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# MEDICINSKI GLASNIK

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# The prevalence of pre-analytical errors in the laboratory of the Cantonal Hospital Zenica in Bosnia and Herzegovina

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## ABSTRACT

**Aim** To identify rates of most common pre-analytical errors and to document possible (different) error rates between inpatients and outpatients.

**Methods** This retrospective study was conducted at the Department of Medical Biochemistry and Immunology Diagnostics, Cantonal Hospital Zenica, from December 2016 until March 2017. Data on rejected blood samples in the laboratory information system were analysed.

**Results** During the 3-month period 35,343 patient blood samples (25,545 inpatients and 9,798 outpatients) were received in the laboratory. The study identified 602 (1.70%) rejected samples because of pre-analytical errors, mostly due to haemolysis, 292 (48.50%), and clotted samples, 240 (39.87%). The remaining 70 (11.63%) samples were rejected because of inappropriate sample volume, inappropriate container and identification errors (7.81%, 2.16% and 1.66%, respectively). The proportion of inpatient rejected samples was 8.7-fold higher than in the outpatient samples. The proportion of inpatient rejected samples because of haemolysis, clotted samples, inappropriate sample volume and inappropriate containers were higher than in the outpatient samples (20.5-, 12.1-, 2.3- and 1.3-fold higher, respectively); proportion of rejected samples because of identification errors was 8.0-fold higher in the outpatient (collection sites outside the hospital) than in the inpatient samples.

**Conclusion** Higher pre-analytical sample error rates were connected with inpatient samples, while higher identification error rates were connected with outpatient samples. Establishment of periodic staff training and introduction of information technology could reduce pre-analytical errors.

**Key words:** diagnostic errors, haemolysis, patient identification systems, pre-analytical phase

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## INTRODUCTION

Diagnostic errors that affect both inpatients and outpatients appear to be the most common, costly and dangerous medical mistakes (1,2). They have an impact on every medical discipline as well as on laboratory medicine (3). Laboratory information plays an important role in medical decision making and it is crucial for diagnostic uncertainty (4). Accordingly, the latest version of the International Standard for medical laboratories accreditation (ISO 15189: 2012) emphasizes the need to “establish quality indicators to monitor and evaluate performance throughout critical aspects of pre-examination, examination and post-examination processes” (5). According to the ISO 15189: 2012 the pre-analytical phase is defined as “steps starting in chronological order, from the clinician’s request and including the examination requisition, preparation of the patient, collection of the primary sample, and transportation to and within the laboratory, and ending when the analytical examination procedure begins” (6).

Pre-analytical phase of the total testing process (TTP) is prone to more errors than analytical phase (7). Pre-analytical phase errors account for 50% to 75% of all laboratory errors (8). On the other hand, analytical phase errors record the significant decrease as a result of several improvements, especially in the internal and external quality control assurance programs (9).

It is widely accepted that the use of Quality Indicators (QIs) minimises the error risk. As basic monitoring and improvement tools they should be integrated in the laboratory improvement strategy (10). Quality Indicators are able to evaluate all key points of TTP including pre-analytical phase (11). The introduction of QIs of the TTP is “a must” in the accreditation process according to ISO 15189 standardisation of medical laboratories (6). Considered as an objective measures, they are fundamental for quantification of the laboratory services quality (11).

Model of Quality Indicators (MQI) proposed by the International Federation of Clinical Chemistry (IFCC) Working Group “Laboratory Errors and Patient Safety” (IFCC WG-LEPS) currently includes 57 QIs (35 pre-, 7 intra- and 15 post-analytical phases). Pre-analytical phase errors basically comprise two traditional QIs categories related to identification and sample problems. Each QIs with its

own priority score (1 = Mandatory; 2 = Important; 3 = Suggested; 4 = Valuable) provides its gradual introduction into routine practice following the order of priority in accordance with their influence to the potential negative clinical outcomes (8,12).

Numerous studies have been conducted worldwide since 1989 in the attempt to demonstrate high pre-analytical phase error rate and how to reduce it (9). There are no studies evaluating pre-analytical errors in any laboratory in Bosnia and Herzegovina.

The aim of this study is to identify the rates of the most common, mandatory, sample and identification pre-analytical errors (haemolysis, inappropriate volume, clotted sample, inappropriate containers and identification errors) and to document possible (different) error rates between inpatients and outpatients.

## MATERIALS AND METHODS

### Materials and study design

This retrospective study was performed during a 3-month period, from December 2016 until March 2017 at the Department of Medical Biochemistry and Immunology Diagnostics, Cantonal Hospital Zenica (Zenica, Bosnia and Herzegovina), serving general and specialized clinical chemistry, haematology, immunology and coagulation testing services. The laboratory is not accredited by the ISO 15189 standard. Data on rejected blood samples in the laboratory information system (LIS) were analysed. The research was done respecting ethical standards of the Declaration of Helsinki. The study approval was obtained from the Ethics Committee of Cantonal Hospital Zenica.

### Methods

For inpatients, phlebotomy was performed by the nursing staff in the clinical wards (outside of the laboratory) and samples were delivered to the laboratory by the hospital delivery personnel. Regarding outpatients, the Department of Medical Biochemistry and Immunology Diagnostics has an outpatient laboratory unit where phlebotomy is performed by laboratory technicians, but also receives (as a core laboratory) numerous samples transported from collection sites (services) outside the hospital, where phlebotomy is also performed by laboratory technicians. Test request forms are

registered into the hospital information system and then transferred into the LIS. Each sample taken from the patient was labelled with a barcode number which is used for identification of the name, surname, gender, age, the type of the tube, sample type, sample collection time and date, site of service where samples were collected, list of the requested tests and name of a doctor who requested tests. After being labelled, samples were subsequently centrifuged, aliquoted and distributed to different laboratory departments. Respective errors, encountered upon admission and later in the testing process, were entered into the LIS, stating that the sample was not processed. The rejected samples were stored in the laboratory for up to 24 hours.

The number and type of errors were retrieved retrospectively from the LIS. Two types of mandatory errors that are recorded into the LIS for every blood sample processed by the laboratory were evaluated: sample errors and identification errors.

As continuously recorded sample errors, according to the sample type (whole blood, serum, plasma) and type of containers for blood sampling, haemolysis, inappropriate volume, clotted sample and inappropriate containers were evaluated for the purpose of this study. Haemolysis was assessed visually by laboratory technicians, and was considered as a sample error, irrespective to the degree of the serum interference and type of test requested. According to the sample type, haemolytic and coagulated samples of any degree were considered unacceptable, and as such were rejected. Identification errors included missing or wrong patient identification data and sample misidentification for all patients and samples.

### Statistical analysis

Data were presented as numbers and percentages. The error prevalence was calculated relative to the total number of errors for each

category (sample type and container type) and expressed as a percentage.

### RESULTS

During the 3-month period 35,343 patient blood samples (25,545 inpatient and 9,798 outpatient samples) were received in the laboratory, of which 602 (1.70%) were rejected because of errors in the pre-analytical phase of laboratory medicine. Stratification of data by the point of collection site revealed that the proportion of rejected samples was higher in the inpatients, 577 (2.26%) than in the outpatients, 25 (0.26%). However, after adjusting for the total number of samples submitted, the proportion of inpatient rejected samples was 8.7-fold higher than in the outpatient samples (Table 1).

**Table 1. Distribution of evaluated and rejected inpatient and outpatient samples**

| Inpatients/<br>outpatients | Collection site                                     | No (%) of samples |            |
|----------------------------|---|-------------------|------------|
|                            |   | Received          | Rejected   |
| Inpatient                  | Clinical wards                                      | 24,968            | 577 (2.26) |
| Outpatient                 | Outpatient laboratory unit in hospital              | 4,882             | 11 (0.22)  |
|                            | collection sites (services) outside of the hospital | 4,891             | 14 (0.29)  |
|                            | Total   | 9,773             | 25 (0.26)  |
| TOTAL                      |   | 34,741            | 602 (1.73) |

Among outpatient samples 4,893 were collected in an outpatient laboratory unit in the hospital, while 4,905 were obtained from collection sites (services) outside the hospital. Stratification of data among outpatients revealed that the proportion of rejected samples was higher in outpatient collection sites outside the hospital, 14 (0.29%) than in the outpatient laboratory unit of the hospital, 11 (0.22%). After adjusting for the total number of samples submitted by both sites, the proportion of rejected samples in the collection sites outside the hospital was slightly (1.3-fold) higher than in the outpatient laboratory unit of the hospital (Table 2).

**Table 2. Distribution of pre-analytical errors in inpatient and outpatient samples**

| Inpatients/<br>outpatients | Collection site                                     | No (%) of samples with identified error |                |                      |                         |                       | Total     |
|----------------------------|---|---|----------------|----------------------|-------------------------|-----------------------|-----------|
|                            |   | Haemolysis                              | Clotted sample | Inappropriate volume | Inappropriate container | Identification error* |           |
| Inpatients                 | Clinical wards                                      | 284 (49.22)                             | 237 (41.07)    | 44 (7.62)            | 10 (1.73)               | 2 (0.35)              | 577 (100) |
| Outpatients                | Outpatient laboratory unit in the hospital          | 8 (32)                                  | 1 (4)          | 0                    | 1 (4)                   | 1 (4)                 | 11 (44)   |
|                            | collection sites (services) outside of the hospital | 0                                       | 2 (8)          | 3 (12)               | 2 (8)                   | 7 (28)                | 14 (56)   |
|                            | Total   | 8 (32)                                  | 3 (12)         | 3 (0.14) (12)        | 3 (12)                  | 8 (32)                | 25 (100)  |
| TOTAL                      |   | 292 (48.50)                             | 240 (39.87)    | 47 (7.11)            | 13 (2.16)               | 10 (1.66)             | 602 (100) |

\*included missing or wrong patient identification data and sample misidentification

Further evaluation of data, according to the number and type of samples and containers showed that 292 (48.50%) out of 602 rejected samples were because of haemolysis, 240 (39.87%) because of clotting, 47 (7.81%) because of inappropriate volume, 13 (2.16%) because of inappropriate container, and the remaining 10 (1.66%) samples were rejected because of identification errors (Table 2). After adjusting for the total number of in- and outpatient samples, the proportion of inpatient rejected samples because of haemolysis, clotting, inappropriate volume and inappropriate container was 20.5-, 12.1-, 2.3- and 1.3-fold higher, respectively, than in the outpatient samples. The proportion of rejected samples because of identification errors was 8.0-fold higher in the outpatient samples (collection sites outside of the Hospital) than in the inpatient samples (Table 2).

## DISCUSSION

We conducted this study with the primary objective of identifying rates of the most common, mandatory, sample and identification errors of blood samples that were rejected in our laboratory, generally and by the point of collection. To our knowledge, this is the first study evaluating these pre-analytical errors in any laboratory in Bosnia and Herzegovina. We detected an overall blood sample rejection rate of 1.70 % in our institution which was around 2.5 times higher than average rejection rate that was reported in similar studies: Atay et al. reported total rejection rate of 0.65 % in a one-year study (13), similar results, with 0.69% rejection rate, were found in an overview of the results of 4 years of the pre-analytical quality control program in 105 laboratories by Alsina et al. (14). The sample rejection rate of 0.3% to 0.8% had also been reported in data from multi-centre quality monitoring programs (15).

According to Joint Commission and the WHO Alliance for patient safety the first goal for clinical laboratories is “to improve patient and sample identification” (16); one of the leading causes of errors in laboratory medicine is identification errors. These errors, due to their potential for misdiagnosis and inappropriate treatment, can have significant consequences for patients, which are associated with the worst clinical outcome. Some studies demonstrate that the quality level of this fundamental step is unsatisfactory, with

the misidentification rate of 1 in 1000 samples (17). Another study showed the misidentification rate of 1 in 2000 samples in transfusion medicine, while much higher rate, approximately 1 in 100, was found in clinical laboratory samples (18).

Bar-coding of sample tubes is recommended as an “evidence-based best practice” since it has been shown that it reduces patient identification errors (19). Dikmen et al. reported 0.3% of misidentification rate in laboratory where electronic bar-coding system is used for identification of patients (20). This procedure is also applied in our institution, and it may be an explanation of far lower rate of 0.03% of identification errors in our laboratory comparing to the above mentioned studies.

The second category of pre-analytical errors includes sample problems. Haemolysis and clotted samples were the primary cause of errors in our laboratory (48.50% and 39.87%, respectively), which is in accordance with other studies. The most commonly reported types of pre-analytical errors in the study of Grecu et al. were also haemolysed samples (46.4%) and clotted samples (43.2%) of similar rate (21). Up to 40–70% haemolytic samples were found according to Lippi G et al. (22). In the study of Alsina et al. (14), 29% and 14% of all rejections were due to haemolysis and to clotted sample, respectively. The main reasons for appearance of haemolysis are vigorous mixing and pneumatic tube transport of the samples as well as forcing of blood through a large-bore needle of a syringe (23). The poor mixing of a content of the vacuum tubes after collecting the blood and keeping them in a horizontal instead the vertical position seems to be the most frequent reason of clotted sample occurrence. Clinical Laboratory Standards Institute (CLSI) recommends that test tubes should be slowly inverted for several times to enable the contact between blood and additives (24). Additionally, the delay of centrifugation for more than 10 minutes after the blood collection as well as use of the conventional syringe/needle/container system instead of vacuum tube system in the blood collection process are frequent reasons for high prevalence of sample coagulation (20).

All blood collection tubes must be filled to the specified volume on the test tubes ensuring the proper blood to additive ratio essential for proper analysis (25). Inappropriate sample volume is the third frequent reason of sample rejection

in our laboratory (7.81%). Other studies showed variation in frequency, from 2.9%, over 22% to 34% (13, 21, 26). Low rate of inappropriateness of container for blood samples in our laboratory (2.16%) is mostly in agreement with other studies (21) probably due to the use of colour coded closures of containers for blood sampling.

Usually, inpatient sample collection is not under control or performed by the laboratory staff. Far higher error rates are demonstrated with clinical ward rather than laboratory staff performing this procedure (27). Our study also showed that the proportion of rejected samples was higher in the inpatients (95.8%) than in the outpatients (4.2%) and that after adjusting for the total number of samples submitted by both sites, the proportion of inpatient rejected samples was 8.7-fold higher than in the outpatient specimens. Similar observations are confirmed in a study of Stark et al. with an error rate of 74.6% for inpatients and 25.4% for outpatients. The proportion of inpatient rejected samples was 5-fold higher than in the outpatient samples (15). We found that all pre-analytical errors, except identification errors, were the most common in inpatients. It is known that the venepuncture in new-borns, children, oncology and patients from intensive care units requires special training and skill (26). This could explain, to some extent, more frequent errors in inpatients. However, since the most common cause of errors is improper venepuncture and handling of blood samples, the reason for this could be insufficient education of the hospital nursing staff in the field of the pre-analytical phase of laboratory medicine. Lillo et al. reported that periodical training and education of the hospital nursing staff by laboratory specialists results in pre-analytical phase improvement (28). Li et al. noted that the incidence of the pre-analytical errors decreased from 1.36% to 0.94% after the step-by-step training program was established (29). Identification errors are far

higher in outpatient samples collected outside of a hospital, probably due to the lack of electronic bar-coding system. In such circumstances laboratories should rely on at least two independent identifiers for proper patient identification (30).

In conclusion, we detected higher overall blood sample rejection rate because of pre-analytical errors in comparison with that reported by others. The study results point the need of QIs introduction even in the non-accredited laboratories despite the lack of official written recommendations of our national scientific community about establishing the QIs for monitoring and evaluation of pre-analytical processes. Additionally, there is a need to establish regular, periodic training of clinical ward staff to reduce errors since higher pre-analytical error rates were demonstrated on samples collected at clinical wards in the hospital. Active participation of hospital workers and laboratory personnel in the process of improvement of pre-analytical quality will enable reduction of potential negative clinical outcomes. On the other hand, establishment of information technology can reduce pre-analytical errors mostly caused by the system-based shortages in outpatients from peripheral collection sites.

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## TRANSPARENCY DECLARATION

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# Development of a novel biofilm classification tool and comparative analysis of result interpretation methodologies for the evaluation of biofilm forming capacity of bacteria using tissue culture plate method

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## ABSTRACT

**Aim** To develop an online biofilm calculation tool (Biofilm Classifier), which calculates the optical density cut off value and accordingly determines the biofilm forming categories for the tested isolates by standardized formulas, as well as to compare the results obtained by Biofilm Classifier to manual calculations and the use of predefined values.

**Methods** The biofilm forming capacity of tested strains was evaluated using tissue culture plate method in 96 well plates, and optical density (OD) value of the formed biofilm was measured on an ELISA Microplate reader at 595 nm on a total of 551 bacterial isolates from clinical specimen.

**Results** Comparative analysis indicated that the manual calculation was 100% in accordance with results obtained by the designed software as opposed to the results obtained by use of predefined values for biofilm categorization. When using predefined values compared to manual biofilm categorization for the determination of biofilm positive and biofilm negative strains the specificity was 100%, sensitivity 97.81%, positive predictive value 100%, negative predictive value 96.04% and accuracy 98.57%.

**Conclusion** Considering obtained results, the use of the designed online calculator would simplify the interpretation of biofilm forming capacity of bacteria using tissue culture plate method.

**Key words:** biofilm, cut-off tissue culture plate method, optical density

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## INTRODUCTION

A gold model for most microbiological examinations is the study of bacteria in pure culture, despite the fact that most bacteria in their natural environment tend to live in associations more commonly known as biofilms (1). A biofilm is an accumulation of microorganisms embedded in a polysaccharide matrix and adherent to a solid biologic or non-biologic surface (1). Due to the increased resistance rates of bacteria embedded in this polysaccharide matrix biofilms have elevated resistance rates to antibiotics and disinfectants (2) and hence they represent a major challenge for microbiologists and clinicians (3). Since biofilms have a significant role in the clinical, industrial and natural setting, the interest in their studying has increased drastically (3).

In the past, there have been many attempts to find simple and reliable methods to detect biofilms. The most commonly used phenotypic assays for the evaluation of biofilm forming capacity today include: the tube test method, Congo red agar method, and tissue culture plate method (TCP) (4), while the detection of biofilm forming genes using polymerase chain reaction (PCR) is amongst the most common genotypic methods. The drawback of the tube test method and Congo red agar method is that they are qualitative tests, they provide results that are neither precise nor sensitive enough. PCR provides more accurate results, however it requires the use of equipment and chemicals that many laboratories do not possess. Therefore, the TCP method is commonly used for the phenotypic evaluation of the biofilm forming potential of species of interest (5,6). Since its very first establishment by Christiansen et al. in 1985 (7) as a quantitative assay for the determination of adherence of staphylococci to medical devices till nowadays, TCP method has been subjected to many modifications and adaptations. Subsequently, scientists in other studies used the values obtained by Christiansen (7) as a referee for the determination of biofilm forming categories (7,8). However, the OD<sub>c</sub> value should be *de novo* calculated for each new experiment considering the minor changes in the experimental conditions (9), yet this is often avoided due to major workload in the laboratory and time efficiency. Accordingly, tube test is often chosen as a qualitative screening test for the evaluation of the

biofilm forming potential of bacterial isolates to avoid calculations needed for TCP. Alternatively, TCP is used, however, biofilm forming categories are determined according to Christiansen's calculations (10).

The aim of our work was to develop an online classification tool for the interpretation of results obtained by the TCP method and at the same time compare the results obtained by this tool to other calculation procedures used for the determination of biofilm forming categories.

## MATERIAL AND METHODS

### Bacterial strains

A total of 551 bacterial strains isolated from clinical specimen were tested. Criteria for inclusion into the study were that the bacteria originated from clinical specimen and that they were isolated in pure culture. The isolated bacterial strains were inoculated in Lauria Bertani (LB) Broth (Liofilchem Bacteriology Products, Roseto/Italy) supplemented with 50% glycerol and kept at -80°C. These bacterial strains were recovered from glycerol stocks by plating on blood agar base (Liofilchem Bacteriology Products, Roseto/Italy) and incubated overnight at 37 °C followed by overnight incubation in tryptic soy broth (TSB) (Liofilchem Bacteriology Products, Roseto/Italy) supplemented with 1% glucose.

### Tissue culture plate method

The TCP method was performed according to current protocols in microbiology (6), by inoculating each bacterial isolate in 5 mL of trypticase soy broth (TSB) supplemented with 1% glucose, aerobically in plastic tubes followed by an incubation at 37 °C for 24 hours. The overnight cultures were diluted in 1:100 ratio in TSB in 96 well polystyrene plates and incubated for additional 24 hours at 37 °C. Samples were arranged in quadruplets. The first quadruplet of uninoculated wells (only media) was used as a negative control. After incubation the trays were washed to remove all planktonic bacteria followed by crystal violet staining (0.1%); 96% alcohol was used as a solvent for crystal violet. Upon a 10-minute incubation 125 µL of the crystal violet/ethanol solution from each well was transferred to a separate well in an optically clear flat-bottom 96-well plate. The optical

density (OD) value was measured on Microplate reader RT-6100 (Rayto Life and Analytical Sciences, Shenzhen/China) at 595 nm.

### Examination of the biofilm forming capacity

The obtained OD of the negative control in quadruplet was used for the calculation of the OD<sub>c</sub> (three standard deviations above the mean OD of the negative control), which was further used for the determination of biofilm forming categories per standardized formulas for manual calculation of biofilm forming categories – which was used as a reference (Table 1).

**Table 1. Comparative analysis of biofilm categorization using three biofilm interpretation methodologies**

| Interpretation method      | No of bacterial strains |      |          |        |
|----------------------------|-------------------------|------|----------|--------|
|                            | Nonadherent             | Weak | Moderate | Strong |
| Predefined value use       | 202                     | 187  | 94       | 68     |
| Manual calculation         | 194                     | 185  | 105      | 67     |
| Online classification tool | 194                     | 185  | 105      | 67     |

### Development and implementation of biofilm classifier

Biofilm Classifier was built in Angular 5, which is an all-encompassing JavaScript framework for building web, desktop, and mobile applications. The whole code was written in Microsoft Visual Studio Code, following the latest updates for faster and more responsive experience.

The program was tested on a database of a total of 551 clinical bacterial isolates. Results obtained on ELISA Microplate Reader were used as inputs for our web application.

### Biofilm classifier tool

Biofilm Classifier available at <http://biofilmclass.com> is an online classification tool that uses the measured OD values of negative control and according to formula ( $3\text{STDEV} + \text{Mean OD neg contol}$ ) calculates the OD<sub>c</sub>. The OD<sub>c</sub> was further used to determine the biofilm forming categories according to predefined formulas for all the other test samples ( $\text{OD} \leq \text{OD}_c = \text{no biofilm producer}$ ;  $\text{OD}_c < \text{OD} \leq 2 \times \text{OD}_c = \text{weak biofilm producer}$ ;  $2 \times \text{OD}_c < \text{OD} \leq 4 \times \text{OD}_c = \text{moderate biofilm producer}$ ;  $4 \times \text{OD}_c < \text{OD} = \text{strong biofilm producer}$ ) (10).

Within the online Classification tool wells of the 96 well plates were grouped into quadruplets (groups of four wells) and labelled with a corresponding letter and number. Since microbiological cultures are usually inoculated vertically in

ELISA test, the first two quadruplets (A1-D1 and E1-H1) represent the negative control (containing only microbiological growth medium) whereas other quadruplets represent the tested samples. A number of tested samples (quadruplets) is required as the initial input and ranges from 2 to 24. Subsequently the obtained OD values from the TCP assay are manually entered and the OD<sub>c</sub> as well as the biofilm forming categories for each sample are determined.

### Statistical analysis

The statistical analysis was carried out using MedCalc online program for the determination of a test's sensitivity, specificity, positive and negative predictive value and accuracy.

## RESULTS

### Comparative analysis of biofilm result interpretation methods

Results of the comparative analysis indicated that the manual calculation was 100% in accordance to the results obtained by the designed software, e. g. online classification tool as opposed to the results obtained by the use of predefined values for the biofilm categorization (Table 1).

The difference in biofilm categorization using predefined values and manual/online classification was less emphasized when the strains were clustered into biofilm positive (weak, moderate and strong) and biofilm negative groups (Table 2). Namely, a total of 8 strains were miss-categorized as biofilm positive using the predefined values for biofilm categorization, which accounts for 1.45% from 551 tested bacterial strains.

**Table 2. Comparative analysis of the three tested biofilm interpretation methodologies**

| Interpretation method   | No (%) of bacterial strains                     |                      |
|---|---|----------------------|
|   | Online classification tool/ manual calculations | Predefined value use |
| <b>Biofilm positive</b> (weak, moderate and strong biofilm forming strains) | 357 (64.79)                                     | 349 (63.34)          |
| <b>Biofilm negative</b> (non-adherent strains)                              | 194 (35.21)                                     | 202 (36.66)          |

Miscategorizations were more emphasized when biofilm positive strains were grouped into three categories (weak, moderate, strong). In this case the difference in categorization occurred in the total number of 2 weak biofilm forming strains, 11

moderate biofilm forming strains and one strong biofilm forming strain (Table 1). This in total yielded a difference in biofilm categorization of 22 strains (14 biofilm positive and 8 biofilm negative) or 4% from the tested 551 bacterial strains using predefined values for biofilm categorization compared to manual calculation as a reference.

Accordingly, the sensitivity and specificity as well as accuracy of the online classification tool compared to manual calculations as a referee was 100% according to statistical analysis.

On the contrary, when using predefined values for biofilm categorization compared to manual biofilm categorization for the determination of biofilm positive and biofilm negative strains - the sensitivity is 97.81%, specificity 100%, positive predictive value 100%, negative predictive value 96.04% and accuracy 98.57%.

The results obtained by comparing manual calculation testing methodologies as a reference using predefined values for each category (to non-adherent stains) for categorization of moderate biofilm forming strains showed the lowest sensitivity, negative predictive value and accuracy, however, it still was over 90% in all cases. The accuracy for weak and moderate biofilm forming categories using predefined values was over 99% (Table 3).

**Table 3. Comparison of the use of predefined values for biofilm category determination to manual calculations using ODc as a reference for each biofilm forming category**

| Results of comparison (%) | Biofilm forming category |          |        |
|---------------------------|--------------------------|----------|--------|
|                           | Weak                     | Moderate | Strong |
| Sensitivity               | 100                      | 90.52    | 100    |
| Specificity               | 98.98                    | 100      | 99.49  |
| Positive predictive value | 98.93                    | 100      | 98.53  |
| Negative predictive value | 100                      | 94.63    | 100    |
| Accuracy                  | 99.48                    | 96.45    | 99.62  |

ODc, three standard deviations above the mean optical density of the negative control

## DISCUSSION

Associations of microorganisms attached to surfaces, more commonly known as biofilms, have received significant attention over the past years due to the role they play in the industrial, natural and clinical setting (1,5). Many biofilm research methodologies have been proposed up to now, genetic and phenotypic (8,10,11). However, due to expenses, the use of phenotypic test is more common for the determination of the biofilm for-

ming capacity of tested microbial strains in laboratory conditions. In the realm of phenotypic testing the use of the tissue culture plate method is considered as a reference method (5). Regardless of that fact, a referent result interpretation methodology for the TCP method is still not defined and established (9).

For the determination of the cut-off value for the TCP method up to now many result interpretation methodologies are encountered and they include: the use of predefined values established by Christiansen in 1985 (8), cut-off calculations based on three standard deviations above the mean OD of the negative control or a biofilm negative strain, considering a strain positive if it is twice the OD of the negative control and some even use the value obtained by the positive control as the starting point (1,2,9, 12-21).

Interpretation procedure that is considered most reliable is the calculation of the cut off based on three standard deviations above the mean OD of the negative control for each 96 well plate separately and subsequent biofilm categorization based upon the use of standardized formulas (10). This falls under the definition of an endpoint titre that is defined as the reciprocal of the highest analyte dilution that gives a reading above the cut off values (22). The fact that no standardized procedure is established for end point titres where there is no positive standard for immunoassay results opens the possibility of use of different calculation procedures as seen in the case of biofilm classification (9,22). In the field of healthcare many automated systems have been developed for the purpose of classification or prediction (23-28).

Since biofilms represent a new frontier in microbiology and are intensively studied, a need to establish result interpretation guidelines for the most commonly used TCP method that would at the same time enable the comparison of data obtained from previous studies would be a milestone in the future studies of this phenomena. Hence the main aim of our study was to develop an online classification tool, available to all, that would aid scientists to determine the biofilm forming capacity of the tested bacterial strains using a common result interpretation method that is not time consuming and is considered most reliable according to previous work (9,22). Besides that, considering the number of studies that employed

the use of predefined values for biofilm classification established by Christiansen (7) in our work we gave a comparison of three evaluation procedures: manual calculation, online classification tool and use of predefined values, and determined their sensitivity, specificity and accuracy.

The results of our study showed that the categorization using the developed online biofilm classification tool were 100% in accordance to the results obtained by the use of manual calculations. The sensitivity and specificity of this calculator both were 100%.

Our study showed that the comparison of the use of predefined values for biofilm categorization to the use of manual calculations missed to classify 1.45% of the strains that produced biofilms. The specificity and positive predictive value were as high as 100%, while the sensitivity was lower at 97.81%, negative predictive value 96.04% and accuracy 98.57%. These parameters were high considering that test results above 95% are considered reliable for the use in laboratory conditions. When comparing manual calculation methodologies as a referee to the use of predefined values for each category (to non-adherent stains) the results of this study for the categorization of moderate biofilm forming strains showed the lowest sensitivity, negative predictive value and accuracy, however, it was still over 90% in all of the cases. The accuracy for weak and moderate biofilm forming categories using predefined values was over 99%. This suggests that the use of predefined values for the biofilm categorization could potentially be used for the determination of biofilm forming categories since it has a sensitivity, specificity and accuracy over 90%. However,

the results can vary to a certain extent and the use of an online tool for exact calculations would aid in the establishment of a referee as a result interpretation methodology for all biofilm classifications using the tissue culture plate method. At the same time using such a referee would allow the comparison of results obtained from different studies and in doing so contribute to the further development of biofilm studies, which represent a new frontier in microbiology today.

The limitation of our study was that only two biofilm result interpretation methodologies were compared while multiple have been used up to now. Hence in our future work we aim to compare the results of all used result interpretation procedures found in literature to enable comparisons of the obtained results.

Due to the fact that biofilms represent a new frontier in microbiology, the establishment of referent testing procedures available and applicable to all in the realm of phenotypic biofilm testing procedures is mandatory for future development of the field.

In our study we developed the first online classification tool for biofilm categorization using TCP method and in doing so set a milestone for establishing a unique result interpretation method for future biofilm studies where the determination of biofilm forming categories for tested samples is a necessity.

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## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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## Effect of intracuff alkalinized 2% lidocaine on endotracheal tube cuff pressure and postoperative throat symptoms in anaesthesia maintained by nitrous oxide

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### ABSTRACT

**Aim** To compare the effects of endotracheal tube cuff inflation media, air, saline and alkalinized 2% lidocaine on increase of cuff pressure (CP) during nitrous oxide maintained anaesthesia and on incidence of postoperative throat symptoms (PTS), and to evaluate the incidence of postoperative throat mucosal injuries (PTMI) depending on cuff inflation medium.

**Methods** Ninety patients who had undergone elective surgery were randomly allocated into 3 equal groups per cuff inflation media: air (group A), saline (group S) and alkalinized 2% lidocaine (group L). The CP was monitored immediately after cuff inflation and further 5, 15, 30, 60 and 90 minutes after intubation. The incidence and intensity of PTS, sore throat, hoarseness, dysphagia and cough were evaluated 2, 6 and 24 hours after extubation. The incidence and intensity of PTMI were evaluated 24 hours after extubation using indirect laryngoscopy examination.

**Results** The highest increase of mean CP was recorded in the group A ( $18.7 \pm 4.9$ ), it was significantly lower ( $6.4 \pm 1.1$ ) in the group S, while it remained stable in the group L ( $0.7 \pm 0.7$ ). All PTS occurred less frequently in the group L: sore throat ( $p < 0.001$ ), hoarseness and dysphagia ( $p < 0.05$ ), but the incidence of cough was not significantly different between the groups. The lowest incidence of PTMI was in the group L ( $p < 0.001$ ).

**Conclusion** The increase of CP contributed to incidence of PTS. The intracuff alkalinized 2% lidocaine was superior to saline and air in the prevention of an increase of CP and reduction of the PTS incidence. There was a strong correlation between the incidence of PTS and PTMI.

**Key words:** cough, dysphagia, hoarseness, sore throat

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## INTRODUCTION

Endotracheal tube provides secure airway, optimal mechanical ventilation and protects from the risk of gastric content aspiration during general anaesthesia. Tracheal intubation is connected with local mechanical irritation, trauma and inflammatory response of the pharyngolaryngeal and tracheal mucosa (1). Preoperative dehydration, trauma from suction before extubation and endotracheal tube cuff pressure (CP) during anaesthesia are additional factors which impair postoperative throat mucosal injuries (PTMI). Anaesthesiologists usually inflate the cuff with air. The cuff makes sure that endotracheal tube stays in place and recommended CP is between 20 - 25 cm H<sub>2</sub>O (2). Higher CP results in the reduction of the tracheal mucosa perfusion and ischemia. CP above 30 cmH<sub>2</sub>O overlaps capillary blood flow through mucosal vessels and induces various mucosal lesions like: erythema, edema, haematoma, erosions, ulceration, granuloma, etc. (3). These lesions provoke an organic basis for patients' postoperative throat symptoms (PTS): sore throat, hoarseness, dysphagia and cough. The PTS is attributed to multiple perioperative conditions (4). The risk factors leading to PTS could be related with patients (elderly age, female gender, history of smoking, diabetes mellitus, hypertension, hypotension, malnutrition, which could aggravate mucosal perfusion and predispose it to mechanical damage of instrumentation in throat and effects of CP (5), with anaesthesia technique (size of endotracheal tube, type of tube, cuff design, value of CP, use of N<sub>2</sub>O in the gas mixture, intubation technique, anaesthesiologist's experience, application of muscle relaxation, movement of the tracheal tube during surgery and excessive pharyngeal suctioning at extubation) (6) and with surgery (type of surgery, surgical technique, insertion of nasogastric tube, patient's position on the operating table and duration of operation (7). During anaesthesia maintained by nitrous oxide (N<sub>2</sub>O), the CP rises because of N<sub>2</sub>O diffuses into cuff more rapidly than it leaves. After 30 minutes of N<sub>2</sub>O anaesthesia, the CP reaches critical pressure of 30 cmH<sub>2</sub>O (8). The overinflation of cuff predisposes the patients to PTS by increasing contact area between cuff and mucosa. The measurement of endotracheal tube CP has not been a part of daily anaesthetic clinical practice. Me-

dical staff pay most attention to outcome of the surgical procedures. The PTSs are not routinely investigated and patients suffer from untreated difficulties. Although the PTSs were considered as minor postoperative complications, they could significantly affect the quality of the recovery period and delay oral intake (9). The examination of larynx after airway instrumentation is not routine practice and PTMIs are often neglected.

As a cuff inflation medium in various concentrations alkalinized lidocaine significantly prevents hyperinflation of cuff and eliminates one of the underlying mechanisms of the postoperative throat adverse events (10). Some efforts for preventing PTS have been made, but conclusive measures have not been elucidated yet. No special medication or procedure has been completely useful for pain control (11).

The aim of this study was to compare the increase of CP during N<sub>2</sub>O anaesthesia, the incidence and intensity of PTS between three cuff inflation media, air, saline and alkalinized 2% lidocaine, and to evaluate correlation between an increase of CP and subjective PTS. Additionally, a comparison of the incidence and intensity of PTMI, which was evaluated by indirect laryngoscopic examination depending on three cuff inflation media, and an evaluation of a correlation between subjective throat symptoms and objective clinical finding were done.

## PATIENTS AND METHODS

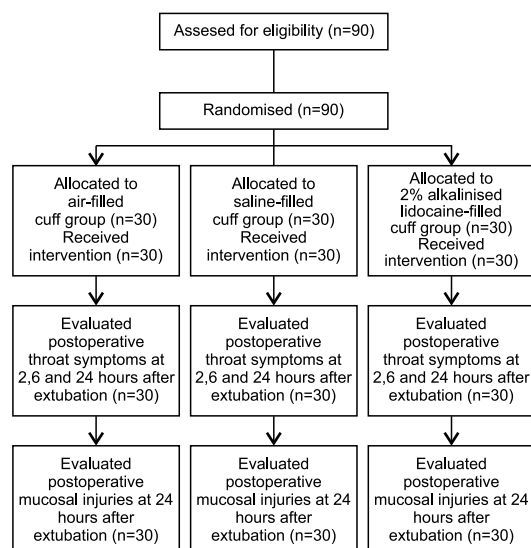
### Patients and study design

This prospective randomized, double-blinded clinical study was conducted in the Department of Anaesthesiology and Intensive Care Unit and the Department of Otorhinolaryngology at the Cantonal Hospital in Zenica, Bosnia and Herzegovina. The study took place during a three-month period, from January to April 2018. The study protocol was approved by the Ethics Committee of the Cantonal Hospital in Zenica.

After obtaining a written informed consent, 90 patients were included in the study. Inclusion criteria were: adult patients aged 18-65 years without predictive signs of difficult intubation, with the American Society of Anesthesiologists (ASA) physical status classes I – III (12), all underwent endotracheal intubation for various elective surgi-

cal procedures, duration not longer than 2 hours, in the supine position. Exclusion criteria were: emergency surgery and surgery in the mouth, throat or neck area, history of smoking, history of preoperative cold, sore throat, cough or hoarseness in the last month, potentially difficult intubation, Mallampati score III and IV (13), more than one attempt needed to achieve tracheal intubation, patients with increased risk of aspiration or gastroesophageal regurgitation, intraoperative nasogastric tube placement, patients with cardiopulmonary, neuromuscular, renal or hepatic disease, body mass index above 40 kg/cm<sup>2</sup>, history of allergy to any study drugs, pregnancy, prone position during operation, administration of succinylcholine in anaesthesia or rapid sequence induction.

The day before the surgery patients were randomized into three equal groups with 30 patients by a nurse who was not involved in the study (Figure 1). A closed envelope contained a code indicating the treatment was used according to computer software randomization. Patients were divided in three groups considering cuff inflation medium: group A (the cuff inflated with air), group S (the cuff inflated with 0.9% saline) and group L (the cuff inflated with alkalized 2% lidocaine). Group A was considered as a control group hence group S and group L were experimental groups.



**Figure 1. CONSORT flow diagram of patients distribution in the study**

## Methods

**Anaesthesia and assessment of CP.** In the operating room, an intravenous cannula of 18 G was inserted to all patients. Standard non-invasive clinical monitoring was performed: pulse oximetry, arterial blood pressure, the electrocardiogram, capnography and neuromuscular block monitoring. Three minutes before induction, all patients were pre-medicated with midazolam 0,05 mg/kg intravenously and preoxygenated with 100% oxygen by facial mask. Anaesthesia was induced with propofol 2 mg/kg, fentanyl 1 µg/kg and atracurium 0,6 mg/kg. After the loss of all four twitches from „train of four“ (TOF) stimulation of the ulnar nerve, endotracheal intubation was made with Machintosh laryngoscope blade size 3 (Machintosh blade, Teleflex/Rüsch, Germany). Trachea was intubated with high-volume low-pressure cuffs endotracheal tube and appropriate inner diameter was chosen individually, for males 8.0-8.5 mm and for females 7.0-7.5mm. No lubricant was used on the tube before intubation. One experienced anaesthesiologist, blinded of experimental protocol, performed endotracheal intubation and anaesthesia in all patients during the study. Another anaesthesiologist, who was not blinded to study protocol, though excluded from the data collection, carefully inflated cuffs in all patients. The cuffs were inflated using the minimal occlusive volume technique with the same coloured syringes in the volume of 20 mL. Previously, the cuffs were completely deflated and after intubation the cuffs were gradually inflated with various medium until the air leak stopped during positive pressure ventilation with tidal volume of 6 mL/kg and peak respiratory pressure to 25 cmH<sub>2</sub>O. In the group A (control group), the cuff was inflated with air. In the group S, the cuff was inflated with 0.9% saline. In the group L, the cuff was inflated with alkalized 2% lidocaine (20 mL syringe filled with mixture 2% lidocaine and 8,4% sodium bicarbonate in 19:1 ratio). The volume of the inflation medium was noted. The intracuff pressure was monitored using portable non-invasive manometer graduated in cmH<sub>2</sub>O and continuously connected to the pilot balloon of the endotracheal tube (Endotest for low pressure cuffs, Rüsch, Germany). Basal value of CP ( $t_0$ ) was documented immediately after cuff inflation. Further, CP was noted 5 ( $t_5$ ), 15 ( $t_{15}$ ), 30 ( $t_{30}$ ),

60 ( $t_{60}$ ) and 90 ( $t_{90}$ ) minutes after intubation. Balanced anaesthesia was maintained as long as necessary for each case using sevoflurane minimum alveolar concentration of 0.5-1 %,  $N_2O$  50% in oxygen, at a total flow of 2 L/min. End tidal carbon dioxide was maintained at 30-35 mmHg. At the beginning of the skin closure, every patient received tramadol chloride 100 mg intravenously, to provide postoperative analgesia. At the end of the surgery, when TOF >0.7 neuromuscular block was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. The patients were extubated fully awake after minimal and gentle mouth suctioning and transferred to the post-anaesthesia care unit. Oral airway devices were not used intraoperatively.

**Assessment of the incidence and intensity of PTS.** The incidence and intensity of PTS were evaluated 2, 6 and 24 hours after extubation according to a 4-point verbal rating scale. Patients were questioned by an observer who was blinded to the study protocol. Sore throat was defined as constant pain or discomfort in the throat independent of swallowing. Intensity of the sore throat was assessed as follows: 0 – no sore throat, 1 – minimal sore throat (less severe than with cold), 2 – moderate sore throat (similar to that noted with cold), 3 – severe sore throat (more severe than with cold). Hoarseness or dysphonia was defined as difficulty in speaking or pain on speaking. Intensity of the hoarseness was scored as: 0 – no hoarseness, 1 – mild hoarseness (noticed by the patient only), 2 – severe hoarseness (noticed by the observer at the time of the interview), 3 – aphonia (inability to speak). Dysphagia was defined as difficulty or pain provoked by swallowing. Intensity of the dysphagia was scored as: 0 – no complaints, 1 – mild dysphagia, 2 – severe dysphagia, 3 – cannot swallow because of pain. Cough was defined as a sudden reflex that forces air out of the throat. Grades of coughing episodes were: 0 – no cough, 1 – one cough, 2 – more than one episode of unsustained coughing, 3 – sustained and repetitive coughing with head lift.

**Assessment of the incidence and intensity of PTMI.** The incidence and intensity of PTMI were evaluated 24 hours after extubation using indirect laryngoscopy. Pharynx, epiglottis, arytenoid and vocal cords were observed. Intensity of PTMI was graded as: erythema (redness of the

mucosa), edema (inflammatory swelling of the mucosa), haematoma (bleeding into mucosa), arytenoid subluxation/luxation (displaced arytenoid with limited movement) and granuloma (granulation tissue into mucosa). Indirect laryngoscopy was performed by an experienced otorhinolaryngologist who was not involved in the study protocol.

The following data were also recorded: age, sex, body weight, ASA physical status class, Mallampati score, type of surgery, volume of intracuff medium, size of endotracheal tube and time from intubation to extubation.

### Statistical analysis

Sample size was estimated using sample size calculator software with 95% confidence interval and power of 80%. Statistical significance was considered as  $p < 0.05$ . Categorical variables were analysed by Pearson's  $\chi^2$  test and presented as frequency and relative number of cases (percentage). The parametric variables were expressed as means and standard deviation and analysed by Student's  $t$  test, one way analysis of variance (ANOVA) and Pearson's correlation as appropriate.

### RESULTS

During the study no patients were excluded from the analysis. All patients were intubated at first attempt. There was no statistically significant difference between demographic parameters in three groups: age, body weight, gender, ASA physical status grade, Mallampati score, type of surgery, size of the endotracheal tube, volume of the intracuff medium and duration of intubation period (Table 1).

Although the basal values of CP were very close between the groups, in the group A basal CP was statistically significantly higher compared to other two groups ( $p < 0.05$ ). Through 90-minute observation period, the highest increase of mean CP was recorded in the group A ( $18.7 \pm 4.9$ ). The CP raised to statistically significant level between each studied time points ( $p < 0.05$ ) in the group A and critical pressure of 30 cmH<sub>2</sub>O was reached 15 minutes after intubation. In the group S, increase of mean CP was statistically significantly lower ( $6.4 \pm 1.1$ ;  $p < 0.01$ ) than in the group A. The mean CP was maintained below the critical pressure of

**Table 1. Demographic characteristics of patients**

| Parameter   | Group A <sup>*</sup>      | Group S <sup>†</sup>      | Group L <sup>‡</sup>      | p     |
|---|---------------------------|---------------------------|---------------------------|-------|
| <b>Male/Female</b> No ( % )                                     | 15/15<br>(50/50)          | 16/14<br>(53.3/46.7)      | 13/17<br>(43.3/56.7)      | 0.733 |
| <b>Age</b> (years (mean (± standard deviation)                  | 50.8<br>(±9.7)            | 47.4<br>(±11.9)           | 50.1<br>(±12.2)           | 0.471 |
| <b>Body weight</b> (kg) mean (± standard deviation)             | 80.4<br>(±10.7)           | 85.6<br>(±11.8)           | 81.7<br>(±11.3)           | 0.177 |
| <b>Type of surgery</b> No ( % )                                 |                           |                           |                           | 0.832 |
| Inguinal hernia   | 8<br>(26.7)               | 10<br>(33.3)              | 10<br>(33.3)              |       |
| Cholecystectomy   | 8<br>(26.7)               | 11<br>(36.7)              | 11<br>(36.7)              |       |
| Mastectomy  | 6<br>(20.0)               | 4<br>(13.3)               | 5<br>(16.7)               |       |
| Transurethral resection of the prostate                         | 8<br>(26.7)               | 5<br>(16.7)               | 4<br>(13.3)               |       |
| <b>Mallampati score class I/II</b> (No / % )                    | 21/9<br>(70/30)           | 24/6<br>(80/20)           | 20/10<br>(66.7/33.3)      | 0.487 |
| <b>ASA status class I/II/III</b> (No / % )                      | 14/13/3<br>(46.7/43.3/10) | 14/13/3<br>(46.7/43.3/10) | 12/14/4<br>(40/46.7/13.3) | 0.978 |
| <b>Tube size</b> mean (± standard deviation)                    | 7.9<br>(±0.5)             | 7.8<br>(±0.5)             | 7.8<br>(±0.6)             | 0.600 |
| <b>Volume cuff media</b> (mL) mean (± standard deviation)       | 4.9<br>(±0.6)             | 4.7<br>(±0.5)             | 4.9<br>(±0.4)             | 0.526 |
| <b>Duration of intubation</b> (min) mean (± standard deviation) | 87.9<br>(±9.9)            | 89.2<br>(±11.3)           | 87.5<br>(±14.5)           | 0.856 |

\*group A, the cuff inflated with air; †group S, the cuff inflated with 0.9% saline; ‡group L, the cuff inflated with alkalized 2% lidocaine; ASA, American Society of Anesthesiologists

30 cmH<sub>2</sub>O during the procedure. In the group L, the mean CP remained stable (0.7±0.7). Post hoc analysis using Student's t test indicated significant difference at all studied time periods between groups (Table 2).

**Table 2. Cuff pressure (cmH<sub>2</sub>O) according to the groups and study time**

| Parameter <sup>*</sup> | Group A <sup>†</sup><br>Mean (±SD)<br>95%CI | Group S <sup>‡</sup><br>Mean (±SD)<br>95%CI | Group L <sup>§</sup><br>Mean (±SD)<br>95%CI | p     |
|------------------------|---|---|---|-------|
| <b>CPt0</b>            | 21.43(±2.19)<br>20.61-22.25                 | 19.53 (±2.90)<br>18.45-20.62                | 18.20 (±1.58)<br>17.61-18.79                | 0.001 |
| <b>CPt5</b>            | 26.90(±3.02)↑<br>25.77-28.03                | 21.80(±3.03)↑<br>20.67-22.93                | 18.80 (±1.27)<br>18.33-19.27                | 0.001 |
| <b>CPt15</b>           | 30.77(±3.31)↑<br>29.53-32.01                | 23.87(±2.87)↑<br>22.79-24.94                | 18.93 (±1.28)<br>18.45-19.41                | 0.001 |
| <b>CPt30</b>           | 34.10(±4.02)↑<br>32.60-35.60                | 25.33(±3.12)↑<br>24.17-26.50                | 8.93 (±1.28)<br>18.45-19.41                 | 0.001 |
| <b>CPt60</b>           | 37.47(±4.54)↑<br>35.77-39.16                | 25.93(±2.99)↑<br>24.82-27.05                | 18.93 (±1.28)<br>18.45-19.41                | 0.001 |
| <b>CPt90</b>           | 39.88(±5.95)↑<br>36.70-43.05                | 26.21(±2.89)↑<br>24.81-27.61                | 19.20 (±1.37)<br>18.44-19.96                | 0.001 |

\*Data was expressed as mean and standard deviation (±SD); CI, confidence interval; CP, cuff pressure (cmH<sub>2</sub>O); t0, immediately after cuff inflation; t5, cuff pressure 5 minutes after intubation; t15, cuff pressure 15 minutes after intubation; t30, cuff pressure 30 minutes after intubation; t60, cuff pressure 60 minutes after intubation; t90, cuff pressure 90 minutes after intubation; †group A, the cuff inflated with air; ‡group S, the cuff inflated with 0.9% saline; §group L, the cuff inflated with alkalized 2% lidocaine; ↑, p<0.05 for the difference between two points of study time within the same group;

The highest incidence of sore throat was noted in the group A, considerably less in the group S (p<0.05) and it was the lowest in the group L (p<0.001) 2, 6 and 24 hours after extubation. The incidence of sore throat dropped by half in the group S (23.3%) and in the group L (13.3%), 6 hours after extubation, while it remained unchanged (60%) in the group A. Twenty-four hours after extubation, sore throat persisted only in the group A.

The peak of hoarseness incidence was recorded 2 hours after extubation: 18 (60%) patients in the group A, 14 (46.3%) in the group S and 7 (23.3%) in the group L. The distribution of hoarseness 6 hours after extubation was only slightly lower in all groups but the difference was still statistically significant (p<0.043). The incidence of hoarseness was not significantly different between the groups, 24 hours after extubation, despite of higher occurrence (30%) in the group A than (6.7%) in the group L.

The incidence of dysphagia was significantly higher in the group A compared to the group S and L, 2 hours (p<0.05) and 6 hours (p<0.001) after extubation, while there was no notable difference between the groups 24 hours after extubation.

There was a trend of decreasing the incidence of postoperative cough in the L group comparing with the group A and the group S, but it was not statistically significant (Table 3).

**Table 3. Incidence of postoperative throat symptoms according to the groups**

| Symptom            | Time after extubation | No (%) of patients   |                      |                      | P     |
|--------------------|-----------------------|----------------------|----------------------|----------------------|-------|
|                    |                       | Group A <sup>*</sup> | Group S <sup>†</sup> | Group L <sup>‡</sup> |       |
| <b>Sore throat</b> | 2h                    | 18 (60)              | 14 (46.7)            | 7 (23.3)             | 0.015 |
|                    | 6h                    | 18 (60)              | 7 (23.3)             | 4 (13.3)             | 0.001 |
|                    | 24h                   | 4 (13.3)             | 0                    | 0                    | 0.015 |
| <b>Hoarseness</b>  | 2h                    | 18 (60.0)            | 14 (46.7)            | 7 (23.3)             | 0.015 |
|                    | 6h                    | 15 (50.0)            | 9 (30.0)             | 6 (20.0)             | 0.043 |
|                    | 24h                   | 9 (30.0)             | 9 (30.0)             | 2 (6.7)              | 0.060 |
| <b>Dysphagia</b>   | 2h                    | 16 (53.3)            | 11 (36.7)            | 7 (23.3)             | 0.050 |
|                    | 6h                    | 15 (50.0)            | 4 (13.3)             | 2 (6.7)              | 0.001 |
|                    | 24h                   | 3 (10.0)             | 4 (13.3)             | 1 (3.3)              | 0.383 |
| <b>Cough</b>       | 2h                    | 7 (26.6)             | 5 (16.7)             | 4 (13.3)             | 0.587 |
|                    | 6h                    | 6 (20.0)             | 3 (10.0)             | 3 (10.0)             | 0.421 |
|                    | 24h                   | 2 (6.7)              | 2 (6.7)              | 1 (3.3)              | 0.809 |

\*group A, the cuff inflated with air; †group S, the cuff inflated with 0.9% saline; ‡group L, the cuff inflated with alkalized 2% lidocaine; ↑, p<0.05 for the difference between two points of study time within the same group;

Most commonly the intensity of PTS was rated with grade 1 as minimal or mild intensity. In the group A, one patient (3.3%) rated sore throat with grade 2 (moderate sore throat) 2 hours after extubation, and two patients (6.7%) 6 hours after extubation. In the group S, two patients (6.7%) declared sore throat with grade 2, 2 hours after extubation. Hoarseness was noted with grade 2 (severe hoarseness) by one patient (3.3%) in the group A and two patients (6.7%) in the group S, 2 hours after extubation. Intensity of dysphagia was declared with grade 1 at all recording times in all groups. Cough was noted with grade 2 (more than one episode of coughing) by one patient (3.3%) in the group S and one patient (3.3%) in the group L two hours after extubation. None of the patients described PTS with grade 3. The increase of mean CP during anaesthesia and incidence of PTS were directly related. Significant correlation ( $\rho=0.450$ ;  $p=0.0001$ ) was found between the increase of mean CP ( $18.7\pm4.9$ ) and overall incidence of PTS ( $4.3\pm2.1$ ) in the group A. In the group S, a notably lower change of mean CP ( $6.4\pm1.1$ ) was associated with lower overall incidence of PTS ( $2.6\pm1.8$ ) and the relation was statistically significant ( $\rho=0.494$ ;  $p=0.0001$ ). In the group L, significant correlation was not found considering that the increase of mean CP was ne-

gligible ( $0.7\pm0.7$ ) and connected with the lowest incidence of overall PTS ( $1.5\pm1.4$ ).

Overall incidence of PTMI was higher in the group A (90%) than in the group S (70%) or in the group L (36.7%). With regard to localisation, PTMI was mostly placed in vocal cord left: 17 (56.7%) patients in the group A, 11 (36.7%) in the group S and five (16.7%) in the group L. With regard to intensity of PTMI, most commonly occurring lesion was erythema. Edema was only noted in the group A. Other lesions, e. g. haematoma, arytenoid subluxation/luxation and granuloma were not noted (Table 4).

A correlation between overall incidence of subjective PTS recorded at all studied time points and incidence of PTMI was excellent. In the group A  $\rho=0.651$  ( $p=0.0001$ ), in the group S  $\rho=0.651$  ( $p=0.0001$ ) and in the group L  $\rho=0.443$  ( $p=0.44$ ). The coefficient correlation for the entire sample was  $\rho=0.733$  ( $p=0.0001$ ).

## DISCUSSION

The presented study investigated the effect of alkalized 2% lidocaine used as a cuff inflation medium on endotracheal tube CP during  $N_2O$  maintained anaesthesia and on PTS.

The results of this study suggest that alkalized 2% lidocaine is better cuff inflation medium comparing to saline or air to prevent increase of CP and postoperative sore throat, hoarseness and dysphagia. Alkalized lidocaine also reduced the incidence of postoperative cough, but with no statistical significance. There was a positive correlation between increase of CP during  $N_2O$  anaesthesia and incidence and intensity of the subjective PTS. Alkalized lidocaine had more superior activity than saline or air in reducing incidence and intensity of PTMI evaluated by indirect laryngoscopy. There was a positive correlation between subjective throat symptoms and objective clinical findings.

In this study many of the risk factors for PTS were controlled by inclusion criteria, exclusion criteria and adjusted anaesthesia airway management in order to reduce bias and minimize the influence of confounding factors as much as possible. The results of demographic data were standardized between the groups. The aforementioned circumstances allowed us to explain our results in light of overwhelming influence of various intracuff media on CP and PTS.

**Table 4. Incidence and intensity of postoperative throat injuries according to the groups**

| Localisation of injuries                       | Intensity of injuries | No (%) of patients |           |           | p     |
|--|-----------------------|--------------------|-----------|-----------|-------|
|  |                       | Group A*           | Group S†  | Group L‡  |       |
| Pharynx  | No lesion             | 11 (36.7)          | 21 (70)   | 26 (86.7) | 0.001 |
|  | Erythema              | 15 (50)            | 9 (30)    | 4 (13.3)  |       |
|  | Edema                 | 4 (13.3)           | 0 (0)     | 0 (0)     |       |
| Epiglottis                                     | No lesion             | 29 (96.7)          | 30 (100)  | 30 (100)  | 0.364 |
|  | Erythema              | 1 (3.3)            | 0 (0)     | 0 (0)     |       |
|  | Edema                 | 0 (0)              | 0 (0)     | 0 (0)     |       |
| Arytenoid                                      | No lesion             | 22 (73.3)          | 23 (76.7) | 26 (86.7) | 0.499 |
|  | Erythema              | 7 (23.3)           | 7 (23.3)  | 4 (13.3)  |       |
|  | Edema                 | 1 (3.3)            | 0 (0)     | 0 (0)     |       |
| Vocal cord right                               | No lesion             | 22 (73.3)          | 26 (86.7) | 29 (96.7) | 0.036 |
|  | Erythema              | 8 (26.7)           | 4 (13.3)  | 1 (3.3)   |       |
|  | Edema                 | 0 (0)              | 0 (0)     | 0 (0)     |       |
| Vocal cord left                                | No lesion             | 13 (43.3)          | 19 (63.3) | 25 (83.3) | 0.006 |
|  | Erythema              | 17 (56.7)          | 11 (36.7) | 5 (16.7)  |       |
|  | Edema                 | 0 (0)              | 0 (0)     | 0 (0)     |       |
| Overall incidence of injuries within the group |                       | 27 (90)            | 21 (70)   | 11 (36.7) | 0.001 |

\*group A, the cuff inflated with air; †group S, the cuff inflated with 0.9% saline; ‡group L, the cuff inflated with alkalized 2% lidocaine;

The CP was not monitored and measured routinely. Anaesthesiologists estimate CP by pilot balloon palpitation, using their own experience, but Jain et al. concluded that it is not an accurate and safe method (14). The increase of CP is responsible for the reduction in mucosal perfusion and occurrence of PTS (15). One of the proposed methods to reduce CP is filling the cuff with alkalinized lidocaine (16). The N<sub>2</sub>O diffuses into cuff and causes spreading of lidocaine outside of cuff. That balance provides stable CP during anaesthesia (17). Outside of cuff lidocaine acts as a local anaesthetic to the mucosa and blunt PTS. Alkalinization of lidocaine with sodium bicarbonate increases pH value of the solution to 7.43 accelerates diffusion through cuff and anaesthetic action of lidocaine to the mucosa (18). Many investigators assessed effectiveness of alkalinized lidocaine on CP and the occurrence of PTS (19). Various methodological approaches are the reason of contradictory findings between the studies. To our knowledge, there is no earlier study which evaluated impact of intracuff alkalinized 2% lidocaine on CP, on the incidence and intensity of PTS in connection with PTMI, in N<sub>2</sub>O maintained anaesthesia and surgical procedures lasting up to 2 hours. The results of this study have shown the absence of CP increase using 2% alkalinized lidocaine as a cuff inflation medium during N<sub>2</sub>O anaesthesia. The saline-inflated cuff kept CP below the critical value of 30 cmH<sub>2</sub>O because liquid does not expand volume when N<sub>2</sub>O diffuses in it, but CP increased statistically significant.

A revealed incidence of postoperative sore throat is 30 – 70% (20). The activation of pain receptors in throat mucosa due to adherence of endotracheal tube and cuff cause PTS. (21). In this study the peak of sore throat was 2 hours after extubation with the incidence between 23.3% in the lidocaine group and 60% in the air group. In the saline group lack of sore throat was not reached despite of the absence of cuff overinflation because of mechanical effects of endotracheal tube on throat mucosa.

Mechanical trauma during endotracheal intubation and influence of CP during anaesthesia cause edema of vocal cords, which leads to postoperative hoarseness in the overall incidence from 20-53% (22). In the present study, the highest incidence of hoarseness (60%) was in relation with the highest value of mean CP (39.88 cmH<sub>2</sub>O).

Hamdan et al. found that the mean CP is most influent factor associated with incidence of vocal symptoms (23). Twenty-four hours after extubation, hoarseness persisted in 30% patients in the air group, while alkalinized lidocaine reduced hoarseness to 7.6%. Some investigators reported persistent hoarseness as many as 11% for up to 96 hours postoperatively (24).

The presumed reasons for onset of dysphagia include neuropraxia of the recurrent laryngeal nerve and mucosal injuries like edema or haematoma (25). Alkalinized 2% lidocaine suppressed postoperative dysphagia better than other two media in this study by limiting CP. Arts et al. suggested that adjustment of CP to 20 mmHg (26 cmH<sub>2</sub>O) decreased the incidence of dysphagia (26).

Cough is provoked by mechanical or chemical factors that act to sensory receptors along the respiratory mucosa with postoperative incidence ranging from 40-90% (27). Cough is a protective airway reflex, but it can lead to arrhythmias, hypertension, increase intraocular and intracranial pressure, bronchospasm, wound dehiscence and postoperative surgical complications (28). The present study detected beneficial effects of alkalinized 2% lidocaine on postoperative cough, but with no statistical significance. D'Aragon et al. have found that alkalinized lidocaine has no influence on incidence of cough (29). Contrary to that study, Souissi et al. achieved significant reduction of postoperative cough but N<sub>2</sub>O-free anaesthesia was conducted and a larger amount of intracuff alkalinized lidocaine was used than in our study (160 mg versus approximately 100 mg), beside the duration of lidocaine diffusion that was up to 2 hours (30). The diffusion time longer than 2 hours would allow effective anaesthetic concentration in the mucosa to produce a reversible block in the transmission of peripheral nerve impulses (31). Respectively, lower incidence of coughing (3.3-26.6%) in the presented study than in the literature could be explained by very strict airway management method during anaesthesia.

With regard to intensity of PTS, patients predominantly expressed mild symptoms, grade one of intensity. The low intensity of symptoms was not the reason to neglect PTS, particularly if the cuff overinflation and throat mucosal injuries were presented.

The observation of PTMI in our study was provided by indirect laryngoscopy examination. Fiberoptic laryngoscopy was available to us, but a more simple, cheaper and less invasive method was used. Efficiency of alkalinized 2% lidocaine in the prevention PTMI was confirmed in the presented study. The left vocal cord is injured more often than the right vocal cord because insertion of endotracheal tube goes from the right angle of the mouth to the left side of glottis (32). In terms of intensity of injuries, the most common finding in our study was erythema in all groups. Edema was recorded only in the air group due to the beneficial effect of saline and alkalinized lidocaine on CP.

Because the symptoms are always subjective, the incidence of PTS in our study was evaluated in relation with the incidence of PTMI. A strong correlation between subjective throat symptoms and objective clinical finding was found.

This study has some limitations. The effects of alkalinized 2% lidocaine on haemodynamic changes during extubation were not observed. Investigators revealed that intacuff alkalinized lidocaine induces significantly less heart rate and blood pressure during extubation, compared with air and saline group in children (33) and adults (34). There was no evaluation of deflating volume of intracuff media at extubation time. The expectation is that deflating volume of liquid media would be less than inflating volume because of the diffusion through the cuff. In the air group,

removed volume would be larger than inflating because of the absorption of N<sub>2</sub>O into cuff (35). We did not have a possibility to detect the serum concentration of lidocaine. The statements of previous investigators that intracuff alkalinized lidocaine has no cumulative effect in the patient's serum were considered. (36).

There was no depression of swallowing reflex, laryngospasm, cuff rupture, any sign of toxicity or any adverse effects during the study, confirming this technique safe and applicable in clinical practice. Further research is needed to evaluate optimal dose of alkalinized 2% lidocaine to obtain significant reduction on the incidence of cough in the aforementioned conditions.

In conclusion, N<sub>2</sub>O maintained anaesthesia is associated with significant increase of CP. The increase of CP contributes to incidence and intensity of PTS. The intracuff alkalinized 2% lidocaine is a better cuff inflation medium than air and saline in limiting CP, the prevention of PTS and PTMI. The incidence of postoperative cough is reduced but not significantly different. The use of intracuff alkalinized 2% lidocaine is a safe and reliable method which could be recommended in daily anaesthesia practice.

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## TRANSPARENCY DECLARATIONS

Competing interest: none to declare

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## Extracorporeal shock wave lithotripsy effect on renal arterial resistive index changing

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### ABSTRACT

**Aim** To investigate a correlation between resistive index (RI) level changes following extracorporeal shock wave lithotripsy (ESWL) in treated and non-treated kidneys depending on the ESWL treatment intensity.

The study was conducted on 60 subjects, which were divided in two groups according to age and treatment protocol.

**Results** In the group of patients younger than 55 years of age there was a significant increase in mean RI values, on the first ( $p=0.001$ ) and second day after the treatment ( $p=0.007$ ). In the group older than 55 years of age, the resulting increase in mean RI levels was also significant on the first ( $p=0.003$ ) and second ( $p=0.011$ ) day following the treatment. The RI values in the non-treated kidney on the first day after the treatment grew significantly ( $p=0.033$ ). In the group older than 55, RI values in the non-treated kidney grew significantly on the first day after the treatment ( $p=0.044$ ). In the group who received 2000 SWs, RI levels grew significantly ( $p=0.044$ ) as well as in the group who received 4000 SWs during the treatment, where the significance was more pronounced ( $p=0.007$ ).

**Conclusion** There is a correlation between RI changes and the degree and localization of changes in vascular elements of the kidney. Post-ESWL treatment changes are existent and reversible, over a period of one week after the treatment.

**Key words:** treatment, renal circulation, safety

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## INTRODUCTION

Extracorporeal Shock Wave Lithotripsy (ESWL), as a treatment option of nephrotic calculosis, affects the pathophysiology of the kidney itself (1). A correct assessment of renal vascular resistance is made by obtaining clear spectra from at least three different intrarenal arteries in various parts of the kidney (2). The resistive index (RI) is most often used for quantification of Doppler spectra and pulsatility index (PI) less frequently (3). Spectra in intrarenal arteries have the same form as the spectra in the main renal artery, but their systolic window is completely filled in, which is not a pathological finding (4). Numerous studies have identified normal RI levels in intrarenal arteries, ranging from 0.58 to 0.64 (5). The process of aging results in a physiological increase of renal vascular resistance, which is not manifested by changes in serum creatinine or creatinine clearance level, so in healthy elderly persons RI levels are 10-15% higher than normal ones (5). In adults, the RI limit is 0.70, while all levels that are equal to or higher than 0.70 indicate an increase in renal vascular resistance, in certain parenchymal renal diseases (6,7). Apart from renal diseases, RI levels may be affected by other conditions, such as hypotension, bradycardia, perirenal or sub-capsular fluid collections (8-10). Available Doppler ultrasound literature is mostly focused on the potential role in evaluating ureteral obstruction, non-obstructive obstructive renal diseases and renal transplant dysfunction (2,6).

The aim of this study was to establish whether there is a correlation between RI level changes following ESWL treatment in the treated and contralateral, non-treated kidneys, depending on the ESWL treatment intensity. Results of this study will point out the safety of the ESWL in the everyday practice, and be a guide for young colleagues for what they can expect right after the treatment.

## PATIENTS AND METHODS

### Patients and study design

The study was conducted on 60 patients of the Urology Clinic, Clinical Center of the University of Sarajevo in the period November 2014 to December 2017. Out of the total of 60 patients, 38 were males (63%), with average age of 42.3 (ranging from 22 to 59 years). A size of kidney

stones ranged from 6 to 18 mm, measured as a mean value of two longest diameters on X ray and ultrasound. Resistive index was monitored on the colour Doppler ultrasound scanner, at the level of interlobar arteries, with the mean value of three measurements for each patient within the set time intervals, before, on the first, second and seventh day following ESWL treatment.

### Methods

Resistive index or Pourcelot index was calculated by using the formula:  $RI = (A - B)/A$ , where A is the peak systolic Doppler shift waveform, and B is the peak diastolic shift waveform.

Resistive index calculation in each patient was done by the investigators.

The obtained RI results concerned the examination of 60 patients, out of whom 41 were set aside when RI was observed in the function of the patient's age.

The results were taken into consideration before the treatment (0), on the first (1) day, second (2) day and on the seventh (7) day following the treatment, while the subjects were divided into groups according to their age and the number of administrated shock waves. Using this method, we monitored the RI movement in two age groups: Group 1 – patients aged < 55 (n = 29) and Group 2 – patients aged ≥ 55 (n = 12).

According to the number of administrated shock waves, we also monitored RI levels in two groups of patients: group of patients who received 2000 SWs (n = 24), and group of patients who received 4000 SWs (n = 36).

In both groups, in terms of the function of both age and number of received SWs, RI levels were monitored in both the treated (ipsilateral), and non-treated (contralateral) kidneys. The resulting mean pre-treatment RI levels, depending on the subjects' age, were as follows: under 25 years of age – 0.563; under 45 years of age – 0.614; under 60 years of age – 0.637; 4% of the patients had levels higher than 0.7, which approximately corresponded to the investigation results and recommendations given by other authors and institutions worldwide (5).

### Statistical analysis

For each group of patients, the average value (Mean), standard deviation (SD), standard error

of the mean (SEM), median value (MED) and percentage differences (P10, 25, 75 and 90%) were determined. Analyzing the significance of the differences in the average value of the groups was carried out using the Student t-test and where it could not be used, the statistical significance of the difference in the median value was tested using the Wilcoxon Signed Ranks test. The values of  $p < 0.05$  were considered significant. In order to select the appropriate test for testing the differences in RI levels between the observed groups, we tested normality in all groups. Since we had less than 50 subjects in groups, instead of the Kolmogorov-Smirnov, we used the Shapiro-Wilks test of normality.

## RESULTS

The normality was confirmed in all analysed groups (Table 1), which allowed the application of t-test for testing the differences in arithmetic means.

**Table 1. Tests of Normality for RI value variations following extracorporeal shock wave lithotripsy (ESWL) treatment, measuring as a function of time (measured before (-1), immediately after (+1), on the second (+2) and seventh (+7) day) in different age groups or following 2000 SWs and 4000 SWs ESWL treatment (measured before (-1) and immediately after the treatment)**

|   | Kolmogorov-Smirnov test |    |       | Shapiro-Wilk test |    |      |
|---|-------------------------|----|-------|-------------------|----|------|
|   | Statistic               | df | Sig.* | Statistic         | df | Sig. |
| <b>Normality RI value variations in the group under the age of 55</b>         |                         |    |       |                   |    |      |
| Ipsilateral (-1)  | .114                    | 29 | .200* | .968              | 29 | .505 |
| Ipsilateral (+1)  | .116                    | 29 | .200* | .969              | 29 | .524 |
| Ipsilateral (+2)  | .124                    | 29 | .200* | .968              | 29 | .508 |
| Ipsilateral (+7)  | .114                    | 29 | .200* | .968              | 29 | .505 |
| Contralateral (-1)  | .114                    | 29 | .200* | .968              | 29 | .505 |
| Contralateral (+1)  | .166                    | 29 | .040  | .957              | 29 | .284 |
| <b>Normality RI value variations in the group older than 55</b>               |                         |    |       |                   |    |      |
| Ipsilateral (-1)  | .231                    | 12 | .200* | .915              | 6  | .473 |
| Ipsilateral (+1)  | .213                    | 12 | .200* | .950              | 6  | .741 |
| Ipsilateral (+2)  | .234                    | 12 | .200* | .921              | 6  | .514 |
| Ipsilateral (+7)  | .231                    | 12 | .200* | .915              | 6  | .473 |
| Contralateral (-1)  | .231                    | 12 | .200* | .915              | 6  | .473 |
| Contralateral (+1)  | .213                    | 12 | .200* | .950              | 6  | .741 |
| <b>Tests of Normality RI value variations following 2000 SWs and 4000 SWs</b> |                         |    |       |                   |    |      |
| Treated kidney (-1)   | .160                    | 24 | .200* | .941              | 24 | .367 |
| Treated kidney 2000   | .154                    | 24 | .200* | .958              | 24 | .621 |
| Non-treated kidney (-1)   | .160                    | 24 | .200* | .941              | 24 | .367 |
| Non-treated kidney 2000   | .160                    | 24 | .200* | .941              | 24 | .367 |
| Treated kidney (-1)   | .125                    | 36 | .200* | .956              | 36 | .493 |
| Treated kidney 4000   | .139                    | 36 | .200* | .959              | 36 | .557 |
| Non-treated kidney (-1)   | .125                    | 36 | .200* | .956              | 36 | .493 |
| Non-treated kidney 4000   | .123                    | 36 | .200* | .949              | 36 | .376 |

\*Lilliefors Significance Correction; lower bound of the true significance; df, degrees of freedom; sig., significance probability

In the group of patients under 55 years a significant increase in mean RI values was found, on

the first ( $p=0.001$ ) and second day ( $p=0.007$ ) after the treatment, whereas the increase was non-significant on the seventh day (7) after the treatment ( $p=0.379$ ), in relation to pre-treatment values ( $0.62 \pm 0.05$ ) (Table 2).

**Table 2. Statistical indicators of resistive index (RI) value variations as a function of time, in the group of 29 patients under 55 years of age, measured before (-1), immediately after (+1), on the second (+2) and seventh (+7) day following extracorporeal shock wave lithotripsy (ESWL) treatment**

|      | Treated (ipsilateral) kidney |        |        |        | Non-treated (contralateral) kidney |        |        |        |
|------|------------------------------|--------|--------|--------|------------------------------------|--------|--------|--------|
|      | (-1)                         | (+1)   | (+2)   | (+7)   | (-1)                               | (+1)   | (+2)   | (+7)   |
| Mean | 0.6228                       | 0.6681 | 0.6584 | 0.6333 | 0.6122                             | 0.6395 | 0.6277 | 0.6177 |
| SD   | 0.0465                       | 0.0503 | 0.0495 | 0.0473 | 0.0457                             | 0.0489 | 0.0474 | 0.0461 |
| SEM  | 0.0086                       | 0.0093 | 0.0092 | 0.0088 | 0.0085                             | 0.0091 | 0.0088 | 0.0086 |
| MED  | 0.630                        | 0.680  | 0.670  | 0.6407 | 0.6193                             | 0.6552 | 0.640  | 0.6249 |
| P10% | 0.568                        | 0.607  | 0.598  | 0.578  | 0.558                              | 0.581  | 0.570  | 0.563  |
| P25% | 0.590                        | 0.628  | 0.620  | 0.600  | 0.580                              | 0.603  | 0.590  | 0.585  |
| P75% | 0.660                        | 0.703  | 0.694  | 0.671  | 0.649                              | 0.676  | 0.660  | 0.655  |
| P90% | 0.682                        | 0.728  | 0.718  | 0.694  | 0.670                              | 0.693  | 0.684  | 0.676  |
| p    |                              | 0.001  | 0.007  | 0.394  |                                    | 0.033  | 0.210  | 0.650  |

SD, standard deviation; SEM, standard error of mean; MED, median; P10%, the first decile; P25%, the first quartile; P75%, the third quartile; P90%, the ninth decile;

In the group of patients older than 55 years, the resulting increase in mean RI levels was also significant on the first and second day following the treatment ( $p=0.001$  and  $p=0.005$ , respectively), and non-significant on the seventh day following the treatment ( $p=0.344$ ), in relation to pre-treatment values ( $0.70 \pm 0.02$ ) (Table 3).

**Table 3. Statistical indicators of resistive index (RI) value variations as a function of time in the group of 12 patients below 55 years of age measured before (-1), immediately after (+1), on the second (+2) and seventh (+7) day following extracorporeal shock wave lithotripsy (ESWL) treatment**

|      | Treated (ipsilateral) kidney |        |        |        | Non-treated (contralateral) kidney |        |        |        |
|------|------------------------------|--------|--------|--------|------------------------------------|--------|--------|--------|
|      | (-1)                         | (+1)   | (+2)   | (+7)   | (-1)                               | (+1)   | (+2)   | (+7)   |
| Mean | 0.7033                       | 0.7562 | 0.7449 | 0.7153 | 0.6914                             | 0.7252 | 0.7106 | 0.6976 |
| SD   | 0.0207                       | 0.0262 | 0.0251 | 0.021  | 0.0203                             | 0.029  | 0.0251 | 0.0205 |
| SEM  | 0.0084                       | 0.0107 | 0.0102 | 0.0086 | 0.0083                             | 0.0119 | 0.0103 | 0.0084 |
| MED  | 0.700                        | 0.756  | 0.7441 | 0.7119 | 0.6881                             | 0.728  | 0.7108 | 0.6943 |
| P10% | 0.685                        | 0.730  | 0.720  | 0.697  | 0.6734                             | 0.6936 | 0.6848 | 0.6795 |
| P25% | 0.693                        | 0.740  | 0.730  | 0.704  | 0.6808                             | 0.706  | 0.6951 | 0.6869 |
| P75% | 0.708                        | 0.764  | 0.752  | 0.720  | 0.6955                             | 0.7358 | 0.7185 | 0.7018 |
| P90% | 0.725                        | 0.783  | 0.771  | 0.737  | 0.7127                             | 0.754  | 0.7362 | 0.7191 |
| p    |                              | 0.001  | 0.005  | 0.344  |                                    | 0.025  | 0.177  | 0.609  |

SD, standard deviation; SEM, standard error of mean; MED, median; P10%, the first decile; P25%, the first quartile; P75%, the third quartile; P90%, the ninth decile;

RI values in the non-treated kidney on the first day after the treatment grew significantly ( $p=0.033$ ), while on the second and seventh day after the treatment the growth was non-significant ( $p=0.21$  and  $p=0.65$ , respectively) in relation to pre-treatment

values ( $0.61 \pm 0.05$ ) (Table 2) in the younger group of subjects. In the group of patients older than 55 years RI values in the non-treated kidney grew significantly on the first day after the treatment ( $p=0.044$ ), while on the second and seventh day after the treatment the growth was non-significant ( $p=0.177$  and  $p=0.609$ , respectively) in relation to pre-treatment values ( $0.69 \pm 0.02$ ) (Table 3).

Due to a small number of observations for patients aged  $>55$ , Wilcoxon Signed Ranks test (non-parametric test for paired samples) was used to check the results, showing the same results as the t-test except for non-treated kidney on the second day of the treatment where the difference in mean RI was significant.

Comparative mean resulting RI levels for treated kidneys, using t-test, showed a significant increase in RI levels in both groups, treated with 2000 SWs (from 0.628 to 0.669;  $p=0.044$ ) or with 4000 SWs (from 0.644 to 0.695;  $p=0.007$ ). In the case of non-treated kidney, we did not confirm the significant increase in RI for patients who received 2000 SWs (from 0.617 to 0.636;  $p=0.330$ ) whereas patients receiving 4000 SW showed a significant increase in RI (from 0.633 to 0.669;  $p=0.042$ ) (Table 4).

**Table 4. Statistical indicators of resistive index (RI) value variations following 2000 SWs and 4000 SWs measured in subjects before (-1) and immediately after extracorporeal shock wave lithotripsy (ESWL) treatment**

|                | Treated (ipsilateral) kidney |          |        |          | Non-treated (contralateral) kidney |          |        |          |
|----------------|------------------------------|----------|--------|----------|------------------------------------|----------|--------|----------|
|                | (-1)                         | 2000 SWs | (-1)   | 4000 SWs | (-1)                               | 2000 SWs | (-1)   | 4000 SWs |
| No of patients | 24                           | 24       | 36     | 36       | 24                                 | 24       | 36     | 36       |
| Mean           | 0.628                        | 0.669    | 0.644  | 0.695    | 0.617                              | 0.636    | 0.633  | 0.669    |
| SD             | 0.053                        | 0.057    | 0.053  | 0.057    | 0.052                              | 0.054    | 0.052  | 0.055    |
| SEM            | 0.0133                       | 0.0141   | 0.0122 | 0.0131   | 0.0130                             | 0.0134   | 0.0120 | 0.0127   |
| MED            | 0.640                        | 0.682    | 0.640  | 0.691    | 0.629                              | 0.648    | 0.629  | 0.666    |
| P10%           | 0.555                        | 0.591    | 0.570  | 0.616    | 0.546                              | 0.562    | 0.560  | 0.593    |
| P25%           | 0.598                        | 0.636    | 0.605  | 0.653    | 0.587                              | 0.605    | 0.595  | 0.629    |
| P75%           | 0.673                        | 0.716    | 0.690  | 0.745    | 0.661                              | 0.681    | 0.678  | 0.718    |
| P90%           | 0.685                        | 0.730    | 0.702  | 0.758    | 0.673                              | 0.694    | 0.690  | 0.730    |
| p              |                              | 0.044    |        | 0.007    |                                    | 0.330    |        | 0.042    |

SD, standard deviation; SEM, standard error of mean; MED, median; P10%, the first decile; P25%, the first quartile; P75%, the third quartile; P90%, the ninth decile;

## DISCUSSION

The results of the presented study have shown that in the group of patients who received 2000 SWs, RI levels grew significantly, as well as in the group who received 4000 SWs during the

treatment. According to most recent information, these changes of RI values following ESWL are a result of cellular infiltration and edema formed around peripheral branches of the renal artery, because of swelling of perivascular tissue so vascular resistance thus may grow too (14-18). RI levels in the non-treated contralateral kidney in the first group of patients who received 2000 SWs did not show any significant changes, while in the other group with 4000 SWs the RI levels grew significantly. In patients under 55 years of age, RI increase was significant on the first and second day after the treatment, whereas it was non-significant on the seventh day, while in patients older than 55 years of age the RI increase practically stood in the same relation to the set temporal determinants, but the significance was more pronounced. RI levels in the contralateral kidney in both age groups showed a significant increase only on the first day after the treatment, while the RI levels on day two and day seven were decreasing. Additionally, the mentioned results in most part confirm the results from other authors' studies. The literature review shows reports addressing the relationship between the ESWL and RI variations after treatment. Knapp et al. found a positive linear correlation between the RI increase following ESWL treatment and the patients age, and concluded that patients older than 65 fall within the risk group for the ESWL treatment due to possibility of elasticity loss in renal tissue and intrarenal blood vessels (10,11). Aoki et al. reported that RI levels measured in interlobar arteries in the region around kidney stone before, 30 min and 7 days after ESWL, showed a significant increase after 30 min (from  $0.656 \pm 0.053$  to  $0.682 \pm 0.053$ ), but eventually return to their pre-treatment levels over a period of seven days (18). A significant RI increase on the contralateral kidney was verified only in patients older than 65, but the changes were of a reversible character over a limited seven-day period of time (18). Nazaroglu et al. found a temporary RI increase three hours after ESWL in both ipsilateral and contralateral kidneys, with the increase being most pronounced in the region near the stone, whereas the lowest increase was reported in the contralateral kidney. After seven days, RI levels returned to normal (1). Beduk et al. reported there was no significant difference in RI levels in renal blood vessels before and after ESWL

treatment by Dornier MPL 9000; the levels were evaluated 24 hours after the treatment (14). Kataoka et al. reported about a significant RI increase in 23 monitored patient's right after Dornier MPL 9000 treatment and found no RI change on contralateral kidney blood vessels (15).

Color Doppler sonography has proven that a non-invasive renal vascular function assessment method may be efficient, and may be used to measure blood flow speed in renal circulation within small parenchymal arteries (15). In our study no significant RI differences between the treated and contralateral kidneys, regardless of patients' age. Post-ESWL RI was elevated by more than 0.7 in more than a half of the elderly patients, which indicates pathological changes. This phenomenon may be attributed to the loss of renal tissue elasticity and intrarenal vascular sclerosis. We assume that the same amount of energy is not that well tolerated by elderly individuals as is the case with younger patients. The differences in results noticed in the works of the foregoing authors depend on numerous factors, including the time of measuring RI, the type of lithotripter used, SW generator power, focal size, quantity of delivered energy, number of delivered SWs and pre-treatment renal function. The discrepancy between the RI monitoring results may be attributed to the different RI measuring techniques. The differences in RI variation reports may be a reflex of pathological changes at each measuring point. The difference in lithotripters may also affect RI changes. Electrohydraulic and electromagnetic

lithotripters more often result in acute sub-capsular hematomas and fibrosis when compared to piezoelectric ones (16-18). Characteristic differences include wider aperture and smaller focal zone. Contralateral non-treated kidneys show significant pre- and post-lithotripsy RI changes in elderly patients. Other studies report of non-significant RI changes in the contralateral, non-treated kidney (17).

Ultrasound has long been a primary diagnostic method in discovering pathologic changes in kidneys. Colour Doppler ultrasound, as a method that provides information on blood flow in kidneys and renal arteries, and non-invasive assessment of vascular resistance, to obtain information on ESWL effect on renal vasculature in both treated as well as non-treated kidneys by measuring RI levels (10-13).

Based on study results, there is a correlation between RI changes and the degree and localization of changes in vascular elements of the kidney, where RI changes are directly correlated with the number of administered shock waves and the administered energy. Post-ESWL treatment changes are existent and reversible over a period of one week after the treatment.

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## TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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## The serum triglyceride to high-density lipoprotein (HDL) ratio in patients with acute coronary syndrome with and without renal dysfunction

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### ABSTRACT

**Aim** To assess triglyceride – to high-density lipoprotein cholesterol (TG/HDL)-C ratio in patients with acute coronary syndrome (ACS) and to verify its association with renal dysfunction.

**Methods** A cross sectional study included 85 ACS patients divided in two groups with (ACS – RD) and without (ACS-nRD) presence of renal dysfunction, and 35 healthy subjects. Blood pressure, blood glucose, C-reactive protein, urea, creatinine, eGFR and serum lipids levels (total cholesterol, triglycerides, LDL-C, HDL-C) was measured in all participants. Based on the values of the measured lipid fractions TG/HDLc ratio was calculated.

**Results** Patients in ACS group had significantly lower HDL-C level ( $p<0.0005$ ) but significantly higher TG level ( $p=0.046$ ) and TG/HDL-C ratio ( $p<0.0005$ ) than controls. There was a significant increase ( $p<0.0005$ ) in TG/HDL-C ratio in ACS-RD group compared to ACS-nRD group. The ACS-RD group had significantly higher level of TG ( $p=0.001$ ), serum urea ( $p=0.02$ ) and creatinine ( $p<0.0005$ ) compared to the ACS-nRD group. With a cut-off level of 1.135 TG/HDL-C ratio had a sensitivity of 77.6% and a specificity of 62.9% in distinguishing between ACS patients and healthy subjects. With cut-off value of 1.905 TG/HDL-C ratio had a sensitivity of 75.9% and a specificity of 78.6% in distinguishing between ACS patients with and without renal dysfunction.

**Conclusion** This study confirms the reliability of the TG/HDL-C ratio as a simple, low cost and useful marker in distinguishing between patients with ACS and healthy subjects and ACS patients with and without renal dysfunction.

**Key words:** eGFR, NSTEMI, STEMI, TG/HDL-C ratio

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## INTRODUCTION

Acute coronary syndrome (ACS) is the acute phase of myocardial ischemia, which includes clinical manifestations of unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) (1). Many factors are involved in the pathogenesis of acute myocardial infarction (AMI), and several studies have indicated a lipid metabolism disorder as one of the key factors in the development of this disease (2). Today, there has been growing interest in the role of the triglyceride (TG) – to – high-density lipoprotein cholesterol (HDL) cholesterol (C) (TG/HDL-C) ratio as a more practical and easy to use atherogenic marker (3). According to Daluz PL et al. (4) this ratio shows promise as an attractive surrogate index of the atherogenicity of the plasma lipid profile. In the general population, an elevated serum TG/HDL-C ratio has been identified as a risk factor for cardiovascular (CV) disease and mortality (5). Previous studies have shown that there is a correlation between TG/HDL-C ratio and insulin resistance, and that TG/HDL-C ratio may be a better predictor of CV events than other lipid parameters, such as TG, low density lipoprotein-cholesterol (LDL-C) or total cholesterol/HDL-C ratio (6).

Renal dysfunction is a strong predictor of end-stage renal disease and CV disease. Recent studies suggest that renal function, measured by the estimated glomerular filtration rate (eGFR), is an independent prognostic factor for CV disease. Renal injury in ACS is a multifactorial phenomenon that could be promoted by underlying renal dysfunction, but it is more often influenced by a number of contributing factors (7). Thus, early identification of renal dysfunction using simple and inexpensive diagnostic tools, is essential for improving diagnosis and risk stratification and for the detection of the fundamental pathophysiological mechanisms that link renal function and ACS.

Today, there are still little data showing the correlation between TG/HDL-C and eGFR values as indicators of renal damage in patients with ACS.

The aim of this study was to assess TG/HDL-C ratio values of the patients with acute coronary syndrome (ACS) and to verify its association with types of ACS and eGFR.

## PATIENTS AND METHODS

### Patients and study design

The cross-sectional, clinical, comparative study was conducted among 85 patients with ACS who were admitted to the Clinic for Heart Disease, Blood Vessels and Rheumatism, University Clinical Centre Sarajevo (UCCS) between January 2015 and January 2017. The diagnosis of ACS was defined by the current guidelines (8), based on cardiac symptoms, electrocardiographic appearance, and biomarkers reflecting myocardial damage. Information about the age, gender and the history of hypertension of the patients were collected from their medical records. Individuals were not eligible for the study if they were younger than 20 years, were unable to provide consent, had a known and active urinary infection, malignancy, febrile disorder, acute or chronic inflammatory diseases, or were taking lipid-lowering therapies during the study period.

The control group consisted of 35 healthy subjects without a family history of coronary heart diseases, dyslipidaemia, hypertension, autoimmune or rheumatic diseases and with normal thyroid, renal and hepatic functions. None of the control subjects had received any medication and none were current smokers or consumers of alcohol. Written informed consent for inclusion in the study was obtained from all patients and healthy controls. The study was carried out in accordance with the Declaration of Helsinki as revised in 2000. The Ethical Committee of the Clinical Centre University of Sarajevo approved this study.

### Methods

Renal function was evaluated by the estimated glomerular filtration rate (eGFR) calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula (9):

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times [\text{Serum Creatinine } (\mu\text{mol/L)} \times 0.0113]^{-1.154} \times \text{Age (years)}^{-0.203} (\times 0.742 \text{ if female})$$

Renal dysfunction was defined as an eGFR < 60 mL/minute/1.73m<sup>2</sup>.

According to eGFR, patients with ACS were divided into two groups: ACS patients with renal dysfunction (ACS-RD group; n = 29) and ACS patients without renal dysfunction (ACS-nRD group; n = 56).

The systolic and diastolic blood pressures (BP) in the arm were measured by well-trained doctors using a calibrated standard mercury sphygmomanometer while the participants were in a sitting position after a 5-min rest.

Blood was collected under aseptic precautions in the morning after overnight fast, after a 30-min rest in a semi-recumbent position from all patients and controls. Blood was taken without stasis from antecubital vein, using the vacutainer technique (10 mL vacutainer tubes; BD Vacutainer Systems, PL6 7BP, Plymouth, UK). Biochemical analyses were performed the same day at the Institute of Clinical Chemistry and Biochemistry, the UCCS. Lipid parameters were determined on automated apparatus (Dimension RxL Max, Dade Behring, Germany) using standard enzymatic methods.

Serum total cholesterol (TC) was measured by the cholesterol oxidase method, while high-density lipoprotein cholesterol (HDL-C) levels were determined by the direct homogeneous enzymatic method. Serum triglyceride (TG) levels were assayed after enzymatic hydrolysis, by the simultaneous enzymatic determination of glycerol. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula ( $LDL-C = TC - HDL-C - TG/5$ ). The reference values for TG, TC, LDL-C, HDL-C (according to manufacturer's instructions) were: TC: 3.1 - 5.2 mmol/L, HDL-C: 1.06 - 1.94 mmol/L, TG: 0.11 - 1.7 mmol/L, LDL-C: 2 - 4.3 mmol/L. In addition, the TG/HDL-C ratio was calculated.

The fasting serum C-reactive protein (CRP) level was determined using the immunoturbidimetric assay (Beckman Synchron LX System). Serum concentration of creatinine (Cr) and urea were determined by kinetic colorimetric tests (Beckman Coulter, Ireland on Olympus AU 400).

### Statistical analysis

The Kolmogorov-Smirnov or Shapiro-Wilk test of normality were used to test the normality and variance homogeneity of data. Data were presented as mean  $\pm$  standard deviation (SD) for normally distributed variables and as median and interquartile ranges for skewed variables. Categorical variables were reported as frequency (percentage) and compared using  $\chi^2$  test as appropriate. The difference in normally distribu-

ted data was tested by independent two-sample t-test. The difference in the values of parameters that showed a skewed distribution was assessed by Kruskal-Wallis, followed by Mann-Whitney U-tst. To determine the accuracy and respective best cut-off values of the TG/HDL-C ratio for differentiating patients with ACS from healthy controls, and ACS patients with renal failure from ACS patients without renal failure the Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. Accuracy rate diagnosing measures were calculated with the 95% Confidence Interval (95% CI). The optimal cut-off values were determined using the Receiver Operator Characteristic (ROC) curve analysis with the Youden index [maximum (sensitivity + specificity - 1)]. A cut-off value with the maximum Youden index of the ROC curve was defined as the optimal the TG/HDL-C ratio cut-off point to diagnose ACS and one separating ACS patients with renal insufficiency from ACS patients without renal insufficiency. A  $p < 0.05$  was considered statistically significant for all comparisons.

### RESULTS

There were no significant differences between patients with ACS and control subjects with respect to gender ( $p = 0.750$ ) or age ( $p = 0.156$ ). Systolic blood pressure, diastolic blood pressure, blood glucose levels, CRP, serum urea and creatinine levels were significantly higher in ACS patients than in controls ( $p < 0.0005$ ). On lipid profiles, patients in the ACS group had significantly lower HDL-C level ( $p < 0.0005$ ), but significantly higher TG level ( $p = 0.046$ ) and TG/HDL-C ratio values ( $p < 0.0005$ ) than the control group. However, TC and LDL-C variables did not differ significantly between the groups ( $p = 0.106$ ,  $p = 0.138$  respectively) (Table 1).

Among patients with ACS, 43 (50.6%) had a diagnosis of STEMI and 42 (49.4%) NSTEMI. Patients in the STEMI group presented with higher values of both systolic and diastolic blood pressure, but the differences were not significant ( $p = 0.318$  and  $p = 0.651$ , respectively). The median serum level of blood glucose, CRP, urea and creatinine were similar in both groups ( $p = 0.306$ ,  $p = 0.453$ ,  $0.989$ , and  $p = 0.840$ , respectively). On the lipid profiles, there were no differences

**Table 1. Demographic data, clinical and biochemical parameters of the study population**

| Variable                      | ACS group         | Control group    | p       |
|-------------------------------|-------------------|------------------|---------|
| Males (n/%)                   | 44 (51.8)         | 18 (51.4)        | 0.750   |
| Females (n/%)                 | 41 (48.2)         | 17 (48.6)        |         |
| Age (years)*                  | 64.11±11.9        | 60.8±10.9        | 0.156   |
| History of hypertension (n/%) | 62/72.9           | -                | -       |
| SBP (mmHg)*                   | 158.5±17.4        | 119.4±9.6        | <0.0005 |
| DBP (mmHg)*                   | 98.7±8.6          | 80.1±7.6         | <0.0005 |
| Blood glucose (mmol/L)        | 7.0 (5.5-8.9)     | 5.0 (4.96-5.4)   | <0.0005 |
| CRP (mg/L)†                   | 7.5 (6.2-9.1)     | 0.8 (0.4-1.5)    | <0.0005 |
| Serum urea (mmol/L)†          | 7.0 (5.4-10.0)    | 4.3 (3.7-5.9)    | <0.0005 |
| Serum creatinine (μmol/L)†    | 88.0 (74.5-111.5) | 64.5 (56.5-79.3) | <0.0005 |
| TC (mmol/L)†                  | 5.2 (4.1-6.3)     | 5.7 (5.1-6.2)    | 0.106   |
| TG (mmol/L)†                  | 1.6 (1.2-2.2)     | 1.5 (0.9-1.7)    | 0.046   |
| HDL-C (mmol/L)†               | 1.0 (0.8-1.2)     | 1.4 (1.2-1.6)    | <0.0005 |
| LDL-C (mmol/L)†               | 3.3 (2.5-4.3)     | 3.6 (3.2-4.4)    | 0.138   |
| TG/HDL-C ratio                | 1.7 (1.2-2.3)     | 0.9 (0.6-1.4)    | <0.0005 |

\*mean ± SD, †median (interquartile range, IQR); ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

in TC, HDL-C, TG, LDL-C and TG/HDL-C ratio between the STEMI and NSTEMI groups ( $p=0.550$ ,  $p=0.323$ ,  $p=0.836$ ,  $p=0.171$ , and  $p=0.501$ , respectively) (Table 2).

**Table 2. Demographic data, clinical and biochemical parameters in the ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) group**

| Variable                   | STEMI group       | NSTEMI group      | p     |
|----------------------------|-------------------|-------------------|-------|
| SBP (mmHg)*                | 160.4±17.9        | 156.6±17.0        | 0.318 |
| DBP (mmHg)*                | 99.1±8.5          | 98.2±8.8          | 0.651 |
| Blood glucose (mmol/L)†    | 6.7 (5.5-8.0)     | 7.7 (5.7-9.2)     | 0.306 |
| CRP (mg/L)†                | 7.3 (6.2-10.4)    | 7.5 (6.3-8.6)     | 0.453 |
| Serum urea (mmol/L)†       | 7.0 (5.6-9.5)     | 7.0 (5.0-10.0)    | 0.989 |
| Serum creatinine (μmol/L)† | 86.0 (75.0-109.0) | 88.5 (74.0-114.3) | 0.840 |
| TC (mmol/L)†               | 5.4 (4.4-6.3)     | 5.1 (4.0-6.3)     | 0.550 |
| TG (mmol/L)†               | 1.5 (1.2-2.3)     | 1.6 (1.1-2.1)     | 0.836 |
| HDL-C (mmol/L)†            | 1.0 (0.8-1.3)     | 1.0 (0.8-1.1)     | 0.323 |
| LDL-C (mmol/L)†            | 3.5 (2.8-4.5)     | 3.1 (2.4-4.0)     | 0.171 |
| TG/HDL-C ratio             | 1.6 (1.0-2.1)     | 1.7 (1.2-2.6)     | 0.501 |

\*mean ± SD, †median (IQR); SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

No significant difference in systolic blood pressure ( $p=0.172$ ), diastolic blood pressure ( $p=0.368$ ), serum blood glucose ( $p=0.08$ ) and CRP level ( $p=0.265$ ) was observed between ACS patients with and without renal dysfunction. The median serum urea and creatinine level was significantly higher in patients in the ACS-RD group than in patients in the ACS-nRD group ( $p=0.02$  and  $p<0.0005$ , respectively). The lipid profile of these patients showed significantly higher

value of TG ( $p=0.001$ ) and TG/HDL-C ratio ( $p<0.0005$ ), while the differences in TC, HDL-C, LDL-C level were not significant ( $p=0.422$ ,  $p=0.409$ , and  $p=0.676$ , respectively) (Table 3).

**Table 3. Demographic data, clinical and biochemical parameters in the acute coronary syndrome (ACS) patients with renal dysfunction (ACS-RD group) and ACS patients without renal dysfunction (ACS-nRD group)**

| Variable                   | ACS-RD group        | ACS-nRD group    | p       |
|----------------------------|---------------------|------------------|---------|
| SBP (mmHg)*                | 162.1±21.2          | 156.6±15.1       | 0.172   |
| DBP (mmHg)*                | 99.8±8.1            | 98.0±8.9         | 0.368   |
| Blood glucose (mmol/L)†    | 8.0 (6.9-11.0)      | 6.4 (5.4-8.2)    | 0.08    |
| CRP (mg/L)†                | 7.2 (6.2-8.8)       | 7.9 (6.3-10.0)   | 0.265   |
| Serum urea (mmol/L)†       | 10.0 (5.8-13.3)     | 6.5 (5.2-8.0)    | 0.02    |
| Serum creatinine (μmol/L)† | 117.0 (104.0-152.5) | 79.5 (70.3-93.5) | <0.0005 |
| TC (mmol/L)†               | 5.6 (4.5-6.2)       | 5.0 (4.0-6.5)    | 0.422   |
| TG (mmol/L)†               | 2.0 (1.5-3.1)       | 1.3 (1.1-1.8)    | 0.001   |
| HDL-C (mmol/L)†            | 1.0 (0.7-1.2)       | 1.0 (0.9-1.2)    | 0.409   |
| LDL-C (mmol/L)†            | 3.4 (2.9-4.1)       | 3.2 (2.4-4.5)    | 0.676   |
| TG/HDL-C ratio             | 2.2 (1.7-2.9)       | 1.4 (1.0-1.9)    | <0.0005 |

\*mean ± SD, †median (IQR); SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

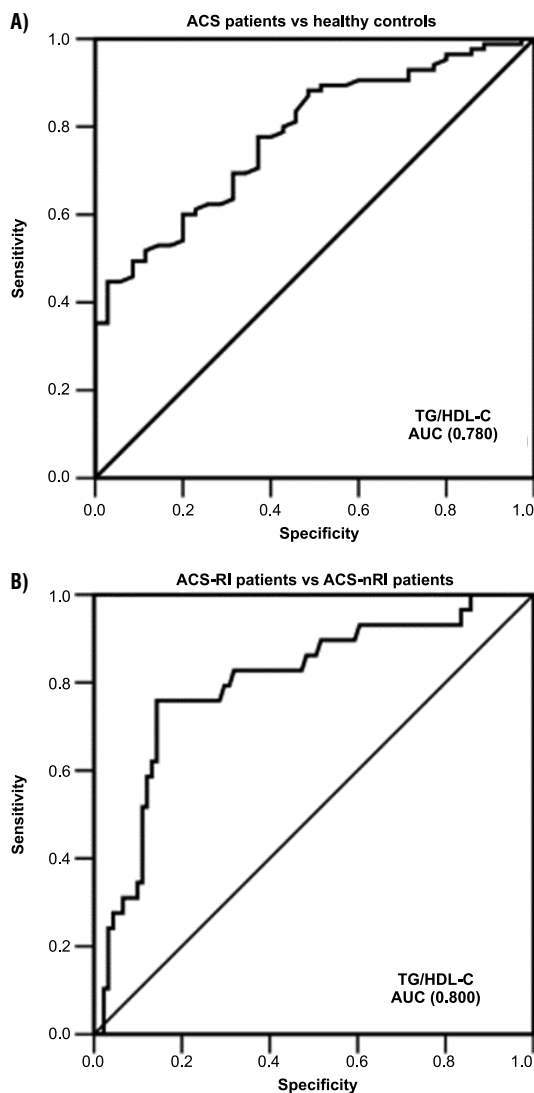
The ROC curve for the TG/HDL-C ratio value in the total sample of ACS patients vs. healthy controls showed significant area under the curve (AUC) (Figure 1A).

The optimal cut-off values for TG/HDL-C ratio in differentiating ACS patients from healthy subjects selected by ROC curve was 1.135, with sensitivity of 77.6%, specificity of 62.9%, positive predictive value of 83.5% and negative predictive value of 53.7% (Figure 1A, Table 4).

**Table 4. Optimal cut-off area under the curve with 95% confidence interval (AUC, 95% CI), sensitivity (SEN), specificity (SPE), positive (PPV) and negative predictive value (NPV), overall accuracy of the TG/HDL-C ratio in differentiating between ACS (acute coronary syndrome) patients and healthy controls and between ACS patients with and without renal dysfunction**

| Variable and cut-off value  | Diagnostic measurements |       |       |       |       |                  | p       |
|---|-------------------------|-------|-------|-------|-------|------------------|---------|
|   | AUC (95% CI)            | SEN   | SPE   | PPV   | NPV   | Overall accurate |         |
| ACS patients vs healthy controls  |                         |       |       |       |       |                  |         |
| TG/HDL-C ratio (≤1.135)   | 0.780 (0.70-0.86)       | 77.6% | 62.9% | 83.5% | 53.7% | 73.3%            | <0.0005 |
| ACS patients with renal dysfunction vs ACS patients without renal dysfunction |                         |       |       |       |       |                  |         |
| TG/HDL-C ratio (≤1.905)   | 0.800 (0.70-0.90)       | 75.9% | 78.6% | 64.7% | 86.3% | 77.6%            | <0.0005 |

TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; AUC, Area under the curve; CI, Confidence interval; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value



**Figure 1. (A) Receiver operating characteristic (ROC) curve of the triglyceride – to high-density lipoprotein cholesterol (TG/HDL)-C ratio for differentiation between the acute coronary syndrome (ACS) patients and healthy controls; (B) ROC curve of TG/HDL-C ratio value for differentiation between ACS patients with (ACS-RI) and without (ACS-nRI) renal dysfunction**

The overall accuracy of the value of the TG/HDL-C ratio in the determination of ACS patients was 73.3%. The TG/HDL-C ratio had fair diagnostic accuracy for differentiation between ACS patients and the healthy control (AUC 0.780;  $p < 0.0005$ ).

The optimal cut-off value for the TG/HDL-C ratio in differentiating ACS with renal dysfunction and ACS patients without renal dysfunction selected by the ROC curve (AUC 0.800;  $p < 0.0005$ ) was 1.905 (sensitivity 75.9%, specificity of 78.6%, positive predictive value of 64.7% and negative predictive value of 86.3%). The TG/HDL-C ratio had good diagnostic accuracy in differentiating

ACS with and without renal dysfunction with an overall accuracy of 77.6% (Figure 2B, Table 4).

## DISCUSSION

The main finding of our study is that the TG/HDL-C ratio is a good diagnostic marker in differentiating ACS with and without renal dysfunction. Analysing the lipid status it was found that the values of TG and the TG/HDL-C and LDL ratio in the ACS-RD group were higher than the values in the serum of patients in the ACS-nRD group. Epidemiological studies have shown a large increase in the number of patients whose ACS development is accompanied by simultaneous renal damage. Around 20% of patients hospitalized with acute myocardial infarction in the USA will develop acute renal dysfunction, which may be partially or completely irreversible (10). The data from the American National Medical Database, which cover a period of 8 years, show that the number of patients with diagnosed terminal renal failure and myocardial infarction increased by 1.5 times, while the mortality rate of hospitalized patients increased from 22 to 25% (11). According to ACTION criteria, renal disease was identified in 31% of patients with non-ST-segment elevation myocardial infarction, and in 43% with ST-segment elevation myocardial infarction. Acute renal damage occurred in 16% and severe renal damage in 4% patients (12).

Renal dysfunction is still characterized by an unclear pathophysiology and insensitive diagnostic tools that make its diagnosis difficult, particularly in the diagnosis of CV disease, especially ACS (13). Today, many researchers are trying to establish the possible role of dyslipidaemia, as one of the main pathways in ACS-RD pathogenesis.

Lipid abnormalities have long been suspected to contribute to atherosclerosis; several studies have established a strong correlation between TC, LDL-C or low HDL-C and the incidence of atherosclerosis-related diseases such as ischemic heart disease and renal failure (14).

The TG/HDL-C ratio, a novel biomarker, has been identified as an indicator of insulin resistance and atherogenic dyslipidaemia (14). Some authors have linked a high TG/HDL-C ratio as an easily obtainable atherogenic marker to coronary atherosclerosis, impaired heart rate recovery after exercise, CV and all-cause death (15,16). Bittner et al (17) reported that the TG/HDL-C ratio is a powerful predictor of total mortality independent

of important prognostic variables in patients with suspected myocardial infarction. They also found a strong relationship between the TG/HDL-C ratio and the severity of coronary artery disease, as well as subsequent CV events.

The results of his study have found that the TG/HDL-C ratio was statistically significantly higher in patients with ACS than in the control group, and the results of the ROC analysis indicated that this ratio is a good biomarker in differentiating ACS patients with and without renal dysfunction. Our results are in accordance with the results of previous studies. Maki et al. (18) found that the ratio of TG to HDL-C independently predicted carotid intima-media thickness (cIMT) progression in subjects at moderate risk of heart disease. TG/HDL-C ratio and HDL-C have been demonstrated by ROC analysis to be useful markers for the detection of the extent of coronary disorders. Recent studies also have shown that the TG/HDL-C ratio is associated with the severity of coronary disease (19).

The association between the TG/HDL-C ratio and renal disease has been established in many studies, but in the presence of the chronic renal dysfunction. Tangvarasittichai et al. (20) reported that an elevated TG/HDL-C ratio was associated with chronic renal disease, and may increase the rate of disease progression and predict decline in renal function and structural damage.

Sonmez et al (21) demonstrated that an elevated TG/HDL-C ratio predicts poor CVD outcome in subjects with CKD, and proposed this ratio as a simple, inexpensive, and reproducible marker of CVD risk in chronic renal diseases.

It is unquestionable that some lipid fractions play a role in the complex pathogenesis of CV and renal disease, but more detailed data about this are still unclear. Some authors have proposed the possible role of free fatty acids (FFA) in the common pathogenesis of these disorders (22).

It is known that FFA promotes lipid accumulation in several non-adipose tissues, primarily including cardiac and renal tissue, a phenomenon called lipotoxicity, which could explain their influence on the development of these two organs (23).

No available data were found in the literature

about lipid status of patients with renal function disorders in addition to ACS. It is important to emphasize that lipid status disorders lead to atherosclerotic changes, which can accelerate the development of heart and renal disease. Olechnowicz-Tietz et al. (24) included 446 patients with both ACS and chronic renal failure, and found that moderate and severe renal function impairment was associated with the rapid development of atherosclerotic changes. The authors consider this to be a major step towards the development of CVD, especially in the case of coronary syndrome. Although a growing body of evidence supports the predictive power of the TG/HDL-C ratio overall and in certain subgroups, very few studies have analysed it in patients with renal function disorders (21, 25). Kim et al. (26) showed that in patients with normal and mild renal dysfunction a higher TG/HDL-C ratio was significantly associated with an increased risk of major adverse CV events. However, in patients with moderate renal dysfunction the TG/HDL-C ratio lost its predictive value.

Since by searching the literature we could not find any similar studies, we could not compare our results with results of other authors. Further longitudinal and comparative studies are needed to investigate the mechanisms underlying this phenomenon.

In conclusion, a connection between heart and renal function exists both in physiological and pathophysiological conditions, and it is two-way and very complex. In patients with ACS, a comorbid decline in renal function aggravates the prognosis and complicates the diagnosis and treatment of these patients. Reduced renal function is a major risk factor with both an increased risk for recurrent CV morbidity and mortality. The TG/HDL-C ratio is a good, useful, low cost and simple biomarker that can be used for recognition of possible future complications in ACS patients, especially disorders of renal function.

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## TRANSPARENCY DECLARATION

Competing of interest: None to declare.

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## Effect of myocardial infarction on the occurrence of erectile dysfunction

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### ABSTRACT

**Aim** To investigate etiological link between acute myocardial infarction (AMI) and the accompanying impotence/erectile dysfunction (ED).

**Methods** Study included 99 male patients (48 who had AMI - patient group, and 51 healthy examinees without previous cardiovascular disease - control group). All patients completed a standardized questionnaire, the International Index of Erectile Function (IIEF-5).

**Results** Older patients had significantly lower IIEF-5 score (negative correlation) ( $p < 0.05$ ), but higher ED degree (significant positive correlation) ( $\rho = 0.522$ ;  $p = 0.0001$ ). In the patient group, 37 (77.1%) patients had ED, while in the control group it was found in 26 (51%) examinees ( $p < 0.05$ ). A clear correlation was found between incidence of ED and diabetes, dyslipidaemia, hypertension and positive family history (they were more common in patients with ED, with no statistically significant difference). There was no statistically significant difference between patients with ED and patients without ED according to the beta-blocker usage ( $p = 0.824$ ): ED was reported in 11 (68%) patients in the group who used carvedilol, 14 (82.3%) in the group who used metoprolol, and nine (81.8%) who used nebivolol.

**Conclusion** Myocardial infarction as well as age are directly related to the occurrence of ED. Cardiovascular risk factors are in direct correlation for the occurrence of erectile dysfunction after myocardial infarction.

**Key words:** cardiovascular disease, impotence, risk factors

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## INTRODUCTION

Development of erectile dysfunction (ED) after acute myocardial infarction (AMI) occurs in one-half to three-quarters of patients (1). Erectile dysfunction essentially has organic cause in the background (only 5-15% of cases have a purely psychogenic cause) (2). Complications following myocardial infarction are well documented, and it is clearly demonstrated that myocardial infarction further increases the risk of an additional cardiovascular incident, but also directly affects the quality of life of the patient (life satisfaction, sleep quality, and activity limitations) (3). The ED and AMI can be taken as different manifestations of the same underlying vascular pathology (atherosclerosis and endothelial dysfunction) (4). Different risk factors such as aging, obesity, sedentary lifestyle, smoking, hypertension, dyslipidaemia, diabetes, and medication (beta-blockers, diuretics and statins) are associated with psychological disorders, cardiovascular disease and sexual dysfunction (5). Integrative and holistic approach, with full consideration of the properties of these conditions, is an adequate way of diagnosis and management of these diseases (6).

Erectile dysfunction is a common clinical problem that is clearly associated with a variety of diseases (cardiac insufficiency, diabetes mellitus, peripheral vascular disease and hypertension) (2). The relationship between ED and coronary vascular disease is endothelial dysfunction, which occurs in penile as well as in coronary arteries, and ED and AMI are considered to be different manifestations of the same pathology (2, 7-11). It is considered that every patient with ED has a cardiovascular risk, until the opposite is proven. The prevalence and significance of ED in patients behind acute myocardial infarction are not sufficiently explored and defined (10). Unfortunately, it is a common condition (10). Variable ED prevalence was reported in cardiac patients (38-78%), mainly after acute myocardial infarction (10). In Bosnia and Herzegovina no studies have been performed in this field.

Aim of this study was to investigate etiological link between AMI and-accompanying ED to point out the importance of this connection (especially with regard to the treatment of ED in the period of cardiac rehabilitation), ED frequency after myocardial infarction, the presence of ED

in dependence on age incidence of risk factors and state of atherosclerotic nature, and the influence of drugs in the therapy of infarction on the development of ED.

## PATIENTS AND METHODS

### Patients and study design

Observational, prospective, analytical and controlled comparative study was performed. The study included 99 male patients divided into two groups. The first group consisted of 48 patients (patient group) aged between 41 and 70 years who had AMI, and had been treated at the Clinic for Heart, Blood Vessel and Rheumatic Diseases at the Clinical Centre of the University of Sarajevo during the period between June 2017 and December 2017. The control group included 51 healthy patients without previous cardiovascular incident who underwent regular general examination.

The inclusion criteria in the study was previous acute myocardial infarction, which occurred at least a month before the study. Exclusion criteria were: an unconfirmed diagnosis of AMI, the existence of endocrine disease and hormonal disorders (as a possible cause of ED), e.g. tumours of the hypothalamic pituitary region and hypogonadism, and possible traumatic lesions of the penile region and spinal cord. Patients with myocardial infarction were further divided into groups: according to age (aged between 40 and 50, 51 and 60 and 61 and 70 years), according to the time of occurrence of ED symptoms in relation to recent AMI (1 to 2 months, 2 to 6 months, 6 months to one year, more than a year after discharge). Anamnestic data was obtained from the history of the disease.

### Methods

All patients completed a standardized questionnaire for the ED assessment, the International Index of Erectile Function (IIEF-5), which consisted of 5 questions (How do you assess your safety that you will be able to achieve and maintain an erection?; When you had erection with sexual stimulation, how often it was hard enough for penetration?; During your sexual intercourse, how often were you able to maintain erection after penetrating?; During sexual intercourse, how difficult was it to maintain your erection to successfully complete the intercourse?; When you had sexual intercourse, how often was it satisfactory for you?) (7).

The answers were scored from 1 to 5. The overall score ranged from 5 to 25: 22-25 points indicate normal erectile function, 17-21 points mild erectile dysfunction, 12-16 mild to moderate erectile dysfunction, 8-11 moderate erectile dysfunction, 1-7 points indicate severe erectile dysfunction. Patients were additionally asked three Yes / No questions (Do you avoid sexual intercourse because of fear that it can cause cardiac problems?; Are you generally in bad mood after the infarction?; Do you know the adverse effects of drugs that could affect sexual function?).

### Statistical analysis

Descriptive statistics,  $\chi^2$  test, student t -test were performed, and the significance of differences for independent continuous variables that did not follow normal distribution was tested with the Mann-Whitney test for independent samples, or the Kruskal-Wallis test, depending on the number of investigated groups (for the analysis of anamnestic data and patient therapy). Spearman's rank correlation coefficient was also used (for assessing the relationship between ED and age of the patient). Values of  $p < 0.05$  were considered statistically significant.

### RESULTS

The average age of the patient group was  $57.1 \pm 7.5$  years (range 40-70). The average age in the control group was  $55.2 \pm 6.9$  years (39-68) ( $p = 0.10$ ).

Based on the data obtained from the IIEF-5 questionnaire, 11 (22.92%) out of 48 patients had no erectile dysfunction, and 16 (33.33%) were positive for erectile dysfunction (mild form). In the control group, 25 (out of 51; 49.01%) patients did not have erectile dysfunction, and in 13 patients (25.49%) erectile dysfunction was found (mild form) (Table 1).

**Table 1. Erectile dysfunction (ED) degree in patients after acute myocardial infarction and control group**

| Patient group          | Stage               | No (%) of patients | Average age (range) (years)            | P            |
|------------------------|---------------------|--------------------|--|--------------|
| <b>Patients (n=48)</b> | Without ED          | 11 (22.92)         | 50.1 $\pm$ 5.3 (41-56)                 | <b>0.001</b> |
|                        | Mild ED             | 16 (33.33)         | 55.4 $\pm$ 7.8 (40-70)                 |              |
|                        | Mild to moderate ED | 10 (20.83)         | 60.6 $\pm$ 3.9 (53-66)                 |              |
|                        | Moderate ED         | 6 (12.5)           | 62.3 $\pm$ 4.8 (54-67)                 |              |
|                        | Severe ED           | 5 (10.42)          | 64.4 $\pm$ 3.4 (60-68)                 |              |
|                        | <b>Total</b>        | <b>48 (48)</b>     | <b>57.1<math>\pm</math>7.5 (40-70)</b> |              |
| <b>Controls (n=51)</b> | Without ED          | 25 (49.01)         | 52.8 $\pm$ 6.4 (39-65)                 | <b>0.001</b> |
|                        | Mild ED             | 13 (25.49)         | 52.8 $\pm$ (44-62)                     |              |
|                        | Mild to moderate ED | 8 (15.68)          | 61 $\pm$ 3.5 (57-66)                   |              |
|                        | Moderate ED         | 3 (5.55)           | 62.7 $\pm$ 3.2 (59-65)                 |              |
|                        | Severe ED           | 2 (3.92)           | 67.5 $\pm$ 0.7 (67-68)                 |              |
|                        | <b>Total</b>        | <b>51 (52)</b>     | <b>55.2<math>\pm</math>6.9 (39-68)</b> |              |

Older patients had lower IIEF-5 score (negative correlation) ( $p < 0.05$ ).

Patients with ED in the patients group were significantly older in comparison to patients without ED ( $59.2 \pm 6.8$  (40-70) vs.  $50.1 \pm 5.3$  (41-56);  $p = 0.001$ ). Older patients have a higher degree of ED compared to the younger ones (significant positive correlation) ( $\rho = 0.691$ ;  $p = 0.0001$ ) (Table 1). In the control group, patients with higher degree of ED (severe) were older than the patients with mild ED ( $p = 0.001$ ), with significant positive correlation ( $\rho = 0.522$ ;  $p = 0.0001$ ).

If we compare the number of patients with and without ED in the control and patients group, it can be noted that 37 (77.1%) patients and 26 (51%) controls had ED.

Statistical analysis by Fisher's exact test and control of results by phi ( $\phi$ ) coefficient test showed that there was no statistically significant difference in the appearance of ED between the observed groups ( $p > 0.05$ ) (although all ED degrees were more represented in the patient group). Erectile dysfunction in 10 (27.02%) patients occurred in the period 3- 6 months after AMI, in eight patients 1-2 months, in seven patients after more than 12 months, in six patients each immediately and 7-12 months after AMI.

The mean IIEF-5 score in the total sample (control and patient group,  $n = 99$ ) was  $18.01 \pm 5.4$  (range 5-25). The IIEF-5 score was statistically significantly lower ( $p = 0.007$ ) in the patient group, with an average of  $16.5 \pm 5.6$  (range 5-25) compared to the control group, with the average of  $19.4 \pm 4.9$  (range 6-25). The IIEF-5 score is obtained through five questions, and represents the degree of erectile dysfunction (the lowest score equals severe ED degree). Out of 48 patients, 40 (83.33%) responded negatively to the question "Do you avoid sexual intercourse because of the fear that it can cause cardiac problems?" ( $p = 0.069$ ). The next questions were related to the presence of reasons for mood swings, or no reasons for mood swings ("Are you generally in bad mood after the infarction?" and "Do you know the adverse effects of drugs that could affect sexual function?") ( $p = 0.2$  and  $p = 0.34$ , respectively).

The prevalence of cardio metabolic risk factors and conditions of atherosclerotic nature in the patient group was: smoking, 37 (77.1%) ( $p = 0.214$ ), diabetes mellitus, 8 (16.7%) ( $p = 0.443$ ), abnor-

mal amount of lipids in the blood (dyslipidaemia), 35 (72.9%) ( $p=0.430$ ), alcohol consumption, 12 (25%) ( $p=0.843$ ), obesity ( $BMI > 24.9$ ), 30 (62.5%) ( $p=0.929$ ), positive family history, 36 (75%) ( $p=0.074$ ), hypertension, 35 (72%) ( $p=0.430$ ). A clear correlation was found between the incidence of ED and diabetes, dyslipidaemia, hypertension and positive family history, e.g. they were more common in patients with ED, with no statistically significant difference. Smoking, alcohol consumption, and obesity were more common in patients without ED.

There was no statistically significant difference between patients with ED and patients without ED according to the beta-blocker usage ( $p=0.824$ ): ED was reported in 11 (68%) of patients in the group who used carvedilol, 14 (82.3%) in the group who used metoprolol, and nine (81.8%) who used nebivolol. Also, there was no statistically significant difference between patients with erectile dysfunction and patients without erectile dysfunction according to the usage of furosemide ( $p=0.610$ ), spironolactone ( $p=0.461$ ) and statins ( $p=0.171$ ).

## DISCUSSION

The presented study included 48 patients who had undergone cardiac rehabilitation after myocardial infarction, and compared with a group of 51 healthy patients of the appropriate age. The results showed that 77.1% of the patients after myocardial infarction reported signs of ED, in comparison with the control group, in 51% ( $p = 0.007$ ). These results correspond to the results showed by Ruzic et al. (8) which found that 82% of patients after myocardial infarction showed a certain degree of ED, with note that patients included in that study had a greater range of years - from 30 to 75. Araujo et al. (9) an extensive Massachusetts Male Aging study showed that 52% of men between 40 and 70 years of age suffered from a certain degree of ED; Montorsi found it in 67% of patients (10). According to the IIEF-5 questionnaire (7), the study conducted by Maroto-Montero (12) showed that 52.6% of patients had a score below 20, what is lower than in our research probably because of the small patient group, but an occurrence of ED degrees is in accordance with our research (12).

Results of our study have shown that the prevalence of ED was related to the age of the patients. In addition, older patients had lower IIEF-5 score.

All patients in our study with ED had at least two risk factors correlating with the appearance of ED. These results partially correspond to the results obtained by Maroto-Montero (12). On the other hand, Dong et al. showed that ED alone significantly increases the risk of coronary heart disease, AMI and mortality itself regardless of the cause (13), probably independently of conventional cardiovascular risk factors (13). Our study has shown no correlation between used drugs in the therapy of infarction and erectile dysfunction. Based on the experience of many studies it is known that propranolol and metoprolol negatively interfere with sexual function (16). In some studies, carvedilol, because of the lower incidence of ED, defined as the drug of choice for patients with this complication (14,15). Nevertheless, other studies showed that nebivolol is the best choice, because of the properties of nebivolol, and the relationship with nitric oxide (16,17). Nebivolol has a particular mechanism of action, which involves release of nitric oxide, resulting in penile vasodilation, and that can be favourable in male subjects with the history of hypertension and ED (16). When it comes to the effects of statins and diuretics on the appearance of ED, different and most often contradictory literature data were found (19). The role of statins and diuretics in the occurrence of ED after myocardial infarction is still dubious, and requests bigger and more controlled trials to confirm their influence (18-20). Our research showed that psychological state of patient (fear, mood swings) could reduce the rate of intercourse, which is also confirmed by results obtained by Lunelli (20), suggesting that 44% of patients reduced the rate due to aforementioned reasons. Kazemi-Saleh (21) in his study of the incidence of depression and fear of sexual intercourse showed that these problems occur in 33.3% of patients, and a correlation between depression and fear of sexual intercourse in men was also noted. Depression, by definition, gives the answer why it can be the cause of ED and its first sign is that the activities that once gave the patient satisfaction and pleasure no longer do that (22).

In conclusion, myocardial infarction, as well as the age, are directly related to the occurrence of ED. It was found that diabetes mellitus, dyslipidaemia, positive family history of cardiac disease and hypertension are more represented in the

patients with erectile dysfunction, which is also the case for smoking, alcohol consumption, and obesity. Influence of therapy, which is prescribed as per a protocol after myocardial infarction, has to be confirmed by larger studies. Although knowing pharmacological properties of drugs, the fact is that therapy should have impact of ED

occurrence. Developing of psychological counselling may be of great importance.

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## TRANSPARENCY DECLARATION

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## Better non-invasive endoscopic procedure: endoscopic ultrasound or magnetic resonance cholangiopancreatography?

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### ABSTRACT

**Aim** To present our experience with a diagnostic ability of endoscopic ultrasound (EUS) and magnetic retrograde cholangiopancreatography (MRCP) in cases of choledocholithiasis verified by endoscopic retrograde cholangiopancreatography (ERCP).

**Methods** This retrospective study was conducted after a collection of data involving 58 suspected choledocholithiasis patients who underwent ERCP from January 2013 to December 2015. Patients who were diagnosed with choledocholithiasis on the basis of clinical symptoms and radiological findings and who underwent ERCP were included in this study. The first group (29 patients) underwent EUS, and the second group (29 patients) underwent MRCP. The ERCP was performed in both groups. Sensitivity, specificity and diagnostic accuracy of EUS and MRCP were determined by comparing them with ERCP, which was considered to be a gold standard.

**Results** Gender representation was in favour of males, 58:42%. The mean age was 55.5 years. In the group 1 (EUS) 22 patients were found to have choledocholithiasis using ERCP. The EUS stone detection rate was 88%. Endoscopic ultrasound showed sensitivity (97%), specificity (67%) and accuracy (88%), positive predictive value (PPV) of 88%, negative predictive value (NPV) of 80%. In the group 2 (MRCP) 16 patients were found to have choledocholithiasis by ERCP. MRCP sensitivity was 81%, specificity 40%, PPV of 74%, NPV of 50%.

**Conclusion** The EUS was a superior non-invasive tool in comparison with MRCP for detecting choledocholithiasis, which was confirmed using ERCP.

**Key words:** choledocholithiasis, cholangiopancreatographies, endoscopic ultrasonography, magnetic resonance

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## INTRODUCTION

Gallstone disease is a common clinical problem. In Europe, ultrasound studies have revealed prevalence of 9–21% and incidence of 0.63/100 persons/year (1,2). Choledocholithiasis or common bile duct (CBD) stones are a frequent complication of gallstone disease and are present in up to 20% of the patients (3,4). The approach used in these patients is most important because CBD stones are a common cause of hospitalization due to recurrent symptoms, cholangitis, and pancreatitis (4). Once the diagnosis of choledocholithiasis is made, stones should be removed by a therapeutic procedure, namely endoscopic retrograde cholangiopancreatography (ERCP), which is the gold standard for the treatment of CBD stones (5). However, although ERCP is highly effective for the extraction of CBD stones, it is associated with a reasonable rate of adverse events, some of them life-threatening, including acute pancreatitis, bleeding, perforation, sepsis (5,6).

For many clinicians, the initial evaluation of patients with suspected choledocholithiasis includes serum liver biochemical tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin) and transabdominal ultrasonography (US) (7-9) to select patients for other procedures, such as magnetic resonance cholangiopancreatography (MRCP) (10) or endoscopic ultrasound (EUS) (11), before they recommend ERCP to the patient; thus, they are trying to avoid the overuse of ERCP, which should not be a diagnostic procedure because it is associated with complications.

In 2010, the American Society for Gastrointestinal Endoscopy (ASGE) published guidelines for the prediction of risk stratification for patients being evaluated for CBD (4), which classifies patients into high risk (>50%), intermediate risk (10–50%), and low risk of choledocholithiasis. Patients at high risk were defined as having any of the very strong predictors of choledocholithiasis (i.e. CBD stones on transabdominal US, clinical ascending cholangitis, or serum bilirubin level >70  $\mu\text{mol/l}$ ) or both strong predictors (i.e. dilated CBD on US, namely >6 mm with gallbladder in situ, and bilirubin level 30-70  $\mu\text{mol/l}$ ). Patients at intermediate risk were those with the presence of 1 strong predictor or any moderate predictor (abnormal liver biochemical tests other

than bilirubin, age older than 55 years, and clinical gallstone pancreatitis). Patients with low risk were those with no predictors present. Based on these guidelines, patients at high risk should directly receive ERCP, patients at intermediate risk should be submitted to less invasive evaluations, namely preoperative MRCP or EUS.

Additionally, there is spontaneous CBD emission in 73% clinical cases in patients with jaundice, biliary colic and cholecystitis (12)

However, in the clinical scenario, many authors advocate for the use of alternative diagnostic strategies for all patients with high and intermediate probability of choledocholithiasis, namely MRCP or EUS before ERCP (13-15).

The ASGE guidelines may lead to an unnecessarily large number of ERCPs, which can be associated with complications. It is clear that the ASGE guidelines should be re-opened for discussion. The optimal cost-effectiveness approach for patients with suspected CBD stones is unknown, but new modalities should be used.

Given the need to redefine the ASGE Guidelines, the focus of recent research is non-invasive techniques in choledolithiasis diagnostics, with the aim of assessing their usability, extending the criteria for their use, with the consequence of using ERCP only as a therapeutic procedure (4). There is a lack of consensus about the optimal non-invasive strategy for patients with suspected choledocholithiasis.

The aim of this study was to present our experience in the diagnostic ability of endoscopic ultrasound (EUS) and magnetic retrograde cholangiopancreatography (MRCP) in cases of choledocholithiasis, verified by ERCP.

## PATIENTS AND METHODS

### Patients and study design

This retrospective comparative observational study involved 58 patients, who attended the Department of Gastroenterology and Hepatology, Clinical Centre University of Sarajevo, Bosnia and Herzegovina, from January 2013 to December 2015. Patients aged 18–65 years were diagnosed with choledocholithiasis on the basis of clinical symptoms and radiological findings and underwent either EUS or MRCP followed by ERCP. The

diagnosis was based on symptoms (most patients complained of upper right abdomen or epigastric pain and jaundice), laboratory findings (elevated bilirubin level, elevated liver enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase), and abdominal ultrasonography examination (most patients were found to have dilated extrahepatic and intrahepatic bile ducts due to suspected choledocholithiasis). All patients were examined by experienced ultrasonographer. Patients with suspected sludge on ultrasonography (US) (presence of echogenic, mobile, nonshadowing debris), ultrasonically unspecified stones in the common bile duct were excluded.

## Methods

The patients were divided into two groups: 29 patients underwent MRCP and 29 patients underwent EUS.

Laboratory findings and abdominal ultrasound were performed for all patients, then the patients were divided into the groups: group 1 included patients with endoscopic ultrasound examination, and group 2 patients with MRCP examination.

After EUS or MRCP were performed, the patients underwent ERCP. The data were obtained from case report forms completed during the procedure.

On the first group, EUS was performed using a radial scope with a frequency of 6–7.5 MHz (Olympus, Japan). On the second group, MRCP was performed using a 1.5 T magnetic resonance imaging (MRI) system (Siemens, Germany), in which no medication or contrast medium was administered. The ERCP was performed with a standard duodenoscope.

Patients who refused to take part in this study and patients with contraindications for ERCP were excluded. The gold standard for the diagnosis of choledocholithiasis was ERCP. The sensitivity, specificity and diagnostic accuracy of EUS and MRCP were determined for the diagnosis of choledocholithiasis. All procedures were performed by experienced doctors.

## Statistical analysis

The positive and negative predictive values (PPV and NPV, respectively) are the

proportions of positive and negative results in statistics and diagnostic tests that are true positive and true negative results, respectively. The PPV and NPV described the performance of a diagnostic test or other statistical measure. The PPV and NPV are not intrinsic to the test; they depend also on the prevalence.

Sensitivity, specificity, PPV, NPV and accuracy were calculated. Positive choledocholithiasis on ERCP was considered as a gold standard.

## RESULTS

Gender representation was 58% : 42%. The mean age was 56.26 years (SD 12.14) in the group 1 (performing EUS) and 54.8 years (SD 12.31) in the group 2 (performing MRCP).

In the group 1 (EUS) among 29 patients with choledocholithiasis on transabdominal ultrasound 22 (75.9%) patients were found to have choledocholithiasis using ERCP, e. g. the EUS stone detection rate was 88%. In the group 2 (MRCP) among 29 patients with choledocholithiasis on transabdominal ultrasound 16 (55.2 %) patients were found to have choledocholithiasis by ERCP, e. g. the MRCP stone detection rate was 74% (Table 1).

**Table 1. Results of endoscopic retrograde cholangiopancreatography (ERCP) according to groups of patients**

| Patients' group<br>(Diagnostic tool) | Finding  | No (%) of<br>patients | ERCP (Gold standard) |                       |
|--------------------------------------|----------|-----------------------|----------------------|-----------------------|
|                                      |          |                       | Finding              | No (%) of<br>patients |
| Group 1 (EUS)                        | Stone    | 25 ( 86.2)            | 22 (75.9)            | 3 (10.3)              |
|                                      | No stone | 4 ( 13.7)             | 1 (3.4)              | 3 (10.3)              |
| Total                                |          | 29                    | 23 (79.3)            | 6 (20.7)              |
| Group 2 (ERCP)                       | Stone    | 22 (75.9)             | 16 (55.2)            | 6 (20.7)              |
|                                      | No stone | 7 (24.1)              | 4 ( 13.8)            | 3 (10.3)              |
| Total                                |          | 29                    | 20 (69.0)            | 9 (31.0)              |

EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography.

After statistical analysis of false positive and false negative, true positive and true negative results, it was shown that EUS had sensitivity (97%), specificity (67%) and accuracy (88%).

The positive predictive value (PPV) and negative predictive value (NPV) of EUS were 88% and 80%, respectively. For MRCP sensitivity was 81%, specificity 40%. The PPV and NPV of MRCP was 74% and 50%, respectively, which was lower than that of the EUS (Table 2).

**Table 2. Comparison of diagnostic values between endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP)**

| Variables compared to ERCP | EUS       | MRCP      |
|----------------------------|-----------|-----------|
| True positive (No, %)      | 22 (75.9) | 16 (55.2) |
| True negative (No, %)      | 4 (13.8)  | 4 (13.8)  |
| False positive (No, %)     | 3 (10.3)  | 6 (20.7)  |
| False negative (No, %)     | 1 (3.4)   | 4 (13.8)  |
| <b>Diagnostic test (%)</b> |           |           |
| Sensitivity                | 97        | 81        |
| Specificity                | 67        | 40        |
| Accuracy                   | 88        | 68        |
| PPV                        | 88        | 74        |
| NPV                        | 80        | 50        |

ERCP, endoscopic retrograde cholangiopancreatography; PPV, positive predictive value; NPV, negative predictive value

## DISCUSSION

This study demonstrated a high diagnostic accuracy of both non-invasive methods, endoscopic ultrasound and magnetic retrograde cholangiopancreatography. Based on the data, we can conclude that the ability of EUS to diagnose true positive patients with choledocholithiasis was higher than MRCP. EUS examination was also better for diagnosing true negative patients than MRCP. The PPV of EUS was 88%, which indicates 88% probability of a patient with choledocholithiasis having positive diagnostic test results; and in MRCP group it was 74%. Thus, in our study, EUS was superior to MRCP for detecting choledocholithiasis, which was confirmed using ERCP.

In a recently published study of Vaynshtein et al. EUS was an excellent screening tool for choledocholithiasis before performing ERCP. In most patients who undergo an early EUS, a subsequent diagnostic ERCP will not be needed. Additionally, alkaline phosphatase (ALP) serum levels higher than 300 IU/L are an independent predictor for the presence of CBD stones (16).

A systemic review from 2017 performed by Gillaca et al. included a total of 18 studies involving 2366 participants. Both EUS and MRCP have high diagnostic accuracy for detection of common bile duct stones. People with positive EUS or MRCP should undergo endoscopic or surgical extraction of common bile duct stones and those with negative EUS or MRCP do not need further invasive tests. The two tests were similar in terms of diagnostic accuracy and the choice of which test to use will be informed by availability and contra-indications to each test. Further studies that are of high methodological quality are necessary to determine the diagnostic

accuracy of EUS and MRCP for the diagnosis of common bile duct stones (17).

In a study of Prachayakul et al. EUS had a sensitivity of 100% and specificity of 80% for detection of CBD stones, and authors concluded that EUS is an accurate diagnostic tool for the detection of CBD stones, and can prevent the unnecessary use of ERCP (18).

Currently there is a need to redefine the ASGE Guidelines, so the focus of recent research are non-invasive techniques in choledolithiasis diagnostics with the aim of assessing their usability. Further, in the scenario of acute cholecystitis, the ASGE guidelines have a low positive predictive value and specificity and leading to an excessive overuse of ERCP as described in the paper of Gouveia et al. concluding that ASGE choledocholithiasis score was not useful for diagnosing choledocholithiasis in patients presenting with acute cholecystitis. Therefore, in patients with acute cholecystitis and suspected choledocholithiasis, this score should not be used and another diagnostic method such as EUS or MRCP should be employed prior to ERCP (19).

The major advantage of MRCP is its completely noninvasive nature compared with EUS, perhaps making it a better test for high-risk patients such as the elderly or the severely ill (17). Nevertheless, a high level of technical expertise is crucial to ensure an accurate review of MRCP images and this method requires a high level of patient cooperation. The presence of air bubbles inside the bile duct is a contributing factor to EUS false negative results (17).

The EUS yields very high-resolution images because of the proximity of the endoscope probe to the internal structures. This high resolution, which exceeds that of MRCP, makes EUS extremely sensitive to small stones. If stones are demonstrated by EUS, therapeutic ERCP can potentially be performed immediately after the completion of EUS while the patient is still sedated (16). However, EUS brings risks of sedation, bleeding, and perforation (17).

There has been much recent interest in performing new guidelines in initial evaluation of patients with suspected choledocholithiasis with less invasive or noninvasive modalities such as EUS and MRCP (17-19).

Choledocholithiasis is often missed on US because it has a relatively low sensitivity (15%–40%), although, its sensitivity is better for detecting CBD dilatation (77%–87%) (20).

The MRCP and EUS are other reliable noninvasive procedures used to evaluate choledocholithiasis and have few risks and complications. The ERCP was still considered as a golden standard. The ideal algorithm for choledocholithiasis diagnostic protocol is still an interest of further research.

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In conclusion, EUS is a superior noninvasive tool in comparison with MRCP for detecting choledocholithiasis, which was confirmed using ERCP.

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## TRANSPARENCY DECLARATION

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## Most common, real life factors affecting effectiveness of omalizumab asthma treatment: a 10-year study

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### ABSTRACT

**Aim** To assess efficacy of omalizumab in moderate to severe asthma and notable factors affecting it, such as treatment compliance during the period of ten years. This retrospective, observational real life study is the first of this kind in the Gulf region and one of the worldwide rare long term omalizumab treatment studies.

**Methods** The treatment for 35 patients started in 2008. Twenty patients (ongoing group) proceeded with treatment and were assessed annually until 2017. Reasons for treatment discontinuation in 15 patients (drop-out group) were also assessed.

**Results** Before starting omalizumab the ongoing group of patients had history of  $\geq 2$  asthma exacerbations per year, which significantly decreased during the first year of the treatment ( $p < 0.001$ ), and for 14 (70%) patients  $\leq 1$  exacerbation stayed during the next 10 years. Since 2014 six (30%) patients had had  $\geq 2$  annual asthma exacerbations ( $p < 0.05$  in 2013;  $p < 0.05$  in 2014;  $p < 0.001$  in 2015;  $p < 0.01$  in 2016;  $p < 0.001$  in 2017). At the same time there was a significant drop in compliance index (CI) ( $p < 0.0001$ ).

**Conclusion** To our knowledge this is the first 10-year study of compliance and effectiveness, which may help finalize some practical suggestions to improve CI in clinical practice and to note acceptable variation in CI. It is important to recognize factors that can possibly affect effectiveness of the treatment and identify the patients who will have the best benefit from a long term omalizumab treatment.

**Key words:** omalizumab, compliance, efficacy, long term, efficacy

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## INTRODUCTION

Over the past four decades, prevalence, morbidity and mortality of asthma have increased significantly (1, 2) and approximately 2-10% of patients with asthma have some form of “severe asthma”, “uncontrolled asthma”, “difficult-to-treat asthma” or “refractory asthma” (3). The prevalence of asthma in Kuwait was estimated to 15% for adults and 18% for children (4).

As there is no cure for asthma, the objective of the treatment is to control the clinical aspects of the disease (5). The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach to asthma control with the treatment being stepped up until control is achieved and maintained. For inadequately controlled asthma patients, that usually means adding oral corticosteroids (OCS) or anti immunoglobulin E (IgE) treatment (6). Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that inhibits the binding of IgE to high-affinity receptors (7). Omalizumab was first approved in 2003 to treat adults and children (12  $\geq$  years of age) with moderate to severe persistent allergic asthma not controlled by inhaled corticosteroids (ICS), lately approved for children aged  $\geq$  6 years (8).

Based on current data it is still unclear when omalizumab treatment should be stopped (9). Omalizumab efficacy is usually evaluated at 16 weeks (10). However, in many patients an extension of the treatment for many years is essential to improve symptoms, medication use, lung function and quality of life outcomes. For this reason the assessment of omalizumab efficacy in real life settings during a prolonged period of time is in the focus (11,12).

The aim of our study was to assess efficacy of omalizumab and notable factors affecting it such as the treatment compliance during the period of ten years. Furthermore, this retrospective and observational real life study is the first of this kind in the Gulf region and one of the worldwide rare long term omalizumab treatment studies.

## PATIENTS AND METHODS

### Patients and study design

This real life, retrospective, observational study, assessed omalizumab effectiveness, in moderate

to severe asthma patients, treatment compliance and factors that possibly affect those two over the period of 10 years. The study was conducted in Al Rashed Allergy Centre in Kuwait, which was the first Medical Institution allowed to apply it in medical treatment of uncontrolled, moderate to severe allergic bronchial asthma by the Ministry of Health in 2008.

The treatment for 35 patients started in 2008. Twenty patients (ongoing group) proceeded with the treatment and were assessed annually until 2017. Reasons for treatment discontinuation in 15 patients (drop out group) were also assessed.

Included patients had been diagnosed with moderate to severe allergic asthma with a poor response to maximal dose of inhaled corticosteroids with long acting beta 2 agonists (ICS\LABA). All patients fulfilled the following criteria: older than 12 years of age, total serum immunoglobulin E of 30-700 IU/ml, presence of atopy to inhalant allergens diagnosed by skin prick test (SPT), obstructive pattern by pulmonary function test, e. g. force expiratory volume in first second (FEV1) less than 80 %, with a bronchodilator response  $>12\%$  and  $>200$  mL, history of more than two asthma exacerbations per year (defined as emergency department/hospital admission or use of systemic corticosteroids). No female patient was pregnant or nursing at time of start with omalizumab treatment.

The Research Ethics Committee of the Ministry of Health of Kuwait approved this study and a signed informed consent was obtained from all study patients prior to start of omalizumab treatment.

### Methods

Compliance to omalizumab (Compliance index, CI) was calculated comparing milligrams of a given dose of medication to milligrams of a presumed dose, per year. If  $CI \leq 50\%$  patient is defined as not compliant, if 50-75% poor compliance, if 76-89% good and if  $\geq 90\%$  high compliance to omalizumab treatment (13).

As factors possibly affecting asthma control, increase in body mass index (BMI), seasonal allergic rhinitis (SAR) and chronic rhino-sinusitis with nasal polyposis were also taken into consideration.

Omalizumab was administered every 2 or 4 weeks, subcutaneously, at the dose calculated taking into account the patients pre-treatment total IgE serum level and body weight. (14). During 10 years of omalizumab treatment, ICS/LABA dose was adjusted with stepping down or up again based on the control of asthma symptoms.

During the following 10 years, annual assessment of CI, number of asthma exacerbations (defined as a worsening of asthma requiring an emergency department/ hospital admission or systemic corticosteroid treatment) (15), FEV1, patient-reported outcomes from the asthma control test (ACT) (16), Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (17) and global evaluation of treatment effectiveness (GETE) (18) were done for ongoing group. Data from patients' files (ACT, AQLQ, annual number of asthma exacerbations) were used to assess efficacy of omalizumab, which is defined with conclusive annual GETE assessment by a physician.

The ACT consists of five questions pertaining to the past 2-4 weeks. The brief questionnaire assesses asthma symptoms (daytime and nocturnal), use of rescue medication, and the effect of asthma on daily functioning. The total score was obtained by summing the scores for each item and ranges from 5 (poor control of asthma) to 25 (complete control of asthma). The minimally important difference of the ACT is 3 points or more (19).

The GETE Questionnaire represents a five-point scale: 1 - excellent (complete control of asthma), 2 - good (marked improvement), 3 - moderate (discernible, but limited improvement), 4 - poor (no appreciable change), and 5 - worsening. The Questionnaire was completed by physicians for every patient. The GETE 4 and 5 point corresponded to "lack of efficacy" and 1 and 2 point corresponded to "clinical efficacy" (20).

The MiniAQLQ contains 15 questions in the four domains. There are five items in the domain Symptoms, four items in the domain Activity Limitations, three items in the domain Emotional Function, and three items in the domain Environmental Stimuli. A change in score of greater than 0.5 was considered clinically important (21).

### Statistical analysis

Non-parametric and parametric methods are used to calculate statistical significance. Kolmogorov-

Smirnov test and Shapiro-Wilk test were used in order to test the normality of distribution of variables. Mean values were shown as arithmetic mean  $\pm$  standard deviation in case of normal distribution of variables (age, body mass index and forced expiratory volume in first second) or median with minimum and maximum value inside brackets in the case of non-normal distribution (immunoglobulin E, doses of omalizumab per month, asthma control test, asthma quality of life questionnaire, number of exacerbations and compliance index). Student's t-test, Mann-Whitney test, Fisher's test and  $\chi^2$  test were used for calculating the difference between the groups. ANOVA test was used to calculate the relative difference distribution variance between variables. The statistical hypotheses were tested at the level of  $\alpha=0.05$ , and the difference between the groups in the sample was considered significant when  $p<0.05$  or less. Statistical significance was depicted as:  $p<0.05$ ,  $p<0.01$  and  $p<0.001$ .

### RESULTS

During the year 2008, total of 35 patients with moderate to severe poorly control asthma on maximum ICS/LABA dose started with omalizumab as add on treatment. All patients fulfilled criteria for stepping up to omalizumab treatment by GINA guidelines at that time (26). Only one patient required daily use of oral corticosteroids prior omalizumab but stopped gradually after 6 months of omalizumab treatment.

Omalizumab was given to eight (22.86%) patients (five in ongoing group) every two weeks and to others every 4 weeks. No significant correlation was observed between monthly number of doses of omalizumab and compliance index in drop out ( $p>0.05$ ; total Pearson coefficient of correlation  $r=0.4141$ ; 95%CI: -0.1247 to 0.7643) nor in ongoing group ( $p>0.05$ ; total Pearson coefficient of correlation  $r=-0.383$ ; 95%CI: -0.7060 to 0.07173).

Until the assessment in 2017, 15 (42.8%) patients (11 females) had discontinued their further treatment for different reasons at different time points. The characteristics of ongoing and dropouts group are presented in Table 1.

The ongoing group was younger ( $p<0.05$ ), but with similar distribution of gender, BMI, IgE and doses of omalizumab per month to later defined drop out group ( $p>0.05$  for all measurements).

**Table 1. Characteristics of the ongoing and dropout group before starting omalizumab**

| Characteristics   | Ongoing group (n=20) | Drop out group (n=15) | p      |
|---|----------------------|-----------------------|--------|
| Age (years) (mean±SD)   | 41.4 ± 8.95          | 51.87 ± 16.37         | 0.021* |
| Females (no; %)   | 15 (75.0)            | 11 (73.3)             | 0.7802 |
| Body Mass Index (kg/m <sup>2</sup> ) (mean±SD)                            | 30.13 ± 6.78         | 30.58 ± 4.29          | 0.8224 |
| Immunoglobulin E (IU/mL) (median) (minimum; maximum)                      | 125 (65; 223)        | 279 (55; 576)         | 0.523  |
| Doses of omalizumab per month (median) (minimum; maximum)                 | 1 (1; 2)             | 1 (1; 2)              | 0.6171 |
| Forced Expiratory Volume in First Second (% of predicted value) (mean±SD) | 77.3±14.5            | 69.7±13.6             | 0.05*  |

\* significant difference

Increased BMI, as comorbidity before starting Omalizumab, was noted in 13 (37.14%) patients (10 from the ongoing group and 3 in the drop-out group). The BMI was not assessed in drop-out group because of a shorter follow up period.

Skin prick test (SPT) results in all patients before starting omalizumab showed a domination of sensitisation to perennial (*Dermatophagoides pteronissinus*, *Dermatophagoides farineii*, *Cat dander*, *Alternaria alternata* spp.) or both perennial and seasonal (*Salsola kali*, *Bermuda grass*) allergens. The SPT positive for only seasonal allergens was found in eight (22.86%) patients (five in the drop-out group).

Before starting omalizumab all patients in ongoing group (n=20) had history of two or more asthma exacerbations per year, which significantly decreased during the first year of treatment (p<0.001) and for 11 (55%) patients one exacerbation remained during next 10 years.

The FEV<sub>1</sub>, ACT and AQLQ improved significantly during 10 years on omalizumab (baseline vs after 10 years: FEV<sub>1</sub> % of predicted value (mimum; maximum): 68.5 (21; 94) vs 72.5 (38; 106) (p<0.01); ACT median (mimum; maximum): 15.5 (8; 21 vs 21 (12; 25) (p<0.0001); AQLQ median (mimum; maximum): 30 (15; 60 vs 77 (31; 87) (p<0.0001). Actually, FEV<sub>1</sub> improved significantly after one year of treatment (p<0.001) and remained similar during next 9 years. Also, ACT improved significantly after one year (2008 vs 2009 p<0.0001), but showed additional improvement after 2 years of treatment (2009 vs 2010 p<0.01) and then remained similar during next 8 years (Table 2).

Over ten years, beside 10 (50.0%) patients with high BMI from the baseline, three (15.0%) expe-

**Table 2. Parameters assessed before (baseline) and after 10 years of omalizumab for ongoing group**

| Parameter   | Baseline      | After 10 years | p        |
|---|---------------|----------------|----------|
| Body Mass Index (kg/m <sup>2</sup> ) (mean±SD)                                  | 30.13 ± 6.78  | 31.32 ± 4.05   | 0.1115   |
| Forced Expiratory Volume in First Second (% predicted value) (minimum; maximum) | 68.5 (21; 94) | 72.5 (38; 106) | 0.0086*  |
| Asthma Control Test (median) (minimum and maximum)                              | 15.5 (8; 21)  | 21 (12; 25)    | <0.0001* |
| Change in Asthma Control Test >3 (no, %)  | -             | 14 (70.0%)     | -        |
| Asthma Quality of Life Questionnaire (median) (minimum and maximum)             | 30 (15; 60)   | 77 (31; 87)    | <0.0001* |
| Change in Asthma Quality of Life Questionnaire >0.5 (no, %)                     | -             | 20 (100)       | -        |

\* significant difference

rienced increase in BMI. Out of four (20.0%) patients that notably reduced BMI over ten years, two (10.0%) experienced increase in the number of asthma exacerbations (after 6th year of omalizumab treatment).

In the drop-out group mean duration of omalizumab treatment was 3±1.65 years, which was discontinued in 8 (22.8%) patients after 2 years. In this group seven (20.0%) patients were discontinued from the treatment due to reasons unrelated to the effectiveness of the treatment (adverse events or new comorbidities). Eight out of 15 (53.33%) patients stopped taking omalizumab due to very poor (n=5) or excellent (n=3) respon-

**Table 3. Drop out according to years of treatment**

| Drop-out according to treatment years | Number (%) of patients in drop out group |
|---------------------------------------|--|
| after 1 year                          | 1 (2.8)                                  |
| after 2 years                         | 7 (20.0)                                 |
| after 3 years                         | 3 (8.5)                                  |
| after 4 years                         | 1 (2.8)                                  |
| after 6 years                         | 3 (8.5)                                  |

se based on GETE (Table 3).

For the ongoing group the number of asthma exacerbations significantly dropped during the first year on omalizumab and it was ≤1 during the first 6 years of the treatment (from 2008 to 2013). From the year 2014, six (out of 20 patients) (30.0%) had ≥2 annual asthma exacerbations (p<0.05 in 2013; p<0.05 in 2014; p<0.001 in 2015; p<0.01 in 2016; p<0.001 in 2017). At the same time there was a significant drop in CI (p<0.0001) (Table 4).

During the period of ten years CI was similar among all 20 patients (p>0.05 for all measurements) except

in 2015, when six patients with  $\geq 2$  exacerbations in 2014 had higher CI than other patients ( $p < 0.05$ ). An increase in CI did not affect annual trend in asthma exacerbations, which remains the same or increased in five of six patients (83.33%).

Average CI in ongoing and drop-out group was similar ( $p > 0.05$ ) (Table 4).

**Table 4. Number of asthma exacerbations and Compliance Index for ongoing group (n=20)**

| Year | Number of Exacerbations<br>(median)<br>(minimum; maximum) | Compliance Index<br>(median)<br>(minimum; maximum) |
|------|---|--|
| 2008 | 0 (0; 1)  | 1 (0.7; 1)   |
| 2009 | 0 (0; 1)  | 1 (0; 1)   |
| 2010 | 0 (0; 1)  | 1 (0; 3)   |
| 2011 | 0 (0; 0)  | 0.9 (0; 1)   |
| 2012 | 0 (0; 1)  | 0.9 (0; 1)   |
| 2013 | 0 (0; 1)  | 0.8 (0; 1)   |
| 2014 | 0 (0; 2)  | 0.8 (0.5; 0.9)                                     |
| 2015 | 0 (0; 3)  | 0.8 (0.2; 1)                                       |
| 2016 | 0 (0; 4)  | 0.8 (0.3; 1)                                       |
| 2017 | 0.5 (0; 4)  | 0.8 (0.4; 0.9)                                     |
| p    | <0.0001   | <0.0001  |

There was no significant correlation in monthly doses of omalizumab (every 2 weeks vs. every 4 weeks) and average CI between six patients with an increase in asthma exacerbations and other 14 patients ( $p > 0.05$ ; patients with  $\geq 2$  exacerbations: total Pearson coefficient of correlation  $r = -0.5356$ ; 95%CI: -0.8850-0.1996; patients with  $\leq 1$  exacerbations: total Pearson coefficient of correlation  $r = -0.2348$ ; 95%CI: -0.7317-0.4250) (Table 4).

In the ongoing group during assessment in 2017, 14 (70%) patients were defined as excellent to good and six (30%) as good to moderate treatment responders (defined by GETE physician assessment).

## DISCUSSION

Although omalizumab is an effective add-on therapy of uncontrolled moderate to severe persistent allergic asthma, most studies discussed its efficacy through relatively short period of time (i.e.  $\leq 4$  years) (22), with the exceptions of a few reports, which proved favourable outcome beyond 4 years of treatment (23,24). A recent study following eight patients up to nine years documented that long-term treatment with omalizumab was associated with continued benefits in reducing symptoms, exacerbations and medication burden without any safety concerns (12). Our overall results also support favourable outcome with excellent to good asthma control in

70% of patients over 10 years. A proportion of patients who discontinued omalizumab treatment due to lack of efficacy was significantly higher in real-life studies than in randomized clinical trials (25). Perhaps strict inclusion and exclusion criteria in randomized clinical trials could alter omalizumab effectiveness in comparison to the real-life settings.

In our study, 42.8% patients dropped out the treatment mostly due to lack of efficacy (after 2 years) or newly diagnosed comorbidities (during 6 years). Response to omalizumab was routinely assessed after 16 weeks of therapy (26) but late responders could benefit from longer period of assessment (27).

After 2 years on omalizumab 14.28% of patients did not show any significant improvement of FEV1, ACT, or annual number of asthma exacerbations in our study. Due to mild improvement in AQOL they decided to continue with the treatment despite overall CI  $< 60\%$ . Disregarding physician's advice these patients have also shown very poor compliance with standard asthma treatment and follow up visits since they stopped with omalizumab. During the same period of 2 years 8.57% of patients had excellent response with high CI, and were advised to stop omalizumab for observational time. Their asthma remained very well controlled with standard asthma treatment (step 4 and step 3 GINA). It seems that a small fraction of patients could be profiled as eligible or ineligible for a long-term treatment during the period of  $\leq 2$  years based on effectiveness and compliance.

Clinical benefits and effectiveness of omalizumab were mostly seen in reduction of asthma exacerbations and ICS dose (28), as well as in improvement of AQOL (29) or FEV1 (30). In this study majority of patients had improvement in FEV1, ACT, AQOL and reduction in asthma exacerbations after the first year on omalizumab. Similar results were documented in our previous 4-year study (11).

Due to different parameters used to assess omalizumab efficacy and controversial data of some studies (31) good predicting markers of omalizumab treatment are still missing (32). Improvement in asthma control with omalizumab led to the reduction of concomitant medication use (33) and in our study 57.14% of patients were stepped down from the maximum dose of ICS/LABA

during the first five years of treatment. However, 30% patients, who were defined during the five-year treatment as good to excellent responders to omalizumab, experienced  $\geq 2$  exacerbations of asthma in the sixth year due to which they were stepped up back to the maximum dose of ICS\LABA; other 70% patients, who were also defined as excellent to good responders, remained like that during all 10 years.

Due to the decrease in asthma control in a relatively high number of patients (30%) we assessed CI, changes in BMI, presence of seasonal allergies and chronic rhinosinusitis with nasal polyposis as possible factors affecting omalizumab efficacy and compliance. For the evaluation of compliance many methods are currently available but none of them could be considered as the gold standard (34). Some studies reported that about 50% of asthma patients are not compliant with the given treatment (35) and CI greater than 80% has been considered as satisfactory (36). One study reported that higher compliance did not correspond to high response rate (13). In our study CI decreased from high to good in all patients over 10 years. We noticed the first mild decrease in CI during the fifth year of the treatment, but in 70% patients CI decrease did not affect asthma control. On the other side, there was no improvement in asthma control for 30% of patients who increased CI after the initial drop. It seems that CI from 0.8-1 presented an acceptable range for asthma control in majority of our patients.

Although in Jason et al. study 4-week dosing regimen achieved better compliance than 2-week regimen (37), in our study there was no significant difference in CI between 2- and 4-week regimens. There was also no effect of dosing regimen on CI among 30% of patients with decreased asthma control.

Caminati et al. highlighted that sensitization to a perennial allergen was missing in more than 20% of patients undergoing omalizumab treatment (25) despite being included in the prescription criteria (14). Domingo et al. proved that omalizumab offered the same clinical benefits regardless of whether asthma was caused by a seasonal or a perennial allergen (38).

In our study 15.0% ongoing group patients had SPT positive only for seasonal allergens (*Salsola kali* and *Bermuda* grass, which are most common

inhalant allergens in Kuwait), but also history of chronic rhinosinusitis (CRS)-with nasal polyposis and they were among 30% of patients who experienced decreased asthma control. Asthmatic patients with CRS and nasal polyposis had more poorly controlled asthma, increased airway obstruction and marked lower airway inflammation (39). Omalizumab reduces the size of nasal polyps and improves the quality of life (40) improving nasal outcomes (symptoms, nasal endoscopy and computed tomography results), but it does not improve pulmonary outcomes (symptoms and pulmonary function test results) (41). In our study 30.0% patients had CRS with nasal polyposis from which 66.67% experienced  $\geq 2$  asthma exacerbations after 5 years being fully controlled on omalizumab. These patients were regularly followed by otolaryngologist. Chronic rhinosinusitis without polyposis was found in 20% patients with excellent response to omalizumab. These data point out complexity and dynamics of asthma control in patients with CRS with nasal polyposis and demand closer follow up of these patients.

We would like to point out a loss of bronchodilator response in one female patient, with spirometry showing dominantly restrictive pattern, after 8 years on omalizumab without any significant changes on her computed tomography (CT) chest. This is opposite to the studies proving that omalizumab decreased airway remodelling in patients with severe asthma (42).

Interestingly, 40-year-old female patient, without comorbidities, with excellent asthma control and good CI, but who had stopped omalizumab due to two pregnancies during the first 5 years and then continued the treatment without significant deterioration in symptoms, lost asthma control ( $\geq 2$  asthma exacerbations annually) during the sixth year on omalizumab.

Molimar et al. noted that 20% of previous responders failed to respond to the reintroduction of omalizumab (43), but Busse et al. reported that 60% of patients remained free of asthma exacerbations at one year after discontinuation of long-term omalizumab ( $\geq 5$  years) (44). The question is whether there is a possible late effect of repeated long term treatment discontinuation (app. one year) on effectiveness and this requires closer monitoring of similar cases.

In conclusion, according to our knowledge this is the first 10-year study of compliance and effectiveness, which may help finalize some practical suggestions to improve compliance in routine clinical practice and to note acceptable variation in compliance index. It is important to recognize factors that can possibly affect effectiveness of the treatment and identify the patients who will have the best benefit from long-term omalizumab treatment.

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## TRANSPARENCY DECLARATION

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## The soluble fms-like tyrosin kinase-1 (sFLT-1) to placental growth factor (PIGF) ratio as a possible indicator for the severity of preeclampsia - single institution experience

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### ABSTRACT

**Aim** To investigate a potential of the clinical use of the soluble fms-like tyrosine kinase 1 (sFLT-1) to placental growth factor (PIGF) ratio from the perspective of a small hospital centre.

**Methods** Maternal serum samples were analysed at 24<sup>1/7</sup>-28<sup>0/7</sup>, and 28<sup>1/7</sup>-32<sup>0/7</sup> weeks of gestation. The level of sFLT-1 and PIGF was determined by immunoassay platform and used to calculate the sFLT-1/PIGF ratio in 35 pregnant women, and divided into subgroups according to preeclampsia occurrence at the time of delivery: preterm ( $\leq 37$  weeks) or term (37-42 weeks'), and matched a control group.

**Results** Patients in the preterm delivery group had a significantly higher incidence of intrauterine growth restriction, lower gestational age at the time of delivery, and lower infant birth weight compared to the other two groups. There was a negative correlation between the sFLT-1/PIGF ratio and GA and between the sFLT-1/PIGF ratio and birth weight at the time of delivery. The value of the sFLT-1/PIGF ratio was significantly higher in the preterm delivery PE group. All the PE group pregnancies ended with caesarean delivery compared to 25% in the control group. However, none of the patients from the PE group had any of the possible complications of preeclampsia nor did they require additional therapy such as blood transfusion or additional non-standard hypertensive therapy.

**Conclusion** The sFLT-1/PIGF ratio could be used as an indicator for the development and estimation of the severity of PE to provide objective evidence for the management of preeclampsia patients, and as a predictive marker of preeclampsia at low cost.

**Key words:** eclampsia, pregnancy complications, placenta, premature birth

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## INTRODUCTION

Preeclampsia (PE) is a heterogeneous, multi-system disorder, which affects both the mother and the unborn child. It affects approximately 3% of pregnant women, along with other hypertensive disorders it affects 5-10% of all pregnancies and remains one of the leading causes of maternal and perinatal morbidity and mortality (1). In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (transaminases up to twice of the normal concentration), new development of renal insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary oedema or new-onset cerebral or visual disturbances. Proteinuria is described as excretion of 300 g or more of protein in 24 hour urine collection (2).

The clinical presentation and course of PE is variable, ranging from mild forms, severe and rapidly progressing PE with the need to end the pregnancy and deliver a preterm baby (3). Consequently, preeclampsia is associated with a high risk of iatrogenic preterm delivery, intrauterine growth restriction, placental abruption and perinatal mortality, along with maternal morbidity and mortality (4).

The pathogenesis of PE is complex, and it likely involves maternal, foetal and placental factors. Abnormalities in the development of placental vasculature early in the pregnancy may result in relative placental underperfusion, hypoxia and ischemia, which then lead to release of angiogenic factors into maternal circulation that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease (5). It is clear that defects in spiral artery remodelling and trophoblast invasion are two separate but related processes characteristic of hypertensive disorder of pregnancy and foetal growth restriction (6). There is growing evidence that imbalance in circulating angiogenic factors, such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) secreted by the placenta, may cause endothelial dysfunction, and may have a major role in the development of PE (7). Maynard et al. (8) demonstrated that high serum levels of sFlt-1 (anti-angiogenic protein) and low levels of PlGF (pro-angiogenic protein), predict subsequent development of PE. Studies

have demonstrated that a high ratio of sFlt-1/PlGF is linked with PE before its clinical onset, and improves the sensitivity and specificity of Doppler ultrasound in predicting PE (9).

Herraiz et al. (10) proposed an algorithm for the intensive follow-up of patients at risk of developing placental dysfunction-related disorders, based on the rational use of the sFlt-1 to PlGF ratio. As in our study, the first measurement of the sFlt-1 to PlGF ratio was undertaken at 24-28 weeks' gestation. On the basis of the sFlt-1 to PlGF ratio values, they suggested that if the sFlt-1 to PlGF ratio is under the "rule out" cut off point (<38) there is a low risk of developing any early-onset PE and women can follow their regular follow up schedule. If the sFlt-1 to PlGF ratio is in the intermediate range (38-85), those women are highly likely to develop clinical manifestations of PE within four weeks. In this case, a new determination of sFlt-1 to PlGF ratio is needed two weeks later and if the sFlt-1 to PlGF ratio is less than 85 this is considered to be safe from pregnancy complications. In case of an sFlt-1 to PlGF ratio above the "rule out" cut-off point (>85) or symptomatic PE the patients should be considered as having placental dysfunction and be managed according to the current guidelines adding regular reappraisals of the sFlt-1 to PlGF ratio every 48-96h for support of clinical management. Similar recommendations for sFlt-1/PlGF ratio use in the clinical diagnosis of PE are given in the NICE Diagnostic Guidance published in 2016. An sFlt-1/PlGF ratio <38 rules out PE for at least a week, a ratio above 85 (early onset PE) or above 110 (late onset PE) is highly indicative of PE, and a ratio of 38-85 (early onset PE) or 38-110 (late onset PE) provides extra information as to which women are at moderate or high risk of developing PE within four weeks using the sFlt-1 to PlGF ratio (11).

Currently, the diagnosis of PE still mainly relies on clinical signs and symptoms, which are variable and non-specific (hypertension, headache, visual disturbance, epigastric pain, reduced foetal movements and a small infant for the gestational age) (12). As a result, frequent laboratory testing (proteinuria, platelet counts, serum uric acid and liver enzymes levels) is usually required with the assessment of foetal wellbeing and unnecessary hospitalization (13). Although no preventive or therapeutic strategy is yet available, quick and reliable detection of the disease allows imme-

diate intervention with steroids for foetal lung maturity, magnesium for seizure prophylaxis and antihypertensive therapy (14).

Therefore, there is still a need for reliable predictors of PE.

The objective of this study was to investigate the value of using the sFlt-1/PIGF ratio for prediction of the presence or absence of PE, and its influence on clinical validation (decision-making for women with suspected PE in routine clinical practice) and to demonstrate the results with presentation of the cost of the test.

## PATIENTS AND METHODS

### Patients and study design

A cohort and randomised study was performed at the Clinical Department of Gynaecology and Obstetrics, University Hospital Centre, Osijek, and at the Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University Hospital Centre Osijek, Croatia, between January 2014 and May 2017.

Osijek University Hospital is a tertiary centre and a teaching hospital for an area covering  $\frac{1}{4}$  of the Croatian territory, and the centre responsible for “in utero transport” for Eastern Croatia.

The course of pregnancy was observed extensively in randomly selected pregnant women. Personal and history data, personal habits, the course and pregnancy outcome were recorded.

All patients were presented with and signed an informed consent.

This study was approved by the Ethics Committee of the University Hospital Centre, Osijek. According to the final pregnancy outcome the pregnant women were divided into two groups: the control group (CTR) and the preeclampsia (PE) group. The control group was selected from women who were normotensive and without proteinuria throughout pregnancy. The diagnostic criteria for PE group were defined as hypertension (systolic blood pressure  $\geq 140$  mm Hg and diastolic blood pressure  $\geq 90$  mm Hg after 20 weeks of gestation) and proteinuria with excretion of 300 mg of protein in 24-hour urine. The study at the beginning included 50 pregnant women, however, only 35 participants were followed to the end of the study.

### Methods

Maternal blood was collected twice at 24<sup>+1</sup> to 28<sup>+0</sup> weeks of gestation (2<sup>nd</sup> trimester) and 28<sup>+1</sup> to 32<sup>+0</sup> weeks of gestation (3<sup>rd</sup> trimester) in serum vacutainer tubes, and immediately centrifuged at 3500 rpm for 10 min. Serum aliquots were stored at -20°C until analysis, which was done in batches of ten samples according to the availability of the test. Levels of sFlt-1 and PIGF in serum samples were determined retrospectively by means of fully automated Elecsys assays on an electrochemiluminescence immunoassay platform (Cobase analyzers, Roche Diagnostics Ltd. Mannheim, Germany) and used to calculate the sFlt-1/PIGF ratio. The minimal detectable levels in the assays of sFlt-1 and PIGF were 15 and 10 pg/mL. The within-run coefficient of variation for the control samples was below 4% in both assays. Between-run coefficients of variation were 2.3 to 5.6 % for sFlt-1 and 2.4-4.6% for PIGF.

Finally, a total of 35 pregnant women, 12 with preeclampsia (PE) diagnosis and 23 control women (CTR), matched for maternal age and gestational age (GA) at the time of blood sampling, were included into sampling and finished the study. The PE group was subdivided into preterm delivery PE (<37 GA) and term delivery PE ( $\geq 37$  GA). Fifteen women were excluded because they did not attend the second blood sampling (n=13) or missing of delivery data (n=2).

### Statistical analysis

Continuous variables were reported as median and categorical variables as numbers (percentage). The normal distribution of the continuous variables was analysed by the Kolmogorov-Smirnov test. Comparison between the defined outcome groups was carried out by the Fisher exact test (categorical variables), Student's t-test (ANOVA) (normal variables), and Mann-Whitney U-test (not normally distributed variables). Differences were considered statistically significant at  $p < 0.05$ . The Spearman correlation coefficient was used to calculate the correlation.

## RESULTS

During the study period between January 2014 and May 2017, 50 women were enrolled. Fifteen women were excluded because they did not attend the second blood sampling (n=13) or there was a lack of delivery data (n=2).

There were no differences in age, body mass index (BMI), smoking habits and family history of PE, PE in previous pregnancies or gestational diabetes between the groups. None of the women had pre-existing hypertension. Five (41.7%) women in the PE group and nine (39.1 %) in the control group were nulliparous (Table 1).

**Table 1. Demographic and clinical characteristics of the study population at sampling**

| Characteristic                   | No (%) of women in the group |                 | p      |
|----------------------------------|------------------------------|-----------------|--------|
|                                  | CTR (n=23)                   | PE (n=12)       |        |
| Age (years) (range)              | 32 (21-41)                   | 31.5 (24-35)    | 0.238  |
| BMI (kg/m <sup>2</sup> ) (range) | 27.2 (23-41.5)               | 29.15 (23-36.4) | 0.849  |
| Nulliparous                      | 9 (39.1)                     | 5 (41.7)        |        |
| Gestational age (week)* (range)  | 26 (25-28)                   | 26 (25-28)      |        |
| Gestational age (week)† (range)  | 30 (28-32)                   | 29 (29-32)      |        |
| Smoking                          |                              |                 |        |
| Past                             | 8 (38.1)                     | 5 (41.7)        | 0.975  |
| Current                          | 4 (19)                       | 2 (16.6)        |        |
| No                               | 9 (42.9)                     | 5 (41.7)        |        |
| Chronic diseases                 |                              |                 |        |
| Yes                              | 4 (17.4)                     | 1 (8.3)         | 0.639  |
| No                               | 19 (82.6)                    | 11 (91.7)       |        |
| Drugs                            |                              |                 |        |
| Metildopa                        | 2 (8.7)                      | 4 (33.3)        | 0.0668 |
| Others                           | 5 (21.7)                     | 0               |        |
| No                               | 16 (79.6)                    | 8 (66.7)        |        |
| Family history of PE             |                              |                 |        |
| Yes                              | 4 (17.4)                     | 5 (41.7)        | 0.456  |
| No                               | 19 (82.6)                    | 7 (58.3)        |        |
| PE in previous pregnancies       |                              |                 |        |
| Yes                              | 5 (21.7)                     | 7 (58.3)        | 0.322  |
| No                               | 18 (78.3)                    | 5 (41.7)        |        |
| GDM in previous pregnancies      |                              |                 |        |
| Yes                              | 0 (0)                        | 1 (8.3)         | 0.343  |
| No                               | 23 (100)                     | 11 (91.7)       |        |

\*second trimester (24<sup>1/7</sup>-28<sup>0/7</sup>); †third trimester (28<sup>1/7</sup>-32<sup>0/7</sup>); CTR, matched controls; PE, preeclampsia; BMI, body mass index; GDM, gestational diabetes;

According to the gestational age at delivery six women in the preeclampsia group had preterm delivery (<37 GA) and six women with PE had term delivery (>37 GA). Women in the preterm PE group had a significantly higher incidence of intrauterine growth restriction, with a significantly lower Apgar score and infant birth weight compared to the other two groups (all p <0.001). All the PE group pregnancies were terminated by Caesarean section, compared to 25% in the control group (p<0.001) (Table 2).

The median serum level of sFLT-1 was significantly higher in the preeclampsia group compared to the women in the control group in both trimesters: 2205 vs 1309 (p=0.047) in the 2<sup>nd</sup> trimester, and 3024.5 vs 1348 (p=0.004) in the 3<sup>rd</sup> trimester.

**Table 2. Characteristics of the study population at delivery**

|                         | No (%) of women in the group |                  |                  | p      |
|-------------------------|------------------------------|------------------|------------------|--------|
|                         | CTR (n=23)                   | PE > 37 GA (n=6) | PE < 37 GA (n=6) |        |
| IUGR                    |                              |                  |                  |        |
| Yes                     | 0                            | 1 (16.7)         | 4 (66.7)         | <0.001 |
| No                      | 23 (100)                     | 5 (83.3)         | 2 (33.3)         |        |
| APGAR                   |                              |                  |                  |        |
|                         | 10 (6-10)                    | 10 (10-10)       | 7 (5-9)          | <0.001 |
| Birth weight (g)        | 3350 (2300-4400)             | 3230 (2400-4420) | 1095 (810-2060)  | <0.001 |
| Gestational age (weeks) | 39 (36-41)                   | 39 (37-40)       | 31 (29-36)       | <0.001 |
| Delivery                |                              |                  |                  |        |
| Vaginal                 | 17 (73.9)                    | 0                | 0                | <0.001 |
| Caesarean section       | 6 (26.1)                     | 6 (100)          | 6 (100)          |        |

CTR, matched controls; PE, preeclampsia; GA, gestational age; IUGR, Intrauterine growth retardation; Appearance, APGAR, Pulse, Grimace, Activity, Respiration, score

ster. In contrast, the median serum level of PIGF was significantly lower in the preeclampsia (PE) group compared to women in the control group in both trimesters: 218.4 vs 478.5 (p=0.006) in the 2<sup>nd</sup> trimester and 151.05 vs 570 (p=0.007) in the 3<sup>rd</sup> trimester. In women with PE, the median sFLT/PIGF ratio was significantly higher compared to the control group in both trimesters: 9.266 vs 2.618 (p=0.004) in the 2<sup>nd</sup> trimester and 25.97 vs 2.599 (p<0.001) in the 3<sup>rd</sup> trimester (Table 3).

**Table 3. Maternal serum concentration of soluble fms-like tyrosine kinase 1 (sFLT), placental growth factor (PIGF) and sFLT/PIGF ratio in women with preeclampsia and matched controls**

|                       | CTR (n=23)           | PE (n=12)             | p     |
|-----------------------|----------------------|-----------------------|-------|
| sFLT (pg/ml) 24-28 GA | 1309 (376.6-2634)    | 2205 (361-4787)       | 0.047 |
| sFLT (pg/ml) 28-31 GA | 1348 (550-2789)      | 3024.5 (394.1-6776)   | 0.004 |
| PIGF (pg/ml) 24-28 GA | 478.5 (135.1-1921)   | 218.4 (29.2-582.1)    | 0.006 |
| PIGF (pg/ml) 28-32 GA | 570 (135-1921)       | 151.05 (15.5-1039)    | 0.007 |
| sFLT/PLGF 24-28       | 2.618 (1.087-6.180)  | 9.266 (0.958-155.092) | 0.004 |
| sFLT/PLGF 28-31       | 2.599 (0.808-17.890) | 25.97 (0.576-217.457) | 0.001 |

CTR, matched controls; PE, preeclampsia; GA, gestational age

Serum levels of PIGF, sFLT-1 and sFLT/PIGF ratio are compared according to the gestational age at delivery, in term and preterm PE. Serum sFLT-1 and sFLT/PIGF ratios were significantly higher in the preterm PE group comparing to term delivery PE women in both trimesters (all p<0.001), and PIGF levels were significantly lower in pre-

term PE women than in term delivery PE women in both trimesters ( $p=0.014$  in the 2<sup>nd</sup> trimester;  $p=0.012$  in the 3<sup>rd</sup> trimester). The median, sFLT/PlGF ratio in preterm PE women was significantly higher compared to term delivery PE women in both trimesters (all  $p<0.001$ ) (Table 4).

**Table 4. Comparison of soluble fms-like tyrosine kinase 1 (sFLT), placental growth factor (PlGF) and sFLT/PlGF ratio in term and preterm preeclampsia**

|                       | PE >37 GA<br>(n = 6)    | PE < 37 GA<br>(n=6)         | p      |
|-----------------------|-------------------------|-----------------------------|--------|
| sFLT (pg/ml) 24-28 GA | 741.5<br>(361-2868)     | 3026.5<br>(2169-4787)       | <0.001 |
| sFLT(pg/ml) 28-31 GA  | 859.6<br>(394.1-3045)   | 5000<br>(2143-6776)         | <0.001 |
| PlGF (pg/ml) 24-28 GA | 306.8<br>(195.6-582.1)  | 59.7<br>(29.2-241.3)        | 0.014  |
| PlGF (pg/ml) 28-32 GA | 287.4<br>(168.2-1039)   | 46.5<br>(15.5-133.9)        | 0.012  |
| sFLT/PlGF 24-28       | 2.330<br>(0.958-9.544)  | 46.643<br>(8.989-155.092)   | <0.001 |
| sFLT/PlGF 28-31       | 3.375<br>(0.576-18.103) | 123.193<br>(33.831-217.457) | <0.001 |

CTR, matched controls; PE, preeclampsia; GA, gestational age

There was a strong, significant negative correlation between the sFLT/PlGF ratio and gestational age ( $-0.679$ ;  $p<0.001$ ) and a moderate negative correlation between sFLT/PlGF ratio and birth weight ( $-0.505$ ;  $p=0.003$ ).

## DISCUSSION

This study supports the theory that preeclampsia results from an imbalance between placental angiogenic and antiangiogenic factors that harm maternal vascular endothelium, resulting in the clinical features of this condition (15). Serum levels of sFlt-1 were significantly higher and PlGF significantly lower in women who developed preeclampsia comparing to women who had a normal pregnancy outcome. The ratio of sFlt-1 to PlGF was also significantly higher in women who developed preeclampsia when compared with women who had a normal pregnancy outcome. Furthermore, serum sFLT-1 and the sFLT/PlGF ratio were significantly higher in the preterm delivery PE group than in the term delivery PE women in both trimesters, and the PlGF level was significantly lower in preterm delivery PE women than in the term delivery PE women, in both trimesters. There was also a statistically significant correlation between the sFlt/PlGF ratio and the week of gestation at delivery, as well as

the sFlt/PlGF ratio and birth weight. Women with higher ratios had premature labour and lower infant birth weight.

The number of caesarean sections among preterm labours was significantly higher, as expected. However, the outcome of the pregnancies and the fact that all the new-borns from the PE group were released home with good perinatal outcomes is encouraging.

In a meta-analysis of clinical studies undertaken in the early period of gestation, Kleinrouweler et al. concluded that the test accuracy of PlGF, sFLT1 and sENG was too poor in terms of sensitivity and specificity for accurate prediction of PE in clinical practice (19), but different studies have shown that calculating the sFlt-1/PlGF ratio improves sensitivity for prediction of PE risk (16).

PreOS was the first study to demonstrate the impact of angiogenic biomarkers (in this cases, sFlt1/PlGF) on physicians' clinical decision-making regarding pregnant women with suspicion of preeclampsia in a routine clinical setting. The study also shows that the sFlt-1/PlGF ratio has the potential to be implemented in clinical practice to guide appropriate management intensity (17).

Recent studies have focused on investigations to identify the subgroup that will develop severe PE requiring delivery within the subsequent 1-4 weeks. In high-risk pregnancies, measurement of serum PlGF or the sFlt-1 to PlGF ratio are highly accurate in identifying the target group (18-20). Close monitoring of such pregnancies for earlier diagnosis of clinical signs of the disease could potentially improve perinatal outcome through interventions such as antihypertensive therapy and early delivery (21).

Although there was a relatively small number of participants, our results suggest that measurement of serum sFlt-1 and PlGF or the sFlt-1 to PlGF ratio is highly accurate in identifying not only the development of severe PE but also women who will have premature labour. Women with PE in our study who had premature labour, lower infant birth weight and low Apgar score had significantly higher sFlt-1 values and sFlt-1 to PlGF ratio than PE women with term delivery and the control group, in both trimesters. PlGF values were significantly lower in women with PE who had premature labour, lower infant birth weight and low Apgar score, than PE women

with term delivery and the control group, in both trimesters.

The results of our study are within the framework of the proposed algorithm and NICE guidelines, considering the sFlt-1/PlGF ratio cut-off and the prediction period. Women with an sFlt-1/PlGF ratio >38 in the 2<sup>nd</sup> trimester and >85 in the 3<sup>rd</sup> trimester developed PE and had preterm delivery within the subsequent 4 weeks.

Despite the ambiguous results from different studies, the sFlt-1 to PlGF ratio could be useful test for identifying potential risk groups among pregnant women with PE symptoms. In addition, the equipment already exists in small hospitals and community health centres (such as in this case electrochemiluminescence immunoassay, ECLIA Cobase 411 analyzer - Roche Diagnostics GmbH Mannheim, Germany, 2014) and testing equipment could be used to determine possible cases that should be sent to the appropriate hospital as “in utero transport” increasing the viability of children and reducing maternal morbidity and mortality.

The cost of sFlt/PlGF testing is approximately 40 Euros (300 HRK), which is acceptable when comparing the cost of usual medications used in the treatment of eclampsia (e.g. the price of a sin-

gle dose (300 mL) of full blood is 500 HRK; the price of basic single-day intravenous antihypertensive therapy with ebrantil (urapidil) is 260 HRK (approx. 34 Euros), with carboprost or mifepriston therapy the price ranges between 150 HRK and 250 HRK (20 and 33 Euros, respectively). The value of lower maternal mortality and morbidity, and the value of low perinatal mortality also add to the arguments for introducing sFlt/PlGF testing.

Appropriate screening, monitoring and routine check-ups during pregnancy may prevent the deterioration of the maternal and foetal condition (15,16).

The results of our study suggest that the sFlt-1/PlGF ratio could be used as an indicator even in smaller hospitals, in countries with a low to moderately well-developed health system, and to serve as a potential tool for the diagnostics and management of patients with preeclampsia.

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## TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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## Perinatal characteristics and prevalence of low birth weight infants in the Federation of Bosnia and Herzegovina: prospective multicentric study

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### ABSTRACT

**Aim** To investigate the prevalence and obstetrical characteristics of low birth weight infants (LBWIs) in ten Cantons of the Federation of Bosnia and Herzegovina (FB&H).

**Methods** The prospective study included newborns of both genders, gestational age (GA) of 22 to 42 weeks and birth weight (BW) of less than 2,500 grams in the period 1 January 2009 to 31 December 2009.

**Results** In the observed period, 22897 neonates were born, out of whom 669 (2.9%) had a BW less than 2500 grams (average BW was 1295 grams; SD  $\pm$  234.2; a coefficient of variation of 0.58). The average GA was 31.4 weeks of gestation. The average lifespan of mothers was 27.7 years (SD  $\pm$  1.2). The average Apgar score (AS) in the first minute was 4.6 (SD  $\pm$  2.1) and in the fifth minute it was 6.6 (SD  $\pm$  1.9). The LBWIs were most commonly delivered by primiparas, 317 (47.5%). Of the 669 LBWIs, 411 (61.4%) were born *per vias naturalis*, with cephalic presentation. The highest number of LBWIs was born in Sarajevo Canton, 3.7%, and Central Bosnia Canton, 3.7%. The lowest prevalence was in Posavina Canton, 1.1%. The largest late fetal mortality was in Central Bosnia Canton, 7.7 %.

**Conclusion** This study has determined a relatively low prevalence of LBWIs and other examined obstetrical characteristics that are in correlation with European and Global World data.

**Key words:** neonate, perinatology, pregnancy

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## INTRODUCTION

According to the World Health Organization, a newborn with a low birth weight infants (LBWIs) is a neonate with a birth weight (BW) less than 2,500 grams, regardless of the duration of pregnancy, and this term refers to preterm infants, newborns with intrauterine growth retardation (IUGR) and newborns small for gestational age (SGA) (1-3). The term *prematurus* is used for infants whose intrauterine growth lasted shorter than 37 weeks of gestation (WG), while the term IUGR implies slowing down of fetal growth (1-3). The term SGA does not indicate the rate of fetal growth, but indicates that the fetus has a low weight and/or length in relation to the gestational age (less than 3 centigrade or below 2 standard deviation adopted standards) (1-3).

The LBWIs is closely related to fetal and neonatal morbidity and mortality. These newborns represent a risk group and have high perinatal mortality, more frequent complications in the neonatal period, higher incidence of congenital anomalies, and they are more prone to infection (4). In later life, they often have suboptimal psychomotor development and more frequent chronic diseases (5).

In spite of the increasing progress of perinatal medicine and the ever-increasing perinatal care, between 9 and 19% of high-risk infants are born annually. Of this number, 80% of newborns are of LBWIs, which is more than 20 million worldwide (6). The frequency of birth LBWIs has its own geographical and social characteristics. It is estimated that more than 95% of LBWIs are born in developing countries, with a birth rate of 16.5%, and among stillbirths 20%, and does not show a tendency to weaken. In the developed part of the world, the birth rate of LBWIs is only 7%. Their participation in neonatal morbidity, mortality and in the most severe form of neuromotor damage, cerebral palsy, whose frequency ranges between 1 and 2/1000 live-born in the general population (7), are also not reduced.

Studies have shown that LBW is a result of an interaction between the biological characteristics of mother and fetus, parents, social environment, and availability of health care during the perinatal period. Furthermore, public health initiatives aimed at reducing the prevalence of births for LBWIs were largely unchanged (8,9). Populati-

on data on the characteristics of LBWIs provide unbiased information that could be applied to improving perinatal care. The quality of data derived from vital statistics records has been found reliable, because of that collection of information on maternal age, infant gender, birth weight, and delivery type are quite valid (10).

There were no studies related to the association of LBWIs and maternal sociodemographic status for the entire Federation of Bosnia and Herzegovina (FB&H). One study investigating LBWIs in Tuzla Canton during 1992-1995 period was found (11).

The aim of this study is to investigate the prevalence and obstetrical characteristics of low birth weight infants (course of pregnancy and childbirth, age of mothers, number of controls in pregnancy, mother's parity and order of birth, canton of childbirth, date and hour of birth, mode of delivery, birth weight, birth length, gestational age, Apgar score in the 1st and 5th minute) in ten Cantons of the Federation of Bosnia and Herzegovina (FB&H).

## PATIENTS AND METHODS

### Patients and study design

This prospective study included newborns of both genders, gestational age (GA) from 22 to 42 weeks and birth weight (BW) of less than 2,500 grams, born in one of the childbirth centres in ten Cantons of the FB&H in the period from 1 January 2009 to 31 December 2009. The standardized formulation compiled the data necessary for this type of research and included data on pregnancy, delivery and incidence to the low birth weight infants (LBWIs).

All newborns included in the study were included in one of three groups based on the GA: Group 1 - preterm infants (22-36 weeks of gestation (WG)), Group 2 - term infants (37-41 WG), Group 3 - post-term infants (42 and more WG).

According to the BW, subgroups of the BW (500-999 grams, 1000-1449 grams, 1500-1999 grams, 2000 to 2499 grams) were formed for each of the three basic groups. Newborns with BW less than 500 grams were not among the living ones.

### Methods

Data on the course of pregnancy and childbirth were collected on the basis of available medical

documentation (pregnancy booklet, mother's disease history, partograms), age of mothers, number of controls in pregnancy, mother's parity and order of birth.

Data on newborns of the LBWIs in the FB&H were collected on the basis of available medical documentation, including the canton of child-birth, date and hour of birth, mode of delivery (vaginal cephalic, caesarean section, vaginal breech, unknown birth), BW, birth length, GA (completed weeks of gestation), Apgar score (AS) in the 1st and 5th minute.

The Ethics and Investigation Committee of the University Clinic Centre Tuzla approved the study.

### Statistical analysis

Standard statistical descriptive statistics (mean value, standard deviation - SD, coefficient of variation - CV) were used in statistical data processing. Quantitative data are intergrouped with the Mann-Whitney U-test, and qualitative data are compared with the  $\chi^2$  test and the exact Fisher test. The prediction power of the BW, GA of pregnancy, birthplace in predicting the results of treatment were determined by specificity, sensitivity, positive and negative predictive value, and the multiple regression analysis was used to compare two dependent on one independent variable. Statistical significance was determined at the level of the difference of 5% and 1%.

### RESULTS

In the period from 1.January.2009 until 31 December 2009 in the FB&H, 22,897 neonates were born, of which 669 (2.9%) had birth weight (BW) less than 2500 grams (ranged from 500 to 2499 grams, with an average of 1295 grams; SD=  $\pm$  234.2, CV=0.58). The average GA LBWIs was 31.4 WG (SD=  $\pm$  5.34, CV=0.17).

The average lifespan of 661 mothers (data were missing for eight mothers) of LBWIs was 27.7 years (SD=  $\pm$  1.2; ranged from 16 to 38 years). The average AS in the first minute for 515 LBWIs was 4.6 (SD=  $\pm$  2.1; CV=0.78). The average AS in the fifth minute was 6.6 (SD  $\pm$  1.9; CV=29) (data were missing for 154 LBWIs) (Table 1).

The LBWIs had a similar gender representation, 345 (51.56%) male and 324 (48.44%) female neonates were born ( $p=0.27$ ). The probability distribution or the relative risk of both genders for

birth with a LBW was equal [RR = 1.133 (95% CI 0.914-1.404)].

**Table 1** Number, arithmetic mean, standard deviation, lowest and highest value of individual characteristics of mothers and low birth weight infants (LBWIs) in the Federation of Bosnia and Herzegovina (FB&H) during 2009

| Characteristics of mothers and newborns | Number of LBWIs | Arithmetic mean | Lowest value | Highest value | Coefficient of variation | Standard deviation |
|---|-----------------|-----------------|--------------|---------------|--------------------------|--------------------|
| Age of mothers (years)*                 | 661             | 27.5            | 16           | 38            | 0.25                     | 1.2                |
| Birth weight (grams)                    | 669             | 1295            | 500          | 2480          | 0.58                     | 243.2              |
| Birth length (cm)                       | 669             | 42.5            | 24           | 50            | 0.21                     | 2.6                |
| WG of pregnancy                         | 669             | 31.4            | 24.8         | 38.8          | 0.17                     | 5.34               |
| AS in 1st minutes†                      | 515             | 4.6             | 0            | 10            | 0.78                     | 2.1                |
| AS u 5th minutes†                       | 515             | 6.6             | 1            | 10            | 0.29                     | 1.9                |

\*The life span for eight mothers was unknown, and they were excluded from this analysis; †Missing data for 154 LBWIs WG, weeks of gestation;

The LBWIs were most commonly delivered by primiparas, 317 (47.5%), followed by second and fourth birth women, 129 (19.3%) and 118 (17.6%), respectively, and the lowest LBWIs were found in third birth women, 105 (15.7%).

The prevalence of births of newborns from the first pregnancy of the mother statistically significantly differed from the birth rate of LBWIs from the second maternal labor ( $p<0.0001$ ) with six times higher relative risk [RR=6.038 (95%CI 4.520-8.065)]. Statistically significant differences were not in the prevalence of newborn births of the LBWIs between the second and third births ( $p=0.033$ ) with an equal relative risk [RR = 1.509 (95% CI 1.048-2.172)]. An important statistically significant difference in the prevalence of births in LBWIs was found between primiparas and multiparas ( $p<0.0001$ ) with a high, seven times higher relative risk [RR=7.216 (95%CI 5.352-9.731)]. The probability of birth of LBWIs was the highest in the primiparas, similar to secundiparas, while the risk was the smallest in the multiparas with a confidence interval of 95%.

A total of 465 (69.5%) LBWIs were delivered vaginally and 141 (21.1%) by Caesarean section (CS) ( $p<0.0001$ ) [RR = 10.875 (95% CI 8.331-14.197)]. Of 669 LBWIs, 411 (61.4%) were born vaginally with the cephalic presentation, 54 (8.1%) vaginal births with a breech presentation ( $p<0.0001$ ) [RR = 57.929 (95% CI 38.784-

86.524)]. No data on the mode of delivery were available for 63 (9.4%) newborns.

The higher number of LBWIs including stillbirths and live births were noticed in Sarajevo Canton, 184 (out of 4898 all births; 3.7%), Central Bosnia Canton, 92 (out of 2462 all births; 3.7%), Una-Sana Canton, 104 (out of 2842 all births; 3.6%) Herzegovina-Neretva Canton, 66 (out of 1870 all births; 3.5%), and Zenica-Doboj Canton, 135 (out of 4186 all births; 3.2%). In the most populated canton, Tuzla Canton, the number of LBWIs was 146 (out of 4898 all births; 2.9%). The lowest number was registered in Posavina Canton, two (out of 255 all births; 1.1%) (Table 2).

**Table 2. Prevalence distribution of stillbirths (and mortality rates) and live births among low birth weights infants (LBWIs) in the Federation of Bosnia and Herzegovina (FB&H) cantons in 2009**

| Canton              | No (%) of LBWIs                       |                  |   |
|---------------------|---------------------------------------|------------------|---|
|                     | Stillbirths<br>(mortality<br>rate, ‰) | Live<br>births   | Total number of<br>LBW births/all<br>births |
| Una-Sana            | 17 (0.6) (6.0)                        | 87 (31)          | 104/2,842 (3.6)                             |
| Posavina            | 0                                     | 2 (0.8)          | 2/255 (1.1)                                 |
| Tuzla               | 15 (0.3) (3.0)                        | 131 (2.7)        | 146/4,898 (2.9)                             |
| Zenica– Doboj       | 9 (0.2) (2.1)                         | 126 (3.0)        | 135/4,186 (3.2)                             |
| Bosna-Podrinje      | 1 (0.4) (4.2)                         | 4 (1.7)          | 5/236 (2.1)                                 |
| Central Bosnia      | 19 (0.8) (7.7)                        | 73 (2.7)         | 92/ 2,462 (3.73)                            |
| Herzegovina–Neretva | 11 (0.6) (5.9)                        | 55 (2.9)         | 66/ 1,870 (3.5)                             |
| West Herzegovina    | 1 (0.1) (1.4)                         | 18 (2.5)         | 19/ 722 (2.6)                               |
| Sarajevo            | 16 (0.3) (3.3)                        | 168 (3.4)        | 184/ 4,898 (3.7)                            |
| Livno               | 1 (0.2) (2.3)                         | 5 (1.1)          | 6/438 (1.7)                                 |
| <b>Total</b>        | <b>90 (3.9) (3.9)</b>                 | <b>669 (2.9)</b> | <b>759/22,897 (3.3)</b>                     |

If the stillborn infants are excluded from a LBWIs the image of the prevalence of a LBWIs is different (Table 2). The highest number of LBWIs was born in Sarajevo Canton, 3.4%, Una-Sana Canton, 3.1%, and Zenica-Doboj Canton, 3%, while in Herzegovina-Neretva Canton the birth rate was 2.9%. In the most populated Tuzla Canton, the birth rate with exclusion of LBWI stillborn was 2.7%, as much as in Central Bosnia and Herzegovina and West Herzegovina Canton, 2.5%. The low prevalence of births of LBWIs was in Bosnia-Podrinje Canton, 1.7%, in Livno Canton, 1.1%, and the lowest one in Posavina Canton, 0.8%.

The highest late fetal mortality rate among the LBWIs was recorded in Central Bosnia Canton, 7.7‰, Una-Sana Canton, 6‰, and in Herzegovina-Neretva Canton, 5.9 ‰. In the two largest cantons, Sarajevo and Tuzla, mortality rates were significantly lower, 3.3‰ and 3‰, respectively.

In Bosnia Podrinje, Livno Canton 10, Zenica-Doboj and West Herzegovina Canton mortality rates of 4.2‰, 2.3‰, 2.1‰ and 1.4‰, respectively, were noticed. No stillbirths were registered in Posavina Canton (Table 2).

## DISCUSSION

The results of this study have shown low prevalence of LBWIs of 2.9%, which is somewhat lower than those of other authors who estimate 4.2-10.6%, depending on geographical area and socio-economic conditions (12,13). In favour of the impact of socioeconomic status in the FB&H Tuzla canton, an increase in LBWIs was recorded in the war period in relation to before and after the war (11). In a study by Tough et al. the LBWIs prevalence in Alberta was 6.4%, and it was greater than the national rate of 5.5% and comparable to the estimates in the United States of 7.0% (14,15). In a study by Sun et al, the incidence of births for LBWIs was 2.8% (16). Very low birth weight (VLBW) infants account for less than 2% (0.6-1.4%) of all live births according to European Perinatal Health Report (13), which correlates with a Croatian study (17).

In our study the birth weight (BW) ranged from 500 to 2499 grams, with an average BW of 1295 grams, and in the study by Filipović Grčić the average BW was 1135.4 g ( $\pm$  250.1 g) (17). In a study by Porta et al. average birth weight was 1100 grams (18). In our study, the birth length ranging from 24 to 50 cm, with an average birth length of 42.5 cm, was less than in the study by Filipović Grčić (17), ranging from 25 to 46 with an average of 36.9. In the study by Skokić et al. (11) both BW and birth length for LBWIs were significantly higher in all periods investigated, pre- and post-war, as well as during the war comparing to our and other studies. This can be explained by the higher average length of gestation in all three analysed periods (11).

In our study the higher average gestational age of 31.4 weeks of gestation was found as compared to studies by Filipović Grčić (17) and Porta et al. (18), the average GA was 29.0 WG and study 29.4 WG.

The average lifespan of 661 mothers of LBWIs in our study was 27.7 years ranging from 16 to 38 years. In the study by Sun et al. the mean maternal age for pregnancy was lower, 25.9 $\pm$ 5.1 ye-

ars old (16), but in Filipović Grčić study it was higher, 29.3 years, ranging from 15 to 44 (17).

The average Apgar score in the first minute for LBWIs in the presented study was 4.6, in the fifth minute it was slightly higher, 6.6, which is lower in first minute and higher in the fifth minute in comparison with Filipović Grčić study with the average 4.9 and 6.5, respectively (17). In the study by Porta et al. it was 6 and 8, respectively (18). The LBWIs in our study had a similar gender representation, similarly to other studies (17,18).

In our study, as well as in others, the highest number of LBWIs was related to vaginal births, however, lower prevalence of Caesarean sections was found in our study (17,18).

Stillbirths were lower in our study in FB&H and in Tuzla Canton in comparison with the pre-war period and the period during the war in Tuzla Canton (11).

FB&H has been administratively divided into ten cantons. Prevalence of LBWIs according to the cantons of the FB&H significantly differed depending on the geographical area. Most of the births were in the two largest cantons in Sarajevo and Tuzla, and the birth rate of the newborn babies was the highest. The low prevalence of LBWIs was found in Bosnian-Podrinje Canton, Livno Canton and the lowest one in Posavina Canton.

The fact that it has been more than 8 years since the research was conducted might be a limitation of the study. However, there is still importance of the results even today, because no recent studies on similar topics have been conducted, while the

investigated topic is not subject to rapid change over time. Currently, we are working on a similar study, and the results of presented study could serve for comparison. The strength of the study is prospective and multi-centre data collection with standards of the primary to tertiary level of care.

This report is our first attempt to prospectively conduct a multi-centric survey of the characteristics of LBWIs in FB&H according to the international definitions, from a low-income, as well as low maternal and infant health care setting.

This study has determined the relatively low prevalence of LBWIs and other examined obstetrical characteristics that are correlated with European and Global World data.

In spite of evident progress in perinatology and significant improvement in perinatal outcome over the past decade, LBWIs remain a major problem in the world, which is the dominant risk factor for infant mortality and/or for subsequent permanent damage. Efforts to prevent the birth of LBWIs have not yielded satisfactory results, and with limited diagnostic and therapeutic options, such a newborn is a significant daily problem of a perinatologist.

Providing adequate care for newborns is an important issue for perinatal medicine.

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## TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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## Hand function in children with unilateral spastic cerebral palsy

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### ABSTRACT

**Aim** To assess hand function and explore the relationship between hand function and neuroimaging findings in children with unilateral spastic cerebral palsy (US CP).

**Methods** Hand function was assessed using Manual Ability Classification System (MACS, I-V). Brain lesions were divided into five groups: brain maldevelopment (MAL), periventricular white matter lesions (PV WM), cortical/subcortical gray matter lesions (C/SC GM), nonspecific and normal findings.

**Results** Of 114 children with US CP (77 boys and 37 girls), 56 were with right-sided and 58 with left-sided involvement. MACS I was found in 49 (42.9%), MACS II in 19 (16.7%), MACS III in 19 (16.7%), MACS IV in 9 (7.9%) and MACS V in 18 (15.8%) children ( $p=0.002$ ). Computed tomography (CT) as the only neuroimaging has been done in 18 (15.8%), magnetic resonance imaging (MRI) at 94 (82.5%) children, whereas 2 (1.7%) children had neither CT nor MRI. The CT showed PV WM in eight (44.4%), C/SC GM lesions in six (33.3%), and normal findings in four (22.2%) children ( $p=0.709$ ). The MRI showed MAL in eight (8.5%), PV WM in 46 (48.9%), C/SC GM in 28 (29.8%), miscellaneous in two (2.1%), and normal finding in 10 (10.7%) children ( $p=0.0001$ ). Mild hand dysfunction (MACS I and II) was assessed in 68 (59.7%) children, of which 33 had PV WM lesions ( $p=0.001$ ).

**Conclusion** Mild hand dysfunction in children with US CP has been significantly associated with PV WM lesions. The type of brain lesion may help to identify its timing and predict the level of hand dysfunction.

**Key words:** cerebral palsy, child, neuroimaging

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## INTRODUCTION

Unilateral spastic cerebral palsy (US CP) occurs after an insult to the developing brain resulting in motor and sensory impairments mainly lateralized to one body side. The upper limb on the affected side may have different functional limitations that can influence child's every day activities and future professional options (1). The timing, size and location of the lesion influence the clinical presentation of upper limb dysfunction (1). The US CP can be caused by different brain lesions (2). Periventricular white matter lesions, depending on the extent of the lesion, may cause mild to moderate motor impairment (2). Grey matter lesions (cortex, thalamus or basal ganglia) may cause moderate to severe motor impairment of the affected limb (3). In addition, the reorganization of the primary motor cortex after the insult plays an important role in the definite upper limb dysfunction (1,2).

Corticospinal tract projections to the affected limb can be contralateral (the typical pattern), ipsilateral or mixed (the affected limb receives motor projections from both hemispheres) (3).

Neuroplasticity and brain organization in children with US CP result in approximately one third of them having impaired hand controlled by ipsilateral hemisphere (4). During the first 18 months of typical postnatal development inter-hemispheric competition reduces the number of ipsilateral corticomotor connections (4). In children with US CP, who have early brain lesions and atypical development, ipsilateral connections may stay intact (4). Ipsilateral projections are associated with poor function (3,5).

Hand asymmetries, the usual clinical sign of unilateral CP, typically do not appear until 4-6 months of age (6).

Hand dysfunction in children with US CP is a serious problem in their everyday activities. Various studies have been performed to evaluate predictive value of brain lesions for the development of hand dysfunction (3,5). Understanding the association between hand dysfunction and brain lesions may assist in the development of novel upper limb habilitation strategies in children with US CP and promote early intervention to minimize motor dysfunction of an affected limb (2).

Our study was conducted in order to explore relevant data about children with US CP, whose

diagnosis and treatment were made in our hospital. The proper analysis of brain lesions may help setting adequate prognosis and realistic therapeutic goals. It is important for pediatricians, neuropaediatricians, physiatrists and physiotherapist, but also other specialists who deal with children suffering from cerebral palsy (orthopedists, psychologists).

The aim of this study was to assess hand function and explore the relationship between hand function and neuroimaging findings in children with unilateral spastic cerebral palsy in the Pediatric Clinic, University Clinical Centre Sarajevo.

## PATIENTS AND METHODS

### Patients and study design

This cross sectional cohort study used data from a prospective longitudinal study on children with unilateral spastic cerebral palsy. The study was performed at the Pediatric Clinic, University Clinical Center Sarajevo (tertiary hospital), during the period 2002-2018.

Inclusion criteria were all children diagnosed with US CP at minimal age of 4 years (born in the period between 1998 and 2013). Exclusion criteria were history of botulinum toxin treatment or hand surgery.

### Methods

Manual abilities were assessed according to the Manual Ability Classification System (MACS) (7), which classifies children's ability to handle objects in everyday activities on a 5-level scale: level I- highest ability - the child handles objects easily and successfully; level II – the child handles most objects, but with somewhat reduced quality and/or speed of achievement; level III – the child handles objects with difficulty, needs help to prepare or modify activities; level IV – the child handles a limited selection of easily managed objects in adapted situations, and level V - most limited ability - the child does not handle objects and has severely limited ability to perform even simple actions (7,8).

Neuroimaging data included magnetic resonance images (MRI) and computer tomography (CT) images. Brain MRI scans were acquired with 1.5 and 3T systems (Avanto, Siemens, Erlangen, Germany) and interpreted by a neuroradiologist. The neuroradiological findings were classified

according to a recommendation of the Surveillance of Cerebral Palsy in Europe (SCPE), based on the predominant pattern of brain injury: maldevelopment (MAL), periventricular white matter lesions (PV WM), cortical/subcortical grey matter lesions (C/SC GM), miscellaneous or normal findings (9).

### Statistical analysis

Standard descriptive methods of statistics and  $\chi^2$  test were used. The significance level of  $p < 0.05$  was used.

### RESULTS

The study has included 114 children with US CP (77 boys and 37 girls) ( $p = 0.007$ ).

The age of the children at the moment of inclusion into the study was 48 months (4 years) at least. The gestational age of the children was at the range between 28 and 40 gestational weeks (arithmetic mean 38.31 gestational weeks).

Right upper limb was affected in 56 (49%) and left one in 58 (51%) children ( $p = 0.893$ ).

The distribution of the patients according to MACS level was: MACS I was found in 49 (42.9%), MACS II in 19 (16.7%), MACS III in 19 (16.7%), MACS IV in nine (7.9%), and MACS V in 18 (15.8%) children ( $p = 0.002$ ).

The CT as the only neuroimaging was done in 18 children (15.7%), the MRI in 94 (82.4%) children, whereas in two (1.7%) children neither CT nor MRI (due to lack of parents' consent).

**Table 1. Distribution of Manual Ability Classification System (MACS) levels according to neuroimaging (MRI) findings**

| MRI finding                  | No (%) of children according to MACS level |           |           |          |          |          |
|------------------------------|--|-----------|-----------|----------|----------|----------|
|                              | Total                                      | I         | II        | III      | IV       | V        |
| <b>MAL</b>                   | 8 (7)                                      | 2 (4.1)   |           | 3 (15.8) | 1 (11.1) | 2 (11.1) |
| <b>PV WM</b>                 | 46 (40.3)                                  | 23 (46.9) | 10 (52.6) | 7 (36.8) | 2 (22.2) | 4 (22.2) |
| <b>C/SC GM</b>               | 28 (24.6)                                  | 9 (18.4)  | 5 (26.3)  | 5 (26.3) | 4 (44.5) | 5 (27.8) |
| <b>Non-specific findings</b> | 2 (1.7)                                    | 1 (2)     |           |          |          | 1 (5.5)  |
| <b>Normal findings</b>       | 10 (8.8)                                   | 8 (16.4)  | 1 (5.3)   | 1 (5.3)  |          |          |
| <b>N/A</b>                   | 20 (17.6)                                  | 6 (12.2)  | 3 (15.8)  | 3 (15.8) | 2 (22.2) | 6 (33.4) |
| <b>Total</b>                 | 114 (100)                                  | 49 (100)  | 19 (100)  | 19 (100) | 9 (100)  | 18 (100) |

MAL, brain maldevelopment; PV WM, periventricular white matter lesions; C/SC GM, cortical/subcortical grey matter lesion; N/A, not available;

The CT showed PV WM in eight (44.4%), C/SC GM lesions in six (33.3%) and normal finding in four (22.2%) children ( $p = 0.709$ ).

The MRI showed MAL in eight (8.5 %), PV WM in 46 (48.9%), C/SC GM lesions in 28 (29.8%), miscellaneous in two (2.1%) and normal finding in 10 (10.7%10.6%) children ( $p = 0.0001$ ) (Table 1).

The correlation between MACS level and type of brain lesion is presented in Table 2.

The mild hand dysfunction (MACS I and II) was assessed at 68 (59.6%) patients, of which in 33 (48.5%) patients PV WM lesion was found ( $p = 0.001$ ).

**Table 2. Correlation between Manual Ability Classification System (MACS) level and neuroimaging (MRI) findings**

| MRI finding                  | No (%) of children according to MACS level |           |          |          | p     |
|------------------------------|--|-----------|----------|----------|-------|
|                              | Total                                      | I+II      | III      | IV+V     |       |
| <b>MAL</b>                   | 8 (7)                                      | 2 (2.9)   | 3 (15.8) | 3 (11.1) | 0.932 |
| <b>PV WM</b>                 | 46 (40.3)                                  | 33 (48.6) | 7 (36.8) | 6 (22.2) | 0.001 |
| <b>C/SC GM</b>               | 28 (24.6)                                  | 14 (20.6) | 5 (26.3) | 9 (33.3) | 0.331 |
| <b>Non-specific findings</b> | 2 (1.8)                                    | 1 (1.5)   | 0        | 1 (3.7)  | 1.000 |
| <b>Normal findings</b>       | 10 (8.8)                                   | 9 (13.2)  | 1 (5.3)  | 0        | 0.051 |
| <b>N/A</b>                   | 20 (17.5)                                  | 9 (13.2)  | 3 (15.8) | 8 (29.7) | 0.388 |
| <b>Total</b>                 | 114 (100)                                  | 68 (100)  | 19 (100) | 27 (100) |       |

MAL, brain maldevelopment; PV WM, periventricular white matter lesions; C/SC GM, cortical/subcortical grey matter lesion; N/A not available

### DISCUSSION

In our US CP-child study, entire birth years, from 1998 born children onwards, were prospectively followed to determine the relationship between the fine motor function as related to the nature of the brain lesion. In this study, which has included 114 children, statistically significant presentation of boys was noticed. The same results have been published by other authors (10-12). The incidence of cerebral palsy is significantly higher in males due to greater vulnerability to hypoxia in males and higher incidence of preterm births in males (11).

Distribution of our patients according to the affected limb is almost equal between right and left side. The same result was published by Arnold and associates (12).

According to the gestational age of children involved in our study, there was a statistically significant presentation of patients with 40 weeks gestational age (arithmetic mean 38.31). The similar results were published by Himpens et al. (13); investigating the relationship between gestational age and type of cerebral palsy, extremely

preterm infants (gestational age 23-27 weeks), predomination of developed bilateral spastic cerebral palsy with no cases of US CP was found. No extremely preterm born children in our study were noticed.

The MACS evaluate child's typical use of hands and upper limbs, not the best use (14). According to the distribution of MACS level, the results of our study have shown statistically significant presentation of MACS I and MACS II patients. Nordstrand, Eliasson and Holmefur published the data for 96 children with US CP and found that mild hand dysfunction (levels I and II) was dominant, similarly to our results, but no levels IV and V were found (15). Klevberg et al. published the data of 64 patients with US CP and found no children with MACS level IV and MACS level V. Our results are similar for mild hand dysfunction (16).

The brain damage is also predictive of outcome. In larger lesions the motor function can be managed via existing ipsilateral tract of contralesional hemisphere (3,8). This possibility for reorganization is unique to the young brain (4).

Cortical malformations which originate in the first two trimesters of pregnancy result in less severe hand impairments than periventricular lesions, which originate early in the third semester of pregnancy. In the cases of unilateral brain damage occurring during the intrauterine period, the functional compensation of the affected hemisphere by the unaffected hemisphere is possible, but it is limited and inferior to normal motor function (8). Neuroplasticity during early brain development decreases with gestational age at which the lesion is acquired (17). This suggests that C/SC lesions, which originate in the late third semester of pregnancy and perinatally, result in more severe hand dysfunction than PV WM lesions (17).

Brain lesion leading to ipsilateral motor control, which occurs during early second trimester of pregnancy (maldevelopment), or a lesion which occurs during early third semester of pregnancy (white matter lesion), conveys better hand function than lesions acquired toward the end of gestation, such as infarct (17).

Neuroimaging is an important part of the diagnostic workup for cerebral palsy. MRI is superior to CT for several reasons (MRI does not involve

exposure to ionizing radiation, it gives extremely clear, detailed images of the brain that CT cannot achieve). In 15.7% children from our study only CT was done, without statistically significant difference between the types of lesions. MRI was done in 82.4% children. The most frequent lesions were PV WM (48.9%) and C/SC GM lesions (29.8%).

The study of Klevberg et al., which included 42 children with US CP, has shown that two most predominant patterns of brain lesions were white matter lesions and gray matter lesions (16). In our study, with larger population involved, white matter lesions were the predominant pattern of brain lesions.

The study of Maileux Lisa et al. including 73 children with US CP, 42 were with periventricular white matter lesions and 29 with cortical/subcortical lesions (2). These results are similar to the results of our study.

The correlation between MACS levels and types of brain lesions may help for further investigations on predictive value of some types of brain lesions for certain levels of upper limb dysfunction. The mild hand dysfunction (MACS I and II) was assessed in 59.6%, of which 48.5% patients had PV WM lesions. Children with PV WM lesions have higher chances of developing better upper limb function than children with C/SC GM lesions (2). The similar results have been published by Holmstrom et al. although the group was small, which included 17 participants with US CP (3).

Neuroradiological findings can be used to make crude prediction of future hand dysfunction in young children with unilateral CP. Impaired function in one hand is a major limitation in children with US CP (18).

The development of affected hand function might be quite different in the parts of the world with limited access to habilitation services, as it is the case in our country (15).

In conclusion, mild hand dysfunction in children with US CP has been significantly associated with periventricular white matter lesions in the brain, with no significant association between severe hand dysfunction and type of brain lesions. Neuroradiological findings may help to predict the development of hand dysfunction in children with US CP.

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## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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## Effects of kinesiotherapy on muscle strengthening in patients with Parkinson disease

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### ABSTRACT

**Aim** To investigate the effect of kinesiotherapy on muscle strengthening in patients with Parkinson's disease.

**Methods** This clinical retrospective – prospective study was based on collected data from medical histories and included 40 patients, who, beside medicaments, had undergone kinesiotherapy. This study analysed age, gender, duration of the rehabilitation and estimation of the gross muscle strength at admittance and discharge using Manual Muscle Test (MMT).

**Results** Females was slightly more represented in the total sample without significant statistical difference. After kinesiotherapy significant statistical difference in muscle strength was observed, average MMT of the upper extremities increased from  $3.25 \pm 0.6$  to  $3.53 \pm 0.8$  and on the lower extremities from  $2.9 \pm 0.8$  to  $3.3 \pm 0.9$ . The analysis of the gender on the higher score of MMT showed that gender does not affect the score of MMT. Correlational analysis of the age and duration of hospitalization on the score of MMT showed that patients with longer hospitalization had better improvement.

**Conclusion** Results of the study showed that kinesiotherapy has positive effect on muscle strength in patients with Parkinson's disease.

**Key words:** rehabilitation, hospitalization, manual muscle test (MMT)

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## INTRODUCTION

Morbus Parkinson - Parkinson's disease (MP) is a progressive disorder of the nervous system that affects movement, characterized by tremor, acinesia, bradykinesia, and rigidity, which create problems to patients with simple everyday activities (1). Bradykinesia is the main cause of functional disability and includes motility of the motor function, such as walking (in small steps and at reduced speed), decreasing font size during writing and problems with balance and position with bent knees and elbows with leaning forward (1,2). The face is hypomobile, like a mask, patients rarely blink and saliva leaks from the corners of their lips, the changes in a direction are very difficult to perform and the entire walk is uncertain, with a tendency to fall down (3). In the further progression of the disease anxiety, sleep disorders, feeling of fatigue, impaired intestinal peristaltic, constipation and incontinence occur (3,4).

The pharmacotherapy used in the treatment acts symptomatically, which means that a therapeutic dose must be corrected depending on the development of the disease, so it can lead to withdrawal or minimization of symptoms with minimal side effects (3).

There is also a surgical method of deep stimulation of the brain, as well as occupational therapy and physical therapy (3,5). The treatment of Parkinson's disease is aimed at preserving the patient's independence and quality of life (4). The use of Levodopa is associated with the occurrence of involuntary movements or dyskinesia, which can cause functional and social deficits, and limit the quality of life of patients (5). Kinesiotherapy is a branch of physical medicine that uses muscle movements and strength for the purpose of healing, improving the condition, preventing disability and achieving a higher degree of functionality, while preventing the occurrence of secondary complications related to the immobility or lack of movements. This method uses the resources of each individual - the strength of their own muscles and movements. It is simple because it does not need special space and equipment. It is increasingly used with success in the patients' rehabilitation (6). The exercises should be adjusted for every patient avoiding the fatigue. It is also important that patients start practicing when they are rest,

appropriately trained and in an adequate space (5). Therapeutic exercises directly affect posture, walk, movements and the performance of daily life activities (7,8). Balance dysfunction and postural instability are common and can lead to increased frequency of falls and injuries that increase the chances of developing comorbidity and disability (8,9). Exercises should be carried out for the whole body: body and extremities, face, speech and breathing exercises. Another exercise benefit is a positive effect on the cardio-respiratory system (9,10). Strong and deep breathing positively influence the strength of the external core muscles. The exhaling phase must be at least twice as long as the inhaling phase (10-12). Coordination exercises are applied because of a disturbed cycle of normal walking due to the reduction and inability to bend, short and clumsy steps, and the inability to coordinate hands and feet during walking (13-15). Passive stretching exercises are performed in order to reduce the possibility of contracting, increasing the range of motion in the joints and relax muscles. By continuous preforming of stretching exercises, flexibility of the body increases and the ability to perform movements in one or more joint systems (16-18). With an appropriate intensity of exercise and a combination with medication and kinesiotherapy, levels of dopamine may be elevated and motor disturbances may be improved (11-13). Previous research has not given precise answers how much kinesiotherapy affects the strength of the muscles individually, because opinions are divided how long, when and where to implement the kinesiotherapy program (14-16). For this reason we decided to show how much kinesiotherapy can affect muscle strength as to continue recovery with a home program after hospitalization.

The aim of study was to investigate the effects of kinesiotherapy on muscle strengthening in patients with Parkinson's disease.

## PATIENTS AND METHODS

### Patients and study design

This research was designed as a clinical, retrospective-prospective study conducted at the Clinic for Physiotherapy and Rehabilitation of the University Clinical Centre of Sarajevo during the period between January and December of 2016 for

the retrospective part and from January to March 2017 for the prospective part of the study. The study involved 40 patients randomly selected that meet the inclusion criteria, e.g. with the diagnosis of Parkinson's disease. The criteria for inclusion in the study were: patients with confirmed diagnosis of Parkinson's disease, patients with kinesiotherapy included as an optional treatment method, patients with complete documentation of the manual muscle test (MMT) value before and after the applied kinesiotherapy.

Patients were diagnosed by a neurologist, and all patients were treated with kinesiotherapy and medication therapy.

### Methods

The age and gender, the time spent on rehabilitation were analysed, and gross muscle strength of the upper and lower extremities at the time of admittance and discharge using the manual muscle test (MMT) was assessed (8). Manual Muscle Test is a non-invasive tool used by health professionals to evaluate neuromuscular integrity, especially muscle strength (8). In performing this test, the muscle or muscle group is isolated, placing the patient in a suitable position for examination, and then applying an external force, while the examiner decides on the force of contraction of the muscle. The grading system is from 0-5: 0 - no muscular activity (preserved 0% of muscle strength); 1- muscle contraction is present in the tract, and can be palpated or visualized (preserved 15% muscle strength); 2 - muscle is capable of overcoming the full range of movement in the joint, if the force of gravity is excluded (in water, suspension, etc.) (preserved 25% muscle strength); 3 - muscular contraction overcomes the full range of motion without the exclusion of gravitational force (preserved 50% muscle strength); 4 - muscle contraction can overcome the full range of motion against gravitational force with mild resistance (preserved 75% muscle strength); 5 - muscle overcomes the full range of movement with the resistance provided by the therapist (preserved 100% muscle strength) (12, 18). We also analysed the difference in the muscle strength of the upper and lower extremities in those patients, and the impact of gender on MMT values.

### Statistical analysis

The results were presented in tables and graphs by the number of cases, percentage, arithmetic mean with standard deviation, standard error of arithmetic mean and range of values. Statistical analysis was carried out using the  $\chi^2$  test, Student's t test, and Pearson's linear correlation coefficient. The results of all tests were considered significant at a probability level of 95% or with  $p < 0.05$ .

### RESULTS

Of the total sample, 25 (62.5%) were females and 15 (37.5%) males ( $p > 0.05$ ).

Out of the total of 40 patients, one (2.5%) was younger than 50, five (12.5%) were aged 50-60 years, seven (17.5%) were aged 61-70, 18 (45%) belonged to the age group 71-80 and seven (17.5%) patients belonged to the age group 81-90 years. In the age group older than 90 years, two (5%) patients were noted. The average age of the patients was 73.9 years (range 39 to 92 years of age) ( $p < 0.05$ ).

The largest number of patients spent 23.2 to 30.8 days in hospital ( $p < 0.05$ ).

The average length of hospitalization was  $27.1 \pm 12.2$  days with the shortest period of 3 days and longest period of 62 days. The length of hospitalization shorter than 10 days was recorded in three (7.5%), while 10-20 days of hospitalization were recorded in seven (17.5%) patients. The largest group of 18 (45%) patients was recorded with the duration of hospitalization of 21-30 days; six (15%) patients were hospitalized for 31-40 days, and in five (12.5%) patients the hospitalization lasted for 41-50 days. Only one (2.5%) patient was hospitalized longer than 50 days.

Comparison of MMT average values at admittance and discharge showed that there was a statistically significant increase in the MMT average measured at both the upper and lower extremities ( $p < 0.05$ ). Thus, the average MMT score measured at the upper extremities increased from  $3.25 \pm 0.6$  to  $3.54 \pm 0.8$ , while the increase at the lower extremities was from  $2.91 \pm 0.8$  to  $3.26 \pm 0.9$  (Table 1).

The MMT (MMT release) difference showed that the MMT increase was somewhat greater at the lower extremities and averaged  $0.35 \pm 0.41$  com-

**Table 1. Comparison of manual muscle test (MMT) values of the upper and lower extremities at the admittance and discharge**

|                    | MMT at admittance |                   | MMT at discharge  |                   |
|--------------------|-------------------|-------------------|-------------------|-------------------|
|                    | Upper extremities | Lower extremities | Upper extremities | Lower extremities |
| Average            | 3.2500            | 2.9125            | 3.5375            | 3.2625            |
| Median value       | 3.25              | 3                 | 3.5               | 3.5               |
| Standard deviation | 0.62017           | 0.75011           | 0.81167           | 0.88425           |
| Minimum            | 1.5               | 1.5               | 1.5               | 1                 |
| Maximum            | 4.5               | 5                 | 4.5               | 5                 |

pared MMT measured at the upper extremities with an average increase of  $0.29 \pm 0.43$  ( $p > 0.05$ ) (Table 2). Gender influence analysis on MMT suggests that the improvement was somewhat higher in females in comparison with males, as measured at the upper extremities,  $0.36 \pm 0.34$  and  $0.17 \pm 0.49$ , respectively, as well as measured at the lower extremities,  $-0.38 \pm 0.36$  and  $0.3 \pm 0.53$ , respectively ( $p > 0.05$ ). This indicates that gender has no influence on MMT improvement (Table 3).

**Table 2. Difference of the manual muscle test (MMT) of upper and lower extremities**

|                    | MMT difference of upper extremities | MMT difference of lower extremities |
|--------------------|-------------------------------------|-------------------------------------|
| Average            | 0.2875                              | 0.3500                              |
| Median value       | 0.5                                 | 0.5                                 |
| Standard deviation | 0.40648                             | 0.42667                             |
| Minimum            | -1                                  | -1                                  |
| Maximum            | 1                                   | 1.5                                 |

$p=0.524$

## DISCUSSION

Numerous studies have dealt with the influence of kinesiotherapy in patients with Parkinson's disease diagnosis, and most of them point out the positive consequences of using kinesiotherapy or its variants in such patients (18). Cugusi et al. conducted a study evaluating the impact of custom physical activity on motor and non-motor functions and the quality of life of patients with Parkinson's disease and have shown an increase in the distance that patients can independently

cross, a significant increase in equilibrium and movement safety as well as a significant increase in muscle strength; the authors concluded that patient-specific exercise program could be effective as an additional method for conventional therapy in order to improve the daily life, motor and non-motor symptoms with a higher quality of life (19). These results are in agreement with results of our research. The effects of physical therapy in relation to placebo or in relation to non-intervention in patients with Parkinson's disease were studied by a meta-analysis whose results were published in 2012, which included 33 studies with a total of 1518 subjects (20). The results indicated a significant improvement in experimental patient groups in terms of increased stroke speed, stroke length, balance, muscle strength, functional mobility, and results on Unified Parkinson's Disease Rating Scale (20). The results obtained in our studies confirm the positive effect of kinesiotherapy, especially on the lower extremities. A study conducted by Baatile et al. who have been concerned with the impact on the quality of life of individuals with Parkinson's disease points the benefits of regular exercise in terms of improving the results measured with Unified Parkinson's Disease Rating Scale (UPDRS) and Parkinson Disease Questionnaire 39 (21). The results of our research show that prolonged use of exercise therapy by kinesiotherapy increases the possibility of prolonged walking and, therefore, more quality activities in everyday life. Training in strength and its impact on bradykinesia and muscle strength in patients with Parkinson's disease were the subject of a 2016 study indicating a significantly reduced bradykinesia and increased muscle strength in older patients with Parkinson's disease as well as a positive effect on the physical function and quality of life (22). Our results agree with this research. Kwok et al. study suggests that exercises lead to great improvement on motor symptoms, postural stability, and

**Table 3. Difference of the manual muscle test (MMT) of upper and lower extremities with regard to gender**

| MMT difference    | Gender (No of patients) | Manual muscle test (MMT) |                    |                |         |         |
|-------------------|-------------------------|--------------------------|--------------------|----------------|---------|---------|
|                   |                         | Average                  | Standard deviation | Standard error | Minimum | Maximum |
| Upper extremities | Males (15)              | 0.1667                   | 0.48795            | 0.12599        | -1.00   | 0.50    |
|                   | Females (25)            | 0.3600                   | 0.33912            | 0.06782        | 0.00    | 1.00    |
|                   | Total (40)              | 0.2875                   | 0.40648            | 0.06427        | -1.00   | 1.00    |
| Lower extremities | Males (15)              | 0.3000                   | 0.52780            | 0.13628        | -1.00   | 1.00    |
|                   | Females (25)            | 0.3800                   | 0.36171            | 0.07234        | 0.00    | 1.50    |
|                   | Total (40)              | 0.3500                   | 0.42667            | 0.06746        | -1.00   | 1.50    |

MMT upper extremities  $p=0.148$ ; MMT lower extremities  $p=0.573$

functional mobility (23). Our research confirms the positive effects of kinesiotherapy. Lee et al. study indicated a significant difference in terms of equilibrium, daily life activities and depressive disorders between the experimental and control group in terms of the positive effect of this type of physical activity on all three examined components in patients with Parkinson's disease (24). The influence of kinesiotherapy on the executive functions of patients with Parkinson's disease in a recently published study suggested that six months of exercise improved some aspects of the executive functions in patients with Parkinson's disease, compared with the control group (25). These, like many other studies, suggest the positive effects that kinesiotherapy has on patients with Parkinson's disease.

However, there are fewer studies suggesting the absence of the effect of this treatment regimen in patients with Parkinson's disease, such as a 2011 study of 28 patients included in a 12-week exercise program where the results affected the cognitive function of the frontal lobe, but not on the quality of life (26).

There is a consensus in literature that regular exercise improves physical and functional abilities in different populations (27, 28). Practicing regular physical activity seems to act preventively on the individual before as well as after the diagnosis of Parkinson's disease (21). Some epidemiological studies suggest that there is an inverse correlation between physical activity and the risk of this disease, the mean and high levels of physical activity are associated with a reduced risk of developing the disease (28). A growing number of studies suggest that treatment with kinesiotherapy brings greater benefits in functional capacity in individuals with Parkinson's disease than iso-

lated drug therapy (28,29). Various types of exercises were suggested by randomized controlled trials in order to minimize the negative effects of Parkinson's disease on motor and functional performance. These studies focused on different approaches to physical therapy, such as specific exercises to improve mobility (30), muscle strength (31, 32), balance (33), aerobic fitness (34), and stroke (35). Some studies are non-exclusive, without strong evidence or a sufficient number of subjects to confirm and measure the effect of kinesiotherapy on daily activities of patients with Parkinson's disease, although in most cases they all indicate the positive impact of kinesiotherapy on almost all aspects of life of these patients (19,20,23).

In this study, we analysed patients who performed kinesiotherapy treatment in hospital, but we were not able to monitor their further progress in the home program. It should be examined how often the kinesiotherapy program can be applied in the hospital conditions in order to prevent weakness in muscle strength.

In conclusion, kinesiotherapy had a positive effect on muscle strengthening for our patients with Parkinson's disease, which is in concordance with previously published results related to positive effects of kinesiotherapy. Daily use of kinesiotherapy is recommended in an individual program with regular check-ups in cooperation with neurologists that provide medication therapy.

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## TRANSPARENCY DECLARATION

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## Effects of adding taxane to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer

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### ABSTRACT

**Aim** To compare the effect of neoadjuvant chemotherapy based on taxane and/or anthracycline to the extent of an objective response in female patients with unresectable breast cancer with evaluation of the toxic profile of applied chemotherapy.

**Methods** One hundred patients with histologically verified breast cancer, treated with neoadjuvant chemotherapy were divided into two groups: a study group A (50 patients), who had received 4 to 6 cycles of taxane-based chemotherapy, and control group B (50 patients), who had received 4 to 6 cycles of anthracyclines-based chemotherapy. Pathohistological response was evaluated after tumour excision and axillary resection at the end of chemotherapy and it was defined as pathologic complete (pCR), partial (pPR), or no response (pNR). Toxic effects were evaluated and quantified by the Common Terminology Criteria for Adverse Events v4.0.

**Results** After neoadjuvant chemotherapy, 8% of patients in the group A achieved pCR, 54% achieved pPR, while 38% of patients had no tumour response to applied chemotherapy. In the group B pCR was achieved in 6%, pPR in 42% of patients, while 51% of patients were pNR to the administered chemotherapy. Significant reduction of tumour mass was achieved in the group of patients treated with taxanes: 20.00 (7.75-30.25) vs. 13.50 (6.00-25.00) mm (p=0.024). Toxicity of chemotherapy in group A and group B was within the limits of grade 2.

**Conclusion** The addition of taxane to anthracycline-based neoadjuvant chemotherapy in patients with breast cancer resulted in a significant reduction in tumour mass compared to the group of patients treated with anthracyclines, but without increasing the overall side effects.

**Key words:** tumour reduction, anthracyclines, taxanes

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## INTRODUCTION

Breast cancer is the most common malignant tumour in women and the second leading cause of cancer death in women (1,2). The mortality rate is about 20.5% with tendency of decrease in the last two decades (3).

Radical mastectomy has long been the leading method in treating breast cancer. Neoadjuvant (preoperative, primary or induction) chemotherapy (NACT) was introduced in early 1970s to treat unresectable, advanced breast cancer. Application of NACT is becoming increasingly common in  $\geq 3$ cm in size and locally advanced (T3, T4 or N2) breast cancer for the purpose of so called "down staging" approach aiming to achieve the reduction in tumour size for better operative outcome and better survival rate (4,5).

The use of anthracyclines (from *Streptomyces peucetius*) in 1980s showed targeted effects on topoisomerase II (Top2), binding it to the DNA with high affinity leading to stabilization of DNA-Top2 complex and double-strand DNA break (6). The anthracycline kinone structure supports the catalysis of oxidation and reduction reactions and the formation of oxygen free radicals that are likely to be involved in antitumor effects as well as the toxicity associated with these drugs (7).

An interest in taxanes began in 1963 when the extract from *Taxus brevifolia* plant showed impressive activity in pre-clinical tumour models. Taxanes vary the degree of tubulin separation constantly on both microtubule ends, thus increasing the dynamic instability (4). The ability of taxanes to induce mitotic interruption is associated with microtubule binding, which is already apparent in submicromolar concentrations (4).

Based on a broad spectrum of clinical studies over the last decade, neoadjuvant chemotherapy (NACT) has shown to increase the breast-conserving surgery and to reduce the mortality rate, however, with the small number of pathological complete responses. Due to promising outcomes, taxanes were incorporated in adjuvant treatment in early breast cancer combined with or sequentially after anthracycline therapy (8,9). In our oncology practice we have applied anthracycline and taxane based neoadjuvant chemotherapy since 2007 in a heterogeneous patient population with advanced breast cancer, which imposed the need for a systematic evaluation of the effects of

this type of chemotherapy on the size of pathohistological response and the safety of its use in locally advanced breast cancer.

The aim of this study was to compare the effect of anthracycline and/or taxane based neoadjuvant chemotherapy on the extent of objective responses in female patients with unresectable breast cancer as well as to evaluate and compare the toxic profiles of both chemotherapy regimens.

## PATIENTS AND METHODS

### Patients and study design

Female patients treated with neoadjuvant chemotherapy based on anthracycline or taxane due to pathohistologically confirmed breast cancer were included in a retrospective-prospective manipulative observational study in the period from January 2010 until June 2014 at the Clinic for Oncology at the Clinical Centre of Sarajevo University. Patients were selected based on similar clinical features (clinical stage of the disease, histological type, tumour molecular profiling, age). Data on tumour features (TNM and molecular profile), type of neoadjuvant chemotherapy and the size of overall tumour response that was evaluated by radiological examination of tumour size (RECIST classification) (10) prior to initiation of chemotherapy and after 4 to 6 cycles of therapy were obtained from the history of patients. According to the type of neoadjuvant therapy, the patients were divided into two groups: study group (A) - 50 patients who received 4 to 6 cycles of taxane-based neoadjuvant chemotherapy and a control group (B) - 50 patients who received 4 to 6 cycles of anthracycline-based neoadjuvant chemotherapy.

### Methods

Pathohistological verification of cancer was done after the core biopsy of initial tumour change. Determining the stage of breast cancer was done based on clinical and radiological findings (mammography, ultrasound, RTG or lung CT scan, CT or MRI of abdomen), and pathohistological staging (11): class 1 - disappearance of all tumour either on macroscopic or microscopic assessment; class 2 - presence of in situ carcinoma; class 3 - presence of invasive carcinoma with stromal alteration such as sclerosis or fibrosis; class 4 - no or few modifications of the tumoral appearance.

Laboratory findings (hematological, biochemical, coagulation factors) and heart ultrasound with determination of ejection fraction of left ventricle (EFLV) were performed on all patients prior to initiation of chemotherapy. After each chemotherapy cycle and before the next cycle, side effects have been recorded and laboratory findings were verified.

The extent of tumour response was clinically monitored after each cycle, and radiologically after three cycles, using the same method as was used initially (mammography, ultrasound or MRI) until completing the chemotherapy protocol. Pathohistological response was evaluated after tumour excision or mastectomy and axillary lymph node dissection. Pathologic response rate to neoadjuvant chemotherapy was assessed as complete (CR), partial (pPR) or no response (pNR) as per Response Evaluation Criteria in Solid Tumours v4.0, RECIST classification (10). Pathologic complete responses (pCR) was defined as having no residual invasive carcinoma in the breast and no tumour in axillary lymph nodes at the end of chemotherapy or pathological lymph nodes (whether targeted or non-targeted) with reduction in short axis <10 mm. Isolated tumour cells (ITC) were allowed in the determination of pCR. Any pathologic partial response (pPR) was defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters, while no response (pNR) have included patients without a pathological therapeutic response or at least a 20% increase in the sum of diameters of target lesions. Toxic effects were evaluated and quantified by the Common Terminology Criteria for Adverse Events (AE) v4.0 (CTCAE), e.g. descriptive terminology of grading (severity) scale for each AE term: nausea grade 1- loss of appetite without alteration in eating habits; nausea grade 2 - oral intake decreased without significant weight loss, dehydration or malnutrition; vomiting grade 1 - intervention not indicated; vomiting grade 2 - outpatient IV hydration; medical intervention indicated (12).

### Statistical analysis

Statistical analysis of the obtained data was performed using the Minitab 17 Software for Windows (Minitab, Inc. 2014). The normality of data distribution was determined by Shapiro-Wilk test. All data were expressed as median and interquartile range. Mann Whitney U test was used to com-

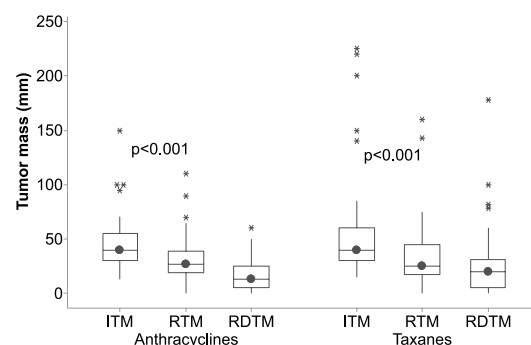
pare the differences in parameters between the two observed groups, while Wilcoxon test was applied in testing the difference between the initial and residual tumour mass within the treated groups. The results are shown as median values with an interquartile range (IQR).  $\chi^2$  test was used to examine differences between groups in the observed properties. The level of significance was set at  $p < 0.05$ .

### RESULTS

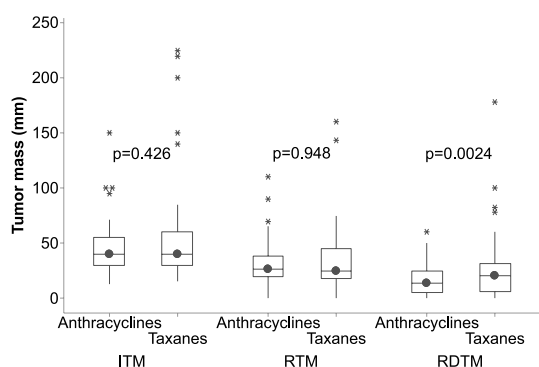
Among 100 female patients the most common type of breast cancer was ductal invasive carcinoma, in 78 (78%) patients. Stage analysis of breast cancer in both chemotherapy groups showed the highest incidence of stage IIIA, 67 (67%, with the ratio 62:72% between group A and group B). Out of 100 patients, 14 (14%) had stage IIB breast cancer, while seven (7%) had stage IIIB. The majority of patients in both groups, 61 (61%) had grade 2 breast cancer; no statistically significant difference was found as to the frequency of different tumour grades in both chemotherapy groups ( $p = 0.656$ ).

Significant reduction of initial tumour mass in the group of patients treated with anthracycline, 40.00 (30.00-55.25) vs. 26.50 (19.25-38.50) mm ( $p < 0.001$ ) as well as in the group of patients treated with taxane, 40.00 (30.00-60.00) vs. 25.00 (17.50-45.00) mm ( $p < 0.001$ ) was found (Figure 1). But, realized difference in tumour mass was significantly higher in the group of breast cancer patients treated with taxanes compared to the group of breast cancer patients treated with anthracycline, 20.00 (7.75-30.25) vs. 13.50 (6.00-25.00) mm ( $p = 0.024$ ) (Figure 2).

Based on the achieved response to chemotherapy regimen, the patients were classified as follows: no pathological response (pNR), partial respon-



**Figure 1. The difference in tumour mass within the breast cancer patient groups treated with anthracyclines or taxanes chemotherapy regimen; ITM, initial tumour mass; RTM, residual tumour mass; RDTM, realized difference in tumour mass**



**Figure 2. The difference in tumour mass in relation to the type of chemotherapy; ITM, initial tumour mass; RTM, residual tumour mass; RDTM, realized difference in tumour mass**

se (pPR) and complete response (pCR). The statistical analysis did not show any significant difference in the frequency of specific forms of therapy responses between the two tested groups ( $p = 0.371$ ). After neoadjuvant chemotherapy, four (8%) patients in the study group (A) /taxane/ achieved complete pathological response, 27 (54%) achieved partial response, and 19 (38%) of patients had no tumour response to the administered chemotherapy. A total of three (6%) patients in the control group (B) /anthracycline/ achieved complete pathological response, 21 (42%) achieved partial pathological response, and 26 (51%) patients had no tumour response to the administered chemotherapy.

The chemotherapy toxicity in both groups (study and control) was within the limits of grade 2. Adding taxanes to anthracyclines did not increase the overall side effects (Table 1).

**Table 1. Adverse effects of chemotherapy according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.0**

| Grasus (G) of adverse effect  | No (%) of patients with therapy |                             | P     |
|-------------------------------|---------------------------------|-----------------------------|-------|
|                               | Anthracyclines                  | Anthracyclines plus taxanes |       |
| nausea G1                     | 10 (20)                         | 12 (24)                     | 0.629 |
| nausea G2                     | 17 (34)                         | 13 (26)                     | 0.383 |
| vomiting G1                   | 8 (16)                          | 10 (20)                     | 0.650 |
| vomiting G2                   | 27 (54)                         | 23 (46)                     | 0.639 |
| diarrhoea G1                  | 11 (22)                         | 12 (24)                     | 0.709 |
| hair loss                     | 50 (100)                        | 45 (90)                     | 0.090 |
| mucositis G2                  | 7 (14)                          | 8 (16)                      | 0.758 |
| change of taste of food G1    | 17 (34)                         | 19 (38)                     | 0.950 |
| stomatitis G1                 | 3 (6)                           | 3 (6)                       | 1.000 |
| loss of appetite G1           | 1 (34)                          | 19 (38)                     | 0.963 |
| bone ache                     | 11 (22)                         | 22 (44)                     | 0.019 |
| weakness G2                   | 7 (14)                          | 9 (18)                      | 0.991 |
| peripheral neurotoxicity G1/2 | 1 (2)                           | 27 (54)                     | 0.001 |
| neutropenia G1                | 7 (14)                          | 3 (6)                       | 0.552 |

In 13 (26%) patients in the taxane-based study group grade 2 nausea was induced, and in 12 (24%) of patients grade 1 nausea was present. The frequency of grade 1 vomiting was present in 10 (20%)

patients in the control group, and grade 2 vomiting in 23 (34%) patients ( $p > 0.05$ ). There were no side effects such as grade 3 and 4 vomiting. A higher level of cytopenia was observed in the anthracycline group, seven (14%). Peripheral neurotoxicity was statistically significantly higher in taxane group with grade 1/2, in 27 (54%) patients ( $p < 0.001$ ) as well as occurrence of bone ache ( $p = 0.019$ ).

## DISCUSSION

The possibility to administer neoadjuvant therapy provides direct information on the clinical (*in vivo*) and pathological response to the therapy. Introduction of postoperative radiotherapy increased the local control of the disease and survival rate, while the combination of systematic chemotherapy with surgery and/or radiotherapy provided even better results, making this approach a standard treatment for patients with locally advanced breast cancer but without satisfactory long-term outcomes (35-55% of local recurrences and 25-45% of five-year survival) (13). A large number of clinical studies have shown that the size of the pathologically detected residual disease and any evidence of residual cancer *in situ* or invasive in the breast and surrounding lymph nodes (after neoadjuvant chemotherapy) is associated with the result of long-term prognosis (8, 14-16). However, no agreement was reached on the precise definition of pathological complete response (pCR).

Changing trends in the treatment of locally advanced breast cancer directly depends on new findings in understanding the biology of the disease (13). In our study, the most common histological type of breast cancer was ductal invasive cancer, and the most common stage of breast cancer was IIIA stage. After neoadjuvant chemotherapy, a complete and partial pathological response was achieved more in the study (A) group (taxane) compared to control (B) group (anthracyclines). With respect to the chemotherapy regimen, significant tumour mass reduction was found in the group of patients treated with the taxane compared to the group of breast cancer patients treated with anthracyclines.

In the study by von Minckwitz et al. (16), the comparison between several defined pCRs has shown that the smallest remaining tumour in breast and lymph nodes correlated with the best survival rate. These, as well as other authors (17,18), have suggested that pCR can serve as a model of the achieved benefits of a chemotherapy regimen compared to another regimen.

Influenced by the hypothesis of Goldie Coldman on the use of a combination of multiple cytostatics, it was assumed that the percentage of resistant tumour cells is decreased in this manner (13). In multiple non-randomized and randomized studies about neoadjuvant (preoperative, primary or induction) chemotherapy (NACT), the following combination was used: cyclophosphamide, methotrexate and 5-fluorouracil (CMF) / fluorouracil, adriamycin and cytoxan (FAC) / doxorubicin and cyclophosphamide (AC) (8,13). Several comparative clinical studies in the adjuvant and metastatic setting have shown that the efficiency of the anthracyclines regimen shows the highest degree of response (protocol B-18, B27) (8,13,19). The results of meta-analysis of multiple randomized clinical trials conducted by Coupone et al. with adding taxane to anthracycline regimen (2,455 patients) showed that the degree of sparing breast surgery significantly increased at the expense of adding taxanes to the NACT regimen (20). The pCR level was also higher in patients who received NACT with taxanes.

The results of the toxicity analyses of cytotoxicity treatment tested in our study proved to be consistent with literature data (9). Serious side effects grade 3 and grade 4 were observed neither in the control nor in the study group.

Anthracyclines are among the most effective cytotoxic drugs developed for the treatment of breast cancer but also among the most toxic drugs ever developed (21,22). They induce nausea, as evidenced by the results of this study. Adding taxanes in neoadjuvant therapy of locally advanced breast cancer causes intense vomiting, which in the early decades was so severe that it required hospitalization and intravenous hydration. The results of this study showed the occurrence of vomiting grade 1 in 20% of patients in the study group and 16% in the control group, and grade 2 in 46% of patients in the study group and 54% in the control group.

Taxanes are potent myelosuppressive drugs and they increase the rate of febrile neutropenia, especially if administered simultaneously with

anthracyclines (23). Taxanes increase the probability of stomatitis, weakness and sensory neuropathy (23). In the study, the frequency of these side effects was not significantly statistically different among chemotherapeutic groups.

Taxane neuropathy may be particularly severe for patients, and data on the expected duration and recovery rate of this complication are limited (23). Neurotoxicity was registered mostly in patients administered with taxane therapy (54%). All side effects in both groups were generally grade 2, without disturbing the quality of life or causing long-term consequences, and they are mostly reversible. By comparing the results in both patient groups, toxic profile is recorded that does not differ between the two groups of patients, regardless of whether the taxanes are sequentially administered, after anthracycline, or simultaneously with anthracycline, except in terms of peripheral neurotoxicity and bone ache. Similar results were also published by other authors (9,16).

Data from the studies BCIRG 001 and GEICAM 9805 show that taxane regimens have a greater negative effect on the quality of life compared to anthracyclines (23,24). These differences in quality of life vanish by the end of neoadjuvant therapy. However, there is no information on the long-term effects of taxane on the quality of life. Future research should investigate whether long-term quality of life depends on the type of neoadjuvant chemotherapy.

In conclusion, application of taxane in neoadjuvant chemotherapeutic treatment of patients with locally advanced breast cancer significantly increases the extent of the objective response compared to treatment with anthracyclines, while at the same time there is no significant increase in toxicity caused by the therapy.

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## TRANSPARENCY DECLARATION

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## Are the single-step resection and primary anastomosis suitable for obstructive colorectal patients in older cases?

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### ABSTRACT

**Aim** To investigate the efficacy and safety of the single-step surgery in elderly patients with obstructive colorectal cancer.

**Methods** All patients who underwent single-step surgery and primary anastomosis for obstructive colorectal cancer in the period between January 2012 December 2017 were evaluated in this study. The patients were divided into two groups: younger than 65 (Group Young) and older than 65 (Group Old). Demographic data, American Society of Anesthesiologists scores (ASA) scores, comorbidities, preoperative albumin levels, type of surgery, postoperative morbidity and mortality, pathological stages, and overall survival rates were investigated.

**Results** A total of 89 patients were included: 49 (54%) were older than 65 (Group Old). In Group Old, the mean age was 75 (65-97), of which 28 (58.3%) were males. There were 41 patients younger than 65 (Group Young) with the mean age of 52.6 (41-64 years of age), of which 21 (51.2%) were males. There was no difference between groups according to albumin level. There was no statistical difference between two groups according to tumour localization, pathological stage and type of surgery, as well as according to surgical complications. The median overall survival rate was 11 months in both groups (0-66) ( $p=0.320$ ).

**Conclusion** Meticulous preparation of older patients (correction of anaemia, electrolyte levels and pH) paves the road for successful surgeries, including single-step resection and primary anastomosis.

**Key words:** anastomosis, colorectal surgery, surgical

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## INTRODUCTION

Majority of patients suffering from colorectal cancer were diagnosed in advanced ages and about 30% of these cases were admitted with mechanical obstruction. Unfortunately, there is limited data in the literature about feasibility of single step surgery with primary anastomosis in elderly patients with obstructive colorectal cancer (CRC) (1,2). Obstructive tumours are usually presented in more advanced stages. Sepsis, dehydration, hemodynamic instability and malnutrition remain major obstacles for successful surgical management of these patients (3). Although, recent advances in technology such as colonic stents and laser applications give us the opportunity to create gastrointestinal system continuity, a significant number of the patients are not suitable for these conservative approaches (3,4).

In right sided colonic malignancies with obstruction general surgical approach is usually single-step resection and anastomosis, however, there is no consensus for left sided tumours (5). In practice, there are four current surgical approaches for the patients with left sided obstructive tumour: loop colostomy/ ileostomy without resection (2/3 step approach), primary resection and Hartman procedure, resection with primary anastomosis (single step surgery), and in selected cases and centres conservative approaches (stent or laser) for palliation (bridge to surgery) (5). Most surgeons did not prefer single-step surgery because of an increasing risk of anastomosis leak secondary to co-morbidities and malnutrition, especially in elderly patients (1). According to the literature, Hartmann procedure is still the most performed surgical procedure in elderly patients with obstructive left sided colorectal cancer (1). Unfortunately, in majority of these patients, colostomies cannot be closed, therefore they have to live with permanent stomas, and in such cases the quality of life is generally measured very low (1). However, some researchers reported very successful outcomes even in elderly patients, who underwent single-step surgery (6).

Aim of this present study was to investigate the efficacy and safety of the single-step surgery in elderly patients with obstructive colorectal cancer.

## PATIENTS AND METHOD

### Patients and study design

All patients who underwent single step surgery and primary anastomosis for obstructive colorectal cancer in the Department of General Surgery of Kartal Research and Education Hospital, Istanbul, Turkey between January 2012 and December 2017 were retrospectively evaluated. The exclusion criteria were patients with mental disability and patients with another malignancy. The patients were divided into two groups according to the age: younger than 65 (Group Young) and patients  $\geq 65$  (Group Old). Demographic data, the American Society of Anesthesiologists scores (ASA) score, comorbidities, preoperative albumin level, type of surgery, postoperative morbidity and mortality, pathological stage, and overall survival rate were investigated. Postoperative mortality was defined as deaths within a period of one month following surgeries.

The study was approved by the Kartal Research and Education Hospital's Ethics Committee.

### Methods

In our clinic, all patients received nasogastric tubes for decompression and foley catheters for urinary status. Personalized fluid resuscitation was applied with careful attention. Central venous catheter was placed and central venous pressure was measured. Plain abdominal graphics, whole abdominal CT scan and colonoscopy were utilized for diagnosis. For colonoscopy examination, fleet enemas was used. Manual decompression was applied for intestinal decompression before single-step resection and primary anastomosis. All patients received single dose 1 gr ceftriaxone and 500 metronidazole, preoperatively, and antibiotics treatment continued for a week.

The American Society of Anesthesiologists scores (7) were evaluated by members of our anaesthesia team. It is a physical status classification system calculated prior to surgery: ASA I - a normal healthy patient; ASA II - a patient with mild systemic disease; ASA III - a patient with severe systemic disease; ASA IV - a patient with severe systemic disease that is a constant threat to life; ASA V - a moribund patient who is not expected to survive without the operation; ASA VI - declared brain-death patient whose organs are being removed for donor purposes.

### Statistical analysis

Data were collected using paper/pencil instruments by the surgeon and entered into a computer by statistical staff. Parameters were evaluated for predictive significance by independent t-tests for continuous variables  $\chi^2$  test for categorical variables. A difference was considered as statistically significant with  $p < 0.05$ .

### RESULTS

A total of 89 patients were included in this study, of which 49 (54%) were older than 65 (Group Old). In the Group Old, the mean age was 75 (range 65-97) years, of which 28 (58.3%) were males. There were 41 (46%) patients younger than 65 years (Group Young) with the mean age of 52.6 (range 41-64); 21 (51.2%) were males. There was no difference in either groups according to gender ( $p = 0.501$ ). The patients in Group Old had significantly higher ASA score ( $p = 0.004$ ) than those in Group Young. Also, comorbidities were significantly higher in Group Old ( $p = 0.337$ ). Most frequent additional disease was hypertension in both groups ( $p = 0.337$ ). In five (12.2%) patients in the Group Old albumin level lower than 3 g/dL was found and 12 (25%) in the Group Young ( $p = 0.220$ ) (Table 1).

**Table 1. Patient characteristics according to age groups**

| Characteristic                    | No (%) of patients in the group |                   | P     |
|-----------------------------------|---------------------------------|-------------------|-------|
|                                   | <65 years (n=41)                | ≥ 65 years (n=48) |       |
| <b>Gender</b>                     |                                 |                   | 0.501 |
| Female                            | 20 (48.8)                       | 20 (41.7)         |       |
| Male                              | 21 (51.2)                       | 28 (58.3)         |       |
| <b>Serum albumin level (g/dL)</b> |                                 |                   | 0.220 |
| 3>                                | 5 (12.2)                        | 12 (25.0)         |       |
| 3 ≤ ~ < 3.5                       | 21 (51.2)                       | 22 (45.8)         |       |
| 3.5 ≤ ~ < 4.0                     | 13 (31.7)                       | 14 (29.2)         |       |
| 4.0 ≤                             | 2 (4.9)                         | 0                 |       |
| <b>Additional diseases</b>        |                                 |                   | 0.337 |
| Hypertension                      | 10 (24.4)                       | 22 (45.8)         |       |
| Diabetes                          | 8 (19.5)                        | 12 (25.0)         |       |
| Heart failure                     | 0                               | 6 (12.5)          |       |
| Asthma                            | 0                               | 4 (8.3)           |       |
| KOAH                              | 0                               | 4 (8.3)           |       |
| CLD                               | 1 (2.4)                         | 1 (2.1)           |       |
| CRF                               | 1 (2.4)                         | 2 (4.2)           |       |
| <b>ASA score</b>                  |                                 |                   | 0.004 |
| II                                | 13 (31.7)                       | 5 (10.4)          |       |
| III                               | 27 (65.9)                       | 33 (68.8)         |       |
| IV                                | 1 (2.4)                         | 10 (20.8)         |       |

KOAH, chronic obstructive pulmonary disease; CLD, chronic liver disease; CRF, chronic renal failure; ASA, American Society of Anesthesiologist

There was no statistical difference between two groups relating to tumour localization, pathological stage and type of surgery ( $p > 0.05$  for all comparisons) (Table 2).

**Table 2. Tumour localization, stage and type of surgery**

| Characteristic         | No (%) of the patients in the group |             | P |
|------------------------|-------------------------------------|-------------|---|
|                        | <65 (n=41)                          | ≥ 65 (n=48) |   |
| <b>Localization</b>    |                                     |             |   |
| Right colon            | 19 (46.3)                           | 17 (35.4)   |   |
| Left colon             | 22 (53.7)                           | 31 (64.6)   |   |
| <b>Stage</b>           |                                     |             |   |
| II                     | 12 (29.3)                           | 21 (43.8)   |   |
| III                    | 14 (34.1)                           | 16 (33.3)   |   |
| IV                     | 15 (36.6)                           | 11 (22.9)   |   |
| <b>Type of surgery</b> |                                     |             |   |
| Right colectomy        | 22 (53.7)                           | 22 (45.8)   |   |
| Left colectomy         | 2 (4.9)                             | 8 (16.7)    |   |
| Anterior resection     | 17 (41.5)                           | 14 (29.2)   |   |
| Segmental resection    | 0                                   | 1 (2.1)     |   |
| Subtotal colectomy     | 0                                   | 3 (6.3)     |   |

The most frequent postoperative complication was surgical site infection in both groups (26.8% v. 27.1%;  $p = 0.979$ ). A rate of anastomosis leaks was 7.3% in the Group Old and 8.3% in the Group Young ( $p = 0.859$ ) ( $p = 0.689$ , 0.653). Respiratory and renal failures were most detected systemic complications in both groups, 12.2% v. 18.8%, respectively (Table 3).

**Table 3. Surgical and systematic postoperative morbidity**

| Type of morbidity         | No (%) of the patients in the group |             | p     |
|---------------------------|-------------------------------------|-------------|-------|
|                           | <65 (n=41)                          | ≥ 65 (n=48) |       |
| <b>Local</b>              |                                     |             |       |
| Surgical site infection   | 11 (26.8)                           | 13 (27.1)   | 0.979 |
| Anastomosis leak          | 3 (7.3)                             | 4 (8.3)     | 0.859 |
| Intra-abdominal bleeding  | 0                                   | 1 (2.1)     | 0.353 |
| Intra-abdominal infection | 2 (4.9)                             | 1 (2.1)     | 0.467 |
| Elongated ileus           | 6 (14.6)                            | 7 (14.6)    | 0.995 |
| Evisceration              | 2 (4.9)                             | 3 (6.3)     | 0.483 |
| <b>Systematic</b>         |                                     |             |       |
| Respiratory               |                                     |             |       |
| Respiratory failure       | 5 (12.2)                            | 9 (18.8)    | 0.397 |
| Pulmonary emboli          | 0                                   | 1 (2.1)     | -     |
| Pneumonia                 | 0                                   | 1 (2.1)     | -     |
| Cardiac                   |                                     |             |       |
| Myocardial infarction     | 1 (2.4)                             | 0           | -     |
| Renal                     |                                     |             |       |
| Acute renal failure       | 5 (12.2)                            | 9 (18.8)    | 0.910 |
| Deep venous thrombosis    | 1 (2.4)                             | 0           | -     |

ASA, American Society of Anesthesiologist

The rate of postoperative early mortality was 2.3% ( $n = 1$ ) in the Group Young and 8.3% ( $n = 4$ ) in the Group Old ( $p = 0.229$ ). The median overall survival rate was 11 months in both groups (range 0-66) with no statistical significance ( $p = 0.320$ ) (Table 4.).

**Table 4. Characteristics of mortality cases**

|                  | <65 (n=41) | ≥ 65 (n=48) | p     |
|------------------|------------|-------------|-------|
| <b>Gender</b>    |            |             | 0.300 |
| Female           | 1          | 2           |       |
| Male             | 0          | 2           |       |
| <b>Stage</b>     |            |             | 0.620 |
| II               | 0          | 1           |       |
| III              | 0          | 1           |       |
| IV               | 1          | 2           |       |
| <b>ASA score</b> |            |             | 0.371 |
| I-II             | 0          | 0           |       |
| III              | 1          | 2           |       |
| IV               | 0          | 2           |       |
| Total            | 1          | 4           | 0.229 |

## DISCUSSION

Usually, majority of colorectal patients admitted with the obstruction are in advanced ages with comorbidities (8). Currently, the majority of literature reviews urgent colorectal cancer patients with comorbidities who received stomas (9-11). If appropriate preoperative preparations are performed, single-step resection and primary anastomosis can be safely applied with low mortality and morbidity rates in even elderly patients (12). Patients admitted for obstructive colorectal cancer require preoperative intestinal decompression for successful resection and anastomosis. Manual decompression and irrigation of colon (on-table lavage) can be safely applied. Studies comparing both methods conclude that manual decompression is simple and can be done within a short period of time. There is no difference between both methods (13,14). We applied manual decompression to all patients. To define synchronous tumours via colonoscopic examinations is highly difficult, manual decompression may be helpful to overcome this situation.

We faced systemic complications more than local in cases with high ASA scores. The same reports can be found in the literature (15). In our study preoperative statistical difference between both groups according to ASA score was not detected following surgeries, in relation with local and systemic complications. Age should not be a contraindication for resection and anastomosis. Iversen et al. reported mortality as 22% in obstructive colorectal cancer cases (16). According to the literature postoperative mortality is related to comorbidities and ASA score more than

age (17-20). In our study short time results were excellent for resection and anastomosis. Total mortality rate was 5.6%.

Application of Hartmann procedure due to high risk of anastomosis leak carry risk of permanent stomas with low quality of life (1). There is no randomized study comparing resection and Hartman procedure. There is no difference between two surgeries according to mortality and morbidity (5). Advances in surgical techniques and preoperative supportive therapies give us the opportunity for successful operations. Primary resection and anastomosis can be safely applied. In our study, mortality rates and the number of anastomosis leaks were significantly lower than in other studies in the literature review (12,21). We believe in experienced hands, dedicated to colorectal surgery, who should do these type of surgeries. In specialized units for colorectal surgery like those in our institution resection and anastomosis should be the choice of treatment.

Single step-resection and anastomosis have excellent results within a short period of time. However, reports on long-term results indicate high numbers of mortality in older cases (22-24). We believe that shortage of long-term survival is related to high numbers of Stage 3 and 4 patients.

In conclusion, meticulous preparation of older patients (correction of anaemia, electrolyte levels and pH) paves the road for successful surgeries, including single-step resection and primary anastomosis. This type of surgery can be safely applied with low mortality and morbidity rates. Older patients will not receive permanent stomas. Age should not play a major role in planning type of surgery. Curative resections should be done by experienced surgeons without hesitation. Despite the absence of screening and chemotherapy regimens in older patients, they should receive effective surgical procedures.

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## TRANSPARENCY DECLARATION

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## Comparison of biomechanical stability of osteosynthesis materials in long bone fractures

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### ABSTRACT

**Aim** To calculate stress and deformation under the force of pressure and bending in the dynamic compression plate (DCP), locking compression plate (LCP), selfdynamisable internal fixator (SIF) and locked intramedullary nail (LIN) in the models of juvidur, beef tibia bone (cadaver) and software of bone model simulator.

**Methods** Juvidur and bone models were used for the experimental study, static tests were performed with SHIMADZU AGS-X tester. CATIA software was used to create a 3D model for the SCA simulator, while software ANSYS to calculate the tension and deformation for compressive and bending forces. Stress and deformation analysis was performed with the use of Finite Element Analysis (FEA).

**Results** Weight coefficients of research methods were different (juvidur=0.3; cadaver=0.5; SCA Simulator=0.2), and weight coefficients of the force of pressure  $K_p=0.5$  and bending forces in one plane  $K_1=0.25$  and  $K_2=0.25$  in another plane, the overall result on the dilatation of DCP, LCP, LIN and SIF on juvidur and veal cadaver models showed that the first ranking was the LIN with a rank coefficient  $K_{U-LIN}=0.0603$ , followed by the IFM with  $K_{U-IFM}=0.0621$ , DCP with  $K_{U-DCP}=0.0826$  and LCP with  $K_{U-LCP}=0.2264$ .

**Conclusion** Dilatation size did not exceed 0.2264 mm, hence the implants fulfilled biomechanical conditions for the internal stabilization of bone fractures. Prevalence goes to the locked intramedullary nailing and Mitković internal fixator in the treatment of diaphyseal, transversal, comminuted fractures in relation to DCP and LCP.

**Key words:** osteosynthesis material, bone, software models, biomechanics

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## INTRODUCTION

Extremities are most frequently exposed to injuries in everyday activities, falls, traffic accidents and in missile injuries. The incidence of limb injury in polytrauma is 58.6% (1). Long bone fractures on the lower extremities are present in 21.9% of traumatised patients (2), while fractures of the long upper extremities are present in 19% (3). The conservative form of treatment lost its primacy over the surgical treatment (4). For decades, the surgical form of osteosynthesis of the closed long-bone fracture is usually performed by internal fixation with the following: dynamic compression plate (DCP), locking compression plate (LCP), internal fixator by Mitković (IFM) and locked intramedullary nailing (LIN). Longstanding experience in clinical and scientific/research work has not yet set clear guidelines on the use of osteosynthetic material for the stabilization of long bone fractures (5). Further development of biomechanical research will probably lead to a concession in the use of osteosynthetic material (6,7).

The aim was to examine the calculation of tension and deformation under the force of pressure, and bending forces in the dynamic compression plates (DCP), locking compression plates (LCP), Mitković internal fixator (IFM) and locked intramedullary nail (LIN) on juvidur and veal cadaver models and software of bone model simulator.

## MATERIALS AND METHODS

### Study Design and Setting

The investigation was carried out at the School of Mechanical Engineering in Niš from January to June 2016 in order to calculate stress and deformation under the force of pressure and bending in the dynamic compression plate (DCP), locking compression plate (LCP), selfdynamisable internal fixator (SIF) and locked intramedullary nail (LIN) in the models of juvidur, beef tibia bone (cadaver) and software of bone model simulator.

### Methods

Geometrically identical, anatomically shaped juvidur and bone models with diameter of 30 mm and the length of 100 mm were used for the experimental study. "The bone" was two juvidur parts at the distance of 10 mm, which were stabilized

by tested osteosynthesis material. A "medullar cavity" was created by drilling the juvidur bar. Models were manufactured in equal, controlled conditions. Such juvidur models provide identical biochemical conditions for all tests of the tested osteosynthesis materials.

Veal cadaver with diameter of 30 mm, length of 100 mm and medullar cavity of 16 mm were used for the experimental study. Osteosynthesis material (DCP, LCP, IFM and LIN) was placed under the same conditions, with two veal bones at the distance of 100 mm. The same manufacturer was used for DCP, LCP and LIN (manufactured by Narcissus, Ada, Serbia), while the other one was used for IFM (manufactured by Traffix Niš, Serbia). Tested osteosynthesis material was placed on juvidur and veal cadaver models; the DCP without locking and the LCP plates with 10 holes. The plates were placed on juvidur, that is, veal cadaver, with three screws on each side of "the fracture", making a total of six screws per plate. The LIN, with the length of 200 mm, was placed in the "medullar cavity" of the juvidur model as well as in the medullar cavity of the veal cadaver with one proximal and distal screw. The same technique was used to place the IFM on juvidur and veal cadaver models. Special fixation clamps for proximal and distal part of juvidur and veal cadaver bone were made to provide more accurate positioning and fixation.

Static tests were performed with the usage of SHIMADZU AGS-X tester with the force of pressure increasing from 0 N to 500 N, and with the subsequent relief. Data and recorded diagram of the change in deflection were written in the software which was the integral part of SHIMADZU AGS-X tester. By dividing the maximum force with the total time, the increase in force per unit of time was obtained.

CATIA software was used to create a 3D model for the SCA simulator, while software ANSYS was used to calculate the tension and deformation for compressive and bending forces. Stress and deformation analysis was performed with the use of Finite Element Analysis (FEA). The tested osteosynthesis material was loaded by the compressive forces of up to 500 N and bending forces up to 250N. We tracked the force and deformation which occurred due to the force of pressure/compression/ or bending and on those bases, we evaluated stability.

Ranking of the DCP, LCP, LIN and IFM was carried out specifically for juvidur, veal cadaver and SCA simulator testing. The ranking was done by determining the minimum rank coefficient, obtained on the basis of the arithmetic mean (mean value) of dilatation in millimetres. The ranking was determined for two cases. The first one, an equal weight coefficient of arithmetic values (mean values) of dilatation for each type of load. The second one, different weight coefficient of arithmetic values including: weight coefficient for the pressure  $K_p=0.5$ ; weight coefficient for bending in one plane  $K_1=0.25$ ; weight coefficient for bending in another plane  $K_2=0.25$ . (6,7) Juvidur model was exposed to the same conditions, compression forces and lateral bending forces in one plane and lateral bending forces in other plane. This research showed that the IFM had the smallest dilatation, 0.2007, followed by the DCP with 0.2602, LIN with 0.2719 and LCP with 0.5459.

The research on the software model in the simulator showed that the LIN had the smallest dilatation with 0.1950, followed by the DCP with 0.1970, the IFM with 0.2238 and the LCP with 0.2394 (7).

### Statistical analysis

On the basis of ranking of biomechanical stability of the tested osteosynthesis materials (LIN, DCP, LCP, IFM) for specific test methods (juvidur, veal cadaver, SCA simulator), the overall ranking of tested osteosynthesis materials was obtained. Overall coefficient rank for each osteosynthesis material and each testing method (SCA simulator, juvidur model; veal cadaver) was determined according to the following algorithm:

$$K_{u-i} = \min_j (K_p * \overline{X_p} + K_1 * \overline{X_{1i}} + K_2 * \overline{X_{2i}})$$

$K_i$  – the overall result for each osteosynthesis material;  $i$  – LIN; DCP; LCP; SIF note of osteosynthesis material;  $j$  – JU - juvidur; TT – veal cadaver; SCA – SCA simulator;

$\overline{X_p}$  – arithmetic value of dilatation (mm) for the force of pressure;  $K_p$  – Pressure Coefficient;

$\overline{X_{1i}}$  – the arithmetic value of dilatation (mm) for the bending force in one plane;  $K_1$  – coefficient of the bending force in one plane;

$\overline{X_{2i}}$  – the arithmetic value of dilatation (mm) for the bending force in the other plane;  $K_2$  – coefficient of bending forces in the other plane.

**Table 1. Biomechanical testing results**

| Rank* | Type of osteosynthesis material    | Rank coefficient† |
|-------|------------------------------------|-------------------|
| 1     | Locked intramedullary nail (LIN)   | 0.0603            |
| 2     | Internal fixator by Mitković (IFM) | 0.0621            |
| 3     | Dynamic compression plate (DCP)    | 0.0826            |
| 4     | Locking compression plate (LCP)    | 0.2264            |

\*order of biomechanical stability of tested osteosynthetic materials;

†dilatation coefficient of tested osteosynthetic materials

### RESULTS

The overall result of the study on the mechanical stability of osteosynthesis material (DCP, LCP, LIN and SIF) on juvidur and veal cadaver models and SCA simulator with weight coefficient test methods (juvidur = 0.3; cadaver = 0.5; SCA = Simulator 0.2) and weight coefficients of forces (pressure  $K_p = 0.5$ ; bending in one plane  $K_1 = 0.25$ ; bending in the other plane  $K_2 = 0.2$ ), showed that the LIN had the smallest dilatation with a rank coefficient  $K_{U-LIN} = 0.0603$ , followed by the IFM with  $K_{U-IFM} = 0.0621$ , DCP with  $K_{U-DCP} = 0.0826$  and LCP with  $K_{U-LCP} = 0.2264$  (Table 1)

### DISCUSSION

Less invasive osteosynthetic material DCP, LCP, LIN, which is used for fracture stabilization has been widely used in clinical practice and nowadays, it provides new opportunities and challenges for modern surgical treatment of fractures (4,5). The plates, screws and pins themselves cannot completely solve all the problems that are encountered in the fracture repair. Bone healing requires a relatively stable environment, precise anatomic reposition and reliable internal fixation (6,7).

Florin et al. have conducted biomechanical tests of DCP, limited contact DCPlate (LC-DCP), LCP and internal fixation bars (CRIF-Formal VetFi) on long bones of horses (8). Studies have shown that DCP, LC-DCP and LCP constructions provide good biomechanical stability and support loads in one cycle (8). Taking into account the biomechanical properties of DCP, LC-DCP and LCP constructs, they have not found statistically significant differences in the examined implants. In addition, they prefer the LCP implants because

of the high yield strength, high stiffness under high-load application, and the least movement at the fracture line (8).

Jiang and associates conducted biomechanical tests on the comminuted fractures of the long femoral bone. The stabilization of the fracture was performed with the use of two kinds of plates: a newly designed locking compression plate (NLCP) and a locking compression plate (LCP). The fracture repair was monitored by computed tomography (CT). After the analysis of the obtained results, the advantage was given to the NLCP plate which gives better biomechanical stability in all three levels in cases of comminuted long bone fractures (9).

When a person weighing 70 kg falls to the ground from a standing position, the energy is about 500J. Eccentric muscle contractions and deformations of soft tissues have the ability to absorb energy and prevent bone fractures in the insignificant, slight falls of young people. Muscles and ligaments of older people are unable to resorb the same energy (10).

Tsutsui et al. conducted biomechanical tests on 15 cadaveric forearms. They stabilized the fracture with the use of the LCP plate. They compared the changes in biomechanical and radiographic properties under cyclic axial loading between groups; one where two rows of distal screws were used, and one where only one row of distal screws was used (11). Cyclic axial compression test was performed (3000 cycles; 0-250 N; 60 mm/min) to measure absolute rigidity and displacement, after 1, 1000, 2000 and 3000 cycles, and values were normalized relative to cycle 1 (11). Biomechanical and radiographic analyses demonstrated that two rows of distal locking screws in the DSS procedure conferred higher stability than one row of distal locking screws (11).

The trauma accounts for about 11% of the diseases in the world, and the fractures are the most presented in trauma. When it comes to the choice of implants, the one that provides micro-movements at the fracture site, as the micromovements stimulate the callus formation, should be used (12). Researchers claim that the future of osteosynthetic material is in biodegradable plates (13). The authors created Auxetic Polymeric Bone Plate, which can be used as an internal fixator for bone fracture (13). It provides micro-movement due to

its counter intuitive behaviour and has the potential to reduce the effect of stress at the fracture site and allow the same range of motion as that of natural bone (13).

Augat et al. have accomplished good results in the treatment of the distal tibia fracture with intermedullary implants when two screws, preferably in crossed configuration, are placed in the distal fragment (14).

The LCP and DC plates rely on completely different mechanical principles in order to ensure the fracture stability and thereby provide different biological environments (15). The LCP plates display good results in metaphyseal fractures, osteoporotic bones and bridging of multifragmented, comminuted fractures as they reduce bone tension with bridging, while DCP plates can still be the method of choice used to stabilize diaphyseal fractures that require perfect reposition (15).

Osteosynthetic material must keep a fracture stable in the internal/external rotation. The internal torque sufficient to ensure adequate stability in the femur of the infant cannot be reliably achieved with the use of 4.5 mm cortical screws (16). The second limiting factor is poor bone cavity of the distal fractural fragment. The construction of LCP plates is significantly more resistant to compression when compared to DCP plates (16).

In a series of 25 calves, LCP was examined in the treatment of closed diaphyseal femur fractures (17). Apart from clinical signs, the fracture repair was monitored radiographically (17). The LCP wedge that was locked in this study was associated with a good prognosis for surgical treatment of femoral fractures regardless of fracture site (17).

Examining the biomechanical stability of a 3.5mm cortical screw that was used to stabilize DC, DCP and LCP to axial forces showed that the screws in the plates maintained physiological loads of the extremities (18). The LCP plate with neutrally placed screws that maintain the planned intrafragmentary gap allows the movement of the fragments up to 15% if the intrafragmentary crack is up to 2 mm (18); this could not achieve with DC and DCP plates (18).

In conclusion, the examined osteosynthesis material has shown that the dilatation size did not exceed 0.2264 mm, hence the implants fulfil the

biomechanical conditions for the internal stabilization of bone fractures. A good technical solution, internal fixator by Mitkovic, enables fast placement, minimal trauma of soft tissue and deperiostation, which gives it the advantage of stabilizing the *diaphyseal long bone fractures* compared to the examined ones.

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## TRANSPARENCY DECLARATION

Conflicts of interest: None to declare

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## Immigrant patients in brief meetings with anaesthetist nurses - experiences from perioperative meetings in the orthopaedic setting

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### ABSTRACT

**Aim** To explore the experience of anaesthetist nurses in brief meetings with immigrant patients in the perioperative setting.

**Methods** The study was conducted through open individualised interviews using open-ended questions. Eighteen anaesthetist nurses (six men and twelve women) participated in the interviews. Their age varied between 35 and 65 and they had worked as anaesthetist nurses for a period between six and twenty eight years. The text was analysed using qualitative content analysis.

**Results** Meetings with immigrant patients made nurses with less experience to prepare more, to study behaviour of these patients and to ask their older colleagues for advice. More experienced nurses acted on the basis of their previous experience and treated the patients in the same way as before. They also emphasised the great responsibility and wider scope of assistance needed by these patients than those born in Sweden. The majority of nurses begin the meetings with these patients by requesting an interpreter, while some nurses begin the meeting directly with the patient and, if they see it is not going well, they request an interpreter.

**Conclusion** Nurses need better guidelines and education in how to deal with the legislation relating to immigrant patients in order to handle the situation more effectively. Training in cross-cultural care should be improved to help nurses deal with stress through co-operation with the Migration Board and others. In order to provide for good communication and patient safety professional interpreters should be used.

**Key words:** anaesthetist nurses, brief meeting, experiences, immigrant patients, qualitative research

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## INTRODUCTION

In the world today, we see massive migrations and we encounter people from other countries on a regular basis. People move from one culture to places that are entirely different in every way. Societies are increasingly multi-cultural (1,2). These changes strike at the roots of society including the health-care system. The provision of health care is based increasingly on a holistic, individual approach, giving each patient equal care (3-6). Entire families are included in individual care (7-10) and communication is seen as increasingly vital in the interaction between the patient, the care provider and the family (11). It is also symbolic and important in interpreting human behaviour (12). The relationship between patients and the anaesthetist nurse in the context of surgery is vital (13) and is based on conversations in which they become acquainted with one another (14,15). The foundation of this is mutual respect and empathy (13). Nurses must be trained well with the ability to help the patient feel secure and at ease, showing that they are available to the patient (16). They need to know who the patient is (17,18) and anything he or she may be worried about (17). If there is any barrier to communication, problems may arise (11). Studies have shown that language barriers, cultural differences, education and family members visiting patients (19,20) may cause difficulties and even lead to the experience of more severe pain (21) in patients suffering from cancer (22), spinal injury (23), vulvodynia (24), migraine (25), arthritis (26), non-specific chronic pain (27,28) and musculoskeletal disorders (29). However, no study has as yet been undertaken from the point of view of the anaesthetist nurses in terms of the perioperative meetings held with immigrant patients, especially in the orthopaedic setting. The nurses have a brief time to communicate with patients about their expectations and their worries and needs. In this study, we aim to bridge this gap to provide a better understanding of the interaction between nurses and patients in that setting. Person-centred care means that the person behind the patient should be seen as a person with his or her own will and own feelings and needs. Person-centred care puts the patient's perception of his/her life situation at the centre (30). The starting point should be to respect the individual patient and find ways to help him/her

to identify and explain his/her own needs. Person-centred care means that the patient should be helped to turn from being a passive party in planning nursing and medical decisions to becoming an active party in planning and decision-making (30). As the focus shifts to the patient, it can lead to increased collaboration in the meeting, improved health and an increase in the patient's sense of satisfaction. The patient's narrative about his/her illness, symptoms and impact on his/her life should be the basis for planning and performing care (30). The meeting will serve as a partnership between patients, relatives and carers. In this partnership, lifestyle, beliefs, values and health will be discussed and will be the starting point for the planning of care. In order for person-centred care to be applied, three steps should be followed (30). Step one means inviting patients to describe their experiences to show them that they are relevant and should be included in the planning or diagnosis. Step two involves sharing experiences and learning from each other by including patients in the decisions to be taken (30). Step three means creating continuity of care by documenting the patients' narratives, perceptions and the common plans that are created (30).

The aim of this study was to explore the experience of anaesthetist nurses in brief meetings with immigrant patients in the perioperative setting.

## MATERIALS AND METHODS

### Study design and participants

This exploratory pilot study is based on a qualitative design. It is part of an earlier study, where nurses were interviewed regarding the brief meetings they hold with immigrant patients at the orthopaedic setting. The study was conducted at the Department of Orthopaedic Surgery, Sahlgrenska University Hospital, Sweden. Anaesthetist nurses were contacted by the first author and asked voluntarily to participate in an open individualised interview. After meeting study participants, the aim of the study was presented. Nurses with at least five-year experience of orthopaedic anaesthesiology were asked to take part in the study, because those who have worked for at least five years will have had more opportunity to meet the immigrant patients. Twenty two anaesthetist nurses were recruited initially, but four were unable

to participate because of shortage of staff and for other personal reasons. An invitation letter with information about the study's aim was sent to 22 anaesthetist nurses. As a result, 18 anaesthetist nurses (six men and twelve women) participated in the interviews. Their age varied between 35 and 65 (median 50) and they had worked as anaesthetist nurses for a period between six and 28 years (median 15 years). In order to obtain information, we performed in-depth individualised interviews.

## Methods

Data were collected by the author through individual interviews, using individualised, open-ended questions, following an interview guide inspired by Kvale (31). The interviews were conducted between March and November 2017 by the first author through face-to-face interviews using open-ended questions. The interviews began with the question "Can you please describe your experience of communication in the brief meeting with immigrant patients?". All the study participants were urged to speak freely using their own words and to respond as comprehensively as possible. The interviewer only interrupted to pose further questions or follow up on the information given by the nurses. The interviews, which were conducted on the surgical ward, lasted between 45 and 75 minutes and were audio-taped and transcribed verbatim.

## Statistical analysis

A qualitative content analysis method in accordance with Graneheim and Lundman (32) was chosen for the analysis and interpretation of data. This method is capable of condensing a large amount of data into a limited number of themes, categories, subcategories and codes. The transcriptions were read carefully in order to identify the informants' experiences and perceptions. The analysis then proceeded by extracting units consisting of one or several words, sentences or paragraphs containing aspects related to each other and addressing a specific topic in the material. Units that related to each other by virtue of their content and context were then abstracted and grouped together into a condensed unit, with a description close to the original text. The condensed text was further abstracted and labelled with a code. After that, codes that addressed si-

milar issues were grouped together, resulting in subcategories. Subcategories that focused on the same problem were merged in order to create more extensive perceptions, which addressed an obvious issue (32). According to Graneheim and Lundman, the interpretation was made primarily at a manifest level. The results were presented with direct quotes from the interviews.

## RESULTS

The analysis of the text resulted in a theme and two main categories and seven subcategories based on how the anaesthetist nurses described communication with immigrant patients at the brief perioperative meeting (Table 2).

**Table 1. Demographics characteristics of participants in terms of education, work and years of experience**

| Characteristic         | Number (%) of participants |
|------------------------|----------------------------|
| <b>Gender</b>          |                            |
| Male                   | 6 (33)                     |
| Female                 | 12 (67)                    |
| <b>Total</b>           | <b>18 (100)</b>            |
| <b>Education level</b> |                            |
| Anesthesia nurses      | 11 (61)                    |
| Master's               | 7 (39)                     |
| <b>Total</b>           | <b>18 (100)</b>            |
| <b>Age</b>             |                            |
| 31-40 years            | 7 (39)                     |
| 41-50 years            | 5 (28)                     |
| 51-60 years            | 4 (22)                     |
| ≥ 60 years             | 2 (11)                     |
| <b>Total</b>           | <b>18 (100)</b>            |
| <b>Experience</b>      |                            |
| ≤ 5 years              | 4 (22)                     |
| 6-10 years             | 5 (28)                     |
| 11-15 years            | 3 (17)                     |
| 16-20 years            | 4 (22)                     |
| ≥ 20 years             | 2 (11)                     |
| <b>Total</b>           | <b>18 (100)</b>            |

**Table 2. Overview of categories, subcategories and theme**

| Category                           | Subcategories                                 | Theme   |
|------------------------------------|---|---|
| Encounters with different cultures | Satisfactory meetings                         | Different challenges in the brief meeting with immigrant patients |
|                                    | Cultural aspects of the meeting               |   |
|                                    | Various forms of communication in the meeting |   |
| Challenges in the meeting          | Frustration in the meeting                    |   |
|                                    | Lack of time for the meeting                  |   |
|                                    | Communication                                 |   |
|                                    | Patient safety                                |   |

## Encounters with different cultures

In this section of the study, all the nurses stated that they prepared to meet with patients a day before. In this way, nurses were able to see which

patients they would have the following day, which made some nurses with less experience nervous and fearful. Meetings with immigrant patients caused nurses with less experience to prepare more, to study the behaviour of these patients and to ask their older colleagues for advice. More experienced nurses acted on the basis of their previous experience and treated the patients in the same way as before.

### **Satisfactory meetings**

Most nurses in this study stated that the meetings with immigrant patients could have had different outcomes, but most meetings ended well and were mutually satisfactory for the patients and the nurses. For nurses with less experience, meetings with these patients required more preparation and study, while, for experienced nurses, this meeting was just one of many meetings. Most inexperienced nurses expressed the desire to meet as many of these patients as possible in order to learn as much as possible about them and to become more skilled in this regard, so they could give better assistance to this type of patients in future. They also emphasised the great responsibility and wider scope of assistance needed by these patients than those born in Sweden. "At the beginning of my career, I asked for only immigrant patients, so that I could learn as much as possible about working with these patients."

Meetings with immigrant patients could unfortunately also have an unpleasant ending, according to the nurses in this study. Some, both those with experience and those with less experience, pointed out the difficulties of working with those patients. "I had one patient who did not want to communicate with men at all and did not want to give me her hand because I am a man... I waited for the interpreter... it took a long time."

### **Cultural aspects of the meeting**

Regarding the cultural aspects of this study, most nurses emphasised that, no matter how large the differences between immigrant patients are, there are also problems with the staff providing assistance to patients they know so little about. Some nurses in the study mentioned that they are also human beings, just like the staff, it is just that they were born far from Sweden and they share the same feelings, pain, suffering and everything

else as patients born in Sweden. Other nurses emphasised that precisely their lack of knowledge of those patients could lead to worry, aggression and frustration in their care providers. Most nurses in this study emphasised that cultural differences are sometimes very large in comparison with patients born in Sweden, but all the nurses in the study respected these differences when providing quality care to these patients.

"Sometimes, when I have a meeting with immigrant patients, I think that they are patients that I will never be able to care for, but they are the same as other patients and just speak a different language and have a different culture than the Swedish culture."

### **Various forms of communication in the meeting**

The brief meetings with immigrant patients sometimes only last a few seconds, sometimes several minutes, while the meeting sometimes takes a great deal of time, depending on the waiting time and the involvement of other people in the meeting. Most nurses emphasised that there are various forms of communication with this type of patients and that, just as anaesthesia is a very varied branch of medicine, these patients also differ greatly from one another. The majority of nurses begin the meetings with these patients by requesting an interpreter, while some nurses begin the meeting directly with the patient and, if they see it is not going well, they request an interpreter. Nurses with less experience almost always consult and seek help from more experienced colleagues to ensure a successful meeting and to reduce waiting and the disruption of the surgical schedule.

"I always order an interpreter for the conversation; first, because it makes it so much easier to communicate with these patients and, secondly, because the interpreter is also a witness and guarantees my work."

"If I have a patient like this on my operating schedule, I always consult an older colleague and the meeting is always successful."

### **Challenges in the meeting**

All the nurses identified and described two phases in meetings with immigrant patients. The first was the phase of preparation by the nurses for the meeting, before they meet the patients, and the

second phase is the direct contact with the patients. The second phase involves several challenges such as a degree of frustration, the lack of time to hold the meeting, waiting for other people who need to attend the meeting, difficulties in communicating with immigrant patients and the effect of all these components on patient safety during preparations for a surgical procedure.

### **Frustration in the meeting**

Most nurses emphasised a certain amount of frustration that could be seen as positive or negative. Frustration in nurses can be seen in the fact that they are unable to provide the right kind of assistance to their patients, who have different expectations. In that case, most nurses align their request for assistance with the policy of the ward or clinic where they are employed. Negative forms of frustration were seen in the fact that nurses encounter problems in the meetings with patients that are caused precisely by the patients. The nurses' frustration may be caused by the fact that the patients do not agree to talk to the nurse, the patients may be mentally ill or suffer from dementia, or they do not understand the language and the interpreter is late for the meeting. All these reasons can take up precious time and disrupt the work schedule, which is not helpful for the patients or the staff.

"I thought I was prepared for the meeting and I was there with the patient... I waited 35 minutes for the interpreter... so much for my meeting."

"I once had a patient with dementia... I asked about allergies to medication and the patient asked me, 'Where is my mum?'"

### **Lack of time for the meeting**

The time that was planned for the brief meeting with patients was often disrupted and, according to the nurses in this study, this most frequently occurred while they were waiting for the interpreter, or there may be other causes that disrupted the meeting and they had to delay the schedule. One of the main causes of lost time was that patients did not acknowledge the staff and female patients asked to communicate and hold the meeting with female staff. The nurses emphasised that, in some cases, they could recover the time by doing other work, but they most frequently wasted precious time waiting for problems to be

resolved before the operation could go ahead. Some of the nurses pointed out that they often wanted to solve the problems and not waste time, but they did not succeed.

"The patient was from an Arabic country... he did not speak a word of Swedish... I waited for the interpreter and time passed... I had no choice but to wait."

### **Communication**

All the nurses emphasised the fact that the brief meeting with immigrant patients was almost impossible because the patients did not understand/speak Swedish. The lack of knowledge of Swedish, waiting for the interpreter, mentally ill patients, the terrible experiences the patients had been through, as well as the influence of religious and cultural factors in communication, were just some of the factors that obstructed the brief meeting with immigrant patients. Communication with these patients differed in relation to the experience and length of time the nurses had worked on the ward. Some nurses had ordered an interpreter the previous day, while others used various aids such as Google Translate, the help of relatives, other staff who spoke the same language as the patient and so on. All the nurses agreed that the best way to communicate with patients was through an interpreter. However, the nurses pointed to difficulties communicating with these patients even if interpreters were present. The difficulties could be seen in the fact that interpreters came late, they did not have enough knowledge of medical terminology, they came from the same state as the patients but were on a different side in the war in that country, which led to the patient rejecting the interpreter, female patients demanded female interpreters, or the interpreter came at the scheduled time, but the patient's operation was postponed due to an urgent case that came up in the meantime.

"We were all waiting for the interpreter because the patient demanded a female interpreter... We waited 45 minutes, but we respected the patient's request."

"To calm the patient, I gave him a 1 mg injection of dormicum... the patient asked me to explain how the drug worked, which I did, but the interpreter did not know how to translate this for the patient with complete certainty."

### Patient safety

All the informants emphasised the fact that immigrant patients' safety during the brief meeting was threatened in comparison with patients born in Sweden. All the informants identified several important factors which could threaten patient safety to some extent. Lack of knowledge of Swedish, waiting for the interpreter to help, talking with patients and the interpreter in front of other patients, lack of knowledge of the patient's previous mental and physical condition and lack of knowledge of the patient's culture, religion and earlier behaviour could all cause fear and insecurity, or lead to the possibility of an error. All the informants also stated that they could suffer additional stress and make mistakes for the same reasons, regardless of whether or not the patient was born in Sweden.

"I had an interpreter beside me, everything was on time, but the patient was fearful and remained silent... time passed... this increased my stress and fear... what could I do?"

"The patient appeared to have a lot of mental and physical problems, but I could only deal with what the patient needed help with at that moment... I don't know what to say... I don't feel that I gave the patient complete assistance."

### DISCUSSION

This study is the first in Sweden to investigate the relationship between anaesthetist nurses and immigrant patients in their communication during the brief perioperative meeting in the orthopaedic setting presenting the characteristics of the informants, their daily work and the difficulties experienced during the brief perioperative meeting. The results showed that many nurses worried because they lacked knowledge about other cultures and how they affect people, but that the meetings they held with immigrant patients were still rewarding. Leininger (1988) (33) pointed out that the basis for a good meeting is knowledge about the patients' different cultures. Nurses need to know about their cultural values, worldview and social structures and how these could affect the patient. Suurmond et al. (2010) (34) stated that, in transcultural care, nurses must be aware of and know about different cultures and people. The authors of the present study believe that knowledge of transcultural care

is important when meeting immigrant patients and that training in transcultural care could result in better meetings. The results showed that the informants wanted their employers to offer relevant training for working with immigrant patients, since the responsibility currently rests with anaesthetist nurses. Hanssen (2007) (35) and Hultsjö and Hjelm (2005) (36) emphasised that knowledge of other cultures is vital when it comes to understanding and meeting people from other cultures. Understanding the patient's culture and religion contributes to increased respect and care. Focusing on culture and religion, however, must not cause the patient to be seen as a representative of a culture or religion, as the patient should be viewed from an individual perspective. The authors believe, however, that applying Leininger's transcultural care theory may lead to an emphasis on the differences rather than the similarities between people, which obstructs person-centred care. Other problems faced in this brief meeting were frustration, shortage of time and communicating with immigrants who did not speak the language and needed an interpreter. In a previous study, we showed that the frustration of staff in the Swedish health-care system does not necessarily arise from immigrant patients (37). The patients may be Swedish, but, at a given moment, staff have to treat them in some way, or the patient behaves towards the staff in a way that causes a measure of frustration in the staff towards them (37). The nurses also mentioned language difficulties and problems with interpreters. In our earlier study of orthopaedic patients, we found that, for patients facing elective total hip replacement, information they receive before surgery is limited. The patients were worried about lack of information they received prior to surgery about implant choice, pain medication and anaesthesia, the lack of time they had to ask the surgeon questions and the stress involved in general (38, 19). In our earlier study of interpreters (39), we have shown that people have high expectations from consultations using interpreters, which are not always met. Interpreters are delayed, they are not professionals, or they are not acquainted with medical terminology and other problems arise when health-care staff or relatives act as interpreters. Anaesthetist nurses need to watch for and note other signs

during the course of the procedure that confirm what the patient has said. They must have an appropriate foundation for clinical assessment and decision-making, so they need information that is adequate in scope, relevance and credibility. When they have informed the patient about the course of the procedure, the patient is more included in decision-making about his/her future care. This can help relieve the patient's stress level and he/she will be more focused on the meeting and less disturbed by distractions (40). Some nurses use interpreters, but others use family members, language applications and other aids. Samarasinghe et al. (2010) (41) described how the nurses in their study believed it was not appropriate for relatives of immigrant patients to interpret for them. Relatives may find it difficult to understand and communicate the information and the responsibility is too great for them. When the symptoms are not all visible, nurses may have difficulty making an assessment and this may affect the patient in overall terms. Since the informants had different solutions to the language problem, asylum seekers and immigrants have different circumstances in their communication. When the nurses do not use interpreters, patient safety may be at risk. Johnstone and Kanitsaki (2006) (42) state that patient safety guidelines should include precise information about cultural and linguistic aspects at the clinical meeting. If this information is missing, the link between the patient's culture, language and safety may be neglected. In our study, we also found that some patients request interpreters from the same language area but also interpreters of the same gender as the patient. This may cause additional problems when ordering interpreters and result in delays to their arrival. Hultsjö and Hjelm (2005), (36) found that it was increasingly difficult to book interpreters, especially if the patients had their own requirements regarding the character of the interpreter. The results of our study also showed that nurses understand and experience the brief meeting with immigrant patients as a challenge, although for the nurses in this study it did not cause any major difficulties. In general, the brief meeting with patients was problematic precisely for the reasons given above. We believe, however, that, in addition to the reasons given above, a fundamental reason why the Swedish health-care

system is threatened with collapse is that it is in the process of a major transition, where normal nurses are easily replaced by nurses from various private firms where money is most important and they are paid for the work they do by the minute. They often combine several working days in order to earn as much as possible and they spend as little time as possible with each patient. Nurses are hired routinely, paid and, the following day, they work somewhere else in a different part of Sweden. Do we ask ourselves where the patients feature in all this, regardless of their racial, religious or other affiliation? The same thing applies to the brief meeting with patients before surgery. The purpose of the meeting is to spend time together to get to know one another, to facilitate the nurse's job and for the patient to resolve any worries or problems (43). It has been shown that nurses are better prepared to deal with the patient on the day of the operation if they have met them before (44,45). The nurse hears about the patient's worries and is therefore able to create a feeling of confidence. They help the patients to deal with their hidden, internal pain that makes them afraid, feel alone and without hope (46). It is utopian in Swedish health care today to believe that, when anaesthetist nurses meet patients the day before surgery, they can resolve all their problems in a full and comprehensive conversation. This is not possible for many reasons. There is a shortage of health-care staff, the need for health care is greater than the number of people employed, cut-backs are taking place in many areas of society, including health care, and the number of procedures undertaken is now more important than the quality and care of patients. This has resulted in the fact that these meetings often take place in a corridor or the bathroom, or that they merely serve to check the patient's identity and ask whether he/she has allergies. We wonder where this will lead and how the patients feel in all the confusion.

In conclusion, nurses expect meetings with immigrant patients to be satisfactory, but they may lead to frustration and stress, since, according to the law, the nurses are expected to provide care for patients in a way that is impossible. Nurses need better guidelines and education in how to deal with the legislation relating to immigrant patients, in order to handle the situation more effectively.

The Migration Board and others should be involved in ensuring that immigrant patients are better informed as well. This would minimise the risk of misunderstandings and improve safety. Training in cross-cultural care should be improved, to help nurses deal with stress through co-operation with the Migration Board and others. In order to pro-

vide for good communication and patient safety, professional interpreters should be used.

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## The relationship between education and self-reported mental and physical health

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### ABSTRACT

**Aim** To investigate the relationship between educational level and self-reported physical and mental health in the population of Sarajevo Canton.

**Methods** This cross-sectional study was carried out in family medicine outpatient departments of the Primary Health Care Centre of Sarajevo Canton, Bosnia and Herzegovina. The study included 300 respondents who were divided into lower- and higher-education groups ( $\leq 12$  years and  $> 12$  years of education, respectively). The SF-36 questionnaire for self-assessment of mental and physical health and a questionnaire for the evaluation of socio-demographic characteristics were used.

**Results** The mean values for the mental component summary (MCS) were significantly lower in the lower education ( $56.86 \pm 23.02$ ) than in the higher education group ( $65.08 \pm 20.91$ ) ( $p=0.001$ ). The mean values for the physical component summary (PCS) were significantly lower in the lower education ( $61.77 \pm 21.60$ ) than in the higher education group ( $74.26 \pm 17.89$ ) ( $p=0.000$ ). On average, females had significantly lower scores than males on both the PCS ( $p=0.00$ ) and the MCS ( $p=0.00$ ). There was significant relationship of low education with self-reported poor mental ( $B=6.547$ ,  $SE=2.481$ ;  $p=0.009$ ) and physical health ( $B=10.870$ ,  $SE=2.248$ ;  $p=0.024$ ). Increased age was associated with poorer PCS and better MCS.

**Conclusion** Educational level is a strong determinant of perceived health. The importance of education should be emphasized to children as vitally important for their future health.

**Key words:** age, schools, female, male, quality of life

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## INTRODUCTION

Health status is an individual's relative level of wellness and illness, taking into account physical, biological and emotional functioning (1). Traditionally, health status has been assessed by physical examination and other objective procedures or tests (2).

Self-reported health status is a measure of how one perceives and reports one's own well-being (3). Self-perception of one's own health has become necessary to consider particular subjective aspects of health to attain a more comprehensive understanding of relevant health and disease processes (4). People's self-perceptions about their health are often more effective than clinical measures for predicting help-seeking behaviours and health service use, because people generally seek health care only when they feel unhealthy (5). Self-rated health has been measured in various ways using single questions or scales (6).

Factors that may contribute to differences in health and in perceived health status include education, age, sex, income psychosocial characteristics, housing and living environment (7).

Many studies show a positive correlation between education and health (8-11). It is usually accepted that more highly educated individuals are healthier and tend to enjoy prolonged life spans (12). Previous studies in less developed regions suggest that even with small amounts of formal schooling (2-3 years), differences in health outcomes arise in comparison to non-schooled individuals (13).

Educational level is a strong determinant of perceived health (14). Higher level of education was found to be associated with higher self-rating of health (15). One study across 22 European countries found that people with low education were more likely to report poor general health and functional limitations. According to the European Social Survey 2003 educational health inequalities are relatively small in Austria, Norway, Sweden, and the United Kingdom, large inequalities were found in Hungary, Poland, and Portugal (16).

The aim of this study was to investigate the relationship between educational level and self-reported physical and mental health in Sarajevo Canton population.

## EXAMINEES AND METHODS

### Study design

This cross-sectional study was carried out in family medicine outpatient departments of the Public Institution Primary Health Care Centre of Sarajevo Canton, Bosnia and Herzegovina (B&H) in the period March – July 2017.

The respondents were patients who used health care services at the Primary Health Care Centre during the course of the study period. The study included 300 respondents on the principle of systematic random sampling. The respondents were divided into lower- and higher-education groups ( $\leq 12$  years and  $> 12$  years of education, respectively).

The inclusion criteria were persons aged 18-65 years who have a medical record in the Primary Health Care Centre of the Sarajevo Canton. The exclusion criteria were persons younger than 18 or older than 65 years, persons who do not have medical records at the Primary Health Care Centre of the Sarajevo Canton and students.

The Ethics Committee of the School of Medicine, University of Sarajevo, approved the study. For this investigation, a written consent of the General Director of the Primary Health Care Centre of the Sarajevo Canton was obtained. An informed consent for participation in the study was taken from all respondents.

### Methods

The respondents were supposed to fill out a questionnaire that included questions about their socio-demographic characteristics and the SF-36 questionnaire (17). Socio-demographic characteristics were included: education, age, gender and self-perceived financial status.

Education was measured by the highest self-reported level of completed education.

Education level was categorized as incomplete elementary school, completed elementary school, completed secondary school, high school/college completed and university completed.

Lower-education group included incomplete or complete elementary and secondary school. Higher-education group included high school / college or university level.

Self-perceived financial status was categorized as a lot worse than average, slightly worse than average, average, slightly better than average and much better than average.

The SF-36 questionnaire was used to measure the self-reported physical health (physical component summary) and self-reported mental health (mental component summary) (17).

The SF-36 Health Survey includes one multi-item scale measuring each of the eight health concepts: physical functioning (10 items), physical role limitations (four items), bodily pain (two items), general health perceptions (five items), energy/vitality (four items), social functioning (two items), emotional role limitations (three items) and mental health (five items). Items and scales were constructed using the Likert method of summated ratings. Answers to each question were scored (some items need to be recoded). These scores were summed to produce raw scale scores for each health concept which were then transformed to a 0 – 100 scale. Higher scores indicate better health (18).

Scoring algorithms were then applied to produce the two summary scores: physical and mental component summary. The physical component summary score was derived from four health concepts: physical functioning, physical role limitations, bodily pain and general health perceptions. Mental component summary score was derived from four health concepts: energy/vitality, social functioning, emotional role limitations and mental health.

All scale questions refer to a four-week period (17).

### Statistical analysis

Testing of the difference in self-perceived financial status between the lower- and the higher-education groups was performed by  $\chi^2$  test.

Testing of the difference in self-reported physical and mental health between the lower- and the higher-education groups, males and females was performed by Kruskal-Wallis test. Linear regression analysis was used to assess the association of self-reported physical and mental health with age, gender, education and self-perceived financial status. Level of significance set at  $p < 0.05$ , and or the confidence level of 95%.

## RESULTS

The study evaluated 300 respondents in two groups of 150 (i. e. lower- and higher-education).

In the total sample, females were slightly more represented than males, 182 (60.7%) and 118 (39.3%), respectively. Mean age of males and females was  $34 \pm 10.34$  years and  $33 \pm 10.43$  years, respectively ( $p = 0.473$ ).

Higher education (more than secondary school) rate of males, 54.2% (64 out of 118) than females was noticed, 47.3% (86 out of 181) ( $p = 0.144$ ). Self-perceived financial status of females in the lower- and higher-education groups was significantly different ( $p = 0.001$ ). Twice as many females with the financial status which was slightly/ much better than average were in the higher education group, 43 (50%), than in the lower education group, 20 (20.9%). Self-perceived financial status of males in the lower- and higher-education groups was not significantly different ( $p = 0.435$ ) (Table 1).

**Table 1. Self-perceived financial status by gender and education level**

| Education level (No) | No (%) of respondents with self-perceived financial status |                             |           |                              |                          | p     |
|----------------------|--|-----------------------------|-----------|------------------------------|--------------------------|-------|
|                      | Lot worse than average                                     | Slightly worse than average | Average   | Slightly better than average | Much better than average |       |
|                      |  |                             |           |                              |                          |       |
| <b>Males (118)</b>   |  |                             |           |                              |                          |       |
| Lower (54)           | 0 (0)  | 4 (7.4)                     | 31 (57.4) | 16 (29.6)                    | 3 (5.6)                  | 0.435 |
| Higher (64)          | 0 (0)  | 6 (9.4)                     | 27 (42.2) | 26 (40.6)                    | 5 (7.8)                  |       |
| <b>Total</b>         | 0 (0)  | 10 (8.5)                    | 58 (49.1) | 42 (35.6)                    | 8 (6.8)                  |       |
| <b>Females (182)</b> |  |                             |           |                              |                          |       |
| Lower (96)           | 2 (2.1)  | 12 (12.5)                   | 62 (64.6) | 18 (18.8)                    | 2 (2.1)                  | 0.001 |
| Higher (86)          | 2 (2.3)  | 4 (4.7)                     | 37 (43.0) | 34 (39.5)                    | 9 (10.5)                 |       |
| <b>Total</b>         | 4 (2.2)  | 16 (8.8)                    | 99 (54.4) | 52 (28.6)                    | 11 (6.0)                 |       |

The mean values for the MCS scores were significantly lower in the lower education than in the higher education group,  $56.86 \pm 23.02$  and  $65.08 \pm 20.91$ , respectively ( $p = 0.001$ ). There was 8-point difference between lower and the higher education groups. Both females and males in the lower education group reported worse mental health than in the higher education group ( $p = 0.002$ , and  $p = 0.511$ , respectively) (Table 2).

The mean values for the PCS scores were significantly lower among the participants with lower education ( $61.77 \pm 21.60$ ) than among the participants in the higher education group ( $74.26 \pm 17.89$ ) ( $p = 0.000$ ). The 12-point difference between lower and the higher education group

**Table 2. Mean values for the mental component summary (MCS) score by gender and education group**

| Gender/education level (No) | Mean value for the MCS score (SD) | p     |
|-----------------------------|-----------------------------------|-------|
| <b>All (300)</b>            |                                   |       |
| Males (118)                 | 68.57 (18.01)                     | 0.000 |
| Females (182)               | 56.05 (23.51)                     |       |
| Lower education (150)       | 56.86 (23.02)                     | 0.001 |
| Higher education (150)      | 65.08 (20.91)                     |       |
| <b>Males (118)</b>          |                                   |       |
| Lower education (54)        | 67.38 (19.84)                     | 0.511 |
| Higher education (64)       | 69.58 (16.37)                     |       |
| <b>Females (182)</b>        |                                   |       |
| Lower education (96)        | 50.95 (22.65)                     | 0.002 |
| Higher education (86)       | 61.74 (23.26)                     |       |

SD, standard deviation

ps was found. Both females and males in lower education group reported worse physical health than in the higher education group ( $p=0.000$  and  $p=0.198$ , respectively) (Table 3).

**Table 3. Mean values for the physical component summary (PCS) score by gender and education group**

| Gender/education level (No) | Mean value for the PCS scores (SD) | p     |
|-----------------------------|------------------------------------|-------|
| <b>All (300)</b>            |                                    |       |
| Males (118)                 | 72.69 (17.57)                      | 0.000 |
| Females (182)               | 64.98 (22.12)                      |       |
| Lower education (150)       | 61.77 (21.60)                      | 0.000 |
| Higher education (150)      | 74.26 (17.89)                      |       |
| <b>Males (118)</b>          |                                    |       |
| Lower education (54)        | 70.41(18.01)                       | 0.198 |
| Higher education (64)       | 74.60 (17.11)                      |       |
| <b>Females (182)</b>        |                                    |       |
| Lower education (96)        | 56.91 (22.02)                      | 0.000 |
| Higher education (86)       | 74.01 (18.54)                      |       |

SD, standard deviation

There was significant relationship of low education with self-reported poor mental health ( $p=0.009$ ) as well as significant relationship of females ( $p=0.000$ ), younger age ( $p=0.024$ ) and slightly worse financial status than average ( $p=0.001$ ) with self-reported poor mental health.

There was significant relationship of low education with self-reported poor physical health ( $p=0.000$ ). There was also significant relationship of female gender ( $p=0.004$ ) and slightly worse financial status than average ( $p=0.000$ ) with self-reported poor physical health. An increase of age was associated with poorer PCS and better MCS (Table 4).

## DISCUSSION

This study explored the relationship between educational level and self-reported physical and mental health. The obtained results indicate that

**Table 4. Linear regression model for the physical and mental component summary**

|  | B       | SE     | 95%CI            | p     |
|--|---------|--------|------------------|-------|
| <b>Mental Component Summary</b>                |         |        |                  |       |
| Age  | 0.270   | 0.119  | 0.036-0.504      | 0.024 |
| Gender: female/male                            | -11.433 | 2.480  | -16.313- -6.552  | 0.000 |
| Education: higher/lower                        | 6.547   | 2.481  | 1.664-11.430     | 0.009 |
| Financial status: lot worse than average       | -13.520 | 10.623 | -34.428-7.389    | 0.204 |
| Financial status: slightly worse than average  | -15.545 | 4.420  | -24.244- -6.845  | 0.001 |
| Financial status: average                      | 0.685   | 2.586  | -4.405-5.774     | 0.791 |
| Financial status: slightly better than average | 0.992   | 2.777  | -4.474-6.458     | 0.721 |
| Financial status: much better than average     | -2.447  | 5.179  | -12.639-7.746    | 0.637 |
| <b>Physical Component Summary</b>              |         |        |                  |       |
| Age  | -0.204  | 0.108  | -0.417 - 0.008   | 0.059 |
| Gender: female/male                            | -6.462  | 2.247  | -10.884 - -2.041 | 0.004 |
| Education: higher/lower                        | 10.870  | 2.248  | 6.446 -15.293    | 0.000 |
| Financial status: lot worse than average       | -16.575 | 9.624  | -35.516 - 2.366  | 0.086 |
| Financial status: slightly worse than average  | -15.523 | 4.005  | -23.404 - -7.641 | 0.000 |
| Financial status: average                      | -1.445  | 2.403  | -6.175 - 3.285   | 0.548 |
| Financial status: slightly better than average | 3.151   | 2.516  | -1.801 - 8.102   | 0.211 |
| Financial status: much better than average     | 3.729   | 4.692  | -5.505 - 12.963  | 0.427 |

B, regression coefficient; SE, standard error; CI, confidence interval

low education was strongly associated with a low self-reported physical and mental health. We found that both male and female with low education had poorer self-reported physical and mental health. These findings are consistent with the literature on the association between education and health, and confirm that low education is a predictor of having low self-reported health (19,20).

More education seems to be associated with reporting better health (7). Those with less than a high school education in the United States are 2.4 times as likely as high school graduates and 4.1 times as likely as those with post-secondary education to rate their health as poor (21). The benefits of education on health may relate to the fact that higher educational attainment can increase the capacity for better decision making regarding one's health, and provide scope for increasing personal resources that are vital for physical and mental health (22). In addition, education is likely to be a determinant of other socioeconomic markers such as income (9). Higher education and income levels have been linked to better health in individuals (23). Recently, the European Community Household Panel reported that income inequality was negatively and consistently related to self-rated health status in the European Union member states in both men and women

(24). In this study, slightly worse financial status than average was significantly associated with poorer self-reported physical and mental health. These findings are similar to the results reported by Parna et al. who found that poor self-reported health is related to poorer self-rated financial situation (25).

This study also demonstrates a relationship of age with poor self-reported physical and mental health. Older age was linked with worse self-reported physical health. These findings are similar to the results reported in previous studies (26, 27). Ageing affected physical health directly and indirectly through increased levels of pathology (28). On the other hand, the results of the study conducted by Wang et al. have shown no relationship between age and self-reported physical health (29).

In this study, increased age was associated with better self-reported mental health, which is consistent with previously reported studies (30, 31). Whitehall II study found significant increases (i.e. improvements) with age in general mental health (32). Furthermore, ageing itself had a protective effect on mental health. Westerhof and Keyes found that older age was correlated with lower positive affect, less feeling of personal growth and purpose in life, less meaning in life and less social coherence and social contribution (33).

In this study, we observed significant relationship of female gender with self-reported poor physical and mental health. We found that, in general, females report poorer health than males.

On average, females had lower scores than males on both the PCS and the MCS. This finding is consistent with the findings of many previous studies. In almost all of them, women have reported

lower levels of self-reported health (34,35). The finding that, on average, females had lower scores than males on both the PCS and the MCS suggests that they may be particularly vulnerable (36). Other studies have found no gender differences in self-reported health in countries such as Finland, the United Kingdom and the United States (21,25,37). In contrast to the findings from previous studies, in France, males rated their health significantly poorer compared to women (38).

Therefore, findings of this study provide evidence on the socio-demographic determinants of self-reported health status. The future studies should extend research on the role of intermediate factors such as living standards, working conditions and health-related behaviours on self-reported health status.

In conclusion, our findings indicate that the low educated groups have a significantly lower self-reported health status. Education is an important mechanism for enhancing the health of individuals and a crucial factor for good perceived health. The health benefits of education have risen in the last years making education even more valuable in achieving better health.

The importance of education, at the very least, a high school education, should be emphasized to children as vitally important for their future health.

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## TRANSPARENCY DECLARATION

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## Ethnic differences in the perception of pain: a systematic review of qualitative and quantitative research

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### ABSTRACT

**Aim** To investigate existence of scientific support for linking differences in the experience of pain to ethnicity.

**Methods** The study was designed as a systematic literature review of qualitative and quantitative studies. The inclusion criteria were scientific studies published in scientific journals and written in English. Studies that described children's experiences and animals were excluded. There were 10 studies, one qualitative and nine quantitative.

**Results** The result was divided into two main sections. The first section presents the results of investigated material regarding different ethnic groups, the groups' different experiences with regard to pain and its treatment focusing entirely on the patients' perspective. Several studies have revealed major differences in the way individuals perceive their pain, using various pain evaluation tools. The second section explained different coping strategies depending on ethnicity and showed that different ethnic groups handle their pain in different ways.

**Conclusion** Healthcare professionals have a duty to pay attention to and understand the patients' experience of their disease and suffering and, as far as possible, mitigate this using appropriate measures. For this purpose, ethnic, cultural and religious differences between different patients need to be understood. It is necessary to continue to study ethnic differences in reporting and predicting pain and its consequences, including the assessment of variables associated with pain, as well as examining the use of prayer as a form of dealing with pain, with an evaluation of various effects of such different influences.

**Key words:** ethnicity, health care professionals, pain perception, pain treatment

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## INTRODUCTION

Ethnic differences in the perception, reporting, experience, discussion and impact of pain have attracted growing attention in recent years. Today in Sweden there is an increasing number of patients from all cultures with different needs. According to the Health Care Act (1), healthcare professionals must provide care on equal terms, and in order to do so, it is very important that healthcare professionals have knowledge of the differences between ethnicities. Health care should be provided with respect to the equal value of all people and the dignity of the individual. Patients with different nationalities, ethnicities, income, gender and age should be given the same care. As today's society becomes increasingly multicultural, it is necessary for healthcare professionals to understand their patients on the basis of the culture they bring with them, especially their values and lifestyle (1). In a previous study, the authors wrote that ethical principles, such as the autonomy principle, the principle of justice and the principle of doing good and not harm, are part of our mind-set. It is important that healthcare staff are aware of this principle in their work (2). Unfortunately, sometimes there is an ethical dilemma where two principles come up against one another and a compromise of some kind is necessary (2). Well-functioning pain treatment is considered of great importance when working with patients (2). There are different situations in practical care work suggesting that nurses make different assessments of pain expression depending on the patient's ethnic background (2). We therefore wanted to investigate whether there are really differences in the experience of pain in patients with different ethnicities. In their study, a group of researchers stated that pain is a complex symptom that occurs within all medical services (3). Pain is a subjective experience as the patient him/herself is able to evaluate it. Different pharmacological studies often neglect the cultural and psychosocial effects of pain such as group cohesion, financial status and the patient's confidence in the treatment (3). Often, healthcare professionals are too interested in physiological and clinical causes of pain and neglect to consider the psychological and cultural components (4). If healthcare professionals do not perceive the description of pain as credible, this increases the patient's loneliness, helplessness and suffering (4). Healthcare

professionals often rely on the patient's expression of pain beyond their own experience, which can make an open and outward reaction appear natural, while another healthcare professional might react completely differently (5). There are other studies from many countries about the way different groups report and experience acute pain, including postoperative pain (6), acute low back pain (7) and exercise-induced angina (8). Moreover, non-white ethnic groups report more pain than whites; African Americans demonstrated lower thermal pain tolerances than whites, that the stimuli are more unpleasant and showed a tendency to rate it as more intense than whites (8). In addition, African Americans had smaller slopes and larger intercepts than whites for ratings of pain unpleasantness (9,10). Women showed a tendency to rate the stimuli as more unpleasant and more intense than men (9,10). Systolic blood pressure was inversely related to pain intensity. After statistically adjusting for systolic blood pressure, gender differences in pain unpleasantness were reduced and gender differences in pain intensity were abolished; race differences were unaltered (9,10). There are also differences between ethnicities in their experience of the severity of chronic pain (11), for example, patients from Africa and the USA, together with Hispanic ethnic groups, claimed greater level of pain than patients with cancer (12), from spinal injury (13), vulvodinia (14), migraine (15), arthritis (16), non-specific chronic pain (17,18) and muscular and skeletal disorders (19-21). It has been suggested that differences in experiencing and communicating pain and distress may arise partially from ethnic differences (22,23).

The aim of this study was to investigate whether there is any scientific support for linking differences in the experience of pain to ethnicity.

## MATERIALS AND METHODS

### Study design and participants

The study was designed as a systematic literature review of qualitative and quantitative studies describing all kind of pain in different ethnic groups. The inclusion criteria were scientific studies published in scientific journals (including an abstract) and written in English, limiting to adult men and women aged from 35 to 65 years.

Exclusion criteria were the studies describing other socially defined groups (besides ethnicity). The studies describe that other socially defined groups, which we found interesting, were used as background and in support of our reasoning in the discussion and conclusions. Also, we excluded studies that described children's experiences and animals as well as studies of experimental pain.

## Methods

The search databases we used were PUBMED, CINAHL and Blackwell Synergy. In addition, books were searched for facts about different ethnicity, differences in the experience of pain to ethnicity, and the Internet was also used as a source of information. During the project planning work, a pilot search was made to see whether there were sufficient substrates to write an entire essay on the chosen topic. The search began with the words: pain, ethnicity, healthcare professionals and perception.

After the articles had been subjected to an initial review, 26 remained. To select the top 10 answers to our questions, the problem was defined using a further exclusion criterion. Since the word "race" is primarily used in American articles, we first thought about excluding these, but, after careful consideration we came to the conclusion that the concept of race in America is sometimes used as a synonym for the concept of ethnic group. Despite the reduction, 13 articles remained and they were checked for quality. We found that two of them were of poor quality. One was rejected after the entire article had been read, when, upon closer examination, we found that it did not answer the questions we had. All authors reviewed the articles individually before they were combined into a common assessment (gradation). The gradation of articles was made depending on how much information we received from each article and how much data was available in each article. The gradation of studies was inversely proportional to the data quantity (key words) in the studies. Depending on the number of key words in the studies, the selected studies were graded as I, II or III: studies with the highest number of key words were graded as grade I, studies with the smallest number of key words as grade III.

Of the ten articles examined, one was qualitative and nine quantitative. The ten were graded and,

when the quality assessment was made, it was found that four were grade I, five grade II and one article was grade III. To make the results more transparent, we chose to divide them into different parts according to content and we undertook so-called thematization (24). In addition, for convenience, we divided the results into two main sections, each representing one issue.

## RESULTS

The first section presents the results of the investigated material regarding different ethnic groups, the groups' different experiences with regard to pain and its treatment focusing entirely on the patient's perspective.

In the second section different coping strategies depending on ethnicity showing how different ethnic groups handle their pain were explained.

### Estimating pain from an ethnic perspective

Several studies have revealed major differences in the way individuals perceive their pain using various pain evaluation tools.

One study has shown that Asians indicate greater pain in relation to African Americans, white Americans and Latin Americans (25). Another study reported that African Americans indicate higher levels of pain than white Americans (26). The same result was found in another study, but there the comparison was with non-African Americans (27). In contrast, other studies have not been able to show any differences in the evaluation of pain (28). Other studies have investigated whether there are differences when the experience of pain is divided into pain intensity and pain relief. They showed that pain intensity does not vary depending on ethnicity, while painfulness varies. It has been shown that the pain rate is greater for African Americans compared with white Americans (29,30).

### Different coping strategies depending on ethnicity

Different ethnic groups handle their pain in different ways. African Americans show a greater tendency to handle their pain with the help of prayers and hope. There was a general tendency among those who participated in the investigation to amplify their pain and African Americans were more likely to do this. These results are in contrast to white Americans (29). The same result

emerged from a study which also reported similar results for Latin Americans (28). In a survey comparing Asians, white Americans, Latin Americans and African Americans, the Asians showed the lowest belief that pain is controllable (25). Another study showed that Indians were found to believe that pain is something that is part of life and therefore not controllable. They often express the will to die because of unbearable pain. Death is nothing to be afraid of as it is a natural part of life (31). One study found that expressions of feelings in relation to pain differ between African Americans and white Americans. African Americans have a stronger connection between their feelings and their pain, feelings such as depression, anger, anxiety and fear. The frustration in a painful situation, on the other hand, was equally strong in both the groups (30). A study also indicated that African Americans showed a greater need for attention for their painful situation from the people around them (29).

#### **Pain associated with wellbeing**

It has been shown that Latin American pain patients exhibit higher levels of wellbeing, the greater the pain is (25). Another study indicated that Afro-Americans, white Americans and Asians, on the other hand, report less wellbeing, the more pain they experience. Indians find proximity to their relatives more important than the treatment, in this case for cancer pain, while Americans see safety in finding the right doctor and the right treatment. The results in the study showed that there was a major difference in the way different groups in society, including people of minority origin, were treated for their pain (31). It was also found that both open and subconscious prejudices existed in the staff in relation to how they treated pain in their patients (27,28,30). In a study conducted in the United States, a comparison was made of different experiences of cancer pain amongst the largest ethnic groups through specific online forums. By allowing patients to discuss their pain with one another in the forum, researchers could see how different groups experienced their pain. What also emerged was that nurses need to be more vigilant in relation to the cultural differences in pain and not treat everyone equally. According to the study, increased attention to differences in pain experience and pain management in different cultures

would give nurses a better opportunity to treat all patients well (29). In the study examining attitudes and problems experienced by Italian nurses in the care of patients with different ethnic and cultural backgrounds it was found that 44.9% of participants had the perception of having a different attitude towards foreign families and their children compared with those who did not have a different ethnic background. Nurses felt that there could be communication difficulties, due to language mediation, and that there were cultural differences that complicated the relationship between the nurse and the patient. They perceived that parents had a more tolerant attitude towards their children's pain (17). In contrast, a study examined whether waiting time and the ethnic background of the patients influenced the assessment of pain management on emergency admission showed major differences, despite equal pain, in how long patients had to wait for pain treatment, depending on their ethnicity; on average, additional 35 minutes passed before Hispanic patients received treatment compared with European-Americans, in terms of both analgesic and opioid treatment. It was also found that men with Hispanic background had to wait much longer for their pain to be documented in patient records (9).

#### **DISCUSSION**

As ethnicity and pain are investigated as a phenomenon, a conscious or unconscious theory arises that ethnicity is linked to the way pain is perceived and described (32). The complexity of medical science can be seen from the perspective of one researcher that pain linked to ethnicity is an idea that is influenced and shaped by doctors, nurses, patients, relatives and research institutions. Other things that affect this idea are the material infrastructure, hospitals, universities, healthcare uniforms and credentials (32). Another study shows that, if pain is interpreted as a social construction, this is reflected in the expression of pain and its management. It has been found that pain is a social and cultural phenomenon. Among other things, people who come from Somalia, especially the men, are relatively untouched by pain. Patients' methods of dealing with their pain differ according to their ethnicity (33). A study of Latin Americans showed that they experience greater wellbeing with greater pain (25). Some

researchers consider that greater wellbeing may be a strange result and believe it is the result of the fact that showing a positive external attitude attracts more attention and therefore results in better care (25). Latin Americans also expressed the greatest satisfaction with their care in the same study, which possibly confirms our assumption (25,31). Asians showed the greatest level of acceptance of their pain, because their beliefs include pain as a common occurrence and something one cannot control. This socially constructed perception could explain why they see pain as uncontrollable in comparison with other ethnicities (25,31).

Those difficulties may also be seen from a social perspective. As Asians live in the part of the world that is relatively medically underdeveloped, where the healthcare system is less established, their perception of pain management is more old-fashioned (25,31,32). They do not have the same need to take a tablet as soon as they feel a headache, as it happens in Sweden and in the western world today. How wellbeing can manifest itself in a painful situation may be perhaps the result of how different ethnic groups use different ways to achieve quality of life and wellbeing. This is important to consider in this situation, since it may mean a great deal for the patient's pain relief. Reportedly, Indians and Americans prioritise different treatments. Despite suffering the same pain, in case of cancer pain, Indians experience greater wellbeing as they may be with their family. Americans would rather devote their time to thinking about their treatment and the choice of doctors. This may be linked to their respective ethnic background and social structure. Indians are mostly Hindus and they think pain is a part of life. Their pain is associated with past life events and is therefore ineffectual. Living through pain is a way for Hindu people to handle their situation. Americans are mostly Christians and their perception of pain is that pain and suffering are a legacy from the death of Jesus on the cross. Many Christians regard pain as a punishment from God, which aggravates their suffering (31).

In the present study, we believe that this may be an expression of why they are more likely to seek relief for their pain. In Sweden, healthcare professionals usually have the initial responsibility for assessing their patients' pain. It is a

nurse who first assesses the patients' pain. Nurse are primary contact with the patients and healthcare professionals who detect changes in pain symptoms. Healthcare professionals must therefore have great responsibility for understanding cultural differences. All studies used in the present study have American background. This has probably contributed to our results and this might be a limitation of the present study. Some things, such as religion and certain values, are common to certain ethnic groups, but even if these are overlooked, people are always shaped to a certain extent by their social environment. To reinforce this, we relate the example of soldiers (34), where individuals, regardless of their previous background, are conditioned to react in a similar way to pain. If there is no interpretation of previous experience, each situation is similar to other comparable situations, or to what other people think is right, which leads us to imagine how things should be (28). There is therefore a risk that, due to their lack of cultural understanding, healthcare professionals are unaware or uncertain about those patients who do not belong to their own social group. Their lack of knowledge about other cultures may possibly explain why they differentiate between different ethnicities. This is further reinforced by the fact that, in a study by Staton et al. (27), in general conditions they more frequently misjudge the pain of their patients than those with more experience.

The same reasoning can be used to explain why they prefer to give opioid preparations to patients from their own ethnic group, when the cause of the pain cannot be directly linked to visual findings such as fractures (35). There may be several reasons why pain treatment is not discussed to the same extent with all ethnicities (27). Even in this case, inexperience and social construction may be the basis. It is a known problem that different ethnicities in Sweden and throughout the world experience and report pain in various ways. This then poses another problem.

The genesis, how we should report and how those with experience and those of us who work in the field of care should help patients who were born abroad with pain problems on a variety of occasions. Healthcare professionals may be unsure about the way people express pain within their specific ethnic group, or they do not know how the patient

is going to react. Another reason that can also be mentioned is the linguistic barrier on both sides. Healthcare professionals may mistakenly assume that the patient does not understand. At the same time, healthcare professionals may have discussed the issue with the patient, but they do not actually have the linguistic knowledge necessary to perceive their true feelings. Everyone in the Swedish healthcare system should treat all patients from the same point of view and not make any differences based on their own prejudices and values. The more people become aware that there are differences in the way patients are treated because of ethnicity, the greater the opportunity to change this. In order to raise awareness, more knowledge is necessary and nurses need to be more aware of their own values and possible prejudices and those of others, which subconsciously and even consciously affect their professional work. In this context, it can be seen just how important it is that this issue is dealt with and examined more closely during the education of nurses in order to lay a good foundation for their future practice. In this profession, it is important to respond to every human being as an individual and see the person as a whole creating an environment and a relationship with the patient that enables him or her to feel confident and make assessments on the right basis.

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In conclusion, healthcare professionals have a duty to pay attention to and understand the patients' experience of their disease and suffering and, as far as possible, mitigate this using appropriate measures. For this purpose, we need to understand the ethnic, cultural and religious differences between different patients. Through our literature review study, we have aimed to help healthcare professionals provide better, more personal care. Since the majority of the studies we found are from the United States, further research is of the utmost importance in order to improve research in Sweden and Europe. The world, including Sweden, is becoming more and more multicultural. It is necessary to continue to study ethnic differences in reporting and predicting pain and its consequences, including the assessment of variables associated with pain as well as examining the use of prayer as a form of dealing with pain, with an evaluation of the various effects of these different influences.

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## Prescription pattern among Iranian community dwelling older adults

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### ABSTRACT

**Aim** To assess prescription pattern among Iranian community-dwelling older adults.

**Methods** This cross-sectional study employed a cluster random sampling to obtain a sample of 1591 patients aged 60 years and over referred to pharmacies in Tehran, 2017. Data were collected using a questionnaire: socio-demographic characteristics, type of pharmacy visited, the municipal district, the university covering the pharmacy, the number and names of prescribed drugs, drug category, type of insurances and physician's socio-demographic profile (age, gender, type of specialization, and work experience).

**Results** The mean age of the patients was 70.51±7.84. A total of 5838 drugs were prescribed, giving an average of 3.73±2.24 drugs per patient (ranging of 1-15). Polypharmacy was noticed in 32.4% patients. Cardiovascular drugs accounted for 20.8% of the prescriptions, antidiabetics 8.8%, nutritional agents and vitamins 7.6%, and analgesics, anti-inflammatory drugs and antipyretics accounted for 7.5%.

**Conclusion** Developing educational programs on geriatric pharmacology general practitioners and more supervision among community-dwelling older adults might have effects on prescription pattern. There is a need for prescriber training and retraining with emphasis on the geriatric population.

**Key words:** aged, general practitioners, medical specialists, prescription pattern

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## INTRODUCTION

The elderly population is growing in our society (1). According to UN Population Division estimates, the proportion of the world's elderly population will increase from 10.5% in 2007 to 21.8% in 2050 (2). Results of the latest census of Iran in 2016 indicate that the elderly population of the country is equivalent to 7,141.91 (3). Drug use in the elderly is fraught with many problems because of the following factors: the physiologic changes of aging and potential drug-drug and drug-disease interactions (4). Polypharmacy and the inappropriate use of medicines in the elderly have been identified as major types of non-rational prescribing in the elderly leading to higher prevalence of adverse drug reactions among them (5-7). These factors have also been shown to be responsible for a disproportionately high rate of adverse drug reactions among elderly patients and its associated increased healthcare costs (8). Provision of financial resources and producing pharmaceuticals are our main priorities in the healthcare plan, but the problem of providing medication will always trouble patients due to problems in prescribing and consuming medication (9). Elderly people are prescribed four times more drugs than other age groups. (10).

There are few studies on the prescription patterns, their costs and loads in Iran (2). This study aimed to determine the patterns of medication prescription in the elderly patients (60 years and above) referred to pharmacies, to recognize the problems and deficiencies, and recommend strategies to train physicians and raise public awareness to modify medication consumption patterns so that a positive step is taken towards better provision of medication needs for this age group.

The results of this study can reveal the patterns of medication prescription in pharmacies of Tehran, which is one of the most important information sources regarding medication prescription for the elderly and its possible deficiencies. It can also draw attention of the authorities to a more efficient training of physicians regarding pharmacology of the elderly and establishing an appropriate relationship with and transfer information to them.

## METHODS

### Study design and population

This cross-sectional study was conducted to assess prescription pattern and their related factors on elderly patients referred to pharmacies in Tehran in 2017.

The study was approved by the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran. The purpose of the study was elucidated and verbal consent was obtained before the participants were interviewed, respecting their autonomy and anonymity.†

### Methods

The questionnaire was used as a source for identifying for prescription pattern. Drug list was first matched with medications available in the Iranian Pharmacopoeia (11), which is updated through the Food and Drug Prescription website of the Ministry of Health (12) every six months. The medications that were unavailable at the Iranian Pharmacopoeia were removed from the list.

The questionnaire was then prepared containing questions on the socio-demographic characteristics of the elderly, the type of pharmacy visited, the municipal district, the university covering the pharmacy, the number of prescribed drugs, the names of drugs and drug category, type of insurances and physician's socio-demographic profile (age, gender, type of specialization, and work experience).

Attempts were made in this study to collect and investigate the prescriptions of individuals aged 60 and above who were referred to the pharmacies of the city of Tehran using random cluster sampling. To do so, the name of all pharmacies covered by Tehran University of Medical Sciences was first listed and each pharmacy was considered as a cluster, then the samples were selected using multistage proportional random sampling. Out of 2169 pharmacies covered by the University of Medical Sciences, 84 were selected randomly. Trained pharmacists and pharmaceutical technicians interviewed 1591 elderly patients aged over 60 years who were referred to pharmacies with prescriptions in their hands after obtaining their consent and then completed the questionnaire.

## Statistical analysis

The study used mainly descriptive analysis. For comparison purposes, ANOVA and t-test were applied for categorical and continuous dependent variables of interest, respectively. A  $p < 0.05$  was considered statistically significant.

## RESULTS

A total of 1591 elderly patients were analysed. The mean  $\pm$ SD of the elderly's age was  $70.51 \pm 8.74$  years. The age groups of 60-74, 75-84 and older than 85 years-old made 72.7%, 21.4 % and 5.9%, respectively. Female and male participants made up 54.1% and 45.9% of the total subjects, respectively. The majority of the elderly had lower education than a primary degree, 36.6%. In addition, a total of 1214 (76.3%) of the elderly were married.

A total of 1568 (98.6%) and 23 (1.4%) of the elderly were insured, and not by the Social Security Organization. The mean  $\pm$  SD of physicians' age and their average work experience was  $53.25 \pm 11.01$  and  $25.5 \pm 10.5$  years, respectively. There was a total of 415 (26.1%) female and 1176 (73.9%) male physicians. Of the total number of physicians, 402 (25.3%) were general practitioners and 1189 (74.7%) were specialists (Table 1).

**Table 1. Demographic characteristic of patients**

| Variables             | Category            | No (%) of patients |          |            |     | Mean  | SD    |
|-----------------------|---------------------|--------------------|----------|------------|-----|-------|-------|
|                       |                     | Females            | Males    | Total      |     |       |       |
| Age (years)           |                     |                    |          |            |     | 70.51 | 7.84  |
| Age group             | 60-74               | 653 (57)           | 503 (44) | 1156 (73)  |     |       |       |
|                       | 75-84               | 163 (48)           | 178 (52) | 341 (21)   |     |       |       |
|                       | +85                 | 45 (48)            | 49 (52)  | 94 (5.9)   |     |       |       |
| Gender                |                     | 861 (54)           | 730 (46) | 1591 (100) |     |       |       |
| Level of education    | No formal education | 317                | 79       | 86         | 21  | 403   | 25    |
|                       | Primary             | 327                | 56       | 256        | 46  | 583   | 37    |
|                       | Secondary           | 155                | 36       | 272        | 64  | 427   | 27    |
|                       | Tertiary education  | 62                 | 35       | 116        | 65  | 178   | 11    |
| Marital status        | Married             | 558                | 46       | 656        | 54  | 1214  | 76    |
|                       | Single              | 20                 | 51       | 19         | 49  | 39    | 2.4   |
|                       | Divorced            | 11                 | 78       | 3          | 22  | 14    | 0.9   |
| Medical Insurance     | Widow               | 272                | 84       | 52         | 16  | 324   | 20    |
|                       | Yes                 | 848                | 99       | 721        | 99  | 1569  | 99    |
| The age of the doctor | No                  | 13                 | 1.5      | 9          | 1.2 | 22    | 1.4   |
|                       | --                  | --                 | --       | -          | --  |       |       |
| Number of doctors     | -                   | 415                | 26       | 1176       | 74  |       |       |
| Work experience       |                     |                    |          |            |     | 25.50 | 10.50 |
| Specialist physician  | General             | 415                | 26       | 1176       | 74  | 402   | 25    |
|                       | Expert              |                    |          |            |     | 1189  | 75    |

The mean number of prescribed medication was  $3.73 \pm 2.24$  32.4% used more than 5 medications, ranging from 1 to 15 (Table 2).

**Table 2. Number of drugs per prescription**

| Number of drugs per prescription | Frequency | Percentage | Mean | SD   |
|----------------------------------|-----------|------------|------|------|
| 1                                | 277       | 17.4       |      |      |
| 2                                | 265       | 16.7       |      |      |
| 3                                | 282       | 17.7       |      |      |
| 4                                | 251       | 15.8       |      |      |
| 5                                | 198       | 12.4       |      |      |
| 6                                | 136       | 8.5        |      |      |
| 7                                | 87        | 5.5        |      |      |
| 8                                | 44        | 2.8        | 3.73 | 2.24 |
| 9                                | 30        | 1.9        |      |      |
| 10                               | 11        | 0.7        |      |      |
| 11                               | 4         | 0.3        |      |      |
| 14                               | 2         | 0.1        |      |      |
| 15                               | 4         | 0.3        |      |      |
| Total                            | 1591      | 100        |      |      |

Cardiovascular drugs accounted for 20.8 % of the prescriptions, antidiabetics 8.8%, nutritional agents and vitamins 7.6%, and analgesics, anti-inflammatory drugs and antipyretics 7.5% (Table 3). The most commonly used medications were insulin, 0.4%, atorvastatin, 2.5%, and aspirin, 2.4%.

**Table 3. Frequency distribution of medication groups in the sample**

| Medication group                                    | Frequency (%) |
|---|---------------|
| Cardiovascular drugs                                | 1562 (20.8)   |
| Antidiabetics                                       | 664 (8.8)     |
| Nutritional agents and vitamins                     | 574 (7.6)     |
| Analgesics anti-inflammatory drugs and antipyretics | 560 (7.5)     |
| Gastrointestinal drugs                              | 394 (5.2)     |
| Antibacterial                                       | 323 (4.3)     |
| Bronchodilators and anti-asthma drugs               | 211(2.8)      |
| Anxiolytic sedatives hypnotics and antipsychotics   | 194 (2.6)     |
| Antiepileptics                                      | 159(2.1)      |
| Antidepressants                                     | 149 (2.0)     |
| Urological drugs                                    | 133 (1.8)     |
| Others  | 915 (36.3)    |
| Total   | 5838 (100)    |

T-test showed that there was a meaningful relationship between having a chronic disease and polypharmacy with the number of prescription drugs ( $p < 0.001$ ).

More frequently drugs were prescribed for people who were insured than others who are not insured. The mean number of prescribed medication was  $3.68 \pm 2.21$  in males and  $3.77 \pm 2.26$  in females with no statistical significance ( $p = 0.411$ ).

Prescribing medication among female doctors was  $3.77 \pm 2.35$  and among male doctors  $3.72 \pm 2.19$  with no significant difference ( $p = 0.664$ ). In addition,

tion, the number of prescribed drugs among general practitioners was significantly higher than that of specialist doctors ( $p=0.021$ ) (Table 4).

**Table 4. The relationship between demographic characteristics of the sample and prescribed number by T- test**

| Variables            | Category | Mean | SD   | t       | df       | p      |
|----------------------|----------|------|------|---------|----------|--------|
| Chronic disease      | Yes      | 3.89 | 2.29 | -6.05   | 605.602  | <0.001 |
|                      | No       | 3.14 | 1.92 |         |          |        |
| Polypharmacy         | Yes      | 6.35 | 1.64 | -48.565 | 747.610  | <0.001 |
|                      | No       | 2.47 | 1.11 |         |          |        |
| Insurance            | Yes      | 3.74 | 2.23 | 1.770   | 21.55    | 0.091  |
|                      | No       | 2.86 | 2.31 |         |          |        |
| Patients' gender     | Female   | 3.77 | 2.26 | 0.824   | 1557.389 | 0.411  |
|                      | Male     | 3.68 | 2.21 |         |          |        |
| Physicians' gender   | Female   | 3.77 | 2.35 | 0.435   | 683.433  | 0.664  |
|                      | Male     | 3.72 | 2.19 |         |          |        |
| Specialist physician | General  | 3.94 | 2.08 | 2.306   | 755.777  | 0.021  |
|                      | Expert   | 3.66 | 2.28 |         |          |        |

SD, standard deviation, t, T- test; df, degrees of freedom

Mean number of prescribed medication in different age groups was  $3.64 \pm 2.19$  for 60-74 year-old group,  $3.93 \pm 2.23$  for 75-84 and  $4.17 \pm 2.64$  for more than 85 years-old group ( $p=0.015$ ).

Mean number of prescribed medication in different education levels was  $4.02 \pm 2.37$  for respondents with no formal education,  $3.60 \pm 2.09$  for primary education,  $3.62 \pm 2.28$  for secondary (diploma) and  $3.78 \pm 2.22$  for tertiary level ( $p=0.018$ ) (Table 5).

**Table 5. The relationship between demographic characteristics of the sample and prescribed N by ANOVA Test**

| Variables         | Category              | Mean | SD    | F/W  | p     |
|-------------------|-----------------------|------|-------|------|-------|
| Education         | No formal Education   | 4.02 | 2.370 | 3.00 | 0.018 |
|                   | Primary               | 3.60 | 2.099 |      |       |
|                   | Secondary (diploma)   | 3.62 | 2.287 |      |       |
|                   | Tertiary (university) | 3.78 | 2.221 |      |       |
| Age group (years) | 60-74                 | 3.64 | 2.198 | 4.19 | 0.015 |
|                   | 75-84                 | 3.93 | 2.236 |      |       |
|                   | +85                   | 4.17 | 2.646 |      |       |

SD, standard deviation; F/W, F ratio/Welch's F

## DISCUSSION

With the improvement of health care and control of diseases, life expectancy has increased and the elderly population is on the rise. This increase accompanied with complications of several chronic diseases and increased medication consumption per capita, which consumes a major part of Iran's healthcare resources.

The average number of drugs prescribed in this study ( $3.73 \pm 2.24$ ) is in the same range as results from other general prescription studies done in

Iran, India, and Nigeria (8, 13-15). Studies carried out among geriatric patients in Turkey, USA, India, Brazil, and Poland found an average of 2.9, 8.1, 4.3, 3.2, and 6.6 drugs per prescription, respectively (16-20).

The preponderance of female patients (54.1%) in this study is similar to the results from similar studies in the USA and Europe (16, 17).

High prevalence of antidiabetics in this study could be due to the high prevalence of diabetes in Iran. Elderly people are referred to physicians more than other age groups due to pain associated with connective tissue and joint problems and they receive analgesics. In most studies, cardiovascular, central nervous system (CNS) and analgesic medications are most common (21-23).

A study from Saboor (2014) showed that CNS medications were the most prevalent (68.2%), followed by vitamins and minerals (66.5%), and cardiovascular (64.7%) (9). Several studies from Malaysia, Denmark and Sweden reported cardiovascular, CNS and neuromuscular medications as most common, respectively (10, 24-26).

In a study by Shah et al. multivitamins and analgesics constituted 10.8% and 9.7% of prescriptions, respectively (27), which is higher than in our study. The study by No Kohan Ahvazi et al. showed that cardiovascular and antibacterial medications are the most commonly prescribed (28).

Although this study showed that the prevalence of drugs prescribed in the individuals with health insurance was higher than those without it, it was not statistically significant. The results of a study in Mexico showed that having Medicare insurance increases the odds of having potentially inappropriate medications (PIMs) differences (29).

This study showed that the number of prescribed drugs is significantly related to at least having one chronic disease, which is similar with results reported in other studies (22, 29-31). Our study showed that the number of drug prescriptions was significantly more common among general practitioners. This can be attributed to the fact that the elderly refer to general practitioners more frequently due to their financial problems and often suffer from various diseases for which the physician has to prescribe many medications.

In conclusion, the results of this study indicate that although the average of prescribed drugs is similar

to those of other countries where similar research has been carried out, it does not diminish the importance of the fact that the high levels of drug use by the elderly could cause many problems in the system. The frequency of prescribing anti-diabetes medication compared with the results of other studies needs to be further investigated. Also, modifying and reviewing the content of pharmacy education in the elderly's healthcare programs may be a good way to reduce the number of prescriptive drugs prescribed by doctors. Increasing the monitoring of how medication is administered by health insurance organizations and the Ministry of Health as a community health custodian can be

a positive step to optimize the administration of the drug in the elderly population.

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## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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## Prevalence and associated factors of potentially inappropriate medications among Iranian older adults

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### ABSTRACT

**Aim** Potentially inappropriate medications (PIMs) in older people are associated with the increased use of health care services. The aim of this study was to investigate the prevalence of PIMs among the elderly being referred to pharmacies in Tehran using the Beers criteria of 2012, and identify factors related to PIMs.

**Methods** This cross-sectional study was conducted on elderly patients (60 years and above) referred to pharmacies in Tehran, in 2017. The Beers' criteria 2012 were used to evaluate PIMs. The logistic regression analysis was used to find sociodemographic predictors of PIMs.

**Results** The mean age of 1591 patients was 70.51 years. The overall prevalence of PIMs was 26.0%. The most frequent PIMs, in order of frequency, included diclofenac (13.5%), <sup>†</sup>alprazolam (9.3%), and chlorthalidone (9.1%) and clonazepam (8.4%). The pain medications were found to be most common PIMs (37.6%). Polypharmacy<sup>‡</sup> (OR=3.64, CI 95%: .81-4.70; p<0.001), number of chronic diseases<sup>§</sup> (OR=2.371, CI 95%: 1.71-3.28; p<0.001) <sup>†</sup>insomnia (OR=1.45, CI 95%: 1.13-1.87; p<0.01) <sup>‡</sup>and type of specialists were found as PIMs risk factors. Internal medicine specialists prescribed PIMs significantly fewer times than other specialists<sup>§</sup> (OR=0.59, CI 95%: 0.40-0.88; p<0.01) <sup>‡</sup>and the orthopedic specialists prescribed PIMs significantly more times than other physicians<sup>§</sup> (OR=3.23, CI 95%: 1.76-5.81; p<0.001) <sup>‡</sup>.

**Conclusion** High prevalence of PIMs among Iranian elderly patients implies a need for the development and operationalization of scientific guidelines for the use of medicines. It is also necessary to hold training courses for physicians to be educated in such cases.

**Keywords:** Beers criteria, elderly, potentially inappropriate medication, potentially inappropriate prescribing

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## INTRODUCTION

The world's population is rapidly aging. According to the UN Population Division estimates, the proportion of the world's elderly population will increase from 10.5% in 2007 to 21.8% in 2050 (1). Results of the latest census of Iran in 2016 indicate that the elderly accounts for 9.2% of the population of the country equivalent to 7,141.91 (2). The phenomenon of increasing population of the elderly in the world including Iran is important in terms of its consequences on different social and economic aspects, including resources of the health sector, and requires a thorough scientific study (2).

The elderly are the largest consumers of healthcare resources in most industrialized and developing countries (3). The extent of drug use has increased in recent populations, especially in the elderly in recent decades. Although the elderly population accounts for a small proportion of the world's population, approximately 40% of prescriptions are related to them in many parts of the world (4). Inappropriate drug prescription is a serious and universal problem in the health care of elderly people as it can increase the risk of adverse drug reactions. Inappropriate drugs refer to drugs in which the risk of an adverse event outweighs its clinical benefit when there is a safer or more effective alternate therapy for the same condition. The use of inappropriate drugs can lead to adverse drug reactions (5).

Inappropriate prescription in the elderly population, considering its direct relationship with high morbidity, mortality and waste of health resources caused by adverse drug reactions, is now considered as a major public health problem (6). Inappropriate drug prescription has become a major health issue in recent years, and numerous tools have been developed to evaluate it (7).

The American Geriatrics Society (AGS) uses the Beers' list to evaluate potentially inappropriate medications (PIMs). The list includes a number of potentially inappropriate medications that should either be avoided in the elderly or used with caution at a low dose with certain diseases or syndromes (8,9). The AGS widely uses the Beers' criteria in the field of clinical geriatric medicine, education and research, and for promoting the quality of indicators. The responsibility

of this society is to continually update the Beers' criteria. The criteria were re-evaluated and updated in 2003, 2012, and 2015 (10,11).

The aim of the present study was to assess the prevalence of PIMs and its related factors in a sample of Iranian elderly people.

## METHODS

### Study design and population

This cross-sectional study was conducted to investigate PIMs and their related factors on elderly patients referred to pharmacies in Tehran in 2017. Attempts were made in this study to collect and investigate the prescriptions of individuals aged 60 and above who were referred to the pharmacies of the city of Tehran using random cluster sampling. To do so, the name of all pharmacies covered by Tehran University of Medical Sciences was first listed and each pharmacy was considered as a cluster, then the samples were selected using multi-stage proportional random sampling. Out of 2169 pharmacies covered by the University of Medical Sciences, 84 were selected randomly. Trained pharmacists and pharmaceutical technicians interviewed 1591 elderly patients aged over 60 years who were referred to pharmacies with prescriptions in their hands after obtaining their consent and then completed the questionnaire.

The study was approved by the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran. The purpose of the study was elucidated and verbal consent was obtained before the participants were interviewed, respecting their autonomy and anonymity.

### Methods

The 2012 Beers Criteria were used as a source for identifying PIMs for the preparation of the questionnaire (11). According to these criteria, drugs that are identified as potentially inappropriate in the elderly are divided into three categories: 1) drugs that the elderly should avoid, 2) drugs that should be avoided by elderly people with certain diseases and syndromes because these drugs can exacerbate certain diseases and infections, 3) drugs that should be used with caution in elderly people (11).

Therefore, this list was first matched with medications available in the Iranian Pharmacopoeia (12), which is updated through the Food and

Drug Prescription website of the Ministry of Health (12) every six months. The medications that were unavailable at the Iranian Pharmacopoeia were removed from the list.

The questionnaire contained questions on the socio-demographic characteristics of the elderly, the type of pharmacy visited, the municipal district, the university covering the pharmacy, the diseases and syndromes mentioned in the Beers list in the Beers' tool including heart failure, syncope, epilepsy, Parkinson's disease, delirium, dementia, fall, stomach disorders, chronic constipation, insomnia, urinary incontinence, prostate hypertrophy as well as the number of prescribed drugs, the names of drugs and drug category, inappropriately prescribed drugs and their drug groups according to the Beers' classification table, and type of insurances and physician's socio-demographic profile (age, gender, type of specialization, and work experience).

## RESULTS

The mean  $\pm$ SD of the elderly's age among 1591 involved in the study was  $70.51 \pm 8.74$  years. The elderly aged 60-70 accounted for majority of the studied population, 72.7%. The female and male participants made up 54.1% and 45.9% of the total subjects, respectively. The majority of the elderly had less than a primary degree (36.6%). In addition, a total of 1214 (76.3%) of the elderly were married. Also, a total of 1568 (98.6%) and 23 (1.4%) of the elderly were insured and not by the Social Security Organization.

The mean  $\pm$  SD of physicians' age and their average work experience was  $53.25 \pm 11.01$  and

$25.5 \pm 10.5$  years, respectively. There was a total of 415 (26.1%) female and 1176 (73.9%) male physicians. Of the total number of physicians, 402 (25.3%) were general practitioners and 1189 (74.7%) were specialists.

The prevalence of PIMs among the elderly referred to the pharmacies of Tehran was estimated to be 26% (412 out of 1591). Among 412 PIMs, one PIM was noticed in 316 (19.9%), two PIMs in 81 (5%), three in 14 (0.9%), and four PIMs in one (0.1%) case. Based on the Beers criteria diclofenac (13.5%), alprazolam (9.3%), chlorthalidone (9.1%) and clonazepam (8.4%), spironolactone (7.1%), prazosin (5.9%), naproxen (5.5%), piroxicam (4.4%), ketorolac and digoxin (2.8%) were among the most frequently prescribed PIMs. Analgesics, medications acting on the central nervous system, and cardiovascular drugs with prevalence rates of 169 (37.6%), 159 (35.3%), and 86 (19.1%) respectively, were among the most common drug groups prescribed for the elderly who were referred to the pharmacies of Tehran (Table 1).

The elderly aged 75-84 years received the highest rate of PIMs (26.1%). The prevalence of inappropriate drug prescriptions in women (24.5%) was higher than men (22.3%), in illiterate individuals (no formal education) (25.1%) as compared to individuals with other educational levels, widow individuals (26.9%) as compared to other groups, and among those who were insured by the Social Security Organization (23.5%). Inappropriate drug prescription in male physicians (24.1%) was slightly higher than female physicians (21.9%). There was no significant relationship among

**Table 1. Distribution of potentially inappropriate medications (PIMs) by drug groups according to 2012 Beers Criteria**

| PIM                        | Therapeutic category PIM | N (%)     | PIM            | Therapeutic category PIM | N (%)     |
|----------------------------|--------------------------|-----------|----------------|--------------------------|-----------|
| Diclofenac                 | Pain medication          | 61 (13.5) | Hydroxyzine    | Anticholinergic          | 9 (1.8)   |
| Alprazolam                 | CNS                      | 42 (9.3)  | Indomethacin   | Pain Medication          | 8 (1.6)   |
| Chlorthalidone             | CNS                      | 41 (9.1)  | Clomipramine   | CNS                      | 8 (1.6)   |
| Clonazepam                 | CNS                      | 38 (8.4)  | Methocarbamol  | Pain Medication          | 8 (1.6)   |
| Spironolactone             | Cardiovascular           | 32 (7.1)  | Zolpidem       | CNS                      | 8 (1.6)   |
| Prazosin                   | Cardiovascular           | 28 (5.9)  | Imipramine     | CNS                      | 7 (1.3)   |
| Naproxen                   | Pain medication          | 26 (5.5)  | Amiodarone     | Cardiovascular           | 6 (1.2)   |
| Piroxicam                  | Pain medication          | 22 (4.4)  | Terazosin      | Cardiovascular           | 6 (1.2)   |
| Ketorolac                  | Pain medication          | 14 (2.8)  | Mefenamic acid | Pain Medication          | 5 (1.0)   |
| Digoxin                    | Cardiovascular           | 14 (2.8)  | Oxazepam       | CNS                      | 5 (1.0)   |
| Clidinium-chlordiazepoxide | Anticholinergic          | 12 (2.4)  | Metoclopramide | Gastrointestinal         | 5 (1.0)   |
| Lorazepam                  | Cardiovascular           | 12 (2.4)  | Amitriptyline  | CNS                      | 4 (0.8)   |
| Diphenhydramine            | Anticholinergic          | 11 (2.0)  | Total          |                          | 473 (100) |
| Ibuprofen                  | Pain medication          | 9 (1.8)   |                |                          |           |
| Meloxicam                  | Pain medication          | 9 (1.8)   |                |                          |           |

CNS, central nervous system

any of the demographic variables. However, polypharmacy was more common in subjects with inappropriate drug prescription (22.2%) than in those without inappropriate drug prescription ( $p < 0.001$ ) (Table 2).

**Table 2. The relationship between demographic characteristics of the sample and potentially inappropriate medication (PIM) test**

| Variables            | Category            | Non- PIM   | PIM        | p      |
|----------------------|---------------------|------------|------------|--------|
|                      |                     | No (%)     | No (%)     |        |
| Patient's gender     | Females             | 651(76)    | 210 (24.5) | 0.302  |
|                      | Males               | 568 (78)   | 162 (22.3) |        |
| Education            | No formal education | 302 (75)   | 101 (25.1) | 0.738  |
|                      | Primary             | 444 (76.2) | 139 (23.8) |        |
|                      | Secondary           | 330 (77)   | 97 (22.7)  |        |
|                      | Tertiary education  | 141 (79)   | 37 (20.8)  |        |
| Marital status       | Married             | 937 (77)   | 277 (22.8) | 0.363  |
|                      | Single              | 31 (80)    | 8 (20.5)   |        |
|                      | Divorced            | 12 (86)    | 2 (14.3)   |        |
|                      | Widow               | 237 (73)   | 87 (26.9)  |        |
| Age group (years)    | 60-74               | 888 (79)   | 268 (20.9) | 0.771  |
|                      | 75-84               | 256 (74)   | 85 (26.1)  |        |
|                      | +85                 | 73 (78)    | 21(22.4)   |        |
| Insurance            | YES                 | 1200 (77)  | 368 (23.2) | 0.494  |
|                      | NO                  | 19 (75)    | 4 (24.9)   |        |
| Polypharmacy         | YES                 | 313 (78)   | 203 (22.2) | 0.001* |
|                      | NO                  | 906 (69)   | 169 (21.3) |        |
| chronic disease      | YES                 | 893 (73)   | 364 (39.3) | 01*    |
|                      | NO                  | 285 (61)   | 49 (15.7)  |        |
| Physician gender     | Female              | 324 (84)   | 91(29)     | 0.377  |
|                      | Male                | 893 (71)   | 283 (14.7) |        |
| Specialist physician | General             | 281(69.8)  | 122 (30.2) | 0.020* |
|                      | Expert              | 897 (75.5) | 291(24.5)  |        |

\*  $p < 0.05$

There was a significant relationship between having chronic diseases with the inappropriate drug prescription found  $p < 0.001$ ). The prevalence of PIMs was significantly higher in general practitioners (30.2 %) than medical specialists (24.5%) ( $p < 0.05$ ) (Table 2).

†Independent sample t-test showed no significant relationship between physicians' age and work experience with inappropriate drug prescription. A significant relationship between epilepsy, falls, insomnia and Parkinson's disease with the inappropriate drug prescription was found (Table 3).

The results of logistic regression analysis (Table 4) showed that people with polypharmacy had 3.5 times the odds of having inappropriate drug prescription than other individuals (OR = 3.64, 95% CI: 2.81-4.70;  $p < 0.001$ ), and those with insomnia had 1.45 times the odds of having inappropriate drug prescriptions (OR = 1.45, 95% CI: 1.13-1.87;  $p < 0.003$ ). In addition, the odds of prescribing inappropriate drugs were 41% lower in internal medi-

**Table 3. The association between a disease and potentially inappropriate medications (PIMs)**

| Disease                       | Category | PIM      | Non-PIM     | p      |
|-------------------------------|----------|----------|-------------|--------|
|                               |          | No (%)   | No (%)      |        |
| Heart failure                 | Yes      | 175 (25) | 541 (75.6)  | 0.366  |
|                               | No       | 197 (23) | 678 (77.5)  |        |
| Syncope                       | Yes      | 17 (22)  | 63 (78.8)   | 0.644  |
|                               | No       | 355 (24) | 1156 (76.5) |        |
| Epilepsy                      | Yes      | 16 (38)  | 27 (62.8)   | 0.03*  |
|                               | No       | 356 (23) | 1192 (77)   |        |
| Delirium                      | Yes      | 20 (28)  | 51 (71.8)   | 0.33   |
|                               | No       | 352 (23) | 1168 (76.8) |        |
| Dementia                      | Yes      | 35 (21)  | 131 (78.9)  | 0.46   |
|                               | No       | 337 (24) | 1088 (76.4) |        |
| History of falls or fractures | Yes      | 51 (31)  | 114 (69.1)  | 0.016* |
|                               | No       | 321 (23) | 1105 (77.5) |        |
| Insomnia                      | Yes      | 194 (28) | 489 (71.6)  | 0.001* |
|                               | No       | 178 (20) | 730 (80.4)  |        |
| Parkinson                     | Yes      | 34 (32)  | 72 (67.9)   | 0.029* |
|                               | No       | 338 (23) | 1147 (77.2) |        |
| Chronic constipation          | Yes      | 157 (25) | 474 (75.1)  | 0.252  |
|                               | No       | 215(22)  | 745 (77.6)  |        |
| Ulcers                        | Yes      | 72 (25)  | 217 (75.1)  | 0.496  |
|                               | No       | 300 (23) | 1002 (77)   |        |
| Chronic kidney disease        | Yes      | 70 (26)  | 198 (73.9)  | 0.246  |
|                               | No       | 302 (23) | 1021 (77.2) |        |
| Incontinency                  | Yes      | 103 (25) | 311 (75.1)  | 0.403  |
|                               | No       | 269 (23) | 908 (77.1)  |        |
| Prostatic hyperplasia         | Yes      | 64 (24)  | 203 (76)    | 0.803  |
|                               | No       | 308 (23) | 1016 (76.7) |        |

\* $p < 0.05$

**Table 4. Multiple logistic regression with dependent variable of potentially inappropriate medications (PIMs) test**

| Variables                 | OR   | 95% CI     | p      |
|---------------------------|------|------------|--------|
| Polypharmacy              | 3.64 | 2.81-4.70  | 0.001* |
| Number of chronic disease | 2.37 | 1.71-3.28  | 0.001* |
| Epilepsy                  | 1.52 | 0.76-3.02  | 0.234  |
| Falls                     | 1.19 | 0.81-1.76  | 0.373  |
| Insomnia                  | 1.45 | 1.13-1.87  | 0.003* |
| Parkinson                 | 1.1  | 0.68-1.80  | 0.69   |
| <b>Type of specialty</b>  |      |            |        |
| Heart specialist          | 0.88 | 0.57-1.35  | 0.549  |
| Gastroenterologist        | 0.65 | 0.27-1.58  | 0.345  |
| Internists                | 0.59 | 0.40-0.88  | 0.009* |
| Endocrinologist           | 0.47 | 0.21-1.06  | 0.068  |
| Neurologist               | 1.45 | 0.92-2.27  | 0.109  |
| Nephrologist              | 0.87 | 0.54-1.39  | 0.555  |
| Infectious specialist     | 0.58 | 0.24-1.36  | 0.208  |
| Ophthalmologist           | 0.6  | 0.17-2.08  | 0.422  |
| Orthopedics               | 3.23 | 1.81-5.76  | 0.001* |
| Emergency Medicine        | 1.98 | 0.89-4.37  | 0.093  |
| Oncologist                | 0.72 | 0.29-1.83  | 0.495  |
| General surgeon           | 1.17 | 0.52-2.63  | 0.712  |
| Pediatrician              | 0.74 | 0.16-3.38  | 0.695  |
| Gynecologist              | 2.34 | 0.64-8.51  | 0.196  |
| Physiatrist               | 2.35 | 0.51-10.73 | 0.272  |
| Others                    | 0.63 | 0.18-2.25  | 0.477  |

\* $p < 0.05$ ; CI, confidence interval; OR, odds ratio; PIMs, potentially inappropriate medications

cine specialists than in general practitioners (OR = 0.59, 95% CI: 0.40-0.88;  $p < 0.009$ ). Orthopedic specialists had 23.3 times the odds of inappropriate drug prescriptions than general practitioners,

which is significant in the regression model (OR = 3.23, 95% CI: 1.71-3.28;  $p < 0.001$ ). Also, people with at least one chronic disease had 2.371 times the odds of experiencing inappropriate drug prescriptions than other elderly people (OR = 2.371, 95% CI: 1.71-3.28;  $p < 0.001$ ).

## DISCUSSION

The aim of the present study was to determine the prevalence of PIMs of drugs and identify factors related to PIMs in pharmacies across the city of Tehran. There have been numerous studies on the use of PIMs in the elderly in the United States as well as in many European and Asian countries (13-17). The discrepancy of the results obtained is partly due to differences in the type of medications used in countries, which have been mentioned as a limitation in these studies (3,18,19). The prevalence of PIMs is different in various studies and ranges from 13 to 40.7% (18). The same prevalence obtained in the present study (26.0%) is similar to those obtained in Japan and South Korea (5,17).

The present study also showed that the prevalence of one, two, three, and four PIMs was 19.9%, 5.1%, 0.9%, and 0.1%, respectively. The results of similar studies carried out in the Czech Republic, Japan, and Ireland are close to these figures (15,20,21). This study showed that diclofenac (13.5%), alprazolam (9.3%), and chlorthalidone (9.1%) and clonazepam (8.4%), spironolactone (7.1%), prazosin (5.9%), naproxen (5.5%), pyroxicam (4.4%), ketorolac and digoxin (2.8%) were among the most frequently prescribed PIMs. This study also showed that analgesics, medications acting on the central nervous system, and cardiovascular drugs with prevalence rates of 37.6%, 35.3%, and 17.1%, respectively, were among the most common drug groups prescribed for the elderly who were referred to the pharmacies of Tehran, which is consistent with the results of studies carried out in the United States and South Korea (14,17). Benzodiazepines are frequently used by the elderly due to the high incidence of insomnia; however, they cause drowsiness and, as a result increase the fall risk in elderly people (22). Older people tend to take more analgesic drugs, because they are more likely to have musculoskeletal pain.

This study showed that PIMs were highly prevalent among the elderly aged 75-84 years, which

is consistent with the results of a study carried out in Slovakia. The prevalence of PIMs in women (24.5%) is slightly higher than that of men (22.3%), which is consistent with the results of many studies, and can be attributed to the fact that women visit physicians more frequently (13,17,18, 23-25).

Although this study showed that the prevalence of PIMs in the individual health insurance was higher than those who did not have insurance, it was not statistically significant. The results of a study in Mexico showed that having Medicare insurance increases the odds of having PIMs differences.

This study showed that the level of literacy has no effect on the prevalence of PIMs; however, the results of a study in Mexico and Heydari et al. study in Iran showed that the prevalence of PIMs is higher in people with low educational levels, and it seems that illiterate and low-literate elderly are more likely to suffer from diseases due to lack of acquaintance with health issues; they thus take more PIMs (17,18,26).

The present study indicated that the prevalence of PIMs was higher in the spouseless elderly (26.9%) than others. Similarly, two other studies also show that PIMs are more common in single subjects (14,18).

The prescription of inappropriate drugs was significantly related to at least having one chronic disease in presented study and had 2.37 times the odds of having PIMs as compared to others, which is similar to results reported in other studies (13,18,25,27). The current study revealed no significant relationship between the physicians' age and the rate of inappropriate drug prescriptions, which was consistent with the results of another study in 2004 (13).

In this study it was found that the prevalence of PIMs was higher in male physicians (no significance). Harvard et al. (2004) also found that male physicians tended to prescribe drugs more inappropriately (26), which may be due to the increased female physicians' attention and awareness of the inappropriate drug prescription. This study showed no significant relationship between physicians' work experience and inappropriate drug prescription, which was also consistent with the results of a study carried out in Taiwan (2004) (5,14).

Our study showed that inappropriate drug prescription was significantly more common among general practitioners. This can be attributed to the fact that the elderly refer to general practitioners more frequently due to their financial problems and often suffer from various diseases for which the physician has to prescribe many medications, or it can be due to general practitioners' lack of familiarity with inappropriate drugs for the elderly.

Highest prevalence of PIMs among orthopedic specialists (43.1%), who had 2.3 times of the odds of prescribing PIMs as compared to the general practitioners was found in our study. This could be due to the pain medications prescribed for the elderly by these professionals. Furthermore, the odds of prescribing inappropriate drugs were 41% lower in internal medicine specialists than in general practitioners suggesting internists are more aware of inappropriate drugs for the elderly. Goulding (2004) also showed that internists had lower inappropriate drug prescriptions as compared to the general practitioners. However,

the results of another study in Japan showed significant inappropriate drug prescriptions among internists (5,13).

In conclusion, the results of this community pharmacy-based study showed that the prevalence of PIMs among elderly people is high. The high prevalence of PIMs indicates developing scientific guidelines for good prescribing in geriatrics patients.

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## TRANSPARENCY DECLARATION

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## Very first patient gift in a general practitioner's career and the impact of this event on physician-patient relationship

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### ABSTRACT

**Aim** To describe experiences, feelings and reactions of general practitioners (GPs) to the very first patient gift in the career, considering the impact on physician-patient relation (PPR).

**Methods** A representative sample of the Croatian GPs (N=265) filled in a supervised paper-based, researcher-led questionnaire. The response rate was 95.7%. Three independent analysts coded and analysed respondents' descriptions. The results were analysed using the descriptive statistics,  $\chi^2$ -test, and  $\phi$ -coefficient of correlation.

**Results** The GPs received the very first patient's gift (FG) already as students (2.6%), during internship (41.5%), and at the latest after being a doctor for one year. After 2-42 years of practice, 95.1% of GPs described their FGs. Typical gifts were coffee and/or sweets (66%). Dominant feeling of GPs on receiving the FG was discomfort (33%); only 22% felt good; just 26% reacted with composure. The outcome regarding the physician-patient relationship (PPR) ranged from the debacle (9%), through mutual discomfort (13%) or a routine reaction (38%), to smiles and mutual pleasure (40%). In 18% they tried to behave properly, considering the patient's best interest, despite their own discomfort. In 29% of cases, the patient took the role of teacher, supporting the young physician. The PPR was not improved in 3/5 of cases where the FG was described.

**Conclusion** Receiving the FG is an impressive and deeply touching event, remembered many years afterwards. Without prior instructions, Croatian GPs mostly reacted in a confused manner. The missed opportunity of improving PPR in 60%, and patients' help instead of teachers' suggest the need for education.

**Key words:** Family Medicine, Gift Giving, Ethics, Education

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## INTRODUCTION

The tradition of giving gifts from patients to physicians is very long. This custom is still deeply rooted in many societies, somewhere even considered as normal or obligatory (1-11). Yet, there is almost no physician who has not asked himself/herself "will I make a mistake if I take a gift, or if I refuse it?" (1,2,9,12-17).

There are some recommendations (2,3,18-20,22,23), and (hypothetic) discussions (1,7,11,12,16,17,21,24-26) on this topic. Some authors state patients' gifts are not acceptable at all (3,18,20), because of the possible influence on the professional distance, further, because of the diminished physician's capacity to treat all patients equally (1,3,11,16-18, 20), and because of the argument that 'every gift has a hidden message about an expected benefit' (18,27).

Existing discussions (1,7,12,17,21,22,24,25) and guidelines (2,3,19,20) mostly agree on some general statements regarding the appropriate professional manner: gifts of low value are more acceptable than expensive or big ones, gifts in kind more acceptable than those in money, and gifts received after a treatment rather than those given before (1,2,3,11,12,17,19-21,23-25). Gifts of an intimate nature should be considered unacceptable as well (2,3,7,11,17,20,24,26).

The main factor in interpreting the meaning of a gift and deciding if it is acceptable or not is the intention for its giving (1,3,11,16,19,22,25,26). Generally speaking, a gift given without a hidden expectation of any benefit for the patient is considered acceptable (1,2,3,7,11,16,17,19,21-26). More or less openly shown expectations of benefits might include: attaining a personal favour, manipulating the physician, or expecting some privileges or priority in the treatment (1,2,11,17,21-24, 27-29).

A physician's feeling of discomfort might also be the reason for avoiding patient gifts (2,3,7,10,11,17,27). This is supported by a challenging opinion that uncomfortable emotions in confusing situations could be read as an internal sign of inappropriate gifts (3,22,26). On the other hand, many authors suggest physicians should avoid to hurt their patients by immediately refusing their gifts, despite their own discomfort or confusion (1,2,10,16,22,28). There is also a cultural element as a decision-factor in accepting gifts (1-5,8,19,20).

In recent years, the number of the reports about the positive therapeutic effects of the patients' gifts has increased (2,28-30), which was recorded even in the cases of the concern-inducing gifts (28). By giving/exchanging gifts with their physicians, patients feel as being not merely objects, but almost friends with physicians, thus improving the physician-patient relationship (PPR) (1-3,11,25,28,29,31). The relatively recently observed positive impact of gift giving on patients' and physicians' feelings and on the PPR (1,3,11,13,25,29,33), and consequently on the therapeutic outcome (2,28-31,34), gives a new meaning to this process. "The importance of congruent relationships between therapists and clients is often enhanced by giving and receiving gifts." (2).

Still, there is no serious comprehensive investigation on patient gifts (2,3,10,13,16,17,20,24) which would better define what should be considered in particular situations as an acceptable gift vs. what is to be refused, and how. Further, the physicians' feelings in gifts-related situations are often mentioned, but rarely explored (2,10,13,15,17, 26-29,34), especially the discomfort (3,7,10-13,15,17,23, 26-28) which might arise from the insufficient knowledge in recognition what lies behind the gift. The unclearness about the gifts mainly encompasses the young doctors. As a rule, they do not get adequate instructions on this matter during their medical education (3,7,10,14,16,23,26). Subsequently, they face with many dilemmas on receiving their first gifts.

It seems important to investigate how the improper manner of the uninstructed physicians influences/changes the PPR on receiving gifts. There has been no similar investigation in Croatia, not even in the world.

The aim of this study is to explore what really happens when young colleagues receive the very first gift, what young physicians feel and how they react, and most importantly, how this event influences the PPR as an important and proven element in treating patients.

## PARTICIPANTS AND METHODS

### Participants and study design

The study was conducted on Croatian general practitioners (GPs) during 2006. The sample was stratified and based on the register of the Croatian Family Medicine Teams. The GPs were chosen

randomly. The GPs with less than two years of experience were considered as not having enough experience for the theme in question. They were excluded with the first question in an initial telephone call and were not allowed to approach. At the time of the study there were 2,358 contracted GPs in total. The sample included a minimum of 10% of all active GPs in Croatia, with proportional gender balance, and as a regional specificity a minimum of 10% of GPs in each of the 21 counties in Croatia. The sample was also representative regarding the proportion of the respondents with or without the vocational training, the percentage of the total patient population, and the proportion of the employed patients under the respondents' care. Without previous intention the sample included participants of a very wide age range from 25-65, a wide variation in terms of the cared population from 352 patients on some islands to 2,200 patients in urban areas, and the inclusion of specific practices (nursing homes, student surgeries, tourist surgeries). The response rate was 95.7%, and the final number was 265 participants.

The study was approved by the Ethics Committee of the Zagreb School of Medicine.

The survey was originally designed in the form of a large questionnaire in order to explore family physicians' experiences and their positive and negative feelings concerning material and non-material gifts given to and received from their patients.

This sub-part of the study investigated GPs' feelings and reactions to the very first gift in the career and the immediate outcome in sense of impact on the physician-patient relationship (PPR). The PPR outcomes are sorted in four basic types: conventional type (just fulfilling social norm), mutual pleasure (good feeling in both patient and physician, recognizing gratuity in small gifts), debacle (misunderstanding, tears, disappointed and hurt patient), and mutual discomfort (confused discomforted patient and physician). An additional type of outcome was Patient-Teacher, meaning the situation when a patient supported an uninstructed confused young physician and helped him/her to cope.

The outcomes are derived from excerpts from answers to the question "How the patient reacted?" and from the description as a whole. The GPs' reactions were derived from excerpts from

their descriptive answers. The questions in this sub-part asked to describe the first gift, the time of receiving it (month or year of being a student or an intern or physician), further the physician's words and feelings and reaction, and patient's words and reaction.

## Methods

The participants were approached by phone after they were chosen (as above described) and assembled in small groups of 2-18 participants. The survey was conducted in field, as a led questionnaire under the supervision and in the presence of the same researcher. The researcher was an experienced GP, therefore capable to understand the issue and to answer the respondents' questions, and not on much higher professional level than participants, so the participants could be more open (according to the results from pilot study). The survey respondents had been informed about the theme in advance, but had not been provided with detailed contents. The respondents had been only requested beforehand to bring with them data about their practice (total number of patients, their breakdown by gender, age and employment status).

The questionnaire was anonymous and instructions were clearly defined beforehand and given immediately before the questionnaire was filled in. Questions were allowed during the survey, but the respondents were not permitted to consult each other about their responses, and no discussion was allowed. A pilot survey was conducted on a group of GPs from different parts of the country.

## Statistical analysis

Answers were analysed by three independent analysts, and coded by a codex of attributions, as given in the Results section. The  $\chi^2$ -test was used to test the differences in remembering between age-groups, and the  $\phi$  coefficient of association for calculating the correlation between observed GPs' emotions/reactions and positive or negative PPR outcomes. The simple results are presented by descriptive statistics.

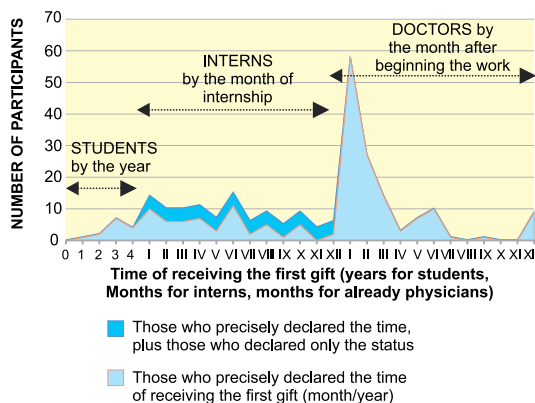
## RESULTS

### Types of the first gifts

The gifts were mostly small and common, in 175 (66.1%) cases coffee and/or sweets, if inclu-

ding their share in the combined gifts. The food is mostly given in rural areas, 24 cases (9.1%). Flowers were typically given to female physicians, 19 (7.2%), drinks to male ones, seven (2.6%). In 15 (5.7%) cases the gifts were a combination of different types, almost all including coffee/sweets. The gifts were predominantly in kind; there were three monetary first gifts.

The respondents did not remember their first gifts or left blank in 13 (4.9%) cases (Figure 1).



**Figure 1. Time-distribution of receiving the first gift**

A total number of 265 GPs were involved in the study. A total number of 15 (5.7%) participants received the first gift as students (at the earliest on the 2<sup>nd</sup> year of medical school at the time), 110 (41.5%) as interns (a range of all months), 133 (50.2%) as physicians (from the 1<sup>st</sup> month until, at the latest, after one year of being a physician) (the most frequent answer was the 1<sup>st</sup> month of being a physician, 58/21.9%), and seven (2.6%) participants had no memory or provided answer. No respondent answered s/he received the first gift after one year of being a doctor (Figure 1).

A total of 163 (62%) participants remembered the first gift, 80 (30%) remembered and described the gift in great details, 9 (3%) remembered but were not quite sure, (4%) did not remember, and 11 (1%) did not answer.

The recall rate of the first patient gift was 95.1% (252) participants. The range of participants' years of practice was 2-42 years (the average 16.23 years); the average of years after graduation was 18.4 yrs. There was no statistically significant difference in remembrance regarding the years after the graduation nor the years of practice ( $p>0.05$ ). In the years of practice only the years of primary care experience were counted, there-

fore, the years after graduation were closer to the elapsed time than the years of practice ( $p=0.147$  and  $p=0.058$ , respectively) (Table 1).

**Table 1. Remembering the first gift regarding the years of practice**

| Remembering description                               | Answer examples/comment   | Number (%)<br>partici-<br>pants | p*<br>(years of<br>practice) | p†<br>(years<br>after gra-<br>duation) |
|---|---|---------------------------------|------------------------------|--|
| <b>Remember</b>                                       | "flowers" or "coffee"   | 163<br>(62%)                    |                              |  |
|   | "bouquet of red and white roses",<br>"7 eggs"   |                                 |                              |  |
| <b>Remember and describe the gift in great detail</b> | "a basket of cherries from the patient's garden",<br>"Zippo cigarette lighter",<br>"one apple",<br>"100g of coffee" | 80 (30%)                        | $\chi^2$ test<br>$p=0.058$   | $\chi^2$ test<br>$p=0.147$             |
| <b>Remember, but are not quite sure</b>               | "Flowers, I think",<br>or "cheese or some other food"   | 9 (3%)                          |                              |  |
| <b>Do not remember</b>                                |   | 11 (4%)                         |                              |  |
| <b>No answer</b>                                      | only two respondents, (both extremely embarrassed and further describing this event in great detail)                | 2 (1%)                          |                              |  |

\*in the years of practice only years of primary care experience were counted; therefore, the years after graduation were closer to the elapsed time ( $p=0.147$ ) than years of practice ( $p=0.058$ ), and the p values were different; the range of participants' years of practice were 2-42 years (the average 16.23); †the average years after graduation 18.4 years

### The outcome of receiving the first patient gift regarding the patient-physician relationship (PPR)

In 19 cases the space for answers was left blank. In one additional case the gift was brought by an intermediary. Thus, it was not possible to reach a conclusion on the outcome. Therefore, the percentages were calculated from the total number, minus these answers and minus those declared as 'don't remember' ( $n=228$ ).

Type F, Patient-Teacher, was only an additional observation, so it was not counted in the sum of total outcomes. It was noted in 62 out of all 265 cases (29%), i.e. in 24% out of 228 completely described answers (Table 2).

The young GPs very often experienced the first gift-giving just as a social norm (86 cases, 38%), sorted as conventional type of outcome (Type A). It might be only a subjective impression of the young physicians who emphasized their surprise with the patients' "normal" reactions in contrast to their own intensive feelings, confusion and excitation. This strong contrast might mask the patients'

real intention and reaction in the young physicians' eyes. The Type E outcome (cannot remember) also indicates strong emotions when receiving the first gift, since these respondents mostly described they were so overwhelmed with their own emotions that they could not recall patient's reaction. The outcome of the type D (mutual discomfort, 30 cases, 13%) often occurred because some patients were "social beginners" similar as young physicians in front of them. This could be illustrated with the situation of "a couple in a dancing room wanting but not knowing to dance, and constantly apologizing for stepping on each other's feet". In such cases patients became "confused by doctor's confusion", as a participant wrote. A good outcome (mutual pleasure) was found in 92 cases, 40% (Table 2). This type of the outcome is positively correlated with GPs positive initial emotions or composure ( $p < 0.001$ ;  $\phi = +0.36$ ).

**Table 2. The outcome of receiving the first patient gift regarding the patient-physician relationship (PPR)**

| The final PPR outcome*  | No (%) of the completely described answers | Examples of the GP's answer   |
|---|--|---|
| <b>A Conventional type</b> of patient answer, fulfilling a social obligation                                | 86 (38%)                                   | Many GPs expressed surprise at the patient's courteous reaction, describing it as 'normal', 'trained', 'routine' – in contrast to their own feelings (overexcited, confused, discomforted). |
| <b>B Mutual pleasure</b> , feeling good, recognising hidden good messages in small gifts                    | 92 (40%)                                   | GP, receiving a bunch of violets: I was glad. I said: "Thank you, they are so beautiful, are they from your garden?" She was happy and pleased that I liked them.                           |
| <b>C Debacle</b> , PPR turmoil. Misunderstanding. Patient's disappointment, feeling of being refused, hurt. | 20 (9%)                                    | I was embarrassed. I didn't think I'd done anything special. 'Sorry, but I'd rather not take this.' The old lady cried and left the gift.   |
| <b>D Mutual discomfort</b>  | 30 (13%)                                   | The patient pushes the gift over the table to me, I push it back to him; both confused.   |
| <b>E Not able to remember</b> the patient's answer†   | 17 (6%) from total                         | I don't remember what he said, but I'll never forget that night.  |
| <b>F Patient as a teacher‡</b> , helping a young doctor to cope, consoling him/her                          | 62 (29%) from total                        | I felt discomfort. I said: "Thank you, you shouldn't have." The patient smiled: "It's only a token of appreciation in the spring"   |

\*The outcomes were derived from excerpts from answers to the question "How did the patient react?" and from the description as a whole; †In 19 cases the space for answers was left blank, in one additional case the gift was brought by an intermediary, thus, it was not possible to reach a conclusion on the outcome. Therefore, the percentages were calculated from the total number, minus these answers and those declared as 'don't remember' ( $n=228$ ); ‡Type F, Patient-Teacher, was only an additional observation, so it was not counted in the sum of total outcomes. It was noted in 29 % from all cases, i.e. in 24% of the completely described

In opposite, GP's negative initial emotions correlated significantly with a bad outcome (Type C, debacle), found in 20 cases, 9% (Table 2). Confusion or discomfort led very often to the refusal of the gift, since young GPs did not recognize patient's gratitude and felt as not deserving the gift. The unnecessary refusal is significantly correlated with bad outcomes ( $p < 0.001$ ;  $\phi = +0.43$ ), with disappointed patients, tears in the eyes and bad feelings in both patients and the doctor.

### GPs' Reactions to the first patient gift

Negative emotions dominated at GPs: discomfort on the first place, in 88 (33%) cases, even embarrassment (18 cases, 7%), shame, feeling of not deserving the gift, confusion including confusion because of not knowing why the gift was given. Surprise was sometimes positive, sometimes negative. Positive emotions occurred less often than the negative ones. One or several attributions were possible for GPs' reactions. The proportions of positive vs. negative emotions could not be compared because of the mixed emotions or multiple positive or negative (happy and ashamed, proud and discomforted, flattered but embarrassed) emotions in the same answer. Due to the possibility of expressing one or more feelings and reactions, the total percentages are normally over 100% (Table 3).

**Table 3. General practitioners' (GPs') reactions to the first patient gift\***

| Type of reaction  | No (%) of GPs |
|---|---------------|
| 1. suitable and composed reaction   | 70 (26)       |
| 2. discomfort   | 88 (33)       |
| 3. extremely embarrassed  | 18 (7)        |
| 4. confused   | 49 (18)       |
| 5. honoured, proud or flattered   | 13 (5)        |
| 6. glad, pleased or cheerful  | 45 (17)       |
| 7. aware of patient's gratitude   | 12 (5)        |
| 8. feeling of not deserving the gift, or just not knowing why it was given  | 17 (6)        |
| 9. surprised  | 48 (18)       |
| 10. trying to do or say something appropriate, with the priority not to hurt the patient, despite own discomfort  | 48 (18)       |
| 11. refusing or trying to refuse the gift (for any reason)  | 40 (15)       |
| 12. From all cases where the first reaction was negative, some of them ended up positively, and in a significant number of these patients support was noted |               |

\*One or several attributions were possible for GPs' reactions. The proportions of positive vs. negative emotions could not be compared because of the mixed emotions or multiple positive or negative emotions in the same answer. Due to the possibility of expressing one or more feelings and reactions, the total percentages were normally over 100%

### The impact of GPs' reactions and emotions on immediate outcome in sense of physician-patient relationship (PPR)

The GPs who reacted with composure significantly differed in immediate outcome to those GPs who reacted non-composedly ( $p < 0.001$ ), and the composure was significantly positively associated with good outcome, i.e. with improved PPR (coefficient of association  $\phi = +0.36$ ).

Positive initial emotions resulted with the same good results in the same values ( $p < 0.001$ ) ( $\phi = +0.36$ ). The GPs who were glad, proud, honoured, pleased, joyful, cheerful, aware of patient's gratitude, flattered or praised, achieved more often good immediate outcome (Type B, i.e. improved PPR or mutual pleasure) (Table 2).

The GPs' discomfort or embarrassment was significantly positively associated with bad outcomes (Types C and D) (Table 2) ( $p < 0.001$ ;  $\phi = +0.35$ ; for both negative initial emotions).

Refusal of the gift (even with the best intention, as the compassion for patient's poverty) was significantly positively associated with bad outcome ( $p < 0.001$ ;  $\phi = +0.43$ ).

**Example.** The GP: "I was embarrassed; I thought it unnecessary and refused the gift". Outcome: It was very hard for the patient. "I'd give more if I had it", he repeated constantly.

The GP: "It was horrible for me. Someone was giving me something small he had, a token of gratitude, and I was refusing it". This GP learned in the hardest way the meaning of a gift and the importance of building the good PPR.

Some of young doctors were aware that they should say or do something appropriate, despite their own discomfort and lack of knowledge. They try to "do it well", considering the patient's best interest, but the results were only insignificantly positive in the sense of bettering the PPR ( $p = 0.244$ ,  $\phi = +0.08$ ), and insignificantly negative in worsening it ( $p = 0.077$ ;  $\phi = -0.07$ ).

**Example.** The GP: "I felt discomfort. I tried to refuse 'in a fine way', but it didn't succeed. The patient was unpleasantly surprised and looked confused by my explanations".

In 62 (29% out of 265) participants the patient supported the young inexperienced doctor and in this way successfully helped to turn up the initial discomfort to mutual pleasure. From all 88 cases

where the GP's first reaction was discomfort, those where the patient's support was noted significantly more ended with the mutual pleasure as a good outcome (Type B) (Table 2) ( $p = 0.0036$ ;  $\phi = +0.31$ ).

## DISCUSSION

### The gift giving is traditional and common

The results of this study have shown that GPs received their very first patient gifts very early (no GP said s/he received it after one year of practice), which confirms the general notion that gift giving in family medicine is often and common (1,7,12). In Croatia it is obviously also a tradition. There are no data to compare this with other countries, but only general observations about cultures where gifts to physicians are not deemed non-ethical, but rather as something normal, polite and socially well accepted or almost obligatory (2,4,5,7-9,24). Examples from Japan (8), Australia (1) and the USA (13) show that the gift-giving tradition is not necessarily restricted to developing countries. In three Baltic countries gifts were given in 14% of all visits to physicians, while a half of the respondents had not seen it as corruption, especially not in case of in-kind gifts (6).

Tradition obligates patients in two ways: first, as a kind of a reward for being treated, and second, to show respect for certain professions, such as physicians and priests, by giving them something. Since treating someone is perceived as something worthy and generous, almost a kind of a gift, it has to be rewarded in an appropriate way (4,5). A patient's gratitude might be expressed even by giving something "which is missing within the medical facilities, such as syringes" or even "a blood-donation by a family member", because "leaving the provider's office without expressing gratitude is culturally not acceptable" (5). In some cultures, the types of gifts are strictly defined, and the refusal is considered very impolite (8).

A gift is sometimes a cultural obligation as a proof of a patient's own dignity (4,5,8,10). It is usually explained as "When I do not have money I do not go to a physician. I will be embarrassed to show up and not be able to pay." (5). The custom of gift giving is especially strong in some countries where people have a feeling that "nobody cares" for them or they "know well that the government's promises are mostly false and disappointing" (5), or where "the formal rules of

health care are pushed to the side” and “marginalized for political reasons” and people just have to accept that “do-it-yourself way” by giving gifts to get the medical help (9).

The local tradition could be very different (2-5,7,9,11,24,35) so cultural differences should be considered when receiving gifts (1,2,4,7-10,16,19,20,24,26). This issue is however largely ignored in medical school curricula (2-4,9,13,14,24) despite all the recommendations in that sense, despite the suggested individual approach on receiving gifts (2,7,10,13,19,22), and despite the advice to act even on a case-by-case basis (16,20).

### **Negative feelings are the most often on receiving the first gift**

The fact that negative feelings were most frequently described in our study was almost expected considering the above-mentioned lack of proper education. In some cases, an extremely unpleasant reaction was provoked, such as running away, blushing, beginning to stutter. One respondent directly described his reaction as a shameful from his current point of view. Discomfort related to receiving gifts is often discussed in literature (3,7,10-13,15,17,23,26-28), but with rare and unclear guidelines how to avoid it, or how to gain useful knowledge and good orientation about the meaning and acceptability of a particular gift. Some advices are logical: “Education, education, education!” (23), similar to those from other authors (1,7,10,14). A very reasonable opinion on using guidelines alone rather than practical teaching was given by an experienced family physician: “Young physicians, and some who are not so young anymore, seem to believe that guidelines are a solution to all problems, even to the challenge of dealing with patients who offer them kindness.” (13).

It should be noted that our study described the experiences with the very first patient gifts, at the beginning of the participants’ careers, which in many cases happened many years ago, when opinions were mostly given from a theoretical and philosophical point of view. Consequently, GPs did not dare to see all the warmth and appreciation hidden in these mostly small gifts (1,2,10,13,16,25,29,33,34), but rather accepted those stiff statements as their own inner ones. In only one case the reaction was indifference. Indifference in the PPR might be worse than

honestly expressed negative emotions, because “affective neutrality breaks the bond that holds people together” (32) and “rigidity, distance and coldness are incompatible with healing” (2).

Better control of emotions could be achieved by improving communication between a physician and a patient, as a specific sub-part of that relationship, because it has been proved that it increases health outcomes and well-being (32,36). Further, it has been observed that accepting even those gifts which were raising a concern for therapists facilitated the therapy process (28).

### **Negative emotions and refusal worse the physician-patient relationship (PPR)**

Negative initial emotions and refusal of the gift are significantly associated with the worsening of the PPR as an immediate outcome. Refusing the gift might hurt the patient (1-4,7,8,10,16,19,21,22,25) and “irrevocably fracture the physician-patient relationship” (1). Many authors advise “not to hurt the patient” as one of the basic principles on receiving a gift (1-3,7,8,12,16,21,22), so it is sometimes suggested to be followed despite own discomfort (1,2,16,22,26). Furthermore, gestures which may hurt patients and worsen the PPR are inadvisable (1,2,7,8,16,31). Sometimes, just once disturbed PPR might compromise the therapeutic effect forever (1,7,26), especially in family medicine (26), since improper behaviour on receiving gifts might induce negative feelings in patients (1-4,7,8,10,16,21) and physicians alike (7,3,24,28).

However, it cannot be said that the reason for worsening the PPR was the mere act of refusing a gift. This could also be caused by an inappropriate way of refusing a gift due to lack of experience or instructions beforehand (4,7,10,16,26), or the fact that young physicians often find their first jobs more easily in an unattractive remote place than in a big city. Highly educated and coming from an urban area, they do not understand the local sub-culture (10). Our study has shown that only exceptionally the young GPs refused gifts in a proper manner, with composure and without an unpleasant outcome. In such cases, not only the words, but the style and intonation were important (1,16,26) such as in the following example: “I politely refused the gift, saying thank you and explaining to the mother of the child that I treat patients equally well, regardless of any gift. She accepted my words well.”

### Positive emotions or composure improve PPR

The outcome of the Type B (mutual satisfaction) was mostly associated with physicians' positive feelings and with recognising patients' gratitude expressed through gifts. A few authors describe pleasant emotions upon receiving gifts, either their own (15,28,29,34) or patients' (34), or they only observed a positive therapeutic effect of gift-giving (2,28,30), without specifically exploring the link between positive emotions and the outcome regarding the PPR.

The most interesting finding (in 29% of all cases) occurred when the patient helped the young GP to understand the meaning of the gift declining confusion. The patient supported and taught the inexperienced doctor how to cope with this situation. Such examples confirm the existence and the beauty of PPR, where both sides, patient and physician, have an important role in this interactive relation (7,16,22,26,32,33). On the other hand, one could ask: why the first teacher on how to interpret and receive the gift was the patient, and not the professor on medical faculty (1,7,10,14,23)?

In general, composure and/or positive emotions upon receiving gifts, significantly improved the PPR. On the other hand, the presence of negative emotions (discomfort, embarrassment, shame) and the subsequent refusal of the gift significantly worsened the PPR, or at least produced a "cold" conventional type of the relationship.

### The recall on the very first patient gift is very high

After 2-42 years of practice 95% of the GPs still remember their first gifts, and 30% describe them in great detail, similarly to rare single examples in the literature (17). Moreover, there was no significant difference in recalling the event, which was neither dependent on the years of practice nor on the years after the graduation.

Some answers sound as this event is an unspent and unspendable stock of joy, still vivid after so many years: 'I was flattered and infinitely happy because I thought it was a sign that I did my job well.' Just this type of an answer explains the very high recall rate on the first gift. Other authors also mention the emotionally coloured long-term recollection of gifts (1,13,17,33,37), as opposed to the opinions of losing the data-bias due to the lapse of time (35). The deep positive

emotional influence on physicians due to intangible gifts was rarely described: for example as providing "the antidote to burnout" (33). These gifts, described as "trust and gratitude, sometimes expressed but more often implied" (13,33), are regularly long remembered (13,17,33,37). GPs keep them with pride "in their shelves full of paintings, photographs, craftwork and cards received from their patients over the years" (1) or "in their treasure chests" (13). It is important to emphasize that in all the above mentioned cases of long and deep emotional recall the gifts were either non-material or small and almost symbolic (1,13,17,33,37) just as most of the first gifts. So, emotions are those that make the gift "valuable" or "unforgotten", not real monetary value.

Drawing from this one can conclude that because the described first gifts are generally of small value (coffee, flowers, chocolate) they should be acceptable (1,3,7,11,17,19,20,21,23,24). It is a pity then that these small and acceptable first gifts, mostly given in a well-intentioned and emotionally warm situation, did not lead to bettering of the PPR in 60% of cases, probably due to the lack of instructions. Despite the fact that in Croatia giving gifts to doctors is a tradition, young physicians found themselves surprised when it happened to them for the first time. This unpreparedness led not only to GPs' own discomfort and confusion, but it often produced a negative outcome for the patient-physician relationship. In some cases patients turned out to be the first teachers for physicians on how to receive gifts, converting GPs' initial discomfort into shared satisfaction. A positive outcome in immediate PPR (smiling, feeling good, accepting and understanding patient's gratitude and appreciation, declining a gift without hurting) was described in only 40% of the completed answers.

In conclusion, since a good physician-patient relationship is a prerequisite for a successful treatment process, these results suggest that education both on the meaning of the patient gifts and proper and professional behaviour, and in accordance to the local culture, is necessary for medical students.

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### TRANSPARENCY DECLARATION

Conflicts of interest: Nothing to declare.

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## Can a place of living of elementary school students determine their health habit?

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### ABSTRACT

**Aim** To determine dietary habits of elementary school students in relation to a place of living and socio-economic status of the family.

**Methods** A prospective study conducted in the Primary Health Center Zenica involved five family medicine teams in urban and five in rural settlement during 2015. Elementary school students aged 10-16 were interviewed by random selection using a questionnaire on the socio-economic status of parents and nutritional habits of adolescents.

**Results** The survey involved 199 respondents, 103 from rural and 96 from urban area. There were significantly more pupils from employed parents who consumed non-carbonated drinks. Students from urban areas more likely consumed fruit every day than children from rural areas. More than half of the respondents did not or rarely consumed vegetables, in this case the village pupils, who consumed much less milk. It would be expected that rural students were more likely to consume fruits, vegetables and milk due to easier access to these foods in the countryside, but the results of this research did not confirm this assumption.

**Conclusion** Changes in traditional family functioning (lower income, unemployment) could be linked with lifestyle changes (low consumption of fruits and vegetables, low consumption of milk both in rural and urban areas, consumption of carbonated drinks), especially in families in rural areas.

**Key words:** adolescents, dietary habits, milk, socio economic status, vegetables

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## INTRODUCTION

Elementary school students (10-16 years of age) often experience eating disorders or an irregular attitude towards food – too little vegetables, fruits and dairy products, too much fast food and snacks and meals at irregular intervals (1). Students of this age group more often consume food outside the house due to lack of time, the dynamics of life and the absence of parents for work (2). Meals that are energy-rich in composition but poor in protective substances, are consumed more and more frequently, so one quarter to one third of energy is generated by feeding snacks (2). An adequate intake of energy and nutrients during childhood and adolescence will not only reduce the risk of developing current health problems (caries, anaemia, growth disorders, obesity), but it will also delay or prevent the onset of chronic illnesses in adulthood (cardiovascular diseases, hypertension, stroke, some forms of malignant diseases, diabetes, osteoporosis) (3).

The most traditional approach about inequities in health is in relation to the individual economic situation (4). In young people (11 to 15 years of age) the role of socioeconomic factors in health is not so clear; some studies have demonstrated the link between a socio-economic status and health outcomes and behaviour (4), some of them showed the protective role of lower socioeconomic status in relation to higher ones (5), while in a series of studies the correlation between socioeconomic status and youth health has not been established (6).

A study conducted in England showed that young people, 11-15 years of age, with a weak feeling of emotional connection with the family and low involvement in the neighbourhood were almost twice as likely to report poor health and low consumption of fruit and vegetables (5). Children from a single-parent family are not only with increased possibility for risky behaviour but also it is more likely their families are poorer, which can additionally affect health and a good subjective feeling in life (5). However, circumstances such as unemployment, time-limiting situations with children (night work, additional jobs to improve income) make even intact families vulnerable and risky for child development (4). In Moldova, only six of 10 respondents indicated that they ate breakfast every weekday and every 10<sup>th</sup> skipped breakfast (6). In Croatia, most elemen-

tary school students (11-15 years of age) do not eat breakfast, fruits and vegetables according to the guidelines for proper nutrition (4).

Looking at the social environment, young people (11-15 years of age) have better relationships with the closest persons and a good level of communication with their parents (7). Young people are the most suitable population group for the adoption of bad eating habits because, due to the lack of time and employment of parents, they increasingly consume food outside the family home, most often as a “fast food” meal (8-10).

Reports about eating habits in Bosnia and Herzegovina (B&H) are scarce. In a survey conducted in Travnik (B&H), young people (11-14 years of age) in a rural area consume fruit every day more frequently than those in the city (11).

The aim of this research was to determine nutritional habits of elementary school students 10-16 years of age (young people) in relation to the place of living and socio-economic status of the family. This research will primarily serve for better planning of preventive and promotional public health activities as well as family medicine employees in their daily work.

## EXAMINEES AND METHODS

### Examinees and study design

This prospective study conducted in the Primary Health Centre of Zenica, Bosnia and Herzegovina, involved five family medicine teams in urban and five in rural settlements during 2015. Family medicine teams were randomly selected. The examinees involved in the study were primary school students aged 10-16 years old, who were checked in a family medicine clinic for any reason.

Consent for participation in the study was given by the Ethics Committee of the Primary Health Care of Zenica. Oral approvals were obtained from the students' parents, who attended the interview too.

### Methods

The questionnaire was created for this research. The questions were clear, unambiguous and precisely formulated. In the first part of the questionnaire, a nurse in the family medicine clinic received answers from the students through an interview (gender, age, socio-economic status). The second part of the questionnaire was filled out

by students independently (knowledge, attitudes and behaviour). The questionnaire was supposed to determine socio-economic conditions in which the adolescents lived (place of residence, employment of parents, family status), which may contribute to knowledge, attitudes and dietary habits of adolescents (non-carbonated and carbonated drinks, fruit, vegetables, milk, breakfast).

### Statistical analysis

For the analysis of the results, methods of descriptive statistics,  $\chi^2$  test and Student t-test were used. Statistical significance was set up for  $p < 0.05$ .

### RESULTS

The survey involved 199 students, 103 (51.8%) from rural and 96 (48.2%) from urban area. The number of female students, who visited the physician in the rural area, was much higher, 66 (62.3%) ( $p < 0.05$ ). Average age of the students in rural and urban area was 13.6 and 13.7 years of age, respectively.

No statistically significant difference was found in the number of students living with both parents, with one parent, or with a guardian (without biological parents). A total of 92 (89.3%) students in the rural area and 88 (91.6%) in the urban area lived with both parents, nine (8.7%) students in the rural area and eight (8.3%) in the urban area lived with one parent, and two (1.9%) students in the rural area with guardians (without biological parents) ( $p > 0.05$ ).

The parents of 59 (57.3%) students in the rural area and 84 (87.5%) in the urban area were employed, 35 (33.98%) in the rural area and 12

(12.5%) in the urban area were unemployed, four (3.8%) in the rural area were pensioners, and five (4.85%) students in the rural area had parents who were also students themselves ( $p < 0.05$ ).

Of the total of 199 students, 168 (84.4%) regularly eat breakfast in the morning: 81 (48.2%) in rural and 87 (51.7%) in urban area ( $p > 0.05$ ) (Table 1).

**Table 1. Consumption of breakfast during a week in relation to the place of living**

| Place of living | No (%) of students per number of days during a week |          |         |         |          |          |         |           |
|-----------------|---|----------|---------|---------|----------|----------|---------|-----------|
|                 | 0 days  | 1 day    | 2 days  | 3 days  | 4 days   | 5 days   | 6 days  | 7 days    |
| Rural           | 3 (75)  | 2 (66.6) | 3 (100) | 3 (75)  | 6 (66.6) | 4 (57.1) | 1 (100) | 81 (48.2) |
| Urban           | 1 (25)  | 1 (33.3) | 0       | 1 (25)  | 3 (33.3) | 3 (42.8) | 0       | 87 (51.7) |
| Total           | 4 (100)   | 3 (100)  | 3 (100) | 4 (100) | 9 (100)  | 7 (100)  | 1 (100) | 168 (100) |

A total of 124 (73.8%) students whose parents are employed have breakfast every day, as opposed to 38 (22.6%) students whose parents were unemployed ( $p < 0.05$ ). Occasional breakfast consumption during a week was similar in both groups (Table 2).

**Table 2. Consumption of breakfast during a week in relation to the working status of parents**

| Working status of parents | No (%) of students per number of days during a week |          |          |         |          |          |         |            |
|---------------------------|---|----------|----------|---------|----------|----------|---------|------------|
|                           | 0 days  | 1 day    | 2 days   | 3 days  | 4 days   | 5 days   | 6 days  | 7 days     |
| Employed                  | 1 (25)  | 2 (66.6) | 1 (33.3) | 3 (75)  | 6 (66.6) | 6 (85.7) | 0       | 124 (73.8) |
| Unemployed                | 2 (50)  | 1 (33.3) | 1 (33.3) | 1 (25)  | 3 (33.3) | 1 (14.2) | 0       | 38 (22.6)  |
| Pensioner                 | 0   | 0        | 0        | 0       | 0        | 0        | 1 (100) | 3 (1.7)    |
| Student                   | 1 (25)  | 0        | 1 (33.3) | 0       | 0        | 0        | 0       | 3 (1.7)    |
| Total                     | 4 (100)   | 3 (100)  | 3 (100)  | 4 (100) | 9 (100)  | 7 (100)  | 1 (100) | 168 (100)  |

**Table 3. Student food habits in relation to the place of living**

| Food                  | Place of living | No (%) of adolescents per number of week/day consumptions |                              |                              |            |             |                   |                        |
|-----------------------|-----------------|---|------------------------------|------------------------------|------------|-------------|-------------------|------------------------|
|                       |                 | Not in the last 7 days                                    | 1-3 times in the last 7 days | 4-6 times in the last 7 days | Once daily | Twice daily | Three times a day | 4 and more times a day |
| Fruit                 | Rural           | 3 (100)   | 17 (56.6)                    | 13 (59.1)                    | 25 (34.2)  | 25 (55.5)   | 10 (76.9)         | 10 (76.9)              |
|                       | Urban           | 0   | 13 (43.3)                    | 9 (40.9)                     | 48 (65.8)  | 20 (44.4)   | 3 (23.1)          | 3 (23.1)               |
|                       | Total           | 3 (100)   | 30 (100)                     | 22 (100)                     | 73 (100)   | 45 (100)    | 13 (100)          | 13 (100)               |
| Vegetables            | Rural           | 6 (31.6)  | 30 (60)                      | 22 (59.5)                    | 27 (39.1)  | 14 (82.4)   | 2 (50)            | 2 (66.6)               |
|                       | Urban           | 13 (68.4)   | 20 (40)                      | 15 (40.5)                    | 42 (60.9)  | 3 (17.6)    | 2 (50)            | 1 (33.3)               |
|                       | Total           | 19 (100)  | 50 (100)                     | 37 (100)                     | 69 (100)   | 17 (100)    | 4 (100)           | 3 (100)                |
| Non-carbonated drinks | Rural           | 23 (47.9)   | 31 (59.6)                    | 16 (55.2)                    | 16 (41)    | 12 (66.6)   | 2 (20)            | 3 (100)                |
|                       | Urban           | 25 (52.1)   | 21 (40.4)                    | 13 (44.8)                    | 23 (59)    | 6 (33.3)    | 8 (80)            | 0                      |
|                       | Total           | 48 (100)  | 52 (100)                     | 29 (100)                     | 39 (100)   | 18 (100)    | 10 (100)          | 3 (100)                |
| Carbonated drinks     | Rural           | 40 (44.5)   | 29 (54.7)                    | 8 (61.5)                     | 14 (58.3)  | 5 (50)      | 2 (100)           | 5 (71.4)               |
|                       | Urban           | 50 (55.5)   | 24 (45.3)                    | 5 (38.5)                     | 10 (41.7)  | 5 (50)      | 0                 | 2 (28.6)               |
|                       | Total           | 90 (100)  | 53 (100)                     | 13 (100)                     | 24 (100)   | 10 (100)    | 2 (100)           | 7 (100)                |
| Milk                  | Rural           | 22 (59.5)   | 37 (66)                      | 26 (72.2)                    | 13 (25)    | 3 (23)      | 1 (50)            | 1 (33.3)               |
|                       | Urban           | 15 (40.5)   | 19 (34)                      | 10 (27.8)                    | 39 (75)    | 10 (77)     | 1 (50)            | 2 (66.6)               |
|                       | Total           | 37 (100)  | 56 (100)                     | 36 (100)                     | 52 (100)   | 13 (100)    | 2 (100)           | 3 (100)                |

**Table 4. Consumption of beverages in relation to family status**

| Beverages             | Parental status | No (%) of students per number of week/day consumptions |                              |                              |            |             |                   |                        |
|-----------------------|-----------------|--|------------------------------|------------------------------|------------|-------------|-------------------|------------------------|
|                       |                 | Not in the last 7 days                                 | 1-3 times in the last 7 days | 4-6 times in the last 7 days | Once daily | Twice daily | Three times a day | 4 and more times a day |
| Non-carbonated drinks | Two parents     | 39 (81.3)  | 47 (90.4)                    | 26 (89.7)                    | 38 (97.4)  | 18 (100)    | 9 (90)            | 3 (100)                |
|                       | One parent      | 8 (16.6)   | 5 (9.6)                      | 3 (10.3)                     | 1 (2.6)    | 0           | 0                 | 0                      |
|                       | Guardian        | 1 (2.1)  | 0                            | 0                            | 0          | 0           | 1 (10)            | 0                      |
|                       | <b>Total</b>    | 48 (100)   | 52 (100)                     | 29 (100)                     | 39 (100)   | 18 (100)    | 10 (100)          | 3 (100)                |
| Carbonated drinks     | Two parents     | 78 (86.7)  | 50 (94.3)                    | 13 (100)                     | 22 (91.7)  | 10 (100)    | 1 (50)            | 6 (85.7)               |
|                       | One parent      | 12 (13.3)  | 2 (3.8)                      | 0                            | 2 (8.3)    | 0           | 1 (50)            | 0                      |
|                       | Guardian        | 0  | 1 (1.9)                      | 0                            | 0          | 0           | 0                 | 1 (14.3)               |
|                       | <b>Total</b>    | 90 (100)   | 53 (100)                     | 13 (100)                     | 24 (100)   | 10 (100)    | 2 (100)           | 7 (100)                |
| Milk                  | Two parents     | 35 (94.6)  | 49 (87.5)                    | 31 (86.1)                    | 48 (92.3)  | 13 (100)    | 1 (50)            | 3 (100)                |
|                       | One parent      | 2 (5.4)  | 5 (8.9)                      | 5 (13.9)                     | 4 (7.7)    | 0           | 1 (50)            | 0                      |
|                       | Guardian        | 0  | 2 (3.6)                      | 0                            | 0          | 0           | 0                 | 0                      |
|                       | <b>Total</b>    | 37 (100)   | 56 (100)                     | 36 (100)                     | 52 (100)   | 13 (100)    | 2 (100)           | 3 (100)                |

Of the total of 199 students, 72.4% consumed fruits daily one or more times: 74 (77.1%) in urban and 70 (68%) in rural areas ( $p < 0.05$ ); 53.3% eat vegetables irregularly or never: 48 (50%) in urban and 58 (56.3%) in rural area; 93 (46.7%) consumed vegetables daily once or more times: 48 (50%) in urban and 45 (43.7%) in rural area ( $p < 0.05$ ). A total of 48 (24.1%) students did not consume non-carbonated drinks: 25 (26%) in urban and 23 (22.3%) in rural areas ( $p > 0.05$ ); 43 (21.6%) consumed carbonated beverages daily once or more times: 17 (17.7%) in urban and 26 (25.2%) in rural areas ( $p > 0.05$ ); 129 (64.8%) did not eat milk regularly: 44 (45.8%) in urban and 85 (82.5%) in rural areas ( $p < 0.05$ ) (Table 3).

It was found that there was no statistically significant difference in the consumption of non-carbonated drinks and in milk consumption relative to the family status (whether the adolescents live with two parents, one parent, or a guardian) ( $p > 0.05$ ), but a statistically significant differ-

ence was found in the consumption of carbonated drinks ( $p < 0.05$ ) (Table 4).

By analysing the consumption of non-carbonated drinks in relation to the working status of the parents, it was statistically significant that more frequently students consumed drinks regularly if their parents were employed, 60 (30.2%) ( $p < 0.05$ ). By analysing the regular consumption of carbonated drinks, it was found that there was no statistically significant difference in relation to the working status of the parents: 30 (15.1%) adolescents with employed parents and 9 (4.5%) with unemployed parents ( $p > 0.05$ ). By analysing milk consumption, there was a statistically significant difference in relation to the working status of parents: 58 (29.1%) students with employed and eight (4%) with unemployed parents consumed milk ( $p < 0.05$ ) (Table 5).

## DISCUSSION

This survey involved 199 respondents from the entire area of the City of Zenica (110,663 inhabi-

**Table 5. Consumption of beverages in relation to employment of parents**

| Beverages             | Working status of parents | No (%) of students per number of week/day consumptions |                              |                              |            |             |                   |                        |
|-----------------------|---------------------------|--|------------------------------|------------------------------|------------|-------------|-------------------|------------------------|
|                       |                           | Not in the last 7 days                                 | 1-3 times in the last 7 days | 4-6 times in the last 7 days | Once daily | Twice daily | Three times a day | 4 and more times a day |
| Non-carbonated drinks | Employed                  | 28 (58.3)  | 34 (65.4)                    | 21 (72.4)                    | 35 (89.7)  | 14 (77.8)   | 9 (90)            | 2 (66.6)               |
|                       | Unemployed                | 17 (35.4)  | 15 (28.8)                    | 8 (27.6)                     | 3 (7.7)    | 4 (22.2)    | 0                 | 0                      |
|                       | Pensioner                 | 1 (2.1)  | 1 (1.9)                      | 0                            | 0          | 0           | 1 (10)            | 1 (33.3)               |
|                       | Student                   | 2 (4.2)  | 2 (3.8)                      | 0                            | 1 (2.6)    | 0           | 0                 | 0                      |
|                       | <b>Total</b>              | 48 (100)   | 52 (100)                     | 29 (100)                     | 39 (100)   | 18 (100)    | 10 (100)          | 3 (100)                |
| Carbonated drinks     | Employed                  | 69 (76.7)  | 37 (69.8)                    | 7 (53.8)                     | 16 (66.6)  | 8 (80)      | 1 (50)            | 5 (71.4)               |
|                       | Unemployed                | 19 (21.1)  | 13 (24.5)                    | 6 (46.2)                     | 7 (29.2)   | 0           | 1 (50)            | 1 (14.3)               |
|                       | Pensioner                 | 1 (1.1)  | 1 (1.9)                      | 0                            | 0          | 1 (10)      | 0                 | 1 (14.3)               |
|                       | Student                   | 1 (1.1)  | 2 (3.8)                      | 0                            | 1 (4.2)    | 1 (10)      | 0                 | 0                      |
|                       | <b>Total</b>              | 90 (100)   | 53 (100)                     | 13 (100)                     | 24 (100)   | 10 (100)    | 2 (100)           | 7 (100)                |
| Milk                  | Employed                  | 26 (70.3)  | 31 (55.4)                    | 28 (77.8)                    | 45 (86.5)  | 9 (69.2)    | 1 (50)            | 3 (100)                |
|                       | Unemployed                | 10 (27)  | 22 (39.3)                    | 7 (19.4)                     | 5 (9.6)    | 3 (23)      | 0                 | 0                      |
|                       | Pensioner                 | 0  | 2 (3.6)                      | 1 (2.8)                      | 1 (1.9)    | 0           | 0                 | 0                      |
|                       | Student                   | 1 (2.7)  | 1 (1.8)                      | 0                            | 1 (1.9)    | 1 (7.7)     | 1 (50)            | 0                      |
|                       | <b>Total</b>              | 37 (100)   | 56 (100)                     | 36 (100)                     | 52 (100)   | 13 (100)    | 2 (100)           | 3 (100)                |

tants). The highest percentage of students both in urban and in rural areas lived with both parents. Parents employment was more frequent in students from the urban area.

In this research it was found that 27.7% of adolescents consumed fruit rarely or never, without major differences between urban and rural areas. The survey conducted in Travnik (Bosnia and Herzegovina) in 2013 showed that many more students (11 to 14 years of age), who consumed fruits were from rural area (11). In a research conducted in 2015 in Croatia a total of 19.4% of students (11 to 15 years of age) declared that their family consumed fruits daily, and 17.9% rarely (12). It was a worrying fact that 13.4% of adolescents stated their family did not consume fruit because it was too expensive (12). In Croatia in 2014, at the age of 15, only a quarter of adolescents eat fruits daily (7), and in 2010, 66% of students did not eat fruit every day (4). A study conducted in Sicily (Italy) showed that higher parental education, occupation, and rural environment were positively associated with students' (12 to 14 years of age) daily consumption of fruits (13). In Poland, it was shown that between rural and urban students (15 to 17 years of age) no difference was observed in frequency of fresh fruit consumption (14). In Moldova, only one third of students (11 to 15 years of age) eat fruits daily and one fifth eat fruits once a week or less (6). High socio-economic status and urban residence was positively associated with intake of high-energy foods, such as foods of animal origin, Western style foods and dairy products (15).

In this study, 53.3% of the students eat vegetables irregularly or never. In Italy it was shown that occupation and rural environment were positively associated with the consumption of vegetables in adolescents (13). In Croatia in 2010, the data showed that three quarters of students (11 to 15 years of age) did not eat vegetables every day (4). In Poland, there were no differences in dietary behaviours concerning frequency of vegetable consumption between rural and urban areas (14).

In this study, 84.4% of students regularly ate breakfast in the morning, more in urban areas. In Croatia in 2014, at the age of 15, only 52% of males and 44% of females ate breakfast every day (7). It is worrying that from 2002 until 2010 a significant proportion of children did not even have breakfast at all (4). Over 90% of the 11-year-old students of both sexes in the Netherlands and Portugal regularly had breakfast on working days, while the same applies to only 50% of students from Slovenia and Romania at the age of 11 (4). In Moldova, girls skip breakfast during the week more often than boys, and this behaviour worsens with age: 17-year-old students have no breakfast 2.5 times more often than those 11-year-old (6). Eating breakfast is significantly more prevalent among boys and girls from more affluent families (15).

In this research it was established that 64.8% of respondents consumed milk irregularly or never; students from the rural areas consumed much less milk than those from the urban areas. It would be expected that adolescents in rural areas are more likely to consume milk due to better access to food in the countryside, but the results of this research do not confirm this (16,17). In Indonesia, rural students reported higher mean intakes of milk products than urban students (18). The proportions of children who consumed milk were higher in urban families in Canada (19).

In this study it was found that 24.1% of students did not consume non-carbonated drinks, and 40.7% did not consume them daily, with statistically significantly more students with employed parents, who consumed non-carbonated juices. In Croatia in 2014 at the age of 15, one quarter of adolescents consumed non-carbonated drinks daily (7). It was observed that students residing in rural areas had a higher prevalence of occasional consumption of natural fruit non-carbonated drinks (20).

In this study there was a statistically significant difference in the consumption of carbonated drinks relative to the family status. In other research the proportion of students exposed to daily consumption of carbonated drinks was higher among those who reported they lived in urban areas (65.0%) compared to those who reported living in rural areas (55.3%) (20). Health behaviours in almost all countries are associated with family affluence, but the patterns emerging for some behaviours vary by region. Higher rates of daily carbonated drink consumption are associated with lower family affluence among girls and boys in the majority of western and northern countries. By contrast, the consumption of carbonated drinks is associated with high family affluence in Eastern Europe and the Baltic states

(21). In Travnik in 2013, adolescents in urban areas consumed two times more often carbonated drinks than adolescents in rural areas (12). In Bangladesh, almost 80% of the tested examinees consumed carbonated drinks rarely or never (17). According to the results of the research conducted by the Institute for Development of Youth, KULT in 2016, there is no accurate data on the prevalence of obesity among the youth in Sarajevo Canton (Bosnia and Herzegovina). According to the CIA data from 2014, it is stated that B&H is rated the 47<sup>th</sup> for the occurrence of obesity in adults (a list of 190 countries) (22). The same source states that 19.2% of adults in B&H are obese (22). However, various organizations dealing with the measurements of these health indicators have made warning estimates for the onset of obesity in B&H in the future in all age groups, and suggest that this issue should be dealt with seriously (20).

In Croatia, students with poor economic status had 70% higher chance of low health self-esteem and life dissatisfaction at the age of 11, while at the age of 15 they had 80% higher chance of low self-esteem, and even 140% higher chance of life dissatisfaction (4). The ways in which an individual relates to social networks and communities has important effects on their health and well-being (5). In other studies, dietary patterns of children were associated with family socioeconomic status, practice of food restriction by parents/guardians and location of residence in urban or rural areas. Better socioeconomic conditions contributed to a more nutritionally inadequate dietary pattern (23). Identifying regional demographics may be useful in tailoring healthy eating programs to the speci-

fic school. Selected food behaviours (consumption of vegetables, fruits, carbonated drinks, milk, breakfast) of elementary school students from Ontario and Alberta improved with increasing school socioeconomic status and varied according to rural/urban school localisation (19). The proper lifestyle of a child, including proper eating habits, should be monitored to ensure proper physical and psychological development. This applies particularly to rural areas which are economically, socially and educationally underdeveloped (24). Those responsible for health-related planning could benefit from knowledge of how their state ranks in comparison to others regarding the consumption of fruits and vegetables by rural population, who are increasingly identified as those at risk for health disparities (25).

In conclusion, Bosnia and Herzegovina is a country in transition, and Zenica-Doboj Canton is one of the poorest in the country. Changes in traditional family functioning (lower income, unemployment) can be linked with changed lifestyles (low consumption of fruits and vegetables, low consumption of milk both in rural and urban areas, consumption of carbonated drinks), especially in families in rural areas. It is necessary to work on health promotion, prevention of diseases, promotion of positive values and the importance of the family to reduce the negative effects of the society.

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## TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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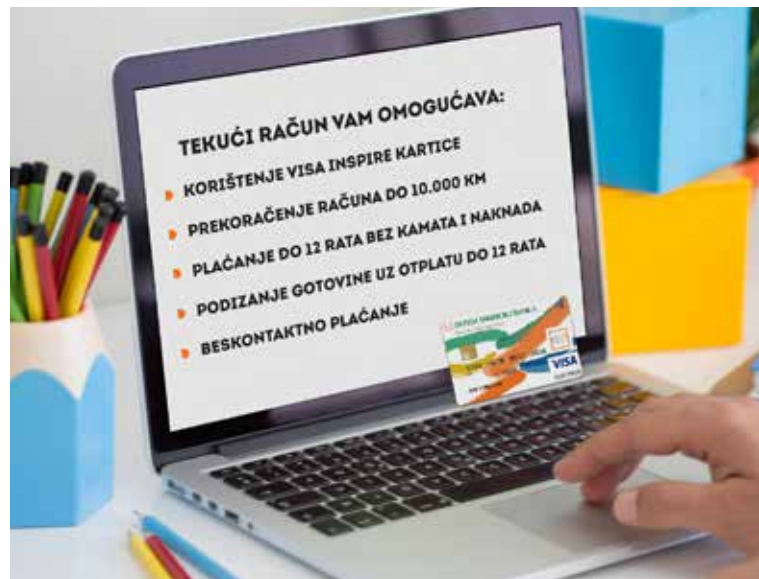
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