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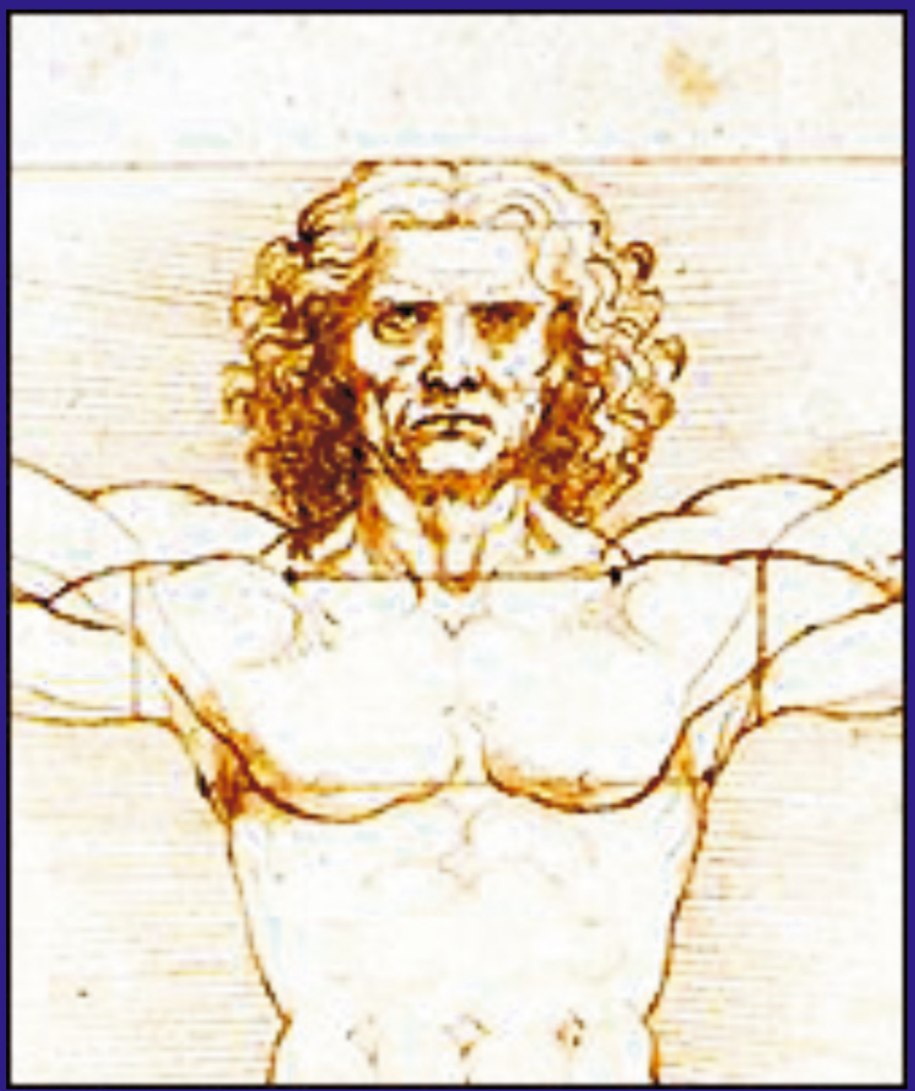

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Original article

KINESTHETIC AND VISUAL IMAGERY IN YOUNG ADULTS WITH CHRONIC NECK PAIN

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Abstract: **Background:** Young adults complain of neck pain almost every year. In recent years the ability of motor imagery (kinesthetic and visual imagery) in many musculoskeletal system problems other than neck pain in young adults has been investigated in the literature. The Cross-Sectional study aimed to question motor imagery ability in young adults with chronic neck pain.

Methods: Two groups were included in the study: the chronic neck pain group (n = 83) and the control group (n = 91). Motor imagery ability of both groups was evaluated with Movement Imagery Questionnaire-3. Additionally, in the chronic neck pain group, pain was evaluated with the Short Form-McGill Pain Questionnaire, disability was evaluated with the Neck Disability Index, and kinesiophobia was evaluated with Tampa Scale for Kinesiophobia.

Conclusions: Internal visual imagery and kinesthetic imagery were significantly different between chronic neck pain and control groups. There was a negative linear relationship between disability and internal visual imagery, external visual imagery, and kinesthetic imagery. Motor imagery ability is reduced in young adults with chronic neck pain. In addition, as the severity of disability increases, the motor imagery ability decreases. Therefore, it is considered appropriate to include a motor imagery training program when treating chronic neck pain in the future.

Keywords: Chronic, Movement, Pain, Young adults.

INTRODUCTION

One of the most commonly reported musculoskeletal problems in young adults is neck pain. The incidence of neck pain has increased in recent years (1, 2). As time progresses in neck pain, there are permanent structural and functional changes in the neuromuscular system of the cervical region (3). Recent studies indicate changes not only in this region, but also in the central region (4, 5). Changes in the central system are considered as neurochemical, structural, and functional changes in the cortical system (6). In recent years, musculoskeletal problems have also been manifested by the influence of motor imagery, an indicator of cortical reorganization (7).

Motor imagery is defined as the mental representation of movement without any body movement. Motor imagery is divided into two. The first is kinesthetic imagery based on feeling the movement, and the second is visual imagery based on visualizing the movement (8). Motor imagery is evaluated by different methods such as laterality judgment, mental chronometer, and questionnaire forms (9). The literature points out that motor imagery decreases in various musculoskeletal problems. The number of studies on individuals with neck pain is insufficient, and the results of these studies are under debate (10).

No studies are evaluating kinesthetic and visual imagery in detail with neck-pained individuals. In the literature, the study conducted on individuals with lower back pain states that motor imagery is affected by disability, kinesiophobia, and pain parameters. To establish successful treatment programs, we need studies evaluating motor imagery, by taking into consideration factors that are related to and affecting it. Our primary aim was to investigate the motor imagery ability of young adults with chronic neck pain. Our secondary aim was to determine the relationship between motor imagery and the factors that are related to and affecting it.

MATERIALS AND METHODS

Our cross-sectional study was carried out at Manisa Celal Bayar University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation. All

students of the department were informed (n = 590). Volunteers were divided into two groups, those with neck pain (chronic neck pain group) and those without neck pain (control group).

Inclusion criteria

Voluntary individuals aged 18-24 years with neck pain for at least 3 months were included in the chronic neck pain group. The control group consisted of healthy individuals aged 18-24 years who had no neck pain for at least 3 months.

Exclusion criteria

In both groups, patients with any neurological disorder, regular medication, and who had spinal surgery were excluded from the study. In addition, individuals in both groups were asked whether they had used any medication for at least 24-48 hours. Patients who were on medication were evaluated on another day.

Outcome measurement

The sociodemographic data of all young adult individuals were evaluated with data record form and motor imagery ability was evaluated with Movement Imagery Questionnaire-3. In addition to these evaluations, the pain level and quality of the chronic neck pain group were evaluated with the short-form McGill Pain Questionnaire, the level of disability was evaluated with the Neck Disability Index, and the kinesophobia was evaluated with the Tampa Scale for Kinesiophobia accompanied by a physiotherapist.

Firstly, gender, age, height, and weight information of the individuals were taken for sociodemographic information, and the duration of neck pain was recorded for months for individuals with neck pain. Both groups were then asked to answer the Movement Imagery Questionnaire-3.

Movement Imagery Questionnaire-3

The imagery influences of the individuals were evaluated with the Movement Imagery Questionnaire-3. The validity and reliability of the questionnaire, which was revised by Williams et al., were performed by Dilek et al. (11, 12, 13). The questionnaire consists of 3 sub-groups: kinesthetic, internal visual, and external visual imagery. The questionnaire, which consists of twelve questions, assesses the imagery ability of the person after 4 different movements. The person is asked to make the movement first and then image it. The higher the score, the more positive the imagery ability of the patient.

The short-form McGill Pain Questionnaire

The quality of pain was assessed by the Short Form McGill Pain Questionnaire. The validity and reliability of the questionnaire in Turkish, which was created by Melzack, were ensured by Yakut et al. (14, 15). The survey consists of three parts. In the first part, the features of pain are asked, 11 of which are sensory and 4 are perceptual. The higher the score, the greater the pain. In the second part of the questionnaire, five groups of words ranging from “mild pain” to “unbearable pain” are used to determine the severity of the person’s pain. In the third part, the current pain intensity of the person is evaluated using VAS (Visual Analog Scale).

Neck Disability Index

Neck Disability Index was used to evaluate the perceived limitation of the individual in daily living activities due to neck pain. The validity and reliability of the Neck Disability Index in Turkish, developed by Vernon and Mior, were made by Aslan et al. (16, 17). An increase in score indicates an increase in the level of disability.

Tampa Scale for Kinesiophobia

The Tampa Scale for Kinesiophobia is a 17-item scale developed to assess the fear of movement / (re)-injury. The validity and reliability of the questionnaire in Turkish, which was prepared by Miller et al., were made by Yılmaz et al. (18, 19). The increase in the score of the person on the scale indicates that the kinesiophobia is also high.

Statistical Methods

Sample size

The size to be included in the study and the smallest sample numbers of the volunteer and control groups were calculated with G Power 3.1. program. In the study conducted by La Touche R et al. (20), the mean and standard deviations of visual motor imagery were calculated with the values of 24.40 ± 2.86 in the low back pain group and 22.48 ± 3.75 in the control group ($d = 0.57$) and $\alpha = 0.05$ significance level was calculated at 80% strength. It was planned to include a minimum of 160 people, having at least 80 people in each group.

Data analysis

Since parametric test assumptions were not provided for numerical variables as descriptive statistics

in the study, median (minimum-maximum), frequency (n), and percentage (%) were given for categorical data. Whether there was a difference between the groups in terms of numerical variables was analyzed by the Mann-Whitney U test, one of the nonparametric tests. Pearson chi-square test was used to evaluate categorical data. The linear relationship between the variables and the strength of the relationship was examined with Significance Testing of the Spearman Rank Correlation Coefficient. A multiple linear regression model was formed by using a forward-selection method with the independent variables which were thought to affect the internal, external, and kinesthetic imagery as dependent variables. The adequacy of the model; Multiple correlation coefficients (R2), the overall significance of the model, and determination of multicollinearity were evaluated with VIF (Variance Inflation Factors) values, determination of autocorrelation was evaluated with the Durbin Watson test. The probability of Type I error was determined to be 0.05. Analyzes were performed using IBM SPSS V22.

RESULTS

There was no significant difference between the chronic neck pain and control groups in terms of age, height, weight and gender distributions (p = 0.173; p = 0.433; p = 0.894; p = 0.479, respectively) (Table 1).

Motor imagery

In terms of internal, external, and kinesthetic imagery values, a significant difference was found between internal visual and kinesthetic imagery, chronic neck pain, and control groups. There was no significant difference in terms of external visual imagery (p = 0.037; p = 0.047; p = 0.108, respectively) (Table 1).

Table 1. *Descriptive Statistics for Demografic Variables*

Variables	CNPG (n = 83)	CG (n = 91)	P value
	Medyan (Min-Max)	Medyan (Min-Max)	
Gender Female, n (%) Male, n (%)	 59 (71.1) 24 (28.9)	 69 (75.8) 22 (24.2)	 0.479[b]
Age (years)	20 (18-24)	20 (18-23)	0.173[a]
Boy (cm)	168 (155-188)	167 (153-187)	0.433[a]
Kilo (kg)	60 (40-97)	60 (40-105)	0.894[a]
IVI	6.25 (3.5-7)	6.50 (4-7)	**0.037[a]**
EVI	6.50 (2.5-7)	6.75 (4-7)	0.108[a]
KI	5.50 (2.25-7)	5.75 (4.25-7)	0.047[a]

a: Mann-Whitney U Test
b: Pearson Ki-Kare Test
CNPG: Chronic neck pain group; CG: Control group; KI: Kinesthetic Imagery; IVI: Internal Visual Imagery; EVI: External Visual Imagery

Table 2. *Results of Chronic neck pain group*

Variables	**CNPG**
	Medyan (Min-Max)
Pain Duration (months)	36 (4-120)
NDI (%)	22 (8-48)
SF-MPQ Sensory score Affective score Present Pain Intensity VAS	 9 (1-20) 2 (0-11) 2 (1-4) 3.50 (0.50-8.50)
TSK	36 (24-47)

CNPG: Chronic neck pain group; NDI: Neck Disability Index; SF-MPQ:Short Form-McGill Pain Questionnaire; TSK: Tampa Scale of Kinesiophobia.

Correlation analysis

A negative linear relationship was found between the kinesthetic imagery score and the Neck Disability Index score (p = 0.003). When the degree of significant correlation coefficient was examined, the correlation was weak (rs = -0,324) (Table 2).

There was a negative linear relationship between internal visual imagery scores and the Neck Disability Index, Tampa Scale for Kinesiophobia scores and neck pain duration (p = 0.020; p = 0.001; p = 0.020, respectively). When the degree of the three significant correlation coefficients were examined, the correlation was weak (rs = -0.255; rs = -0.371; rs = 0.254) (Table 2).

A negative linear relationship was found between the external visual imagery score and Neck Disability

Index and Tampa Scale for Kinesiophobia scores (p = 0.005; p = 0.009). When the degree of significant correlation coefficients was examined, the correlation was weak (rs = -0.302; rs = -0.284) (Table 2).

Regression analysis

A multiple linear regression model was established with independent variables (duration of pain, disability, kinesophobia, pain quality) which were thought to affect kinesthetic imagery. According to the established regression model, two significant variables were found. The Neck Disability Index and Short Form McGill Pain Questionnaire's perceptual influence together can explain 18.4% of the kinesthetic imagery dependent variable (p < 0.001; R2 = 0.184) (Table 3).

A multiple linear regression model was established with independent variables (duration of pain, disability, kinesophobia, pain quality) which were thought to affect internal visual imagery. According to

Table 3. *Correlation Between Movement Imagery Questionnaire-3 Results And NDI, MPQ, TSK*

	n = 83	**IVI**	**EVI**	**KI**
NDI	r_s	-0.255	-0.302	-0.324
	p	**0.020**	**0.005**	**0.003**
TSK	r_s	-0.371	-0.284	-0.197
	p	**0.001**	**0.009**	0.075
SF-MPQ Sensory Score	r_s	-0.136	-0.157	0.080
	p	0.219	0.156	0.470
SF-MPQ Affective Score	r_s	-0.135	-0.137	0.003
	p	0.223	0.218	0.976
SF-MPQ Present Pain Intensity	r_s	-0.046	-0.090	-0.150
	p	0.681	0.418	0.176
SF-MPQ Visual Analog Score	r_s	0.009	-0.157	-0.206
	p	0.939	0.156	0.062
Neck pain duration (months)	r_s	-0.254	-0.126	-0.207
	p	**0.020**	0.258	0.061

r_s: Spearman's Correlation Coefficient, KI:Kinesthetic Imagery; IVI:Internal Visual Imagery; EVI:External Visual Imagery; NDI: Neck Disability Index; MPQ: Short Form-McGill Pain Questionnaire; TSK: Tampa Scale of Kinesiophobia

Table 4. *Regression Analysis of Movement Imagery Questionnaire-3*

IVI	R^2		**Anova p value**		
	0.170		0.001		
Independent Variables	Unstandardized Coefficients		p	95,0% Confidence Interval for B	
	B	Standart Error		Lower Bound	Upper Bound
TSK	-0.054	0.018	**0.004**	-0.090	-0.017
Neck pain duration (months)	-0.008	0.004	**0.031**	-0.015	-0.001
EVI	**R^2**		**Anova p value**		
	0.149		< 0.001		
Independent Variables	Unstandardized Coefficients		p	95,0% Confidence Interval for B	
	B	Standart Error		Lower Bound	Upper Bound
NDI	-0.043	0.012	**< 0.001**	-0.066	-0.020
KI	**R^2**		**Anova p value**		
	0.184		< 0.001		
Independent Variables	Unstandardized Coefficients		p	95,0% Confidence Interval for B	
	B	Standart Error		Lower Bound	Upper Bound
NDI	-0.052	0.012	**< 0.001**	-0.066	-0.020
MPQ Affective Score	0.099	0.046	**0.037**	-0.077	-0.028

KI: Kinesthetic Imagery; IVI: Internal Visual Imagery; EVI: External Visual Imagery; NDI: Neck Disability Index; MPQ: Short Form-McGill Pain Questionnaire; TSK: Tampa Scale of Kinesiophobia

the established regression model, two significant variables were found. the Tampa Scale for Kinesiophobia and duration of pain can explain 17% of the internal visual imagery dependent variable ($p = 0.001$; $R2 = 0.170$) (Table 3).

A multiple linear regression model was established with independent variables (duration of pain, disability, kinesophobia, pain quality) which are thought to affect external visual imagery. According to the established regression model, only 1 variable was found. Neck Disability Index can explain 14.9% of the external visual imagery dependent variable ($p < 0.001$; $R2 = 0.149$) (Table 3).

DISCUSSION

As a result of our study, we found out that kinesthetic and internal visual imagery ability has decreased in young adults with chronic neck pain. In addition, there has been a low correlation between disability and internal visual, external visual, and kinesthetic imagery. It has been seen that visual imagery has a negative linear relationship with kinesiophobia. In addition, it has been seen that the visual imagery of the neck decreases as the pain duration increases and the kinesthetic imagery decreases as the sensory intensity of the pain increases.

Motor imagery ability

In a review of studies evaluating motor imagery in musculoskeletal problems, it has been seen that motor imagery was affected in lower extremity-upper extremity-facial pain-low back pain patient groups. The results differ only in neck pain. (7). In line with our results, Elsig et al. show that motor imagination is reduced in adults with chronic neck pain (21). Two different studies indicate that motor imagery is not affected in patients with neck pain (22, 23).

In studies evaluating individuals with neck pain, it has been observed that the groups have been classified into recurrent neck pain (21), whiplash (23), and whiplash with non-specific neck pain groups (22). In two studies that evaluated the same whiplash patient group, it was reported that motor imagery was not affected (22, 23). However, it supports the presence of motor imagery in non-whiplash diagnoses.

When we examine the literature methodologically, unlike in our study, it has been seen that motor imagery has been assessed from the neck (21), neck and foot (23), or hand region (22) of the patients. We think that the results might be different with the heterogeneity of the methods of the studies. (21, 22, 23). In our study, the motor imagery of the whole body was evaluated.

In terms of determinants (24) that make a difference in the cortical system such as age (25) and gender, our study consists of women between 18-24 years of age, with a ratio of 71-75%. All other studies were conducted with an adult age group. Gender is another factor that determines the innate difference in the cortical system (26). Gender ratios of studies indicating no motor imagery influences are close to each other (22, 23). In the study of Elsig et al. together with our study, where it is supported that there is a motor imagery influence, the female gender constitutes the majority of the groups (21). Differences created by different sexes and ages in the cortical system might also affect the results of our studies.

Factors Affecting Motor Imagery

The relationship between disability and motor imagery

In our study, there was a negative linear relationship between disability and all imagery types. In addition, a 1-unit increase in disability results in a 0.04 decrease in external visual imagery. Elsig et al. also show a negative linear relationship with disability, similar to our motor imagery results (21). There is no different study showing the relationship between disability and motor imagery level in neck-pained individuals. It has been seen that the results of the study evaluating the visual and kinesthetic imaging abilities of lower back pain patients- a group of otherwise diagnosed patients, and our results are similar (20). Even if the number of subjects is insufficient, there is a relationship between disability and imagery even in a group with different diagnoses. This shows that motor imagery decreases as the level of restriction increases during daily life activities.

The relationship between kinesiophobia and motor imagery

In our study, the increase of kinesiophobia decreases internal visual imagery and external visual imagery. In addition, a 1-unit increase in kinesiophobia reduces internal visual imagery by 0.05 units. In the study of Touche et al., it has been seen that there is a significant relationship between visual imagery and kinesiophobia in lower back pain patients, the same as in our study. Touche et al. assessed visual and kinesthetic imagery the same as in our study (20). However, the questionnaire used does not examine the types of visual imagery. But in our study, information on the two types of visual imagery, i.e. internal and external visual imagery levels, can be obtained.

The relationship between pain and motor imagery

In our study, as the duration of pain increases, the level of internal visual imagery decreases. Our study is the first to describe the relationship between pain and visual and kinesthetic imagery types. Among the studies, only Elsig et al.'s study shows that the increase in pain duration results in a decrease in motor imagery (21). It is reported in the literature that pain that is becoming chronic in any part of the body continues cortical reorganization (27, 28, 29). Our study supports that motor imagery, which is a part of cortical influence, is affected by the process of pain becoming chronic.

It is also seen that one unit of sensory influence of pain reduces kinesthetic imagery by 0.09 units. Therefore, an increase in the perceived pain intensity indicates that kinesthetic imaging ability decreases. In the literature, there is not any study explaining this relationship, either.

Strengths, limitations, and recommendations for further research

In the literature, our study is the first to assess the young adult age group according to types of motor imagery (internal visual, external visual, and kinesthetic imagery). In the studies examined, it has been observed that motor imagery evaluation was limited to a small region of the body. Our study evaluates the imaging ability of the whole body. Moreover, there is an insufficient number of cases in studies evaluating individuals with neck pain (21, 23). Our study is the only one with the highest number of cases as well as evaluating the young adult group only.

Our study is a descriptive study evaluating people according to the survey results. We did not evaluate motor imagery performance times during the assessment of motor imagery ability. In addition, the female gender was dominant in both groups.

Further studies are needed considering the factors that may affect the level of motor imagery such as gender and age in future studies due to cortical differences. Studies are showing the positive effects of motor imagery training on different parameters in the treatment of chronic neck pain (30). In our study, it is shown that kinesthetic and internal visual imagery training can be added to treatment programs.

CONCLUSION

As a result of this study, internal visual imagery and kinesthetic imaging ability decreased in young adults with chronic neck pain. With the increase in disability, the overall motor imagery ability is reduced. Visual imaging ability is also affected by the increase of kinesiophobia.

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Sažetak

KINESTETIČKE I VIZUELNE SLIKE KOD MLADIH ODRASLIH OSOBA SA HRONIČNIM BOLOM U VRATU

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Uvod: Mladi se žale na bol u vratu skoro svake godine. Poslednjih godina u literaturi se istražuje sposobnost motoričke slike (kinestetičke i vizuelne slike) kod mnogih problema mišićno-skeletnog sistema, pored bolova u vratu, kod mladih.Studija preseka imala je za cilj ispitivanje sposobnosti motoričke slike kod mladih odraslih osoba sa hroničnim bolom u vratu.

Metode: U istraživanje su uključene dve grupe: grupa sa hroničnim bolom u vratu (n = 83) i kontrolna grupa (n = 91). Sposobnost motoričkih slika obe grupe je procenjena pomoću Upitnika o slikama pokreta-3. Pored toga, u grupi sa hroničnim bolom u vratu, bol je procenjen kratkim MekGil upitnikom za bol, invalidnost je procenjena indeksom invalidnosti vrata,a

kineziofobija je procenjena Tampa skalom za kineziofobiju.

Zaključak: Unutrašnje vizuelne slike i kinestetičke slike bile su značajno različite između grupe sa hroničnim bolom u vratu i kontrolne grupe. Postojala je negativna linearna veza između invaliditeta i unutrašnjih vizuelnih slika, spoljašnjih vizuelnih slika i kinestetičkih slika. Sposobnost motoričkih slika je smanjena kod mladih odraslih osoba sa hroničnim bolom u vratu. Pored toga, kako se težina invaliditeta povećava, sposobnost motoričke slike se smanjuje. Stoga se smatra prikladnim uključiti program obuke motoričkih slika kada se u budućnosti leči hronični bol u vratu.

Ključne reči: hronični, pokret, bol, mladi.

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PULMONARY ARTERY DIAMETER ON CHEST CT PREDICTS IN-HOSPITAL MORTALITY IN PATIENTS WITH COVID-19 PNEUMONIA

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Abstract: **Background:** Enlargement of the pulmonary artery (PA) could be helpful in risk stratification by the chest CT on the admission of COVID-19 patients.

Methods: This study aimed to associate PA diameter and overall mortality in COVID-19 pneumonia. We designed a retrospective study between January 2021 and May 2021 in tertiary-level hospitals in Gebze, Turkey. Subjects were evaluated in two groups according to their survivor status (survivors and non-survivors). Then biochemical, demographic, and clinical values were compared via the groups to define the predictive value of PA diameter on chest CT images.

Results: In the enrolled 594 COVID-19 in-hospital patients (median age was 45 (34-58) years, 263patients (44.3%) were female. 44 patients (7.4%) died during hospitalization. Multivariate Cox-proportion regression model yielded main PA ≥ 29 mm on admission showed that as independent predictors of death (long rank <0.001, median survival time 28 days). Cumulative survival rates were MPAD ≥ 29 mm 45% and < 29 mm 90% yielded (p < 0.001).

Conclusions: PA dilatation is strongly linked with in-hospital mortality in hospitalized patients with COVID-19 infection. Thus increased PA diameter on chest CT at admission may guide rapid and early diagnosis of high-risk patients.

Keywords*:* COVID-19, Computed tomography, pulmonary artery, mortality, pneumonia.

INTRODUCTION

The coronavirus 2019 (COVID-19) infection has become a global health problem that affects large populations in a short time over the world (1, 2). Its clinical presentation ranges from asymptomatic patients to acute respiratory failure, multiple system dysfunction, and death. It also impairs the vascular endothelial structure and function (3). Severe complications more frequently occur in advanced age, smoking, and comorbidities like hypertension (HT), diabetes mellitus (DM), cardiovascular disease, cardiac arrhythmia, dementia, cancer, chronic kidney, cerebrovascular, and respiratory disease (4, 5, 6). Chest computed tomography (CT) may have a crucial role in diagnosing and prognosis of this infection (7, 8). CT is widely used, especially in the emergency department, to make a risk assessment, and evaluate lung involvement and differential diagnosis. PA enlargement is a predictor of hemodynamic instability such as; right ventricular failure, pulmonary hypertension (PH), and embolism (9, 10, 11). Although PA dilatation reflects vascular injury, abnormal coagulation, hypoxia, and inflammation, the optimal cut-off value of PA diameter in COVID-19 patients is unknown. We hypothesized that the enlargement of PA could be helpful in risk stratification on the admission to hospital in the COVID-19 patient population. Therefore, we aimed to relationship PA diameters and in-hospital mortality of COVID-19 pneumonia.

MATERIAL and METHODS

Patients population

This study planned a retrospective and observational between January 2021 and May 2021. Five hundred ninety-four COVID-19 patients, diagnosed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests and non-cardiac gated thoracic CT scans, were enrolled in the study. Baseline laboratory findings were obtained from the hospital's electronic database system. Complete blood counts and biochemical parameters including blood glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), high sensitive CRP (hs-CRP), ferritin, fibrinogen, D- Dimer, and high sensitive cardiac troponin I (hs-cTnI) were evaluated on admission. For patients under 18 years old, CT images

cannot be evaluated, pneumonia other than COVID-19 infection, non-hospitalized patients, and history of PH and thromboembolism were excluded. The study conforms to the principles in the Declaration of Helsinki and the local ethics committee's approval.

CT imaging

Thoracic CT imaging was performed using a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems, Japan) with 3-mm reconstructed slice thickness. CT images were obtained in the supine position, end of inspiration, and hands raised by the side. Tube current and voltages were 300 mA, and 120 kV, respectively, and gantry rotation time was 0.4s. All images were unenhanced and non-gated. The main PA diameter (MPAD), left PA diameter (LPAD), and right PA diameter (RPAD) were measured at the level of PA bifurcation from CT images by two cardiologists who were bound to the study (Figure 1).

Statistical analysis

Data were analyzed via the SPSS 22.0 version (SPSS Inc, Chicago, Illinois). The mean and standard deviation were used to describe continuous variables with normal distribution. Median, minimum, and maximum values were used to describe without normal distribution. Categorical variables were described with frequency and percentage. Continuous variables between two dependent groups were compared using Paired t-test and Wilcoxon t-test according to their distribution. Student t-test and Mann-Whitney U test were used to compare continuous variables with normal and without normal distribution respectively. Receiver operating characteristic (ROC) curve analyses were used for the optimal cut-off point of MPAD, LPAD, and RPAD. The area under the ROC curve (AUC) was reported with a % 95 confidence interval (CI). Pearson Chi-Square and Fisher's Exact tests were used in group comparison. Multivariable cox regression analysis was employed to assess the relationship between CT parameters (MPAD, LPAD, RPAD) and death as the outcome, summarized by hazard ratios (HR) and associated 95% confidence intervals. Survival analyses were calculated by the Kaplan-Meier method, and differences in the parameters were evaluated using a log-rank test. P-value was set at 0.05 in all statistical analyses.

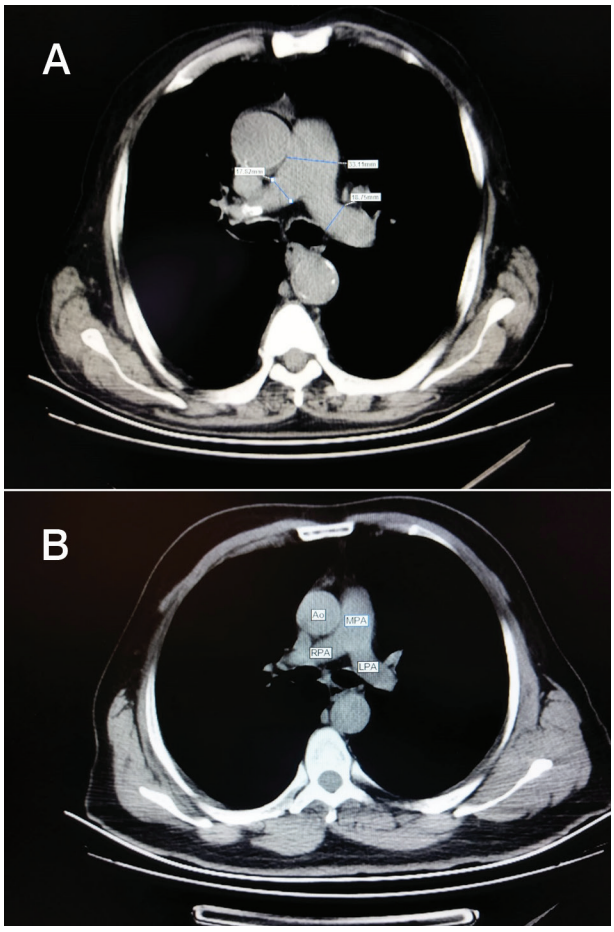


Figure 1. A-B: *From chest CT the diameter of the main, left and right pulmonary artery was measured at the level of bifurcation on the mediastinal window*

RESULTS

A total of 594 SARS-CoV-2 patients were hospitalized and divided into two groups according to their survival status [survivor (n = 550) and non-survivor (n = 44)]. Baseline characteristics, and clinical and laboratory parameters of the study population are demonstrated in Table 1. The median age was 45 (34-58), and 263 patients (44.3%) were female. One hundred eighty-five patients (31.1%) were smokers, 79 patients (13.3%) had DM, 133 patients (22.4%) had HT, 14 patients (2.3%) had congestive heart failure (CHF), and 66 patients (11.1%) had chronic obstructive pulmonary disease.

Non-survivors were older [median age 72 (63–80) vs 44 (33–55), $p < 0.001$] and had a higher prevalence of HT (50% vs 21.2%, $p < 0.001$), CHF (18.2% vs 1.1%, $p < 0.001$), coronary artery disease (CAD) [13.6% vs 2.9%, $p < 0.001$] and chronic obstructive pulmonary disease (34.1% vs 9.8%, $p < 0.001$). DM was similar frequency in the groups [18.2% vs 13.6%, $p = 0.397$]. Compared to survivors, non-survivors had higher fever [37.5 (38.3 - 36.8) vs 37.2 (36.4 - 38.0)C, $p = 0.019$], and heart rate [98 (91 - 106) vs 94 (89 - 102), $p = 0.04$], lower systolic blood pressure [110 ± 11 mm/Hg vs 114 ± 8 mm/Hg, $p = 0.002$], and lower oxygen saturation on admission [90 (83 - 97) vs 94 (91 - 97), $p < 0.001$]. On laboratory examination, non-survivors had higher fasting blood glucose [134 (106 - 235) vs 100 (87 - 115)

Table 1. *Baseline patient characteristics and clinical features of cohort*

Survival	Non-survival	Total	P value
Age (years) 45 ± 15	71 ± 13	47 ± 17	< 0.001
Gender n (%) (male/female) 44-56	45.5-54.5	41.1-55,9	0.85
DM, n (%) 71 (13.6)	8 (18.2)	79 (13.9)	0.397
HT, n (%) 111 (21.2)	22 (50)	133 (23.5)	< 0.001
CHF, n (%) 6 (1.1)	8 (18.2)	14 (2.5)	< 0.001
CAD, n (%) 15 (2.9)	6 (13.6)	21 (3.7)	< 0.001
CPD, n (%) 51 (9.8)	15 (34.1)	66 (11.6)	< 0.001
Smoking, n (%) 171 (32.7)	14 (31.8)	185 (32.6)	0.905
Saturation O (%) 94 ± 3	90 ± 7	93 ± 4	< 0.001
Fewer (D) 37.2 ± 0.8	37.5 ± 0.8	37.2 ± 0.8	0.019
Heart rate (mn) 96	98	96	0.053
SBP (mm/hg) 114.99 ± 8.96	110.16 ± 11.05	114.61 ± 9.22	0.002
MPA (mm) 25.74 ± 3.48	32.11 ± 4.45	26.23 ± 3.95	< 0.001
RPA (mm) 17.81 ± 3.25	24.11 ± 4.18	18.30 ± 3.73	< 0.001
LPA (mm) 17.65 ± 2.96	23.75 ± 3.77	18.12 ± 3.44	< 0.001
Glucose (mg/dL) 100 ± 89	134 ± 106	101 ± 90	< 0.001
Creatinine (mg/dL) 0.8 ± 0.7	1.2 ± 0.8	0.8 ± 0.7	< 0.001
BUN (mg/dL) 12 ± 10	33 ± 19	13 ± 10	< 0.001
AST (U/L) 23 ± 17	31.5 ± 23	24 ± 18	< 0.001
ALT (U/L) 22 ± 16	20 ± 13.5	22 ± 16	0.352
Troponin (ng/mL) 0.001 ± 0.003	0.03 ± 0.13	0.013 ± 0.042	< 0.001
Ferritin (µg/L) 100.1 ± 41.6	401.0 ± 153.5	109.0 ± 43.5	< 0.001
Hs-CRP (mg/L) 7.2 ± 1.7	93.2 ± 43.8	7.8 ± 1.9	< 0.001
WBC 103/µL 6708 ± 2677	11803 ± 6572	7108 ± 3436	< 0.001
Hemoglobin (g/dL) 13.6 ± 1.6	11.5 ± 2.6	13.4 ± 1.8	< 0.001
Thrombocyte (103/µL) 233 ± 81	245 ± 129	234 ± 85	0.344

CAD: coronary artery disease, CHF: chronic heart failure, CPD: chronic pulmonary disease, DM: diabetes mellitus, HT: hypertension, SBP: systolic blood pressure, MPA: Main pulmonary artery, RPA: Right pulmonary artery, LPA: left pulmonary artery, D: degree, mn: minute

mg/dL, p < 0.001], creatinine [1.2 (0.8 - 2.2) vs 0.8 (0.7 - 0.9) mg/dL, p < 0.001], AST [31.5 (23 - 46.5) vs 22 (17 - 30) U/L, p < 0.001], D-Dimer [1.2 (0.52 - 3.1) vs 0.37 (0.27 - 0.68) ng/ml], hs-CRP [93.2 (43.8 - 192) vs 7.4 (2 - 22.6) mg/L, p < 0.001], ferritin [401 (153.5 - 585) vs 98 (41 -220.1) ng/mL, p < 0.001], white blood cell count (WBC) [11.8 ± 6.5 vs 6.6 ± 2.6 x103/ml, p < 0.001], fibrinogen [447 (389 - 525) vs 382 (321 vs 446) mg/dl] and hs-cTnI [30 (9 - 132) vs 1 (0.1 - 3) pg/mL, p < 0.001] levels. However, hemoglobin levels [11.5 ± 2.6 vs 13.6 ± 1.6 g/dL, p < 0.001] were lower in non-survivors, and ALT levels were similar in both groups (20 (13.5 - 37.5) vs 22 (16 - 36) U/L, p = 0.352). MPAD [32.11 ± 4.45 vs 25.74 ± 3.48, p < 0.001] LAPD [23.75 ± 3.77 vs 17.65 ± 2.96, p < 0.001], and RPAD [24.11 ± 4.18 vs 17.81 ± 3.25, p < 0.001] were significantly higher in non-survivor group compared to survivor group. The mean hospital stay was 5 (3-7) days and hospitalization period was longer in non-survivor group [8 (4-12) days vs 5 (3-7) days (p < 0.001)].Cumulative survival rates were MPAD > 29 mm 45% and < 29 mm 90% respectively (p < 0.001) (Figure 2). Receiver operator characteristic curve of main, left and right PA diameter for predicting deaths. MPA ≥ 29 mm, with 79.55% sensitivity and 87.19% specificity. Area under the rock curve (AUC) was 0.879 (p < 0.001) (Figure 3) At cox's regression analysis adjusted with ages, comorbidities, oxygen saturation, fewer, hs-cTnI and inflammatory parameters were predicting in-hospital mortality (Figure 4, Table 2).

Table 2. *At cox's regression analysis adjusted with ages, comorbidities, oxygen saturation, fewer, hs-cTnI and inflammatory parameters were predicting in-hospital mortality*

Variable	HR [95% CL]	P value
MPA	1.252 [1.180-1.327]	< 0.001
MPA + age	1.168 [1.085-1.258]	< 0.001
MPA + age + HT + CAD	1.158 [1.072-1.250]	< 0.001
MPA + age + HT + CHF	1.156 [1.074-1.244]	< 0.001
MPA + age + HT + CPD	1.168 [1.081-1.262]	< 0.001
MPA + HT + sat + fewer	1.244 [1.161-1.332]	< 0.001
MPA + glucose + crea + CRP	1.217 [1.134-1.306]	< 0.001
MPA + hs-cTnI + fibrinogen + D-dimer	1.305 [1.033-1.650]	0.026

MPA: Main pulmonary artery, HT: hypertension, sat: saturation, CAD: coronary artery disease, CHF: chronic heart failure, CPD: chronic pulmonary disease, crea: creatinine.

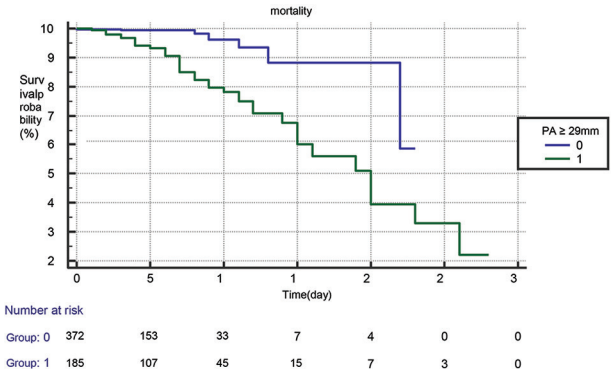
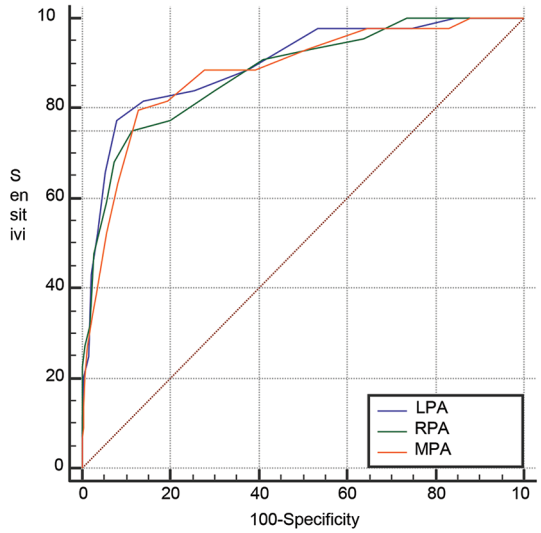
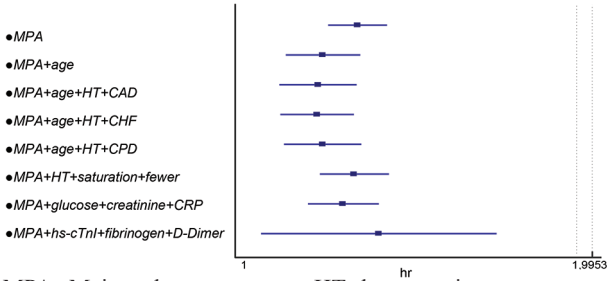


Figure 2. *Kaplan-Meier survival curves for PA trunk diameter showed that PA diameter ≥ 29 mm was significant predictor of mortality (long-rank p < 0.001, median survival time was 28 days)*



MPA: Main pulmonary artery, RPA: Right pulmonary artery, LPA: Left pulmonary artery

Figure 3. *Receiver operator characteristic curve of main, left and right pulmonary artery diameter for predicting deaths. MPA ≥ 29 mm, with 79.55% sensitivity and 87.19% specificity. Area under the rock curve (AUC) was 0.879, (p < 0.001)*



MPA: Main pulmonary artery, HT: hypertension, sat: saturation, CAD: coronary artery disease, CHF: chronic heart failure, CPD: chronic pulmonary disease, crea: creatinine.

Figure 4. *At cox's regression analysis adjusted with ages, comorbidities, oxygen saturation, fewer, hs-cTnI and inflammatory parameters were predicting in-hospital mortality*

DISCUSSION

The role of chest CT imaging in the COVID-19 infection is apparent as to determine the prevalence and severity of the disease, early screening, and making different diagnoses. In a study by Fang et al., the sensitivity of chest CT with COVID-19 was 98% (12). Multifocal bilateral distribution of ground-glass opacities, consolidations, air bronchogram, crazy-paving pattern, pulmonary vascular enlargement, linear opacification, and airway and pleural changes are the typical CT evidence of COVID-19 (7, 8).

We showed that MPAD ≥ 29 mm was an independent predictor of the severity of the COVID-19 infection. The enlargement of PA was considered to be a specific determinant of mortality and in-hospital duration and was found to be a negative correlation with the oxygen saturation at the time of admission. PA enlargement detected by CT imaging is a finding that helps predict worse outcomes (13). Although PA enlargement is associated with poor prognosis in acute pulmonary edema, embolism, and heart failure, insuf-

ficient data on its prognostic significance and optimal cut-off PA diameter in COVID-19 infection. A normally mean PA diameter calculated in a healthy population was 26.1±2.4 mm in men and 22.9±1.9 mm in women (14). This value was 25.74 ± 3.48 mm in the entire study group. A study conducted by Esposito et al., which included 1461 patients, determined that an MPAD ≥ 31 mm in COVID-19 patients was an independent predictor of mortality (15). The study by Zhu et al. demonstrated that MPAD ≥ 29 mm is a significant predictor of mortality (10). Truong et al. demonstrated that the predictive value of MPAD of 31 mm or greater in diagnosis PH and associated with 2-3 fold increased mortality risk compared to normal (11). In parallel, we found similar findings in our study cohort with an MPAD ≥ 29 mm, and this patient has more inflammation, heart injuries, and co-morbid disease. MPAD predicted worse outcomes in various regression models adjusted with age, comorbidities, clinical status, and inflammatory parameters.

COVID-19 negatively affects the endothelial system by activating multiple inflammatory, pro-thrombotic, and thrombotic cascades**.** Erdoğan et al. have suggested that disrupted endothelial system, increased inflammatory process, myocarditis, and active coagulopathy are linked with the severity of infection (16). Increased inflammatory status is accompanied by the severity of the infections, and high mortality (13, 16). It also caused deterioration in lung functions and a related increase in PA pressure. In addition, many patients had elevated inflammatory parameters, liver enzymes, CPK, and prothrombin time (13). Furthermore, Cai et al. demonstrated the increase in liver enzymes from severe pneumonia might be related to increased pulmonary pressure (17). In our cohort, similar to these results, AST and inflammatory levels; hs-CRP, ferritin, troponin, BUN, WBC, D-Dimer, and creatinine levels were significantly associated with PA diameter. Although thrombocytopenia is a common finding in COVID-19 patients in previous studies, no correlation was found between platelet count and PA diameter in our study (18, 19).

Although the etiology of PH is not known exactly, as possible causes; pulmonary small vessel thrombosis, vasculopathy, hypoxemia, and vasoconstriction were reported as the leading cause of PH in COVID-19 disease. PH can rapidly worsen right heart function and impair oxygenation, thus the length of hospital stay is prolonged, and the risk of the patient's multi-organ failure, bacterial infections, sepsis, hypercoagulation, and thrombosis**.** We found that severe CT findings of pneumonia and relation with hypoxemia were correlated with higher MPAD.

COVID-19 maybe affects the cardiovascular system. The underlying mechanism of cardiac damage is not clearly understood. Possible reasons are; increased cardiac stress due to acute respiratory distress and progressive hypoxemia, direct myocardial toxic effect of the COVID-19 increased inflammatory status, or their combination. In addition, SARS-CoV-2 infects host cells with angiotensin-converting enzyme 2 receptors and can cause myocardial damage. It has been shown that cardiovascular complications and heart failure may be responsible for 40% of deaths in COVID-19 patients (20).

There is a need for criteria to predict the prognosis of the disease in these patients. Thus increased MPAD may guide rapid and early diagnosis and treatment of high-risk patients.

In our study, pulmonary disease, CAD, CHF, and HT at the time of admission adversely affected the prognosis in COVID-19 patients. On the contrary, the presence of DM did not affect the prognosis in our patient population.

Limitation of the study

Although our study emphasized the association of PA diameter with mortality, there are several limitations. We did not have information about the clinical status of the patients before admission to the hospital. There was also no follow-up data. Follow-up and repeated measurements of the PA diameter will provide further information. Also, our cohort included only hospitalized patients, so it cannot be used for all patients. The frequency of pulmonary embolism that could lead to PA enlargement was unknown. Furthermore lack of data on electrocardiography and echocardiography imaging.

CONCLUSIONS

Chest CT imaging in the diagnosis of COVID-19 is obvious, simple, and of great value in early screening. A rapid diagnosis of high-risk COVID-19 patients is crucial, especially in order to dissolve the patient density in the emergency department. An enlargement of PA on chest CT may be an indicator of hemodynamic instability and worse outcomes. It should be considered that these patients may be at high risk, and should be evaluated carefully.

Abbreviation

ALT — Alanine aminotransferase
AST — Aspartate aminotransferase
CAD — Coronary artery disease
CT — Computed tomography
CHF — Congestive heart failure
DM — Diabetes mellitus
hs-CRP — high-sensitive CRP

HT — Hypertension
LPAD — Left pulmonary artery diameter
MPAD — Main pulmonary artery diameter
PA — Pulmonary artery
PH — Pulmonary hypertension
RT-PCR — Real-time reverse transcriptase-polymerase chain reaction test
RPAD — Right PA diameter
WBC — White blood cell count

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Sažetak

DIJAMETAR PLUĆNE ARTERIJE NA CT-u GRUDNOG KOŠA KAO PREDIKTOR MORTALITETA HOSPITALIZOVANIH PACIJENATA SA COVID-19 PNEUMONIJOM

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Uvod: Proširenje plućne arterije (PA) može biti od pomoći u stratifikaciji rizika pomoću CT grudnog koša pri prijemu pacijenata sa COVID-19.

Metode: Ova studija je imala za cilj da poveže prečnik PA i ukupni mortalitet kod pacijenata sa COVID-19 pneumonijom. Osmislili smo retrospektivnu studiju između januara 2021. i maja 2021. u bolnicama na tercijarnom nivou u Gebzeu, Turska. Ispitanici su evaluirani u dve grupe prema statusu preživelih (preživeli i nepreživeli). Upoređivane su biohemijske, demografske i kliničke karakteristike između ovih grupa kako bi se definisala prediktivna vrednost prečnika PA na CT grudnog koša.

Rezultati: Od 594 hospitalizovanih pacijenata sa COVID-19 (srednja starost je bila 45 (34-58) godina, 263 pacijenta (44,3%) su bile žene. 44 pacijenta (7,4%) su umrla tokom hospitalizacije. Na osnovu multivarijantnog regresijskoga modela Cox proporcije, PA ≥ 29 mm pri prijemu pokazao se kao nezavisni prediktori smrti (long rank < 0,001, srednje vreme preživljavanja 28 dana). Kumulativne stope preživljavanja bile su MPAD ≥ 29 mm 45% i < 29 mm 90% (p < 0,001).

Zaključak: Dilatacija PA je usko povezana sa bolničkim mortalitetom kod hospitalizovanih pacijenata sa infekcijom COVID-19. Povećani prečnik PA na CT-u grudnog koša pri prijemu može omogućiti brzu i ranu detekciju visokorizičnih pacijenata.

Ključne reči: COVID-19, kompjuterizovana tomografija, plućna arterija, mortalitet, pneumonija.

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SOCIOECONOMIC DETERMINANTS OF GENDER DIFFERENCES IN SELF-REPORTED HEALTH STATUS AMONG OLDER POPULATION

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Abstract: **Introduction:** Self-reported health status is considered one of the highly significant indicators of general health and overall quality of life.

Aim: to examine whether there are gender differences in self-reported health status among the older population depending on the socioeconomic determinants.

Methods: The analysis was carried out based on the data collected from the fourth National Health Survey of the population of Serbia, which was designed as a cross-sectional study. The research was conducted in accordance with the methodological guidelines and research instruments of the European Health Interview Survey.

Results: A statistically significant correlation was observed between gender and the self-reported health status of the respondents. Women were significantly more likely to report poor self-rated health (27.8%), whereas men reported better self-rated health (21.3%). The results of the multivariate logistic regression analysis showed that poor self-rated health status among women was more likely to be affected by age, educational level, and region, whereas age and economic status were significant factors associated with poor self-rated health status among men.

Conclusion: Taking into consideration the fact that the advantages of increased life expectancy will achieved only if these extra years of life gained through increased longevity are spent in good health, the importance of conducting additional research on gender differences is more than evident, particularly in terms of providing meaningful insight into the development of action plans devised to deal with gender differences in health status, simultaneously promoting healthy and active aging for both men and women.

Keywords: self-reported health status, elderly, gender, national health survey.

INTRODUCTION

The world's older population continues to grow at an unprecedented rate. The part of the global population older than 65 is expected to increase from 9.3% in 2020 to 16 % in 2050 (1). The rapid growth of the older population has far-reaching implications across all spheres of society due to their various needs. Aging is associated with an increase in the number of dependent old people in terms of their economic, health, and social dependency, along with increasing demand for the relocation of resources to a long-term care facility (2). All the above-mentioned facts have a significant negative impact on the economic stability of the health care system and therefore on society as a whole (3). Accordingly, simple but valid health status measures need to be implemented to assess and predict health outcomes in the elderly so that it could be easier to deal with the financial burden of aging populations, posing a challenge to both social and health services (4).

Self-reported health status (SRHS) is considered one of the highly significant indicators of general health and the overall quality of life. Subjective measurement, that is, self-reported health status, is a multi-dimensional concept including an individual evaluation of various health dimensions such as phys-

ical, emotional, and social functioning, not only the assessment of current health conditions in its narrow meaning (5, 6). This particular indicator has been used in national health surveys ever since the 1950s and has been recommended by the WHO and European Commission as a highly reliable and valid indicator of residents' health status (7). Numerous research has shown that despite its simplicity – this indicator, in particular, is one of the more significant predictors of population mortality or morbidity rates, functional limitations, and use of health protection (6, 8).

The nature of inequalities between men and women based on their gender and age indicates that age is considered a more cultural and socio-historical category, being less perceived as a biological and natural process by itself. Gender is regarded as a significant health determinant which additionally shapes the patterns of developing diseases, approach to health protection, and medical treatment availability as well (4). The roots of inequalities in health related to gender are numerous, mutually intertwined, and complex. Biological and genetic factors partly contribute to differences in health status later in life. However, social variables a significant source of health inequalities (9).

Poor availability of published evidence on gender-specific characteristics of health in old age and the impacts of aging on health status is reported in our country. Actual information on the manners in which sex and gender differences between men and women play a role in influencing their health status in advanced age is not sufficiently known. The key factor is related to researching gender differences in health status among older people, considering some of the relevant factors of population aging, such as premature mortality rates among men, along with the feminization of advanced age.

Our research aims to examine whether there are gender differences in self-reported health status among the older population depending on socioeconomic determinants such as the following: age, marital status, educational level, and economic status.

MATERIAL AND METHOD

Data source and type of study

The analysis of gender differences in self-reported health status among the population aged 65 or over was carried out based on the data collected from the fourth National Health Survey (NHS) of the population of Serbia which was designed as a cross-sectional study and conducted on the territory of the Republic of Serbia in 2019. The population living on the territory of the Autonomous Province of Kosovo and Metohija along with persons living in collective households and institutions were not included in the abovementioned survey. The research was conducted in accordance with the methodological guidelines and research instruments of the European Health Interview Survey third wave (EHIS wave 3) (10).

Sampling

In the study, we used a two-stage stratified random sample. The sample comprised all the households included in the 2011 population census results. The mechanism used for obtaining a random household sample and respondents resulted from a combination of two sampling techniques: stratified random sampling and multistage sampling. Primary sampling units comprised census circles selected based on the probability proportional to their size. In the first stage, 600 census circles were selected in total. The second stage units were households. Ten household addresses to be surveyed (+ 3 reserved addresses) were selected within each of the census circles.

The health survey included 5.114 households in total (out of 6.335 contacted households, the response rate of households was 80.7%), with a total number of 15.621 persons recorded, out of which there were 13.589 persons aged 15 and over along with 1.493 children aged from 5 to 14 years. The number of surveyed persons aged 65 or more was 3743.

Research instrument

The European Health Interview Survey third wave (EHIS wave 3) was used as a research instrument. Data were collected using three kinds of a questionnaire: a household questionnaire, a questionnaire for adults at the age of 20 or more, and a questionnaire that adults completed on their own.

The dependent variable in this study was self-reported health. Demographic characteristics (age, gender, marital status, region) and socioeconomic characteristics (educational level, economic characteristics of households) were used as independent variables.

Ethical standards in health surveys were harmonized with the international (the Declaration of Helsinki) and legislative country-specific norms and standards. The researchers were obliged to issue a printed document on the health survey and the Ethical Committee's approval of its conducting. In addition, each one of the respondents provided their informative consent through which they accepted to be part of the research in question.

Statistical data analysis

All the data of interest were presented and analyzed by adequate statistical methods. The Chi-square

test was used to compare proportions between groups. The bivariate and multivariate logistic regression analyses were used to examine the association between self-reported health status and a series of independent variables. Statistically significant results were considered to be the ones with a probability of less than 5% ($p < 0.05$). All the statistical calculations were performed using the Statistical Package for Social Sciences software (SPSS Inc, version 18.0, Chicago, IL)

RESULTS

Out of 3743 respondents at the age of 65 or more, 932 respondents (24.9%) reported poor self-rated health (20.0% bad and 4.9% very bad), whereas 1167 (31.2%) respondents reported good self-rated health (28.2% good and 3.0% very good).

There was a statistically significant association between genders and the self-reported health status of the respondents themselves ($\chi^2 = 63.231$, $p < 0.001$). Women were more likely to assess their health as bad (27.8%) (5.5% very bad and 22.3% bad), whereas men tended to assess their health from a more positive perspective (21.3%) (4.1% very bad and 17,2% bad) (Figure 1).

Analysis of variance (an ANOVA test) demonstrated that there were statistically significant differences in the mean values of age and self-reported health status ($p < 0{,}001$). The mean age in years of respondents with poor self-reported health was 75.2 ± 6.9, whereas the mean age in years of respondents with good self-reported health was 70.1 ± 5.2.

Respondents' self-reported health status by gender and demographic and socioeconomic characteristics are summarized in Table 1. The age of respondents is inversely proportional to good health, which means that the percentage of men and women reporting poor health increases with age. A significantly higher proportion of women among older age groups report poor self-rated health (SRH) compared to men. For instance, every second woman in the 85-89 age group reported

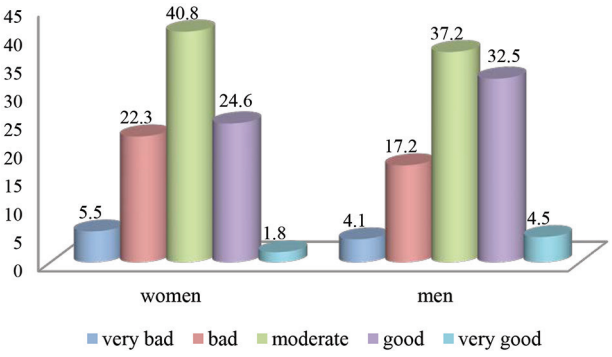

Figure 1. *Respondents' self-reported health status by gender*

poor self-rated health (42.5%), whereas 25.3% of men in the same age group rated their health as poor. On the other hand, men among younger age groups were more likely to report good self-rated health. There were statistically significant differences in self-reported health status among different age groups between both genders.

The analysis of self-reported health status of older respondents by marital status revealed statistically significant associations between marital status and health status in both men and women.

The analysis of the self-reported health status of respondents by educational attainment showed a significant inverse correlation, meaning the lower the level of education was, the worse the respondents' self-reported health status was, with the more emphasized differences observed in the female population. Therefore, 47.4% of older women with no education reported having poor self-rated health, whereas the percentage of men with the same characteristics was significantly lower (32.6%). As regards the highest level of educational attainment (a magister degree/ Ph.D.), even 63.3% of men who had completed this educational level rated their health as good, compared to 53.3% of women.

As regards the well-being index, the respondents belonging to the lower social classes more frequently reported poor self-rated health, with more emphasized gender differences. Women belonging to the lowest social class reported having poor self-rated health (39.1%) compared to 35% of men. On the other hand, men and women belonging to the highest social class reported having good self-rated health (47% of men and 43.2% of women).

The citizens of Šumadija and Central Serbia reported to have the worst self-rated health status. One-third of older women (30%) and 22,9% of men in this particular region rated their health as poor.

The results of bivariate logistic regression analyses of poor self-reported health by gender indicated that the association between demographic and socioeconomic determinants and poor health was more expressed in women for the majority of determinants (Table 2). With the population aging, every year of age increased the risk of poor health by 5,1% among women and 3.2% among men. Widows had a 20.4% higher risk of rating their health as poor when compared to men who revealed no statistically significant association between marital status and self-reported health status. The higher the level of education was, the less risk of poor self-rated health was (52.2% among women, 38.8% among men). Women living in the south had a 47.4% higher risk of poor health when compared to women living in the north (OR = 1.474), whereas men

Table 1. *Respondents' self-reported health status by gender and demographic and socio-economic characteristics*

Variables	Self-reported health status (%)									
	very good		good		moderate		bad		very bad	
	men	women	men	women	men	women	men	women	men	women
Age (years)										
65-69	6.4	2.2	37.7	32.4	36.6	41.0	14.2	18.1	2.7	4.4
70-74	4.3	1.9	33.6	26.9	37.4	44.4	16.8	19.8	4.9	4.1
75-79	4.3	2.2	27.6	18.8	39.8	40.9	16.5	26.5	5.0	6.4
80-84	1.4	0.7	26.8	17.6	33.8	38.1	27.2	27.0	5.2	8.6
85-89	1.3	0.7	22.5	10.6	39.8	31.2	21.7	33.3	3.6	9.2
90+	0.0	0.0	12.5	7.1	37.5	40.5	12.5	21.4	8.3	0.0
men: $\chi^2 = 108.084$, $p = < 0.001$; women: $\chi^2 = 199.144$, $p < 0.001$										
Marital status										
single	8.1	2.3	21,6	37.2	48.6	30.2	10.8	7.0	2.7	9.3
married	5.1	1.8	34.0	29.6	36.5	39.6	16.8	20.9	3.9	5.2
widowed	2.2	1.7	25.8	19.7	39.1	42.2	16.6	24.4	5.9	5.5
separated/divorced	0.0	2.6	43.6	26.3	34.5	40.8	18.2	18.4	3.6	6.6
men: $\chi^2 = 88.145$, $p < 0.001$; women: $\chi^2 = 54.399$, $p < 0.001$										
Level of education										
no education	0.0	1.2	6.5	8.7	41.3	27.2	23.9	35.3	8.7	12.1
incomplete elementary school	1.2	0.8	25.7	15.2	32.7	39.5	24.0	30.1	7.6	7.3
elementary school	1.1	1.2	25.1	21.4	41.7	42.3	21.5	25.2	5.5	5.8
middle school	6.5	2.7	35.2	32.2	36.6	44.0	15.0	15.0	3.4	3.3
high school/college	5.5	3.0	40.5	37.9	35.8	40.9	13.5	12.9	1.8	2.6
magister degree/PhD	10.0	0.0	53.3	53.8	30.0	23.1	6.7	15.4	0.0	7.7
men: $\chi^2 = 131.368$, $p < 001$; women: $\chi^2 = 221.711$, $p < 001$										
Wellbeing Index										
I (the poorest)	0.7	1.1	21.8	14.4	36.6	41.1	26.1	29.9	8.9	9.2
II	2.5	1.1	30.2	21.4	37.2	38.5	19.8	26.9	5.0	6.1
III	6.5	2.0	34.0	25.1	39.1	43.4	15.9	20.3	1.9	5.0
IV	5.6	3.1	36.2	26.2	35.6	42.9	14.7	17.0	2.8	4.1
V (the richest)	7.1	1.9	39.9	41.3	37.2	36.9	9.8	1.6	2.4	1.6
men: $\chi^2 = 101.141$, $p = 0.001$; women: $\chi^2 = 122.675$, $p < 0.001$										
Region										
Vojvodina	5.5	1.8	32.5	24.7	35.9	39.9	16.4	20.0	4.5	6.7
Belgrade	7.7	2.3	35.7	32.7	35.7	3.3	13.5	19.2	3.4	4.6
South and Eastern Serbia	3.0	1.6	34.1	24.3	36.5	40.8	19.5	23.9	3.4	6.1
Sumadija and Western Serbia	2.6	1.8	27.5	24.6	40.4	40.8	18.7	22.3	5.3	5.5
men: $\chi^2 = 35.067$, $p = 0,009$; women: $\chi^2 = 50.340$, $p < 0.001$										

Table 2. *Odds ratios (OR) and their 95% confidence intervals (CI) of poor self-rated health were estimated according to demographic and socioeconomic characteristics by gender*

Variables	Gender	Univariate model		Multivariate model	
		OR (95%CI)	p	OR (95%CI)	p
age	women	1,051 (1,031 -1,063)	< 0,001	1,037 (1,019 -1,057)	< 0,001
	men	1,032 (1,013 -1,054)	0,001	1,029 (1,007 -1,0468)	0,009
widow /widower	women	1,204 (1,010 – 1,441)	0,039		
	men	1,189 (0,927 – 1,543)	0,171		
education	women	0,488 (0,417 – 0,569)	< 0,001	0,7623 (0,519 -0,738)	< 0,001
	men	0,612 (0,519 – 0,712)	< 0,001		
wellbeing index	women	0,804 (0,749 – 0,857)	< 0,001		
	men	0,753 (0,691 – 0,818)	< 0,001	0,873 (0,759 – 0,925)	< 0,001
region	women	1,474 (1,228 – 1,751)	< 0,001	1,227 (1,004 – 1,498)	0,047
	men	1,368 (1,124 – 1,741)	0,004		

had a 36.8% higher risk of poor health (OR = 1.368). As regards men, their economic status was the only determinant revealing a greater association with poor health when compared to women.

The results of multivariate logistic regression analyses indicated that the following factors influenced poor self-rated health status in women: age, educational attainment, and region, whereas the factors influencing men were primarily: age and economic status (Table 2).

DISCUSSION

Previous studies have shown that self-reported health among older men and women is a valid measure of the objective health status of respondents, a significant predictor of survival in advanced age along with being a powerful predictor of healthy longevity (4,6). The perception of health status varies in different cultures and countries. The results of this particular survey showed that older people widely assessed their health status as poor and very poor (40%), whereas 22.3% of the respondents reported having good health. The survey conducted in Spain showed that approximately 25% of the older population considered themselves healthy (11). In Russia, this figure is only 10%, while in Finland, 39% of the elderly population rate their health as good (12). Women were more likely to report poor health status than men (45.9% to 32.2%). The abovementioned results were in accordance with the findings of the majority of other authors who confirmed that there was a larger percentage of older women who reported having poorer health status when compared to the health status of men (13, 14).

Such findings in the health literature could be explained by the fact that women, due to the higher level of awareness of health issues and disease symptoms, were more likely to report poorer self-rated health when compared to men. In addition, women showed a tendency to be prone to providing socially more desirable responses compared to men. Case and Paxson indicated that gender differences in self-rated health could be explained by the differences observed in the distribution of chronic conditions faced by both men and women, respectively, that is, by the fact that women genuinely showed poorer health status compared to men (15). As was expected with aging, years of life represented a key factor that was inversely proportional to health status, which meant that the prevalence of chronic diseases turned out to rise sharply with age, along with the increase in the share of adults reporting poor self-rated health.

Josefsson et al. established that among the respondents aged from 65 to 79, one out of three reported having a long-standing illness or health problems having lasted for more than six months. This proportion rose sharply with age, among women in particular, whereas half of the women respondents at an advanced age (the 80-84age group) suffered from chronic diseases (13).

Goldman et al. showed that women who became widowed early in life had poorer self-rated health status than those who were married. On the other hand, never-married women had better health outcomes than those who were married (16). Interestingly, single women living alone reported having better self-rated health status when compared to other married women, which could partially reflect the severe burden associated with taking care of their families which were more likely to be experienced by the majority of married women.

The respondents with middle and low educational levels had a higher prevalence of chronic diseases,

and they more often had poorer self-rated health status compared to those with higher education levels, which was in accordance with the data obtained from the available literature indicating that higher educational attainment correlated with good health status (17). These inequalities in self-reported health status observed according to education level may be explained by the fact that persons with higher educational attainment were more likely to be given adequate employment opportunities and become high-paid employees (18). Persons with higher educational attainment revealed a higher level of health literacy, had a healthier lifestyle and were able to make better use of available information while facing everyday problems which could harm their health (19).

Numerous studies indicated that populations with lower socioeconomic status had higher mortality rates along with a higher prevalence of the majority of illnesses. This regularity occurred in both genders and all age groups regardless of whether the research was focused on the association between mortality and morbidity and education level, income, or social status (20, 21).

Borg and Kristensen emphasized that lower socioeconomic status, measured based on the level of educational attainment and occupation, was associated with poorer self-rated health status among both men and women (22), given that women experienced a lot of cumulative adversities in their lifetime. In patriarchal societies, women often have inferior or secondary status compared to men. Older women have lower chances of receiving an education, particularly in developing countries, which results in lower incomes. Accordingly, women find themselves in a typically less favorable socioeconomic position compared to their male colleagues, and these problems in particular can explain their worse self-rated health status at an advanced age. This places a socioeconomic obstacle before them when it comes to approaching and making use of healthcare services and preventive healthcare measures in their lifetime, which may result in worse health status at an advanced age. In this manner, socioeconomic status determines the level of exposure to agents causing health deterioration, simultaneously defining individual resources for health promotion (23).

The current scientific literature on gender inequalities in health emphasizes the fact that education plays a more significant role in health status among women compared to men (23), whereas marital status has a more significant role in the mortality of men compared to the mortality of women (24). Accordingly, it was demonstrated that lower socioeconomic status had a significantly larger impact on the health status and mortality outcomes of men when compared to women (25).

Several studies (26, 27) demonstrated that statistically significant gender differences in self-reported health status were observed even after adjusting for all SES variables, whereas other studies showed that gender differences in self-reported health status were more in favor of women after adjusting for the role of socioeconomic factors (28). It was revealed not only that women tended to report worse self-rated health than men, particularly ones belonging to groups with privileged socioeconomic status (27), but the fact that socioeconomic status significantly contributed to expanding the above-mentioned disparity (28).

CONCLUSION

Taking into consideration the fact that the advantages of increased life expectancy will be entirely achieved only if these extra years of life gained through increased longevity are spent in good health, the importance of conducting additional research on gender differences is more than evident, particularly in terms of providing meaningful insight into the development of action plans devised to deal with gender differences in health status, simultaneously promoting healthy and active aging for both men and women.

From the point of view of health inequalities, the values of this indicator, in particular, may point out the need to create sound policy measures to minimize the existing differences observed among the groups of the population characterized by different gender, age, educational levels, economic status, place of residence along with other social and demographic characteristics.

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Licensing

AUTHOR CONTRIBUTIONS

SI, SR, and KJ developed research questions, designed the study, and prepared the manuscript. DA, MI, AM, and MP participated in the presentation and interpretation of the results and reviewing of the manuscript.

Sažetak

SOCIJALNO-EKONOMSKE DETERMINANTE RODNIH RAZLIKA U SAMOPROCENI ZDRAVLJA KOD STARIJE POPULACIJE

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Uvod: Procena sopstvenog zdravlja je jedan od veoma značajnih pokazatelja ukupnog zdravstvenog stanja i kvaliteta života.

Cilj: Ispitati postojanje rodnih razlika u samoproceni zdravlja kod starih osoba u zavisnosti od društveno-ekonomskih faktora.

Metode: Kao osnov za analizu korišćeni su podaci iz četvrtog nacionalnog Istraživanja zdravlja stanovništva Srbije urađenog po tipu studije preseka. Istraživanje je sprovedeno u skladu sa metodologijom i instrumentima Evropskog istraživanja zdravlja.

Rezultati: Postoji statistički značajna povezanost između pola i samoprocene zdravlja ispitanika. Žene su značajno češće procenjivale svoje zdravlje kao loše (27,8%), dok su muškarci pozitivnije ocenjivali svoje zdravlje (21,3%). Rezultati multivarijantne logističke regresije pokazuju da na lošiju samoprocenu zdravlja kod žena utiču godine starosti, stepen obrazovanja, regija, dok kod muškaraca utiču godine starosti i materijalno stanje.

Zaključak: Obzirom na to da su prednosti dužeg očekivanog životnog veka u potpunosti postignute samo u slučaju da se ove dodatne godine prožive u dobrom zdravlju, jasno je da su potrebna dodatna istraživanja rodnih razlika da bi se obezbedio smisleni uvid u razvoj akcionih planova koji rešavaju rodne razlike u zdravstvenom statusu i koji promovišu zdravo, aktivno starenje i za muškarce i za žene.

Ključne reči: procena sopstvenog zdravlja, stare osobe, rod, nacionalno istraživanje zdravlja.

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NEONATAL SEIZURES: ETIOLOGY, TREATMENT AND PROGNOSIS

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Abstract: **Introduction:** Seizures are one of the most common pathologies in newborns. Their incidence is 1.5–3.5/1000 for term infants and 10–130/1000 for preterms. The most common causes of seizures in term infants are hypoxic-ischemic encephalopathy (HIE), cerebrovascular insult (CVI), cerebral malformations (CM), and metabolic disorders. For preterm infants: intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and infections. Clinical characteristics are diverse and subtle, and subclinical forms are common. The drug of the first choice is phenobarbitone. Newborns with seizures are more prone to developing neurological disturbances such as epilepsy and cerebral palsy.

Methods: This is a clinical, observational research, one-year, retrospective, cross-sectional study conducted in the Department of neonatal intensive care and neonatology of the Clinic of Pediatrics KCUS. The study included 43 newborns who met the inclusion criteria.

Results: We found that 7.19% of hospitalized newborns had seizures. A number of seizures were recorded in the group of term infants with an earlier time of seizures. The most common etiological causes were: HIE, IVH, infections, and CM. There was a frequent occurrence of metabolic disorders such as acidosis, blood sugar, and mineral (Ca, K, Na, and Mg) disorders. The median of the first day of onset of seizures in full-term infants is on the fourth day, while in premature infants it is on the sixth day of life. Phenobarbitone was mainly used to stop seizures, with great success. Overall mortality in children with seizures was 37.21%.

Conclusions: Seizures are common in newborns, which, depending on the etiological cause, increase mortality, especially in preterm infants. Seizures in term infants occur earlier than in premature infants. The most common etiology of seizures in term infants are infections, hypoxemic-ischemic encephalopathy, intracranial hemorrhage, cerebral malformations, and cerebrovascular insult. In premature infants these are hypoxemic-ischemic encephalopathy, intracranial bleeding, and infections. In the initial treatment of neonatal convulsions, phenobarbitone is most often used, which has proven to be successful in the majority of cases.

Keywords: neonatal seizures, etiology, treatment, prognosis, mortality.

INTRODUCTION

Neonatal seizures are one of the most common phenomena that are considered a consequence of the sensitivity and vulnerability of the brain during rapid growth and development, as well as the effects of many harmful factors (1, 2). They can be associated with long-term neurological consequences, an increased risk of developing epilepsy, cerebral palsy, intellectual disability, and/or learning disabilities (3). Acute symptomatic seizures are defined as a consequence of acute brain injuries, such as stroke, trauma, or brain infection, while provoked seizures are defined as a consequence of transient and reversible changes in brain function of metabolic or toxic origin (1). Although rare, unprovoked neonatal seizures may occur, which may be secondary to structural abnormalities of the brain, which would correspond to structural epilepsies or genetic conditions (1). Clinically, neonatal seizures are described as abnormal, stereotyped, paroxysmal, and recurrent dysfunctions in the central nervous system (CNS), which occur in the first 28 days after birth in term infants or before 44 gestational weeks in preterm infants (2, 4, 5).

Seizures occur most often in the neonatal period, especially in the first week of life, more often than in other periods (4, 5). The incidence is 1.5 - 3.5/1000 for term newborns and 10 –(130/1000 for preterms (5, 6). Etiological factors that can lead to seizures in new-

borns are diverse and can be divided into perinatal, genetic, vascular, infectious, metabolic, and seizures associated with malformations, drugs, and seizures of unknown cause (2, 6). The etiology of neonatal seizures is different in term and premature infants (5). Hypoxemic - ischemic encephalopathy (HIE), cerebrovascular insult (CVI), cerebral malformations (CM), and metabolic disorders are the main causes of seizures in term infants (5). In premature infants, some of the main causes are intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and infections (5). Determining the etiological factor is extremely important because some of them require immediate treatment but also affect the prognosis of the disease (7). According to the revised ILAE classification from 2017, seizures can be classified through several levels, where the first level of the epilepsy classification framework is the type of seizure and is divided into focal onset, generalized onset, and unknown onset (8). The second level of classification represents the type of epilepsy, and it is divided into generalized epilepsy, focal epilepsy, a combination of generalized and focal epilepsy, and unknown epilepsy (8). According to the 2021 modification of the ILAE classification, infantile-onset epileptic syndromes are divided into two large groups: self-limited epileptic syndromes, where spontaneous remission is likely to occur, and developmental epileptic encephalopathy (DEE), where there is impairment in development (9).

Clinical picture: obvious manifestations of neonatal seizures occur only in a small number of newborns due to their immature CNS. Brain connections are less developed, so seizures may not spread to the motor cortex, which would lead to outwardly visible signs of epileptic seizures (10). Clinical signs of neonatal seizures may be subtle or even absent. Also, infants may exhibit frequent proximal movements such as rapid eye movements, automatism, and sleep-related myoclonus, which may mimic seizures (10). Clinical signs are often focal and include limb or facial movements that may be clonic, myoclonic, or tonic (10).

More types of clinical neonatal seizures that are more difficult to detect are the so-called “subtle” seizures and they account for 50% of all seizures (10, 11). They are more common in preterm than in term children (2). They include eye movements and autonomic signs of seizures represented by tachycardia, bradycardia, or apnea (10).

Tremors and other non-convulsive movements should be distinguished from neonatal seizures (3). Characteristics that help in differentiation are the absence of abnormal eye movements, which can be provoked by stimulating the child, can be stopped by mild passive flexion of the limbs, there are no EEG abnormalities, they are not associated with tachycardia, bradycardia, or hypertension (2).

Diagnosis and treatment: The diagnosis is made based on the clinical picture, anamnestic data, and EEG. Due to the growing body of evidence that neonatal seizures contribute to an unfavorable neurodevelopmental outcome, the focus is increasingly on early detection and treatment. In treatment, phenobarbitone is the first drug of choice. The initial intravenous dose is 20 mg/kg, which is usually given for 10 to 15 minutes (12, 13). In refractory cases, benzodiazepine preparations (lorazepam, diazepam, midazolam) are used (12, 13). Lidocaine is an effective drug for treating refractory seizures as a second or third-line choice (12, 13). Levetiracetam is a new anticonvulsant drug that has become the drug of choice for treating refractory neonatal seizures, and in some centers, it is also used as a second-line drug before benzodiazepines and lidocaine (13). According to the available data, levetiracetam appears to have few side effects and no interactions, and it is available in intravenous form (13).

Outcome: newborns with seizures have a high risk of death in the neonatal period, ranging from 10 to 35%. Seizures can cause loss of neurons and reduce neurogenesis and dendritic density of the spinal cord (14, 15). Epilepsy is a common outcome in infants with seizures, occurring after a latent period in approximately 25%. Infants with cerebral palsy who survive neonatal seizures are eight times more likely to develop epilepsy (15). Global developmental delay is reported in approximately 40% of children who survived neonatal seizures in a single center (15). In a population-based study of the outcomes of infants with seizures, 20% had an intellectual disability, and 27% had a learning disability (15). Long-term outcome in children with neonatal seizures depends on EEG activity, response to anticonvulsant therapy, and ARGAR score (14). More recently, genetic testing of newborns with seizures is increasingly available, which may allow targeted treatment of newborns with genetic epilepsies (1).

MATERIAL AND METHODS

This is a clinical, observational, one-year, retrospective, cross-section study. The research included newborns who were hospitalized in the Neonatal Intensive Care and Neonatology department from January 1st to December 31st, 2021. Out of 598 hospitalized newborns, 43 had seizures and are included in the research. The diagnosis of seizures of the newborns included in the study was made based on a clinical picture. We have analyzed data regarding sex, gestational age, delivery mode, birth weight, and APGAR score.

We have also analyzed the etiology and predisposing factors for seizures, the day of life in which seizures were noted, and the characteristics of seizures. We have analyzed laboratory findings (FBC, minerals, blood gases, D-dimer, blood culture), brain US, brain MRI, and EEG.

Statistics

The data were processed using the Excel program and presented in tables and graphics. Statistical analysis and hypothesis testing were done using IBM SPSS software. The Chi-square test was used for binary variables, t-test was used for continuous variables. Statistics tests were carried out at the 95% significance level.

RESULTS

Out of the total number of hospitalized neonates (598), 43 (7.19%) had seizures. There were 251 preterm infants, of which 17 (6.77%) with convulsive attacks, and 347 term infants, of which 26 (7.49%) with seizures. The increased incidence of seizures in the group of term infants compared to premature infants is not statistically significant. $\chi 2$ test = 0.1131, P = 0.736639 (P > 0.05). Of the total number of newborns with seizures, 18 (41.86%) were female and 25 (58.14%) were male. The increased incidence of seizures in the group of male infants compared to female infants is not statistically significant. $\chi 2$ test = 0.3436, P = 0.557731 (P > 0.05). Six full-term newborns had a seizure on the first day of life, followed by the second and fourth days of life. The mean value of the first day of onset of seizures in term infants is 6.69 days, while the median is four days of life.

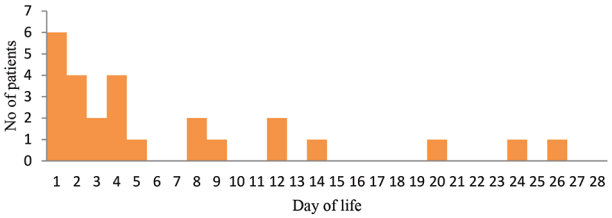

Figure 1. *Time of occurrence of the first seizure in full-term infants*

Five premature infants, had seizures on the seventh day of life, followed by the second, fifth, and sixth days of life. The mean value of the first day of onset of seizures in premature infants is 6.7 days, while the median is six days of life. The median of the first day of onset of seizures between the categories of term infants and premature infants is not statistically significant. T-test = 0.0068, P = 0.9946 (P > 0.05, CI 95% from -4.04 to 4.06)

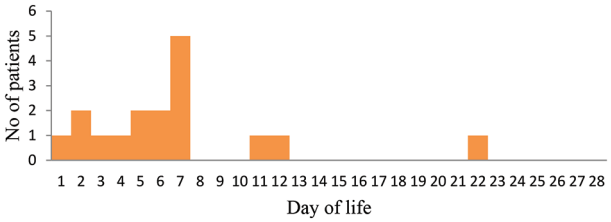

Figure 2. *Time of occurrence of the first seizure in premature children*

Of the total number of term infants with seizures, nine had HIE, five had some type of intracranial hemorrhage, five had some cerebral malformation, and three had cerebrovascular insult. Ten term infants had some infectious disease. Three infants had an early neonatal infection, two had sepsis and meningitis caused by E. Coli, two had Herpes simplex virus sepsis, and one developed encephalitis. Two infants had meningitis of unknown cause. One newborn had a Cytomegalovirus infection.

Of the total number of premature infants with convulsions, seven had some type of intracranial hemorrhage, six infants had hypoxemic-ischemic encephalopathy, while cerebrovascular insult and cerebral malformations were not recorded in premature infants. Of the total number of premature infants, three had some type of infectious disease. Two infants had sepsis and one had meningitis. Of the metabolic disorders, which were recorded in newborns with seizures, we found 10 with hypoglycemia, 24 with acidosis, 14 with hypocalcemia, 7 with hyponatremia, and 5 with hypomagnesemia. Of the total number of cases of hypomagnesemia, four cases were combined with hypocalcemia (80%).

Eight patients had elevated D-dimer values. There were three whose mothers have recently recovered from COVID-19 infection. All of the newborns had some type of thrombosis (sagittal sinus, transverse sinus, and/or the internal carotid artery). Table 1 shows patients with elevated D dimer and their risk factors.

18 patients had an EEG registration performed (41.86%), out of which 11 had normal results (61.11%), and seven infants had epileptic activity recorded on the EEG (38.89%).

The initial treatment for seizures was phenobarbitone in 25 newborns (58%), five (12%) got unspecified anticonvulsants, and one (2%) received diazepam during transport in an ambulance. 12 infants received no drugs. Out of 25 newborns who received phenobarbitone, in 21 cases (84%) seizures have stopped. The other four had additional drugs: midazolam, levetiracetam, and pyridoxine. One infant received three different anticonvulsive drugs.

Out of 43 infants with seizures, 16 (37.21%) were cured without repeated attacks and therapy. In 11

Table 1. *Patients with elevated D dimer and their risk factors*

Patient	Mother's diseases	Infant's diseases
1	Hyperthyroidism, elevated blood pressure, recovered from COVID 19 infection	Internal carotid artery thrombosis, cystic leukomalacia
2	Thrombophilia, recovered from COVID 19 infection	Transverse sinus thrombosis, thrombophilia, thalamostriate vasculopathy
3	No data	E. coli sepsis, meningitis
4	Seizures since the age of 14	No proven diseases
5	Elevated blood pressure, recovered from COVID 19 infection	Sagittal and transverse sinus thrombosis
6	No data	Sagittal sinus thrombosis
7	No data	Thalamostriate vasculopathy, an anatomical variation of the internal carotid artery
8	No proven diseases	Meningitis

(25.58%) newborns, therapy was continued with some of the anticonvulsants to keep the seizures under control. Death was recorded in 16 (37.21%) newborns. Of the total number of deaths in children with convulsions, there were 13 premature and three term children. RR = 0.62 (term infants), RR = 1.61 (preterm infants). The increased mortality of premature newborns with seizures compared to full-term newborns is statistically significant. $\chi 2 = 59.4099$, $P < 0.00001$, ($P < 0.05$).

DISCUSSION

According to research conducted by Carlotta Spagnoli, Raffaele Falsaperla, and others, in 2018, neonatal seizures occur in up to 1.5-3.5/1000 full-term infants and 10-130/1000 premature infants (16). In our research, the prevalence of attacks among premature infants was 6.77%, and among term children 7.49%. A common problem is the failure to recognize subtle seizures, which are more prevalent in premature infants, and subclinical seizures, which occur in both full-term and premature infants. In our study, of the total number of newborns with convulsive attacks, there were more male newborns (58.14%).

The onset of seizures in premature infants tends to occur later than in term infants (16). It is believed that the difference in the onset of seizures in premature and term infants is a consequence of the different etiology of seizures (16). In our research, it was found that the median of the first day of onset of seizures in full-term infants is on the fourth day, while in premature infants, it is on the sixth day of life. Our sample, although small, is consistent with the results of larger studies.

Research by C. Glass, A. Shellaas, and others, published in 2017, included 611 infants with seizures (17). Hypoxemic-ischemic encephalopathy was described as the most common etiological cause of seizures among premature and full-term infants, and intracranial bleeding in premature newborns (17). Cerebrovascular insults were more often diagnosed in term infants, while intracranial infections were more common in premature infants (17). In our work, it was noted that the largest number of term newborns had hypoxemic-ischemic encephalopathy, followed by intracranial bleeding and then cerebral malformations. Cerebrovascular insult was recorded in three cases in term infants. Some infants had more than one etiological factor.

In the Iraqi study from 2018, 203 newborns with seizures were included, of which 28 had hypocalcemia (13.79%) (18). In our study, we had hypocalcemia in 14 newborns, or 32.56%. In a study from 2017 that included 150 newborns with recorded seizures (19) 5.3% of newborns with hypomagnesemia were discovered. 33 87% of hypomagnesemia cases were associated with hypocalcemia, which implies a mutual connection in the pathophysiology of these disorders. In our sample, 11.63% of cases of hypomagnesemia were recorded, of which 80% were associated with hypocalcemia. Studies such as the one by K. Williams and A. Singh found 16.81% of children with seizures to have a reduced pH value (20). The same study concluded that in univariate analysis, acidosis was significantly associated with seizures. We recorded acidosis in 24 infants (55.81%). In the current literature, increasingly frequent reports of neonatal seizures have been observed in newborns of mothers who had a COVID-19 infection during pregnancy. One of the reports published in 2022 presents a case of central venous sinus thrombosis of a newborn whose mother had a COVID-19 infection in the first month of pregnancy (21). Also, Parul Jain, Anup Thakur et al. published a 2020 case report of a newborn, COVID 19 of a positive mother, who was diagnosed with acidosis and thrombocytopenia at birth, associated with intracranial

bleeding (22). Manas Kumar Nayaka, Santosh Kumar Panda et al. in study 2021 included 162 COVID 19 positive mothers (23). Nine infants of positive mothers developed infection and eight had neonatal seizures. We recorded three cases of mothers who suffered from COVID-19 during pregnancy and whose newborns had seizures. Some type of intracranial thrombotic process (arteriae carotis internae thrombosis, sinus transversus thrombosis, and sinus sagittalis et transversus thrombosis) was detected by the MRI technique in the mentioned newborns. The presented cases could point to a connection between the mother's COVID-19 infection and an increased predisposition to the occurrence of thrombotic incidents in newborns, which should be the subject of further research.

In 2007, Ajay Kumar, Ashish Gupta, and Bibek Talukdar published a study in which 90 infants with a clinical picture of seizures were included within one year (24). Of the 60 EEG recordings performed, only one-third had an abnormal finding. In our work, we noted that 41.86% of children with realized EEG registration, 38.89% had an abnormal EEG finding.

In 2019, E. Baudou, C. Rakovi, and others published a study based on the follow-up of 319 newborns with neonatal seizures (6). 243 newborns received anticonvulsant therapy, of which one-third received monotherapy and two-thirds polytherapy (6). Phenobarbitone was prescribed in 199 cases (82%), diazepam in 111 (46%), and phenytoin in 79 cases (32%). 86% of infants primarily treated with diazepam needed second-line therapy, which in most cases was phenobarbitone. In maintenance therapy, valproic acid 50%, carbamazepine 11%, levetiracetam 7%, phenobarbitone 2%, and 2% others. In 28% of cases, no maintenance therapy was prescribed. Another study published in 2020 by researchers Cynthia Sharpe, Gail E. Reiner, and others, was based on a randomized cohort study of infants with seizures, who were randomly divided into two groups (25). In one group, the infants received phenobarbitone therapy while in the second group received levetiracetam. 80% of infants randomized to phenobarbitone had seizures stopped within 24 hours, compared to 28% of infants randomized to levetiracetam. By increasing the dose of levetiracetam from 40 to 60 mg/kg, a 7.5% improvement in effectiveness was achieved. In our study, 25 infants received phenobarbitone in the initial treatment (58%). For five children we do not have exact information on which drug it was, one newborn received diazepam as an initial treatment, to which he responded positively. 12 infants were without initial treatment (28%). Of the total number of infants who received phenobarbitone in the initial treatment, 21 infants responded successfully (84%). Of the cases in which there was no success in stopping the attack with phenobarbitone, in one case it was stopped with midazolam, in another with levetiracetam, and in two cases pyridoxine was used which stopped the attack in one newborn, while it did not in the other. The infant who did not respond to either phenobarbitone or pyridoxine therapy, was treated with levetiracetam, also without success.

The conclusion of a systematic review (26) comparing the efficacy and safety of levetiracetam and phenobarbitone in the treatment of neonatal seizures is that levetiracetam shows promising results, with better efficacy in seizure control and safety, and with fewer side effects than phenobarbitone, which is currently used as a first-line drug in neonatal seizures. The researchers state that long-term follow-up studies are needed to determine the neuroprotective effect of levetiracetam on neonatal brain development, leading to a better neurodevelopmental outcome compared to phenobarbitone. In a study published by Renée A. Shellhaas, Courtney J. Wusthoff et al. in 2021, 282 infants with a history of neonatal seizures were followed (27). In this large study of infants who survived neonatal seizures, the majority (87%)) did not develop post-neonatal epilepsy before 24 months. Infants who developed epilepsy had up to three times the risk of developing a neurodevelopmental disorder. Another study on the neurodevelopment of infants after neonatal seizures was published in 2011 by researchers Jarred Garfinkle and Michael I. Shevella, who observed 120 newborns (28). Of the total number of newborns (120), 45% did not have any neurodevelopmental disorders, 31% had cerebral palsy, 43% had developmental delays, and 32% had epilepsy. A similar study was conducted in 2015 at the Sarajevo Pediatric Clinic, where the neurodevelopment of 100 infants with neonatal seizures was monitored (29). 62.33% of the children showed a developmental discrepancy. This research concludes that neonatal seizures have a strong predictive association with short-term and long-term causes of mortality and morbidity. According to a 2020 study by Monica E. Lemmon, and Sonia L. Bonifacio et al., among 611 infants followed with seizures, 90 infants (15%) died during hospitalization (30). The most common etiology of fatal seizures in infants was: hypoxemic–ischemic encephalopathy. Research from 2016 (31) shows mortality in the first year of life, of infants with seizures in the neonatal period, of 23%. Death was more common in premature infants (33.3%) than in term infants (17.9%). Mortality was higher among male full-term infants than among female full-term infants. In our work, the mortality of children with recorded convulsions was 37.2% (72.9% of which were premature) of which a fatal outcome was recorded, had some type of intracranial hemorrhage, then hypoxemic-ischemic encephalopathy, and cerebral malformations.

CONCLUSIONS

In our study, we observed a higher prevalence of seizures in term than in premature infants, which is probably a consequence of not recognizing subtle and subclinical seizures and a small sample, but also a larger total number of hospitalized term infants. Seizures in term infants occur earlier than in premature infants. The most common etiology of seizures in term infants are infections, hypoxemic-ischemic encephalopathy, intracranial hemorrhage, cerebral malformations, and cerebrovascular insult. In premature infants, these are hypoxemic-ischemic encephalopathy, intracranial bleeding, and infections. Among the metabolic disorders in patients with convulsions, acidosis, hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia (alone and in combination with hypocalcemia) were found to be the most common. The occurrence of thrombosis (art. carotis internae, sinus sagittalis, sinus transversus), followed by seizures, in newborns whose mothers suffered from the COVID 19 infection, due to the greater number of recorded cases, should be the subject of further research. In the initial treatment of neonatal convulsions, phenobarbitone is most often used, which has proven to be extremely successful in the majority of cases. According to many studies, levetiracetam gives promising results, with better efficacy in seizure control and safety, fewer side effects, and better neurodevelopmental outcomes compared to phenobarbitone. Increased mortality of infants with neonatal seizures was observed, compared to the total number of recorded deaths, especially in the group of premature infants (76.47%). The highest mortality rate is for newborns who had some type of intracranial bleeding as an etiological cause.

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Sažetak

NEONATALNE KONVULZIJE: ETIOLOGIJA, TRETMAN I PROGNOZA

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Uvod: Konvulzije su jedna od najčešćih patologija u novorođenčadi. Njihova učestalost je 1,5-3,5/1000 za terminsku dojenčad i 10-130/1000 za nedonoščad. Najčešći uzroci konvulzija u terminske dojenčadi su hipoksično-ishemijska encefalopatija (HIE), cerebrovaskularni inzult (CVI), cerebralne malformacije (CM) i metabolički poremećaji, a u nedonoščadi: intraventrikularno krvarenje (IVH), periventrikularna leukomalacija (PVL) i infekcije. Kliničke karakteristike su raznolike i suptilne, a česti su subklinički oblici. Lek prvog izbora je fenobarbiton. Novorođenčad s konvulzijama sklonija su razvoju neuroloških poremećaja poput epilepsije i cerebralne paralize.

Metode: Ovo je kliničko, opservacijsko istraživanje, jednogodišnja, retrospektivna, studija preseka, sprovedena na Odeljenju za neonatalnu intenzivnu negu i neonatologiju Klinike za pedijatriju Kliničkog centra Univerziteta u Sarajevu. Istraživanje je obuhvatilo 43 novorođenčadi koja su zadovoljila kriterijume uključivanja.

Rezultati: Otkrili smo da je 7,19% hospitalizovane novorođenčadi imalo konvulzije. Velik broj napada zabeležen je u grupi terminske novorođenčadi s ranijim početkom konvulzija. Najčešći etiološki uzroci bili su: HIE, IVH, infekcije i CM. Česta je bila pojava metaboličkih poremećaja poput acidoze, poremećaja šećera u krvi i minerala (Ca, K, Na i Mg). Medijan prvog dana početka konvulzija u donošene dece je četvrti dan, dok je u nedonoščadi šesti dan života. Fenobarbiton se uglavnom koristio za zaustavljanje konvulzija, s velikim uspehom. Ukupna smrtnost u dece s konvulzija bila je 37,21%.

Zaključak: Kod novorođenčadi su česte konvulzije koje, zavisno od etiološkog uzroka, povećavaju mortalitet, naročito kod nedonoščadi. Konvulzije se u donošene dece javljaju ranije nego u nedonoščadi. Najčešća etiologija konvulzija u donošene dece su: infekcije, hipoksemično-ishemijska encefalopatija, intrakranijalno krvarenje, cerebralne malformacije i cerebrovaskularni inzult. U nedonoščadi to su: hipoksemično-ishemijska encefalopatija, intrakranijalna krvarenja i infekcije. U početnom lečenju neonatalnih konvulzija najčešće se koristi fenobarbiton, koji se pokazao uspešnim u većini slučajeva.

Ključne reči: neonatalne konvulzije, etiologija, lečenje, prognoza, mortalitet.

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THE ASSESSMENT OF PATIENTS WITH NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE BY USING THE BRAVO® PH MONITORING SYSTEM

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Abstract: **Background and aim:** Gastroesophageal reflux disease (GERD) is a common disease in the world. GERD is always treated with drugs. The Bravo® wireless pH monitoring system is a good technique. The Bravo® may affect increasing the specificity and sensitivity in the diagnosis of GERD with its 48-hour recording feature. In this study, we aimed to assess the diagnostic performance of the Bravo® pH monitoring system in patients with non-erosive GERD.

Materials and Methods: Patients with non-erosive reflux disease (normal endoscopy) whose symptoms persisted after PPI treatment (at least two months) were included in the study. All patients had upper gastrointestinal system endoscopies performed in our clinic between January 2013 and December 2019. All patients had a 48-hour Bravo® wireless pH monitoring record.

Results: Twenty-three patients (M: 18 (78.3%; Age: 35.7 ± 11) were included in the study. All patients completed the 2-day recording protocol. During and after the procedure, no patient showed any adverse effects of the Bravo® procedure. We diagnosed GERD in 13 of 23 patients by Bravo® capsule. According to the Bravo® pH-meter recordings; Total time pH < 4 (minute) was 187 ± 190, the total number of refluxes was 90 ± 61, the percentage of time with pH < 4 was 7.1 ± 7.22, the number of long reflux events were 8.1 ± 8, the duration of the longest reflux episode during pH < 4 (minute) was 31 ± 49, the Demeester score was 20.8 ± 19.3 detected.

Conclusion: Based on the results of the current study, the Bravo® pH monitoring system is a practical and effective diagnostic technique for non-erosive GERD. Further prospective studies would be useful for comparing the differences between 24-hour and 48-hour pH recording results.

Keywords: Gastroesophageal Reflux, Esophagus, Reflux.

INTRODUCTION

The leakage of gastric acidic juice or alkaline secretions into the esophagus is named gastroesophageal reflux. Gastroesophageal reflux, which is a physiological event, is defined as gastroesophageal reflux disease (GERD) when it causes symptoms. The most important preventive factor in the pathological transformation of gastroesophageal reflux in physiological conditions is the mechanical barrier at the lower esophageal sphincter (LES). GERD can occur when this mechanical barrier is weakened by LES insufficiency, hiatus hernia, or temporary LES relaxation. The prevalence of GERD has been reported in 10-29% in the western world. In the GORHEN study (3214 cases in 20 provinces in Turkey) the frequency of GERD has been reported as 23% (1, 2, 3). One or both of the classic GERD symptoms (pyrosis, regurgitation), once a week or more often, is sufficient for diagnosing GERD. GERD is always classified into two groups according to endoscopy. Erosive reflux disease (ERD) is defined in cases with erosion or ulceration in the endoscopic examination. Non-erosive reflux disease (NERD) is defined by determining acid exposure for 24 hours or more with new diagnostic methods such as pH-meter, impedance, and Bravo® pH measurement. In NERD cases, response to proton pump inhibitor (PPI) therapy is low (3, 4, 5).

GERD should be investigated with intraesophageal monitoring in cases that has no response to PPI treatment, in cases with extraesophageal symptoms, or in cases where an operation is planned for GERD, especially if there is no evidence of upper GI endoscopic

examination (non-erosive reflux disease) because objective evidence is needed. For this purpose, conventional catheter-based pH-meters and the Bravo® wireless intraesophageal capsule pH-meter can be used. The conventional method may restrict the patient's diet and physical activity, and the catheter may migrate. Patients with Bravo® wireless intraesophageal capsule pH-meter do not experience such problems with its 48-hour recording feature (6-10).

In this study, we aimed to assess the diagnostic performance of the Bravo®pH monitoring system in patients with non-erosive GERD.

MATERIAL AND METHOD

Study population

In this study, patients with NERD whose symptoms persisted after PPI treatment (at least two months), were included. All patients had undergone upper gastrointestinal system endoscopy in our clinic between January 2013 and December 2019. All patients had undergone a 48-hour Bravo® wireless pH monitoring. Since the study was retrospective, patient data were obtained from the digital database of our hospital.

Cases under the age of 18, presence of malignancy in the upper gastrointestinal system endoscopy or presence of reflux due to gastric outlet obstruction, cases with motility disorder, cases who underwent Nissen fundoplication, and cases with connective tissue disease (scleroderma, etc.), were not included in the study. The local Ethics Committee approval was obtained (2021.371.IRB1.161).

Bravo® (Esophageal capsule Ph meter) (Medtronic, Shoreview, MN, USA)

The Bravo® pH monitoring system has several items: pH receiver kit; capsule with a delivery system, an internal battery, and transmitter; vacuum pump; suction tubes; calibration stand, buffer solution; infrared receiver device; and software. Drugs (proton pump inhibitors and H2-blockers) must be discontinued for 14 days. Antacids should be stopped at least 24 hours before the operation. Patients must fast (at least 8 hours). The capsule-shaped probe (6 mm × 5.5 mm × 25 mm) that will measure pH is attached to the 6 cm proximal of the LES during the endoscopic examination performed while the patient is sedated. The main parameters measured are listed as percent of the total time of pH < 4; the total number of reflux periods in both positions; duration of reflux period; the number of long reflux periods (longer than 5 minutes); symptom score; and the mean duration of reflux period. A reflux period is defined as a drop in pH below 4, lasting for ≥ 10 seconds. In addition to the possibility of measuring in more physiological conditions due to its catheter-free nature, it provides the opportunity to measure intraesophageal pH-meter until it falls. The capsule always detaches from the esophagus spontaneously (2 days to 2 weeks). It measures 2-5 days until the capsule falls. The day in which reflux is detected the most is taken into account. For this reason, it has been shown that the sensitivity has increased by 30% with the concept of "worst day". Complications such as chest pain (3%-5%), failure of the capsule to hold, and premature or no fall (0-3%) may develop. The contraindications for Bravo® are known as pregnancy, history of bleeding diathesis, the presence of esophageal strictures, esophageal varices, diverticula of the esophagus, and severe esophagitis with metaplasia. For patients with a history of previous upper GI surgery, Zollinger-Ellison syndrome, active malignancy, or Crohn's disease, the Bravo®pH monitoring system was not recommended (11-14).

Statistical Analysis

The data distribution characteristics were reviewed before the statistical analysis. Non-parametric group data were listed as the median (interquartile range). The Wilcoxon signed-rank test is used for comparing paired data. The statistical significance is defined as a P value of less than 0.05.

RESULTS

All twenty-three patients had undergone the 2-day recording protocol. No side effects were observed after or during the Bravo® procedure (chest pain, dysphagia, bleeding, etc.). The indications for pH testing were PPI responsiveness symptoms such as chest pain, refractory heartburn, and laryngeal symptoms. We diagnosed GERD in 13 of 23 patients by Bravo® capsule. According to Bravo® pH-meter records; Total time pH < 4 (minute) was 187 ± 190, the total number of reflexes was 90 ± 61, the percentage of time with pH < 4 was 7.1 ± 7.22, the number of long reflux events was 8.1 ± 8, the duration of the longest reflux episode during pH < 4 (minute) was 31 ± 49, the Demeester score was 20.8 ± 19.3 detected.

The demographics of the patients and results of Bravo® capsule presented in Table 1.

We also compared Day 1 and Day 2 results and found no statistically significant difference between the two days (Table 2).

Table 1. *Demographics of patients and Bravo capsule pH results*

Age	35.7 ± 11
Gender (Male)	18 (78.3%)
Patients with extraesophageal symptoms	9 (39.1%)
Total time pH < 4 (minute)	187 ± 190
Total number of refluxes	90 ± 61
Percentage of time with pH < 4	7.1 ± 7.22
Number of long reflux events	8.1 ± 8
Duration of longest reflux episode during Ph < 4 (minute)	31 ± 49
Demeester score	20.8 ± 19.3

Table 2*. The comparison of Day 1 and Day 2 results of the Bravo Capsule pH Meter*

	Day 1	**Day 2**	**P Value**
Total time pH < 4 (minute)	88.09 ± 74	103 ± 138	0.9
Total number of refluxes	50.6 ± 32	45.6 ± 29	0.58
Percentage of time with pH < 4	6.7 ± 5.5	7.9 ± 10	1
Number of long reflux events	4.1 ± 4	3.8 ± 4.6	0.72
Duration of longest reflux episode during pH < 4 (minute)	17.5 ± 14	20.8 ± 48	0.21
Demeester score	18.4 ± 13.6	19.5 ± 21.8	0.7

DISCUSSION

Conventional pH-meter limits the daily life activities, diets, and physical activities of the patients, thus causing a decrease in their quality of life. Bravo® allows the patient to continue his daily activities and does not reduce his quality of life. Bravo® is better tolerated, longer records can be undertaken, and this can increase the diagnostic sensitivity. Because the conventional catheter pH meters may cause discomfort in patients, it may lead them to eat less and behave differently in their daily lives during the process. Patients with Bravo® wireless intraesophageal capsule pH-meter do not experience such problems, so the Bravo® procedure provides "real" measurement. On the other hand, it is important to stay in place because it has been shown that conventional catheter pH meters can be displaced within hours. Measurement differences may be in conventional catheter pH meter and Bravo® capsule pH meter because recording intervals are different in these two methods. The recording interval is 4 seconds for a conventional pH meter and 6 seconds for Bravo® pH-meter. In a study, Azzam et al. compared the conventional and capsule pH monitoring, reported as no significant difference was detected between the two methods for the diagnosis of GERD, and they also reported as they detected longer reflux durations in the capsule group. Hakanson et al. reported as the esophageal acid exposure time detected in capsule pH was approximately half of the value that was found with the catheter ($p < 0.05$)in a study. According to the current medical literature, catheter pH monitoring has 79%-96% sensitivity and 85%-100% specificity. Bravo's endoscopic application is easy, and it stands out with its long-term recording capability. Pandolfino et al. reported 78.3%-100% sensitivity and 84.5%-94.8% specificity for this method. Bravo® has advantages over conventional catheters in these respects, but Bravo® is expensive, and the number of applications remains low compared to other methods. Rare complications such as chest pain, failure of the capsule to hold, and premature or no fall may develop (8-18). In our study, patients tolerated the Bravo® procedure well, consistent with the literature.

Several studies in the medical literature had presented the positive effect of extended 48h pH monitoring for the diagnosis of GERD. Many studies are comparing the results of days one and two of the Bravo® procedure, but the results of these studies are contradictory. Pandolfino et al., in a study that included 37 patients with GERD and 39 controls, stated no significant difference between the 1st and 2nd day data in terms of acid exposure (11). Bechtold et al. reported that they detected higher acid reflux in Day 1 recordings compared to Day 2 recordings (19). In some studies, more reflux was detected in the 2nd day measurements (20-22). According to our study, no significant difference was found for acid reflux and Bravo® capsule parameters in the 1st and 2nd day recordings.

After the procedure, some patients may have throat discomfort, bleeding, odynophagia, dysphagia, mild foreign body sensation, and eating and chest discomfort. If the patients have severe odynophagia and

chest pain (< 2% cases), a chest X-ray may be useful for excluding perforation. Sometimes, in up to 15% of cases, technical failure may occur (data transmission decrease, attachment problems, early capsule dislodgement, detachment failure). The need for capsule removal may be indicated in patients whose chest discomfort is intolerable and persistent (6%) (14, 21, 22). In our study no major complications or serious side effects were observed after the procedure, and all patients tolerated the Bravo® capsule well. It was not necessary to remove the capsule in any of the patients.

The study has some limitations. The most important one is the retrospective nature of the study. The data of the patients (demographic, anthropometric, procedure history, treatment history, etc.) could not be obtained sufficiently. Another limitation is that the majority of the current study is male, and the study results may not be generalizable to the whole population.

In conclusion, the Bravo® pH monitoring system is an effective, practical, and safe diagnostic procedure. In our study, no significant difference was found between the first- and second-day values for acid reflux. Nowadays, few studies have compared the merits of 24 versus 48-hour wireless capsule pH monitoring. Many factors may affect the result, for example, the sedation given during endoscopy for capsule placement on the first day can increase the acid reflux in the distal esophagus. Further prospective studies would be useful for comparing the differences between 24-hour and 48- hour pH recording results and investigating the effects of sedation on 24-hour and 48-hour wireless pH monitoring.

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ANALIZA PACIJENATA SA NEEROZIVNOM GASTROEZOFAGEALNOM REFLUKSNOM BOLEŠĆU KORIŠĆENJEM BRAVO® PH SISTEMA ZA MONITORING

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Uvod i cilj: Gastroezofagealna refluksna bolest (GERB) je uobičajena bolest u svetu. GERB se uvek leči lekovima. Bravo® bežični sistem za praćenje pH vrednosti je dobra tehnika. Bravo® može uticati na povećanje specifičnosti i osetljivosti u dijagnozi GERB-a sa svojom funkcijom snimanja od 48 sati. U ovoj studiji, imali smo za cilj da procenimo dijagnostičke performanse Bravo®pH sistema za praćenje kod pacijenata sa neerozivnim GERB-om.

Materijali i metode: U studiju su uključeni pacijenti sa neerozivnom refluksnom bolešću (normalna endoskopija) čiji su simptomi perzistirali nakon tretmana PPI (najmanje dva meseca). Svim pacijentima je urađena endoskopija gornjeg gastrointestinalnog sistema u našoj klinici u periodu od januara 2013. do decembra 2019. Svi pacijenti su imali 48-časovni Bravo® bežični zapis o praćenju pH vrednosti.

Rezultati: U studiju su uključena 23 pacijenta (M: 18 (78,3%; Starost: 35,7 ± 11). Svi pacijenti su završili dvodnevni protokol snimanja. Tokom i nakon procedure, nijedan pacijent nije imao štetne efekte od Bravo® procedure. Dijagnostikovali smo GERB kod 13 od 23 pacijenta sa Bravo® kapsulom. Prema snimcima Bravo® pH metra, ukupno vreme pH < 4 (minuta) je 187 ± 190, ukupan broj refluksa bio 90 ± 61, procenat vremena sa pH < 4 je bio 7,1 ± 7,22, broj dugih refluksnih događaja je bio 8,1 ± 8, trajanje najduže epizode refluksa tokom pH < 4 (minuta) je bilo 31 ± 49, Demeester skor je bio 20,8 ± 19,3.

Zaključak: Na osnovu rezultata trenutne studije, Bravo® pH sistem za praćenje je praktična i efikasna dijagnostička tehnika za neerozivni GERB. Dalje prospektivne studije bi bile korisne za poređenje razlika između 24-časovnih i 48-časovnih rezultata pH snimanja.

***Ključne re**či:* gastroezofagealni refluks, jednjak, refluks.

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Case report

MANAGEMENT OF NEGLECTED VICIOUS CAT BITE IN A CHILD: A CASE REPORT

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Abstract: **Introduction:** Cat bites make up 10% of all animal bites and have a high incidence of infection. Cat bites can cause severe deep bacterial infection in closed spaces such as tendon sheath, joints, and bones due to their sharp teeth. Generally, cat bite wound infections are reported at 30%-60%, which is double compared to rat or dog bites. However, cat bites are easily misjudged due to their minimal appearance of tissue injury. **Case Report:** We hereby present a case of a neglected cat bite wound complicated with infection in a healthy child. The wound was debrided in the operation theatre, and a ten-day course of antibiotics was completed. No further infection was noted and the child was discharged home well. **Conclusion:** There is no exact algorithm of treatment for cat bites. However, cat bites are nasty wounds that should be treated early and aggressively. Empirical oral or intravenous antibiotics should be started immediately, and adequate surgical debridement is indicated to provide a better outcome as there are no standardized protocols for initial management.

Keywords: Cat bites, Infection, Wound, Antibiotic Treatment.

INTRODUCTION

Cat bites make up 10% of all animal bites and have a high incidence of infection (1). Cat bites are commonly seen in adult women and high incidences are seen in extremities (1, 3). Cat bites can cause severe deep bacterial infection in closed spaces such as tendon sheath, joints, and bones due to their sharp teeth (1, 2, 3). *Pasteurella multocida* is the most common Gram-negative, non-spore-forming coccobacillus found in cat bite infections, and it occurs hastily within the first 24 hours after the bite (1). Generally, cat bite wound infections are reported at 30-60%, double compared to rat or dog bites (3). However, cat bites are easily misjudged due to their minimal appearance of tissue injury (3). Hereby, we present a case of a neglected cat bite wound complicated with infection in a healthy child.

CASE REPORT

A previously healthy 7-year-old child was brought to the emergency department, Hospital Shah Alam, Malaysia, by her mother with a history of being bitten by a stray cat a week prior, and no medical consultation was made. Subsequently, the mother noticed the wound was worsening, and the patient developed a fever. Upon admission, vital signs were stable, and no documented temperature in the ward. Clinical examination revealed diffuse swelling over the medial aspect of the left ankle with multiple puncture wounds, serous discharge, and an area of fluctuance in the middle. The surrounding skin was warm, erythematous, and tender upon palpation. Noted pus discharge upon milking from the wound edges. Laboratory examination showed leukocytosis with the number of WBCs in the blood at 18×10^9/L, and an increased level of C-Reactive Protein was 20 mg/L. The plain radiograph of the left ankle was normal and no bony involvement was noted. The patient started on intravenous Amoxicillin-clavulanate. Meticulous wound debridement was performed until healthy skin margins were obtained. Postoperatively the wound was healthy and subsequently healed by secondary intention. Tis-

Figure 1. *Pre operative wound over the left ankle*

Figure 2. *Post operative wound over the left ankle*

sue culture and sensitivity were reported as no growth. The child completed 5 days of intravenous antibiotics in the ward. The child was discharged after a week in the hospital with a five-day course of oral Amoxicillin-clavulanate (Figure 1 and 2).

Parents have signed consent for the case presentation and publication.

DISCUSSION

Clinical evaluation and culture of the bite remain the mainstay of the diagnosis and management. Naturally, polymicrobial infections are seen in animal bites. Nevertheless, infections caused by cat and dog bites are usually due to aerobic and anaerobic microorganisms (1). The commonest microorganisms that have been discovered in infected cat bite wounds are *Pasteurella sp.* (3). These bacteria are normal oral flora in this type of mammal and are present in 70% to 90% of healthy cats (3). Post Exposure to antibiotic prophylaxis in most cases remains controversial (1). However, a wise approach is crucial in managing higher-risk bites such as cat bites and bites on the hand (1). Management of cat bites depends on the site and severity of the wound and infection, close observation, outpatient oral antibiotics, intravenous antibiotics and finally, surgical debridement or irrigation is needed accordingly (1, 2). There is no exact algorithm of treatment for cat bites. However, according to Infectious Disease Society of America, guidelines state that soft tissue and skin infection are suggested to prescribe preemptive antibiotics 3-5 days in the immunocompromised patient, especially in injuries that involve the bone, joint, tendon and capsule, and genitalia, face, hand and foot (2). 7-10 days of antibiotic course is sufficient in soft tissue infection (2). However, the final decision for antibiotic therapy depends on the severity of the wound and the clinical progress of the patient (2). First-line prophylactic antibiotic therapy in animal bites is known to be Amoxicillin-clavulanate (1, 3). Patients who are allergic to penicillin can replace it with doxycycline or a combination of clindamycin and fluoroquinolone (1). The majority of the wounds can be managed with oral antibiotics and without hospitalization or surgical debridement (3). Yet, it's highly recommended to debride a cat bite wound and close it with secondary intention because of its high risk for infection (1, 3).

CONCLUSION

Cat bites are nasty wounds that should be treated early and aggressively. A proper clinical assessment and management are critical to prevent further complications. Empirical oral or intravenous antibiotics should be started immediately and adequate surgical debridement is indicated to provide a better outcome as there are no standardized protocols for initial management, antibiotic of choice, or algorithm of management for hospitalized patients for cat bite injury.

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LEČENJE ZANEMARENE RANE OD UJEDA MAČKE KOD DETETA: PRIKAZ SLUČAJA

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Uvod: Ujedi mačaka čine 10% svih ujeda životinja i imaju visoku učestalost infekcije. Ujedi mačaka mogu izazvati ozbiljnu, duboku bakterijsku infekciju u zatvorenim prostorima kao što su omotač tetiva, zglobovi i kosti zbog njihovih oštrih zuba. Generalno, infekcije rane od ugriza mačaka se beleže u 30-60%, što je dvostruko više u poređenju sa ujedom pacova ili pasa. Međutim, mačji ugriz se lako pogrešno proceni zbog minimalnog izgleda povrede tkiva. **Prikaz slučaja:** Predstavljamo slučaj zanemarene rane od ujeda mačke komplikovane infekcijom kod zdravog deteta. Rana je obrađena u operacionoj Sali, a pacijent tertian deset dana antibioticima. Dalja infekcija nije zabeležena i dete je otpušteno kući. **Zaključak:** Ne postoji tačan algoritam za lečenje ujeda mačaka. Međutim, ujedi mačaka su gadne rane koje treba lečiti rano i agresivno. Sa empirijski oralnim ili intravenskim antibioticima treba započeti odmah, a adekvatan hirurški debridman je indikovan da bi se obezbedio bolji ishod pošto ne postoje standardizovani protokoli za inicijalnu terapiju.

Ključne reči: ujedi mačaka, infekcija, rana, lečenje antibioticima.

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Letter to editor

MAY 25-31, INTERNATIONAL THYROID AWARENESS WEEK & MAY 25, WORLD THYROID DAY, 2022: INDETERMINATION OF INDETERMINATE CYTOLOGY, AUS/FLUS, FN, SUSP, IN THYROIDOLOGY?

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May 25, World Thyroid Day, WTD, was officially accepted at the Annual General Meeting of the European Thyroid Association (ETA) before the September 2007 Congress in Leipzig, Germany. Although the date also refers to the establishment day of ETA in 1965, the aim is to create awareness about thyroid diseases on this day. After World Thyroid Day was first celebrated by ETA, in 2010, the American Thyroid Association (ATA) declared its support for this day. In addition, on May 25-31, International Thyroid Awareness Week, ITAW, is celebrated worldwide with the mentorship of Thyroid Federation International.

The "thyroid gland", commonly used terminology simply "thyroid", is an important endocrine organ localized in front of the neck, extending laterally on both sides. This butterfly-shaped and delicate (1) vital organ is responsible for many metabolic activities that are critical for the organism through the secretion of thyroid hormones. Therefore, "thyroid health" becomes extremely important. As such, thyroid gland disorders continue to affect all age groups globally and possess a wide spectrum of signs and symptoms. Among these, hypothyroidism, thyrotoxicosis with or without hyperthyroidism, goiter, congenital thyroid diseases, thyroiditis, retro/substernal goiter, follicular nodular thyroid disease with primary and secondary thyroid carcinomas are noteworthy. Family history, genetic and familial predisposition, radiation exposure to the head & neck and thorax region during the first two decades particularly in children and women (0-20 years of age), iodine deficiency, and some drugs such as amiodarone are known as the leading factors to the thyroid gland disorders. Nevertheless, the Public Health Update reported that more than 200 million people worldwide are facing thyroid disorders, and over 50% of them remain undiagnosed.

To achieve an accurate diagnosis for disorders and also carcinomas with their metastasis and recurrences before histopathology and during postoperative follow-up of this small, delicate, and papillon vital organ that can affect the whole organism: *(i) biochemical essays* (fT3, fT4, tT3, tT4, TSH, Tg, anti-Tg, anti-TPO, calcitonin, TSI/TRAb, US-guided-Tg/calcitonin washout); *(ii) imaging modalities* (sonography, strain, and shear wave elastography, SWE, scintigraphy and CT, MRI, 18-FDG PET/CT, and ^{131}I-WBS, when necessary) and (*iii) cytopathologic examinations* have been utilized. However, thyroid and neck US and cytopathological examination, in particular, still maintain their importance today. Indeterminate cytology (Category III, IV, V, The Bethesda System for Reporting Thyroid Cytopathology, TBSRTC, 1st and 2nd ed.s) (2, 3) in cytopathology and follicular nodular thyroid disease, in general, is one of the controversial topics which remains to be a significant topic for thyroidologists (4,5). The latest ATA guidelines, 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (6), recommended repeat FNA cytology, molecular tests with further surveillance or diagnostic surgery, considering worrisome sonographic and clinical features with patient preference, as novel approaches in Endocrine Surgery, Endocrine Pathology, and Thyroidology to resolve the challenging issue, Category III, TBSRTC (AUS/FLUS, atypia of undetermined/follicular lesion of undetermined significance), which is at the center of the aforementioned controversion *(Recommendation 15A, Weak recommendation, Moderate-quality evidence; 15B, Strong recommendation, Low-quality evidence).*

Of note, some authors and authorities have advocated the potential need for separation in TBSRTC in terms of Category III, AUS/FLUS (7, 8, 9). We very recently also postulated the so-called subdivision concept in Category III, TBSRTC, *id est*, *(i) Category II-IA*: AUS/FLUS without nuclear atypia (*AUS/FLUS wo NA*), and *(ii) Category IIIB*: AUS/FLUS with nuclear atypia (*AUS/FLUS w NA*) within the possible forthcoming 3rd ed., the 202X TBSRTC (10, 11). *Mater artium necessitas*. Therefore, a novel risk of malignancy, ROM, for each diagnostic category of possible forthcoming TBSRTC would selectively enrich the different management proposals in Thyroidology. As a matter of fact that this issue merits further investigation. *Bene diagnoscitur bene curatur.*. *Dum vivimus servimus*..

Keywords: Thyroid gland, World Thyroid Day, Awareness, International Thyroid Awareness Week, Indeterminate cytology, AUS/FLUS, TBSRTC, Endocrine Surgery, Endocrine Pathology, Thyroidologists, Thyroidology.

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada.

U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

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Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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