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THE IMPACT OF KNOWLEDGE ON THE FORMATION OF ATTITUDES TOWARDS AGEING AND THE ELDERLY AMONG STUDENTS OF THE UNIVERSITY OF SPLIT

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Introduction: With the global trend of increasing ageing of the population, there is a corresponding increase in the health problems associated with elderly population. Older people need ever more health services. According to the research, the factors that influence health care practice of the health workers for the elderly in geriatric hospitals included knowledge, attitude, and gerontologic education. The *aim* of this study was to determine whether education in gerontology affects attitude towards ageing and the elderly among students at the University of Split. An additional objective was to determine the extent to which the student socio-demographic status (age, sex, domicile), different education and experience of living with the elderly affect their attitude towards ageing and the elderly. ***Subjects and Methods:*** The population included in this study consisted of 301 students of the University of Split, 153 of whom attended the Faculty of Maritime Studies and 148 the School of Medicine. The research was conducted using an anonymous questionnaire, during the period from December 1, 2020 to March 31, 2021. A total of 45 students had attended training in gerontology, while 265 had none. Information was collected through a questionnaire that consisted of 3 parts: one investigating their socio-demographic characteristics, another one looking into their attitudes towards the elderly (the Kogan score scale), and Palmer's competence test. ***Results:*** A difference in attitude was observed between students who had undergone training in gerontology compared to those who had none. Socio-demographic factors, different education and the experience of living with the elderly also affected student attitudes. Overall, the School of Medicine students had a more positive attitude than those of the Faculty of Maritime Studies. The level of statistical significance was set at $p<0.05$. ***Conclusion:*** Education in gerontology helps form a more positive attitude towards the elderly among students, meaning that educational programs should be changed with the aim of reducing stigmatization of the elderly.

Key words: attitudes, ageing, education

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INTRODUCTION

People nowadays live longer and exhibit a growing need for an improved quality of life. Contagious disease prevalence has decreased as medical science evolved. As a result of successful vaccination, administration of antibiotics and other forms of treatment, the morbidity and mortality caused by contagious diseases have decreased. On the one hand, progress in medicine, coupled with discovery of a number of medications, application of various forms of treatment, and new diagnostic and therapeutic opportunities, provides for better knowledge and earlier disease detection, as well as better and more effective treatment of chronic illnesses. On the other hand, the issue of care for an ever-increasing number of chronic patients is rising in importance. Population ageing is a global phenomenon; however, this issue is predominantly discussed in developed countries (1). In fact, most developed countries have low fertility and birth rates as a result of demographic transition. Extended life expectancy has contributed to the rise in the share of elderly persons

in the total population. Medical advances, especially in prevention and treatment, have also played a major role in increasing life expectancy, along with improved socioeconomic conditions, which has resulted in decreased mortality rates (2). Accelerated and continuous growth of elderly population is a demographic trend that increases the need for medical and social services, since the elderly are the most frequent users of such services (3). An ageing population thus turns into a key issue of social development, with a substantial expected impact on the situation in health care, social care and social policy throughout the 21st century. Population ageing is a highly complex process that entails major economic, social and political consequences (4). At the global level, the number of elderly persons is continuously rising as a result of progress in medicine that has led to extension of life expectancy to between 80 and 90 years (1).

A longer life brings along opportunities, not only for the elderly and their families, but also for the society as a whole (5). Additional years of life provide an opportunity to start new activities, such as further education, a new career, or pursuit of a neglected passion from the past. Elderly persons contribute to their families and communities in many ways. The scope of these opportunities and contributions largely depends on a single factor, i.e., health (4).

DEMOGRAPHIC PROFILE OF CROATIA AND THE WORLD

The United Nations data available in the World Population Prospects 2019 point to an eight-year increase in average life expectancy between 1990 and 2019. In 2019, global average life expectancy stood at 72.6 years. An even higher increase is expected by 2050, with average life expectancy estimated at 77.1 years (6).

According to data of the Bureau of Statistics of the Republic of Croatia, average life expectancy in the Republic of Croatia stood at 78.2 years in 2018 (7). According to the 2011 census, the Croatian population is 41.7-year-old on average, making the Croatian people one of the oldest peoples in Europe (8). The rise in life expectancy has increased the average age of the Croatian population by 10 years over the last 50 years. According to the 2011 census, the share of persons aged 65 or over (17.7%) is, for the first time ever, higher than the share of young persons pertaining to the 0-to14-age group (15.2%). Worldwide, in 2018, the number of persons over 65 exceeded the number of children under 5 (6). The share of the very old has risen in the Republic of Croatia as well, from 0.8% in 1953 to 3.9% in 2011 (7).

OLD AGE – SOCIOLOGICAL ISSUES

An increase in the number of elderly people in a population also leads to greater need for long-term care, ultimately resulting in increasing health care and social care costs (5). Due to this fact, it is assumed that ageing will have a serious impact on social security and economy, with healthcare and social care costs reaching substantial proportions. One of the key characteristics of old age is retirement, i.e., greater social dependence (9).

The social context within which elderly persons and families function is also changing, which *inter alia* impacts the nature of certain types of social relations, as well as the institutions providing part of the supporting infrastructure accessible to the elderly. Demographic and social trends – such as changes in propensity for marriage and starting a family, increasing frailty of human relations, disturbances within nuclear family, earlier adulthood – have an impact on the quantity and type of support available to the elderly and on their need for support (10).

An increasingly popular concept is ageism, a phenomenon characterised by the lack of recognition or limitation of rights of the elderly (9). Ageism is segregation based on calendar age, non-acceptance of individual approach to the elderly after turning a certain age, determining capacity and attribution of social roles based on chronological age (9). People are prone to prejudice when they lack specific information concerning an elderly person other than their age, which is seemingly obvious (3). It is extraordinarily important to consider the (lack of) capabilities of an elderly person that is being cared for, to eliminate prejudice concerning the elderly and to recognize their individuality while responding in accordance with the specific needs of the elderly person (11).

OBJECTIVES AND RESEARCH ASSUMPTIONS

The objective of this research was to examine the impact of education in gerontology on the formation of student attitudes towards elderly persons and the process of ageing. This examination was performed by means of a survey that looked into the respondent education in gerontology, their demographic data, and the impact thereof on their attitudes towards the elderly. We wanted to determine whether differences in attitudes towards ageing and elderly persons existed among groups of students, and whether they were in any correlation with different levels of education in gerontology or with personal experience of living with the elderly. The first hypothesis was that attitudes of

the School of Medicine students towards ageing were more positive compared to those of students of the Faculty of Maritime Studies of the University of Split, partly due to education in gerontology in the course of studies. The second hypothesis was that negative attitudes of the School of Medicine students towards ageing and the elderly were linked to the preferred residency upon completion of studies, and that students did not wish to specialize in gerontology as a result of such negative attitudes.

METHOD

Sample

The respondents were students of the University of Split enrolled in the School of Medicine or the Faculty of Maritime Studies in the academic year 2019/2020. The research was conducted with an anonymous questionnaire, during the period from December 1, 2020 to March 31, 2021. The site of research was the University of Split. In total, 301 male and female students participated in the survey. Informed consent was obtained from all subjects.

Instrument

Attitude is defined as an acquired, relatively permanent and stable organization of positive or negative emotions, evaluations and responses to an object. The structure of attitude consists of three components: cognitive component, which pertains to the knowledge concerning the object of attitude; emotional component, pertaining to the emotional perception of the object of attitude; and behavioural component, which pertains to action in regard to the object of attitude (12).

As a means of looking into student attitudes, the authors conducted a cross-sectional, online survey, accessed by students of the two mentioned faculties, from all programmes and years of study. The survey was anonymous and participation voluntary. Out of a total of 1,470 students of the Faculty of Maritime Studies in the academic year 2019/2020, 153 (10.40%) students responded to survey invitation. Of the total of 1,216 students of the School of Medicine in the same academic year (in Medical Doctor, Pharmacy and Dental Medicine study programmes), 148 (12.58%) students completed the survey. The survey questionnaire consisted of three parts: a part looking into respondent socio-demographic characteristics, a part examining their attitudes towards the elderly (Kogan's Attitudes Towards Old People scale, ATOP scale), and a knowledge/competence test (Palmer's questionnaire). Attitudes towards ageing and elderly persons were examined using the Kogan's ATOP scale. This scale contains a set of questions, where respondents are asked to choose the number that most accurately describes their stance on the question asked, the options being: 1=Strongly disagree, 2=Partly disagree, 3=Disagree, 4=Agree, 5=Partly agree, and 6=Strongly agree. The same questionnaires were also used as a research instrument in the survey undertaken among Slovenian nursing students (13).

Procedure

Descriptive statistics methods were used, i.e., arithmetic mean and standard deviation for values in line with normal distribution; in case of deviation from normal distribution, the median was used as median value, and interquartile range as a dispersion indicator. Distribution normality was examined by using the Kolmogorov-Smirnov test. Furthermore, χ^2-test was used to test distribution balance based on socio-demographic characteristics.

Differences in the level of knowledge and relations with the elderly were tested using the MannWhitney U test and Kruskal-Wallis test as versions of parametric tests for determining normal distribution values. The impact of the selected characteristics on relations with the elderly was tested using logical regression, i.e., the stepwise procedure. Links between numerical values were determined using Pearson correlation coefficient.

In the empirical part of the research, we tested the defined assumptions using quantitative methods in biomedicine. The paper also includes tables, detailing the structure of respondent answers to survey questions.

Statistical software STATISTICA 12 (2013, StatSoft, USA) was used for analytical purposes, while the level of significance was set at $p<0.05$.

RESULTS

Of the overall number of respondents (N=301), 53.16% were female and 46.84% were male students, and the difference was not statistically significant ($\chi^2=1.20$; $p=0.273$). In terms of age, the greatest number of respondents were in the 18-22 age group. In fact, there were 196 more students in this age group than in the ≥33 age group (19; 6.31%), which was the least represented student agegroup in the sample ($\chi^2=208.05$; $p<0.001$).

The greatest number of students (n=153; 50.83%) were enrolled in the Faculty of Maritime Studies, while only 5.65% (n=17) were enrolled in the Faculty of Pharmacy. Tests confirmed the uneven distribution of students according to study programme ($\chi^2=269.15$; $p<0.001$).

The majority of respondents had attended a grammar school (n=174:127), i.e., 47 more than a vocational secondary school, yielding a statistically significant difference (χ^2=7.34; p=0.007).

The number of students who had no training in gerontology was significantly higher (n=211; 256/49) and tests confirmed the difference to be statistically significant (χ^2=147.91; p<0.001).

Significantly more respondents (n=209) had experience living with the elderly (≥65), compared with 92 respondents who had no such experience. The difference was statistically significant (χ^2=45.48; p<0.001) (Table 1).

Table 1. *Respondent socio-demographic characteristics*

		n	%	χ^2	p*
Sex	F	160	53.16	1.20	0.273
	M	141	46.84		
Age group (yrs)	18-22	215	71.43	208.05	<0.001
	23-27	67	22.26		
	≥33	19	6.31		
Domicile	Urban area	241	80.07	108.84	<0.001
	Rural area	60	19.93		
Course enrolled	Medicine	100	33.22	269.15	<0.001
	Dental Medicine	31	10.23		
	Pharmacy	17	5.65		
	Faculty of Maritime Studies	153	50.83		
Secondary education	Grammar School (Lycee)	174	57.81	7.34	0.007
	Vocational	127	42.19		
Education in gerontology	No	256	85.05	147.91	<0.001
	Yes	45	14.95		
Experience living with an elderly person (>65)	Yes	92	30.56	45.48	<0.001
	No	209	69.44		
Total	301100.00				

*χ^2-test

The difference in results depending on the course enrolled was based on Kogan's ATOP scale and Palmer's competence test. According to Kogan's ATOP scale, the results were higher by 6 points in students of Medicine than in students of Maritime Studies (Z=4.17; p<0.001), which means that medical students had more positive attitudes towards the elderly. Medical students had 4.65 points more than their Maritime Studies counterparts (Z=5.32; p<0.001) in Palmer's competence test as well, which means that they knew more about ageing and the elderly. These differences in test results between the two groups of respondents served to prove that there was a correlation between positive attitudes and knowledge about ageing and the elderly in students of medical sciences (Table 2).

Table 2. *Difference in student attitudes according to the course enrolled*

	Faculty				Z	p*
	Maritime Studies		School of Medicine			
	Median	IQR	Median	IQR		
Kogan's ATOP Scale	120.00	(116.00-128.00)	126.00	(119.00-135.00)	4.17	<0.001
Palmer's competence test	62.79	(58.14-69.77)	67.44	(2.79-74.41)	5.32	<0.001

*Mann-Whitney U test

Table 3 shows differences in the results achieved by students according to sex. Kogan's ATOP scale median was by 4 points lower in men than in women (Z=2.21; p=0.027).

The Palmer's scale median was by 4.65 points lower in men than in women (Z=3.97; p<0.001). These results indicate that male students had fewer positive attitudes and a lower degree of knowledge about ageing and the elderly than their female counterparts, and the difference was statistically significant.

Table 3. *Differences in student attitudes depending on demographic characteristics*

	Sex				Z	p*
	Male		Female			
	Median	IQR	Median	IQR		
Kogan's ATOP scale	121.00	(117.00-129.00)	125.00	(116.00-135.00)	2.21	0.027
Palmer's competence test	62.79	(58.14-69.77)	67.44	(62.79-72.09)	3.97	<0.001

*Mann-Whitney U test

Table 4 shows difference in the results according to respondent domicile. Kogan's ATOP scale median was by 3 points higher in respondents living in urban areas (Z=2.21; p=0.027), showing that they had more positive attitudes towards ageing and the elderly than respondents living in rural areas. The Palmer's test median was by 0.01 points higher in respondents living in rural areas, but without a statistically significant difference (Z=1.06; p=0.288).

Table 4. *Differences in student attitudes depending on their domicile*

	Domicile				Z	p*
	Urban area		Rural area			
	Median	IQR	Median	IQR		
Kogan's ATOP scale	123.00	(117.00-134.00)	120.00	(116.00-126.50)	2.21	0.027
Palmer's competence test	65.11	(60.47-72.09)	65.12	(60.47-69.77)	1.06	0.288

*Mann-Whitney U test

In Palmer's competence test, students aged 18-22 achieved poorer results than their counterparts aged 23-27 or ≥33(H=5.46; p=0.654). Such results indicate that older students knew somewhat more about ageing and the elderly, but the difference was not statistically significant (Table 5).

Table 5. *Differences in student perception according to age groups*

Palmer's competence test				
Age group (yrs)	Median	IQR	H	p*
18-22	65.12	60.47-69.77	5.46	0.654
23-27	67.44	62.79-74.42		
≥33	67.44	62.79-72.09		

*Kruskal-Wallis test

Table 6 shows difference in the results on attitudes towards ageing and the elderly between different student age groups. Kogan scores were by 6 points higher in respondents aged 23-27 than in those aged 18-22 or ≥33 (H=12.80; p=0.002). These results indicate that older students had more positive attitudes towards ageing and the elderly, and this difference was statistically significant.

Table 6. *Comparison of Kogan scores according to student age group*

Kogan score				
Age group (yrs)	Median	IQR	H	p*
18-22	121.00	(116.00-132.00)	12.80	0.002
23-27	127.00	(120.00-137.00)		
≥33	121.00	(116.00-128.00)		

*Kruskal-Wallis test

Considering difference in the results according to previous education in gerontology, Kogan median score was by 7.50 points higher in respondents who had attended gerontology training than in those who had none (Z=2.65; p=0.008). Respondents who had been educated in gerontology showed a more positive attitude and more knowledge about ageing and the elderly, and the difference was statistically significant, confirming the first hypothesis of our research (Table 7).

Table 7. *Differences in student perception depending on education in gerontology*

	Education in gerontology				Z	p*
	Some		None			
	Median	IQR	Median	IQR		
Kogan's ATOP score	129.00	(120.00-135.00)	121.50	(116.00-132.00)	2.65	0.008
Palmer's competence test	65.12	(62.79-74.42)	65.12	(60.47-72.09)	1.50	0.134

*Mann-Whitney U test

Difference in student attitudes also depends on their experience of living with the elderly, as well as on the student gender. Gender had a statistically important impact on the Kogan scale values: female students had 1.898 times greater chances of Kogan scores higher than 133 (B=1.898; p=0.038), which indicated a more positive attitude towards ageing and the elderly in females than in males, and this difference was statistically significant. With every further year at university, the likelihood of a Kogan scale score higher than 133 increased by 1.234 (B=1.234; p=0.017), which means that the longer a respondent had been studying, the more positive their attitudes would be, and the difference was statistically significant.

Kogan median score was by 4 points higher in respondents who had lived with an elderly, but the difference was statistically nonsignificant (Z=1.36; p=0.173).

Palmer's competence test results showed the same median in both study groups, which means that there were no statistically significant sex differences in the level of knowledge about ageing and the elderly (Z=0.76; p=0.448) (Table 8).

Table 8. *Differences in student attitudes depending on their experience of living with the elderly*

	Experience of living with the elderly				Z	p*
	Some		None			
	Median	IQR	Median	IQR		
Kogan score	124.00	(117.00-133.00)	120.00	(115.50-133.00)	1.36	0.173
Palmer's competence	65.12	(60.47-72.09)	65.12	(60.47-72.09)	0.76	0.448

*Mann-Whitney U test

From the point of view of the preferred residency (among medical students), the highest Kogan score concerning ageing and the elderly, and consequently the most positive attitude was recorded in respondents who wanted to become radiology specialists, while those interested in emergency medicine had the lowest score, but the results were not statistically significant (H=14.62; p=0.931) (Table 9).

Table 9. *Differences in student perception depending on their preferred residency following completion of their studies*

Preferred residency	n	Median	IQR	H	p*
Radiology	2	141.00	134.00-148.00	14.62	0.931
Clinical Pharmacy	2	133.00	125.00-141.00		
Internal Medicine	15	131.00	117.00-137.00		
Family Medicine	10	130.50	120.00-142.00		
Sports Medicine	2	130.50	119.00-142.00		
Psychiatry	6	130.00	125.00-135.00		
Dermatology	8	128.00	109.00-136.00		
Paediatrics	9	128.00	119.00-132.00		
Gerontology	2	127.00	119.00-135.00		
Gynaecology	8	126.50	115.50-141.00		
Neurology	3	126.00	112.00-142.00		
Cardiology	6	124.50	122.00-133.00		
Oncology	8	123.50	117.00-131.50		
Surgery	15	123.00	117.00-135.00		
Anaesthesiology	2	121.00	121.00-121.00		
Infectious Disease Medicine	1	121.00	121.00-121.00		
Pathology	1	113.00	113.00-113.00		
Microbiology	1	108.00	108.00-108.00		
Emergency Medicine	1	106.00	106.00-106.00		

*Kruskal-Wallis test

DISCUSSION

The attitudes and effect of gerontology education on students of Medicine and of Maritime Studies in Split were examined using Kogan's ATOP scale and Palmer's questionnaire. In addition to the impact of knowledge, the questionnaire also examined the effect of some socio-demographic factors on the formation of attitudes concerning ageing and elderly persons among students (3).

School of Medicine students were selected due to the possibility of their earlier education in the area of gerontology, and due to the awareness of social groups with increased needs. Students of the Faculty of Maritime Studies were selected as a comparative group, representative of the general population with no gerontology education during the course of their studies.

Two hypotheses were defined. According to the first hypothesis, attitudes of the School of Medicine students concerning ageing are more positive than those of students of the Faculty of Maritime Studies of the University of Split, partly due to gerontology education in the course of studies, and this hypothesis was confirmed. The second hypothesis was that negative attitudes of the School of Medicine students concerning ageing and the elderly are linked with the preferred residency upon completion of the studies, and that students do not wish to become specialized in gerontology due to their negative attitude. This hypothesis was rejected.

Attitudes concerning ageing and elderly persons are formed under the influence of various factors (14). Since the number of elderly persons is on a rise, there is a growing need to change negative attitudes among the public towards ageing and elderly persons (15). Academic findings and research see the average age of the population of a given community as the first indicator and benchmark of the quality of life. Extension of life expectancy is a major achievement. Each individual, regardless of age, wants to live as many years as possible, but without the negative connotations of old age, and with the highest achievable quality of life (16).

When considering the elderly, it is often forgotten that most people in this population group are in the period of early old age, when changes caused by ageing are not pronounced to such a degree that they would substantially limit their daily activities, except for cases of complications caused by chronic illness (11).

In this study, students expressed their own attitudes concerning ageing and elderly persons using the Kogan scale, by selecting the number closest to their perception of a given claim. They agreed most with the claim that most elderly persons have their own habits that cannot be changed. On the other hand, students agreed least with the claim that most elderly persons allow their homes to become shabby and unpleasant.

The impact of knowledge on the formation and change of attitudes has already been proven (17). Palmer's questionnaire comprised claims that respondents assessed as true or false. There were 34 claims where more than 50% of the respondents knew the correct answer, and four claims where the majority of the respondents did not know the correct answer. Student responses included stereotypes and fallacies most frequently connected

with social life of the elderly, and correct answers were typically those pertaining to physical condition of the body and changes arising due to ageing.

In case of our respondents, there was a positive and statistically significant link between the results of Kogan and Palmer scales, i.e., persons with a higher degree of knowledge concerning aged persons had more positive attitudes towards ageing and the elderly, and the opposite was true as well. Fallacies in connection with ageing include lack of knowledge on the plasticity of the central nervous system and decay of brain activity excluding neurological disorders (18). Elderly persons can learn, but their motivation and learning methods differ, which requires adaptation of teaching methods to their age and needs. While the manner in which they memorize new data and written material can be considered through proper teacher training, various games help maintain mental fitness, just as in other organic systems (19). It is important to point out that elderly persons do not memorize new data as young persons do; however, their learning capacity, as well as long-term memory are preserved. It is therefore extraordinarily important to initially assess the psychological independence of a person, and to exclude depression and neurological disorders that are frequent in old age (11).

Among our respondents, a more positive attitude towards ageing and the elderly was recorded in medical students than in students of Maritime Studies.

Age, sex and domicile have also been shown to have an impact on the formation of attitudes concerning ageing and the elderly (20). Male students scored lower median values in both Kogan scale and Palmer questionnaire, when compared to female students. Furthermore, female students exhibited a more positive attitude towards ageing and the elderly compared to their male counterparts (1.898 times higher probability for Kogan scores higher than 133; B=1.898; p=0.038). In most cultures, the role of woman in family is to care for the children, the ill, the old and disabled persons; as a result of upbringing, female children have a pronounced sensitivity for the needs of other family members (21).

Each subsequent year of the study increased the probability that a person would achieve a Kogan scale score higher than 133 by 1.234 times (B=1.234; p=0.017), which points to a conclusion that a more positive attitude among students is developed in the course of years of the study.

Respondents from urban settlements showed a more positive attitude towards ageing and the elderly compared to respondents residing in rural settlements, but difference in knowledge (Palmer's test) was not determined. This result was contrary to our expectations. In fact, rural areas are frequently perceived through the prism of a traditional form of life and nurturing of family values, where care for the needs of each family member is pronounced and, in line with that, we expected respondents living in rural areas to have more positive attitudes concerning ageing and the elderly.

Students were divided into three age groups, i.e., 18-22, 23-27 and ≥33 years. The youngest age group (18-22 years) showed a lower level of Palmer scale results (knowledge) compared to older age groups. The highest results on Kogan scale were achieved by the 23-27 age group, which means that attitudes towards ageing and the elderly turned more positive as life experience increased. However, if students had no gerontology training scheduled in their study programme, the chance to form positive attitudes will remain unused (22).

Experience of living with the elderly did not result in differences in Kogan scale and Palmer questionnaire results between persons who had such experience and those who did not.

Desired residency among students of the School of Medicine did not influence their attitudes concerning ageing and the elderly. Tests showed no statistically significant difference (H=14.62; p=0.931), which means that attitudes towards ageing and the elderly are not linked to professional preferences/preferred residency, rejecting the second hypothesis. This outcome might be the consequence of poor information about residency opportunities upon completion of studies.

The reason why relatively few students chose Gerontology as future residency in the course of professional life is probably grounded in insufficient information concerning the opportunities and education methods in this branch of medicine, and probably also due to insufficient attractiveness of the specialty (23).

We compared the results obtained through our survey with two existing pieces of research. An earlier research from Slovenia compared attitudes towards ageing and the elderly between Croatian and Slovenian nursing students (13). The total number of respondents in the Slovenian study amounted to 825 nursing students, 408 of whom were from Croatia and 417 from Slovenia. The same questionnaires were applied as in our research. As regards important characteristics of the two groups, it is important to point out that 22.55% of the Croatian student group had no education concerning care for the elderly, compared with only 8.39% of the total number of Slovenian students covered by the study who had no such education. In accordance with

that, 81.86% of Croatian students believed that additional educational programmes were needed concerning ageing and the elderly, with 70.74% of Slovenian students believing the same.Differences in student attitudes towards ageing and the elderly were identified as depending on training in gerontology, i.e., on differences in educational programmes between Croatia and Slovenia. Slovenian respondents had substantially better indicators as regards perception and attitudes of students compared to Croatian respondents/students, while respondents with prior education in care for the elderly also exhibited substantially better attitudes and perception compared to those who had no prior education (13).

Whenever results differ according to on sex, domicile, type of study and employment, such results obtained in the Slovenian study are similar to the ones identified in our research. Answers from the Slovenian survey show that female respondents perceive ageing and elderly persons substantially better than men. However, in the Slovenian study, respondents residing in rural areas showed better results (more positive attitudes and a higher level of knowledge) compared to those living in urban areas, which is opposite to our findings.

Links between professional preferences following completion of the studies on the one hand, and attitudes towards ageing and the elderly on the other, were not found in the mentioned Slovenian survey either.

Attitudes of medical students towards ageing and elderly persons were also examined in a study performed in Turkey, involving students of the School of Medicine. The research encompassed 324 students of the fourth, fifth and sixth year of medical faculty, and attitudes were examined using Kogan scale (24). The Turkish respondent median value on Kogan's scale was lower than that of our respondents from the School of Medicine, suggesting a more benevolent attitude towards ageing and the elderly at the University of Split. In addition, the Kogan scale result was higher for female students compared with male students, which is identical to our results. No differences were found concerning other socio-demographic factors. The use of the same instrument for the examination of attitudes in three culturally different environments is interesting in terms of the diverse character of the results obtained. Differences in Kogan scores on the examined attitudes revealed when comparing the data obtained point to the need to educate young people and to adapt educational programmes. Through this research, we have shown that knowledge is the only effective measure in combating prejudice and negative stereotypes. Correct information is the only cure against ill-informed beliefs. That is why young people need to be made aware of societal problems and of the increasingly older community as early as possible. Moreover, Medicine, Dental Medicine and Pharmacy students need to be better acquainted with the possibilities of resolving health issues of elderly persons through study programmes (23).

Comparative analysis of surveys is even more interesting considering that respondents were chosen among students of Nursing (Slovenia and Croatia) and Faculties of Medicine (in Croatia and Turkey). Our research provides an additional dimension by providing comparison with students of the Faculty of Maritime Studies, whose education is not founded on healthcare programs, and whose attitudes are not impacted by their professional knowledge but rather by general health literacy. A positive impact on the formation of attitudes and knowledge shown in the survey was found among first-year medical students who had obtained education in the optional course of Gerontology.

Our research found that there was a difference in attitudes between students who were exposed to educational contents from gerontology and those who were not. The group that was not exposed to gerontology training had a negative attitude compared to the group having had gerontology lessons. This paper confirms that providing truthful and timely information is the best method of preventing negative attitudes and stigmatization of the groups that have increased needs in the society.

POTENTIAL LIMITATIONS AND GAPS

This was a cross-sectional study involving students of two faculties of the University of Split at one point in time. Although the male to female ratio of respondents was approximately the same (160/53.16% females; 141/46.84%; p=0.273 males), it is possible that medical students have more positive attitudes towards and more knowledge of ageing and the elderly due to the fact that there is a greater share of female than male students at that faculty. The female group of students is also made up of a part of female students of Maritime Studies since the overall number of medical students was 148, and the total number of female respondents 160. According to a research conducted in Croatia, males make up the majority of enrolled students (73.1%) only in regular and full-time university specialist courses in the field of technical sciences. The highest ratio of females at the Faculty of Maritime Studies is in the Maritime Management study programme. In the areas such as biomedicine and health, males make up less than one-third (28.06%)of all students enrolled (25), and the situation at the University of Split is in line with the trends at the national level.

CONCLUSION

The attitudes among students of medical sciences are generally more positive in two categories: they scored 6 points higher on Kogan scale than their Maritime Studies counterparts, and had 4.65 points higher test results in Palmer's competence questionnaire, which means that individuals who know more about the issue at stake tend to have a more positive attitude towards it. Student attitudes and knowledge differ depending on their demographic characteristics (age, sex, domicile, and study year).

Differences in attitudes exist depending on whether students had gerontology courses; it has been proven that students who attended such courses have a more positive attitude than those who had none.

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SAŽETAK

UČINAK ZNANJA NA FORMIRANJE STAVOVA O STARENJU I STAROSTI U STUDENATA SVEUČILIŠTA U SPLITU

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Uvod: Prisutan globalni trend starenja stanovništva rezultira sve većim udjelom starog stanovništva i sve većim potrebama za zdravstvenim uslugama, što opterećuje zdravstveni sustav. Stavovi zdravstvenih radnika bitan su čimbenik koji utječe na njihovo ponašanje. Prema dostupnim istraživanjima čimbenici utjecaja na rad zdravstvenih radnika prema starim osobama u gerijatrijskim ustanovama uključuju znanje, stav i gerontološko obrazovanje. ***Cilj:*** Cilj istraživanja bio je ispitati utjecaj izobrazbe iz područja gerontologije na formiranje stavova studenata prema osobama starije životne dobi i prema procesu starenja. Uz izobrazbu iz gerontologije ispitali smo kako demografski čimbenici (spol, dob, boravište), različiti obrazovni sadržaji kojima su studenti bili izloženi i suživot s osobama starije dobi utječu na formiranje stava studenta prema starenju i starijoj životnoj dobi. ***Ispitanici i metode:*** Istraživanje je obuhvatilo studente Sveučilišta u Splitu, a pristupio mu je 301 student. Istraživanje je provedeno anonimnim anketnim upitnikom u razdoblju od 1. prosinca 2020. do 31. ožujka 2021. godine. Najveći broj studenata je na studijskim programima Pomorskog fakulteta (n=153). Istraživanju je pristupilo i 148 studenata Medicinskog fakulteta. Studenata koji su prošli izobrazbu iz gerontologije bilo je 45, a 265 nije imalo nikakav oblik izobrazbe iz gerontologije. Podatci su dobiveni anketnim upitnikom koji se sastojao od 3 dijela, i to dijela koji se odnosi na sociodemografska obilježja, dio kojim se ispituje stav prema starijim osobama (Koganova ljestvica) te testa znanja (Palmerov upitnik). Za testiranje statističke značajnosti primijenjeni su χ2-test, Mann Whitneyev U test i Kruskal-Wallisov test. ***Rezultati:*** Stavovi studenata Medicinskog fakulteta, različitih studija, statistički su značajno pozitivniji u odnosu na ispitanike Pomorskog fakulteta. Postoje razlike u stavovima prema starenju i starijim osobama među skupinama studenata s obzirom na različitost obrazovnih sadržaja iz gerontologije. Čimbenici kao što su demografski čimbenici, obrazovni čimbenici, različiti obrazovni sadržaji kojima su studenti bili izloženi te suživot s osobama starije dobi značajno utječu na stavove o starenju i starijoj životnoj dobi kod studenata. ***Zaključak:*** Postojanje obrazovnog sadržaja iz gerontologije utječe na formiranje pozitivnog stava o starenju i starijoj životnoj dobi među studentima te bi, s obzirom na demografske promjene u društvu, trebalo prilagoditi obrazovne programe, što bi trebalo rezultirati smanjenjem stigmatizacije osoba treće životne dobi.

Ključne riječi: stavovi, starenje, izobrazba

BIOETHICAL DECISION-MAKING IN CLINICAL NURSING PRACTICE

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Introduction: Nursing as a profession and vocation is understood as humanity, altruism and dedication. Nurses possess 4 types of responsibilities: human, legal, ethical and professional, within which protective models are oriented to the well-being of the patient. The values, rules and principles within nursing practice are regulated by codes of ethics. *Aim:* To determine the influence of knowledge, positive attitude and love for the profession, as well as practices based on high moral and ethical principles in graduate nurses on making ethical decisions in work with patients. *Material and methods:* The study was conducted among 106 graduate nurses of the Clinical Center of the University of Sarajevo. The study was descriptive, transverse according to the cross-sectional type. The study was conducted in the period from June 1, 2019 to September 30, 2019. Statistical data processing was performed using the χ2-test, Fisher test, Mann-Whitney U test, and other tests. *Results:* The majority of respondents (89.4%) stated that they chose nursing profession out of love and desire to help sick people. The largest number of respondents make ethical decisions independently in the implementation of appropriate health care (84%), 62.3% are considered religious, but 77.7% of them believe that religiosity does not affect ethical decision making. Half of the respondents stated that they were in a situation to act as a legal protector for patients in case they noticed that they could be harmed. The majority of respondents (84%) did not have a situation to make wrong ethical decision in their practice. *Conclusion:* Our study confirms that in order to make ethical decisions in working with patients, graduate nurses must have quality knowledge, a positive attitude and love for the profession, and a practice based on high moral and ethical principles.

Key words: knowledge, attitudes, practice, nurse, ethical decisions

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INTRODUCTION

In the last few decades, the health care system has undergone major structural changes that have affected almost every profession. Such changes have also affected the profession of nurses based on empathy and vocation. The nursing profession is slowly laying an increasingly strong academic foundation for the advancement and recognition of a distinct profession that is recognized and acknowledged in health care and the community (1).

Today, nursing is a recognized profession that no one disputes. As a profession, nursing requires strict education with the need for further work on autonomy, and the possibility of complex education up to the doctorate degree. Nursing as a profession is in the process of professional proving and seeking greater reputation and autonomy in relation to the physician, as well as recognition of its unique role in patient health care (2).

A nurse should be a professional who has the appropriate knowledge, experience and competencies to do the job. Professionalism requires responsibility, accuracy, conscientiousness, dedication and continuous education. Although nurses who have successfully completed the education prescribed by the law of their country, passed all the necessary exams to register and

obtain approval for self-care, today they do not have support from strong interest groups, their work is undervalued, they insufficiently advocate for themselves, which suits all subjects in health care (3).

Being a nurse means having a sense of human values and desire to behave and live by social rules and moral norms. In the process of their work, nurses must combine their knowledge with science on the one hand, and morality and caring for people on the other (4). In their work, nurses should adopt principles, basic rules, and a culture of behavior, and emphasize moral norms and principles that respect human dignity and patient rights (5). Throughout the long history of nursing, the character virtues of nurses have always been emphasized. Florence Nightingale points out that the proper functioning of health care requires fulfillment of two conditions: a good knowledge of care, as well as specific medical skills, and the high moral maturity of nurses. A person who conscientiously cares for others develops and acquires specific virtues that allow them to perform that care with ease and perseverance. Love, care, sacrifice, honesty, sincerity, trust, devotion, diligence, patience, are just some of the virtues that explicate the value of caring for others (6).

The ability to make ethical decisions is a matter of moral excellence of nurses. From the very beginning of the faculty education of nurses, it is necessary to encourage students to develop a moral vision, which must provide them with the possibility of moral reflection, development of moral intuition, critical thinking and political resourcefulness. The main goal of ethical teaching is to provide all relevant information related to the morals, education, sensitivity and responsibility of nurses who must be able to make ethical decisions in practice. The second goal is to prepare future nurses to be able to identify and respond properly to ethical dilemmas in the field of health care. In order to achieve all this, it is important to encourage the integration of personal value systems with professional values, to know ethical concepts in nursing, ethical methodology, and standards of ethical behavior (7). Everything technically feasible in biomedicine does not mean that it is always ethically acceptable.

Virginia Henderson emphasizes that "the nurse is temporarily the consciousness of the unconscious, the love of life of the suicidal, the leg of the amputee, the eyes of the newly blind, a means of locomotion for the newborn, knowledge and confidence for the young mother, a voice for those too weak to speak, and so on" (8).

Until adoption of the first code, the guide for ethical behavior of nurses was an oath by Florence Nightingale, compiled in 1983 and modeled on the Hippocratic Oath (9).

The principles of ethical reasoning of deontological theory arise from the intention of the action taken by the one who makes the decision. Reasoning based on duty, law and intuition draws its frames from deontological theories. The most fundamental universal approach is respect for people (10).

Good communication is an important prerequisite for a good partnership, but also for a better work atmosphere, a positive patient attitude about their own illness, and for active patient action in their own treatment (11).

The partnership raises awareness and motivates the patient to take an active role in taking responsibility for their own health, which stems from being well informed by the nurse.

Cooperation is also important for good partnership in the field of improving the work process of the entire health care team and in the field of shaping common attitudes and interests. Part of that health team should be the patient in a special manner (12).

AIM

To determine the influence of knowledge, positive attitude and love for the profession, as well as practices based on high moral and ethical principles in graduate nurses on making ethical decisions in working with patients.

MATERIAL AND METHODS

The study was conducted among graduate nurses of the Clinical Center of the University of Sarajevo. The instrument used in the study was an original author's questionnaire, created on the basis of a review of professional and scientific literature, and experiences from clinical practice, with the help of which the knowledge, attitude and practice of graduate nurses in the process of making ethical decisions in working with patients have been identified. The questionnaire was created in Google forms. The questionnaire was available to all respondents on a personal e-mail, or e-mail of the institution in which they work.

It was not possible to find out identity of the respondents from the answers received. The study was descriptive, transverse according to the cross-sectional type. The study was conducted in the period from June 1, 2019 to September 30, 2019.

Nominal and ordinal variables in the study were analyzed by the χ^2-test, and in the absence of the expect-

ed frequency, Fisher exact test was used. The SPSS for Windows version 22.0 software was used on statistical data analysis (SPSS Inc., Chicago, IL, USA) and Microsoft Excel version 2019 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The study included 106 employees of the Clinical Center of the University of Sarajevo, of which 16 men and 90 women working in various organizational units and disciplines. The majority of respondents knew that there was an Ethics Committee in their institution (70.5%), and there were no significant differences among different jobs or socio-demographic groups. The χ^2-test yielded uniform answers to this question depending on the workplace of the respondents (p=0.085).

Respondents answered the question why they decided to choose the nursing profession. A vast majority of them (89.4%) stated that they had chosen their profession out of love and desire to help sick people. Respondents with the academic degree Master of Science somewhat more often (p=0.001) claimed that they were dealing with this call because they were not able to enroll another school due to difficulty of the subjects.

The questionnaire examined the system of values in the society and at the workplace. Judging by the answers of the respondents, the system of values in the society relies on „nobility and doing good deeds" and „knowledge", which were the answers offered by 42.5% and 35.8% of respondents, respectively.

There was no difference among different groups of respondents (Pearson's χ^2-test, p=0.256), including age. Nevertheless, in the society in which the respondents live, position and power are valued, as indicated by 47.2% of the respondents.

The questionnaire examined the method and conditions of participation in ethical decision making. Table 1 shows the results of decision-making practice in ethical situations. The largest number (n=59) of respondents stated that they used to help patients to become familiar with their disease and cope with it, and a slightly smaller number (n=48) to help them alleviate pain and suffering. There were no significant differences among different disciplines, except for the case when respondents „help make decisions about treatment and health care". Employees at the surgical and neuropsychiatric disciplines more often answered positively to this question (p=0.040).

The majority of respondents believed that knowledge and skills were most important for making ethical decisions, which was confirmed by 55.7% of respondents.

Table 1. *Practice of respondents in the process of ethical decision-making within certain medical disciplines at the Clinical Center of the University of Sarajevo*

		Medical discipline					Total
		Surgical discipline	Internalist discipline	Neuropsychiatry discipline	Discipline for gynecology and obstetrics	Unknown	
The practice of helping patients get to know their disease and cope with it	n	25	9	14	5	6	59
	%	42.4	15.3	23.7	8.5	10.2	
The practice of helping patients alleviate pain and suffering	n	27	7	2	4	8	48
	%	56.3	14.6	4.2	8.3	16.7	
Decision making practices for treatment and health care	n	22	2	6	1	8	39
	%	56.4	5.1	15.4	2.6	20.5	
The practice of communication with the patient and family, and education in order to make the right ethical decisions	n	14	3	3	0	6	26
	%	53.8	11.5	11.5	0.0	23.1	
Total	n	50	15	16	10	14	105

Somewhat less, 25.5% of them, believed that it was work experience. There was no difference among medical disciplines, but it was recorded among different jobs. Head nurses more often considered that knowledge and skills were most important (67%), while a large number of ward nurses, but not the majority, believed that it was work experience (34%).

The questionnaire sought to examine the knowledge of graduate nurses in independent ethical decision-making. The largest number of respondents stated that they made decisions independently in the implementation of appropriate health care (n=84), and a smaller number (n=33) in choosing the best method of treatment and care. There were no significant differences among medical disciplines, except for the case of indepen-

dence of decision-making in the treatment of dying patients. A significantly higher number of employees of neuropsychiatric disciplines (p=0.005) answered this question in the affirmative manner.

Also, this was more often recorded in male (p=0.010) and ward nurses (p=0.012).

The majority of the surveyed staff, 61.5% of them, occasionally participated in ethical decision-making. More often, head nurses were the only ones to answer this question in the affirmative manner.

Most respondents had time to communicate with patients; 89.6% of them answered „yes" or „partially". Employees without academic degree had the least time to do it.

A small number of respondents confirmed that they had obstructions by doctors in making ethical decisions in the health care process (7.5%).

Table 2. *Knowledge and practice related to making ethical decisions within certain medical disciplines at the Clinical Center of the University of Sarajevo.*

		Medical discipline					Total
		Surgical discipline	Internalist discipline	Neuropsychiatry discipline	Discipline for gynecology and obstetrics	Unknown	
Knowledge and skills	n	29	13	9	3	5	59
	%	56.9	86.7	56.3	30.0	35.7	55.7
Competences	n	1	0	0	2	2	5
	%	2.0	0.0	0.0	20.0	14.3	4.7
Work experience	n	10	2	6	3	6	27
	%	19.6	13.3	37.54	30.0	42.9	25.5
Empathy	n	4	0	1	0	1	6
	%	7.8	0.0	6.3	0.0	7.1	5.7
Good communication	n	7	0	0	2	0	9
	%	13.7	0.0	0.0	20.0	0.0	8.5
Total	n	51	15	16	10	14	106

DISCUSSION

Fry describes different characteristics of independence. The term can refer to one's own choice, freedom of action, personal freedom, and ability to control oneself. To be independent means to determine one's own laws in terms of valid moral principles.

Respecting independence means respecting the individual's right to self-government according to a plan set by the individual and followed (13).

Nurses should respect independence, first by establishing the principles of independence as a guideline for action. For example, the nurse shows respect for the patient independent choice before beginning a procedure or treatment. The treatment offered must be the one that the patient/family would choose or that corresponds to the procedure that the patient/family would like to undergo (14).

The opinion of nurses in team work is partially respected. A very small number do not agree with this statement, and more often it was about respondents who did not work in managerial positions.

Therefore, it can be said that the nurse is an equal member of the team that participates in making ethical decisions for patients, and their opinion is sometimes respected and sometimes not.

The nurses in the team are often patient advocates. Advocacy is an active support to a significant goal. It is often used in a legal context in terms of defending the basic human rights of those who cannot speak for themselves (15).

The article says that medicine has become money, and man a wallet. Regardless of advances in medical science, nurses are expected to be empathetic, to understand and support the patient, and to be guided by high ethical principles.

Also, the same article mentions that the nurse should be subordinate to the authority of generally recognized humanistic values or the good of the patient, and not to the authority of the physician and other team members (16).

The study conducted by Markovic in 2018 through an online survey questionnaire among 872 participants

showed that 364 of them (41.7%) perceived the nursing profession as a true calling. Those who perceived the nursing profession as a true vocation were significantly older than those who perceived the profession as a profession and vocation (17).

It is interesting to note that when asked about the experience of nurses/technicians in terms of role within the business environment, as many as 536 (61.5%) participants stated that a nurse was a full member of a multidisciplinary team. The results obtained differ from Deming's study, according to which the public perceives nurses as persons dependent exclusively on doctors' orders, which ultimately leads to depreciation of the profession.

The results showed that most participants understood the importance of the nursing profession in the society and consequently believed that secondary education simply did not meet the needs of today's health care users (17-20).

In our study, the influence of religious beliefs on ethical decision-making was examined. Two-thirds of respondents were considered religious, most of them younger and middle-aged. Interestingly, more than half of the employees over the age of 54 were "partially" religious, while younger ones were more likely reluctant to answer questions of this kind. However, regardless of religiosity, most employees were not affected by ethical decision-making. A small number of respondents would not participate in a procedure that was not justified from their religious point of view. Although there were significant differences among particular socio-demographic groups of respondents, they could be directly related to the degree of religiosity, given that these are feelings that individuals have regardless of their level of education or job. Respect for personality is a special model in the nursing profession.

In a study conducted in Brazil, the lack of competence in the team was the most common source of employee moral distress, followed by disrespect for patient autonomy and insufficient working conditions, and denial of the role of the nurse in advocating for palliative patients (21).

CONCLUSION

Most of the respondents stated that they chose the nursing profession out of love and desire to help sick people, and as a system of values in the society, most of them considered „nobility and doing good deeds", and „knowledge".

Chief nurses-technicians believe that knowledge and skills are the most important characteristics that a graduate nurse must possess in order to be able to make competent decisions.

It should be emphasized that the majority of respondents did not have a situation to make a wrong ethical decision in their practice.

This study affirmatively responded to the set goal that in order to make ethical decisions in working with patients, it is necessary to have quality knowledge, build a positive attitude and love for the profession, and practice based on high moral and ethical principles.

Likewise, the study showed that graduate nurses in most cases (56.6%) were equal team members in the ethical decision-making process.

The bioethical principles of fairness, innocence, charity, and autonomy were assessed as insufficient to solve the problems related to use. A new principle derived from Pellegrin's philosophical propositions is the so-called principle of 'sustainable being'. This principle is appropriate for the practice that is being developed and is compatible with deontological, consequentialist, and relational ethics theories. To form a standard of behavior and a moral imperative for 'keeping beings', the term 'care' is associated with care in genetic health care. Subsidiarity is the principle by which decisions are made and problems are solved in the form of categories and at the levels at which they arise. The principle of subsidiarity refers to the determination of the ability to achieve the common good. What an individual can do alone, the society must not deny him. This principle tells us that community members have the right to help in things they cannot do, but as members, they must be protected from the domination of the community itself that surrounds them.

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SAŽETAK

BIOETIČKO ODLUČIVANJE U KLINIČKOJ SESTRINSKOJ PRAKSI

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Uvod: Sestrinstvo kao profesija i poziv shvaćeno je kao humanost, altruizam i predanost. Medicinske sestre imaju 4 vrste odgovornosti i to: ljudska, pravna, etička i profesionalna, a unutar kojih se prožimaju zaštitnički modeli usmjereni na dobro bolesnika. Vrijednosti, pravila i načela unutar sestrinske prakse regulirani su etičkim kodeksima. ***Cilj:*** Utvrditi utjecaj znanja, pozitivno izgrađenog stava i ljubavi prema struci, kao i prakse zasnovane na visokim moralnim i etičkim načelima kod diplomiranih medicinskih sestara na donošenje etičkih odluka u radu s bolesnicima. ***Materijal i metode:*** Istraživanje je provedeno među 106 diplomiranih medicinskih sestara Kliničkog centra Univerziteta u Sarajevu. Istraživanje je deskriptivno, transverzalno prema tipu poprečne *(cross-sectional)* studije. Istraživanje je provedeno u razdoblju od 1. lipnja 2019. do 30. rujna 2019. godine. Statistička obrada podataka učinjena je uz primjenu χ^2-testa, Fisherova testa, Mann-Whitneyeva U testa i drugih testova. ***Rezultati:*** Većina ispitanika (89,4 %) izjavila je da su sestrinsku struku odabrali iz ljubavi i želje da pomažu bolesnim osobama. Najveći broj ispitanika samostalno donosi etičke odluke kod provođenja odgovarajuće zdravstvene njege (84 %), 62,3 % se smatra religioznim, međutim 77,7 % ih smatra da religioznost ne utječe na donošenje etičkih odluka. Polovina ispitanih navodi kako su bili u situaciji da se ponašaju kao pravni zaštitnik bolesnika kada primijete da bi im se mogla nanijeti šteta. Većina ispitanika (84 %) nije bila u situaciji da u svojoj praksi donesu pogrešnu etičku odluku. ***Zaključak:*** Rad potvrđuje da za donošenje etičkih odluka u radu s bolesnicima diplomirane medicinske sestre moraju imati kvalitetno znanje, izgrađen pozitivan stav i ljubav prema struci te praksu zasnovanu na visokim moralnim i etičkim načelima.

Ključne riječi: medicinska sestra, etičke odluke, znanje, praksa

PATENT FORAMEN OVALE AND ISCHAEMIC STROKE IN YOUNG ADULTS – A RETROSPECTIVE STUDY

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Objective: Ischaemic stroke is the most common type of stroke. One of the risk factors is patent foramen ovale (PFO), which is normally open in parallel intrauterine circulation and represents the right-to-left flow (shunt), and is closed by the septum primum tissue or persists after establishment of postpartum circulation. If it does not close at the end of the first year, it is called atrial septal defect (ASD) and represents left-to-right flow in circulation. This defect remains open with varying degrees of left-to-right flow in some patients. It is thought to be present in about 50% of young patients who experience ischaemic stroke. It is caused by the mechanism of paradoxical embolization, but by the right-to-left flow. The factors affecting the likelihood of stroke in these patients are as follows: PFO size, increase in the right atrial pressure due to various factors that may transiently cause right-to-left flow, or even open virtually closed fossa ovalis. A possible concomitant aneurysm of the interatrial septum at the level of fossa ovalis has a special place in the development of paradoxical embolism. The accompanying factors that increase the likelihood of ischaemic stroke in patients with PFO are severe physical exertion, agitation, pulmonary hypertension, immobilisation, pregnancy, and congenital or acquired coagulation disorders. *Methods:* This retrospective study was based on the analysis of patients aged 18-49 years hospitalised due to ischaemic stroke at the Maribor University Medical Centre in the period from 2010 to 2019 inclusive. Differences between the 2 groups were analysed. Group 1 consisted of patients with proven PFO and group 2 of patients in whom no right-to-left flow was demonstrated. The results of the research were analysed by JASP 0.14.1. and IBM SPSS Statistics 28 software. The level of statistical significance was set at $p<0.05$. *Results:* This study included 196 patients with 198 ischaemic stroke events. PFO was present in 23 (11.7%) patients. Arterial hypertension was more common in group 2 patients (17.4% vs. 53.2%, $p<0.05$). Group 1 patients were significantly younger than group 2 patients (36.478 (7.223) vs. 42.214 (7.043) years, $p<0.05$). Disease outcome was more favourable in group 1 as compared with group 2 patients (1.000 (0.603) vs. 1.728 (1.574), $p<0.05$). *Conclusions:* Persistent foramen ovale is a more common cause of ischaemic stroke in younger people and plays a key role in this age group. Arterial hypertension is probably a more common cause of ischaemic stroke in elderly patients. The outcome of the disease is more favourable in the group of patients with PFO.

Key words: ischaemic stroke, patent foramen ovale, young adults, risk factors, paradoxical embolism

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INTRODUCTION

Ischaemic stroke (IS) is the most common type of stroke. It accounts for 71% of all strokes. It is one of the most common causes of death and disability (1). Ischaemic stroke in young adults is usually defined as an IS which occurs in adults aged between 18 and 50 years. Some studies include patients aged up to 55 years. It occurs in 7-8/100,000 people in Europe and up to 100/100,000 people in Sub-Saharan Africa. Even though IS in young adults is not as common as in older population, it still represents 10%-18% of all IS cases (2-4). The incidence of IS in young adults continues to increase in higher-income countries (5).

Although patients may have different causes of IS, the cause still remains undetermined in 40% of cases (6,7). These cases are referred to as cryptogenic stroke. In these patients, it is important to pursue a stroke mechanism to be able to choose an improved therapy op-

tion in order to reduce the stroke recurrence risk (8). Most cryptogenic strokes appear to be embolic, thus the term embolic stroke of undetermined source (9).

Atrial septumis formed during embryogenesis by two membranes growing from the atrial walls, leaving an oval shaped fenestration (foramen ovale), which serves as a right-to-left shunt in the foetal circulation. It is sealed during the first year of life by fusion of both membranes. The failure of this process leads to an interatrial slit-like channel, called patent foramen ovale (PFO) (10). It is present in 20%-30% of general population. Studies report that the percentages of PFO presence tend to be even higher in people with cryptogenic IS (11,12). Some report that the percentage could be near 50% in young patients (12). In these cases, IS occurs as a consequence of paradoxical embolization. Criteria for paradoxical embolization include proven arterial infarction, absence of embolus in left heart, proof of venous thrombosis or pulmonary embolism, and right-to-left shunt (11,12). The occurrence of IS may be influenced by PFO size, shunt flow, tunnel length and PFO accompanied by atrial septum aneurysm. Accompanying factors that increase the probability of IS in patients with PFO are immobilization, pregnancy, congenital and acquired hypercoagulable conditions (6,13). PFO has also been associated withrecurrent IS cases (5).

Although most of the times PFO does not cause any problems, it has been associated with cryptogenic stroke, migraine, peripheral embolism, and Alzheimer's dementia (10). On the other hand, many cases of PFO in patients with IS also represent incidental findings and are not the cause of the event (14).

Considering PFO treatment, most studies imply that PFO closure on its own does not affect the prevalence of recurrent stroke (15,16). Other studies report that PFO closure in addition to medical therapy appears to be cost-effective compared to medical therapy alone (17).

AIM

The study was conducted to determine the incidence of PFO in young adults who had suffered an IS and to compare risk factors for stroke in patients with this heart malformation to risk factors of patients without PFO.

METHODS

This retrospective study was based on data on all patients who were hospitalised at the Maribor University Medical Centre due to IS during the period from 2010 and 2019 inclusive. Included patients were aged 18-49 inclusive at the time of the event. If a single person suffered more than one stroke event in the monitoring time, the second event was considered as a relapse. Individuals who did not meet the time or age interval criteria were excluded. Patients who suffered other types of strokes, e.g., haemorrhagic stroke or venous sinus thrombosis, or were hospitalised due to other causes, were also excluded.

The study was approved by the Ethics Committee of the Maribor University Medical Centre in Maribor, Slovenia (UKC-MB-KME-45/21).

In this study, we compared characteristics of patients with proven PFO (group 1) with characteristics of patient group without it (group 2). Only patients with a sonographically confirmed PFO or PFO history were included in group 1.Patients with PFO had it confirmed with transoesophageal echocardiography (TEE). Echocardiography was performed either during hospitalisation or on an outpatient basis after discharge but noted in the discharge letter.

Data were obtained from the MEDIS hospital database. Alongside the information on PFO, the data contained information on patient gender, age, location of the lesion according to circulation, year of hospitalisation, duration of hospitalisation, relapse, National Institutes of Health Stroke Scale (NIHSS) score at admission, NIHSS score at discharge, difference between both scores, modified Rankin Scale (mRS) score (measured at discharge), and risk factors for ischaemic stroke, such as family history, obesity, experience of transient ischaemic attack (TIA), arterial hypertension, diabetes mellitus and HbA1c, dyslipidaemia, migraine, malignant disease, infection, alcohol use, smoking cigarettes, illicit drug abuse, pregnancy, hormonal therapy, immunosuppressive therapy, immunoglobulin therapy, Down syndrome, Marfan syndrome, morphological heart abnormalities (heart or ascending aorta aneurysm, myxoma, heart valve changes, heart hypertrophy, heart dilatation), heart congestion, heart rhythm disorders, increased value of homocysteine, decreased values of vitamins D and B12, folates, protein C, protein S, factor V Leiden mutation, prothrombin gene mutation, presence of antibodies (anti-b2GPI-IgG,anti-b2GPI-IgM, anti-b2GPI-IgA, anti-cardiolipin-IgG, anti-cardiolipin-IgM, cryoglobulins, myeloperoxidase, ANCA, ANA, ENA, anti-SS-A, anti-SS-B, anti-Sm, anti-RNP, anti-Jo-1, anti-Scl-70, anti-dsDNA, lupus anticoagulant), and primary central nervous system angiitis.

Events that occurred in patients with clinical presentation of stroke in the past were marked as relapses. Lesions in the carotid artery, anterior or medial cerebral

artery or their branches were classified as 'anterior circulation'. Lesions in the posterior cerebral artery, basilar or vertebral artery or their branches were classified as'posterior circulation'. Those with an IS or TIA in parents or siblings were considered to have a positive family history. The group with a positive family history was divided into three subgroups depending on the time of event occurrence (before the age of 50, at 50 or later) and an undefined group of patients, whose age at the event was unknown. The days spent at the Maribor University Medical Centre were considered as the length of hospital stay. Obesity was defined by body mass index ≥30. The group of people with diabetes was divided into a group of patients with type 1 diabetes and a group with patients with type 2 diabetes. Normal HbA1c values were determined as NGSP<6.0% and IFCC <42 mmol/L. Dyslipidaemia was considered as values of total cholesterol >5.7 mmol/L, high-density lipoprotein (HDL) <0.9 mmol/L, low-density lipoprotein (LDL) >4.9 mmol/L or triglycerides (TG) >1.7 mmol/L. Malignant diseases of any type within five years prior to the event were considered as malignant diseases. In the group of infectious diseases, the events with clinically or laboratory proven infection during hospital stay or a week prior to the event were taken in consideration. Alcohol consumption was divided into groups of harmful drinking and occasional drinking. Smoking was considered as regular smoking of cigarettes at the time of the event or in the past. Oral contraceptives, therapy with sex hormones and erythropoietin therapy were considered as hormonal therapy. Heart rhythm disorders were divided into two groups of atrial fibrillation and other rhythm disorders. Increased homocysteine was determined at values above 15 μmol/L, decreased vitamin D at values below 47.7 nmol/L, decreased vitamin B12 at values <132 pmol/L, decreased folates at values <6.1 nmol/L, and decreased protein C and protein S at values <70 IU/dL. Disease outcome was determined by NIHSS and mRS scales.

The results of the research were analysed by JASP 0.14.1. The level of statistical significance was set at $p<0.05$. The values of skewness and kurtosis between -2 and 2 were used to evaluate the normality of distribution.

RESULTS

Among 196 patients with 198 IS events, who were included in the study, PFO was found to be present in 23 (11.7%) patients included in the study. In 2011 and 2015, there was one case each, in 2014, 2016, 2018 and 2019 there were three cases, in 2017 four, and in 2013 there were five cases of IS with PFO. Thirteen (56.5%) patients with PFO were men, who also predominated in the group of patients without PFO, accounting for 66.5% of the patients included in the study.

None of the patients with PFO suffered from diabetes mellitus, increased HbA1c, malignant disease, Down syndrome, Marfan's syndrome, arterial dissection, arteriovenous malformations, myxoma or infection. None of them were illicit drug users, pregnant or taking immunoglobulin therapy. None of them had *decreased* vitamin Dor B12, folates, or protein C levels. There was no case of factor V Leiden mutation in the PFO group. None of these patients died in the hospital.

Five (21.7%) out of 23 PFO patients were obese compared to 25 (14.5%) out of 173 patients in the non-PFO group. There were 2 (8.7 %) relapse cases in the PFO group and 18 (10.4 %) in the non-PFO group. Only one (4.3%) patient in the PFO group had a medical history of TIA prior to IS, and 17 (9.8%) patients in the non-PFO group had a history of TIA. In both groups, a more common location of lesion was anterior circulation. In the PFO group,15 (65.2%) cases of IS occurred in anterior circulation, 6 (26.1%) in posterior, and two (8.7%) cases in both circulations concomitantly. In the non-PFO group, 110 (63.6%) cases of IS occurred in anterior circulation, 60 (34.7%) in posterior, and 3 (1.7%) in both circulations. Out of 23 PFO patients, 16 (69.9%) had no family history of IS or TIA, two (8.7%) had relative suffering from an ischaemic cerebrovascular event before age 50, four (17.4%) had relative suffering from an ischaemic cerebrovascular event after age 50, and one (4.3%) patient had relative suffering with an ischaemic cerebrovascular event that occurred at unknown age.

In the PFO group, four (17.4%) patients had a medical history of arterial hypertension, while in the non-PFO group arterial hypertension was present in 92 (53.2%) patients. In the PFO group, 12 (52.2%) patients had dyslipidaemia, two (8.7%) suffered from migraine, three (13.0%) consumed alcohol moderately, and 20 (87.0%) patients did not consume alcohol at all. Six (26.1%) PFO patients were smokers, four (17.4%) used hormonal therapy, two (8.7%) were on immunosuppressive therapy, one (4.3%) patient had a heart aneurysm or ascending aorta aneurysm, one (4.3%) had heart valve *abnormality*, two (8.7%) had heart hypertrophy, one (4.3%) had heart dilatation, and one (4.3%) had heart congestion. None of the patients in this group had atrial fibrillation; however, five (21.7%) of them had other heart rhythm disorders.

Among PFO patients, two (8.7%) had elevated homocysteine levels, four (17.4%) had decreased protein S levels, and one (4.3%) had a prothrombin gene mutation. Frequencies of risk factors are presented in Tables 1, 2 and 3.

Table 1. *Risk factors for ischaemic stroke in patients with and without patent foramen ovale (PFO): Gender, Obesity, Arterial Hypertension, Dyslipidaemia, positive family history*

		Gender		Obesity		Arterial hypertension		Dyslipidaemia		Positive family history	
		male	female	no	yes	no	yes	no	yes	no	yes
		Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %
PFO	**no**	66.5%	33.5%	85.5%	14.5%	46.8%	53.2%	42.2%	57.8%	93.6%	6.4%
	yes	56.5%	43.5%	78.3%	21.7%	82.6%	17.4%	47.8%	52.2%	69.6%	30.4%

Table 2. *Risk factors for ischaemic stroke in patients with and without patent foramen ovale (PFO): Alcohol consumption, Migraine, Smoking, elevated homocysteine levels, decreased protein S levels*

		Alcohol		Migraine		Smoking		Elevated homocysteine		Decreased protein s	
		no	yes	no	yes	no	yes	no	yes	no	yes
		Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %
PFO	**no**	68.8%	31.2%	94.8%	5.2%	62.4%	37.6%	96.5%	3.5%	91.9%	8.1%
	yes	87.0%	13.0%	91.3%	8.7%	73.9%	26.1%	91.3%	8.7%	82.6%	17.4%

Table 3. *Risk factors for ischaemic stroke in patients with and without patent foramen ovale (PFO): Prothrombin gene mutation, Hormonal therapy, Immunosuppressive therapy, Structural heart malformations*

		Prothrombin mutation		Hormonal therapy		Immunosuppressive therapy		Structural heart malformations	
		no	yes	no	yes	no	yes	no	yes
		Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %	Row N %
PFO	**no**	98.8%	1.2%	95.4%	4.6%	96.5%	3.5%	77.5%	22.5%
	yes	95.7%	4.3%	82.6%	17.4%	91.3%	8.7%	8.7%	91.3%

Echocardiography after the event was performed in 137 (69.9%) study patients; 62.8% of these had transthoracic echocardiography (TTE), 3.6% had TEE,and 33.6% had both. It was performed either during hospital stay or on an outpatient basis.

Mean (SD) age of IS patients with PFO was 36.478 (7.223) years compared to 42.214 (7.043) in the non-PFO group with IS. Median (interquartile range, IQR) length of hospital stay was 15.000 (8.500) in the PFO group and 18.000 (16.000) in the non-PFO group. Mean (SD) NIHSS at admission was 4.435 (4.273) in PFO patients and 6.295 (4.833) in the non-PFO group. At discharge, median (IQR) value of NIHSS was 1.000 (2.000) in the PFO group and 2.000 (3.000) in the non-PFO group. Median (IQR) difference between both NIHSS values was -2.000 (4.000) in the PFO group compared to -2.000 (5.000) in the non-PFO group. Mean (SD) mRS at discharge was 1.000 (0.603) in IS patients with PFO compared to 1.728 (1.574) in the IS group without PFO.

Relations between the variables mentioned above and the presence of PFO were statistically analysed. PFO patients with IS were less likely to suffer from arterial hypertension than non-PFO patients $\chi^2(1)=10.405$, p=0.001. Median (IQR) age of patients who suffered from hypertension was 46.00 (5.25), and our study showed that hypertension was significantly more common in older patients (U=2796.000, p<0.001). The research also showed that patients with PFO were more likely to be younger than non PFO-patients (T=3.659, p<0.001).

Although NIHSS values, both at admission and at discharge, tend to be more favourable in patients with PFO, our study showed it to be statistically nonsignificant. mRS values at discharge tended to be lower (and therefore more favourable) in PFO patients than in non-PFO patients (T=2.193, p=0.029).

DISCUSSION

Considering all IS patients included in this study, PFO was found in 11.7% of them, which is lower than most researches show, as it is reported to be present in up to 50% of young adult patients with IS (11,12,17). It might be due to a reason that almost one-third of all patients did not undergo echocardiography; some of them had it done outside Maribor UMC, and some did not respond to the invitation to do it on an outpatient basis. In some cases, it was not performed because the

diagnosis was clear (e.g., arterial dissection). Some studies show that PFO is present in 13.6% (18) or even in 20%-30% of general population (11,12).

There were more men than women with PFO in our research; however, it was not statistically significant because there were more male patients in the study. Other studies confirm that more male than female young adults suffer from IS with PFO (19).

The study also showed that the mean age of stroke patients with PFO was lower compared to the mean age of IS patients without PFO. According to other studies, PFO appears to be a more important risk factor in younger patients, i.e., IS patients younger than 40 (20,21). Our study indicated that IS patients with PFO were less likely to have a medical history of arterial hypertension. This is due to the fact that arterial hypertension plays a more important role as a risk factor for IS in older population, where all other traditional risk factors also play a more significant role in the IS pathogenesis than in young adults.The relation between age and arterial hypertension was also verified in this study and it appears to be statistically significant. Hypertension is more likely to appear in older patients, while PFO is usually found in younger patients. Another study points to the fact that PFO patients have a lower atherosclerotic burden compared to non-PFO patients suffering from IS (22).

Stroke patients with PFO seem to have a significantly better outcome than other young adults with IS, which has been confirmed in other studies (23). This might be due to younger age, less comorbidities, and milder clinical presentation (NIHSS).

CONCLUSION

Patent foramen ovale is an important factor that plays a vital role in some IS pathogenesis cases, especially in young adults. Therefore, it should be considered in young adults with IS presentation who lack traditional and modifiable risk factors. PFO solely cannot be the only risk factor for stroke; it is a common finding in general population and it requires a hypercoagulable state to increase the risk of paradoxical embolism with consequences (e.g., IS). We found that arterial hypertension appeared to be more common in IS not caused by PFO. In addition, we observed that IS patients with PFO tended to be younger than non-PFO patients and have a better outcome according to mRS. More studies on risk factors associated with PFO are needed to further research the impact of PFO on IS probability in an individual, as the results of many studies tend to be contradictory.

There were some limitations to our study; to begin with, sampling was carried out by convenience. The study was based on a Caucasian population. Moreover, the sample was very small, which resulted in limited statistical analyses; some of the expected values were small; this may have led to the p-value not being accurate. The study was retrospective, i.e., data could not have been collected directly from patients, instead medical database findings were used. Some data might be inaccurate due to their subjective nature and the inability to verify such data, e.g., medical history of smoking, using illicit drugs, and alcohol abuse.

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SAŽETAK

PERZISTIRAJUĆI OVALNI OTVOR *(FORAMEN OVALE)* I ISHEMIJSKI MOŽDANI UDAR U MLADIH OSOBA − RETROSPEKTIVNO ISTRAŽIVANJE

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Pozadina: Ishemijski moždani udar je najčešći tip moždanog udara. Jedan od čimbenika rizika jest perzistirajući ovalni otvor (engl. patent foramen ovale, PFO) koji je normalno otvoren u paralelnoj intrauterinoj cirkulaciji i predstavlja desno-lijevi pretok (shunt), a nakon postpartalne uspostave serijske cirkulacije zatvara se tkivom septuma primuma ili perzistira. Ako se ne zatvori završetkom prve godine naziva se defektom septuma atrija (engl. atrial septal defect, ASD) i u serijskoj cirkulaciji predstavlja lijevo-desni pretok. Ovaj defekt ostaje otvoren s različitim stupnjem lijevo-desnog pretoka u dijela bolesnika. Smatra se da je prisutan u oko 50 % mladih bolesnika koji dožive ishemijski moždani udar. Uzrokovan je mehanizmom paradoksalne embolizacije, ali desno-lijevim pretokom. Čimbenici koji utječu na vjerojatnost moždanog udara kod ovih bolesnika su sljedeći: veličina PFO, porast tlaka u desnoj pretklijetki zbog različitih čimbenika koji mogu u tim posebnim okolnostima prolazno izazvati desno-lijevi pretok ili čak otvoriti virtualno zatvorenu ovalnu fosu nepotpuno sraštenom preklopnicom (flap). Posebno mjesto u nastanku paradoksalne embolije ima moguća popratna aneurizma interatrijskog septuma na razini ovalne fose. Popratni čimbenici koji povećavaju vjerojatnost ishemijskog moždanog udara kod bolesnika s PFO su teži tjelesni napori, uzbuđenje, plućna hipertenzija, ali i imobilizacija, trudnoća te prirođeni ili stečeni poremećaji koagulacije. ***Metode:*** Riječ je retrospektivnoj studiji analize bolesnika u dobi od 18 do 49 godina hospitaliziranih zbog ishemijskog moždanog udara u razdoblju od 2010. do 2019. godine u UKC Maribor. Analizirane su razlike između dviju skupina: skupina 1 s dokazanim PFO u odnosu na skupinu 2 kod koje nije dokazan desno-lijevi pretok na razini ovalne fose. Analiza je provedena pomoću programa JASP 0.14.1. i IBM SPSS Statistics 28. Za statističku značajnost korištena je granična vrijednost p<0,05. ***Rezultati:*** U ovo istraživanje bilo je uključeno 196 bolesnika sa 198 događaja ishemijskog moždanog udara. PFO bio je prisutan u 23 (11,7%) bolesnika. ***Rezultati:*** Arterijska hipertenzija bila je češće prisutna u bolesnika u skupini 2 (17,4 % : 53,2 %, p<0,05); bolesnici skupine 1 bili su značajno mlađi od bolesnika skupine 2 (36,478 (7.223) : 42,214 (7.043) godina, p<0,05); ishod bolesti bio je povoljniji u bolesnika skupine 1 nego u skupini 2 (1,000 (0,603) : 1,728 (1,574), p<0,05). ***Zaključak:*** Perzistirajući ovalni otvor je češće uzrok ishemijskog moždanog udara kod mlađih osoba te ima ključnu ulogu u toj dobnoj skupini. Arterijska hipertenzija je vjerojatno češći uzrok ishemijskog moždanog udara u starijih bolesnika. Ishod bolesti je povoljniji u skupini bolesnika s PFO.

Ključne riječi: ishemijski moždani udar, perzistirajući ovalni otvor, mlade osobe, čimbenici rizika, paradoksalna embolija

ANALYSIS OF OVERALL SURVIVAL IN PATIENTS WITH LUNG CANCER BEFORE THE INTRODUCTION OF TYROSINE KINASE INHIBITORS AND IMMUNOTHERAPY IN THE REPUBLIC OF CROATIA – A SINGLE INSTITUTION STUDY

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We analyzed outcome in patients with lung cancer (LC) in the period before the introduction of tyrosine kinase inhibitors and immunotherapy in the Republic of Croatia in comparison to similar studies abroad and created a basis for future analysis. At the Pathology Department, Split University Hospital Center, 1165 patients were diagnosed with LC during the 2012-2016 period. Data on age, gender, biopsy specimen, histologic type, and stage of disease were collected. Overall survival of each patient was calculated from the date of biopsy until death or the last day of follow-up.There were 74% of male and 26% of female patients. Median age was 66 years, younger than in other similar studies. In 78% of patients, the diagnosis of LC was based on brochoscopic biopsy. Adenocarcinoma (ADC) was diagnosed in 42.9%, squamous cell carcinoma (SCC) in 32.7%, and small cell lung carcinoma (SCLC) in 16.7% of cases. In females, ADC was more common than SCC ($p<0.001$). The mean survival was 22.3 months, median 10 months, and 5-year survival rate was 16.5%. Patients older than 74 years had shorter mean survival compared to younger patients, with the risk of death 1.1 times higher for each increasing age range group ($p<0.001$). The risk of death was 1.34 times higher in males than females ($p<0.001$), and 1.12 times higher for SCLC than ADC/SC ($p=0.005$). Gender, age, and histologic type were confirmed as independent prognostic factors. Women lived on average 8 months longer than men (28 vs. 20.4 months). The 5-year survival rate of 16.5% in the Split-Dalmatia County was better than the one recorded at the national level (10%).

Key words: lung cancer, overall survival, personalised therapy, Croatia

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INTRODUCTION

The incidence of lung cancer (LC) in the Republic of Croatia is high, similar to the rest of the world. In 2015, there were 2998 newly diagnosed patients, 72.3% of males and 27.3% of females (1). Smoking increases the risk of all types of LC. The incidence of LC is higher in urban areas, probably due to air pollution. The incidence of LC is higher in people of lower socioeconomic status and education because they have more frequent smoking habit and are more exposed to other risk factors (2). Discovery of activating mutations (*EGFR, ALK, ROS1*) in adenocarcinoma (ADC) and tyrosine kinase inhibitors (TKI) led to reflex testing for these mutations in laboratories worldwide (3-5). These analyses have been used in our institution since 2012, but positive results did not directly affect the treatment, as it was not approved by our national health authorities. Upon discovery of the checkpoint inhibitors, testing for PD-L1 expression in non-small cell lung cancer (NSCLC) was initiated (6). In 2017, we introduced immunohistochemical analysis of PD-L1 into routine diagnostics of NSCLC. Unlike TKI therapy which was introduced several years after testing, immunotherapy (IT) was administered soon after fast approval of health authorties in Croatia (7). In this study, we analyzed overall survival (OS) in LC patients during the 2012-2016 period. The aim was to compare our results with similar studies abroad and create a basis for comparison with the period from 2017 onwards, when targeted TKI and IT became a new paradigm of individualized therapy.

PATIENTS AND METHODS

The study included 1165 LC patients who were subsequently diagnosed from January 1, 2012, till December 31, 2016 at the Department of Pathology, Forensic Medicine and Cytology, Split University Hospital Center (below, Department of Pathology). Patient data included age, gender, date and type of biopsy, and histopathologic diagnosis. Patients who had small biopsy followed by operative material analysis were included in the cohort only once. For 565 patients, the initial stage of disease was successfully recorded in hospital documentation. Follow-up was completed on December 1, 2017. Patient status (alive or dead) was determined from database of the coroner's office of the Split University Hospital Center and Vital Statistics Registry of the Split-Dalmatia County. Overall survival was calculated in months from the date of biopsy to the day of death or the last day of follow-up. Crude incidence rates of LC in the Split-Dalmatia County were calculated using the 2011 census of the Central Bureau of Statistics of Croatia. Age-standardized incidence rates were calculated with the help of the standard world and European population according to the World Health Organization 2000 (8). The SPSS Statistics for Windows® software package (version 22.0, IBM, Armonk, NY, USA) and Microsoft Excel for Windows (Microsoft Corporation) were used on data processing. The χ^2-test, Kruskal-Wallis test, Kaplan-Meier curve, log-rank test, and Cox regression analysis were used on data processing. Results were interpreted at a significance level of $p<0.05$.

RESULTS

The study included 1165 patients with LC diagnosed at the Department of Pathology from 2012 to 2016. Median age was 66 (min-max: 27-95) years. There were 860 (74%) male and 305 (26%) female patients (Table 1). Patient distribution did not differ significantly in various age range groups ($\chi^2=3.0$; $p=0.386$).

Table 1. *Analyzed variables according to gender of patients with lung cancer*

			Gender		
		Total	**Male (N=860)**	**Female (N=305)**	**p***
Age (years) n (%)	≤60	319 (27.6)	224 (26.3)	95 (31.1)	0.386
	>60 to ≤66	289 (25)	218 (25.6)	71 (23.3)	
	>66 to ≤74	296 (25.6)	224 (26.3)	72 (23.6)	
	>74	253 (21.9)	186 (21.8)	67 (22)	
Histologic type n (%)	ADC	500 (43)	332 (38.6)	168 (55.3)	**<0.001**
	SC	381 (32.7)	327 (38)	54 (17.8)	
	SCLC	195 (16.8)	142 (16.5)	53 (17.4)	
	NEC	20 (1.7)	10 (1.2)	10 (3.3)	
	Other	57 (4.9)	41 (4.8)	16 (5.3)	
	Combined	11 (0.9)	8 (0.9)	3 (1)	
Biopsy specimen n (%)	(trans) bronchal	915 (78.5)	683 (79.4)	232 (76.1)	
	CT-guided TTB	89 (7.6)	60 (7)	29 (9.5)	
	Lobectomy	143 (12.3)	106 (12.3)	37 (12.1)	
	Metastasis	18 (1.5)	11 (1.3)	7 (2.3)	

*χ2-test; TTB = transthoracic biopsy

Patients with ADC were most common, 500 (42.9%). Squamous cell carcinoma (SCC) was diagnosed in 381 (32.7%), small cell lung carcinoma (SCLC) in 195 (16.7%), neuroendocrine carcinoma (NEC) in 20 (1.7%), combined cancer in 11 (0.9%) and other malignant lung tumors in 57 (4.8%) cases. Distribution of LC types differed significantly between the sexes ($\chi^2=48.8$; $p<0.001$). In women, ADC was more common than SCC. Biopsy material was obtained in 78.5% by bronchoscopy, as transbronchial biopsy, followed by computer tomography (CT)-guided transthoracic biopsy (TTB), lobectomy, or biopsy of metastatic tumor. Patient age was significantly different in various types of LC ($\chi^2= 17.2$; $p=0.004$) (Table 2).

Table 2. *Distribution of patients according to age and biopsy specimen in different types of lung cancer*

	Type of lung cancer						
	Adeno	**Squamous**	**Small cell**	**Neuro endocrine**	**Other**	**Mixed**	**p**
Patients (N)	498	380	191	20	56	11	
Age (years) (min-max)	65 (27-91)	67 (44-86)	65 (36-95)	61 (49-81)	66 (39-82)	70 (60-81)	**<0.004***
Age (years)							0.106†
≤60	155 (31.1)	86 (22.6)	53 (27)	10	14 (25)	1	
>60 to ≤66	119 (23.9)	96 (25)	53 (27.7)	5	15 (26.8)	1	
>66 to ≤74	120 (24.1)	105 (27.6)	57 (24.6)	2	16 (28.6)	6	
>74	104 (20.9)	93 (24.5)	38 (19.9)	3	11 (19.6)	3	
Biopsy specimen							
Bronchial	368 (73.6)	306 (80,3)	181 (92.8)	14	38 (66.7)	7	
Transthoracic	47 (9.4)	31 (8.1)	6 (3.1)	2	3 (5.3)	0	
Lobectomy	74 (14.8)	44 (11)	3 (1.5)	3	15 (26.3)	4	
Metastasis	11 (2.2)	0 (0)	5 (2.6)	1	1 (1.8)	0	

†χ2-test; *Kruskal-Wallis test

Median age of NEC patients was 61 (min-max: 49-81) years, i.e., 6 years younger than in SCC (Z=2.9; p=0.004; r=0.14), and 9 years younger than in mixed cancer (Z=2.8; p=0.005; r=0.5). Distribution according to age range was not significantly different among particular LC types (χ^2=22.1; p=0.106). In all LC types, bronchial biopsy was the most common diagnostic specimen.

In the Split-Dalmatia County, a slight increase in the overall incidence rates of LC and incidence in both men and women was observed during the study period (Figure 1).

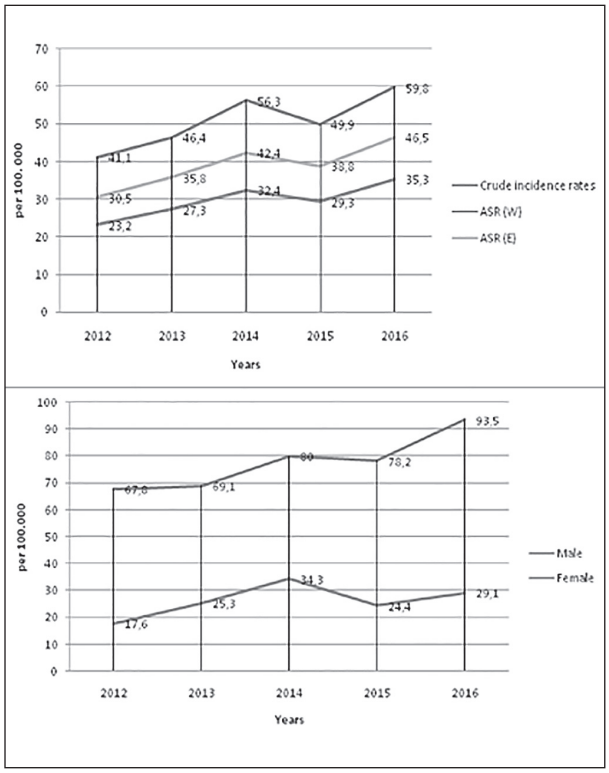

Figure 1. *Overview of incidence rates from 2012-2016: total (upper panel) and by gender (lower panel). Crude incidence rates, ASR(W) – age-standardized incidence rates by the standard world population, ASR(E) – age-standardized incidence rates by the standard European population.*

Median follow-up was 10 (min-max: 1-69) months. During follow-up, 852 (73%) patients died. All variables were compared with the outcome and the results are shown in Table 3.

Table 3. *Comparison of study variables in patients with lung cancer and outcome*

		Alive (N=313)	Dead (N=852)	p*
Gender n (%)	male female	205 (65) 108 (35)	655 (77) 197 (23)	**<0.001**
Age range (years) n (%)	≤60 >60 to ≤66 >66 to ≤74 >74	90 (29.2) 84 (27.3) 91 (29.5) 43 (14)	229 (27) 205 (24.1) 205 (24.1) 210 (27.4)	**<0.001**
Histologic type n (%)	ADC SC SCLC NEC Other Combined	141 (45.2) 107 (34.3) 40 (12.8) 4 (1.3) 18 (5.8) 2 (0.6)	359 (42.1) 274 (32.2) 155 (18.2) 16 (1.9) 39 (4.6) 9 (1.1)	0.278

* χ2-test

The share of patients aged >74 years was 1.56 times higher in the group of deceased patients as compared with the alive ones (χ^2=15.87; p=0.001). The share of women in the group of alive patients was 1.5 times higher than the share of women in the group of deceased patients (χ^2=14.8; p<0.001). Distribution of patients according to LC type did not differ significantly (χ^2=6.3; p=0.278).

The mean OS was 22.3 (SE: 0.79; 95% CI: 20.7-23.8) months, median 10 (SE: 0.60; 95% CI: 8.8-11.2) months, and 5-year OS rate was 16.5 (Figure 2). The average survival was by 8 months higher in women than in men (LR: 13.9; p<0.001).

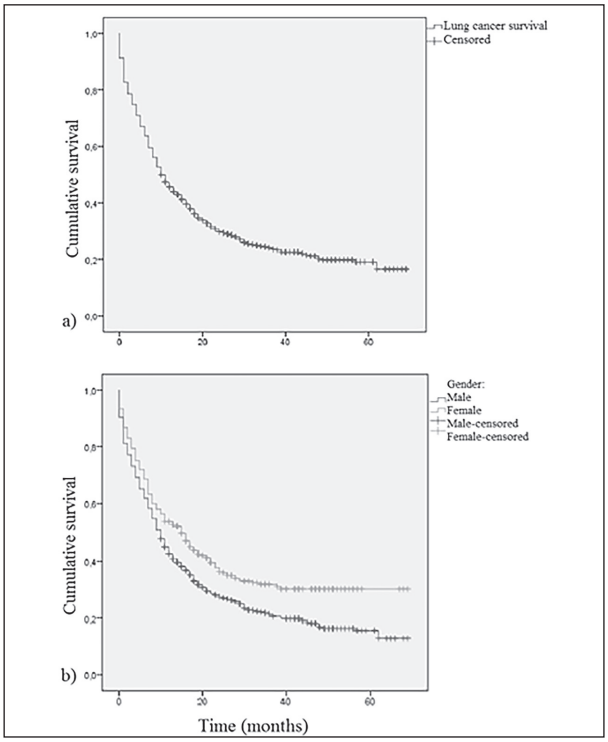

Figure 2. *Kaplan-Meier curve of survival of patients with lung cancer: total (upper panel) and by gender (lower panel).*

The variables analyzed were compared to OS (Table 4). The groups of patients according to age range had significant difference in OS (LR: 20.9; p<0.001).There was no significant difference in OS between the ≤60 years, >60 to ≤66s and >66 to ≤74 age groups (LR: 0.085; p=0.059). In these groups, the mean survival was 23.8 months (SE: 0.93; 95% CI: 22-26) and median 12 months (SE: 0.85; 95% CI: 10-14), i.e., significantly higher than in group >74 years (LR: 20. 9; p<0.001). A significant difference in OS was found between LC types (LR: 9.1; p=0.028). There was no difference between ADC and SCC (LR: 0.140; p=0.708), and between SCLC and NEC (LR: 0.052; p=0.820). The mean survival in ADC/SC was 22.9 months (SE: 0.92; 95% CI: 21-25), median 12 months (SE: 0.95; 95% CI: 10-14). The mean survival in SCLC/NEC was 18.4 months (SE: 1.7; 95% CI: 15-21.7), median 8 months (SE: 0.7; 95% CI: 6.6-9.3). The median in SCLC/NEC was by 4 months lower than in ADC/SCC (LR: 8.9; p=0.003) (Figure 3).

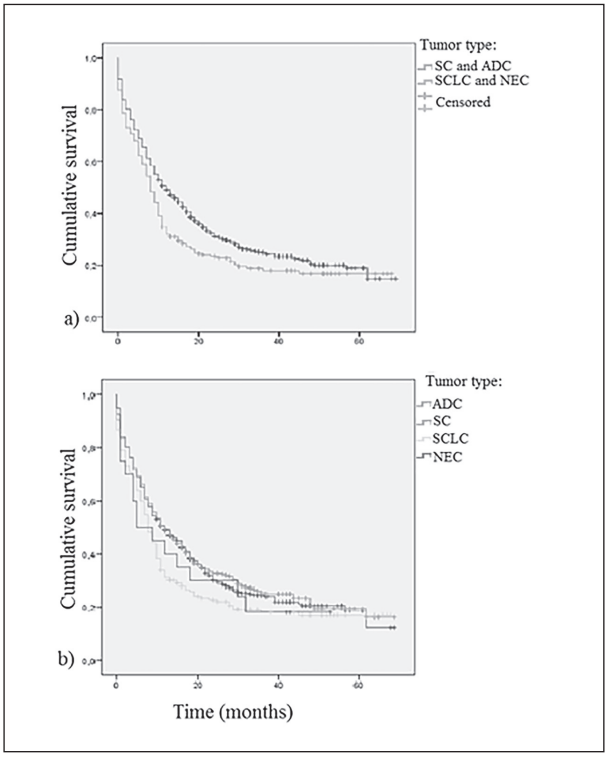

Figure 3. *Kaplan-Meier curve of survival of patients with lung cancer according to histologic type.*

Patients diagnosed in stage IV of disease had a significantly worse OS (LR: 110.574; p<0.001). Patients diagnosed in stage I to stage IIIC had mean survival of 23.03 months (SE: 1.025; 95% CI: 21-25), median 18 months (SE: 1.729; 95% CI: 14.6-21.4). Patients diagnosed in stage IV had mean survival of 9.26 months (SE: 0.788; 95% CI: 7.7-10.8), median 5 months (SE: 0.569; 95% CI: 3.9-6.1) (Figure 4).

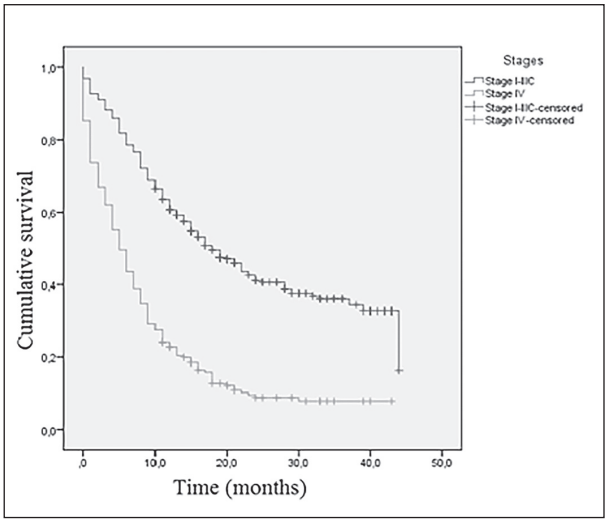

Figure 4. *Kaplan-Meier curve of patients with lung cancer according to stage of disease.*

The risk of death was 1.34 times higher for men than women (p<0.001). As the age range group was higher, the risk of death increased by 1.13 times compared to the previous age group (p<0.001). The risk of death was 1.12 times higher in patients with SCLC/NEC than with ADC/SC (p=0.001).

Table 4. *Study variables according to overall survival*

	Survival				
	Mean (SE); 95% CI	**Median (SE); 95% CI**	**p***	**HR; 95% CI**	**p†**
Gender					
Male	20.4 (0.9) 18.7-22	10 (0.6) 9-11	<0.001	1.34 1.14-1.57	**<0.001**
Female[1]	28 (1.7) 25-31	15 (1.8) 11-19			
Age group (years)					
≤60	24 (1.6) 21-27	11 (1.3) 8.5-13.5	<0.001	1.1 1.07-1.2	**<0.001**
>60 ≤66	23.5 (1.6) 20-27	13 (1.6) 9.9-16			
>66 ≤74	23.4 (1.7) 20-27	11 (1) 8.9-13			
>74	16 (1.4) 13-19	7 (0.9) 5.2-8.8			
Histologic type					
AC	22.5 (1,2) 20-25	12 (1.2) 9.6-14	0.028		
SCC	23.4 (1,4) 20.6-26	12 (1.3) 9.5-14.5		1.12 1.04-1.21	**<0.005****
SCLC	18 (1.8) 14.8-22	8 (0.7) 6.7-9.3			
NEC	17.2 (4.3) 8.6-25.7	5 (4) 1-12			

*Log rank test; †Cox regression; [1]reference level

**Cox analysis investigated the risk of death in SCLC and NEC compared to AC and SCC together. According to LR test, there was no statistically significant difference in survival length between AC and SCC, or between SCLC and NEC.

The risk of death did not differ significantly between SCC and ADC (p=0.715). The risk of death was 1.13 times higher in patients with SCLC than ADC (95% CI: 1.03-1.24; p=0.01). The risk of death did not differ significantly between NEC and ADC (p=0.534). The risk of death did not differ significantly between SCLC and NEC (p=0.827). The risk of death for SCLC was 1.3 times higher than for SCC (95% CI: 1.07-1.6; p=0.008). The risk of death did not differ significantly between SCC and NEC (p=0.452). The risk of death was 1.13 times higher in patients with SCLC than in those with ADC, SCC and NEC combined (95% CI: 1.04-1.24; p=0.005). Results of the Cox multivariate regression analysis suggested that patient gender, age, and histologic type were statistically significant parameters for outcome (Table 5).

Table 5. *Results of multivariate Cox regression analysis in patients with lung cancer*

	HR; 95% CI	p*
Gender Male Female[1]	1.34 (1.14-1.59)	**<0.001**
Age (years) ≤60 >60 to ≤66 >66 to ≤74 >74	1.13 (1.06-1.2)	**<0.001**
Histologic type AC SCC SCLC NEC	1.4 (1.2-1.7)	**<0.001****

[1]Reference level; *Cox regression
**Cox analysis investigated the risk of death in SCLC and NEC compared to AC and SCC together. According to LR test, there was no statistically significant difference in survival length between AC and SCC, or between SCLC and NEC.

DISCUSSION

Lung cancer is the most common and lethal malignancy in the world, thus an important health problem. It is mostly caused by tobacco use, so reducing the prevalence of smoking worldwide has priority in fighting the disease. Most patients are diagnosed at an advanced stage of the disease (9); in our cohort, 80.1% of patients were in stage III or IV. Early LC stages have a more favorable prognosis, with 5-year survival rates of 70%-90% for small, localized tumors (10-12). Earlier diagnosis should be a priority. The large American National Lung Screening Trial from 2011 showed that screening with low-dose CT reduced LC mortality (13). The study showed that after positive screening results, LC stages Ia and Ib were diagnosed most frequently. In Croatia, the screening program for early detection of LC with low-dose CT started in 2020, and we are hoping to see lower percentage of patients diagnosed in advanced stages (14).

In the Split-Dalmatia County, LC occurs at a younger age than in the rest of the world; in our cohort, median age was 66 years, compared to median age of 70 in the USA (15). We also observed a higher ratio of men to women affected with LC than in the rest of the world (male: female 2.8:2.13) (16). In the world, there is a downward trend in the incidence of LC in men and an increased incidence in women (17). According to the model reported by Lopez *et al*., it takes 40 years for changes in smoking rates (prevalence) to affect epidemiological LC statistics (18). Today, developed countries have a declining trend of LC incidence in men owing to decreased tobacco use in the last several decades. Since the smoking epidemic in women started later, a decreasing incidence is not yet observed. According to Janković *et al*., Croatia followed the world trend of a decreasing incidence of LC in men and increasing incidence in women from 1988 to 2013 (19,20). However, our study showed a slight increase in the incidence in both genders in the Split-Dalmatia County from 2012 to 2016. The incidence of LC in 2012 worldwide (age-standardized rates according to the standard world population) was 23.1/100 000, 30.4/100 000 in Croatia, and 23.2/100 000 in the Split-Dalmatia County (16).

The most common type of primary LC in our cohort was ADC (43%), and its proportion was increased in the monitored period. This result is in line with the world literature where ADC is the most common type, with a trend of increasing incidence, followed by SCC (21). In men, the proportion of ADC is slightly higher than SCC (38.6% *vs*. 38%), while in women the difference was significant (55.3% *vs*. 17.8%). These results correspond to the results of other world studies according to which a decreased incidence of SCC in men has been observed in recent decades in favor of ADC. The changes in the incidence are attributed to a decrease in the smoking rate and change in the quality of cigarette filters (22). The incidence of ADC in women is higher than SCC worldwide, which was confirmed by this study (21). The incidence of SCLC was 16.7%, which corresponds to data from the world literature (23). A few neuroendocrine carcinomas were diagnosed at a younger age, median age 61 (min-max: 49-81) years, which is consistent with literature data. According to the studies by Travis *et al*., most atypical carcinoids occur between 45 and 55 years (23), and patients with large cell NEC have a median age of 60 years at the time of diagnosis (24). LC is the leading cause of death from all malignancies (16). In most countries, the 5-year survival rate of patients with LC is 10%-20%, and in Croatia it is 10% (25). In our cohort, the mean survival was 22.3 months, median

10 months, and the 5-year survival rate is 16.5%. In the 2010-2014 period, the best 5-year survival of patients with LC was recorded in Japan (32.9%) (25). The following 12 countries had a 5-year survival rate of 20%-30%: USA, Canada, Mauritius, China, Korea, Taiwan, Israel, and in Europe Latvia, Iceland, Sweden, Switzerland and Austria. Countries that had a 5-year survival rate of less than 10% were India, Thailand and Bulgaria (25). According to these data, 5-year survival of LC in the Split-Dalmatia County was 16.5% *versus* 10% at the national level. The literature shows that female gender is a favorable prognostic factor for OS. A meta-analysis by Nakamura *et al*. including 86 800 patients with NSCLC found a significantly longer survival in women (26). In several studies on SCLC, female gender had a favorable prognostic significance (27-29). In our study, women had 8 months longer mean survival than men (LR: 13.9**;** p<0.001), which is in line with data from the world literature. Also, the proportion of women was 1.5 times higher in the group of alive patients than in the deceased ones (p<0.001), and the number of men was higher in the deceased group. In a large Norwegian study involving 40 118 patients with all types of LC, the risk of death was 1.14 times higher for men than for women (95% CI: 1.109-1.166; p<0.001) (30). In our study, these results were confirmed, with the risk of death for men 1.34 times higher than for women (95% CI: 1.14-1.57, p<0.001). According to data from the world literature, older patients with LC have a worse prognosis than younger patients (31-33). In our study, patients older than 74 had a significantly worse survival than patients aged ≤74 (p<0.001). Also, in the group of deceased, there was a significantly higher number of patients older than 74 than in the group of alive patients (27.4% *vs*. 14%) (p=0.001). There was no difference between ADC and SCC in median survival, which was 12 months (p=0.708), and this result is consistent with the literature (30,33). Patients with SCLC had lower median survival, 8 months (95% CI: 6.7-9.3), which correlates with data from the literature (15,30).

CONCLUSION

During the 2012-2016 period, the incidence of LC in the Split-Dalmatia County was slightly increased in both sexes, and patient age of 66 years was somewhat younger than in similar studies. Gender, age, and type of cancer were independent prognostic factors, confirming the results of other clinical and population studies. The 5-year survival rate of 16.5% was higher than at the national level. A limitation of this study was its epidemiologic descriptive character, while its strength were real clinical data from one center with a large catchment population. This study may provide a basis for future analyses with new personalized therapies.

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SAŽETAK

ANALIZA OPĆEG PREŽIVLJENJA BOLESNIKA S KARCINOMOM PLUĆA PRIJE UVOĐENJA INHIBITORA TIROZIN KINAZE I IMUNOTERAPIJE U REPUBLICI HRVATSKOJ – STUDIJA IZ JEDNE USTANOVE

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Analizirali smo ishod ispitanika s karcinomom pluća u razdoblju prije uvođenja inhibitora tirozin kinaze i imunoterapije u Republici Hrvatskoj, rezultate usporedili sa sličnim studijama i stvorili osnovu za buduće analize. Na Odjelu za patologiju KBC-a Split od 2012. do 2016. godine karcinom pluća je dijagnosticiran u 1165 bolesnika. Prikupljeni su podatci o dobi, spolu, bioptičkom uzorku, histološkom tipu karcinoma i stadiju bolesti. Ukupno preživljenje za svakog bolesnika izračunato je od datuma biopsije do datuma smrti, odnosno posljednjeg dana praćenja. Sedamdesetčetiri posto ispitanika bili su muškarci, a 26 % žene, medijan dobi 66 godina (manji nego u sličnim studijama). U 78 % slučajeva dijagnoza je postavljena bronhoskopskom biopsijom. Adenokarcinom (ADC) je dijagnosticiran u 42,9 %, skvamozni karcinom (SCC) u 32,7 % i karcinom malih stanica (SCLC) u 16,7 % slučajeva. U žena je ADC bio češći od SCC (p<0,001). Prosječno preživljenje bilo je 22,3 mjeseca, medijan 10 mjeseci, a stopa petogodišnjeg preživljenja 16,5%. Bolesnici u skupini starijih od 74 godine imali su kraće prosječno preživljavanje u odnosu na mlađe skupine, s rizikom smrti 1,1 puta većim za svaku višu dobnu skupinu (p<0,001). Rizik smrti bio je 1,34 puta veći za muškarce nego za žene (p<0,001), a 1,12 puta veći za SCLC od ADC/SC (p=0,005). Spol, dob i histološki tip karcinoma potvrđeni su kao neovisni prognostički čimbenici. Žene su u prosjeku živjele 8 mjeseci duže od muškaraca, 28 naspram 20,4 mjeseca. Petogodišnja stopa preživljenja od 16,5 % u našoj kohorti bila je bolja nego na nacionalnoj razini, 10 %.

Ključne riječi: rak pluća, opće preživljenje, personalizirana terapija, Hrvatska

NEUROLOŠKA OČITOVANJA COVID-19

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Uvod: Krajem 2019. god. otkrivena je nova bolest nazvana COVID-19 (od engl. *Corona Virus Disease-2019*). Bolest je uzrokovana novim koronavirusom SARS-CoV-2 (od engl. *Severe acute respiratory syndrome coronavirus 2*), a s obzirom na brzo širenje od strane Svjetske zdravstvene organizacije (SZO) ubrzo je proglašena pandemija. Na početku pandemije ustanovljeno je da se COVID-19 osim dišnim simptomima može očitovati simptomima drugih organskih sustava. Između ostalog COVID-19 može se očitovati neurološkom simptomatologijom, a neurološki simptomi mogu se javiti i kao komplikacija COVID-19 te nakon preboljenja same bolesti. ***Cilj:*** nastojali smo prikupiti najnovije spoznaje o COVID-19 i neurološkim očitovanjima i komplikacijama. Također, željeli smo istaknuti i moguće razlike pri postavljanju dijagnoze i liječenja. ***Metode:*** Pretražili smo bibliografsku bazu podataka MEDLINE s ključnim riječima neurološki simptomi, komplikacije, COVID-19 sve do 2020. godine. ***Rezultati:*** Do sada su prema izvješću SZO ustanovljena 23 neurološka simptoma i 14 neuroloških dijagnoza. Prema podatcima SZO do sada je 1/3 hospitaliziranih bolesnika imala neurološke simptome. Kod bolesnika starijih od 66 godina najčešća je dijagnoza bila encefalopatija, a očitovala se agitacijom, smetenošću, delirijem te poremećajima stanja svijesti. Također, encefalopatija je bila pokazatelj lošijeg ishoda bolesti. Incidencija ishemijskih i hemoragijskih moždanih udara bila je veća kod COVID-19 pozitivnih bolesnika u odnosu na opću populaciju što se objašnjava proupalnim odgovorom i povećanom sklonosti koagulaciji tijekom bolesti. Prethodni čimbenici rizika za moždani udar kao što su pušenje, šećerna bolest i arterijska hipertenzija pridonose mehanizmu nastanka moždanog udara i lošijem ishodu. Manje učestali bili su neuromišićni poremećaji kao što su kljenut facijalnog živca i Gillian Barréov sindrom. Druge infektivne bolesti kao što je meningoencefalitis javljale su se rjeđe. Poremećaji mirisa i okusa obično bi se povukli unutar dva mjeseca. Dijagnostika i liječenje neuroloških očitovanja COVID-19 ne razlikuje se od uobičajenih postupaka. Nema specifičnog lijeka za liječenje neuroloških poremećaja tijekom COVID-19. Važno je napomenuti da bolesnici koji već imaju određenu neurodegenerativnu bolest i veći stupanj onesposobljenosti mogu imati lošiji ishod COVID-19. Također, kod dijela kroničnih neuroloških bolesti moguće je da se tijekom COVID-19 liječenje mora promijeniti. ***Zaključak:*** Tijekom pandemije neurolozi su se susreli i s različitim načinima reorganizacije bolničkog sustava liječenja neuroloških bolesnika, praćenja kroničnih neuroloških bolesnika, liječenja kroničnih bolesnika zbog pandemije te hitnih neuroloških stanja kod COVID-19 pozitivnih bolesnika. Zato je neurološka struka morala reorganizirati i osigurati neurološku dijagnostiku i liječenje za ostale bolesnike.

Ključne riječi: COVID-19, očitovanja, simptomi, liječenje, komplikacije

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UVOD

Krajem 2019. godine u Narodnoj Republici Kini pojavila se bolest dišnog sustava uzrokovana novim koronavirusom (SARS-CoV-2). Do tada nepoznata bolest nazvana je COVID-19 (od.engl. *Coronovirus Disease-2019*). S obzirom da se radi o virusu koji se širi dišnim putem, bolest se brzo širila pa je tako početkom ožujka 2020. Svjetska zdravstvena organizacija (SZO) proglasila pandemiju. Kasnije je ustanovljeno da se bolest može očitovati i simptomima drugih organskih sustava. Klasičan prikaz bolesti uključivao je oslabljeni

osjet mirisa i okusa, kašalj i rjeđe proljev. Jedan dio bolesnika očitovao se blažom kliničkom slikom, a kod drugog dijela bolesnika klinička slika je uključivala upalu pluća, dišno i srčano zatajivanje, posljedično višestruko zatajivanje organa i smrt. Osim navedenog, medicinska zajednica u cijelom svijetu susrela se s bolesti nepoznatog tijeka i s nepoznatim komplikacijama te je brzo bilo potrebno organizirati zbrinjavanje bolesnika koji su bolovali od COVID-19. Usporedno je na ovu temu objavljen i veliki broj znanstvenih istraživanja. Ubrzo je primijećeno da veliki dio bolesnika, neovisno o dišnim simptomima, pokazuje i neurološku simptomatologiju. Neurološki simptomi mogu se pojaviti i kod hospitaliziranih bolesnika i kod onih na kućnom liječenju. Osim toga, neurološki simptomi se mogu javiti tijekom, ali i nakon akutne bolesti COVID-19 (sindrom post-COVID-19). Raspon neuroloških simptoma varira od blažih (npr. poremećaj mirisa i okusa) do težih (encefalopatija). Ovdje iznosimo neurološke manifestacije COVID-19 i njihovo daljnje praćenje i liječenje (1).

NEUROLOŠKI SIMPTOMI I COVID-19

Smatra se da akutna faza COVID-19 traje do 4 tjedna, a neurološki simptomi koji se mogu javiti tijekom bolesti uključuju: glavobolju, vrtoglavicu, poremećaj okusa i mirisa, delirij, moždani udar, komu, epileptične napadaje i Guillain-Barréov sindrom (GBS). Kod određenih bolesnika dio simptoma može trajati dulje od 12 tjedana. Tada govorimo o tzv. post-COVID-19 sindromu. S obzirom na raznolikost neurološke simptomatologije SZO je pokušala objediniti prikaze bolesnika i objavljenu literaturu o tom sindromu. Razumije se da se ti podatci stalno mijenjaju, ali dobiven je približni dojam neuroloških očitovanja COVID-19. Prema podatcima SZO analizirano je ukupno 145 721 bolesnika s akutnim COVID-19. Kod svih bolesnika je bolest COVID-19 bila potvrđena putem RT - PCR testa (od engl. *real time reverse transcription polymerase chain reaction*). Većinom se radilo o hospitaliziranim bolesnicima (86 %). Opisana su 23 akutna neurološka simptoma (tablica 1) i 14 neuroloških dijagnoza (tablica 2) (2,3). Prema podatcima istraživanja kod jedne trećine bolesnika bila su prisutna neurološka očitovanja, a kod jednog na 50 bolesnika došlo je do razvoja moždanog udara. Kod bolesnika starijih od 60 godina, najčešća neurološka dijagnoza bila je akutno smeteno stanje/delirij (3). Kod bolesnika starijih od 60 godina prisutnost neurološke bolesti bila je povezana sa značajno povišenom smrtnosti. U svim dobnim skupinama vjerojatnost pojave akutnog smetenog stanja/delirija, moždanog udara, epileptičnog napada i poremećaja pokreta povećavala se s težinom kliničke slike COVID-19. Poremećaji okusa i mirisa bili su statistički značajno povezani s blažom kliničkom slikom. Ograničavajuće kod sakupljanja gornjih podataka bila je nedostatnost podataka o bolesnicima koji nisu bili hospitalizirani.

Tablica 1. *Neurološki simptomi u COVID-19.*

Simptom	Postotak prevalencije (%)	95% CI (%)
Znakovi kortikospinalnog oštećenja*	65	58-71
Agitacija	45	3-93
Umor	32	30-35
Mialgija ili umor	31	25-37
Poremećaj okusa	21	15-29
Mialgija	20	18-23
Poremećaj okusa ili mirisa	19	13-25
Glavobolja	18	10-28
Glavobolja i vrtoglavica	13	12-15
Akutno smeteno stanje/delirij	12	8-17
Poremećaj stanja svijesti	11	7-16
Vrtoglavica	7	5-8
Tinitus	7	1-10
Poremećaj vida	5	1-9
Poremećaj sluha	4	1-5
Poremećaj osjeta	3	1-5
Kognitivni poremećaj	2	0-5
Lezija moždanog živca	2	0-8
Hemiplegija/pareza	2	0-10
Neuralgija	1	0-3
Epileptični napad	1	0-2
Ataksija	1	0-2

*hiperrefleksija, klonus i bilateralni ekstenzornni plantarni odgovor

Preuzeto i modificirano prema: WHO. [Internet]. Neurology and COVID-19: Scientific brief. c 2021-09 [cited 17 Jan 22]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Neurology-2021.1

Tablica 2. *Neurološke dijagnoze u COVID-19.*

Dijagnoza	Postotak prevalencije (%)	95% CI (%)
Neuropsihijatrijski poremećaji	24	2-61
Lezija skeletnog mišića*	5	1-12
Miopatija**	2	0-4
Moždani udar	2	1-2
Ishemijski moždani udar/TIA***	1	1-2
Poremećaj pokreta	1	0-1
CIN/polineuropatija****	1	0-2
Epileptični status	1	0-5
Hemoragijski moždani udar	0,31	0,15-0,50
Encefalitis	0,30	0-1
Guillain-Barreov sindrom	0,28	0-1
Parainfektivni radikulitis	0,23	0-1
Cerebralna venska tromboza	0,12	0-2
Sindrom reverzibilne posteriorne encefalopatije (PRES)	0,12	0.02-0.27

*praćena povišenom kreatin kinazom i rabdomiolizom; **uključuje CIN, PRES i tranzitornu ishemijsku ataku; *** TIA tranzitorna ishemijska ataka, **** CIN-critical illness myopathy

Preuzeto i modificirano prema: WHO. [Internet]. Neurology and COVID-19: Scientific brief. c 2021-09 [cited 17 Jan 22]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Neurology-2021.1

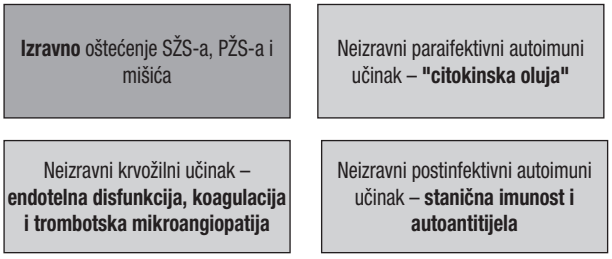
Osim akutnih neuroloških očitovanja opisivane su i neurološka post-COVID-19 očitovanja. Prema SZO retrospektivno je analizirano 1733 COVID-19 bolesnika otpuštenih s bolničkog liječenja. Kod 19,6 % bolesnika bili su prisutni neurološki simptomi post-COVID-19 sindroma. Najčešće su kod bolesnika bili prisutni: umor ili slabost mišića (63 %), smetnje spavanja (26 %), anksioznost i depresija (23 %) te smetnje hoda (24 %). Druga prospektivna studija uspoređivala je COVID-19 pozitivne bolesnike koji su bili liječeni u jedinici intenzivnog liječenja i bolesnike koji su bili na kućnom liječenju. Najučestaliji simptomi nakon otpusta bili su amnezija (30 %), disegzekutivni sindrom (33 %), ataksija (11 %) i tetrapareza (18 %) (3,4). Ono što je važno napomenuti je to da su podatci o neurološkim komplikacijama nakon preboljelog COVID-19 ograničeni jer je bilo teško pratiti ishod svih otpuštenih bolesnika, a posebno je teško bilo pratiti ishode asimptomatskih bolesnika (4). Također, određeni bolesnici s već prileţećim neurološkim bolestima (npr. moždani udar i demencija) bili su pod povećanim rizikom od težeg ishoda COVID-19, a kod određenih neuroloških bolesti može doći do pogoršanja zbog COVID-19 te posljedično do težeg i/ili smrtnog ishoda. Prema podatcima SZO od neuroloških bolesti najveća prevalencija za teži ishod zbog COVID-19 bila je kod cerebrovaskularnih i neurodegenerativnih bolesti (3,5,6).

PATOGENEZA NASTANKA NEUROLOŠKOG OŠTEĆENJA

Smatra se da je mehanizam nastanka neuroloških oštećenja zbog COVID-19 uzrokovan izravnim učinkom virusa i neizravnim, sistemskim odgovorom organizma na infekciju (7). Mehanizmi neizravnog puta uključuju oštećenje središnjeg (SŽS) i perifernog živčanog sustava (PŽS) te oštećenje mišića. Patogeneza oštećenja neizravnim putem može biti uzrokovana: krvožilnim putem, paraupalnim autoimunim putem (tzv. "citokinska oluja") i postinfektivnim autoimunim procesom koji podrazumijeva stvaranje protutijela (sl. 1.). Smatra se da virus dolazi do SŽS-a hematogenim ili olfaktornim putem te se kasnije umnožava u SŽS-u. U prilog tome idu analize u kojima je virus pronađen u moždanom deblu, produljenoj moždini i respiratornim centrima te na mjestima izlazišta moždanih živaca. Naime, autopsije bolesnika umrlih od COVID-19 i akutnog respiratornog zatajenja prikazale su hiperemiju i edem te degeneraciju tkiva u području produljene moždine. Nadalje, različiti imunomodulatorni učinci započinju produkciju protutijela na glijalne stanice i neurone što dovodi do para- i post-upalnog zbivanja. Smatra se da tada dolazi i do interakcije između dišnog sustava. Sve to dovodi i do hipoksije koja je između ostalog uzrokovana dodatno središnjim mehanizmima živčanog sustava. Slijedom dolazi i do pogoršanja dišne funkcije te hipoksičnog oštećenja mozga (7,8). Osim navedenog pretpostavljeno je da se pojedini koronavirusi mogu sinaptički širiti s kemo- i mehanoreceptora u plućima u područje produljene moždine (9).

Periferni živčani sustav može biti zahvaćen direktnim i indirektnim imunološkim odgovorom. Virus se veže za receptor angiotenzin-konvertirajućeg enzima 2 (ACE 2) što mu omogućava ulazak u stanice. ACE je enzim koji konvertira angiotenzin II u angiotenzin I. ACE je izražen na stanicama mišića te kad se SARS-CoV-2 veže na mišićne stanice dolazi do promjene regulacije ACE 2 i pretjerane reakcije renin-angiotenzin-puta što rezultira oksidativnim stresom i širenjem krvnih žila (1,2). Također, kada se SARS CoV-2 veže na ACE dolazi do oštećenja krvožilnog endotela što dovodi do srčanih i cerebrovaskularnih poremećaja (8). Bolesnici na intenzivnoj njezi često razviju znakove citokinske oluje koja se klinički prezentira vrućicom, povišenim upalnim biljezima (D-dimer, feritin)

i povišenim proupalnim citokinima (IL 6, TNF alfa). Proupalni citokini klinički dovode do pojave smetenosti i poremećaja stanja svijesti. Osim toga, proupalno stanje dovodi do pojave sklonosti trombozama (7,8,).



Sl. 1. *Patogeneza neurološkog oštećenja u COVID-19*

Preuzeto i modificirano prema: Leven Y, Bösel J. Neurological manifestations of COVID-19 - an approach to categories of pathology. Neurol Res Pract 2021; 26;3(1):39.

ENCEFALOPATIJA

Encefalopatija je poremećaj stanja ili sadržaja svijesti koji može biti uzrokovan izoliranom ili potpunom zahvaćenošću mozga (10). Kod bolesnika pozitivnih na COVID-19 encefalopatija je bila učestala kod onih koji su bili liječeni na intenzivnoj njezi. Smatra se da encefalopatija može biti prvi početni simptom COVID-19. Prema jednom istraživanju kod 28 % bolesnika kod kojih je postavljena dijagnoza COVID-19, 28 % ih je kao početni simptom imalo encefalopatiju. Encefalopatija je bila prisutna kod 31,8 % hospitaliziranih bolesnika. Bolesnici s encefalopatijom bili su stariji od 66 godina u odnosu na one bolesnike kod kojih nije bila prisutna encefalopatija, imali su kraće vrijeme od početka bolesti do hospitalizacije, češće su to bili muškarci, a pri prijmu su imali već postojeće rizične faktore za moždani udar (postojeća neurološka bolest, tumorska bolest, cerebrovaskularna bolest, kronična bubrežna bolest, šećerna bolest, zatajenje srca, arterijska hipertenzija i pušenje) (8,11).

Neuroradiološkm prikazom, magnetskom rezonancijom (MR) mozga i/ili kralježnice kod COVID-19 encefalopatije prikazani su različiti nespecifični znakovi: klasični znakovi ishemijskog i hemoragičnog moždanog udara, leptomeningealna imbibicija, poremećaji u tehnici snimanja FLAIR (od engl. *fluid attenuated inversion recovery*), oštećenja medijalnog temporalnog režnja, difuzne lezije bijele tvari, citoksične lezije bijele tvari (8,12).

Encefalopatija COVID-19 može se očitovati različitom kliničkom slikom: delirijem, somnolencijom te poremećajem stanja svijesti. Mogu se pojaviti znakovi oštećenja kortikospinalnog puta (povišeni refleksi, ekstenzorni plantarni odgovor) ili epileptične atake (8).

Što se dijagnostičkog pristupa tiče. kod bolesnika s encefalopatijom potrebno je uvijek isključiti encefalopatiju uzrokovanu hipoksijom, lijekovima te toksičko-metaboličkim uzrocima. U slučaju prisutnog fokalnog ili lateralizirajućeg neurološkog deficita potrebno je učiniti slikovne pretrage (MR mozga i/ili kralježnice), elektroencefalogram (EEG) u svrhu prikaza mogućih subkliničkiih epileptičnih napadaja i lumbalnu punkciju u svrhu isključivanja infekcije SŽS-a.

Liječenje encefalopatije kod COVID-19 ne uključuje nužno kortikosteroidnu ili imunomodulatornu terapiju. Za sada nema jasnih dokaza da kortikosteroidna terapija ili imunomodulatorna terapija pomaže kod COVID-19 encefalopatije.

Prognoza kod COVID-19 bolesnika s encefalopatijom je loša. Jedna trećina bolesnika ostane nakon otpusta subjektivno kognitivno oštećena (8).

CEREBROVASKULARNE BOLESTI

Incidencija ishemijskog moždanog udara povećana je kod COVID-19 pozitivnih bolesnika te je prema nekim podatcima varirala od 0,4 do 2,7 %. Incidencija hemoragijskog moždanog udara varirala je od 0,2 do 0,9 %. Incidencija tromboze venskih sinusa iznosila je 0,08 % (13).

Općenito se smatra da COVID-19 pridonosi povećanom riziku za moždani udar. Kod srednje teške kliničke slike rizik od COVID-19 iznosio je <1 %, a kod bolesnika na intenzivnom liječenju 6 %. Najčešće do moždanog udara dolazi nakon jednog do tri tjedna od početka simptoma COVID-19.

Rizični čimbenici za moždani udar uključuju ranije poznate rizične čimbenike za moždani udar, a to su: arterijska hipertenzija, hiperlipidemija, atrijska fibrilacija i šećerna bolest.

Smatra se da su ishemijski moždani udari bili nepoznatog uzroka (kriptogeni) što je vjerojatno posredovano dodatnim mehanizmima povećane sklonosti koagulaciji i proupalnom odgovoru koji su prisutni zbog COVID-19.

Povećana sklonost koagulaciji i proupalno stanje za vrijeme infekcije COVID-19 dokazani su na temelju povišenih vrijednosti D-dimera u prvih nekoliko tjedana trajanja bolesti. Opisani su porast slučajeva tromba u aorti, karotidnoj i bazilarnoj arteriji. Pokazana je i povećana učestalost reokluzije nakon mehaničke trombektomije. Sljedeći mehanizam nastanka moždanog udara uključuje kardioemboliju. Smatra se da kardioembolija može uzrokovati ishemijski mož-

dani udar na izravan način zbog miokarditisa ili zbog poremećenog upalnog odgovora organizma.

Hemoragijski moždani udar primijećen je u slučaju kada nastane kao sekundarna hemoragizacija zbog neprepoznatog ishemijskog moždanog udara u 0,9 % slučajeva. Zamijećeni su i slučajevi spontanog intracerebralnog i subarahnoidnog krvarenja zbog koagulopatije i antikoagulacije (8, 12).

U dijagnostičkom pristupu važno je naglasiti da je svakog bolesnika sa sumnjom na moždani udar na početku pri prijmu potrebno testirati na SARA-CoV-2 neovisno o simptomima. Bolesnik može biti asimptomski nosilac što je kasnije organizacijski važno za daljnji smještaj i/ili izolaciju bolesnika. Potrebno je držati se važećih smjernica za liječenje moždanog udara i ne odgađati laboratorijsku i hitnu slikovnu dijagnostiku. Što se liječenja tiče potrebno je provesti trombolizu i/ili mehaničku trombektomiju u skladu s važećim lokalnim smjernicama (1,8).

Daljnja dijagnostička obrada tijekom hospitalizacije ne smije se razlikovati u odnosu na bolesnike koji ne boluju od COVID-19. Nakon akutnog liječenja važno je uvesti ranu antitrombotsku terapiju u dozama sukladno važećim smjernicama. Ono što je važno imati na umu je da je rizik za naknadno krvarenje nešto veći kod COVID-19 pozitivnih bolesnika. Kod bolesnika kod kojih je ustanovljena fibrilacija atrija potrebno je uvesti antikoagulantnu terapiju u punoj dozi. Ranije se mislilo da liječenje bolesnika ACE inhibitorima ili blokatorima angiotenzinskih receptora može pridonijeti težim ishodima, no pokazano je da nema kontraindikacija za njihovu primjenu te se oni mogu nastaviti primjenjivati u važećim indikacijama. U sekundarnoj prevenciji važan je nastavak antitrombotske terapije te prevencija rizičnih faktora.

Što se prognoze tiče, pokazano je da su bolesnici s moždanim udarom i COVID-19 imali veći neurološki deficit, a mortalitet i neurološka osposobljenost bili su veći kod bolesnika s COVID-19 u odnosu na bolesnike koji nisu bolovali od COVID-19 (14).

Samo saznanje da hitan bolesnik boluje od COVID-19 ne bi trebalo mijenjati pristup u dijagnostici i liječenju akutnog moždanog udara već bi u hitnoj službi organizacijski trebale postojati prostorije za izolaciju i pravodobno i pravovremeno zbrinjavanje COVID-19 pozitivnih bolesnika.

NEUROMIŠIĆNE BOLESTI

Pojava neuromišićnih bolesti kao što je Guillan-Barr**é**ov sindrom (GBS) opisivana je nakon infekcije COVID-19, premda je nepoznata njihova točna povezanost i učestalost (15). Većina bolesnika s GBS i COVID-19 prezentirala se progresivnom mišićnom slabošću koja se razvijala nakon jednog do četiri dana. Razmak od početka same bolesti i razvoja mišićne slabosti bio je između 5 do 16 dana (16). U međunarodnoj studiji IGOS (od engl. *International GBS Outcome Study)* navedeno je da se 73 % bolesnika prezentiralo senzomotornim simptomima, a kod 64 % bolesnika bila je prisutna kljenut facijalnog živca. Ističe se mogućnost da GBS kod COVID-19 pozitivnih bolesnika ima progresivniju težu kliničku sliku s potrebama mehaničke ventilacije. Za sada je još nedovoljno dokazano je li veća potreba za mehaničkom ventilacijom bila zbog upale pluća ili GBS (15,16).

Kod bolesnika s progresivnom slabošću ekstremiteta i smetnjama respiracije koje nisu potvrđene radiološkim pretragama pluća uvijek treba pomisliti na GBS. Ostali dijagnostički kriteriji za GBS se ne razlikuju od postojećih kriterija za GBS. U likvoru je prisutna odsutnost leukocita uz povišene proteine. Sinteza intratekalnog imunoglobulina oligoklonskih vrpci nije tipičan nalaz. Elektromioneurografija (EMNG) pokazuje ili aksonalnu varijantu GBS ili demijelinizacijsku varijantu. MR kralježnice može prikazati imbibiciju korjenova.

Što se liječenja tiče, preporučuje se intravenska primjena imunoglobulina (0,4 mg/kg tjelesne težine) ili terapijska izmjena plazme (1,8).

Od ostalih neuromišićnih bolesti mogu se javiti izolirane neuropatije ili neuropatije koje zahvaćaju više živaca (kljenut facijalnog živca, okulomotorne neuropatije, neuropatije vagusa, akcesornog živca, lezija hipoglosusa, različite neuropatije kranijalnih živaca i sl.). Oštećenja mišića mogu se prezentirati povećanjem kreatin kinaze (CK) u serumu, mijelitisom te umorom. Na kraju infekcije COVID-19 opisana je polineuropatija kritične bolesti, tzv. "*critical illnes neuropathy*" te miopatija kritične bolest. Sama neuropatija i miopatija koje nastaju u jedinicama intenzivnog liječenja povezane su s komplikacijama (sepsa, hiperglikemija i višestruko zatajivanje organa), parenteralnom prehranom te primjenom određenih sedativa, anestetika i mišićnih relaksansa, a incidencija se povećava s povećanjem trajanja liječenja u jedinici intenzivnog liječenja te težinom bolesti. Klinički je kod bolesnika prisutna atrofija i slabost mišića, a laboratorijski vrijednosti CK mogu biti povišene. Liječenje se sastoji od primjene plazmafereze i/ili imunoglobulina.

Na posljetku, opisani i su i slučajevi oštećenja perifernih živaca zbog lošeg namještanja bolesnika u jedinicama intenzivnog liječenja (17).

POREMEĆAJI MIRISA I OKUSA

Simptomi poremećaja mirisa često su početna prezentacija COVID-19. Gubitak mirisa/smanjen osjet mirisa i poremećaji okusa mogu se pojaviti iako nema prisutne nosne kongestije, a rijetko su izolirano prisutni kao jedini simptom. Prema određenim podatcima javljaju se u 80 % bolesnika (18). Kao prvo u nosnoj šupljini su prisutne visoke koncentracije virusa te posljedično dolazi do upale njušnih živaca i receptora. Studije su pokazale i veliki broj ACE receptora na jeziku (u odnosu na gingivu i sluznicu obraza) na koje se SARS-CovV-2 veže. Slikovne MR pretrage prikazale su različita oštećenja olfaktornih bulbusa. Različite studije pokazale su da gubitak mirisa traje u prosjeku 8 dana; 83 % bolesnika oporavilo se u prosjeku nakon 37 dana nakon početka simptoma, a 84 do 96 % bolesnika u razdoblju 4 do 8 mjeseci od gubitka mirisa (8,19).

EPILEPSIJA

Opisani su slučajevi epileptičnih napadaja i epileptičnog statusa zbog COVID-19. Smatra se da do epileptičkog napadaja tijekom COVID-19 dolazi zbog izravnog ili neizravnog djelovanja virusa (hipoksija, poremećaj acidobazne ravnoteže i/ili elektrolita) (1). Naime, u jednoj studiji opisano je 40 % bolesnika oboljelih od COVID-19 koji ranije u anamnezi nisu bolovali od epilepsije ili druge neurološke bolesti (8,20). U rijetkim slučajevima epileptički napad bio je početni simptom COVID-19. Opisivani su rijetki, ali mogući slučajevi epileptičkog statusa (8,21). Liječenje epileptičnog napadaja i epileptičnog statusa treba provoditi prema važećim smjernicama vodeći se ciljem zaustavljanja napadaja što prije. Lijekovi prve linije uključuju diazepam i lorazepam. Primjena antiepileptika druge i treće linije podrazumijeva antiepileptike širokog spektra te hitan bolnički nadzor i bolničko zbrinjavanje (1).

AKUTNI DISEMINIRAJUĆI ENCEFALOMIJELITIS (ADEM)

Akutni diseminirajući encefalomijelitis (ADEM) je rijetka akutna demijelinizacijska bolest koja se najčešće javlja nakon infekcije ili cijepljenja. Obično je bolest jednofaznog tijeka, a klinička slika varira od žarišnih neuroloških ispada do pojave encefalopatije. Bolest je karakterizirana demijelinizacijskim lezijama bijele tvari, leđnoj moždini i bazalnim ganglijima uz moguću imbibiciju kontrasta. U likvoru mogu biti prisutni povišeni proteina te rijetko poliklonske vrpce. Kod sumnje na ADEM važno je diferencijalno dijagnostički razmišljati i o drugim demijelinizacijskim bolestima (1).

Do sada je opisano nekoliko slučajeva s kliničkom i slikovnom slikom ADEM-a kod COVID-19 pozitivnih bolesnika. Bolest je uključivala mijelitis sa zahvaćenosti mozga ili bez nje. Opisani su i slučajevi hemoragičnog encefalomijelitisa. Pokušano je liječenje visokim dozama kortikosteroida, intravenskih imunoglobulina i/ili izmjenom plazme s različitim prognozama.

Za sada se kod ADEM-a preporuča primjena pulsne kortikosteroidne terapije (1-2 g/dan) u trajanju 3 do 5 dana, a ako ne dođe do poboljšanja. primjenjuju se imunoglobulini (0,4 g/kg/tjelesne težine) ili terapijska izmjena plazme (1,8).

MENINGOENCEFALITIS

Kod COVID-19 infekcije u rijetkim slučajevima opisivani su virusni i autoimuni encefalitisi. Klinička slika većinom je uključivala glavobolju, umor i vrućicu. Opisivani su slučajevi mogućih meningoencefalitisa kod kojih SARS-COV-2 nije dokazan ili je nalaz bio lažno negativan. Bolesnici su uspješno reagirali na terapiju kortikosteroidima, terapiju izmjenom plazme i/ili intravenskim imunoglobulinima (1,22).

ČIMBENICI RIZIKA ZA TEŽI OBLIK COVID-19

Šećerna bolest, arterijska hipertenzija i pušenje pridonose lošijem ishodu COVID-19 tako da bolesnici koji već na početku bolesti imaju rizične faktore podložniji i samom lošijem ishodu. Također, smatra se da bolesnici koji od ranije boluju od ostalih srčanokrvožilnih bolesti imaju lošiji ishod. Bolesnici koji na početku bolesti imaju poznatu lošiju srčanu ili plućnu funkciju, neuromišićnu bolest, bulbarnu slabost ili veću neurološku onesposobljenost (npr. bolesnici koji boluju od amiotrofične lateralne skleroze, multiple skleroze) mogu također imati lošiji ishod nakon COVID-19 infekcije (8).

ZAKLJUČAK

Zaključno možemo reći da je povezanost SARS-CoV-2 s neurološkim sustavom nedvojbena. Dio bolesnika s COVID-19 i neurološkom simptomatologijom bio je prepoznat već na početku. Pandemija COVID-19 nedvojbeno je promijenila način rada i organizaciju medicinske zajednice. Tako su se i neurolozi susreli s različitim načinima reorganizacije bolničkog sustava liječenja neuroloških bolesnika, praćenja kroničnih neuroloških bolesnika, liječenja kroničnih bolesnika zbog pandemije te liječenja hitnih neuroloških stanja kod COVID-19 pozitivnih bolesnika. Velik dio etiolo-

gije, patogeneze i liječenja neuroloških bolesti ostaje i dalje neistražen te zahtijeva trajno praćenje i edukaciju.

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SUMMARY

COVID-19 AND NEUROLOGICAL MANIFESTATIONS

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Introduction: At the end of 2019, a new disease called COVID-19 was discovered. The disease was caused by the new coronavirus SARS-CoV-2. Due to its rapid spread, a global pandemic was soon declared by the World Health Organization (WHO). At the beginning of the pandemic, it was established that COVID-19 usually presented with respiratory symptoms but that it could also be presented with symptoms of other organs. COVID-19 can be manifested by neurological symptoms. Neurological symptoms can also occur as a complication due to COVID-19 and persist long after the disease has been overcome. *Aim:* We aimed to analyze scientific papers on neurological manifestations and complications in COVID-19 positive patients. We also wanted to highlight the possible differences in neurological diagnosis and treatment strategies. Methods: We searched MEDLINE database using the following key features: "neurological manifestations", "neurological symptoms" and "COVID-19" back to the year 2020. *Results:* According to a WHO report, 23 neurological symptoms and 14 neurological diagnoses have been described so far. One-third of hospitalized patients had neurological symptoms. Encephalopathy was the most common neurological condition in patients older than 66 years. Those patients presented with different symptoms including agitation, delirium, and consciousness disorders. According to some studies, encephalopathy was also a predictor of poor outcome. The number of cases of strokes (ischemic and hemorrhagic) was higher in COVID-19 positive patients than usual. This fact is explained by the tendency to a hypercoagulable state and proinflammatory process while having COVID-19. Also, a great number of patients have already had some risk factors (smoking, hypertension, diabetes mellitus), which contributed to the pathogenesis of stroke and also poorer outcomes. Less often neurological manifestations include neuromuscular disorders such as Guillain-Barré syndrome and facial palsy. Guillain-Barré syndrome mostly presented with sensorimotor manifestations. Other infective diseases such as meningoencephalitis occurred in rare cases. Hyposmia, anosmia, and dysgeusia occurred in most cases but resolved mostly within two months of infection. The diagnosis and treatment of neurological manifestations caused by COVID-19 do not differ from the usual diagnostic methods and treatment strategies. There is no specific drug to be used during COVID-19 infection and certain neurological diagnoses. Important information is that patients who already have certain neurodegenerative diseases and a higher degree of neurological disability may have worse outcome while having COVID-19. Also, in several neurological patients with a pre-existing neurological diagnosis, the strategy and treatment of the underlying neurological disease had to change depending on whether or not the person had COVID-19. *Conclusion:* In conclusion, during the pandemic, neurologists met with different ways to reorganize the hospital system for treatment of neurological patients, monitoring of chronic neurological patients, treatment of chronic patients due to the pandemic, and emergency neurological conditions in COVID-19 positive patients. Also, the neurologists had to organize normal functioning of neurological diagnostic methods and treatment for other patients.

Key words: neurologic manifestations, COVID-19, symptoms, treatment, complications

NEUROLOŠKO OČITOVANJE SINDROMA POST-COVID-19

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Uvod: Krajem 2019. otkrivena je nova bolest nazvana COVID-19. Bolest je uzrokovana novim koronavirusom SARS-CoV-2. Ubrzo je Svjetska zdravstvena organizacija (SZO) proglasila pandemiju. Osim dišnih simptoma uočeno je da se bolest može očitovati i neurološkom simptomatologijom te da se tijekom i nakon liječenja COVID-19 mogu javiti neurološke komplikacije. Nakon preboljenja COVID-19, neovisno o težini kliničke slike, dio bolesnika žali se na zaostale neurološke simptome. U tim slučajevima govorimo o post-COVID-19 sindromu. Za simptome koji se javljaju tjednima ili mjesecima nakon COVID-19 simptoma u literaturi su korišteni različiti termini kao što su npr. od "dugi-COVID", "post–COVID sindrom", "posljedice SARS-CoV-2 infekcije". Simptomi podrazumijevaju različita očitovanja organskih sustava koji se jave i/ili traju dulje od 4 tjedna. ***Cilj:*** Napraviti pregled trenutnih znanstvenih činjenica povezano sa sindromom post-COVID-19. ***Metode:*** Pretražili smo bazu podataka MEDLINE s ključnim riječima: post-COVID-19, neurološka očitovanja i dugi COVID-19 u vremenu od 2020. godine. ***Rezultati:*** Prema podatcima koje smo prikupili postoje četiri stadija COVID-19. Akutni COVID-19 podrazumijeva simptome i znakove bolesti koji traju do 4 tjedna. Produljeni simptomatski COVID-19 podrazumijeva simptome i znakove koji traju od 4 do12 tjedana. Post-COVID-19 sindrom podrazumijeva simptome i znakove koji se jave nakon akutne bolesti te traju dulje od 12 tjedana, a nisu objašnjeni drugom dijagnozom. Sindrom post-COVID-19 podrazumijeva znakove i simptome koji se pojavljuju tijekom ili nakon COVID-19 te traju dulje od 12 tjedana, a nisu objašnjeni drugom dijagnozom. Simptomi se mogu preklapati i varirati u intenzitetu. Dugi COVID podrazumijeva COVID-19 i sindrom post-COVID-19. Što se neuroloških post-COVID-19 očitovanja tiče, kod bolesnika su najčešće prisutni slabost i umor, mialgija, smetnje raspoloženja i smetnje spavanja. Također, u literaturi se navode i trajna glavobolja, smetnje koncentracije koje su nazvane moždanom maglom (od engl. brain fog), parestezije, poremećaj ili gubitak okusa, poremećaj ili gubitak mirisa te smetnje autonomnog živčanog sustava. Postoji nekoliko pretpostavljenih načina kojima virus dođe do središnjeg živčanog sustava: njušni, dišni i probavni. Središnji živčani sustav može biti oštećen izravno i neizravno. Moždana magla i smetnje pamćenja objašnjeni su središnjom i respiratornom hipoksijom te proupalnim odgovorom organizma. U slučaju sumnje na sindrom post-COVID-19 pri postavljanju dijagnoze uvijek treba uzeti u obzir i ostale moguće dijagnoze. U mnogim slučajevima potrebno je učiniti magnetsku rezonanciju (MR) mozga i vratne kralježnice. Ponekad je potrebno u dijagnosticiranje bolesti uključiti i ostale specijaliste. ***Zaključak:*** Sindrom post-COVID-19 može se očitovati nizom neuroloških poremećaja kao što su kognitivni simptomi, nesanica i promjene raspoloženja, disautonomija, smetnje mirisa i okusa, sindrom postintenzivne skrbi.

Ključne riječi: post-COVID-19, neurološko očitovanje, simptomi, patofiziologija, dijagnoza, liječenje

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UVOD

Krajem 2019. otkrivena je nova bolest nazvana COVID-19 (od engl. *Corona Virus Disease-2019)*. Bolest je uzrokovana infekcijom teškim akutnim respiratornim sindromom koronavirusa 2 (od engl. *Severe acute respiratory syndrome coronavirus 2*, SARS-CoV-2), a s obzirom na brzo širenje Svjetska zdravstvena organizacija (SZO) ubrzo ju je proglasila pandemijom. Klinička slika bolesti uključuje uglavnom respiratorne simptome, ali moguća su i očitovanja drugih organskih sustava. Između ostalog, bolest se može očitovati neurološkom simptomatologijom, a tijekom i nakon liječenja

COVID-19 mogu se javiti i neurološke komplikacije. Također, jedan dio bolesnika ima zaostale neurološke simptome tjednima i mjesecima nakon preboljenja COVID-19. Navedeni zaostali simptomi ne ovise o težini kliničke slike COVID-19 ili o mogućoj prethodnoj hospitalizaciji zbog liječenja. U navedenim slučajevima govorimo o sindromu post-COVID-19 (1). U ovom preglednom radu razjasnit ćemo definiciju i različita očitovanja sindroma post-COVID-19.

DEFINICIJA SINDROMA POST-COVID-19

Za različita očitovanja koja se javljaju tjednima ili mjesecima nakon simptoma COVID-19 u literaturi su korišteni različiti termini kao što su npr. "*long-COVID*", *"post–COVID siydrome*", "posljedice SARS-CoV-2 infekcije". Simptomi podrazumijevaju različita očitovanja koja se jave i/ili traju dulje od 4 tjedna. Jedno retrospektivno istraživanje na uzorku od 273 618 bolesnika proučavalo je učestalost simptoma post-COVID-19 nakon 90 i 180 dana nakon preboljenja bolesti. Simptomi su redom uključivali: smetnje disanja, opću slabost/umor, bolove u prsima, glavobolju, difuzne bolove u tijelu, probavne smetnje, bolove u mišićima, smetnje kognicije i anksioznost/depresiju.

Prema smjernicama NICE (od engl. *National Institute for health and care Excellence*) za simptome koji traju duže od 12 tjedana nakon COVID-19 predložen je termin sindrom post-COVID-19 (3,4).

Navedene smjernice NICE obuhvaćaju pregled simptomatologije COVID-19:

- Akutni COVID-19 podrazumijeva simptome i znakove bolesti u trajanju do 4 tjedna.
- Produljeni simptomatski COVID-19 podrazumijeva simptome i znakove bolesti koji se javljaju i traju u vremenu 4 do 12 tjedana.
- Sindrom post-COVID-19 podrazumijeva simptome i znakove koji se pojavljuju tijekom ili nakon bolesti te traju dulje od 12 tjedana, a nisu objašnjeni nekom drugom dijagnozom. Navedeni simptomi bolesti mogu varirati i preklapati se te mogu uključivati različite organske sustave: srčano-krvožilni, dišni, probavni, živčani, mišićno-koštani, endokrinološki, urološki, kožni, otorinolaringološki, hematološki i psihijatrijski. Također, simptomi mogu biti praćeni općim simptomima upale kao što su generalizirana bol, umor i/ili trajna vrućica. Sama dijagnoza sindroma post-COVID-19 može se razmotriti i prije 12 tjedana je u tijeku obrada moguće druge dijagnoze
- Dugi COVID-19 obuhvaća simptome koji se javljaju nakon preboljenja COVID-19 te samim time podrazumijeva termin produljeni simptomatski COVID-19 i post-COVID-19 (4,5) (tablica 1).

Tablica 1. *Predloženi kriteriji za postavljanje dijagnoze sindroma post-COVID-19*

Kriteriji
• Znakovi i simptomi koji se razvijaju tijekom ili nakon infekcije COVID-19, ali se mogu pojaviti i nakon 12 tjedana
• Česta pojava preklapajućih simptoma koji mogu s vremenom varirati • Pojava simptoma različitih organskih sustava: kardiovaskularni, respiratorni, gastointestinalni, živčani, muskuloskeletni, endokrinološki, urološki, kožni, otorinolaringološki, hematološki i psihijatrijski • Pojava općih simptoma kao što su generalizirana bol, umor i/ili trajna vrućica
• Za postavljanje dijagnoze nije nužno u povijesti bolesti imati COVID-19 potvrđen PCR testom. • Dijagnoza se može razmotriti i prije 12 tjedana, dok se još razmatra druga moguća dijagnoza

Preuzeto i modificirano prema: Carod-Artal FJ, García-Moncó JC. Post-COVID-19 syndrome: epidemiology, diagnostic criteria and pathogenic mechanisms involved. Rev Neurol 2021; 72(11): 384-396.

Nakon pojave pandemije jedan dio bolesnika se žalio na trajne neurološke simptome post-COVID-19. Prema jednom istraživanju bolesnici su se najviše žalili na kroničnu slabost i umor, mialgiju, simptome depresije i smetnje spavanja. Ostali simptomi uključivali su glavobolje slične migrenama koje često nisu povoljno odgovarale na uobičajene analgetike. Također, 38 % bolesnika žalilo se na trajne glavobolje nakon 6 mjeseci. 1/10 bolesnika imala je smetnje okusa i mirisa nakon 6 mjeseci. Dio bolesnika žalio se na varirajuće kognitivne smetnje, tzv. moždana magla (od engl."*brain fog*") (6,7). Prema najnovijim podatcima bolesnici s blažim simptomima COVID-19, koji nisu bili hospitalizirani zbog upale pluća ili hipoksije također su se žalili na neurološke simptome iz čega se može zaključiti da se neurološka post-COVID-19 očitovanja mogu javiti i nakon preboljenja blažeg COVID-19 (6). U drugom se istraživanju od 180 bolesnika više od 50 % žalilo se na jedan trajni simptom u trajanju od 125 dana. Najčešće se radilo o umoru i gubitku mirisa (24 %) (3,8). U još jednom istraživanju od 100 bolesnika, koji nisu bili hospitalizirani zbog COVID-19, od simptoma su najčešće nakon 6 tjedana zaostajali tzv. moždana magla (81 %), glavobolja (68 %), osjećaj utrnulosti (60 %), gubitak okusa (59 %), gubitak mirisa (55 %) i bolovi u mišićima (55 %) (6,9).

Unatoč navedenim primjerima teško je navesti točnu incidenciju i prevalenciju neuroloških očitovanja post-COVID-19. Razlozi za to su teškoće pri samim prospektivnim i retrospektivnim istraživanjima. Naime, ponekad je teško procijeniti radi li se samo o izoliranom simptomu ili skupini simptoma te radi li se o stvarnom simptomu ili samo o subjektivnom osjećaju pacijenta. Također, teško je procijeniti kognitivnu disfunkciju određenom mjernom ljestvicom te ustanoviti simptome putem telefonskih posjeta (5). U tablici 2 sažeta je predložena klasifikacija neuroloških simptoma post-COVID-19 (tablica 2).

Tablica 2. *Predložena klasifikacija neuroloških simptoma sindroma post-COVID-19*

Neurološke dijagnoze i simptomi	
1. Glavobolja • Tenzijska glavobolja • Kronična dnevna glavobolja	**5. Poremećaji spavanja/nesanica**
2. Moždani živci • Gubitak mirisa/poremećaj mirisa • Poremećaj okusa • Šum u uhu • Gubitak sluha/djelomični gubitak sluha • Vrtoglavica • Smetnje ravnoteže • Poremećaj fonacije	**6. Poremećaji autonomnog živčanog sustava** • Poremećaji termoregulacije • Ortostatske smetnje • Smetnje tijekom vježbanja • Sindrom posturalne ortostatske tahikardije • Ostalo
3. Mišićnoskeletni sustav • Mialgija • Slabost mišića • Kronični umor • Poremećaji pokreta • Parestezije ekstremiteta • Bol (lumbalni dio leđa, kosti i zglobovi, generalizirana bol)	**7. Kognitivne smetnje i moždana magla** • Smetnje pamćenja • Smetnje pažnje • Smetnje koncentracije • Smetnje donošena odluka • Sporije vrijeme reagiranja • Jezične smetnje
4. Poremećaji pokreta • Tremor ekstremiteta • Smetnje koordinacije	**8. Psihološke i psihijatrijske smetnje** • Anksioznost • Depresija • Posttraumatski stresni poremećaj • Ostalo

Preuzeto i modificirano prema: Carod-Artal FJ, García-Moncó JC. Post-COVID-19 syndrome: epidemiology, diagnostic criteria and pathogenic mechanisms involved. Rev Neurol 2021; 72(11): 384-396.

NEUROPATOGENEZA SARS-COV-2 INFEKCIJE

Smatra se da SARS-CoV-2 može doći do središnjeg živčanog sustava (SŽS) na nekoliko načina. Virus se veže za receptor angiotenzin-konvertirajućeg enzima 2 (ACE2) što mu omogućava ulazak u stanice. U SŽS receptor ACE2 je prisutan u krvnim žilama mozga te njušnom epitelu. S obzirom na navedeno, smatra se da virus može doći do mozga ovim putovima:

- Njušni put. Virus se veže za završetke aksona u olfaktornom području te se širi prema moždanoj kori (10)
- Hematogeni put. Otpuštanjem proupalnih citokina dolazi do oštećenja krvno-moždane barijere što dopušta virusu da dođe do mozga. Jedna od teorija je ta da virus može doći do mozga i putem pleksusa horioideusa smještenim u moždanim komorama. Periciti – stanice koje povezuju endotel s astroglijom - mogu biti mjesta replikacije virusa odakle se virus može širiti u astrocite i ostale stanice parenhima mozga (11)
- Probavni put. S obzirom na to da su receptori ACE nađeni u enterocitima, smatra se da se virus putem njih širi do vagusa i retrogradnim transportom do moždanog debla (12).

Mehanizmi neuropatogeneze COVID-19 uključuju izravna oštećenja virusa i oštećenja nastala zbog sistemskog odgovora organizma na upalu, upalu središnjeg živčanog sustava, mikrožilne tromboze i posljedično propadanje moždanog tkiva. U istraživanjima se nakon biopsije pokazalo da SARS-CoV-2 uzrokuje promjene u krvnim žilama i moždanom tkivu čime utječe na stanje krvno-moždane barijere i cerebrospinalni likvor te uzrokuje upalu neurona, glije i krvnih žila mozga. Tijekom COVID-19 dolazi do aktivacije makrofaga, neutrofila i aktivacije komplementa što dovodi do sklonosti prokoagulaciji i posljedičnom pretpostavljenom većem riziku od moždanog udara. Također, dolazi do "citokinske oluje", tj. jakog imunološkog odgovora i lučenja proupalnih citokina. Jedan od najznačajnijih je IL-6 (interleukin 6) za koji se smatra da je i prediktor za klinički lošiju prognozu. Lučenjem proupalnih citokina dolazi do dodatnog oštećenja krvno-moždane barijere i aktivacije mikroglije te daljnjeg lučenja dodatnih proupalnih citokina i samim time napredovanja proupalnog procesa u krug (13).

Mehanizmi neuropsiholoških i kognitivnih posljedica uključuju imunološki odgovor organizma na SARS-CoV-2, stres prije i tijekom infekcije te mogući virusni učinak na središnji živčani sustav. Na početku se smatralo da kognitivne smetnje mogu biti posljedica neuroinvazivnosti SARS-CoV-2, no za sada su slučajevi encefalitisa rijetki. U jednom istraživanju od 35 bolesnika s trajnim neurološkim simptomima nakon COVID-19 u usporedbi sa 44 zdrave osobe putem pozitronske emisijske tomografije (PET) pokazan je smanjeni metabolizam fluorodeoksiglukoze (FDG) u moždanoj kori. Bolesnici s trajnim simptomima pokazali su smanjeni metabolizam u području sulkusa orbitalisa i rektusa te u području olfaktornog sulkusa, girusa cingularisa, temporalnom režnju, amigdali, hipokampusu, ponsu, moždanom deblu i malom mozgu (14). Između ostalog girus cingularis odgovoran je za emocije, pamćenje i donošenje odluka, a smanjen metabolizam FDG-a u njegovom području mogao bi biti uzrok nastanka moždane magle (5,15). Još jedan od neizravnih mehanizama oštećenja je hipoksija do koje dolazi zbog respiratornog zatajenja. Tijekom hipoksije najranjivije su moždane strukture hipokampusa (koji je odgovoran za pamćenje) i mali mozak.

Što se tiče umora, smatra se da do njega dovodi nekoliko mehanizama. Umor može biti uzrokovan psihološkim čimbenicima (anksioznost, depresija, poremećaji spavanja), središnjim (poremećaji prijenosa neurotransmitera, upalni odgovor), perifernim čimbenicima (promjenama strukture mišića) (16).

Smatra se da SARS-CoV-2 može dovesti i do oštećenja autonomnog živčanog sustava. Najčešći simptomi vezani uz sindrom post-COVID-19 i autonomni živčani

sustav uključuju palpitacije, probavne smetnje, ortostatsku hipotenziju te sindrom posturalne ortostatske tahikardije (POTS). Smatra se da virus na ranije navedene načine dolazi u područje moždanog debla tzv. areje postreme gdje se nalaze središta za regulaciju disanja i krvožilnog sustava. Drugi mehanizam kojim može doći do oštećenja je taj da se u proupalnom stanju organizma luče citokini koji djeluju i na povećanje aktivnosti simpatičkog živčanog sustava (17,18). Međutim, i teorije nastanka umora i autonomne disfunkcije zahtijevaju još detaljnija ispitivanja i dokaze.

POČETNI ALGORITAM POSTUPANJA KOD SINDROMA POST-COVID-19 NEUROLOŠKIM OČITOVANJIMA

Pri početnoj evaluaciji sindroma post-COVID- 19 uvijek treba usporedno razmišljati i o diferencijalnoj dijagnostici stanja koja se mogu očitovati s glavnim vodećim simptomom. U složenijim slučajevima preporuča se multidisciplinarni pristup različitih specijalista ovisno o simptomima bolesnika.

U daljnjem tekstu bit će iznešeni početni algoritmi postupanja kod neuroloških očitovanja post-COVID-19 (tablica 3).

Tablica 3. *Početni algoritam postupanja kod sindroma post-COVID-19 s neurološkim* očitovanjem

Kognitivne smetnje
• KKS, vitamin B12, vitamin D3, TSH
• Teži oblici: HIV, RPR, vrijednosti folne kiseline i tiamina, neurofiziološko testiranje
• Neuroslikovne pretrage (MR mozga i/ili kralježnice)
Disautonomija
• KKS, elektroliti, metabolički parametri, TSH
Nesanica i smetnje raspoloženja
• KKS, TSH, status željeza
• obrada za opstruktivnu apneju kod spavanja
Anosmia/hiposmija
• Potrebno isključiti ostale respiratorne bolesti i alergije

KKS - kompletna krvna slika; TSH - tireoidni stimulirajući hormon; HIV - virus humane imunodeficijencije; RPR - rapid plasma reaginin; MR - magnetska rezonancija

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Kognitivni simptomi

Što se kognitivnih smetnji tiče bolesnici se mogu žaliti na kognitivne promjene kao što su npr. moždana magla, smanjenje koncentracije ili smetnje pamćenja. Početna dijagnostika uključuje kompletnu krvnu sliku (KKS), vitamin B12, vitamin D3, tireoidni stimulirajući hormon (TSH). U slučaju da su kod bolesnika prisutne srednje teške do teške kognitivne smetnje od laboratorijskih pretraga potrebno je učiniti: test na virus humane imunodeficijencije (HIV), brzi test na plazmatski reaginin (RPR, od engl. *rapid plasma reaginin*), vrijednosti folne kiseline i tiamina, neurofiziološko testiranje. Neuroslikovne pretrage, magnetska rezonancija (MR) mozga i/ili kralježnice potrebno je učiniti u slučaju kada je kod bolesnika bio prisutan srednje teški do teški oblik COVID-19, ako su bolesnici stariji od 50 godina ili ako imaju izolirani neurološki deficit. Važno je napomenuti da bi nalaz MR mozga/kralježnice mogao biti nejasan i nespecifičan, pogotovo ako u bolesnika postoje srčano-krvožilni čimbenici rizika.

Nesanica i promjene raspoloženja

Promjene raspoloženja i nesanica su relativno česte nakon preboljenja COVID-19. Istraživanja su pokazala da su bolesnici liječeni na intenzivnoj njezi skloni depresiji, anksioznosti i postraumatskom odgovoru. Iako su teže psihološke i psihičke posljedice prisutne nakon bolesnika koji su preboljeli teži oblik COVID-19, one se mogu javiti i nakon preboljenja blažih oblika. Smetnje prilagodbe mogu izazvati anksioznost koja posljedično može dovesti do smetnji spavanja i umora te tako u krug dolazi do poremećaja raspoloženja. Za početak se preporuča psihoterapijski pristup (npr. kognitivno bihevioralna terapija). Početna laboratorijska obrada bi trebala uključivati KKS, TSH, status željeza, obradu za opstruktivnu apneju u snu. U slučaju potrebe za lijekovima, kod nesanice se preporuča melatonin, a u slučaju potrebe za antidepresivima preporučuju se mirtazapin, gabapentin ili amitriptilin. Ovi antidepresivi se mogu propisati bolesnicima koji se žale na parestezije i učestale glavobolje.

Disautonomija

Disautonomija, nespecifične vertiginozne tegobe ili palpitacije mogu se javiti kod dijela bolesnika koji se oporavljaju od COVID-19, a njihova učestalost je za sada nepoznata. Početna obrada uključuje KKS, metaboličke parametre, TSH. Potrebno je fizikalnim pregledom i mjerenjem krvnog tlaka odrediti ima li bolesnik ortostatsku hipotenziju te dalje odrediti potrebu za tilt-up table testom. Liječenje bi se trebalo temeljiti na dovoljnom unosu vode, povećanju unosa soli i po potrebi nošenja kompresivnih čarapa. U slučaju POST mogu se primijeniti midodrin, fludrokortizon ili beta blokatori. Ako simptomi potraju, potreban je pregled kardiologa i/ili multidisciplinarnog tima.

Smetnje mirisa i okusa

Smetnje mirisa obično se spontano oporave unutar 7 do 10 dana. Uvijek se treba voditi mišlju da smetnje mirisa mogu uzrokovati i druge respiratorne bolesti te

alergije zbog čega ih je pri evaluaciji potrebno isključiti. Kod većine bolesnika unutar 2 mjeseca dođe do oporavka smetnji mirisa, a ako smetnje traju dulje, potrebno je u liječenje uključiti specijalista ORL (3,19).

Sindrom postintenzivne skrbi

Osim ranije navedenih pojmova, u literaturi se opisuje tzv.sindrom postintenzivne skrbi (PICS, engl. *postintensive care syndrome*) koji uključuje simptome generalizirane slabosti, smetnje pamćenja i koncentracije, depresiju, anksioznost i postraumatski stresni poremećaj. PICS je bio poznat i prije COVID-19, ali njegova točna incidencija je nepoznata. Smatra se da kod bolesnika sa sindromom post-COVID-19 iznosi oko 60 % vezano za kognitivne i psihološke simptome te 25 do 60 % vezano za neuromišićne smetnje. Također, smatra se da PICS može trajati više godina te samim time otežavati povrat k svakodnevici (5,20).

Bolesnici koji prebole sindrom akutnog respiratornog distresa i teže oblike COVID-19 kasnije mogu razviti simptome kronične boli. Također, smatra se da do postraumatskog stresnog poremećaja može doći kod bolesnika liječenih na intenzivnoj njezi, ali i kod obitelji bolesnika. Navedeno je pripisano dugotrajnoj razdvojenosti i zabrani posjeta tijekom pandemije (5,21).

ZAKLJUČAK

Sindrom post-COVID-19 je pojam s kojim ćemo se kao znanstvena zajednica u budućnosti sigurno susretati. Saznanja o neuropatogenezi infekcije SARS-CoV-2 te COVID-19 će se sigurno u budućnosti još povećavati. Samim time, mijenjat će se dijagnostički pristup i način liječenja sindroma post-COVID-19. Važno je odmah na početku kod bolesnika uočiti subjektivne tegobe, učiniti dijagnostičku obradu te pokušati prikazati objektivno simptome na koje se bolesnik žali. Također, važno je tijekom utvrđivanja sindroma post-COVID-19 usporedno provoditi i diferencijalnu dijagnostiku kako bi se prepoznala moguća druga dijagnoza.

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SUMMARY

NEUROLOGICAL MANIFESTATIONS OF POST-COVID-19 SYNDROME

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Introduction: At the end of 2019, a new disease named COVID-19 was discovered. The disease is caused by the new coronavirus SARS-CoV-2. A global pandemic was soon declared by the World Health Organization (WHO). The disease mostly presents by respiratory simptoms. It can also be presented by neurological symptoms and neurological complications may occur during and after treatment of COVID-19. Regardless of COVID-19 symptoms, some patients complain of persistent symptoms. In such cases, we talk of so-called post-COVID-19 syndrome. Various terms have been used in the literature for the spectrum of symptoms that occur weeks or months after COVID-19 symptoms, such as "long-COVID", "post-COVID syndrome", "consequences of SARS-CoV-2 infection". Symptoms include various manifestations of organ systems that occur and/or last longer than 4 weeks. *Aim:* Our aim was to analyze scientific papers on the topic of post-COVID-19 syndrome. We also wanted to describe the proposed pathophysiological mechanisms of post-COVID-19 syndrome and highlight the possible diagnostic algorithm. *Methods:* We searched the MEDLINE database using the following key features:„post-COVID-19“, „neurological manifestations“ and „long-COVID-19“ back to the year 2020. *Results:* Accoding to our findings, there are several stages of COVID-19. Acute COVID-19 includes acute disease that lasts for 4 weeks. Ongoing symptomatic COVID-19 includes symptoms that last for 4 to 12 weeks. Post-COVID-19 syndrome involves signs and symptoms that occur during or after COVID-19 infection, last for more than 12 weeks, and cannot be explained by another diagnosis. Symptoms can affect different organ systems and may overlap and fluctuate in intensity. The term „long COVID-19“ describes ongoing symptomatic COVID-19 and post-COVID-19 syndrome. Neurological manifestations of post-COVID-19 syndrome include weakness and fatigue, myalgia, mood disorders, and sleep disturbances. Persistent headaches, impaired concentration ("brain fog"), paresthesias, dysgeusia, hyposmia and disorders of the autonomic nervous system have also been reported in the literature. There are several proposed routes for SARS-CoV-2 to reach the central nervosu system: olfactory, hematogenous and gastointestinal. The central nervous system can be damaged directly and indirectly. "Brain fog" and memory difficulties are explained by central and respiratory hypoxia (especially), as well as proinflammatory body response. In case of post-COVID-19 neurolgical symptoms, there always have to be a diagnostic approach that considers and searches for alternative diagnosis in the patient context. Basic laboratory workup with possible later extension has to be done. Also, proper neuroimaging methods, mostly brain and/or spine magnetic resonance imaging, should be performed. In some cases, a multidisciplinary approach may be required. *Conclusion:* We have made a review of neurological post-COVID-19 symptoms and their pathophysiological mechanism with the initial care proposed. We would also like to note that there still are numerous data on the topic that will certainly be revealed with time.

Key words: post-COVID-19, neurological manifestations, symptoms, pathophysiology, diagnosis, treatment

LIJEČENJE ANEMIJE U KRONIČNOJ BUBREŽNOJ BOLESTI 2021.

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Anemija kronične bubrežne bolesti (KBB) je multifaktorska i uključuje poremećaj željeza (apsolutni ili funkcionalni manjak), nedostatnu proizvodnju eritropoietina, gubitak krvi, stanje kronične inflamacije s povišenim hepcidinom i čimbenike vezane uz prisutno kronično stanje hipoksije (*hypoxia-inducible factor,* HIF). Temelj današnjeg liječenja anemije KBB čini primjena eritropoietina uz liječenje preparatima željeza, no više razine hemoglobina (Hb >130 g/L) povezane su s povišenim rizikom neželjenih kardiovaskularnih i cerebrovaskularnih događaja, trombozama vaskularnih pristupa kao i činjenici progresije u završni stadij KBB-a i ukupne smrtnosti. Liječenje anemije u bolesnika s KBB temelji se na postojećim smjernicama KDIGO (*Kidney Disease: Improving Global Outcomes*) iz 2012. godine. Hrvatske smjernice za liječenje anemije KBB-a objavljene su 2014. godine. Od tada do danas, temeljem brojnih istraživanja i kliničkom praksom došlo je do novih izmjena u suvremenom shvaćanju liječenja anemije KBB-a. Hipoksija-inducibilni faktori-inhibitori domene prolil hidroksilaze (HIF-PHI) nova su klasa oralno primijenjenih lijekova za liječenje anemije KBB-a, aktivirajući put osjetljivosti na razinu kisika HIF-a. Dokazana je njihova učinkovitost u prekliničkim i kliničkim studijama u korekciji i održavanju razine Hb u predijaliznih/dijaliznih bolesnika smanjujući razinu hepcidina i modulirajući metabolizam željeza, a smatra se da imaju i učinke izvan eritropoeze. Slijedom navedenog, ptikazujemo osvrt i preporuke za liječenje anemije KBB-a prilagođene trenutnim spoznajama 2021. godine.

Ključne riječi: anemija, kronična bubrežna bolest, lijekovi za stimulaciju eritropoeze, željezo, hepcidin, hipoksija, inducibilni faktori (HIF)

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UVOD

Kronična bubrežna bolest (KBB) i pridružena joj anemija najčešće se otkrivaju prekasno i u poodmaklom stadiju bolesti, često na tercijarnoj razini zdrastvene zaštite. Internacionalne studije ukazuju na visoku prevalenciju anemije koja progredira s pogoršanjem KBB-a koja poprima pandemijske razmjere, a definirana je sniženom razinom hemoglobina (Hb) <12g/dl u 30 %, 46 % i 72 % u bolesnika sa stadijem KBB G3B, G4 i G5 koji nisu na dijalizi (ND) (1)

S obzirom na javnozdravstveno značenje, neophodno je povećati svijest o toj bolesti te potaknuti skrining na ranu dijagnozu i pravovremeno liječenje već na razini primarne razine zdravstvene zaštite. Liječenje anemije u bolesnika s KBB temelji se na postojećim smjernicama KDIGO (*Kidney Disease: Improving Global Outcomes*) iz 2012. te skupine ERBP ((*European Renal Best Practice*), koja je objavila osvrt na smjernice KDIGO iz 2013 (2,3). Posljednja inačica hrvatskih smjernica vezanih uz liječenje anemije KBB-a objavljena je 2014. godine (4). U njima su dane jasne preporuke temeljem tadašnjih spoznaja o važnosti liječenja anemije u KBB, u ukupno 4 poglavlja: Poglavlje 1 se odnosi na dijagnozu i evaluaciju anemije u KBB s preporukom učestalosti pretraga koje su danas od iznimne važnosti u svakodnevici Covid pandemije i nerijetko potrebe telemedicinskog praćenja a to je 1 x godišnje praćenje u bolesnika s KBB stadij G3 a i b, 2 x godišnje u KBB stadij G4-G5 u predijaliznoj fazi odnosno KBB-ND, svaka 3 mj u KBB stadij 5HD (bolesnici na hemodijalizi, KBB-DD) i 5PD (bolesnici na peritonejskoj dijalizi). Poglavlje 2. se

odnosi na liječenje anemije KBBa željezom i u njemu je jasno navedna ciljna razina vrijednosti Hb između 100-120 g/l, s jasnim individualnim pristupom za liječenje i lijekovima koji stimuliraju eritropoezu (LSE) s posebnim osvrtom na posebne skupine bolesnika (s anginom pektoris i dijabetičare s asimptomatskom anginom pektoris,..). Navedena je jasna preporuka praćenja statusa željeza svakih 3 mjeseca tijekom liječenja LSE, a češće u slučaju promjene doze LSE te praćenja učinka intravenske terapije željezom. Navedena je jasna indikacija kada se ne primjenjuje liječenje intravenskim željezom (stanje sistemske infekcije, feritin>500ng/ml i TSAT> 30%). U poglavlju 3 je detaljno dana preporula o načinu primjene LSE i to subkutana primjena u bolesnika na dijalizi (DD) i to peritonejskoj dijalizi (PD) i KBB-ND bolesnika s anemijom, iv. primjena na programu hemodijaliznih bolesnika (HD) s oprezom kod primjene LSE u visokorizičnoj populaciji (periferna arterijska bolest, moždani udar, asimptomatska ishemijska bolest srca, maligna bolest) u koje je potrebno približavanje donjoj granici preporučene razine Hb (100-120 g/L). U poglavlju 4 i potrebi za transfuzijom krvi jasno su navedene indikacije s posebnim osvrtom na perioperacijsko zbrinjavanje bolesnika s anemijom u KBB i na skupine s rizikom za primjenu LSE.

Od tada 2014. godine do danas, temeljem istraživanja i kliničkom praksom, došlo je do brojnih novih izmjena u suvremenom shvaćanju liječenja anemije KBB povrh ere LSE koji omogućuju bolesnicima liječenja anemije uz postizanje stabilne željene razine Hb bez fluktuacija Hb na potpuno novi način djelovanja putem dvije nove skupine lijekova što predstavlja revoluciju u pristupu liječenja anemije u KBB-u posebice što svjedočimo da je anemija u KBB-u prisutna u 60 % ND i 93 % DD bolesnika (5-8).

PROŠLOST-SADAŠNJOST LIJEČENJA ANEMIJE I POSTOJEĆI PROBLEMI

Anemija je često stanje u bolesnika s KBB-om i udružena je sa značajno povišenim rizikom kardiovaskularnih neželjenih događaja i sniženom kvalitetom života, a poznato je da pravovremeno liječenje anemije može usporiti daljnje napredovanje KBB-a (8-11).

Anemija KBB-a se primarno smatrala samo uzrokovana nedostatkom željeza, potom kao jednostavni poremećaj uslijed manjka eritropoietina zbog oštećenja bubrežne funkcije/tkiva i gubitka stanica koje produciraju eritropoietin u bubrezima, no danas je poznata činjenica kako se radi o mnogo složenijem procesu s kroničnim inflamatornim stanjem (5,10).

Do danas kliničke smjernice za liječenje anemije u KBB primarno se vežu za postizanje ciljne vrijednosti Hb 100-120g/l, a u cilju smanjenja potrebe za transfuzijama krvi kod bolesnika s teškom anemijom (Hb<90g/L) kao i omogućavanje bolje kvalitete života (2-4).

Anemija u KBB-u je posljedica disregulirane homeostaze željeza, kao i smanjenog preživljenje crvenih krvnih stanica, stoga je dugogodišnji pristup početnog riješavanja anemije u KBB razumljiv.

Primjena željeza kao jednog od uzroka anemije KBBa je jasno definirana: intravenozna primjena željeza ovisi o težini nedostatka željeza, prijašnjem odgovoru i nuspojavama pri terapiji željezom, i.v. primjena željeza po obrascu visoka/ kratka doza indicirana je u bolesnika na hemodijalizi (KBB-DD). Parenteralna (iv. infuzija) primjena željeza kontraindicirana je u bolesnika s aktivnom infekcijom, a smjernice za liječenje transplantiranih bolesnika s KBB-om iste su kao smjernice za liječenje anemije KBB-ND bolesnika (11). Dodatni problem je što višak željeza može dovesti do stvaranja reaktivnih vrsta kisika, što može oštetiti mnoge stanične komponente, stoga je balans liječenja iznimno važan. Realnost svakodnevice i jedan od osnovnih problema je, a što su pokazala i dodatna istraživanja da se još uvijek danas nedostatno liječi anemija KBB-a s deficitom željeza unatoč jasnim preporukama parenteralne primjene iv. željeza a radi bolje učinkovitosti i sniženja kardiovaskularnih incidenata posebno u bolesnika na hemodijalizi (12,13). Razlog je najčešće problem sigurnosti parenteralne primjene željeza s mogućim razvojem (iako rijetkih) hipersenzitivnih ozbiljnih neželjenih štetnih događaja. Bolesnici s KBB imaju značajne dodatne čimbenike koji doprinose rezistenciji u sadašnjem liječenju anemije koja je učestalija i u ranijem stupnju KBB-a kod bolesnika posebno s dijabetesom zbog kroničnog inflamatornog odgovora na koji nije moguće utjecati današnjom terapijom anemije KBB-a te neučinkovitosti primjene terapije željezom.

Razmatrajući studije s primjenom eritropoietina nailazimo na probleme: Iako je liječenje ***lijekovima koji stimuliraju eritropoezu (LSE)*** u početku bilo iznimno obećavajuće, te je postignuto značajno smanjenje transfuzijskog liječenja anemije (problem politransfundiranih bolesnika i povišene senzibilizacije) i omogućena adekvatna priprema bolesnika za transplantacijsko liječenje posebno u preemptivnom transplantacijskom programu te je stoga učinkovito u dijela bolesnika s anemijom KBB-a koji održavaju vrijednosti unutar zadanog raspona (Hb 100-120g/L), na globalnoj razini nije dokazano očekivano smanjenje smrtnosti (10). Ranije studije (npr. CHOIR iz 2008 godine) s LSE pokazale su da je potpuni ispravak anemije KBBa s postizanjem razine Hb > 130g/L povezan sa značajnim neželjenim kardiovaskularnim kliničkim događajima (14).

Dodatni problem s primjenom lijekova iz LSE je da dio bolesnika nije imao nikakav učinak na porast razine Hb i nije bilo jasno radi li se pridruženim komorbiditetnim stanjima ili toksičnosti primjene LSE (hiporesponzivnost) (15).

Postaje jasno poslijednjih godina da dio bolesnika unatoč ispravku manjka željeza i primjeni LSE ne uspijeva postići željenu stabilizaciju razine Hb a većinom se radi o bolesnicima sa šećernom bolesti, kardiorenalnom sindromu odnosno pridruženim komorbiditetnim stanjima koji predstavljaju većinu današnje populacije s anemijom u KBB-u (15).

Stoga je razumno bilo težiti pronalasku novih lijekova obzirom na multifaktorijalni uzrok anemije u KBB u podlozi koje je kronična inflamacija s poremećajem željeza (apsolutni ili funkcionalni manjak) kao i nedostatna proizvodnja eritropoietina i rezistencija na liječenje LSE s centralnom ulogom hepcidina i novim igrača vezanih uz stanje kronične hipoksije (16-18).

BUDUĆNOST LIJEČENJA ANEMIJE

Posljednjih godina utvrđeno je da anemiji u KBB najviše doprinose povišena razina hepcidina koji blokira apsorpciju željeza iz crijeva (stoga peroralna terapija željezom ne može biti adekvatna u većine bolesnika s anemijom KBB-a) i čimbenici indukcije hipoksije (hypoxia-inducible factor, HIF) koji imaju mnogostruke značajke (10).

Hepcidin je peptid od 25 aminokiselina, koji se proizvodi u jetri a ima ključnu ulogu u regulaciji razine željeza primarno onemogućavajući prekomjerno nakupljanje, regulirajući eritropoezu i stanje upalnog odgovora (16). Važan je regulator dostupnosti željeza koji dovodi do smanjenog transporta željeza i povećane sekvestracije željeza. Regulacija hepcidina posredovana je razinama željeza u plazmi i jetri, potrebom za eritropoezom (Epo) i upalnim stanjem. U normalnim uvjetima prepunim željeza, hepcidin se veže na feroportin (FPN)-izvoznik željeza koji je potreban za oslobađanje željeza iz enterocita, makrofaga i hepatocita u plazmu ili izvanstanični prostor, te uzrokuje njegovu razgradnju, što dovodi do zadržavanja unutarstaničnog željeza. Proizvodnja hepcidina regulirana je na transkripcijskoj razini putem gena za hepcidin (antimikrobni peptid -*HAMP*), koji kodira hepcidin, a reguliran je koštanim morfogenetskim proteinom (BMP) koji se veže za receptore tipa I i II BMP-a. Upalni citokin, interleukin-6, izravno se veže na *HAMP* promotor, čime se potiče ekspresija hepcidina u uvjetima upale, koji veže FPN na površini makrofaga i enterocita, što rezultira internalizacijom i naknadnom degradacijom FPN-a, čime se smanjuje izvoz željeza u cirkulaciju, ograničavajući dostupnost željeza za ključne biološke procese, uključujući eritropoezu (16,19).

Apsolutni nedostatak željeza nastaje kada se željezo iscrpi iz tijela, kao što je gubitak krvi. Nasuprot tome, nedostatak funkcionalnog željeza je stanje u kojem su ukupne zalihe željeza dovoljne, ali željezo nije učinkovito mobilizirano iz rezerva uskladištenja, što se javlja u uvjetima kronične upale čije je obilježje povišena razina hepcidina ili kada se eritropoeza stimulira u velikom, suprafiziološkom stupnju, kao što je to slučaj tijekom liječenja lijekovima LSE (20,21). Smanjenje razine hepcidina u prisutnosti hipoksije i/ili ograničenja željeza omogućuje veću dostupnost željeza za eritropoezu. Izlučivanje hepcidina se smanjuje kako se povećava stupanj KBB-a, dok se proizvodnja hepcidina povećava u upalnim stanjima poput KBB-a. Stoga je KBB stanje kronične inflamacije, gdje je razina hepcidina trajno povišena. Potvrđen je i dodatni *učinak inhibitora SGLT2 u liječenju anemije bolesnika s dijabetesom i KBB-om djelujući na sniženje razine hepcidina* svojim pleomorfnim dodatnim učincima povrh regulacije glikemije (17). Temeljem studije Ghanima i suradnika iz 2020 godine liječenje dapagliflozinom značajno je smanjilo koncentraciju hepcidina i feritina u cirkulaciji bolesnika a uzrokovalo je značajno povećanje razine inhibitora hepcidina, eritroferona uz prolazno povećanje eritropoietina (17). Dodatno je uočeno da liječenje dapagliflozinom povećava razinu transferina u plazmi i ekspresiju transferinskih receptora u mononuklearnim stanicama ispitanika, bez promjene u ekspresiji staničnog transportera željeza, feroportina. Uočeno je da dolazi i do smanjenja ekspresije faktora-1alfa izazvano hipoksijem u mononuklearnim stanicama, uz povećanje ekspresije njegovog infibitora, prolil hidroksilaze-2 uz zaključak da liječenje dapagliflozinom osim odlične regulacije dijabetesa i postizanja ciljne razine HbA1c dovodi do povećanje eritropoeze supresijom hepcidina i modulacijom ostalih regulatornih proteina koji utječu na metabolizam željeza (17).

Lijekovi koji djeluju modulirajući aktivnost hepcidina (*antagonisti ili inhibitori hepcidina*) u budućnosti će zasigurno utjecati na ishode liječenja anemije u KBB i omogućiti dostupnost željeza za eritropoezu. Nekoliko hepcidinskih antagonista je u razvoju za liječenje anemije KBB-a, od kojih je obećavajući polietilen glikoliran antikalin protein (PRS-080#22) koji se veže i antagonizira hepcidin. U kliničkom ispitivanju faze 1 u bolesnika s anemijom i KBB-DD, povećano serumsko željezo i TSAT te smanjena razina slobodnog hepcidina uočeni su nakon jednog tretmana PRS-080#22 koji se dobro podnosio i u bolesnika s KBB-om kao i kod zdravih dobrovoljaca (22).

Inhibitori HIF-PH

Nekoliko novih terapija anemije KBB-a je iz faze istraživanja danas prešlo u klinički primjenu.

Dobro je poznata činjenica da u stanju hipoksije dolazi do povećanja eritrocita koje je posredovano hormonom Epo. Molekularni mehanizmi regulacije indukcije Epo u stanjima hipoksije s otkićem regulatorne sekvence Epo gena za koji se pokazalo da veže nuklearni faktor hipoksije naziva HIF-1 i koji je od krucijalne važnosti za razumijevanje hipoksije, otvorio je put istraživanja u tome smjeru i omogućio novi pogled na shvaćanje anemije KBBa i potencijalne terapijske smjerove. HIF je heterodimerni faktor transkripcije s tri podjedinice koji je reguliran HIF-prolil hidroksilazom (PH), koja uzrokuje razgradnju u uvjetima prepunim kisika. U hipoksičnim uvjetima, HIF-α regulira gene koji kodiraju EPO i proteine odgovorne za transport željeza, kao što je feroportin, čime se olakšava eritropoeza i korištenje željeza. Stabilizacija HIF-a inhibitorima HIF- PH jedna je od strategija za povećanje ekspresije EPO- a u bubregu i liječenja anemije KBB-a (22-24).

Svi do sada istraženi inhibitori HIF-PH pokazali su učinke snižavanja razine hepcidina. Naime HIF neizravno smanjuje ekspresiju *HAMP-a*, gena za kodiranja hepcidina, indukcijom eritropoeze, a HIF također modulira homeostazu željeza regulacijom gena (24,25).

U randomiziranim istraživanjima te meta analizama obuhvaćeno je 6 inhibitora HIF-PH.

ROXADUSTAT

U randomiziranom, dvostruko slijepom ispitivanju faze 3 bolesnika s KBB-ND, veća smanjenja razine hepcidina uočena su u skupini liječenih roxadustatom u odnosu na placebo. Razine željeza u serumu bile su stabilne i slične u obje skupine, dok su se transferin i TIBC povećali, a feritin smanjio u skupini roxadustata (26). Slično tome, u randomiziranom, otvorenom ispitivanju faze 3 u bolesnika s KBB-DD, veće smanjenje razine hepcidina uočena su u onih liječenih roxadustatom u usporedbi s epoetinom alfa. Razine željeza u serumu bile su stabilne, a razina transferina povećana, dok se TSAT smanjio u skupini na roxadustatu (27).

DAPRODUSTAT/ MOLIDOSTAT/ VADADUSTAT/ ENARODUSTAT/ DESIDUSTAT

Podaci ispitivanja za ostale HIF-PH inhibitore, uključujući daprodustat, molidustat, vadadustat, enarodustat i desidustat, u skladu su s nalazima dobivenim za roxadustat. U bolesnika s KBB-ND, liječenje navedenim HIF-PH inhibitorima dovelo je do povećanja razine Hb, TIBC i/ili koncentracije retikulocita, kao i do smanjenja hepcidina, feritina, serumskog željeza i/ili TSAT-a (28-32). Slično tome, u bolesnika na dijalizi koji su prethodno liječeni s LSE-e a potom daprodustatom ili vadadustatom razine Hb su ostale stabilne ili povećane, dok su se hepcidin, feritin i/ili TSAT smanjili, a TIBC povećao (33, 34). U randomiziranom, otvorenom ispitivanju faze 2b u bolesnika koji su primili molidustat i suplementaciju željeza, razine hepcidina, TSAT-a i TIBC-a ostale su stabilne, dok se feritin smanjio a koncentracija željeza se povećala. U bolesnika koji su primali molidustat, ali bez suplementacije željezom, hepcidin i feritin su se smanjili, dok su se koncentracija željeza i TIBC povećali, a TSAT je ostao stabilan (31).

DJELOTVORNOST INHIBITORA HIF-PH

Analiza objavljena 2021.godine koja je uključivala meta analizu 12 istraživanja faze 2 i 3 randomizirana istraživanja učinkovitosti djelovanja inhibitora HIF-PH u bolesnika koji nisu na dijalizi (KBB-ND) u odnosu na placebo pokazala je slijedeće: skupina koja je aktivno liječena stabilizatorima HIF-a pokazala je statistički značajne promjene razine TSAT% (-4.51), feritina (-47.29 ng/ml), hepcidina (-0.94 ng/ ml), uz održan TIBC (+9.15 mg/ dl), bez promjena u razini željeza u serumu u odnosu na komparativnu skupinu ispitanika (35).

Druga meta-analiza 15 istraživanja faze 2 i 3 pokazala je značajno sniženje razine feritina ($P < 0.01$) u bolesnika na dijalizi u odnosu na kontrolnu skupinu, no ne i kod bolesnika s KBB-ND (P ¼ 0.11) (36). Sniženje razine hepcidina ukupno za sve inhibitore HIF-PH u odnosu na kontrolu za bolesnike na dijalizi nije bilo značajno (P ¼ 0.15) no dokazana je statistički značajna razlika za bolesnike koji su liječeni roxadustat-om ($P < 0.01$). Metanaliza 19 studija učinkovitosti liječenja u bolesnika s KBB-ND pokazala je značajno sniženje razine hepcidina u odnosu na kontrolu u svih 6 skupina ispitivanih HIF-PHIs ($P < 0.05$) uz značajan porast razine Hb demonstrirajući neinferiornost u odnosu na LSE (37).

OSVRT NA NAJVAŽNIJE STUDIJE FAZE 3 KLINIČKIH ISTRAŽIVANJA

Na globalnoj razini navesti ćemo samo najveća istraživanja vezana uz najveći broj ispitanika koji su liječeni roxadustatom i vadadustatom. U fazi 3 istraživanja

s roxadustatom danas postoji 8 studija, 4 s KBB-ND bolesnicima (Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis (ALPS), A Study of FG-4592 for the Treatment of Anemia in Chronic Kidney Disease Patients Not Receiving Dialysis (ANDES), and Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, Not on Dialysis (OLYMPUS) u usporedbi s placebo kontrolom; Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa (DOLOMITES) u usporedbi s LSE kao kontrolom skupinom) uz 4 studije u bolesnika s KBB-DD (Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients (HIMALAYAS), Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, on Dialysis (ROCKIES), and Evaluation of Efficacy and Safety of Roxadustat in the Treatment of Anemia in Stable Dialysis Subjects (SIERRAS] u usporedbi s kontrolom na epoetinu, i Roxadustat in the Treatment of Anemia in End Stage Renal Disease Patients on Stable Dialysis (PYRENEES) u usporedbi s epoetinom ili darbopoetinom) (10). Rezultati studija su objavljeni 2021. godine uz dokazanu učinkovitost nove skupine lijekova, smanjenje potrebe za transfuzijama za 63 % uz dobar sigurnosni profil s obzirom da je hiperkalijemija bila prisutna u 10.9 % ispitanika na roksadustatu u odnosu na 7.1 % u kontrolnoj skupini (38,39)

Vadadustat je u fazi 3 kliničkih istraživanja na globalnoj razini obuhvatio 2 velika programa. Prvi je za bolesnike s KBB-DD: Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects with Dialysis-dependent CKD (INNO2VATE) (40). Drugi je za bolesnike s KBB-ND: Efficacy and Safety Study to Evaluate Vadadust for the Correction of Anemia in Subjects with Nondialysis-dependent CKD (PRO2TECT) u kojima je dokazana neinferiornost vadadustata u odnosu na darbopoetin (41)

Daprodustat je u fazi 3 kliničkih istraživanja obuhvatio 5 sudija s KBB bolesnicima: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat (ASCEND) studija, uključujući bolesnike s KBB-ND, KBB-DD, uzimajući u obzir kvalitetu života te različito doziranje lijeka s dokazanom učinkovitosti (42).

Iako je do sada ukupno 6 inhibitora HIF-PH istraživano u liječenju anemije KBB-a, tri su odobrena za daljnju kliničku primjenu u svijetu.

Roxadustat je dobio regulatorno odobrenje u Kini za liječenje anemije KBB-a u predijaliznih kao i dijaliznih bolesnika s KBB-ND i KBB-DD (43).

U Japanu je roxadustat odobren za bolesnike s anemijom koji se liječe dijalizom (KBB-DD) a vadadustat i daprodustat odobreni su za primjenu u bolesnika s KBB-DD i KBB-ND (44).

DISKUSIJA

Današnje liječenje anemije KBB-a može poremetiti homeostazu željeza uslijed često funkcionalnog nedostatka željeza a i samo liječenje željezom može dodatno povećati razinu hepcidina koji je ključan za anemiju u KBB (20,21).

Nove mogućnosti liječenja anemije KBB-a usmjerene su na druge mehanizme kao što su HIF-PH inhibitori, koji omogućuju povećanu aktivnost HIF puta, poboljšanjem homeostaze željeza uslijed smanjenja razine hepcidina, povećanjem apsorpcije željeza dodatnim reguliranjem duodenalnog citokroma B te povećanjem transporta željeza dodatnom regulacijom transferina i transferinskog receptora (24,26-34). Hepcidin antagonisti koji su u razvoju izravno ciljaju hepcidin ili komponente njegovog ekspresijskog puta za povećanje dostupnog željeza u bolesnika s anemijom KBB-a (22). Lijekovi iz skupine HIF-PHI aktiviraju put osjetljivosti razine kisika HIF i pokazali su učinkovitost u prekliničkim i kliničkim studijama u korekciji i održavanju razine Hb u liječenju anemije KBB-a (35-39.) Liječenjem lijekovima iz skupine HIF-PHI smanjujemo razinu hepcidina i moduliramo metabolizam željeza, osiguravajući povećanje ukupnog kapaciteta vezanja željeza i razine transferina, smanjujući potrebe primjene željeza, a smatra se da imaju i učinke izvan eritropoeze (25).

Lijekovi iz skupine HIF stabilizatora pokazali su dobar učinak liječenja anemije u slu čaju neadekvatnog odgovora na liječenje LSE, stoga je u budućnosti indicirano primijeniti HIF stabilizatore u slučaju upale, kao i neadekvatnog odgovora uz liječenje LSE (hiporesponzivni i rezistentni bolesnici na liječenje LSE). Posebne skupine bolesnika s neodgovarajućim odgovorom na sadašnje liječenje LSE trebale bi obuhvatiti pacijente s teško liječivom anemijom KBB uslijed kronične inflamacije najčešće izraženo kod bolesnika s dijabetesom, kardiorenalnog sindroma (KRS), te u skupini transplantiranih bolesnika s KBB, obuhvaćajući upravo one vulnerabilne skupine bolesnika koje sadašnjim liječenjem anemije ne mogu postići ciljne vrijednosti Hb.

Također treba razmišljati i o problemu polifarmacije kod bolenika s KBB te primijeniti one lijekove koji su pokazali učinkovitost i neinferiornost u odnosu na sadašnje liječenje anemije u KBB a primjenjuju se oralno

i nekoliko puta tjedno, misleći prije svega na roxadustat. Zbog različitosti u farmakokinetici za HIF-PH inhibitore, roxadustat se primjenjuje 3x tjedno, dok ostali imaju primjenu jednom dnevno (vadadustat, daprodustat, enarodustat, desidustat, molidustat) (25).

U budućnosti liječenja anemije u KBB najviše obećava primjena upravo ove skupine lijekova, stabilizatora HIF-a koji stimuliraju eritropoezu endogenim putem, reguliraju metabolizam željeza te imaju učinak na sniženje hepcidina, gdje postoje jasne preporuke njihove primjene u Kini i Japanu, no još uvijek su nedostupni u svakodnevnoj praksi zbrinjavanja nefroloških bolesnika unatoč dokazane učinkovitosti i neinferiornosti u odnosu na LSE (45,46).

ZAKLJUČAK

Osnova za nove preporuke liječenja anemije u KBB-u, temelji se na novim istraživanjima i randomiziranim studijama proteklih godina vezanim primarno za lijekove iz skupine inhibitora HIFa, a koje su pokazale sigurnost i učinkovitost liječenja anemije KBB-a u predijaliznih i dijaliznih bolesnika. Stoga postoji veliki potencijal i u Hrvatskoj za uvođenje nove terapije u redovito zbrinjavanje svakodnevice izazova liječenja sve većeg broja bolesnika s anemijom KBB-a. Nove spoznaje nameću potrebu i izrade novih smjernica za liječenje anemije 2021.godine u Hrvatskoj.

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SUMMARY

TREATMENT OF ANEMIA IN CHRONIC KIDNEY DISEASE 2021.

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Multiple factors are involved in the pathogenesis of anemia in chronic kidney disease (CKD), including iron deficiency, inadequate production of erythropoietin (Epo), hepcidin, and hypoxia-inducible factors (HIFs). Renal anemia is the result of CKD and deteriorates with disease progression. Erythropoiesis-stimulating agents administered either subcutaneously (sc.) or intravenously (iv.), along with iron therapy, are currently the cornerstones for treating anemia, but higher hemoglobin (Hb >130 g/L) increases the risk of cardiovascular and cerebrovascular events, vascular access thrombosis, progression to end-stage renal disease, and overall mortality. Treatment of anemia in patients with CKD is based on current guidelines. The latest version of Croatian guidelines for anemia was published in 2014. Since then, on the basis of research and clinical practice, there have been numerous changes in modern understanding the treatment of anemia in CKD. Hypoxia-inducible factor-prolyl hydroxylase domain inhibitors (HIF-PHIs) are a new class of orally administered drugs for the treatment of anemia in CKD. HIF-PHIs activate the HIF oxygen-sensing pathway and are efficacious in correcting and maintaining Hb, reduce hepcidin and modulate iron metabolism, and are predicted to have effects beyond erythropoiesis. Consequently, we hereby publish a review on the recent recommendations for treating anemia in CKD 2021.

Key words: anemia, chronic kidney disease, erythropoiesis stimulating agents, iron, hepcidin, hypoxia-inducible factors

Acta Med Croatica, 75 (2021) 303-307 *Proffesional Paper*

PATIENTS REFERRED TO NEPHROLOGY SPECIALIST WITH INCOMPLETE DIAGNOSTIC WORKUP – HOW BIG IS THE PROBLEM?

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In daily work, we notice an increasing number of patients referred to a nephrologist without diagnostic tests necessary for proper assessment and treatment plan. Our aim was to show how many patients are referred to a nephrology specialist for the first time with complete diagnostic workup. We included 184 patients (89 male and 95 female) newly referred to the Merkur University Hospital nephrology specialist due to chronic kidney disease (CKD, stages 3A and above) from 2017 until 2020. We analyzed blood pressure values, 24-h ambulatory blood pressure monitor (ABPM) and laboratory test results (hemoglobin, hematocrit, glucose, potassium, creatinine, sodium, cholesterol, calcium, urates, and urine) of patients having presented them at the check-up. Most of the referred patients had CKD stage G3 (G3A 15 patients, G3B 82 patients, 52.15%), while 71 (38.17%) patients had CKD stage G4 and 18 (9.67%) patients CKD stage 5. Women were statistically significantly older (74.08 vs. 70.49 years, p<0.05) with higher heart rate (76.11 vs. 70.76 bpm, p<0.05) than men. Although 160 (86.02%) patients had verified arterial hypertension, only 44 (23.66%) patients had ABPM results. Ninety (48.39%) patients had their urate levels measured; 104 patients had their urine analyzed, of which 28 (26.92%) patients had no albumin values, and 76 had albumin values measured in urine (A1 (8.65%), A2 (51.92%), and A3 (12.50%)). Hematuria was found in 49 (47.11%) patients. Only 14.52% of patients referred for the first time to the nephrology specialist had complete diagnostic test results mandatory for successful first clinical check-up. Multicenter data should be obtained to get more consistent results.

Key words: chronic kidney disease, primary care physicians, referral to nephrologist

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INTRODUCTION

In a modern clinical care setting, where precision and efficiency are the key measures, there is a growing pressure on physicians to do increasing amounts of quality work in as short time as possible. This situation combined with the fact that many modern healthcare settings suffer from patient overload and increasingly longer waiting lists to clear, has led to the fact that a proper, standardized specialist examination in Croatia should take 15 minutes or less, according to the Croatian Bureau of Health Insurance. Within that short timeframe, it is expected that a physician takes thorough medical history, completes quality physical examination, reviews laboratory results brought by the patient, establishes a differential diagnosis and therapy plan, and makes records of all these steps. A patient referred with incomplete diagnostic workup, i.e., visiting a specialist for the first time without having done all diagnostic tests necessary for quality diagnostic workup, therefore poses another obstacle in the already arduous task for the physician. Faced with a patient with incomplete diagnostic workup, the specialist has a difficult choice of either making diagnoses and therapy modifications with incomplete data or scheduling the patient for a return visit with the results of all the missing necessary diagnostic tests done at the earliest possible date, thus taking up another time slot in the already overfilled clinic schedule. There are multiple variables influencing the quality and completeness of patient referrals, including but not limited to primary care physician (PCP) education regarding diagnos-

tic tests necessary for quality specialist examination, availability of facilities where these diagnostic tests can be performed, and patient compliance in completing this diagnostic workup. Several studies investigated incomplete referrals and their repercussions on the healthcare system. The article by Forrest *et al*. (1) from 2007 showed that only 80% of patients referred to a specialist completed the examination they were referred to, with the main reason for noncompletion being the lack of patient compliance. Another article by Patel *et al*. (2) from 2018 paints a much darker picture, showing that out of a very large patient sample of 103,737 people referred to a specialist, only 34.8% completed the examination they were referred to. The authors report on the problems with patient access to clinical facilities, long wait times, and geographical distance to hospitals as the main negative predictors of incomplete referrals and unfinished diagnostic processes. Besides compliance and other patient-related variables, PCP education and thoroughness, as mentioned above, play a very important role (3).

Being aware of the potential problems and difficulties mentioned above that incomplete referrals can bring about, we decided to check how many referred patients had complete test results necessary for successful check-up of chronic kidney disease (CKD) in a single nephrology clinic operating as part of a tertiary care center in Zagreb.

METHODS

In this cross-sectional study, we included 184 patients (89 male and 95 female) newly referred from family medicine practice to the Merkur University Hospital nephrology specialist due to CKD (stages 3A and above) from 2017 until 2020. All analyzed patients lived and were referred from Croatia. All patients from the patient pool were referred by a single PCP, who is experienced in nephrology referrals and current guidelines. We analyzed blood pressure values measured at the check-up, number of 24-h ambulatory blood pressure monitor (ABPM) test results done before check-up, and laboratory test results (hemoglobin, potassium, sodium, calcium, creatinine, cholesterol, urates, and urine) of patients having presented them at the check-up. Glomerular filtration rate was estimated with the CKD-EPI formula, while CKD and albuminuria stages were graded by KDIGO classification from 2020 (4). The number of patients having ultrasound findings, parathyroid hormone (PTH), phosphate, and high-sensitivity C-reactive protein (hsCRP) levels were not analyzed because these data were missing in more than 90% of patients. Data were expressed as mean and percentage, and Student's t-test was used on parametric variable analysis performed by Statistica v. 10.0.

RESULTS

Most of the referred patients had CKD3 stage (3A 15 patients, 3B 82 patients, 52.15%), while CKD4 stage was found in 71 (38.17%) and CKD5 in 18 (9.67%) patients. Women were statistically significantly older (74.08 *vs*. 70.49 years, $p<0.05$) with higher heart rate (76.11 *vs*. 70.76 bpm, $p<0.05$) than men, and had significantly higher values of cholesterol (5.86 *vs*. 4.78 mmol/L for total cholesterol, $p<0.01$; 3.66 *vs*. 2.54 mmol/L for LDL cholesterol, $p<0.01$, and 1.31 *vs*. 1.11 mmol/L for HDL cholesterol, $p=0.05$). There were no statistically significant differences between genders in other examined parameters. Differences between CKD stages are listed in Table 1.

Table 1. *Mean values of examined parameters for chronic kidney disease (CKD) stage 3B and 4. The last two columns describe the rate of patients with values above or below normal values.*

	CKD stage 3B (N=82)	CKD stage 4 (N=71)	p	Threshold value	Values above (%)
Age (years)	73.36±10.97	72.39±11.66	0.596	/	/
SBP (mm Hg)	138.04±16.86	135.84±25.64	0.539	≥140	52.22
DBP (mm Hg)	81.33±10.37	77.7±12.44	0.058	≥90	22.78
HR (/min)	72.37±14.19	75.13±15.73	0.321	≥80	35.21
BMI (kg/m^2)	27.76±6.96	32.52±6.64	0.012	≥30	45.71
Hemoglobin (g/L)	130.67±17.26	116.21±22.88	<0.001	≥135 males, ≥120 females	54.16
Hematocrit	0.38 ± 0.06	0.34±0.06	0.005	<0.41 males, <0.36 females	76.47
Potassium (mmol/L)	4.71±0.56	4.75±0.72	0.750	>5.00	28.22
Sodium (mmol/L)	138.16±3.31	137.73±3.73	0.549	≤136	18.85
Calcium (mmol/L)	2.31±0.26	2.17±0.36	0.122	≤2.0	4.28
Glucose (mmol/L)	7.01±2.14	6.57±2.18	0.306	≥7.0	34.64
Uric acid (mmol/L)	468.97±116.55	505.14±154,62	0.248	>420	69.23
LDL cholesterol (mmol/L)	3.22±1.20	2.92±0.99	0.430	>2.6	56.25

The number of patients having certain test results significantly varied depending on CKD stage. The rate of patients having test results was 26.67% in CKD stage 3A, 12.20% in CKD stage 3B, 15.49% in CKD stage 4, and 11.11% in CKD stage 5 not on dialysis (Table 2). Although 160 patients had verified arterial hypertension (86.02%), only 44 (23.66%) patients had ABPM results (9 were dippers, 20.45% non-dippers). Anemia significantly depended on CKD stage and was found in 77 (45.83%) and hyperkalemia in 46 (28.22%) patients. Ninety (48.39%) patients had their urate levels measured, of which 63 (70.0%) had hyperuricemia (more pronounced in men, 499.54 *vs.* 436.36 mmol/L, $p<0.05$); 104 patients had their urine analyzed, of which 28 (26.92%) patients had no albuminuria levels, 9 (8.65%) patients had A1, 54 (51.92%) patients had A2, and 13 (12.50%) patients had A3. Hematuria was found in 49 (47.11%) patients.

The rate of CKD patients having test results was as follows: potassium 87.63%, glucose 68.28%, complete blood account 66.67%, albuminuria 55.91%, uric acid 48.92%, calcium 37.63%, and LDL 25.81% (Table 2). Only 14.52% of patients referred for the first time to the nephrology specialist had complete diagnostic test results (Figure 1).

Table 2. *Rate of patients having test results in each chronic kidney disease stage from stage 3A to stage 5 not on dialysis*

	CKD stage 3A (N=15)	CKD stage 3B (N=82)	CKD stage 4 (N=71)	CKD stage 5 (N=18)
APMB measurement	4 (26.67%)	12 (14.63%)	14 (19.72%)	14 (77.78%)
Complete blood count	12 (80.00%)	40 (49.78%)	54 (76.06%)	18 (100.00%)
Potassium	13 (86.67%)	67 (81.71%)	66 (92.96%)	17 (94.44%)
Calcium	7 (46.67%)	27 (32.93%)	28 (39.44%)	8 (44.44%)
Glucose	9 (60.00%)	50 (60.98%)	53 (74.65%)	15 (83.33%)
Uric acid	8 (53.33%)	48 (58.54%)	29 (40.85%)	6 (33.33%)
LDL cholesterol	6 (40.00%)	27 (32.93%)	13 (18.31%)	2 (11.11%)
Albuminuria	8 (53.33%)	39 (44.56%)	43 (60.56%)	14 (77.78%)
Total	**4 (26.67%)**	**10 (12.20%)**	**11 (15.49%)**	**2 (11.11%)**

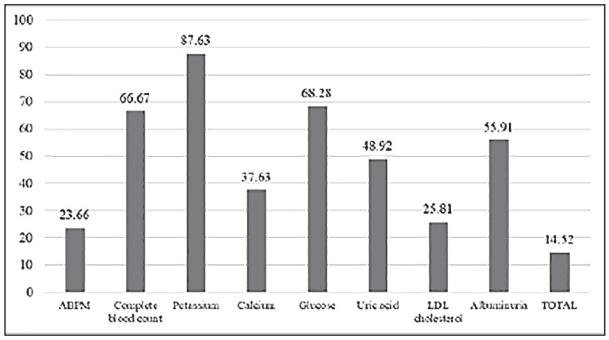

Figure 1. *Rate of patients with CKD having test results. ABPM = ambulatory blood pressure monitor.*

DISCUSSION

Chronic kidney disease is a growing population health concern worldwide (4). With early identification and effective management, kidney disease progression can be slowed down or prevented. Most patients with risk factors for CKD are treated within primary healthcare (5). There are challenges in providing optimal CKD care in the primary care setting (PCPs). Effective co-management of patients with CKD between PCP and nephrologists is increasingly recognized as a key strategy to ensure efficient and high-quality CKD care (3, 6).

While the results of laboratory tests analyzed are congruent with clinical presentation and features of CKD established in modern literature, the percentages of patients having the results of diagnostic tests necessary for a quality first-time examination by a nephrologist in a tertiary care center paint a bleak picture. It is well known that in CKD, the complications of the compromised kidney function and morphology present a significant detriment to both the patient physical health and quality of life (7). The various sequels of CKD, including anemia, hyperkalemia, arterial hypertension, etc. should therefore be carefully and regularly monitored, evaluated, and treated in order to prevent further deterioration of the patient presenting clinical state (8). Among the most worrying results identified in this research is the fact that less than one-fourth of the patients presenting with arterial hypertension had an ABPM result. Complete blood count as a basic and routine laboratory test with results available within 30 minutes and an indicator of the severity of anemia was missing in about one-third of the patients. Albuminuria, which is an important marker and indicator of glomerular dysfunction, was evaluated in only about half of the patients. Still, the most worrying result is, without any doubt, that only 14.52% of the patients who presented for the first-time nephrologist examination had done all diagnostic tests necessary for a proper examination and adequate for the nephrologist to form an opinion and treatment plan. A first-time examination without having an insight into the necessary diagnostic test results requires either repeat visits within a short time period, requiring from the patient to do and bring along all those test results, or, in the worst-case scenario, making a conclusion and treatment plan using incomplete data, which may imply that some more subtle comorbidities and complications remain undetected and unaddressed. Looking at the available literature, it should be noted that incomplete referrals and data on clinical examinations in hospitals are not endemic to a specific area or country, but are a worldwide issue mostly connected with the lack of communication between PCPs and hospital physicians, administrative obstacles for the patient in reaching the healthcare facilities and

services required, and patient compliance (3, 9). For example, a study by Al Shamsi *et al*. from 2018 showed that among 181,192 Saudi Arabian patient referrals and documents examined, more than 50% contained incomplete patient information and data (9). The effect those incomplete referrals can have on a larger scale can best be inferred from a study by Buja *et al*., where the authors concluded that incomplete and inappropriate patient referrals to the Emergency Department by PCPs increased wait times, delayed referral acceptance, and significantly reduced the quality of the services provided (10). Although this article raises important questions about the chain of referrals from a PCP all the way to a tertiary clinic physician and the efficiency of the Croatian healthcare system, it should be noted that it suffered from some limitations. Being a single-center study analyzing only a single nephrology clinic, the results of this study cannot be generalized to the Croatian healthcare system. Also, since all the patients from the patient pool were referred by a single PCP, who is experienced in nephrology referrals and current guidelines, it is hard to infer the efficiency and quality of referrals of PCPs in general. Multicenter data should be obtained in future studies in order to either confirm or deny the results of this study and the allegations inferred from them. These findings reinforce prior observations of low adherence to guideline-recommended practices in healthcare systems and underscore the urgent need for improved patient management (5, 6). The nephrology workforce has focused attention on patients with kidney diseases (11). If there is not enough time for patients and communication, along with the lack of guidelines for primary care, the question is what can we do at this moment? We need better communications between us. We need to invest additional efforts for education of PCPs and other hospital specialists to increase the number of patients with complete workup results on the first nephrology specialist check-up for CKD. The findings of this article suggest the need for time-efficient strategies that promote better collaboration among all members of the healthcare team for CKD patients.

CONCLUSION

Our results show that only 14.52% of patients referred for the first time to a nephrology specialist had complete diagnostic test results mandatory for the successful clinical check-up and management of CKD. The most important component of the system is communication between primary care and specialist care providers. Poor communication between them can cause significant issues with coordination of ineffective care. Multicenter data should be obtained to get more consistent results.

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SAŽETAK

PACIJENTI UPUĆENI NEFROLOGU S NEPOTPUNOM OBRADOM – KOLIKA JE VELIČINA PROBLEMA?

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U svakodnevnom radu uočavamo sve veći broj pacijenata upućenih nefrologu bez potrebne obrade. Stoga smo analizirali koliko je pacijenata adekvatno pripremljenih na primarnoj zdrastvenoj zaštiti upućeno na prvi pregled nefrologu. Uključeno je 184 pacijenata (89M, 95F) upućenih u Kliničku bolnicu Merkur zbog kronične bolesti bubrega (KBB, stadij G3A i više) u razdoblju od 2017. do 2020. godine. Kod pacijenata su pri upućivanju analizirani podatci postojanja laboratorijskih parametara (hemoglobin, hematokrit, glukoza, kreatinin, kalij, natrij, kalcij, kolesterol, urati, urin) uz podatak o nalazu kontinuiranog mjerenja krvnog tlaka (KMAT). Analiza podataka prikazana je u postotcima, srednjim vrijednostima uz Studentov t-test. Većina upućenih pacijenata bila je unutar KBB stadija G3 (15 pacijenata u G3a, 82 pacijenta u G3b, 52,15 %). U KBB G4 bio je 71 pacijent (38,17 %), a 18 ih je bilo u KBB G5 (9,67 %). Žene su bile statistički značajno starije (74,08 vs. 70,49 godina, p<0,05) s višom srčanom frekvencijom (76,11 vs. 70,76/min, p<0,05) nego muškarci. Iako je bilo 160 pacijenata (86,02 %) s hipertenzijom, svega 44 (23,66 %) je imalo KMAT. Devedeset pacijenata (48,39 %) imalo je određenu vrijednost urata, od čega ih je 63 (70,0%) imalo hiperuricemiju (M /499.54 vs. F /436.36 mmol/L, p<0,05). Analizu urina imalo je 104 pacijenta, od kojih s određenom razinom albuminurije (A) kako slijedi: stadij A1 utvrđen je u 9 (8,65 %), A2 u 54 (51,92 %) i A3 u 13 (12,50 %) pacijenata, a 28 (26,92%) nije imalo određenu A. Hematurija je utvrđena u 49 od 104 pacijenta koji su imali analizu urina (47,11 %). Podatci su pokazali da je svega 14,52 % pacijenata koji su upućeni na prvi pregled nefrologu pripremljena, odnosno ima potrebne laboratorijske analize krvi i urina za prvi pregled. Potrebna je multicentrična studija koja će pokazati kolika je veličina problema.

Ključne riječi: kronična bubrežna bolest, primarna zdravstvena zaštita, upućivanje nefrologu

BRUGADA SYNDROME ACCOMPANIED WITH CORONARY HEART DISEASE

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Brugada syndrome is a congenital disorder that can lead to sudden cardiac death. It is characterized by spontaneous or provoked typical ECG features and the occurrence of malignant ventricular arrhythmias, most commonly manifested by syncope or sudden death. The use of an implantable cardioverter-defibrillator is the only effective therapy for arrhythmic death prevention. The coexistence of Brugada syndrome and coronary heart disease is rarely described in the literature. We present a case of a patient with coexistence of two different heart conditions, symptomatic Brugada syndrome and coronary heart disease.

Key words: Brugada syndrome, syncope, coronary heart disease

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INTRODUCTION

Brugada syndrome is an inherited disorder of ion channels in cardiomyocytes, and most common are mutations in the SCN5A gene. It is characterized by specific features on ECG, can cause syncope and sudden cardiac death due to ventricular arrhythmias (1-3). Most patients have no structural changes in the heart or they are minimal, but cases of coexisting significant coronary heart disease, as well as ischemia-induced Brugada-like ECG features have been described (1,2,4,5). The diagnosis of Brugada syndrome is based on specific spontaneous ECG features or features occurring during test performance with sodium channel blockers application (e.g., ajmaline, procainamide, flecainide) (2). Brugada syndrome was first described more than 25 years ago. The definition and ECG diagnostic criteria have changed over time; today, we distinguish three types of ECG features, as follows: type 1 is diagnostic and consists of concave elevation of the ST-segment and J point by >2 mm at its peak, followed by negative T-wave with little or no isoelectric separation in one or more right precordial leads (V1 and V2); type 2 consists of high ST-segment elevation after J point (2 mm), which is followed by gradual descending ST-segment elevation (1 mm above the baseline), and positive or biphasic T wave, saddle configuration; and type 3 has a saddle or concave elevation of the ST segment of <1 mm in the right precordial leads (1). The use of an implantable cardioverter defibrillator is effective therapeutic choice for prevention of sudden cardiac death due to arrhythmias (6). Although this syndrome typically manifests with arrhythmia and syncope episodes in younger age (1,2), we report a case of coexistence of two different heart conditions, Brugada syndrome and coronary heart disease in a 60-year-old patient.

CASE REPORT

A 60-year-old male was admitted to the coronary unit through the emergency department due to recurrent syncope. A few hours before admission while watching TV in a sitting position, the patient suddenly lost consciousness and spontaneously recovered. He had a similar event a few years before but did not report to the physician. He asserted to have occasional mild chest discomfort during physical activity. However, chest pain, shortness of breath, or any other symptom he did not report on the day of admission, but he consumed small amounts of alcoholic beverages the day before admission. He had well controlled arterial hypertension for several years, taking angiotensin-converting enzyme (ACE) inhibitor, diuretic and calcium channel blocker. His father died at the age of 57 by sudden death; he had a pacemaker implanted but the exact cause of death was uncertain.

The patient was generally in good health, afebrile, eupneic, normal neurological status, with audible murmur over the heart apex, intensity II/VI. The 12-channel ECG recorded showed a typical pattern for type 1 Brugada syndrome, i.e., right branch block and concave ST-segment elevation in V1 and V2 leads higher than 2 mm (Figure 1), without criteria for acute ischemia. All laboratory tests were within the reference values including repeated cardiac enzymes; echocardiography showed left ventricular ejection fraction of 53% and mild mitral regurgitation. Coronary angiography revealed the existence of hemodynamically significant stenosis (IFR 0.86) of middle segment left anterior descending (LAD) artery at bifurcation with first diagonal artery (D1), including D1 ostium with 75% lumen stenosis. Percutaneous coronary intervention was performed with dilatation of LAD and D1 and implantation of by drug-coated balloon (Figure 2). Diagnostic workup ruled out the existence of neurovascular disease as a cause of syncope. No ventricular or supraventricular arrhythmias, or atrioventricular conduction disturbances were observed by ECG monitoring, and existence of reflex syncope was also excluded. We implanted a single-chamber cardioverter defibrillator for prevention of sudden cardiac death due to possible ventricular arrhythmias associated with Brugada syndrome.

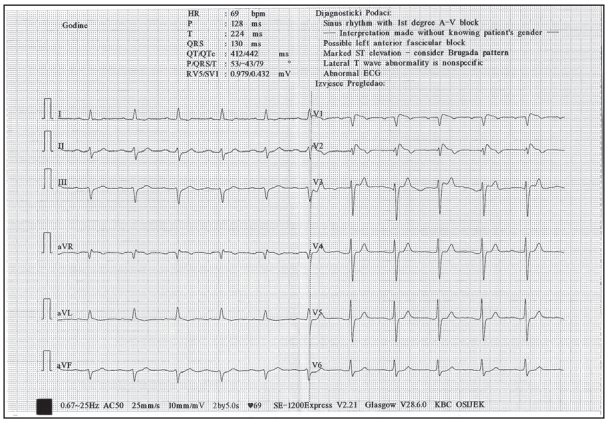

Fig. 1. *ECG type I: Brugada – concave elevation of ST segment in V1-V2 leads.*

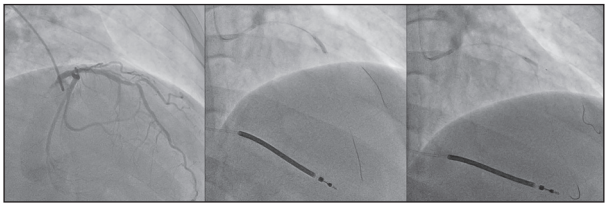

Fig. 2. *Percutaneous coronary intervention on LAD and D1 arteries. Left image: coronary angiography showing significant bifurcation LAD/D1 stenosis; middle image: drug-coated balloon dilatation in LAD covering bifurcation with D1; right image: drug-coated balloon dilatation in proximal D1.*

Three months after implantation of the cardioverter-defibrillator, the patient was in good health, had no syncope or recorded arrhythmias.

DISCUSSION

The incidence of Brugada syndrome has been estimated to five cases *per* 10,000 people; it is the cause of 4%-12% of total cardiac deaths and 20% of sudden cardiac deaths (2,4,7,8). Only a few published studies and case reports describe its coexistence with coronary heart disease. One smaller study including 55 cases with Brugada type ECG has reported significant coronary disease in 5 cases, yielding a 9.1% prevalence (10). Another retrospective analysis of 200 Brugada type ECG cases has reported significant coronary disease in 20% and coronary vasospasm in 11% of cases, with higher association of coronary disease in type 1 Brugada ECG pattern (11). The diagnosis of Brugada syndrome was based on a typical type 1 ECG pattern followed by recurrent syncope (6), although we did not prove the occurrence of ventricular arrhythmias by ECG monitoring. Type 1 ECG pattern does not require an arrhythmia provocation test with sodium channel blockers for diagnosis confirmation, whereas provocation test confirmation is necessary for types 2 and 3 (6). In our hospital, electrophysiological study was not available. Thorough clinical examination and tests failed to find another explanation for syncope. Coronary angiography showed significant coronary heart disease on LAD/D1 and successful revascularization was performed on those vessels. Although the patient reported occasional angina symptoms, acute coronary syndrome was not diagnosed at hospital admission (absence of symptoms or typical ischemia related ECG features on the day of admission, and normal troponin according to the 0-3 protocol), and the ECG remained unchanged after revascularization. We consider coronary heart disease in this patient to have been a concomitant accidental finding, which was not the cause of syncope or Brugada related ECG pattern. Diagnosis of acute coronary syndrome in Brugada type ECG and *vice versa* can be challenging due to ECG pattern overlap. In several published case reports, Brugada type ECG was masking anterior wall infarction (LAD and LMCA occlusion), as well as conus branch occlusion inducing ventricular arrhythmia in Brugada type ECG pattern (12-14). Diseases such as myoprecarditis can also mimic Brugada type ECG, and structural heart abnormalities can coexist with Brugada syndrome. We have previously reported on right ventricular structural abnormalities in a patient with Brugada type ECG induced with propafenone testing (15). Coexistence of Brugada syndrome and coronary spasm was found in 17% of Brugada cases in a small Japanese study (16).

Episodes of both entities usually occurred during the night and it was concluded that coronary spasm represented a risk factor for cardiac events in Brugada patients (16). Due to the increased risk of sudden arrhythmic death, syncope, type I ECG pattern and male gender, the patient received implantable cardioverter defibrillator (ICD). ICD is the only effective therapy to prevent sudden arrhythmic death for Brugada syndrome (2,6), and even with strong suspicion of ventricular arrhythmia existence we consider ICD implanting justified. In our opinion, considering recurrent syncope only as a symptom of successfully threated coronary disease and discharging patient without ICD implantation could endanger patient life. Although our patient's father died of sudden death at the age of 57, this fact itself does not support the existence of Brugada syndrome in the family (6). The ECG sample analysis of the patient's relatives did not detect any specific patterns associated with Brugada syndrome, while genetic analyses were not available. The question of the hereditary component in this case remained unanswered.

In conclusion, we believe that there were two different diseases in this case, mildly symptomatic/asymptomatic coronary disease and symptomatic Brugada syndrome, both recognized and successfully treated. Although the assumed malignant rhythm disorder can occur at an age when it is usually associated with ischemic heart disease, we consider that Brugada syndrome most likely was the cause of the malignant rhythm disorder in this case.

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SAŽETAK

BRUGADIN SINDROM UDRUŽEN S KORONARNOM SRČANOM BOLESTI

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Brugadin sindrom je nasljedni poremećaj koji može dovesti do iznenadne srčane smrti. Obilježen je spontanim ili provociranim tipičnim promjenama u EKG-u te pojavama malignih ventrikulskih aritmija koje se najčešće manifestiraju sinkopom ili iznenadnom smrću. Primjena implantabilnog kardioverter defibrilatora je jedina učinkovita terapija za sprječavanje aritmijske smrti. Koegzistencija Brugadina sindroma i koronarne bolesti je vrlo rijetko opisana u literaturi. Donosimo prikaz bolesnika s koegzistencijom dviju srčanih bolesti: simptomatskog Brugadina sindroma i koronarne bolesti.

Ključne riječi: **Brugadin sindrom, sinkopa, koronarna srčana bolest**

DELIRIUM AFTER COVID-19 IN A KIDNEY TRANSPLANT RECIPIENT

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Delirium can manifest as a neurological complication after COVID-19 in immunocompromised patients. To date, several reports have described delirium associated with SARS-COV-2 infection in older patients. Herein we present a case of a younger adult with a kidney transplant, who became disoriented, confused, and restless after acute COVID-19 and was admitted to the psychiatric ward for delirium management. He recovered and had a stable allograft function in follow-up.

Key words: delirium, COVID-19, kidney transplantation

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) pandemic, is still spreading rapidly throughout the world as several countries are dealing with a new wave of new Omicron variant (1). It is known that immunosuppressed patients such as kidney transplant recipients are at a greater risk of COVID-19 infection with high morbidity and mortality. The disease presentation is atypical and data on the post-COVID-19 period in this population are still scarce. In this report, we describe a case of delirium in a kidney transplant recipient post-COVID-19 infection.

CASE REPORT

A case of a 47-year-old man with unknown primary kidney disease is reported. He underwent kidney transplantation in 2006 after two years of hemodialysis. The immunosuppressive protocol included tacrolimus, mycophenolate mofetil, and a steroid. The post-transplant course was complicated by renal allograft artery stenosis that required stent implantation, and new-onset diabetes after transplantation. At the end of March 2021, he received the second dose of the Pfizer vaccine. Two weeks later, he developed persistent fever above 39 °C, with no specific symptoms. The reverse transcriptase-polymerase chain reaction was positive for SARS-CoV-2, and chest x-rays revealed bilateral interstitial COVID-19 pneumonia.

The mycophenolate mofetil dose was decreased, and he was discharged from the hospital one week later in good condition with a stable allograft function. However, one week later, he complained of being uncomfortable and disoriented in space and time at home. He was confused, restless and aggressive. It was necessary to engage police for admission to the psychiatry ward. He claimed to be depressed and was anxious about the outcome of his kidney allograft. Intimidated by his stay at psychiatry ward, he could not relax and was tense. His will, interests, and instincts were diminished. The patient was distracted and often absent but denied any memory problems. After acute delirium, the psychiatrist's conclusion revealed anxiety and depressive disorder of the neurotic level, predominated by repression and denial in defenses, and occasional application of dissociative defense mechanism accompanied by difficulties in adjustment. Computed tomography of the brain was unremarkable except for a zone of sclerosis with a diameter of 7 mm in the area

of the sella turcica. His neurological status was unremarkable, as well as his cerebrospinal fluid findings. Quetiapine was introduced in his therapeutic protocol. Seven days later, his psychiatric status improved, and he was discharged from the hospital.

DISCUSSION

Delirium is a significant mental condition that causes flawed thinking and decreased awareness of the environment. The Confusion Assessment Method (CAM) is widely used as an instrument and diagnostic algorithm to identify delirium. It is based on four cardinal features: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. A diagnosis of delirium, according to the CAM, requires the presence of features 1, 2, with either 3 or 4 (2). Ticinesi *et al*. report delirium as a common complication of COVID-19 and a marker of severe disease course, especially in older patients with neuropsychiatric comorbidity (3, 4). In their retrospective analysis, they found that 11% of patients admitted for suspected COVID-19 pneumonia developed delirium during hospitalization. They were mostly older (median age 82 years) and had more neuropsychiatric comorbidities and worse respiratory status at baseline. Older patients are more likely to present with delirium during COVID-19 infection with the occurrence of up to 22% (5), and this was also the case before the SARS-CoV-2 pandemic era, while a large number of patients with delirium have always been diagnosed in acute hospitals (6).

Our patient is relatively young, and additional mechanism can be involved in the pathogenesis of delirium in this case. Kotfis *et al*. report that, indeed, patients with COVID-19 are more likely to develop delirium as a result of direct central nervous system (CNS) invasion, induction of CNS inflammatory mediators, the secondary effect of other organ system failure, the impact of sedative strategies, prolonged mechanical ventilation time, and social isolation to name those (7). Immunosuppression may have had an important role in the development of delirium in our case. It was necessary to exclude opportunistic CNS infections and toxicity of drugs.

The outcome in COVID-19 patients presenting with delirium includes a high mortality rate, and this can be exacerbated by institutionalized measures such as family and social distance and isolation in intensive care units. Garcez *et al*. report that the overall occurrence of delirium was independently associated with in-hospital death reaching up to 55% in COVID-19 patients presenting with delirium compared to 30% in the group without delirium. The length of hospital stay, ventilator utilization, and admission to the Intensive Care Unit also increased in patients with delirium compaired to the non presenting group (5, 7, 8). In their multicenter cohort study, Pun *et al*. report that the use of sedatives such as benzodiazepine, mechanical ventilation, use of restraints, opioid administration, vasopressor infusions, and antipsychotics was each associated with a higher risk of delirium. In contrast, family visitation (in person or virtual) was associated with a lower risk of delirium (8, 9). Delirium has also been a significant predictor of acquired dementia after critical illness (9).

CONCLUSION

No cure is yet approved for the management of COVID-19. Supportive therapy and increased herd immunity through vaccination remain the first-line option in fighting the pandemic. Delirium prevention and management should be a priority during the COVID-19 pandemic, thus avoiding long-term neurological complications and decreasing readmission and health care supply consumption. Kidney transplant recipients may be at an increased risk of developing delirium even at a young age.

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SAŽETAK

DELIRIJ NAKON AKUTNOG COVID-19 U BOLESNIKA S TRANSPLANTIRANIM BUBREGOM

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Delirij se može manifestirati kao neurološka komplikacija nakon COVID-19 kod imunokompromitiranih bolesnika. Do danas je u nekoliko istraživanja opisan delirij u starijih osoba nakon infekcije COVID-19. Prikazali smo mlađeg bolesnika s presatkom bubrega koji je nakon preboljene infekcije SARS-CoV-2 postao dezorijentiran, zbunjen, nemiran i agresivan te je primljen na psihijatrijski odjel zbog liječenja delirija. Stanje bolesnika se postupno popravilo, a funkcija presatka bubrega ostala je stabilna.

Ključne riječi: delirij, COVID-19, transplantacija bubrega

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Rukopis i popratno pismo šalju se u elektroničkom obliku, isključivo e-poštom na adresu actamedicacroatica@amzh.hr. Priloge koji se šalju treba označiti prezimenom prvog autora uz dodatak što prilog sadrži (npr. Horvati-pismo; Horvat-rad; Horvat-slike; Horvat-tablice; Horvat-literatura). Rukopisi koji ne udovoljavaju tehničkim zahtjevima oblikovanja biti će vraćeni autoru na doradu bez razmatranja sadržaja.

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Slike moraju imati redni broj koji ih povezuje s tekstom i ime prvog autora rada. Prikazuju se zasebno u svojoj datoteci u JEPG ili TIF formatu razlučivosti ne manje od 300 dpi.

Upute za pisanje popisa literature

Članak u časopisu (navedite sve autore ako ih je 5 ili manje, ako ih je više, navedite prva 3 i dodajte: i sur.: Smerdelj M, Pećina M, Hašpl M. Surgical treatment of infected knee contracture after war injury. Acta Med Croatica 2000; 53: 151-5.

Suplement časopisa

Djelmiš J, Ivanišević M, Mrzljak A. Sadržaj lipida u placenti trudnica oboljelih od dijabetesa. Acta Med Croatica 2001; 55 (Supl. 1): 47-9.

Knjige i monografije

Guluyer AY, ur. Health indicators. An international study for the European Science Foundation. Oxford: M. Robertson, 1983.

Poglavlje u knjizi

Weinstein I, Swartz MN. Pathogenic properties of invading microorganisms. U: Sodeman WA, ur. Pathologic physiology: mechanism of disease. Philadelphia: WB Saunders, 1974, 457-72.

Disertacija ili magistarski rad

Cigula M. Aktivnosti nekih enzima u humanom serumu kao pokazatelji apsorpcije žive (disertacija). Zagreb: Medicinski fakultet, 1987, str. 127.

Članak sa znanstvenog skupa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. U: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG (ur.). Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002; 182-91.

Članak objavljen u online znanstvenom časopisu

Terauchi Y, Takamoto I, Kubota N. Glucokinase and IRS-2 are required for compensatory beta cell hyperplasia in response to high-fat diet-induced insulin resistance. J Clin Invest [Internet]. 2007;117. [cited 2007 Aug 12]. Available from: http://www.jci. org/cgi/content/full/117/1/246

Internetska stranica

Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc. c2000-01 [cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Baza podataka na internetu

Who's Certified [Internet]. Evanston (IL): The American Board of Medical Specialists. c2000 [cited 2001 Mart 8]. Available from: http://www.abms.org/newsearch.asp

Softver (program)

Epi Info [kompjutorski program]. Verzija 6. Atlanta, GA. Center for Disease Control and Prevention, 1994.

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References – examples

Journal article (list all authors if there are 5 or less; list the first 3 authors and add et al. if there are 6 or more authors): Smerdelj M, Pećina M, Hašpl M. Surgical treatment of infected knee contracture after war injury. Acta Med Croatica. 2000;53:151-5.

Journal supplement

Djelmiš J, Ivanišević M, Mrzljak A. Sadržaj lipida u placenti trudnica oboljelih od dijabetesa. Acta Med Croatica. 2001;55 (Suppl 1):47-9. (in Croatian)

Books and monographs

Guluyer AY, editor. Health Indicators. An International Study for the European Science Foundation. Oxford: M. Robertson, 1983.

Chapter in a book

Weinstein I, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA, editor. Pathologic Physiology: Mechanism of Disease. Philadelphia: WB Saunders, 1974;457-72.

Doctoral dissertation or MS thesis

Cigula M. Aktivnosti nekih enzima u humanom serumu kao pokazatelji apsorpcije žive. Doctoral dissertation. Zagreb: School of Medicine, 1987; p. 127. (in Croatian)

Conference paper

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic Programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002;182-91.

Article in online journal

Terauchi Y, Takamoto I, Kubota N. Glucokinase and IRS-2 are required for compensatory beta cell hyperplasia in response to high-fat diet-induced insulin resistance. J Clin Invest [Internet]. 2007;117. [cited 2007 Aug 12]. Available from: http://www.jci.org/cgi/content/full/117/1/246

Web site

Cancer-Pain.org [Internet]. New York: Association of Cancer Online Resources, Inc. c2000-01 [cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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Software

Epi Info [computer program]. Version 6. Atlanta, GA: Center for Disease Control and Prevention, 1994.

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Sadržaj

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