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ABO BLOOD TYPE ANALYSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Tobacco smoking is major risk factor for development of chronic obstructive pulmonary disease (COPD), which appears in 15-20% of smokers. Apart from smoking, exposure to polluted air and various *noxae*, and several genetic factors influence its development as well. The ABO blood type distribution varies among populations in the world, but also within subpopulations. A large number of studies have shown a correlation between blood types and the pathology of various diseases. These markers, used in population genetic research, have mainly shown deviations in the representation of blood groups in different diseases, compared to the general population. The aim of this study was to determine the ABO blood types distribution in patients with COPD compared to the general population, and their possible association with COPD stage, patients' nutritional status and lung function impairment. This observational, prospective study included 150 patients (68.7% men and 31.3% women), average age 64.80 ± 8.38 years, diagnosed with COPD. Data were collected at the Clinical Center of Montenegro in Podgorica and at the Special Hospital for Lung Diseases Brezovik in Niksic. Determination of blood types of the ABO system and Rh factors for all subjects was performed at the Blood Transfusion Center in Podgorica. Apart from patients' tobacco smoking status (duration of smoking and the number of cigarettes smoked per day expressed in pack/years for current smokers and former smokers), we also analyzed their exposure to various other *noxae*, their body

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mass index, and lung function in correlation to ABO blood type and Rh factor, and performed statistical analysis. We found a significant difference in the distribution of ABO blood types in patients with COPD compared to the general population. The highest frequency of blood type A was found in patients with COPD. We also found the lowest average values of spirometry parameters in that group, which represented majority of those patients with respiratory insufficiency having the most severe stage of the disease. Combined blood types A, B and AB were significantly more common in patients with COPD in comparison to blood type O, which is the least represented (23.3%). The least obstructive disturbance of pulmonary ventilation was found in the patients with B type. Respiratory insufficiency showed differences in gender representation, found in 40.4% of women, and in 25.2% of men with terminal phase of COPD. The prevalence of AB, higher than expected, decreases with the severity of the disease.

Key words: chronic obstructive pulmonary disease – COPD, ABO blood type, Rh factor, lung function, respiratory insufficiency

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of common diseases with high global morbidity and mortality. Its main characteristic is poorly reversible airway obstruction, confirmed by spirometry, and that includes obstruction of the small airways and emphysema (BARNES *et al*., 2015). These lead to air trapping and dyspnea (shortness of breath) in response to physical exertion. Underlying mechanisms are associated with chronic inflammation and accelerated ageing of the lungs. An abnormal repair mechanism might be driven by oxidative stress. Cigarette smoking is the most common risk factor for COPD, found in about 90% of the patients.

Following the World Health Organization estimates, almost 210 million people in the world suffer from COPD (WHO, 2018). The prevalence is 1-4% of the global population with gradual increase up to 11.7% among older than 40 years (GOLD, 2018). It is on further increase in subjects above the age of 60 years. COPD is a bit more frequent in men than in women. It is the fourth on the list of the leading causes of mortality in the world (EUROPEAN DATABASE, 2020). About three million people die annually from the preventable disease. COPD mortality rate is on continual increase during the last several decades. It is mostly due to world epidemic of tobacco smoking.

Although tobacco smoking is major risk factor for developing COPD, not all smokers develop COPD but only 15-20% of them (SILVERMAN, 2006). Thus, host factors may contribute to heterogeneous susceptibility to tobacco smoke contents or to the other risk factors that lead to COPD: air pollution, exposure at working place, recurrent respiratory infection etc. It is evidence based that genetic factors may play a role in predisposition and development of COPD. Current genetic studies suggest the complexity of the host environment interactions (SORHEIM, 2010). Despite several candidate genes, COPD susceptibility has not been fully elucidated (VESTBO 2013; HALL *et al.*, 2019; SILVERMAN 2020). Natural history of COPD depends on age, gender,

and race, and the impact of comorbid conditions (MASELLI, 2019). Smoking cessation is the best preventive measure for rapid disease progression and for worsen quality of life and death.

Numerous studies have highlighted the different frequency between the ABO blood types and Rh systems in patients with different diseases in relation to the general population. Thus, the selective advantage of blood type O in the fight against malaria (ANSTEE, 2010) and cholera (KAPER *et al*., 1995) has been shown, and negative correlation of O blood group in relation to ulcer and cancer (BJORKHOM *at al*., 2001). The selective advantage of blood group A in smallpox explains the higher prevalence of blood type A in Europe. Some studies have brought ABO blood types into correlation with tuberculosis (VOLKOVA *et al*., 1991; PESUT and MARINKOVIC 2009). The other studies explored and confirmed association of particular ABO blood type with top sportsmen and young intellectuals (MARINKOVIC and CVJETICANIN, 1991), prevalence of O blood type during selection of elite water polo players (CVJETICANIN and MARINKOVIC, 2009) while no significant association was found for congenital hip dislocation (CVJETICANIN and MARINKOVIC, 2005) and lung cancer (PESUT and MARINKOVIC, 2009). Current studies examined if there was an association with ABO blood type and COVID19, its development and severity (DAI, 2020; ZHAO *et al.*, 2020). In a recent study (LATZ *et al.*, 2020), according to their ABO blood type, some patients were more likely to be test positive for SARS CoV-2.

Current studies show that susceptibility to COVID19 and its severity, and cardiovascular disease may depend on ABO blood type (DAI, 2020; ZHAO *et al.*, 2020).

About 16% of Europeans have a negative Rh factor (VAGNER *at al*., 2000; FLEGEL, 2011), and several recent studies have pointed to the specifics of the Rh genotype on the human phenotype and the health (KANKOVA *et al*., 2010; FLEGR *at al*., 2015; FLEGR, 2016). Negative Rh factor correlates with the negative health of the subjects, who are also significantly more sensitive to the effects of smoking and infection. Rh-negative factor is a combination of negative heterozygotes and homozygotes, and as detected, the health of Rh-negative homozygotes is significantly worse than Rh-positive heterozygotes (FLEGR, 2015). The RhD allele, alone or in association with other alleles, protects heterozygotes (DANIELS, 2005). However, a binary cohort study on a sample of almost 900,000 of subjects who received transfusions in Denmark and Sweden in the time interval 2003-2012, showed, that there was no difference in the mortality of Rh negative and Rh-positive individuals (HELMIN *et al*., 2017).

MATERIAL AND METHODS

Patients and methods

This observational, prospective study included 150 patients (68.7% male and 31.3% female, average age 64.80 ± 8.38) diagnosed with COPD according to GOLD (Global initiative for chronic obstructive lung diseases) criteria (GOLD, 2018). After the approval by the Ethics Committee of the Clinical Center of Montenegro, the data we collected at the Clinical Center of Montenegro in Podgorica and the Special Hospital for Lung Diseases Brezovik in Niksic, the national reference institution for lung diseases in Montenegro. Determination of blood types of

the ABO system and Rh factors for all subjects we performed at the Blood Transfusion Center in Podgorica. We analyzed data from the patients' medical charts for socio-demographic features, risk factors for developing COPD (tobacco smoking, exposure to various *noxae*), body mass index (BMI), spirometry findings and indicators of respiratory failure. Tobacco smoking status was set as smoker, former smoker and never smoker. In smokers and former smokers, we have expressed total exposure to tobacco smoke contents by measure pack/years. One pack/year denotes one year of smoking 20 cigarettes (a pack) daily.

Statistical analysis

We used standard statistical procedure, and compared the means and variance in two groups of patients, patients with COPD and general population they belonged to. In order to determine the differences values, the variability type, we applied common testing set ($\chi 2$, S2, t-test, F-test and Z-test, respectively).

Statistical analysis of the data was done using the statistical program IBM SPSS Statistics 21.0. Data processing included methods of descriptive and inferential statistics. We presented numerical features using means (arithmetic mean, median) and measures of variability (range of values, standard deviation), and attributive features using frequencies and percentages. Testing of differences in frequency distribution for attribute features was performed using a nonparametric chi-square test. Student's *t*-test was applied to compare the mean values for the numerical features of the two groups. Mutual comparison was also performed using the Tukey test. We used Z-test for testing the significance of the proportions' differences in the samples of patients and general population. The significance levels were set at $0.01<p\leq 0.05$ (statistically significant) and $p\leq 0.001$ (highly statistically significant).

RESULTS

Study group consisted of 150 patients with COPD (68.7% male, 31.3% female), average age 64.80 ± 8.38 (33-82, range) whose diagnoses were established by GOLD criteria. The patients' distribution by sex and age is presented in Table 1 together with GOLD classification by disease stages, and Figure 1 illustrates patients' distribution by COPD stage. Every second COPD patient was aged 60 to 69, and more than a quarter of them aged 70 to 79, and 28.6% of patients aged 80 to 89 years.

Due to the small number of patients with a mild stage of the disease, in the further analysis, the categories of mild and moderate stage of the disease were merged into one category. Male subjects dominated in all stages of the disease mild/moderate (60.0%), severe stage (76.1%) and very severe (66.7%). Men are not only significantly more numerous in the total sample of COPD patients (68.3%), but they are also the most numerous patients in a very severe stage of the disease (66.7%). There were 33.3% of female subjects in a very severe stage of the disease, with an average body mass index of 23.13 (SD = 3.72).

In our study, the average duration of COPD was 7.42 years (SD = 4.27) from establishing the diagnosis. Patients with COPD in a very severe stage are treated for a slightly longer time, almost nine years on average (8.83 SD = 4.09).

Table 1. The structure of patients with COPD in relation to the stages of the disease by sex and age

Features	COPD stage								p
	Mild/Moderate (n=55)		Severe (n=71)		Very severe (n=24)		Total (n=150)		
	n	%	n	%	n	%			
Gender									$\chi^2 = 3.767$, p=0.152
Male	33	60.0	54	76.1	16	66.7	103	68.7	
Female	22	40.0	17	23.9	8	33.3	47	31.3	
Age group									
20-29									
30-39	1	1.8	1	1.4	0	0.0	2	1.3	
40-49	1	1.8	1	1.4	2	8.3	4	2.7	
50-59	10	18.2	11	15.5	5	20.8	26	17.3	
60-69	27	49.1	37	52.1	11	45.8	75	50.0	
70-79	15	27.3	20	28.2	6	25.0	41	27.3	
80-89	1	1.8	1	1.4	0	0.0	2	1.3	
Age ($\bar{x}$±SD)	64.65 ± 8.77		65.51 ± 7.98		63.04 ± 8.70		64.80 ± 8.38		F = 0.787, p = 0.457

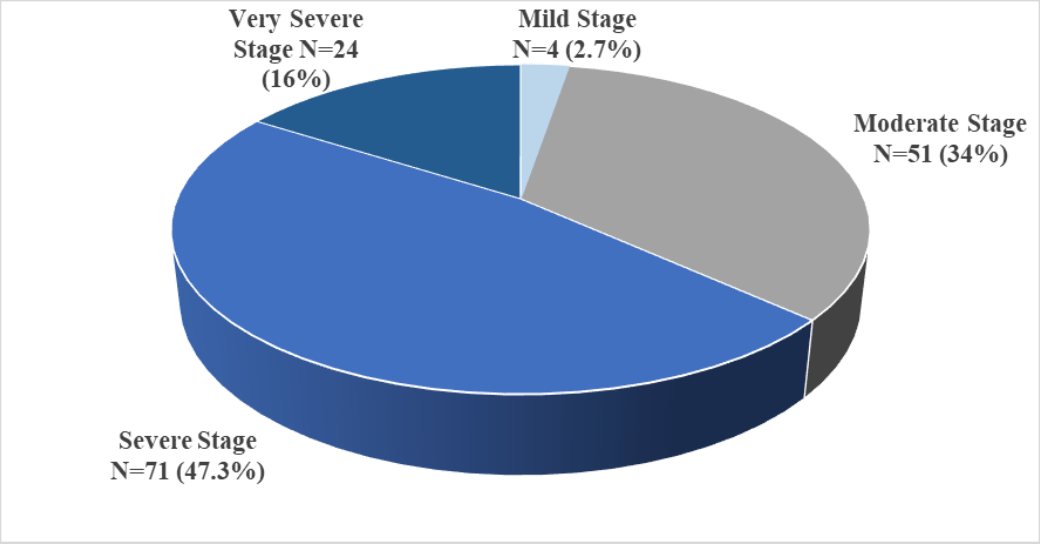
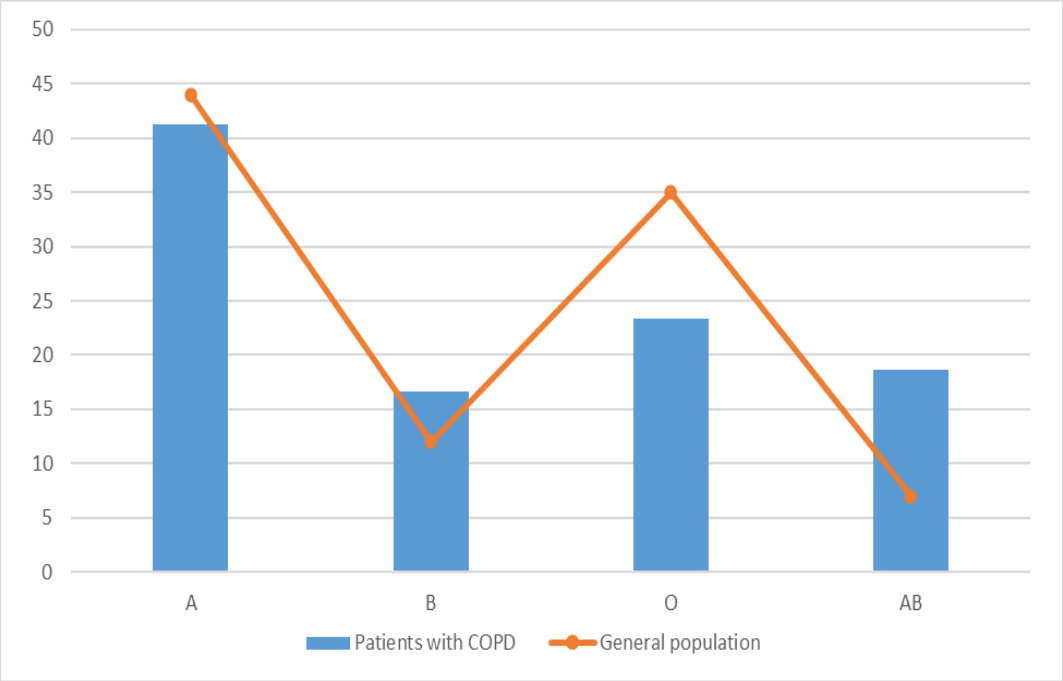


Figure 1. The structure of patients with COPD in relation to the stages of the disease

Being related to the terminal stage of the disease, respiratory insufficiency showed differences in gender representation. It is present in 40.4% of female patients, and in 25.2% of male patients.

The distribution of blood types in subjects with COPD shows that the most common blood type in both genders is A (41.3% in total), followed by O (in total 23.3%), and least number of subjects had B blood type (16.7% in total). The distribution of blood types in our sample of patients is different in relation to the general population (Figure 2). The most significant difference between patients and the general population group is in the representation of AB blood type ($p<0.001$), and the least difference is in A blood type ($p=0.505$). The O blood type is the least represented in patients with COPD in relation to the general population ($p=0.003$).



p value between sample of patients with COPD and the general population: A blood type $p=0.505$; B blood type $p=0.077$; O blood type $p=0.003$; AB blood type $p<0.001$.

Figure 2. Distribution of ABO blood types in the sample of patients with COPD (N = 150) and the general population

Highly significant difference between sample of patients with COPD and the general population is found for proportions of AB blood type ($p<0.001$) and O blood type ($p=0.003$) while the differences of A blood type ($p=0.505$) and B blood type ($p=0.077$) are not significant.

We determined a significant difference in the representation of blood types in relation to the stage of the disease ($\chi^2 = 41.652$, $p<0.001$). The prevalence of AB blood type decreases with the severity of the disease (23.6% mild/moderate down to 12.5% in very severe stage). The representation of blood type A is the highest in subjects with the severe stage of the disease (87.5%), and the lowest in subjects with mild and moderate stages of the disease (20.0%). Blood type B distribution is significantly more common in the moderate/mild stage of the disease compared to the severe/very severe stage of the disease (7.4%). Blood types B and O were not present in COPD patients in the very severe stage of the disease (Table 2).

Table 2. ABO blood type and Rh factor distribution in relation to the stage of the disease

Blood type	COPD stage			Total (n=150); n (%)
	Mild/Moderate n (%)	Severe n (%)	Very severe n (%)	
AB^+	9 (16.4)	8 (11.3)	2 (8.3)	19 (12.7)
A^+	6 (10.9)	27 (38.0)	15 (62.5)	48 (32.0)
B^+	15 (27.3)	1 (1.4)	0 (0.0)	16 (10.7)
0^+	9 (16.4)	17 (23.9)	0 (0.0)	26 (17.3)
Rh^+	39 (70.9)	53 (74.6)	17 (70.8)	109 (72.7)
AB^-	4 (7.3)	4 (5.6)	1 (4.2)	9 (6.0)
A^-	5 (9.1)	3 (4.2)	6 (25.0)	14 (9.3)
B^-	3 (5.5)	6 (8.5)	0 (0.0)	9 (6.0)
0^-	4 (7.3)	5 (7.0)	0 (0.0)	9 (6.0)
Rh^-	16 (29.1)	18 (25.4)	7 (29.2)	41 (27.3)
Total	55 (100.0)	71 (100.0)	24 (100.0)	150 (100.0)

The total sample of COPD patients characterizes the distribution of positive Rh factors in almost ¾ patients (72.7%; Table 3). In relation to the stage of the disease, the presence of Rh+ factor varies, but not statistically significantly. Rh-negative A blood type is most prevalent in subjects in a very severe stage of the disease (25%).

The presence of respiratory insufficiency in relation to blood types of the ABO system was shown to be statistically significant. Almost half of the subjects of blood type A (46.8%) have respiratory insufficiency, and then it decreases in the subjects of AB, O and B blood group (respectively 25.0% vs. 17.1% vs 12%).

Analysis of spirometry parameters in relation to gender, blood type and degree of nutrition showed a significant difference in the values of all parameters in relation to blood types (Table 4). Thus subjects with disease and blood type B have the highest values of the forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1).

Table 3. Distribution of ABO blood types and Rh factor in the sample of patients with COPD and the general population

Blood Type %	COPD patients	General population	p value
A	41.3	44	0.505
A +	32	36	0.307
A-	9.3	8	0.557
B	16.7	14	0.077
B+	10.7	12	0.624
B-	6.0	2	0<0.001
O	23.3	35	0.003
O+	17.3	28	0.004
O-	6.0	7	0.631
AB	18.7	7	<0.001
AB+	12.7	6	0.001
AB-	6.0	1	<0.001
Rh+	72.7	82	0.00303
Rh-	27.3	18	0.00303

The FVC value showed statistically significant and highest values in subjects with B blood type in relation to AB blood type ($p = 0.014$), A ($p<0.001$) and O ($p = 0.021$) blood type.

The average values of FEV_1 are significantly lower in patients with blood type A compared to patients with AB blood type ($p=0.018$), compared with patients with B blood type ($p <0.001$) and in relation to patients with O blood type ($p <0.010$).

Patients with COPD with blood type A have a significantly lower average value of the FEV_1/FVC ratio, which is a real indicator of the existing obstructive ventilation disturbance, compared to blood type AB ($p=0.002$) and blood type O ($p=0.010$). The ratio has the highest values in blood type B, which is significantly higher compared to patients with blood type AB, A and O blood types. The spirometry parameters values indicate more severe stages of the disease, with the lowest average values in individuals with blood type A.

Table 4. Parameters of spirometry in relation to gender, blood type and body mass index (BMI)

Spirometry parameters	Features	n	Mean	SD	Min	Max	p
	Gender						
FVC (%)	Male	103	76.50	19.25	40.40	121.00	t=0.205
	Female	47	77.21	21.18	31.70	133.33	p=0.838
FEV_1 (%)	Male	103	45.48	15.20	20.50	83.80	t=0.504
	Female	47	44.19	12.69	20.10	66.30	p=0.615
FEV_1%FVC	Male	103	47.23	11.34	22.28	68.10	t=1.663
	Female	47	50.61	11.98	26.89	69.68	p=0.098
	Blood type						
FVC (%)	AB	28	74.64	19.20	42.60	109.00	F=5.689
	A	62	72.39	19.89	31.70	117.00	p=0.001
	B	25	90.61	20.11	55.70	133.33	
	0	35	76.14	15.83	51.50	104.10	
FEV_1 (%)	AB	28	48.18	14.99	25.50	83.80	F=7.719
	A	62	39.00	14.58	20,10	83.10	p<0.001
	B	25	52.48	10.31	30.50	79.20	
	0	35	48.07	12.36	30.60	78.70	
FEV_1%FVC	AB	28	53.58	12.25	26.89	69.68	F=6.036
	A	62	44.23	10.68	22.28	67.77	p=0.001
	B	25	47.70	11.65	32.41	69.68	
	0	35	51.67	10.29	26.35	68.10	
	BMI						
FVC (%)	Malnourished	14	79.88	20.17	31.70	108.30	F=1.375
	Normally fed	75	79.29	20.69	37.40	133.33	p=0.253
	Pre-obesity	46	72.33	18.39	41.30	106.40	
	Obesity	15	74.36	18.20	48.70	114.60	
FEV_1 (%)	Malnourished	14	40.56	11.62	21.00	60.90	F=0.970
	Normally fed	75	46.30	15.70	20.10	83.80	p=0.409
	Pre-obesity	46	43.59	13.05	21.80	79.20	
	Obesity	15	47.75	14.07	29.60	78.70	
FEV_1%FVC	Malnourished	14	42.96	13.11	25.17	67.77	F=1.929
	Normally fed	75	47.86	11.75	22.28	69.68	p=0.127
	Pre-obesity	46	49.08	11.75	26.89	68.08	
	Obesity	15	52.95	6.79	41.24	61.91	

DISSCUSSION

In this study, we found significant differences in the prevalence of blood types of the ABO system and Rh factor in patients with COPD compared to the general population. Statistically, the most significant difference we found in the prevalence of AB blood type between patients with COPD and the general population (Rh^+ Rh^- $p<0.001$). The B blood type is the least represented in the sample of patients with 16.7%, while its proportion in the general population is significantly higher (37%). In relation to the general population having blood type O frequency of 35%, in the sample of patients we found a proportion of 23.3%. There was also a significant difference between Rh factors, and a higher prevalence of negative Rh factors in patients with COPD compared to the general population.

The data on the ABO blood type distribution and its association with COPD, viral infections, asthma, and tuberculosis vary. In Garratty's study, through review of previous works, tuberculosis is more prevalent in people with blood types O, B; bacterial infections are more prevalent in people with blood types B, and AB. Viral infections are associated with a higher incidence of blood type A and AB (GARRATTY, 2005).

BJANZADEH *et al.* found no association between ABO system blood types and asthma, while MROCZEK *et al*. found a lower incidence of O blood type in patients with asthma and chronic obstructive pulmonary disease (BJANZADEH *et al.*, 2009; MROCZEK *at al*., 2018). Data from the study by MROCZEK *et al*. showed a higher incidence of blood type A in patients with COPD and asthma, compared to the general population and coincides with the data in our study. It also coincides that the combined blood types A, B and AB are significantly more common in patients with asthma and COPD, compared to blood type O, which is the least present.

The spirometry parameters from our study indicate more severe stages of the disease with the lowest average values in individuals having blood type A. It is still not determined whether the explanation here regarding the level and reduced activity of alkaline phosphatase in blood type A could be acceptable for these data, (SUN *et al*., 2019). It has long been known that blood type A can further inactivate the action of alkaline phosphatase (BAYER *et al*., 1980).

Negative Rh factor often negatively correlates with various diseases. The results of this study might also point to such conclusions (Rh negative A blood type is most prevalent in subjects in a very severe stage of COPD), but this should be investigated in more detail. The Rh-negative phenotype was associated with a slower response to *Toxoplasma gondii* infection in the study of soldiers in the Czech Republic (FLEGR *et al*., 2009; FLEGR *et al*., 2018). A study conducted in Spain (Basque Country) highlighted the negative correlation between Rh-negative factor and liver transplantation (HANVESAKUL *et al.*, 2008).

The frequency of RhD^+ and RhD^- phenotypes appears to have been influenced by migration and genetic drift rather than natural selection (SINGLETON *et al*., 2000; TOUINSSI *et al.*, 2009). A higher incidence of cardiovascular disease and cancer (excluding cervical cancer) in Rh-negative homozygotes was observed in an environmental regression analysis, while being less susceptible to congenital malformations and neuropsychiatric disorders (HALMIN *et al*., 2017).

ABO blood type studies stay an actual topic of research. They have shown that ABO blood types are associated with cardiovascular disease, cancer, severe malaria (*Plasmodium*

falciparum), but also with depression and anxiety (LIUMBRUNO *et al.*, 2013; HANSEN *et al.*, 2005; YAMAMOTO *et al*., 2012; FRY *et al*., 2008; RICH *et al.*, 2013; *et al*., 2014). During the COVID19 pandemic, susceptibility to SARS CoV-2 dependent on ABO blood type has been demonstrated as well (DAI, 2020; ZHAO *et al.*, 2020).

It is to be expected that future research will re-examine the predisposition to developing COPD and the role of blood type antigens ABO and Rh system (MROZECH *et al*., 2018). Future studies should investigate the complexity of ABO blood type antigens, their interaction with other genes as well as genes located near the ABO locus. Genes in the immediate vicinity of the ABO gene locus are genes of muscular dystrophy, aortic valve disease, colon cancer, but also longevity (SADAHIRO *et al*., 2014; DIZDAROGLU, 2015; TZORTZAKI *et al*., 2012).

CONCLUSION

We found significant differences in the representation of blood types of the ABO system and Rh factor in patients with COPD compared to the general population. The most significant statistical difference is found in decreased prevalence of AB blood type in the patients compared to the general population. From all blood types, the B blood type is the least present in the sample of patients in relation to the general population. COPD patients with B blood type have the least disturbed lung function, contrary to those with A blood type, especially if Rh negative. The latter patients are found in the highest proportion in the terminal phase of the disease. Thus, Rh-negative patients with A blood type require particular clinicians' attention and care from the very beginning of the disease. Found frequency of O blood type in the patients group is significantly lower compared to the general population.

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ANALIZA KRVNIH GRUPA SISTEMA ABO KOD BOLESNIKA SA HRONIČNOM OPSTRUKTIVNOM BOLEŠĆU PLUĆA

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Izvod

Hronična opstruktivna bolest pluća (HOBP) je oboljenje čiji su ispoljavanje i razvoj uslovljeni sredinskim, genetičkim i socioekonomskim faktorima. Sistem krvnih grupa ABO bi mogao da bude jedan od faktora genetske predispozicije za bolest. Cilj ove studije bio je da utvrdi postoji li razlika u zastupljenosti krvnih grupa sistema ABO u uzorku obolelih od HOBP u odnosu na opštu populaciju i da li ima povezanosti pojedinh tipova sa težinom kliničke slike i plućne funkcije bolesnika. Studija je obuhvatila 150 obolelih od HOBP (103 muškarca – 68.7% i 47 žena – 31.3%), prosečne starosti 64.80 ± 8.38 godina (raspon: 33-82) i prosečnog indeksa telesne mase 24.54 ± 4.63. Značajno je veća učestalost krvne grupe AB u odnosu na opštu populaciju ($p<0.001$). Najučestalija krvna grupa u uzorku obolelih je krvna grupa A (41.3%), kao i u opštoj populaciji, a najmanje zastupljena je krvna grupa B (16.7%). Nismo našli obolele sa krvnim grupama B i O među obolelima sa veoma teškim stadijumom bolesti. Oboleli sa krvnom grupom A imali su najniže vrijednosti FEV1%FVC kao pokazatelja bronhoopstrukcije, naročito ako su Rh-negativni, dok je kod bolesnika sa grupom B plućna funkcija bila najviše očuvana. Potrebna su nova istraživanja da otkriju ulogu ABO antigena u nastanku i toku hronične opstruktivne bolesti pluća.

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