

COVID-19 AND COMORBIDITIES

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Funding: none**Competing interests:** none**ABSTRACT**

Background: The coronavirus disease-2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus). The virus has spread globally, causing millions of deaths.

Aim: This study was made with the aim of revealing the clinical features of COVID-19, as well as assessing the impact of comorbidities in patients infected with SARS-CoV-2.

Methods: In this analysis the data was obtained from the hospital information system (BIS), involving patients who were hospitalized for treatment of moderate to severe COVID-19 infection at the Infectious Diseases Clinic of the Tuzla University Clinical Center (UCC) between January 1 and April 8, 2021.

Results: Four hundred infected patients were included in the study, 345 (86.2%) of whom had comorbidities, and 27 (6.8%) without comorbidities. The most common symptom was fever in 248 (62%), followed by dyspnea in 212 (53%), and cough in 168 (42%). The most prevalent comorbidities were cardiac 273 (68.3%), then endocrinological 135 (33.8%), surgical 66 (16.5%), neurological 69 (15%), oncological 48 (12%), nephrological 44 (11%), and pulmonary 40 (10%). The existence of a significant association between the presence of comorbidities and the patients suffering from COVID-19 on mechanical ventilation due to treatment complications was determined, $p=0.000$ ($p<0.05$) at the 95% significance level.

Conclusion: We assessed the prevalence of comorbidities in patients with COVID-19 and found that underlying disease, including cardiac and endocrinological diseases, may be a risk factor for severe forms of COVID-19.

Key words: COVID-19, clinical features, comorbidities, risk factors

INTRODUCTION

During the last few decades, the world witnessed the emergence of new viruses that posed serious health risks [1]. The SARS-CoV-2, previously known as the new coronavirus, broke out in Wuhan (China) and caused great morbidity and mortality at the global level [2, 3]. It appeared for the first time at the end of 2019 and caused the disease named COVID-19, omitting the geographical location and association with certain animals from the name in order to avoid prejudice, inaccuracies and stigma [3], WHO has declared the SARS-CoV-2 epidemic on March 11, 2020.

Common symptoms of COVID-19 include fever, sore throat, cough, lung infection and, in severe cases, acute respiratory distress syndrome, sepsis and death. SARS-CoV-2 predominantly affects the lungs, but it can also affect other organs such as the brain, heart and gastrointestinal system. It has been observed that 75%

of hospitalized patients with COVID-19 have at least one comorbidity related to COVID-19. The most common comorbidities reported are hypertension, neurological disorders (NDs), diabetes, cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs). COVID-19 also results in hypercoagulability problems such as gangrene, stroke, pulmonary embolism and other related complications [4].

Several studies on the comorbidities of patients infected with SARS-CoV-2 indicate that hypertension, diabetes, obesity, neoplasms, chronic kidney disease, and COPD as leading risk factors for the fatal outcome of the disease [5, 6].

The US Centers for Disease Control and Prevention (CDC) also includes immunocompromising conditions and liver disease as potential risk factors for severe COVID-19 [7], although specific data on the risks associated with these conditions are limited.

There are several risk factors associated with COVID-19, for example the male population has a higher rate of infection with SARS-CoV-2 compared to females [6]. Studies have shown that an increasing frequency of severe and fatal COVID-19 is observed within elderly population [5], and this phenomenon is partly attributed to pre-existing comorbid conditions.

At admission, 20–51% of patients reported having at least one comorbidity, with diabetes (10–20%), hypertension (10–15%), and other cardiovascular and cerebrovascular disorders (7–40%) being the most prevalent [8–10].

Individuals with chronic underlying illness may have severe outcome risks as high as 10-fold as compared to individuals without any comorbidity [11].

The goal of our work was to show the most common comorbidities in patients hospitalized due to COVID-19.

SUBJECTS AND METHODS

Subjects

A retrospective observational study was conducted that included data from BIS from 400 subjects who were hospitalized for treatment of moderate to severe COVID-19 at the Infectious Diseases Clinic of the UCC Tuzla in the period between January 1 and April 8, 2021. This period was chosen because it is normally the peak of acute respiratory infections in our area. The patients were older than 18 years.

The subjects were divided into two groups, depending on the presence of comorbidities before hospitalization:

1. **Group 1:** subjects who had verified comorbidities/comorbidities before hospitalization.
2. **Group 2:** subjects who had no verified comorbidity/comorbidities before hospitalization.

The study was approved by the Ethics Committee of UCC Tuzla before data collection. Also, this study is part of a project carried out in UCC Tuzla during 2021 which involved COVID-19 and comorbidities.

Methods

The following data analyzed for all 400 subjects: age, sex, symptoms (fever, cough, headache, sore throat, dyspnea, weakness, loss of appetite, loss of sense of smell and taste, vomiting, diarrhea, dizziness), presence of comorbidities during hospitalization (cardiovascular, gastrointestinal, nephrological, endocrinological, hematological, pulmonary, neurological, surgical, orthopedic, urological, psychiatric, ophthalmological, otorhinolaryngological). The influence of comorbidities on the occurrence of complications and the outcome of treatment (recovery or death) was analyzed. The assessment of the frequency of comorbidities was based on previous medical documentation. An analysis was also conducted to identify significant

indicators of the severity of the disease of COVID-19, admission to the intensive care unit (ICU), mechanical ventilation and mortality.

The diagnosis of COVID-19 was confirmed by a polymerase chain reaction (PCR) test on nasal and oropharyngeal swab samples taken at the time of admission to the hospital.

Chronic GI patients who are participants in transplant programs were not included in this study (we did not have all needed data for these patients because they were primarily not treated at the Clinic for Infectious diseases).

Statistical data processing

Non-parametric and parametric methods were used to calculate statistical significance. After statistical normality test, continuous variables were presented as mean with standard deviation (SD), while variables with skewed distribution as median with interquartile range (IQR, 25th–75th quartile). Categorical variables are presented as percentages. Differences in categorical variables were tested with the Chi-square test. One-way analysis of variance (ANOVA) was used to compare continuous variables with a normal distribution, and the Mann-Whitney test for continuous variables with a skewed distribution. All statistical hypotheses were tested at the 95% confidence level, i.e., 5% risk ($p < 0.05$). Statistical data processing was carried out using the statistical tool IBM SPSS Statistics v.23. The obtained results are presented in the form of a table and graph.

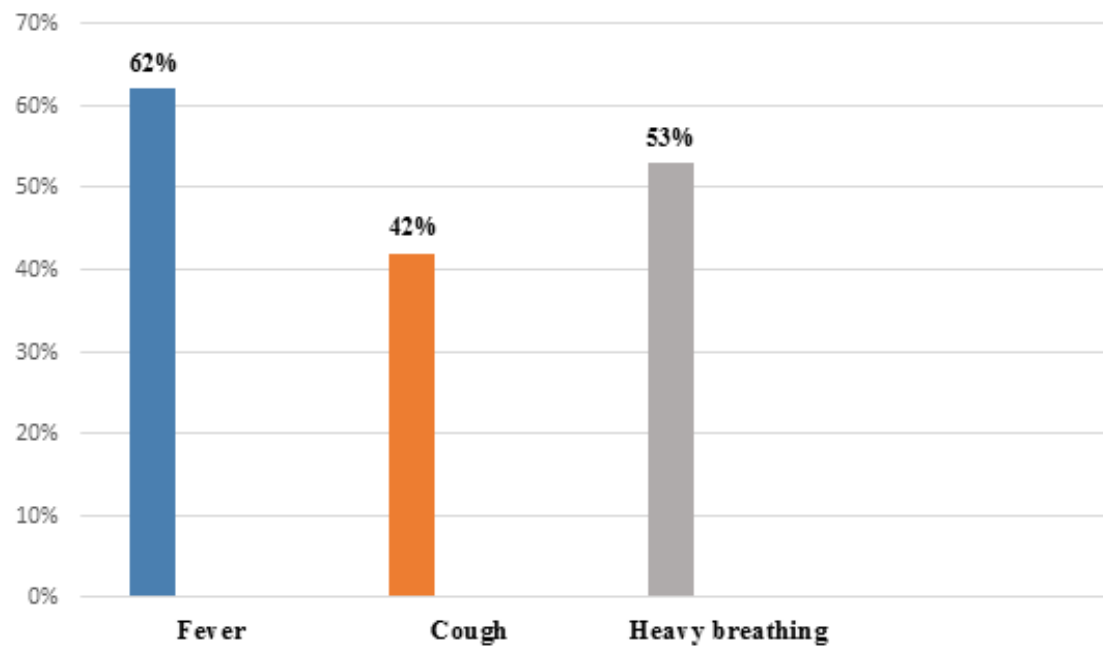
RESULTS

The research included a total of 400 subjects hospitalized for treatment of moderate to severe COVID-19 infection from January 1st to April 8th 2021., of which 221 (55.2%) were men and 179 (44.8%) were women, aged 22–91 years. The arithmetic mean for age is 68.03 ± 12.491 (SD) and the median is 69 years. The length of hospitalization ranged from a minimum of 1 day to a maximum of 27 days. Median length of hospitalization is 5 years, arithmetic mean is 5.78 ± 5.11 (SD) years. For 78 respondents, data on the duration of hospitalization is not known (Table 1).

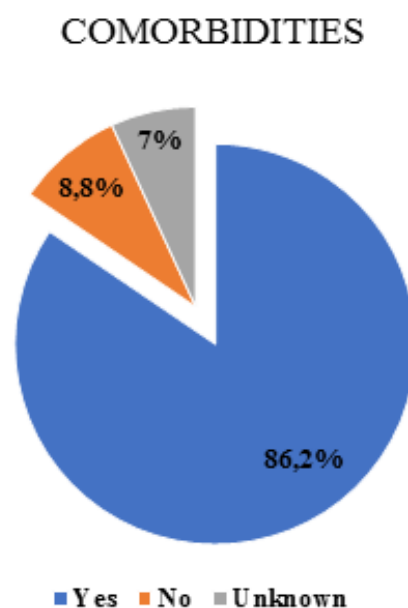
Table 1. Demographic data of the patient and length of hospitalization

	N	Min.	Max	Aritm. mean	SD	Median
Sex	Male	221				
	Female	179				
Age (years)		22	99	68,3	± 12,15	69
Length of hospitalization (days)		1	27	5,78	± 5,11	5

The most common symptom is fever 248 (62%), followed by dyspnea 212 (53%), and cough 168 (42%) (Figure 1.)

**Figure 1.** Prevalence of symptoms in patients with COVID-19

There were 345 (86.2%) subjects with comorbidities, 27 (6.8%) without comorbidities, and we lack information on the existence of comorbidities for 28 (7%) subjects (Figure 2).

**Figure 2.** Prevalence of comorbidities in patients with COVID-19

The most common comorbidities are cardiovascular, which 273 (68.3%) subjects have, with arterial hypertension as a primary disease in this group, followed by endocrinological 135 (33.8%) subjects, with diabetes mellitus type 2 as a primary disease in this group, surgical 66 (16.5%), which refers to post-surgical complications and complications during the surgical procedure, neurological 60 (15%), oncological 48 (12%), nephrological 44 (11%), pulmonary 40 (10%), CVD 22 (5.5%), psychiatric 18 (4.5%), gastroenterological 18 (4.5%), hematological 17 (4.3%), orthopedic 15 (3.8%), urological 13 (3.3%), ophthalmological 6 (1.5%), neurosurgical 3 (0.8%) and otorhinolaryngological 3 (0.8%) (Figure 3).

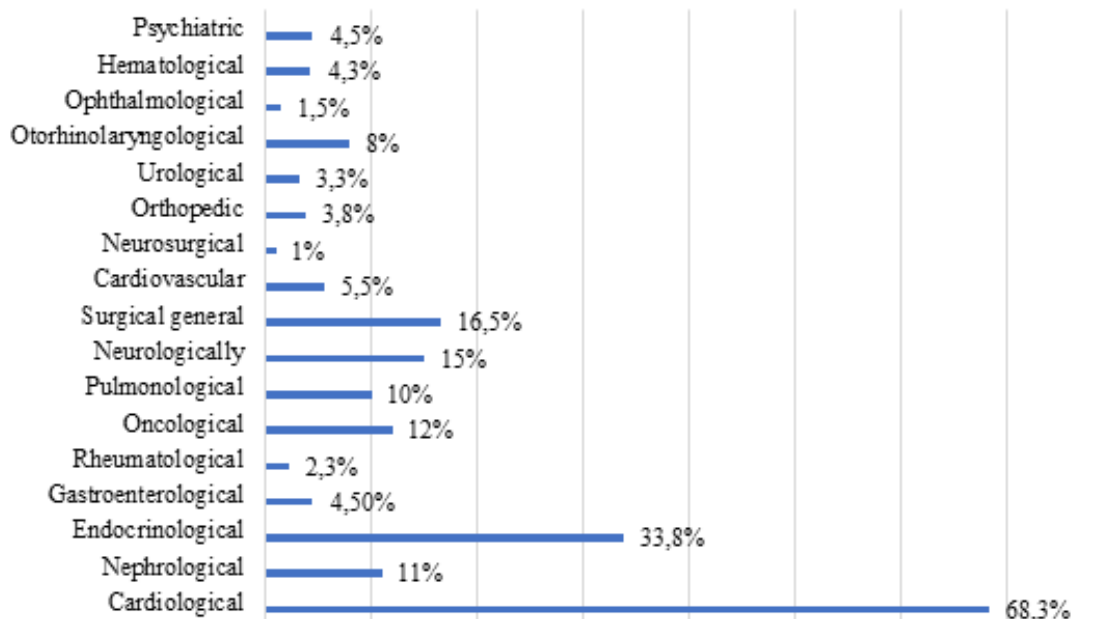


Figure 3. Types of comorbidities in patients with COVID 19

Thirty-seven (9.3%) subjects were on mechanical ventilation, while for 97 (24.2%) subjects we do not have information on whether they were on mechanical ventilation or not. Other subjects, 266 of them (66.5%) were not on mechanical ventilation (Figure 4).

MECHANICAL VENTILATION

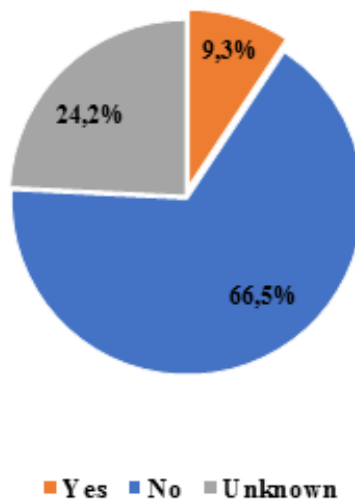


Figure 4. Distribution of patients according to necessity for mechanical ventilation

The outcome of the treatment is known for 325 (81,3%) subjects and the largest number of them is in the recovered category, 195 of them (48.8%). Sixty (15%) subjects were transferred to Pulmonary Respiratory Centre (PRC), 7 (1.8%) subjects requested discharge at personal request, and 63 (15.8%) subjects have died. For 75 (18.8%) subjects we do not have data on the outcome of treatment because of patient privacy regulations of Pulmonary Respiratory Centre UCC Tuzla (Figure 5).

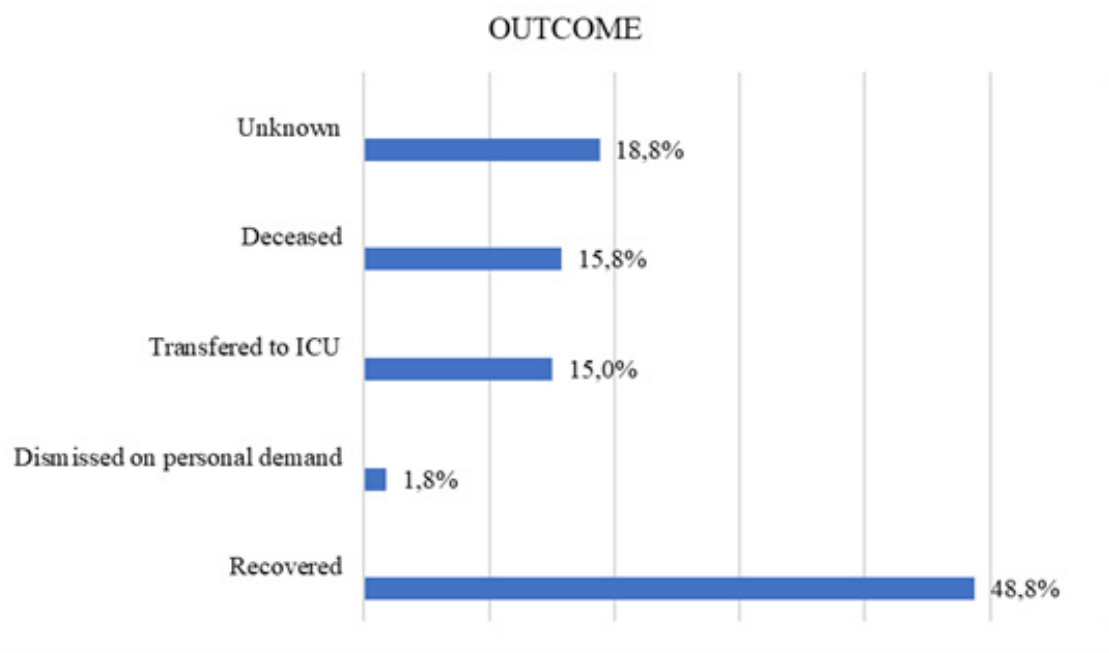


Figure 5. Outcome of the treatment of patients with COVID-19

Of the 60 subjects who were transferred to PRC due to complications, 47 (78.3%) of them had comorbidities, and Pearson’s chi-square test determined the existence of a significant statistical association, given that $p=0.002$ ($p<0.05$), and between the existence of comorbidities and the occurrence of complications in the treatment of subjects suffering from COVID-19 (Table 2.)

Table 2. Outcome of patients with COVID-19 regarded to the presence of comorbidities

		Outcome				
		Recovered	Transferred to PRC	Requested discharge	Lethal outcome	Data unknown
Comorbidities	Yes	164	47	7	63	64
	No	19	7	0	0	1
	Data unknown	12	6	0	0	10
Summary		195	60	7	63	75

Out of a total of 37 subjects who were on mechanical ventilation, 25 of them (67.5%) had comorbidities. Pearson’s chi-square test also determined the existence of a statistically significant association between the presence of comorbidities and the connection of patients suffering from COVID-19 on mechanical ventilation due to treatment complications, and given that the p-value is $p=0.000$ ($p<0.05$) at the level significance of 95% (Table 3).

Table 3. Use of mechanical ventilation in patients with COVID-19 considering the presence of comorbidities

		Mechanical ventilation		
		Yes	No	Data unknown
Comorbidities	Yes	25	236	84
	No	8	18	1
	Data unknown	4	12	12
Summary		37	266	97

In order to examine the impact of comorbidities on the outcome of the treatment of patients suffering from COVID-19, we used a one-way analysis of variance (ANOVA) and the application of Post Hoc multiple correlation, specifically the Tukey test, which allowed us to gain insight into the existence of differences between individual categories related to treatment outcome, depending on the presence of comorbidities. Thus, it is found that there is a statistically significant difference between the category "Recovered" and the category "Died" since the p value is less than 0.05, $p=0.044$; and at a significance level of 95%. Also, there is a statistically significant difference between the category "Transfer to PRC" and the category "Died", where $p=0.012$, i.e., $p<0.05$ at the 95% significance level (Table 4). We can therefore conclude that the existence of comorbidities in patients with COVID-19 affects the outcome of treatment.

Table 4. The impact of comorbidities on the outcome of treatment of patients with COVID-19

(I) Outcome	(J) Outcome	Mean Difference (I-J)	Std. Error	Signif.	95% Confidence Interval
					Lower Boundary
Recovered	Transferred to PRC	-.096	.081	.755	-.32
	Discharged per request	.221	.210	.832	-.35
	Died	.221*	.079	.044	.00
	Data unknown	-.059	.074	.930	-.26
Transferred to PRC	Recovered	.096	.081	.755	-.12
	Discharged per request	.317	.218	.594	-.28
	Ex. letalis	.317*	.098	.012	.05
		.037	.095	.995	-.22

DISCUSSION

Bosnia and Herzegovina has recorded a total of 399,227 inhabitants infected with the SARS-CoV-2 since the beginning of the COVID-19 pandemic, and of these numbers, 178,328 new infections were recorded for the period from January 1, 2021 to December 30, 2021 [12].

This research included a total of 400 subjects who suffered from COVID-19 in the period of 01.01. until 08.04.2021., and required hospital treatment, which according to our knowledge, is the study with the largest number of subjects infected with the SARS-CoV-2 conducted at the UCC Tuzla. The average age of the subjects is 69 years, which corresponds to the global trend of the dominant representation of patients requiring hospitalization in the seventh decade of life.

Of the total number of subjects, 55% were male and 45% females, which correlates with the previously known facts about the higher expression of comorbidities of a predominantly cardiovascular nature in men, as well as the higher expression of angiotensin-converting enzyme 2 receptors (ACE-2 receptors), which are the main binding sites for the spike protein SARS-CoV-2 viruses. The average length of stay in the hospital is 5 days [13], which also correlates with the average hospitalization worldwide of 7 days, and we should keep in mind that we do not know the length of hospitalization for 19.5% of subjects.

Out of a total of 400 subjects, 62% had fever as the leading symptom, 53% dyspnea, and 42% dry cough.

When we compare our subjects with the observational study from the ZOE COVID study 2021, which includes subjects from the United Kingdom of predominantly white race from an area of relatively similar climatic conditions and lifestyle in a period when the Delta strain of the SARS-CoV-2 is dominant in the world, we observe that in relation in the afore mentioned study, our subjects had dominant respiratory symptoms with fever, while the other group had more dominant general symptoms such as pain in muscles and joints, nausea, poor appetite, etc. [14].

There are 86.2% of subjects with comorbidities, 6.8% without comorbidities, and we do not have information on the existence of comorbidities for 7% subjects. As the leading group of comorbidities, we have CDs in first place with 68.3%, followed by endocrinological diseases with 33.8%, and various surgical conditions with 16.5% of subjects. The representation of cardiovascular patients follows the global trend of dominant comorbidities, because CDs are the leading pandemic of non-infectious diseases, and changes in a society during the pandemic, which included the restriction of an active life, the inaccessibility of primary and secondary levels of health care for the purpose of regular controls and optimization of therapy, and emphasized stressors due to media pressure and devastating reports during the acute phase of the pandemic in 2021, resulted in a worsened quality of life, and thus an increase in patients with hypertension, hyperlipoproteinemia, diabetes and obesity, which are known pro-inflam-

matory conditions with impaired phagocytic ability of the immune system cell. The increase in patients with comorbidities resulted in an increase in the degree of complications during infection with the SARS-CoV-2. The leading cardiovascular comorbidity is arterial hypertension (29.5%) followed by chronic coronary disease (22.5%) and obesity (11.4%) [15], and the data correlated with our group of respondents. This group had the highest mortality rate due to complications of their former known diseases during the COVID-19. After that, patients with diabetes mellitus had a high mortality rate. However, the third leading comorbidity in our group is patients who required surgical intervention, followed by patients who are being treated for a neurological disease, which contradicts studies we have used in comparison, who list respiratory diseases as third leading group of comorbidities, with COPD as generally the second leading comorbidity after arterial hypertension. In our group of subjects, respiratory diseases occupy the seventh place with a representation of 10%. However, even if respiratory diseases are positioned lower on the table of comorbidities in our research, they are the third in terms of mortality rate. It is interesting that our group of respondents has a high level of comorbidities related to nephrological diseases with a representation of 11%, while in the world, renal diseases are the most common after arterial hypertension, COPD, chronic coronary syndrome, liver diseases, malignancy, and asthma [15].

Tenth place in our group of comorbidities is occupied by chronic gastrointestinal diseases with 4.5%, which correlates with global data on the insignificance of the incidence of complications of comorbidities of a chronic gastrointestinal nature (primarily Crohn's disease and ulcerative colitis) [16].

Regarding the complications of acute respiratory distress, we had 9.3% of subjects on mechanical ventilation support, and that 66.5% did not require the same, with unknown information on mechanical ventilation for 24.2% of patients due to the imperative privacy of patients treated in the PRC, where all our clinical units for mechanical ventilation and respiratory support are located. We did not receive data on non-invasive methods of oxygenation through the patient's medical history. When we compare our data with the knowledge of much higher incidences of mechanical ventilatory support worldwide with a prevalence of about 47.2% in China [13], 16% in the UAE [17], and 15-30% in a large group of patients included in the ISARIC database survey (which includes over 40,000 respondents in 43 countries) [18], what we notice in addition to the lower incidence of setting an indication for mechanical ventilation support, is a significantly higher mortality with 15.8%, while in the mentioned studies the mortality rate was 4.3% for China, 2.7% for UAE, 30.7% for ISARIC survey. The higher mortality rate among our respondents can be explained by the higher incidence of comorbidities, but it is more in favor of inadequate and insufficient equipment to support life-threatening patients, which is a problem of a non-medical nature and is not within the scope of the medical staff's activities.

CONCLUSION

This study showed that the majority of hospitalized COVID-19 patients belong to the older age group and have had comorbidities present at the time of hospitalization. The most common of them are cardiovascular and endocrinological. The presence of comorbidities affected the higher incidence of patient transfer to the ICU, placement on mechanical ventilation, as well as mortality itself. The information we received will hopefully play an important role in management and decision-making to resolve complications in order to reduce the further economic and health burden of the COVID-19 pandemic in the elderly population with already existing comorbidities.

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