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Coronavirus Pandemic

The main predictive factors of worse outcome in patients with COVID-19 infection hospitalized in temporary COVID hospital

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Abstract

Introduction: After the Serbian community hospitals had reached their full capacity during the pandemic, new institutions were enrolled into the coronavirus disease 2019 (COVID-19) system as temporary COVID hospitals (TCH). These hospitals usually had no intensive care units (ICU) and no possibility to treat severely ill patients. The aim of this study was to identify risk factors at the time of triage that could help identify patients that will require ICU treatment and cannot be treated in a TCH.

Methodology: In this retrospective study, a total of 158 patients with COVID-19 infection were enrolled. The demographic information, underlying comorbidities, laboratory findings, chest X-rays, computed tomography scans, and clinical outcomes were obtained from medical records. Deterioration of a patient's condition was regarded as a need for further transfer to ICU.

Results: During the hospitalization 15.2% of patients required transfer to ICU. Patients with deterioration were significantly older and there was no difference between genders. We observed a higher prevalence of hypertension, other cardiovascular diseases, lower lymphocyte and platelet counts, and higher IL-6 and troponin T in patients with deterioration. The multivariate logistical regression model showed that only age was an independent risk factor for deterioration and with each year of age, the risk for poor outcome increased by 8%.

Conclusions: Patients with cardiovascular risk factors, low lymphocyte and platelet counts, high IL-6 and troponin T and, especially, increased age should not be treated in a TCH because of the high possibility for deterioration and need for transfer to an ICU.

Key words: COVID-19; infection; predictive factors.

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Introduction

Serbia was faced a unique early second coronavirus disease 2019 (COVID-19) outbreak from 1stJune to 1st September 2020. During this period, the weekly average number of new cases reached a maximum of over 400, and the maximum number of new deaths was 13. In addition, the highest weekly average number of hospitalized patients was almost 5000 and the highest weekly average number of patients in intensive care units (ICU) was 185 [1] (Figure 1). During that time, COVID-19 vaccines and specific antiviral therapy were not available, and there were no dedicated COVID-19 hospitals. After the community hospitals had reached their full capacity, the Government of the Republic of Serbia and its Ministry of Health enrolled new institutions into the COVID-19 system. The Institute of Rheumatology in Belgrade, a tertiary health care institution responsible for the care and treatment of several thousand patients with different musculoskeletal disorders and rheumatic diseases, was among them. Our Institute was dedicated to treating patients with mild to moderate COVID-19 illness since there was no ICU and central oxygen supply system, according to the plan of the Ministry of Health. Furthermore, after treating a total of 158 patients we encountered a wide variety of different disease courses and a significant number of severe ones. In the end, we wondered if there were any clinical, laboratory or imaging predictive markers that could indicate the course of COVID-19 before hospital admission.

Therefore, the aim of this study was to analyze the data we had accumulated in our first COVID-19 rotation that could potentially help us recognize high-risk patients at the time of triage and admission in temporary hospitals and thus prevent complications associated with transportation to the intensive care unit.

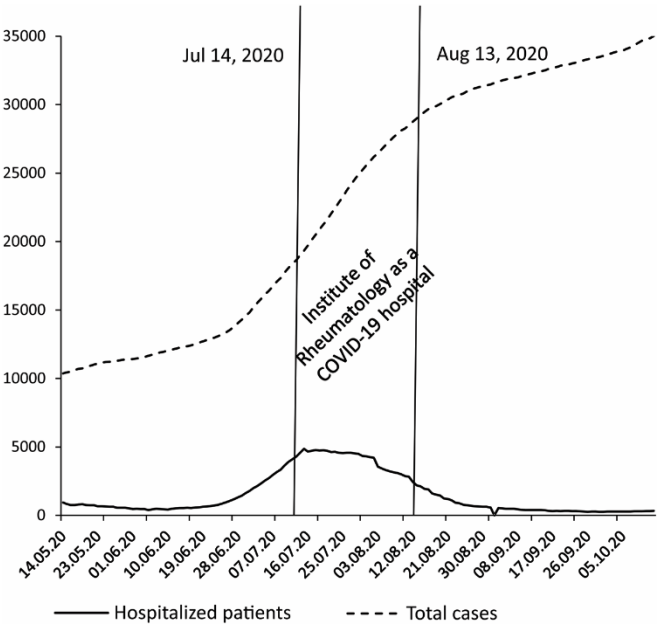
Methodology

In this retrospective cohort study, a total of 158 patients diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and admitted to the Institute of Rheumatology (IR), a temporary COVID hospital (TCH), from July 14th to August 13th 2020 were enrolled. This study was approved by the Ethics Committee of the Institute of Rheumatology (Ethical approval number 132/9, 2022).

The basic demographic information, underlying comorbidities, laboratory findings, chest X-rays, computer tomography (CT) scans, applied therapy and clinical outcomes were obtained from hospital medical records.

Obesity, diabetes, hypertension, other cardiovascular diseases (coronary heart disease, arrhythmias, cardiomyopathies), and previously diagnosed respiratory diseases (chronic obstructive pulmonary disease - COPD, bronchial asthma) were recorded as coexisting chronic diseases. The white blood cells (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute platelet count (PLT), C-reactive protein (CRP), peak CRP level, interleukin-6 (IL-6), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin (fer), D-dimer and troponin T were observed in the laboratory findings on admission. Chest X-ray findings were analyzed by radiologists to diagnose interstitial changes, ground glass opacities, spotty consolidation, early fibrosis and pleural effusion. CT was performed and CT severity score was calculated in 17 out of 158 patients [2].

Figure 1. Prevalence of COVID-19 infected cases and number of hospitalized patients in Serbia from 14th May 2020 to 5th October 2020.



The patients were treated following the National COVID-19 Treatment Guideline, version 8 [3] which was approved by the Ethics Committee of the University Clinical Centre of Serbia on July 8th,2020. Treatment recommendations included antimalarials, antibiotics, corticosteroids, convalescent plasma from recovered COVID patients, anticoagulants, IL-6 inhibitors, conventional oxygen therapy, and vitamins.

The disease severity was defined according to the National COVID-19 Treatment Guideline, version 8. The disease severity was divided in four types: mild – type 1, moderate – type 2, severe – type 3 and critical-type 4 and 5 according to symptoms, laboratory findings and imaging results. When patients had modest clinical symptoms as well as confirmed radiographic signs of pneumonia with or without hypoxia at the time of admission they were identified as having type 2 moderate disease. Patients were considered as having type 3 of disease when they had fever, serious hypoxia, multiple opacities verified by chest X-ray (or specific CT changes), but with an adequate response on oxygen therapy (fingertip oxygen saturation > 90% after one hour of oxygen therapy via nasal cannula or face mask with flow rate 10-15 liters per minute). Patients with moderate and severe COVID infection were hospitalized in the IR. Deterioration of patient condition was regarded as a need for further treatment in the progressive care unit or ICU despite applied care and therapy (onset of the acute respiratory distress syndrome, ARDS).

Categorical data are presented with absolute and relative numbers. Numerical data are shown as described with arithmetic mean and standard deviation (sd), or median with range (from minimum to maximum), depending on the distribution. Normal distribution was evaluated by mathematical and graphical methods. Two independent groups were compared with Student t-test or Mann Whitney U test for numerical variables, depending on the distribution, as well as with Chi-square or Fisher's exact test for categorical variables. In order to evaluate factors influencing the possibility of disease deterioration, univariate and multivariate logistic regression model (backward Wald model) was used and calculated B, OR, 95% CI of OR, and p value were presented. All statistical methods were considered significant if $p \leq 0.05$. Statistical analysis was performed in IBM SPSS (version 21.0).

Results

Among the 158 patients there were 94 men (59.5%) and 54 women (40.5%), with the mean age of 56.6 ± 25.2 years. Most of the patients were in the age group 51-60 years and the highest frequency of deterioration was recorded in the age group 81-90 years, where 62.5% of patients had severe form of the disease (Figure 2). During the hospitalization, 24 (15.2%) patients were required to transfer to another hospital in order to be treated in progressive care and intensive care units. There was a statistically significant difference in the average age of COVID-19 patients with and without deterioration (68.7 ± 11.8 years vs. 54.4 ± 14.7 years, $p < 0.001$) (Table 1). Based on the presence of deterioration of the disease, patients were compared in relation to demographic characteristics, the presence of comorbidities and certain laboratory parameters at the time of admission (Tables 1 and 2). No significant difference was observed with respect to deterioration between patients of different gender, $p = 0.745$ (Table 1). A statistically significant higher prevalence of hypertension ($p = 0.020$) and other cardiovascular

Figure 2. Distribution of COVID-19 disease deterioration according to age.

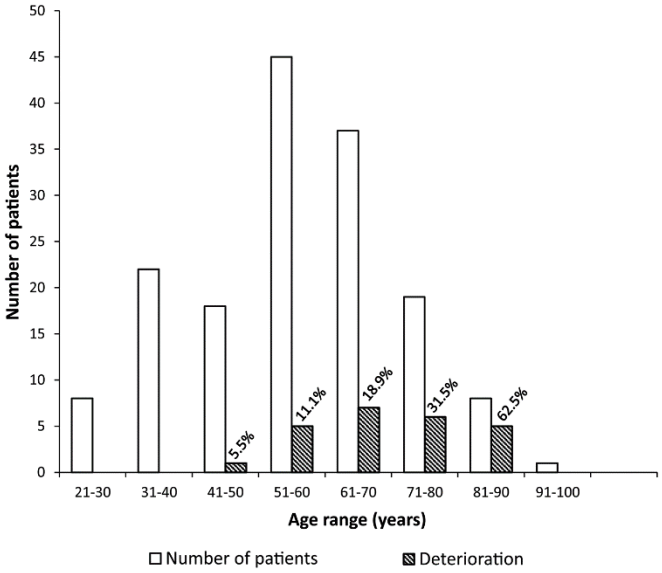


Table 1. Demographic characteristics and comorbidities.

Characteristic	Total n = 158	Group		p^*
		Deterioration n = 24	No deterioration n = 134	
Age (years), $\overline{x}$ ± sd	56.60 ± 25.17	68.71 ± 11.79	54.43 ± 14.71	**< 0.001***
Gender, n (%)				
Male	94 (59.5)	15 (62.5)	79 (59.0)	0.745
Female	64 (40.5)	9 (37.5)	55 (41.0)	
Obesity, n (%)	34 (21.5)	6 (25.0)	28 (20.9)	0.652
Hypertension, n (%)	84 (53.2)	18 (75.0)	66 (49.3)	**0.020***
Diabetes mellitus, n (%)	31 (19.6)	7 (29.2)	24 (17.9)	0.201
Other CVDs, n (%)	25 (15.8)	12 (50.0)	13 (9.7)	**< 0.001***
Pulmonary diseases, n (%)	13 (8.2)	4 (16.7)	9 (6.7)	0.102

*$p < 0.05$ was considered statistically significant; n: number of patients.

Table 2. The laboratory findings of COVID-19 patients at the time of admission.

Characteristic	Total n = 158	Group		p^*
		Deterioration n = 24	No deterioration n = 134	
WBC $\times 10^9$/L,med (min-max)	5.5 (1.6-15.4)	5.8 (2.8-15.4)	5.5 (1.6-14.0)	0.576
Neu $\times 10^9$/L,med (min-max)	3.9 (0.7-11.5)	4.5 (1.9-10.5)	3.8 (0.7-12.2)	0.217
Lym $\times 10^9$/L,med (min-max)	1.2 (0.3-6.7)	0.8 (0.4-2.6)	1.3 (0.3-6.7)	**0.004***
Plt $\times 10^9$/L,med (min-max)	191.0 (88.0-510.0)	154.0 (99.0-507.0)	197.0 (88.0-510.0)	**0.002***
CRP (mg/L),med (min-max)	28.7 (0.4-213.)	36.5 (13.2-175.7)	27.3 (0.4-213.0)	0.078
CRP peak (mg/L),med (min-max)	43.6 (1.8-213.0)	63.1 (13.8-145.3)	39.3 (1.8-213.0)	0.122
IL6 (ng/L),med (min-max)	18.5 (1.5-700.0)	46.4 (1.9-700.0)	14.6 (1.5-209.0)	**0.001***
Ferritin (µg/L),med (min-max)	279.2 (6.7-2587.4)	279.2 (167.3-2011.8)	295.1 (6.7-2587.4)	0.091
D-dimer (µg/mL),med (min-max)	0.35 (0-9.3)	0.5 (0-9.3)	0.3 (0-5.7)	0.157
LDH (U/L),med (min-max)	223.5 (70.0-1040.0)	239.0 (149.0-359.0)	218.0 (70.0-1040.0)	0.326
AST (U/L),med (min-max)	28.0 (11.0-172.0)	30.5 (13.0-119.0)	27.5 (11.0-172.0)	0.534
ALT (U/L),med (min-max)	31.0 (10.0-269.0)	27.0 (10.0-95.0)	32.0 (11.0-279.0)	0.244
Troponin T (ng/mL),med (min-max)	7.5 (3.0-82.0)	17.0 (7.0-82.0)	6.0 (3.0-17.0)	**0.001***

*$p < 0.05$ was considered statistically significant; n: number of patients.

diseases ($p < 0.001$) was noted in patients with deterioration. No statistically significant difference was observed with regards to the presence of obesity, diabetes mellitus and chronic lung disease (Table 1). It was also identified that patients with deterioration differ from those without deterioration in absolute lymphocyte count ($p = 0.004$), absolute platelet count ($p = 0.002$), interleukin-6 (IL-6) level ($p = 0.001$) and troponin T level ($p = 0.001$) (Table 2). No significant difference was detected in the values of the absolute neutrophil count, CRP, peak CRP value, AST, ALT, LDH, ferritin and d-dimer (Table 2).

The radiological characteristics are shown in Table 3. We noted that COVID-19 patients with clinical deterioration had more frequently described spotty consolidations on chest radiography compared to those without deterioration ($p = 0.007$). There was no statistically significant difference in the distribution of other radiographic characteristics (interstitial changes, ground glass opacities, fibrosis and pleural effusion) between COVID-19 patients with and without deterioration. In patients who had a chest CT scan, there was no significant difference in the values of CT severity score between the groups with and without deterioration.

Median duration of the disease before hospitalization was seven days and the median time of hospitalization until the onset of worsening of the disease was four days. Patients with clinical deterioration had significantly shorter time of

Table 3. Radiologic lung findings.

Characteristics	Total n = 158	Group		p^*
		Deterioration n = 24	No deterioration n = 134	
CT score,med (min-max)	14.0 (2.0-21.0)	10.5 (2.0-19.0)	14.0 (2.0-21.0)	0.881
Interstitial changes, n (%)	103 (68.2)	17 (85.0)	86 (65.6)	0.083
Ground glass, n (%)	95 (62.9)	13 (65.0)	82 (62.6)	0.836
Spotty consolidation, n (%)	95 (62.9)	18 (90.0)	77 (58.8)	**0.007***
Fibrosis, n (%)	8 (5.3)	2 (10.0)	6 (4.6)	0.314
Pleural effusion, n (%)	6 (4.0)	1 (5.0)	5 (3.8)	0.580

*$p < 0.05$ was considered statistically significant; n: number of patients.

Table 4. Hospitalization and therapy.

Parameter	Total n = 158	Group		p^*
		Deterioration n = 24	No deterioration n = 134	
Length of illness (days)med (min-max)	7.0 (1.0-27.0)	6.5 (2.0-14.0)	7.0 (1.0-27.0)	0.088
Illness deterioration (day)med (min-max)	4.0 (1.0-10.0)	4.0 (1.0-10.0)	/	NA
Length of hospitalization (days)med (min-max)	10.0 (1.0-22.0)	6.0 (1.0-22.0)	10.0 (1.0-22.0)	**< 0.001***
O_2 supplement (days)med (min-max)	6.0 (0-20.)	4.5 (0-20.0)	7.0 (0-19.0)	0.658
Corticosteroide therapy,n (%)	109 (69.0)	20 (83.3)	89 (66.4)	0.099
Convalescent plasma, n (%)	17 (10.8)	4 (16.7)	13 (9.7)	0.311
Tocilizumab, n (%)	23 (14.6)	10 (41.7)	13 (9.7)	**< 0.001***
Favipiravir, n (%)	4 (2.5)	3 (12.5)	1 (0.7)	**0.001***

*$p < 0.05$ was considered statistically significant; n: number of patients; NA: not applicable.

Table 5. Predictors of deterioration.

Characteristic	Multivariate regression analysis - Step 1			
	B	OR	95%CI OR	*p*
Age	0.075	1.078	1.04-1.12	< 0.001
Lymphocytes	-1.286	0.276	0.10-0.77	0.014
Platelets	-0.008	0.992	0.98-0.99	0.034
IL-6	0.020	1.020	1.01-1.03	0.004
D-dimer	0.337	1.401	1.02-1.92	0.035
Troponin T	0.234	1.264	1.08-1.48	0.004
Spotty consolidation	1.842	6.312	1.41-28.34	0.016
	Multivariate regression analysis - Step 7			
Age	**0.077**	**1.080**	**1.01-1.15**	**0.019***

*$p < 0.05$ was considered statistically significant.

hospitalization with median value of 6 days, compared to patients without the deterioration, for whom median hospitalization time was 10 days ($p < 0.001$) (Table 4). In the group of patients with the disease deterioration, 47% received tocilizumab ($p < 0.001$) and 12.5% favipiravir ($p = 0.001$), while in the group of patients without deterioration, these medications were applied in 9.7% and 0.7%, respectively. Concerning the need for oxygen therapy, corticosteroid therapy and the application of convalescent plasma, there was no statistically significant difference between the groups (Table 4).

Univariate and multivariate logistical regression analysis were performed with the intention of detecting factors that would predict the risk of deterioration in COVID-19 patients. All variables that were proven as statistically significant in the univariate analysis were included in the multivariate model: patient age, absolute lymphocyte count, absolute platelet count, IL-6 level, troponin T level and spotty consolidation on chest radiography. The last step of multivariate logistic regression model showed that only the age of the patient could be considered a statistically significant risk factor for the onset of deterioration in COVID-19 infection ($p = 0.019$). It was observed that with each year of age above the mean age, the risk of worsening the disease course was increased by 8%.

Discussion

The global rise in the number of COVID-19 patients has put a lot of pressure on the health systems of most countries, urging the health service to undergo a number of changes, including the formation of TCHs. A large number of temporary hospitals do not have adequate resources for the treatment of more severe forms of the disease, such as intensive care units. Appropriate transport of the most severe patients could be significantly limited due to overloaded capacities during the pandemic, and any delay in transport to intensive care units further increases the possibility of a fatal outcome [4]. For this reason, an adequate triage of patients is of the highest significance, so that patients who are expected to have severe worsening of the disease should not be sent for treatment in a TCH. Our study was conducted in order to determine the factors which affect the development of unfavorable outcomes and can be identified during triage.

During the period of the early second COVID-19 outbreak in the Republic of Serbia, our hospital functioned as a TCH, and within a short period of time it was transformed from a highly specialized tertiary health care center for the treatment of rheumatic diseases into a hospital for a large number of patients with a new and not fully understood infectious disease. As our hospital was intended to treat patients with type 2 and 3 [3] disease severity, there were no organized intensive care units. Among the patients examined in this study, median time from the manifestation of the first symptoms of SARS-CoV-2 infection to the admission to hospital was seven days. The further course of the disease was complicated in 15.2% of patients by the development of clinical deterioration of the disease, which on average took place on the fourth day of hospitalization. While patients with severe forms of the disease were expected to require significantly longer hospital stay [5], the length of hospitalization of these patients in our hospital was shorter (median of 6 days) compared to patients without deterioration (median of 10 days). The reason for this discrepancy is that the patients who had a significant deterioration of illness and who required intensive treatment were transferred to another hospital with appropriate capacities in a short period of time from progression onset.

Recent studies demonstrated that gender-based differences are likely to play a role in fatality resulting from COVID-19. It had been observed that males have a higher risk of developing more severe clinical forms and increased mortality during SARS-CoV-2 virus infection. However, our study did not reach this conclusion [6-10].

The most common comorbidity among the patients in this study was arterial hypertension, which was observed in 53% of patients, with a statistically significant higher frequency in patients with illness deterioration. Hypertension was present in 79% of cases with deterioration compared to 49% of those without deterioration. A study by Basu *et al*. showed that hypertension is an independent risk factor for increased mortality during SARS-CoV-2 virus infection [8]. The authors explained that the endothelial damage is the main culprit that triggers further events leading to multiple organ failure (acute respiratory distress syndrome, kidney damage, thromboembolic events) that characterizes the progressive forms of SARS-CoV-2 infection. People with pre-existing arterial hypertension have already significantly impaired endothelial function, leading to the development of a more severe form of the disease. The development of the severe clinical form of COVID-19 in our patients was associated with the presence of chronic cardiovascular disease, which is consistent with the findings of Pranata, Kim and their associates [11,12]. In our study obesity was not associated with an

unfavorable outcome, although some authors have described obesity as a poor prognostic factor of COVID-19 [13].

The pathogenesis of COVID-19 is not yet sufficiently elucidated, but a virus-mediated hyperinflammatory response has been shown to play a significant role in the disease severity [14]. While observing the laboratory characteristics at the time of admission to hospital, we noticed that patients with later illness deterioration had higher values of IL-6 and troponin T, and lower values of the absolute lymphocyte and platelet counts. Lymphopenia is an expected finding during viral infection including SARS-CoV-2 infection. A study by Lee *et al.* showed that people with lymphopenia had a higher risk of death from SARS-CoV-2 virus infection, with a direct correlation between the degree of lymphopenia and the likelihood of an adverse outcome [15]. As an important mediator of inflammation, IL-6 has been described in various studies as a laboratory parameter whose increase precedes and warns of the development of cytokine storm. Therefore, higher values at hospital admission can be considered as a poor prognostic factor [16-18]. Troponin T is a marker of myocardial necrosis and enables the recognition of acute coronary syndrome in persons with nonspecific chest pain. In our study, troponin T levels were measured in patients with problems that may indicate myocardial affection (mid-chest pain, chest tightness and dyspnea). We observed that troponin T levels were significantly higher in subjects with clinical deterioration of COVID-19 disease. Elevated troponin values have been observed to be associated with a poor prognosis [19,20]. This is thought to be due to direct SARS-CoV-2 myocardial damage as well as right ventricular failure caused by acute lung disease, which is supported by histological findings [21].

There is no single specific radiological finding that unequivocally indicates the existence of COVID-19 pneumonia [22]. However, while reviewing the radiographic characteristics in persons with worsening the course of the disease, a higher prevalence of spotty consolidations was observed, which were localized bilaterally, mainly in the peripheral part of the lung parenchyma. Some studies have highlighted this type of radiographic change as the most common in patients with COVID-19 pneumonia, with a tendency to consolidate in the later stages of the disease and in parallel with the development of clinical deterioration [23].

The 8th version of the National Guideline for the Treatment of COVID Infection was utilized during the period when the IR was functioning as COVID hospital. Taking into account the significant role of interleukin-6 in pathogenesis of inflammatory response as a part of SARS-CoV-2 infection, cytokine storm, lung fibrosis, and T lymphocyte dysfunction, this molecule quickly became a targeted therapy for COVID-19. Considering this, a monoclonal antibody against IL-6 receptor, tocilizumab, was implemented in therapeutic approach to COVID-19 [16,24]. According to the aforementioned guideline, the use of tocilizumab was only approved for people with significant increase in the value of inflammatory parameters (IL-6 > 40 ng/L and/or CRP > 50 mg/L or triple increase of value in 48 h). Therefore, patients with deterioration, who had a higher mean value of IL-6, more often received tocilizumab (47%) compared to patients without deterioration (9.7%). Likewise, the application of favipiravir, an antiviral drug designed for the treatment of RNA virus infection (inhibitor of viral RNA polymerase) was more frequently used in the group of patients with deterioration, if the deterioration occurred within 7 days of the first symptoms. Although some authors have unequivocally emphasized the importance of utilizing corticosteroid therapy in the treatment of COVID-19 [25], in our study we did not observe a significant difference between the two groups of patients in the frequency of administration of corticosteroids.

Older age is a risk factor for many infectious and non-infectious diseases. Our study demonstrated through both univariate and multivariate analysis that age is an independent risk factor for developing more severe clinical forms of COVID-19 disease. Specifically, for each year of life in addition to the mean age of the patients, the chance for illness deterioration increased by 8%. Jackson *et al.* showed that old age was the strongest predictor of death caused by COVID-19 disease. In addition, the risk is 12 times higher in people over 65 years old compared to people under 45 years old [26]. The experiences of other medical centers also indicate older age as an independent risk factor for more severe clinical forms of the disease [6,27,28]. The explanation can be found in the involution changes that occur with aging, weakened immune response, and associated comorbidities that make the elderly population more vulnerable.

Conclusions

With this retrospective research, we have attempted to establish predictive factors that could help to more quickly and accurately identify the potential development of severe forms of the disease. Among the possible risk factors for the deterioration, we identified

older age as the main factor. Comorbidities such as arterial hypertension, elevated values of IL-6 and troponin T, and the reduced value of the absolute lymphocyte and platelet counts also had significant contribution. These are the factors that physicians should focus on while performing triage of COVID-19 patients in order to anticipate the progression of the disease. This is of great significance because progression of the disease occurred relatively quickly and it required a polymodal therapeutic approach (oxygen therapy, tocilizumab, favipiravir, corticosteroid and symptomatic therapy) and often application of intensive treatment measures. The TCH usually do not have intensive care units and transport to other facilities is often slow or insufficiently available which is a risk for patients whose condition rapidly deteriorate. Therefore, we suggest that older patients and possibly patients with hypertension, elevated IL-6, and troponin T, and reduced value of the absolute lymphocyte and platelet counts should not be hospitalized in TCHs because of a higher risk of deterioration and need for transport to specialized centers.

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