ORIGINAL ARTICLE

Early predictors of severity and mortality in COVID-19 hospitalized patients

Sehveta Mustafić[1,2], Edin Jusufović[2,3], Fatima Hukić[1,2], Emir Trnačević[1,4], Anja Divković[1,4], Alma Trnačević[2,5]

[1]Department of Laboratory Diagnostics, University Clinical Centre Tuzla, [2]Faculty of Medicine, University in Tuzla, [3]Department of Pulmonology, Public Educational and Health Centre, [4]Pharmaceutical Faculty, University in Tuzla, [5]Department of Infectious Diseases, University Clinical Centre Tuzla; Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To identify laboratory tests for early detection and the development of more severe illness and death in COVID-19 hospitalized patients.

Methods A prospective study was done on 66 hospitalized COVID-19 patients (males: 54.5%; mean age 70.1 ± 9.6 years) who were stratified into: moderate (n=36; 54.5%), severe (n=12; 18.2%), and critically ill (n=18; 27.3%). Besides clinical findings, a wide spectrum of laboratory parameters was monitored at admission and control during the first seven days of hospitalization and used to predict progression from non-severe to severe illness and to predict the final outcome.

Results Critically ill patients showed a higher control value of white blood cell count, C-reactive protein, lactate dehydrogenase, ferritin, but lower lymphocyte count and O_2 saturation. Patients with fatal outcome (23; 34.85%) showed a higher control value of neutrophil, lactate dehydrogenase, ferritin, and lower lymphocyte and O_2 saturation. Progression from moderate to severe or critical illness was predicted by increasing lactate dehydrogenase (95% CI 0.5803 to 0.8397;p=0.003729), increase in ferritin (95% CI 0.5288 to 0.8221;p=0.03248), and by drop in O_2 saturation (95% CI 0.5498 to 0.8179;p=0.01168). A fatal outcome was predicted by increase in ferritin (95% CI 0.5059 to 0.8195;p=0.04985), as well as by drop in O_2 saturation (95% CI 0.5916 to 0.8803; p=0.001861).

Conclusion Increase in ferritin, and drop in O_2 saturation could be the most important prognostic parameters for the development of more severe clinical illness and death in COVID-19 hospitalized patients.

Key words: ferritin, LDH, O_2 saturation,SARS-CoV-2

Corresponding author:
Sehveta Mustafić
Department of Laboratory Diagnostics,
University Clinical Centre Tuzla
Prof. Ibre Pašića bb, 75 000 Tuzla,
Bosnia and Herzegovina
Phone: +387 35 303 516;
E-mail: sehveta.mustafic@ukctuzla.ba
ORCID ID: https://orcid.org/0000-0001-6889-271X

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that has been declared a global public health emergency by the World Health Organization (WHO) on February 28, 2020.

Although the majority of patients with COVID-19 have a mild influenza-like illness or may be even asymptomatic, a small proportion of patients develop severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and can even die (1-3). Pre-existing comorbidities such as medical histories of cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, obesity, immunocompromised, renal disease, and liver disease are associated with severe disease and may have an impact on the overall outcomes (1,4).

It was shown already at the early stage of the pandemic that routine laboratory biomarkers could provide some estimation. These laboratory tests include haematological, haemostaseological, biochemical and immunological parameters that are at least partially associated with a severe or mild course of the disease (5). Immune dysregulation and prolonged inflammation might be the key drivers of the poor clinical outcomes in patients with COVID-19(6). Virus particles spread through the respiratory mucosa, initially using the ACE2 receptor at ciliated bronchial epithelial cells, and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral white blood cells and immune cells such as lymphocytes (7,8).

There is consensus that in severe COVID-19 infection, an exacerbated pulmonary and systemic inflammatory response occurs, with increased serum levels of inflammatory markers, such as C-reactive protein (CRP), lactic dehydrogenase (LDH), ferritin, D-dimer, and IL-6 (3,9,10), all of which may result in the cytokine storm (10,11). A hyperinflammatory environment has been a hallmark of COVID19 infection and is thought to be a key mediator of morbidity (12). Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm (13).

Many patients deteriorate rapidly after a period of relatively mild symptoms, emphasizing the need for early risk stratification (2,3). COVID-19 is associated with severe respiratory compromise and mortality of up to 21% in hospitalized patients (14). So, it is necessary to urgently identify reliable predictors of the disease severity and mortality. Comorbidities and laboratory markers have been proposed for risk stratification (15,16). There is mounting evidence that in critically ill patients, there are characteristics of hyperinflammation, which consist of elevated serum C-reactive protein (CRP), and hyperferritinemia and many others. Laboratory biomarkers to forecast the severity of COVID-19 are essential in a pandemic, because resource allocation must be carefully planned, especially in the context of respiratory support readiness (17).

Careful evaluation of laboratory indices at baseline and during the disease course can assist clinicians in formulating a tailored treatment approach and promptly provide intensive care to those who are in greater need.

The aim of this study was to identify laboratory tests for early detection and the development of more severe illness and death in COVID-19 patients hospitalized at the University Clinical Hospital Centre Tuzla.

PATHIENTS AND METHODS

Patients and study design

This prospective study from the University Clinical Hospital Centre Tuzla (July to September 2020) included 66 hospitalized patients aged 18 years or older with laboratory confirmed COVID-19 infection, and pneumonia confirmed by chest X-ray or computerized tomography (CT), with moderate, severe or critical degree of illness. COVID-19 infection was diagnosed according to the diagnosis and treatment of coronavirus disease 2019 (COVID-19) recommended by the National Health Commission of China (China National Health Commission, 2020)(18). The laboratory confirmed patient was defined as a positive result on high throughput sequencing or real-time polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. The illness severity of COVID-19 (mild, moderate, severe and critical) was defined according to the

Chinese management guideline for COVID-19 (version 7.0) (18).

For intra-hospital determining progression of the disease, the patients were divided in two groups: non-severe (moderately ill) and severe (severely and critically ill). Patients with non-severe illness were defined as COVID-19 confirmed patients with moderate clinical symptoms (cough, fever, respiratory symptoms, with imaging finding of pneumonia, who needed hospital treatment). Patients with "severe" illness were defined as COVID-19 confirmed patients with one of the following conditions: respiratory distress with respiratory rate (RR)>30/min, blood oxygen saturation <93% at rest, arterial oxygen partial pressure (PaO_2)/fraction of inspired O_2 (FiO_2) <300 mmHg, respiratory failure with mechanical ventilation, shock, or other extra pulmonary organ failures requiring intensive care unit (ICU) monitoring. The observed end-point was defined as recovery or death recorded as "survivors" or "non-survivors". Survival time was defined as from illness onset to death. The mortality group of non-survivors included patients who died during their hospital stay. The patients with proven haematology disorders or with malignancy were excluded.

Patient's clinical data were collected from the Medical Records, Laboratory Information System (LIS) and Picture Archiving and Communication System (PACS). Final data were extracted 28 days after finishing the observation.

The study was approved by the Institutional Ethics Committee of the University Clinical Hospital Centre Tuzla (No 02-09/2-25/20).

Methods

A total of 50 indicators were collected from the patients at hospital admission, including age, gender, pre-existing conditions (respiratory disease, cardiac or vascular disease, diabetes, kidney disease or other comorbidities), presenting symptoms (cough, dyspnoea, fatigue and weakness, symptoms from gastrointestinal tract) and clinical findings (fever, blood pressure, medium arterial pressure-MAP, respiratory rate-RR, heart beats, Glasgow coma score). Fever was defined as axillary temperature of 37.3°C or higher.

Initial laboratory analysis at hospital admission of COVID-19 infection included: pH derived from *capillary blood sample, capillary* partial pressure of carbon dioxide ($cPCO_2$), *capillary* partial pressure of oxygen (cPO_2), *capillary* blood oxygen saturation ($cSaO_2$), white blood cell count (WBC), haematocrit (HCT), platelet count (PLT), medium platelet volume (MPV), absolute value of neutrophil (NEU), neutrophil percentage (NEU%), absolute value of lymphocyte (LYM), lymphocyte percentage (LYM%), neutrophil to lymphocyte ratio (NLR), absolute value of monocyte (MON), monocyte percentage (MON%), c-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), blood urea nitrogen (BUN), sodium, potassium, creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), high sensitive troponin I (hsTNI). The same laboratory findings were also observed during the first week of their hospitalization and the worst findings were observed (control value).

Chest X-ray radiography or CT imaging was employed to evaluate the ground-glass opacity and pulmonary infiltrate.

Anti-SARS-CoV-2 antibodies IgG were also tracked. IgG antibodies were measured between the 15th and 21st day of their hospitality stay with SARS-CoV-2 IgG chemiluminescence test kit (ABBOTT diagnostics, North Chicago, Illinois, United States). The SARS-CoV-2 IgG assay is an automated, two-step chemiluminescent microparticle immunoassay, designed for qualitative detection of immunoglobulin class G (IgG) antibodies to the nucleocapsid protein of SARS-CoV-2. The resulting chemiluminescent reaction is measured as a relative light unit (RLU). There is a direct relationship between the amount of IgG antibodies to SARS-CoV-2 in the sample and the RLU detected by the system optics. This relationship is reflected in the calculated index (S/C). The presence or absence of IgG antibodies to SARS-CoV-2 in the sample is determined by comparing the chemiluminescent RLU in the reaction to the calibrator RLU. The Architect ci8200 system calculates the calibrator mean chemiluminescent signal from 3 calibrator replicates and stores results. The results are reported by dividing the sample result by the stored calibrator results. The default results units for the SARS-CoV-2 IgG assay is index (S/C). The cut off value is 1.4 Index (S/C). Values < 1.4 are interpretative (considered) as negative, and values ≥ 1.4 as positive results.

Clinical and laboratory findings at admission and control laboratory findings were analysed and compared between different stages of the disease (moderate, severe, critical) and used to predict progression from "non-severely" to "severely" ill and to predict the final outcome in these patients.

Statistical analysis

Non-parametric and parametric methods are used to calculate statistical significance. The distribution value was determined using Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test, Mann-Whitney test, Fisher's test and $\chi 2$ test were used for calculating the difference between the groups. ANOVA test was used to calculate the relative difference distribution variance between variables. The risk factors related to the development of severe or critical clinical picture and mortality were assessed using binary logistic regression analysis. Receiver operating characteristics (ROC) analysis was used to determine the optimum value of the predictive score, and the Hanley and McNeil methods were used to calculate the area under the curve. Qualitative variables were expressed as numbers and percentages, while quantitative variables were expressed as means and standard deviations and/or medians and interquartile ranges. Variables included in the logistic models were categorized into two levels (0 for no and 1 for yes). The difference between the groups was considered significant when $p<0.05$.

RESULTS

A total of 66 patients with the coronavirus disease 2019 were enrolled: 36 (54.5%) males and 24 (45.5%) females, with mean age of 70.1±9.6 years were enrolled (the youngest patients was male, 41 years old; the oldest patient was female, 89 years old). Critically ill patients were younger (64.4±8.1 years) than moderately (71.5±10.1 years) and severely ill patients (74.3±5.8 years). However, moderately, severely and critically ill patients showed similar gender distribution (males: 52.8%, 41.7% and 66.7%, respectively). On the other side, patients with non-fatal and fatal outcome showed similar age (69.9±9.9 vs70.4±9.2 years), and gender distribution (males: 46.5 vs. 69.6%).

According to the guidelines (18) all patients were stratified into: moderate (n=36; 54.5%), severe (n=12; 18.2%), and critically ill (n=18; 27.3%) patients. Critically ill patients were younger, had more comorbidities, treatment period was longer, and had more frequent fatal outcome than moderately or severely ill patients (Table 1). Cardiovascular comorbidities were the most common in all groups, followed by diabetes, and respiratory co-

Table 1. Clinical characteristics of hospitalized COVID-19 patients with different clinical presentation according to severity of illness and outcome

Clinical characteristic	Severity of illness			p	Outcome		p
	Moderate (n=36; 54.5%)	Severe (n=12; 18.2%)	Critical (n=18; 27.3%)		Non-fatal (n=43; 65.15%)	Fatal (n=23; 34.85%)	
Comorbidities (No; %)							
Diabetes mellitus	13 (36.1)	5 (41.7)	10 (55.6)	0.3944	16 (37.2)	12 (52.2)	0.2997
Respiratory comorbidities	7 (19.4)	2 (16.7)	2 (11.1)	0.7408	7 (16.3)	4 (17.4)	1.0000
Cardiovascular comorbidities	28 (77.8)	12 (100)	13 (72.2)	0.1472	34 (79.1)	19 (82.6)	1.0000
Renal comorbidities	6 (16.7)	0 (0.0)	2 (11.1)	0.3056	4 (9.3)	4 (17.4)	0.4346
Other comorbidities	14 (38.9)	8 (66.7)	16 (88.9)	0.0017	15 (34.9)	23 (100)	<0.0001
p	< 0.0001	< 0.0001	< 0.0001	-	<0.0001	<0.0001	-
Total (median [min, max])	2 [1, 4]	2.5 [1, 4]	2.5 [1, 4]	0.0078	2 [0, 4]	3 [1, 4]	0.0019
Symptom (No; %)							
Cough	17 (47.2)	6 (50.0)	9 (50.0)	0.975	20 (46.5%)	12 (52.2%)	0.797
Breathing disorder	24 (66.7)	8 (66.7)	13 (72.2)	0.9111	29 (67.4%)	16 (69.6%)	1.0000
Gastrointestinal symptoms	13 (36.1)	6 (50.0)	9 (50.0)	0.5241	17 (39.5%)	11 (47.8%)	0.6045
Weakness and fatigue	30 (83.3)	10 (83.3)	18 (100)	0.1814	36 (83.7%)	22 (95.7%)	0.2444
p	0.0054	0.2231	0.0028	-	<0.0001	0.0022	-
Signs							
Fever (No; %)	23 (63.9)	8 (66.7)	13 (72.2)	0.8290	27 (62.8)	17 (73.9)	0.4211
SBD* (mmHg) (median [min, max])	120 [80, 172]	120 [90, 150]	120 [86, 150]	0.8746	120 [86, 172]	120 [80, 150]	0.6766
DBP†(mmHg) (median [min, max])	72.5 [60, 118]	70 [60, 86]	80 [50, 100]	0.5189	75.5 [50, 118]	70 [60, 90]	0.8151
MAP‡(mmHg) (median [min, max])	95 [70, 145]	97.5 [75, 118]	101.25 [79.5, 200]	0.2071	95 [75, 145]	80 [60, 200]	0.5372
Pulse (number/minute) (median [min, max])	84 [63, 134]	82 [76, 100]	81.5 [69, 113]	0.7759	83.5 [63, 105]	83 [69, 134]	0.9155
Glasgow coma score(median [min, max])	15 [10, 15]	15 [10, 15]	15 [15, 15]	0.2213	15 [10, 15]	15 [10, 15]	0.8723
Days in hospital (median [min, max])	15.5 [1,46]	18 [7,28]	24.5 [8,55]	0.0078	17 [7, 55]	19 [1, 34]	0.8526
Fatal outcome (No; %)	6 (16.7)	5 (41.7)	12 (66.7)	0.0012	-	-	-

*Systolic blood pressure; †Diastolic blood pressure; ‡Mean arterial pressure

morbidities (Table 1).The most common symptom in all groups was weakness and fatigue, followed by breathing disorder, and cough (Table 1).

Control values (at the first week of hospitalization) of lymphocytes, haematocrit, platelets, sodium and O_2 saturation were lower than initial values, but control values of leukocytes, neutrophils, neutrophils/lymphocytes ratio, monocytes, mean platelet volume, CRP, AST, ALT, urea, creatinine, potassium and pCO_2 were higher than initial values among all examined groups. Control values of pH and pO2 were lower than initial values, but control values of LDH were higher than initial values among severe and critically ill patients. Ferritin was higher on control in critically ill patients, only. Creatine kinase was lower on control among moderately and critically ill patients, but creatine kinase-MB was lower on control in moderately ill patients, only. When comparing specific groups, critically ill patients showed higher initial haematocrit, creatine kinase-MB, and neutrophils/lymphocytes ratio, as well as higher control mean platelet volume, leukocytes, CRP, ferritin, but lower lymphocytes and O_2 saturation than other two groups. On the other hand, moderately ill patients showed lower control urea, creatinine, and pCO_2 than other two groups. Anti-SARS-CoV-2 IgG showed similar distribution among moderately, severe and critically ill patients (Table 2; SDC).

Patients with fatal outcome had more comorbidities than patients with non-fatal outcome. However, in both groups, with fatal and non-fatal outcome, the most common were cardiovascular comorbidities followed by diabetes, and then respiratory comorbidities. Also, in both groups the most common symptom was weakness and fatigue, followed by breathing disorder, and cough (Table 1).

Control values of absolute number of lymphocyte, lymphocytes (%), sodium and O_2 saturation were lower than initial values, but control values of absolute neutrophils, neutrophils/lymphocytes ratio, absolute and percentage of monocytes, LDH, ferritin, and creatine kinase-MB were higher than initial values among both groups of patients, with fatal and with non-fatal outcome.

Supplemental Digital Content (SDC) 1.Table 2. Laboratory findings between hospitalized COVID-19 patients with different clinical presentation

Supplemental Digital Content (SDC) 2. Table 3. Laboratory findings between COVID-19 patients with non-fatal and fatal outcome

Control values of AST, ALT, urea and creatinine were higher than initial values in patients with fatal outcome only (Table 3; SDC). However, the patients with fatal outcome showed higher levels of control neutrophils, neutrophils/lymphocytes ratio, LDH, ferritin, creatinine, creatine kinase, and both initial and control creatine kinase-MB, but lower levels of control monocytes (%) and O_2 saturation, as well as initial and control lymphocytes and initial neutrophils/lymphocytes ratio comparing to patients with non-fatal outcome. Anti-SARS-CoV-2 IgG showed also similar distribution between patients with fatal and non-fatal outcome (Table 3; SDC).

Binary logistic regression analysis showed that the risk factors (significantly associated with progression from moderately to severely or critically ill) were an increase in LDH and ferritin, as well as a drop in O_2 saturation. The risk factors significantly associated with mortality were the drop of ferritin and O_2 saturation (Table 4). Progression from moderate to severe or critical illness was predicted by increasing LDH (area under the curve-AUC 0.71; 95% confidence interval - CI95% 0.5803 to 0.8397;p=0.003729), increase in ferritin (AUC 0.6755;CI95% 0.5288 to 0.8221; p=0.03248), and by drop in O_2 saturation (AUC 0.6838; CI95% 0.5498 to 0.8179; p=0.01168).

In the prediction of progression to severe or critical form of the disease for LDH increase values of >18.5 and >54.5, sensitivity and specificity was 70.0% and 62.86%, as well as 63.33% and 74.29%, respectively. On the other hand, for ferritin increase values of >433.5 and > 730.7, sensitivity and specificity was 53.57% and 69.57%, as well as 42.86% and 82.61%, respectively. At the same time, in the prediction of the disease progression to severe or critical form, sensitivity and specificity were 53.33% and 79.41%, and

Table 4. Binary logistic regression analysis of factors related to the development of progression from moderately to severely or critically ill and to fatal outcome

Variable	95% confidential interval		p
	Lower	Upper	
Progression to severely or critically ill			
Increase of LDH	2.194	67.224	0.005
Increase of ferritin	1.314	100.768	0.029
Drop in O2 saturation drop	3.431	102.119	0.0012
Fatal outcome			
Increase of ferritin	1.004	26.111	0.022
Drop in O2 saturation drop	1.05	24.601	0.041

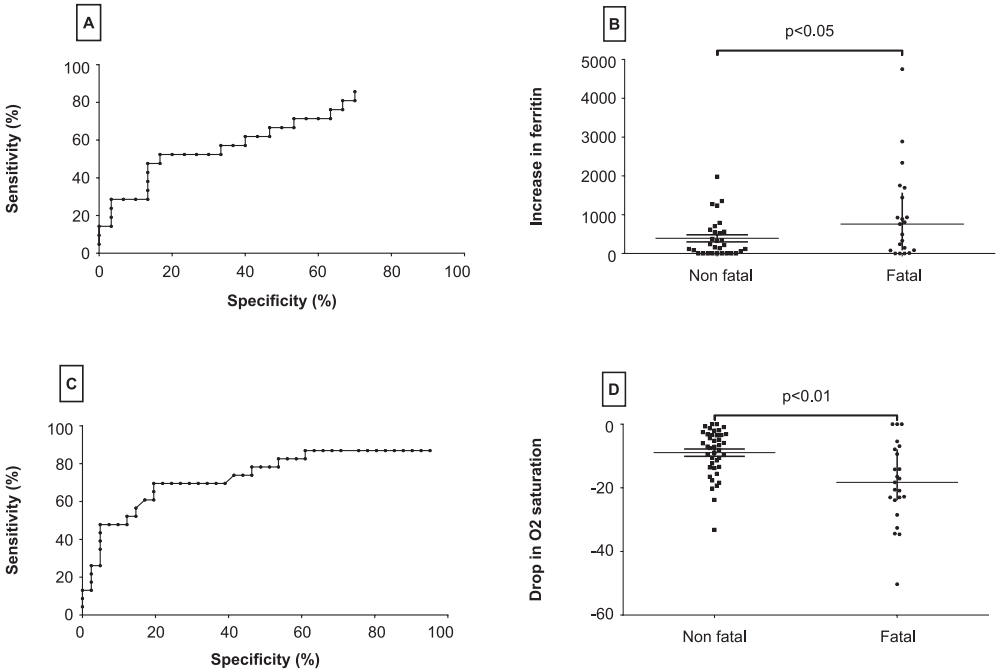

Figure 1. ROC curve analysis of increase in ferritin (A and B) and drop in O2 saturation (C and D) in patients with fatal outcome

56.67% and 64.71% for the drop in O_2 saturation of <-14.15 and <-11.00, respectively.

Fatal outcome was predicted by increase in ferritin (AUC 0.6627; CI95% 0.5059 to 0.8195; p=0.04985), as well as by drop in O_2 saturation (AUC 0.7359; CI95% 0.5916 to 0.8803; p=0.001861) (Figure 1). In the prediction of fatal outcome, sensitivity and specificity was 57.14% and 66.67 %, and 52.38% and 83.33%, respectively, for ferritin increase values of >433.5 and >730.7, but for a values of drop in O_2 saturation of <-18.00 and <- 13.95 they were 52.17% and 87.8%, and 69.57% and 80.49%, respectively.

DISCUSSION

One of the risk factors most strongly associated with severe COVID-19 and death is advanced age. The median age of patients in our study was 71 years, compared to 76 years of Italian, Americans, British and Spanish patients (19). Mandeep et al. (20) showed that out of the total of 8910 patients 80.9% were below 60 years of age and 5.8% died in the hospital. Although the majority of patients in our study were of older life age, there were no significant differences between survivors and non-survivors. In our study in the critically ill group, the patients were younger, had more comorbidities, were treated longer, and had more frequent fatal outcome than moderately or severely ill patients. This finding suggests that comorbidities associated with aging rather than advanced age itself contribute to a worse prognosis.

However, crude case fatality ratio obtained by dividing the number of deaths by the number of cases can be misleading (21). During a growing epidemic, the final clinical outcome of most of the reported cases is typically unknown (22). The in-hospital mortality of severe and critically ill patients with COVID-19 could be up to almost 40% (23). The mortality rate in our study was 34.85%. In our analysis those patients at highest risk for severe disease and death included people over the age of 64 years and those with underlying conditions. In Fei et al. (23) study in-hospital death was higher in patients with diabetes or coronary heart disease.

In contrast to many previous studies which relied on single data points, we estimated the association between longitudinal measurements at admission and control repeated measurements of laboratory markers and clinical outcomes. Several clinical and laboratory variables used in this study showed differences between different stages of the disease already at admission but those were even more significant during the hospital stay.

Among haematological parameters, lymphopenia is clearly associated with disease severity.

The same as the other papers published previo-

usly (26, 27), our data showed that the lymphocyte percentage descends with the disease development, which indicates the direct result of viral infection. We also found that both the higher white blood cell count and absolute value of neutrophil during first seven days of hospitalization were associated with the higher risk of severity (28). Although not significant, haematological abnormalities found in this study were more prominent among severe versus non-severe cases. These results were consistent with three other descriptive studies that were conducted in China (2,3,29). Huang et al. and Wang et al. (2,3) highlighted an association between lymphopenia and a need for ICU care, whereas Wu et al. (29) showed an association between lymphopenia and acute respiratory distress syndrome (ARDS) development. It has also been reported that patients with severe disease and fatal outcomes present with a decreased lymphocyte/white blood cell ratio both on admission and during hospitalization compared with those who survived (29). Contrary to non-survivors, survivors demonstrated a nadir of lymphocytes count on day 7 from symptom onset and subsequent restoration (23). Therefore, serial assessment of lymphocyte count dynamics may be predictive of the patient outcome. In our study baseline lymphocyte count was significantly higher in survivors than non-survivors; in survivors, whereas severe lymphopenia was also observed in non-survivors, but was not an independent predictor of mortality.

Coagulation disorders are relatively frequently encountered among COVID-19 patients, especially among those with severe disease (23,30). Although a few studies showed a correlation between thrombocytopenia and severity of the COVID-19 disease, in our study there was no significant thrombocytopenia on admission but there was a slight fall-down during hospitalization in all examined groups. A meta-analysis of nine studies has suggested that thrombocytopenia is significantly associated with the severity of the COVID-19 disease, and a more sizeable drop in platelet counts was noted especially in non-survivors (31).

Inflammatory biomarker characteristics of patients with laboratory confirmed SARS-CoV-2 infection have been described, and serum ferritin seems to be relevant for assessing the disease severity and outcome of patients (5). Of the inflammatory biomarkers we monitored serum level of CRP, LDH and ferritin.

In our study, increased CRP value was associated with severe COVID-19, but it is not independent of mortality. In the study Guan et al. (9) disease severity was associated with elevated CRP, and the primary composite endpoint (admission to an intensive care unit, use of mechanical ventilation, or death) in their study was also associated with elevated CRP. Also, Deng et al. (30) found that patients in the death group exhibited significantly higher CRP level on admission, and CRP levels remained high after the treatment in the non-survivors.

Elevated LDH indicates cell death and injury and is associated with a poor host immune response, resulting in a higher susceptibility to severe viral infections (32,33). Since LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation (34). Early data in COVID-19 patients have suggested significant differences in LDH levels between patients and without severe disease (35). As the increasing experience with COVID-19 worldwide, numerous studies found that LDH was associated with the severity and poor outcomes of COVID-19 (32,34,36,37). In this study, we also proved that serum LDH was an independent prognostic factor for patients with COVID-19.

There are multiple publications showing that higher ferritin levels, along with other pro-inflammatory markers are correlated with worse outcomes and may even help predict these outcomes (23,38-40). Particularly critically ill patients may exhibit an extreme increase in ferritin levels as an indication of a macrophage activation syndrome (41). This condition is most commonly triggered by viral infections, which might lead to a hypothesis of SARS-CoV-2 inducing this hyper inflammatory syndrome (42).

Our data showed that the common top predictors of progression from non-severe to severe disease were an increase in LDH and ferritin, and reduction in O_2 saturation. At the same time, the best predictors of mortality were an increase of ferritin levels and a drop in O_2 saturation. The similar data were found in a retrospective analysis of Ruan et al. clinical predictors of mortality in 150 patients, higher ferritin concentrations correlated with fatal disease development compared to pa-

tients that were discharged (40). However, in our study hyperferritinemia was observed in majority of patients on admission, as well as throughout the clinical course, and increased with illness deterioration. Levels of serum ferritin were clearly elevated in non-survivors compared with survivors on admission. The similar data were also found by Kappert et al. (5).

We also found that a decrease of O_2 saturation in capillary blood sample is also strongly associated with severity of disease and mortality. Severe respiratory failure and death caused by COVID-19 may result from damaged alveoli and oedema formation, negatively affecting the lung's ability to oxygenate blood, as reflected in reduced oxygen saturation (43). In studies by Han et al. and Erez et al. the common top predictors of ICU admission and mortality were elevated LDH and ferritin, and reduced SpO_2 (32,33). Xie et al. also reported age, lymphocyte count, LDH and SpO_2 to be independent predictors of mortality but a risk score was not developed (44).

It was previously reported that the serum antibody in COVID-19 had potential diagnostic value and the higher titter of antibody was independently associated with a worse clinical classification (45). In our study there was no statistically significant difference in antibody levels between severe and non-severe patients nor between patients with fatal and non-fatal outcome. The number of patients was small in the present study, which might result in less accurate results. More cases and time period tests are needed to verify these results. The similar data were found by Shang at al. (26).

In conclusion, timely analysis of the laboratory characteristics associated with COVID-19 can assist in the clinical prognosis. The increase in ferritin, increase in LDH and drop in O_2 saturation could be the most important prognostic parameters for the development of more severe clinical illness and death in COVID-19 hospitalized patients. Early identification and adequate treatment of COVID-19 patients at high risk for acute respiratory failure are paramount to avoid acute respiratory distress syndrome and end-organ damage, and can probably reduce the death rate.

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Conflict of interests: None to declare

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