Le Infezioni in Medicina, n. 1, 49-54, 2023
doi: 10.53854/liim-3101-7

Clinical characteristics and risk factors for mortality in COVID-19 patients during the first wave of the COVID-19 pandemic in Rome, Italy: a single-center retrospective study

Emanuele Rando, Alessandra Oliva, Francesca Cancelli, Claudia D'Agostino, Giulia Savelloni, Maria Rosa Ciardi, Camilla Ajassa, Guido Siccardi, Gioacchino Galardo, Claudio M. Mastroianni

Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Article received 20 December 2022, accepted 27 January 2023

SUMMARY

Background: Since the beginning of 2020, the SARS-CoV-2 pandemic has become a serious public health problem. Numerous studies have highlighted the main clinical features of COVID-19, mainly the huge heterogeneity of the clinical manifestations that can vary from asymptomatic infection to serious viral pneumonia with a high mortality rate. The aim of this study was to analyze retrospectively the clinical characteristics and assess the risk factors for mortality in an Italian cohort of patients with COVID-19.
Methods: Retrospective analysis including patients with COVID-19 admitted to the Infectious Diseases wards of Azienda Ospedaliera Universitaria Policlinico "Umberto 1", Rome, from March 2020 to May 2020. The data were part of an electronic anonymous web-based database processed by SIMIT (Italian Society of Infectious and Tropical Diseases).
Results: 258 patients were included in the analysis, and 34 (13.2%) died. The median age was 62 (IQR, 52-74), 106 (40%) were women, and 152 (60%) were males, 172 (66.7%) had at least one co-morbidity. The most common signs and symptoms were: fever [221 (85.6%)], cough [135 (52.3%)], and dyspnea [133 (51.5%)]. The PaO2/FiO2 ratio was often altered [352 (IQR, 308-424)]. Lymphopenia [lymphocyte counts, 875/μL (IQR, 640-1250)] and high levels of D-dimer [mg/dL, 874 (IQR, 484-1518)] were found. Non-survivors were older than survivors [median age, 74 (IQR, 67-85)] vs. 61 (QR, 51-72)], mostly men [25 (73.5%)] and more frequently with more than 2 comorbidities [21 (61.8%) vs. 94 (42.1%)]. In the multiple logistic regression model, the variables associated with in-hospital mortality were age [OR, 3.65 (95% CI, 1.22-10.89)], male gender [OR, 2.99 (95% CI, 1.18-7.54)], blood urea [OR, 2.76 (95% CI, 1.20-6.35)] and a low PaO2/FiO2 ratio [OR, 0.28 (95% CI, 0.12-0.62)].
Conclusion: The mortality rate in COVID-19 was 13,2%. The risk factors associated with in-hospital mortality were advanced age, male sex, increased blood urea, and the PaO2/FiO2 ratio reduction.

Keywords: COVID-19, SARS-CoV-2, asymptomatic infection, viral severe pneumonia.

INTRODUCTION

In December 2019, several cases of pneumonia with unknown etiology were reported in the city of Wuhan, the capital of Hubei Province in China [1]. Subsequently, the origin of this outbreak was recognized thanks to the isolation of a new coronavirus called SARS-CoV-2 [2]. In February 2020,

Corresponding author
Alessandra Oliva
E-mail: alessandra.oliva@uniroma1.it

the World Health Organization (WHO) named COVID-19 (COronaVIrus Disease 19) the disease caused by this virus [3]. The disease has a spectrum of heterogeneous manifestations ranging from asymptomatic to severe respiratory failure with a need for mechanical ventilation.
The epidemic suddenly spread, initially in China and subsequently in the rest of the world. In Italy, the first isolation of the virus in an Italian patient was found on 20 February 2020 in the Lombardy region. As of 16 January 2023, the number of cases reported worldwide, and deaths from SARS-CoV-2 infection were 666,879,519 and 6,723,297, respectively. In Italy, 25,363,742 cases and 185,993 deaths have been recorded at this date [4].
Some clinical studies conducted since 2020 have highlighted the main features of COVID-19. The initial clinical manifestations of the infection can be numerous and dependent on the different organs involved reflecting the expression of the ACE-2 receptor in the organism [5].
The purpose of our study was to further contribute to the available knowledge about the clinical characteristics of the infection by investigating first the clinical course, symptoms, and major laboratory alterations and second the relationship between these factors and in-hospital mortality.

PATIENTS AND METHODS

Ethics
The research was conducted according to the Declaration of Helsinki and national and institutional standards. The Internal Review Board (IRB) of the Ethical Committee of Azienda Ospedaliera Universitaria Policlinico "Umberto I", Rome, Italy, approved the study (Protocol ID: 109/2020).

Study design and data collection
This study was a retrospective observational study, including all patients with a confirmed SARS-CoV-2 infection admitted to the Infectious Diseases wards of the Azienda Ospedaliera Universitaria Policlinico "Umberto I" in Rome from March to May 2020.
The data were part of an electronic, anonymous, web-based database processed by SIMIT (Italian Society of Infectious and Tropical Diseases).
The information collected included demographic data, comorbidities (arterial hypertension, diabetes, coronary disease, heart failure, vasculopathy, cerebrovascular disease, dementia, asthma, COPD, peptic ulcer, connective disease, hepatopathy, hemiplegia, tumour in the last 5 years, AIDS, metastatic disease), date of symptoms onset, presenting signs and symptoms (fever, cough, dyspnea, asthenia, diarrhoea, ageusia/anosmia, arthromyalgia, vomiting and nausea, syncope and lipothymic episodes, headache), vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure), Glasgow Coma Scale (GCS), blood gas analysis (pH, PaO2, PaCO2, PaO2/FiO2 ratio, lactates, HCO3-), laboratory data (hemoglobin, hematocrit, leukocytes, polymorphucleates, lymphocytes, monocytes, platelets, serum creatinine, blood urea, glycemia, AST, ALT, total bilirubin, plasma albumin, blood potassium and sodium levels, LDH, troponin, INR, aPTT, ferritin, D-dimer, fibrinogen, CRP, CPK). Charlson Comorbidity Index, qSOFA, polymorphic/lymphocyte ratio, and glomerular filtrate estimation (EGRF) were also calculated.

Statistical analysis
The categorical variables were analyzed by referring to frequencies and percentages, the continuous variables to the median and the values of the interquartile deviation. In the primary analysis, for comparison of the survivors and deceased, test χ^2 and Kruskal-Wallis test were performed when appropriate.
A multiple logistic regression model was created to evaluate the effect of age, sex, PaO2/FiO2 ratio, haemoglobin levels, and blood urea on in-hospital mortality. These variables have been identified, starting from a first set, on the basis of the model selection process as those constituting the best subset for the construction of the same, referring to the prediction error of the model as a metric of its efficiency. The standardized odds ratio and 95% confidence intervals (CI) for each variable have been calculated. The confidence intervals were not constructed considering the model selection process and therefore cannot be considered sufficiently reliable. The analyses were conducted with Python, in particular with the SciPy and statsmodels libraries.

RESULTS

Of the 258 patients included in the analysis, 106 (40%) were women, while 152 were men (60%).

The median age was 62 (IQR, 52-74). Overall, 172 (66.7%) of them had at least one comorbidity, while 115 (44.6%) had two or more comorbidities (Table 1). Of these, the most frequent were: hypertension [114 (44.2%)], peripheral artery disease [52 (20.2%)], coronary artery disease [38 (14.7%)], COPD [33 (12.8%)], cancer in the last five years [25 (9.7%)], heart failure [24 (9.3%) and dementia [22 (8.5%)]. The median Charlson Comorbidity Index of the total population was 1 (IQR, 0-3).

The death occurred in 34 patients (13.2%). Non-survivors were older than those who survive [median age, 74 (IQR, 67-85)] vs. [61 (IQR, 51-72); p<0.001]. Men accounted for the majority of non-survivors [25/34 (73.5%)]. Non-survivors had more frequently two or more comorbidities when compared to survivors [28 (82.3%) vs. 144 (64.6%)], including dementia [12 (35.3%) vs. 10 (4.5%); p<0.001] and heart failure [7 (20.6%) vs. 17 (7.6%); p=0.04] Finally, the Charlson comorbidity index (CCI) of non-survivors was higher than that of survivors [6 (IQR, 4-7) vs. 3 (IQR, 1-5); p<0.001] (Table 1).

The median duration of the days elapsed since symptoms onset and hospitalization was 6 (IQR, 3-9). The most frequent signs and symptoms of presentation were fever [221 (85.6%)], cough [135 (52.3%)], dyspnea [133 (51.5%)] followed by asthenia [41 (15.9%)], diarrhoea [33 (12.8%)], ageusia and/or anosmia [29 (11.2%)] and arthromyalgias [23 (8.9%)].

Non-survivors experienced reduced time from symptoms onset to hospitalization when compared with survivors [3 days (IQR, 1-4) vs. 7 (IQR, 3-10); p<0.001]. In addition, they were less likely to present with fever [22 (64.7%) vs. 198 (88.8%); p=0.04].

The PaO2/FiO2 ratio was frequently below 400

Table 1 - Demographic and clinical characteristics.

Characteristics	*All (n=258)*	*Non-survivors (n=34)*	*Survivors (n=223)*	*p value*
Age	62 (52-74)	74 (67-85)	61 (51-72)	<0.001
Male	152 (60)	25 (73.5)	127 (57)	0.15
Female	106 (40)	9 (26.5)	96 (43)	
Comorbidities ≥1	172 (66.7)	28 (82.3)	144 (64.6)	0.1
Comorbidities ≥2	115 (44.6)	21 (61.8)	94 (42.1)	0.048
Diabetes	46 (17.8)	7 (23.5)	39 (17.5)	0.62
Hypertension	114 (44.2)	14 (41.2)	100 (44.8)	0.92
Coronary artery disease	38 (14.7)	9 (26.5)	29 (13)	0.06
Heart failure	24 (9.3)	7 (20.6)	17 (7.6)	0.04
Peripheral artery disease	52 (20.2)	8 (23.5)	44 (19.7)	0.54
Cerebrovascular disease	16 (6.2)	3 (8.8)	13 (5.8)	NS
Dementia	22 (8.5)	12 (35.3)	10 (4.5)	<0.001
Asthma	10 (3.9)	0 (0.0)	10 (4.5)	NS
COPD	33 (12.8)	6 (17.6)	27 (12.1)	0.38
Peptic ulcer	5 (1.9)	0 (0.0)	5 (2.2)	NS
Connective tissue disease	0 (0.0)	0 (0.0)	0 (0.0)	NS
Liver disease	10 (3.9)	4 (11.8)	6 (2.7)	NS
Hemiplegia	7 (2.7)	3 (8.8)	4 (1.8)	NS
Cancer (last 5 years)	25 (9.7)	5 (14.7)	20 (8.9)	0.39
AIDS	1 (0.4)	0 (0.0)	1 (0.4)	NS
Metastasis	5 (1.9)	2 (5.9)	3 (1.3)	NS
CCI	3 (1-6)	6 (4-7)	3 (1-5)	<0.001

Data are n (%) or median (IQR).
AIDS: acquired immunodeficiency syndrome; COPD: Chronic Obstructive Pulmonary Disease; CCI: Charlson Comorbidity Index.

[352 (IQR, 308-424)]. At hospital admission, there were no differences between the non-survivors and survivors in heart rate, systolic and diastolic blood pressure, respiratory rate, Glasgow Coma Scale, and qSOFA. By contrast, non-survivors showed a lower PaO2/FiO2 ratio than survivors [249 (IQR, 168-326) vs. 367 (314-438); p<0.001], as well as a lower SpO2 [92% (IQR, 87-97) vs. 97% (IQR, 94-98); p<0.001] (Table 2).

Overall, the most frequently observed laboratory abnormalities were lymphopenia [lymphocyte counts, 875/µL (IQR, 640-1250)], high levels of D-dimer [mg/L, 874 (IQR, 484-1518)], and ferritin [µg/L, 518 (IQR, 254-1027)]. When compared to survivors, non-survivors experienced more frequently laboratory alterations (Table 3); specifically they showed lower hemoglobin levels [11.4 g/dL (IQR, 10.2-13.7) vs. 13.9 g/dL (IQR, 12.8-14.9); p<0.001] and haematocrit [34.4% (IQR, 30.7-41.1) vs. 40.6% (IQR, 37.7-43.4); p<0.001], higher serum creatinine values [1.0 mg/dL (IQR, 0.8-1.4) vs. 0.9 mg/dL (IQR, 0.7-1.0); p=0.003], lower creatinine clearance [52.5 mL/min (IQR, 42.4-69.9) vs. 64.4 mL (IQR, 52.84.2); p=0.008], higher blood urea [24 mg/dL (IQR, 18-33) vs. 13 mg /dL (IQR, 11-19); p<0.001], as well as lower albumin [3.2 g/dL (IQR, 2.9-3.4) vs. 3.8 g/dL (IQR, 3.4-4.1); p<0.001], higher ferritin values [1638 µg/L (IQR, 622-2371) vs. 480 µg/L (IQR, 254-923); p<0.001], and higher C-reactive protein levels [10.57 mg/L (IQR, 4.35-22.84) vs. 3.37 mg/L (IQR, 1.03-9.44); p<0.001].

The multiple logistic regression model showed that age, male sex, and blood urea were associated with an increased risk of in-hospital mortality. For age, the odds ratio was 3.65 (95% CI, 1.22-10.89); for male sex, 2.99 (95% CI, 1.18-7.54); for blood urea, 2.76 (95% CI, 1.20-6.35). The odds ratio for the PaO2/FiO2 ratio was 0.28 (95% CI, 0.12-0.62) (Table 4).

DISCUSSION

This study highlighted several clinical findings of COVID-19 presentation and investigated risk factors associated with in-hospital mortality in a population of hospitalized patients with COVID-19 at Policlinico "Umberto I" of Rome, Italy. Specifically, of the 258 patients included in this cohort, death occurred in 34 cases (13.2%); the majority of admitted patients [172 (66.7%)] had at least one comorbidity, and 115 (44.6%) had two or more comorbidities. Non-survivors were older [median age 74 (IQR, 67-85)] and more likely to have two or more comorbidities than survivors. Of interest, non-survivors experienced less frequent fever at presentation and lower median time between clinical onset and hospitalization [3 days (IQR, 1-4) vs. 7 days (IQR, 3-10)]. The demographic and clinical data reported here have also been confirmed by previous studies [6-11].

Table 2 - Presenting vital and arterial blood gas parameters.

Parameters	*All (n=253)*	*Non-survivors (n=34)*	*Survivors (n=219)*	*p value*
Heart rate	90 (80-103)	90 (80-115)	90 (80-100)	0.4
SBP	130 (120-140)	120 (110-130)	130 (120-140)	0.1
DBP	80 (70-80)	70 (70-80)	80 (70-80)	0.3
Respiratory rate	18 (16-20)	20 (16.5-22)	17 (16-19)	0.03
GCS	15 (15-15)	15 (14-15)	15 (15-15)	<0.001
qSOFA	0.0 (0.0-0-0)	0.0 (0.0-0.75)	0.0 (0.0-0.0)	0.03
pH	7.46 (7.44-7.49)	7.44 (7.39-7.47)	7.47 (7.44-7.49)	0.036
PaO_2, mmHg	80 (68-96)	68 (58-98)	81 (69.0-95)	0.2
$PaCO_2$, mmHg	34 (31-37)	35 (33-40)	34 (31-37)	0.1
PaO_2/FiO_2	352 (308-424)	249 (168-326)	367 (314-438)	<0.001
Lactate mmol/L	1.0 (0.8-1.2)	1.0 (0.8-1.5)	1.0 (0.7-1.2)	0.7
HCO3-, mmol/L	25 (23-26)	26 (24-29)	24 (23-26)	0.1
SpO_2	97 (94-98)	92 (87-97)	97 (94-98)	<0.001

Data are expressed in median (IQR).
SBP: Systolic blood pressure; DBP: diastolic blood pressure; GCS: Glasgow coma scale; qSOFA: quick sequential organ failure assessment.

Table 3 - Laboratory findings.

Laboratory findings	*All (n=253)*	*Non-survivors (n=34)*	*Survivors (n=219)*	*p value*
Hb, g/dL	13.8 (12.4-14.8)	11.4 (10.2-13.7)	13.9 (12.8-14.9)	<0.001
Hct, %	40.4 (36.7-43.4)	34.4 (30.7-41.1)	40.6 (37.7-43.4)	<0.001
WBC, n°/µL	5680 (4382-7207)	6920 (4830-8355)	5610 (4310-7120)	0.12
PMN, n°/µL	4030 (2872-5700)	4830 (3007-6440)	3970 (2840-5679)	0.26
LYM, n°/µL	875 (640-1250)	840 (557-1092)	880 (640-1290)	0.29
Monocytes, n°/µL	310 (250-450)	310 (232-462)	310 (250-450)	0.76
PMN/LYM	4.8 (2.8-7.0)	5.1 (3.6-10.3)	4.4 (2.7-6.9)	0.09
Platelets, x1000/µL	193 (160-244)	169 (140-220)	195 (162-247)	0.06
Creatinine, mg/dL	0.9 (0.7-1.1)	1.0 (0.8-1.4)	0.9 (0.7-1.0)	0.003
eGFR, ml/min	63.3 (52.0-83.1)	52.5 (42.4-69.9)	64.4 (52.6-84.2)	0.008
Blood Urea, mg/dL	14 (11-21)	24 (18-33)	13 (11-19)	<0.001
Glycemia, mg/dL	102 (90-126)	115 (94-141)	101 (90-126)	0.16
AST, U/L	26 (20-40)	25 (20-50)	26 (20-39)	0.57
ALT, U/L	22 (16-34)	18 (13-43)	22 (16-34)	0.69
Total bilirubin, mg/dL	0.46 (0.24-0.69)	0.44 (0.32-0.67)	0.48 (0.35-0.69)	0.95
Albumin, g/dL	3.8 (3.4-4.1)	3.2 (2.9-3.4)	3.8 (3.4-4.1)	<0.001
Potassium, mmol/L	4.0 (3.7-4.3)	4.0 (3.6-4.3)	4.0 (3.7-4.4)	0.57
Sodium, mmol/L	138 (135-141)	139 (137-142)	138 (135-140)	0.07
LDH, U/L	290 (230-390)	359 (267-512)	285 (228-375)	0.030
Troponin, mcg/L	0.014 (0.006-0.029)	0.027 (0.018-0.046)	0.012 (0.006-0.025)	0.002
INR	1.03 (0.99-1.08)	1.06 (1.02-1.13)	1.02 (0.99-1.07)	0.06
aPTT	0.96 (0.89-1.06)	1.08 (0.93-1.20)	0.95 (0.88-1.04)	<0.001
Ferritin, µg/L	518 (254-1027)	1638 (622-2371)	480 (254-923)	<0.001
D-dimer, mg/L	874 (484-1581)	1345 (670-2054)	862 (467-1549)	0.08
Fibrinogen, mg/dL	528 (402-556)	488 (369-537)	537 (402-556)	0.07
CRP, mg/L	3.84 (1.21-9.89)	10.57 (4.35-22.84)	3.37 (1.03-9.44)	<0.001
CPK, U/L	93 (51-157)	75 (43-143)	96 (53-159)	0.18

Data are expressed in median (IQR).
Hb, haemoglobin; Hct, haematocrit; WBC, white blood cells; PMN, polymorphonucleate; LYM, lymphocytes; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; aPTT, activated partial thromboplastin time; CRP, C-reactive protein; CPK, creatine phosphokynase.

Table 4 - Risk Factors for in-hospital mortality.

Risk Factors	*OR (95% CI)*	*p value*
Hb	0.57 (0.24-1.34)	0.199
PaO_2/FiO_2	0.28 (0.12-0.62)	0.002
Blood Urea	2.76 (1.20-6.35)	0.017
Age	3.65 (1.22-10.89)	0.020
Male	2.99 (1.18-7.54)	0.020

OR, odds ratio; CI, confidence interval; Hb, haemoglobin.

It is worth noticing the more severe involvement of male individuals; some studies had indeed shown a similar gender imbalance, especially in those with increasing age [9-11].
Differences in oxygen saturation and PaO2/FiO2 ratio were found, which were significantly lower in non-survivors; there were also differences in laboratory tests, including lower hemoglobin values, as well as a higher blood urea value, decreased blood albumin levels, increased levels of LDH, ferritin

and finally C-reactive protein. Lower hemoglobin value has already been described in the literature in patients suffering from severe forms of the disease; however, another study did not show any change in the affinity of hemoglobin for oxygen during the course of the disease [12-14].

In the logistic regression model, the factors associated with a higher risk of in-hospital mortality were advanced age, male sex, increased blood urea, and the PaO2/FiO2 ratio decreased at presentation. This study, therefore, confirms data previously reported in other publications, especially regarding age and male sex, adding important information on the parameter of blood urea. The latter had been found to be related to an increased risk of hospital death, but the evidence for this is scarce so far [15]. Nonetheless, some limitations of this study should be considered. Most of all, this is a retrospective study and data were collected during the first wave of COVID-19 epidemic in Italy, possibly not reflecting the changes induced by new variants during subsequent waves. For this reason, the study conclusions may not be valid nowadays after two years of the pandemic. However, this work contributes to highlighting the most interesting features of pathology and providing potential variables of interest in the formulation of a disease severity score.

Declaration of interest

None to declare.

Funding

This work was supported by Gilead Sciences Srl which provided unconditional support for data collection.

REFERENCES

[1] Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol*. 2020; 92 (4), 401-402. doi: 10.1002/jmv.25678.

[2] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020; 5 (4), 536-544. doi: 10.1038/s41564-020-0695-z.

[3] Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. [cited 2020 May 31]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

[4] Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins. [Internet]. [cited 2023 Jan 16. Available from: https://coronavirus.jhu.edu/map.html

[5] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med*. 2020; 14 (2), 185-192. Doi: 10.1007/s11684-020-0754-0.

[6] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395 (10223), 507-513. Doi: 10.1016/S0140-6736(20)30211-7.

[7] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published correction appears in JAMA. 2021 Mar 16; 325 (11), 1113]. *JAMA*. 2020; 323 (11), 1061-1069. Doi: 10.1001/jama.2020.1585.

[8] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28; 395 (10229), 1038] [published correction appears in Lancet. 2020 Mar 28; 395 (10229), 1038]. *Lancet*. 2020; 395 (10229): 1054-1062. Doi: 10.1016/S0140-6736(20)30566-3.

[9] Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. *J Immunol*. 2017; 198 (10), 4046-4053. Doi: 10.4049/jimmunol.1601896.

[10] Ozma MA, Maroufi P, Khodadadi E, et al. Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period. *Infez Med*. 2020; 28 (2), 153-165.

[11] Ochani R, Asad A, Yasmin F, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. *Infez Med*. 2021; 29 (1), 20-36.

[12] Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. *Ann Hematol*. 2020; 99 (7), 1421-1428. Doi: 10.1007/s00277-020-04103-5.

[13] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020; 382 (18), 1708-1720. Doi: 10.1056/NEJMoa2002032.

[14] Daniel Y, Hunt BJ, Retter A, et al. Haemoglobin oxygen affinity in patients with severe COVID-19 infection. *Br J Haematol*. 2020; 190 (3), e126-e127. Doi: 10.1111/bjh.16888.

[15] Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020; 97 (5): 829-838. Doi: 10.1016/j.kint.2020.03.005.