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Markers associated with an unfavourable outcome in SARS-CoV-2 infection: Insights from a Romanian military hospital

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Abstract

Background and objectives. *The use of affordable and simple tools to identify patients with severe forms of COVID-19 is imperative worldwide. The aim of the present study was to identify factors associated with the unfavourable progression of SARS-CoV-2 infection in the Military Emergency Clinical Hospital "Dr. Victor Popescu", Romania.*

Materials and methods. *Data from 166 patients admitted with a positive SARS-CoV-2 reverse transcription-quantitative PCR test were retrospectively collected. The presence of lung changes on chest X-ray scans was the criterion used to divide the subjects into two groups: patients with no radiological findings (group 1; n=45) and patients with radiological features of pneumonia (group 2; n=121).*

Results. *The mean age (P<0.0001) and body mass index (P=0.0109) were significantly higher in group 2 compared with group 1. Ageusia and headache, as clinical manifestations of COVID-19, were significantly prevalent (P=0.005 and P=0.007, respectively) in group 2; in the same group, cardiovascular risk factors and established cardiovascular disease were highly prevalent. In SARS-CoV-2 patients with radiological lung changes, correlations were identified between neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (P<0.001; CI 95%, 0.137-0.471) and fibrinogen (P=0.009; CI 95%, 0.054-0.406), respectively. Only the platelet-to-lymphocyte ratio (PLR) was identified as a marker of X-ray changes (P=0.029). Within group 2, and for patients with unfavourable disease progression, the NLR were significantly correlated with intensive care unit admission (P<0.0001) and were highly correlated with mortality (P=0.001). Increased lactate dehydrogenase (LDH) values had the same tendency.*

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Conclusions. *An unfavourable progression of SARS-CoV-2 infection can be expected in middle-aged, obese patients, and in those with elevated levels of inflammatory markers and LDH. Abnormally increased NLR and PLR values may also serve as potential indicators of disease severity; however, further evaluation in a larger patient sample is required to determine the predictive role of these rations in SARS-CoV-2 infection.*

Keywords: COVID-19 infection, pneumonia, inflammatory markers, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, outcomes

INTRODUCTION

Coronavirus 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) strain of the family of coronaviruses, which can infect both humans and animals [1]. In humans, infection can take various forms, from asymptomatic or mild respiratory symptoms such as fever, dry cough, nasal congestion, and headache, to severe cardiovascular and pulmonary complications, such as acute respiratory distress syndrome and cardiogenic shock [2,3].

Respiratory failure followed by cardiovascular complications is the main cause of mortality in COVID-19 patients. Patients at high risk of developing a severe form of the disease are the elderly and those with comorbidities, such as diabetes mellitus, hypertension, malignancy, and chronic heart or lung disease. The most common manifestation of the disease is pneumonia, which is preceded at onset by fever, dyspnoea and myalgia, and is accompanied by imaging findings of pulmonary infiltrates [4].

A recent study published by Lippi and Plebani revealed changes in levels of certain laboratory parameters of patients tested positive for SARS-CoV-2 and indicated that some of these parameters could serve as predictive markers of an unfavourable outcome [5]. Above mentioned authors focused on 11 studies that reported abnormal laboratory tests results, the most frequent of which were lymphopenia (35-75% of cases), lactate dehydrogenase (LDH; 27-92% of cases), erythrocyte sedimentation rate (up to 85% of cases) and D-dimer (36-43% of cases). In terms of prediction, a range of factors were found to be correlated with unfavourable outcomes, including increased white blood cell (WBC) and neutrophil count, and decreased lymphocyte count in complete blood count (CBC) results; LDH, alanine aminotransferase, aspartate aminotransferase, creatinine, cardiac troponins and D-dimer levels, prothrombin time, as well as inflammatory markers procalcitonin and C-reactive protein (CRP), were also found to be increased [5].

In 2020, Velavan and Meyer reported that several laboratory parameters, including low lymphocyte count, serum levels of CRP, D-dimer levels, serum ferritin and IL-6 levels, may distinguish mild cases from severe forms of COVID-19. These parameters are useful in risk stratification, as they can predict severe disease [6].

Certain prognostic scores have been shown to predict the development of severe disease; the APPACHE II score estimating intensive care unit (ICU) mortality has been found to be more useful than the SOFA and CURB-65 scores [7]. At the same time, other studies have sought to find new prognostic scores for disease progression, such as COVID-GRAM and The Coronavirus Clinical Characterization Consortium (4C) Mortality Score. COVID-GRAM was validated on a cohort of 1,600 Chinese patients, while the 4C Mortality Score was validated in the UK on a prospective cohort study of 60,000 patients. Abnormal chest X-ray features, age, hemoptysis, dyspnoea, unconsciousness, number of comorbidities, malignancy, neutrophil-to-lymphocyte ratio (NLR), LDH levels and direct bilirubin levels are the variables tested upon admission used by the COVID-GRAM score, while the 4C Mortality Score includes demographics, clinical observations and blood parameters available at the time of hospitalization (age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow Coma Scale score, urea and CRP levels) [8,9].

The initial report of the international registry RISC-19-ICU, created to provide a near real-time assessment of patients becoming critically ill from COVID-19, demonstrated that procalcitonin and IL-6 levels were similar in survivors and non-survivors, while only creatinine, D-dimer, lactate, potassium, and ischemic heart disease were predictors of mortality in critically ill patients with COVID-19 [10].

Inflammation plays a critical role in the pathophysiology of SARS-CoV-2 infection, contributing to the progression of viral pneumonia [11,12]. Thrombotic arterial events and venous thromboembolism are present in COVID-19 infected patients as a consequence of SARS-CoV-2 virus or as a consequence of systemic inflammatory response syndrome (SIRS) and they lead to a higher rate of morbidity and mortality. The optimal approach for the use of anticoagulants (unfractioned heparin – UFH, low molecular weight heparin – LMWH or direct oral anticoagulants – DOACs) in thromboprophylaxis or

treatment of these life-threating conditions in high-risk ICU patients (SIC score ³4) is uncertain [13]. Nowadays the current use of DOACs (apixaban, rivaroxaban, dabigatran) in thromboprophylaxis is unconfirmed due to their reasonable drug-drug interactions with antiviral, immunosuppressants or other investigational regimens used in treatment of COVID-19 patients [14]. However, DOACs have a predicted lower pharmacokinetic and pharmacodynamic variability, standardized methods for determining plasmatic concentrations are available in accredited laboratories and the net benefits is terms of reduced bleeding and superior efficacy are undoubtful [15-17].

The immune response is triggered following infection to reduce the ability of the virus to reproduce inside the cells of the human body. Therefore, recent data has suggested that biomarkers that can evaluate inflammation and immune status may be indicators of the prognosis of patients with COVID-19. Peripheral WBC count, NLR and platelet-to-lymphocyte ratio (PLR) have also been described as potential predictors of systemic inflammatory response in other illnesses that exhaust the immune system [18]. A retrospective study of the clinical characteristics of 93 laboratory-confirmed cases with COVID-19 concluded that advanced age and NLR could be considered independent biomarkers for poor clinical outcomes [19].

The aim of the present study was to identify markers associated with the poor prognosis of SARS-CoV-2 infection among patients with pulmonary chest X-ray changes at the time of admission.

MATERIAL AND METHODS

Patient data collection

Data were obtained from electronic or paper-based medical records of 166 adult patients admitted to the Infectious Disease Department of the Military Emergency Clinical Hospital "Dr. Victor Popescu" (Timisoara, Romania) between July and September 2020. At index admission, the cohort was divided into two groups based on chest X-ray findings: Group 1 included 45 patients (29 male) with no radiological features and group 2 included 121 patients (71 male) with radiological signs of pneumonia.

Demographic data, medical history (including comorbidities), symptoms, clinical signs and laboratory test results were collected from all patients. The existence of a minimum of one positive COVID test using reverse transcription-quantitative (RT-q) PCR, irrespective of sex, was considered the inclusion criterion. Symptomatic or suspected cases with negative or inconclusive tests were excluded from the study.

The study was conducted according to the ethical standards of the 1975 Declaration of Helsinki. The research was approved by the Medical Council of the Military Emergency Clinical Hospital "Doctor Victor Popescu", Timisoara, Romania, approval number A2952/2021. Written informed consent was obtained from all patients at the time of admission, according to local regulatory standards.

SARS-CoV-2 infection diagnosis

SARS-CoV-2 infection was diagnosed according to the World Health Organization directives and guidance for Coronavirus disease issued by the National Institute of Public Health of Romania [20]. The presence of SARS-CoV-2 in respiratory specimens (nasal and pharyngeal swabs) was confirmed using a GeneFinder™ COVID-19 Plus RealAmp kit (OSANG Healthcare Co., Ltd.) on a 7500 Fast Real-Time PCR Detection system (Applied Biosystems; Thermo Fisher Scientific, Inc.), according to the manufacturer's instructions.

Laboratory data: Biochemical tests were performed on study enrolled patients' blood samples using an Abbott Architect C4000 system (Abbott Diagnostics), while the selected parameters in the CBC were analysed on a Beckman Coulter DxH (Beckman Coulter, Inc.), a scalable, fully automated haematology analyser system. The same blood samples obtained at admission were used to calculate the NLR and PLR. Plasma fibrinogen levels were measured by a coagulometric assay using a commercially available kit (Technoclone Herstellung von Diagnostika und Arzneimitteln GmbH) on a Sysmex® CA-600 device (Sysmex Corporation). CRP and serum ferritin values were assessed by immunoturbidimetry (Konelab™ Prime 60I; Thermo Fisher Scientific, Inc.). Quantitative values of D-dimer were measured via a fluorescence immunoassay using a Finecare™ D-Dimer Rapid Quantitative test (Guangzhou Wondfo Biotech Co. Ltd.). All laboratory investigations were performed in an ISO 15189 accredited laboratory.

STATISTICAL ANALYSIS

Continuous variables are expressed as the mean ± standard deviation (SD.) To assess the statistical significance of differences between the groups, a Student's paired t-test was used for parametric data; Mann-Whitney U test and Spearman's rank Rho correlation were used for non-parametric data. P-values were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. All statistical data were analysed using GraphPad Prism version 8.4.3 software for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com).

RESULTS

The average age in group 1 was 34.20±11.62 years old, with 64.45% (29/45) of cases being men. In group

2, the average age was 44.97±12.19 years old, with 58.68% (71/121) cases being men. The demographic characteristics, symptoms and laboratory findings of the studied cases are presented in Table 1.

The patients' symptoms at the time of admission showed that headache, along with ageusia, were significantly prevalent in those who did not present radiological signs of pneumonia (group 1; Table 1).

The main identified comorbidities of patients included in the study are depicted in Table 2.

A comparative analysis of NLR and PLR mean values in the studied population is shown in Figure 1. No statistically significant difference was observed in the NLR between the two groups (p=0.054), whereas a significant difference was observed in the average PLR value between groups 1 and 2 (p=0.029).

TABLE 1. *Baseline characteristics, laboratory features and symptoms of the study participants.*

A. Baseline characteristics

Variable (unit)	Mean ± SD or percentage		*p*-value
	Group 1 (45 cases)	Group 2 (121 cases)	
Age (years)	34.20±11.62	44.97±12.19	0.0001
Gender			0.593
Male (%)	64.45	58.68	
Female (%)	35.54	41.32	
Body mass index (kg/m^2)	25.7±4.57	27.91±5.44	0.0109

B. Laboratory findings

Variable, unit (reference value)	Patients (n)		Mean ± SD		*p*-value
	Group 1	Group 2	Group 1	Group 2	
WBC, x10^3/mm^3 (3.8-11.8)	45	121	6.25±3.08	7.10±3.51	0.134
Neutrophils, x10^3/mm^3 (1.9-8.2)	45	121	3.69±2.73	4.48±3.51	0.131
Platelets, x10^3/µL (179-408)	45	121	227.23±65.16	238.46±75.42	0.351
Lymphocytes, x10^3/mm^3 (1.1-3.1)	45	121	1.99±0.77	1.77±1.02	0.070
CRP, mg/dL (0.00-0.50)	44	120	0.4±0.56	2.70±4.94	<0.0001
Fibrinogen, mg/dL (196-372)	42	117	286.02±69.1	368.05±122.10	<0.0001
LDH, U/L (125-220)	39	113	176.61±35.11	214.98±60.910	<0.0001
Serum ferritin, ng/mL (female, 20-300; male, 15-160)	26	74	203.51±185.51	439.26±514.91	0.001
AST, U/L (5-34)	42	119	28.11±27.47	27.51±16.74	0.895
ALT, U/L (0-55)	42	120	38.16±37.19	40.50±35	0.725
Creatinine, mg/dL (0.57-1.11)	45	121	0.85±0.16	0.91±0.42	0.186
D-dimer, mg/L (0.0-0.5)	12	25	0.29±0.21	0.38±0.45	0.388

C. Symptoms

Symptom	Group 1 (%)	Group 2 (%)	Odds ratio (95% confidence interval)	*p*-value
Fever	37.78	53.72	0.523 (0.265-1.033)	0.081
Shiver	15.56	13.22	1.209 (0.473-3.244)	0.800
Sweating	8.89	14.05	0.596 (0.208-1.781)	0.442
Anosmia	31.11	18.18	2.032 (0.949-4.431)	0.090
Ageusia	28.89	9.92	3.690 (1.457-8.476)	0.005
Dry cough	28.89	43.8	0.521 (0.257-1.078)	0.108
Dyspnea	6.67	7.44	0.888 (0.249-3.537)	>0.999
Gastrointestinal symptoms	20	10.74	2.077 (0.868-5.009)	0.128
Myalgia	22.22	19.01	1.217 (0.529-2.839)	0.664
Headache	33.33	14.05	3.059 (1.401-6.558)	0.007
Angina	13.33	10.74	1.278 (0.453-3.530)	0.596
No symptoms	13.33	14.88	0.880 (0.330-2.403)	>0.999

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; n, number of patients; SD, standard deviation; WBC, white blood cells;

TABLE 2. *Comorbidities identified in all subjects. Numerals express number of patients*

	HTN	Established CVD	Diabetes mellitus	GI diseases	CRD	Tuberculosis	CLD/CKD	Malignancy
Group 1	3/45	0	1/45	1/45	0	0	0	0
Group 2	38/121	13/121	7/121	7/121	9/121	2/121	4/121	3/121

Abbreviations: CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic respiratory disease; CVD, cardiovascular disease; GI, gastrointestinal; HTN, arterial hypertension

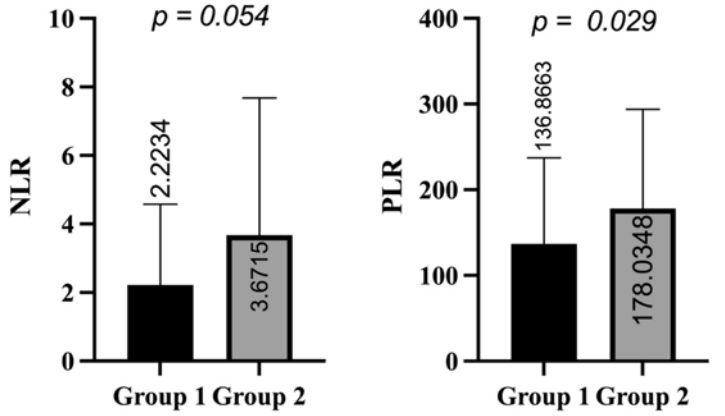

FIGURE 1. *Mean NLR values in the studied cohort (a); mean PLR values in the studied cohort (b). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio*

The correlations between NLR, PLR and inflammatory markers (CRP, serum ferritin and fibrinogen) are presented in Tables 3 and 4, respectively. Using Spearman's Rho correlation in group 2, significant correlations were observed between NLR and two inflammatory markers [CRP (p<0.001) and fibrinogen (p=0.009)], and between PLR and CRP (p<0.001).

TABLE 3. *Correlations between NLR and CRP, and fibrinogen and serum ferritin (Spearman's Rho correlation) in all studied patients*

Parameter	Spearman's Rho correlation	NLR		CRP		Fibrinogen		Serum ferritin	
		Group		Group		Group		Group	
		1	2	1	2	1	2	1	2
NLR	r	1	1	0.011	0.314	-0.238	0.238	0.153	0.202
	p-value	<0.0001	<0.0001	0.942	<0.001	0.128	0.009	0.454	0.083
	n	45	121	44	120	42	118	26	74
	95% CI	1.000 to 1.000	1.000 to 1.000	-0.294 to 0.315	0.137 to 0.471	-0.512 to 0.079	0.054 to 0.406	-0.259 to 0.519	-0.033 to 0.417
CRP	r	0.011	0.314	1.000	1.000	0.464	0.599	-0.049	0.428
	p-value	0.942	<0.001	0.000	0.000	0.002	<0.001	0.811	<0.001
	n	44	120	44	120	42	73	26	73
	95% CI	-0.294 to 0.315	0.137 to 0.471	1.000 to 1.000	1.000 to 1.000	0.177 to 0.678	0.464 to 0.706	-0.438 to 0.355	0.213 to 0.603
Fibrinogen	r	-0.238	0.238	0.464	0.599	1.000	1.000	0.300	0.504
	p-value	0.128	0.009	0.002	<0.001	<0.0001	<0.0001	0.136	<0.001
	n	42	118	42	117	42	118	26	73
	95% CI	-0.512 to 0.079	0.054 to 0.406	0.177 to 0.678	0.464 to 0.706	1.000 to 1.000	1.000 to 1.000	-0.110 to 0.623	0.303 to 0.661
Serum ferritin	r	0.153	0.202	0.049	0.428	0.300	0.504	1.000	1.000
	p-value	0.454	0.083	0.811	<0.001	0.136	<0.001	<0.0001	<0.0001
	n	26	74	26	73	26	73	26	74
	95% CI	-0.259 to 0.519	-0.033 to 0.417	-0.438 to 0.355	0.213 to 0.603	-0.110 to 0.623	0.303 to 0.661	1.000 to 1.000	1.000 to 1.000

Abbreviations: CRP, C-reactive protein; n, number of patients; NLR, neutrophil-to-lymphocyte ratio; r, correlation coefficient

TABLE 4. *Correlations between PLR and acute phase proteins (CRP, fibrinogen, and serum ferritin).*

Parameter	Spearman's rho correlation	PLR		CRP		Fibrinogen		Serum ferritin	
		Group		Group		Group		Group	
		1	2	1	2	1	2	1	2
PLR	r	1.000	1.000	0.226	0.320	0.408	0.146	0.129	0.062
	p-value	<0.0001	<0.0001	0.140	<0.001	0.797	0.114	0.528	0.598
	n	45	121	44	120	42	118	26	74
	95% CI	1.000 to 1.000	1.000 to 1.000	-0.084 to 0.496	0.144 to 0.477	-0.275 to 0.348	-0.040 to 0.323	-0.282 to 0.501	-0.175 to 0.293
CRP	r	0.226	0.320	1.000	1.000	0.464	0.599	-0.049	0.428
	p-value	0.140	<0.001	<0.0001	<0.0001	0.002	<0.001	0.811	<0.001
	n	44	120	44	120	42	117	26	73
	95% CI	-0.084 to 0.496	0.144 to 0.477	1.000 to 1.000	1.000 to 1.000	0.177 to 0.678	0.464 to 0.706	-0.438 to 0.355	0.213 to 0.603
Fibrinogen	r	-0.238	0.238	0.464	0.599	1.000	1.000	0.300	0.504
	p-value	0.128	0.009	0.002	<0.001	<0.0001	<0.0001	0.136	<0.001
	n	42	118	42	117	42	118	26	73
	95% CI	-0.275 to 0.348	-0.040 to 0.323	0.177 to 0.678	0.464 to 0.706	1.000 to 1.000	1.000 to 1.000	-0.110 to 0.623	0.303 to 0.661
Serum ferritin	r	0.129	0.062	-0.049	0.428	0.300	0.504	1.000	1.000
	p-value	0.528	0.598	0.811	<0.001	0.136	<0.001	<0.0001	<0.0001
	N	26	74	26	73	26	73	26	74
	95% CI	-0.282 to 0.501	-0.175 to 0.293	-0.438 to 0.355	0.213 to 0.603	-0.110 to 0.623	0.303 to 0.661	1.000 to 1.000	1.000 to 1.000

Abbreviations: CI, confidence interval; CRP, C-reactive protein; N, number of values; PLR, platelet-to-lymphocyte ratio; r, correlation coefficient

Out of the 121 patients in group 2, 17 (14.05%) were transferred to the ICU [10 patients aged 18-49 years (38.4±7.04) and 7 patients aged 50-64 years (58.57±3.41)]. The average body mass index among the patients transferred to the ICU was 27.12 kg/m^2. Hypertension, other cardiovascular disease, and diabetes were the most common comorbidities in patients with unfavourable outcomes. Laboratory parameters of ICU vs. non-ICU patients are presented in Table 5.

Acute phase proteins and predictors of the systemic inflammatory response were also assessed in ICU survivors vs. non-survivors (table VI), and significantly increased values for serum ferritin and NLR were detected in the deceased cases (p=0.014 and p=0.001, respectively).

A body mass index of >30 kg/m^2 was present in all deceased patients (5 cases, mean age 53.40±8.23 years old).

DISCUSSION

The present study, conducted in a single hospital, identified certain risk factors for moderate or severe forms of SARS-CoV-2 infection. Advanced age, comorbidities (such as hypertension and cardiovascular disease) and high values of certain biological variables (LDH, serum ferritin, fibrinogen, D-dimers) have been considered as independent risk factors by various studies published worldwide [21-24].

TABLE 5. *Acute phase proteins and predictors of systemic inflammatory response in patients with pneumonia features on X-ray scans (group 2)*

Parameters, unit (reference value)	Patients, n		Mean ± SD		*p*-value
	ICU	Non-ICU	ICU	Non-ICU	
Fibrinogen, mg/dL (196-372)	17	104	7.24±4.62	3.09±3.60	0.0001
CRP, mg/dL (0.00-0.50)	17	104	6.51±9.70	2.08±3.35	0.002
Serum ferritin, ng/mL (women, 20-300; men, 15-160)	8	66	1,106.00±950.80	358.50±378.50	0.014
LDH, U/L (100-190)	17	104	254.80±121.20	208.60±56.46	0.014
NLR	17	104	7.24±4.62	3.09±3.60	<0.0001
PLR	17	104	257.00±111.20	165.10±111.70	0.002

Abbreviations: ICU, intensive care unit; CRP, C-reactive protein; LDH, lactate dehydrogenase, NLR, neutrophil-to-lymphocyte ratio, PLR, platelet-to-lymphocyte ratio

TABLE 6. *Main laboratory findings in ICU non-survivors vs. survivors.*

Parameters, unit (reference value)	Patients (n)		Mean ± SD		*p*-value
	ICU non-survivors	ICU survivors	ICU non-survivors	ICU survivors	
Fibrinogen, mg/dL (196-372)	5	116	443.80±290.40	363.90±111.20	0.971
CRP, mg/dL (0.00-0.50)	5	115	9.72±14.98	2.40±3.95	0.070
Serum ferritin ng/mL (women, 20-300; men, 15-160)	5	70	1,110.00±809.00	400.90±477.80	0.014
LDH, U/L (100-190)	5	116	400.20±93.42	206.60±56.50	<0.0001
NLR	5	116	9.64±3.97	3.41±3.82	0.001
PLR	5	116	218.60±89.54	176.30±116.70	0.175

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; n, number of patients; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation

Chronological age has been identified as an independent risk factor for severe forms of SARS-CoV-2 infection and mortality. The results of the present study reveal that patients with COVID-19 infection in group 2 (with radiological signs of pneumonia) are older than those in group 1 (milder disease and no radiological changes; p<0.001). Ho et al reported that COVID-19 positive cases aged >75 years had a 13-fold mortality risk [95% confidence interval (CI), 9.13-17.85] compared with those aged <65 years in a cohort of 470,034 patients [25]. The increased risk was explained by a low forced expiratory volume in 1 second, high systolic blood pressure, low handgrip strength and multiple long-term conditions. Statistical analysis showed that these risk factors were strongly associated with COVID-19-related mortality among older participants. Study participants aged >75 years without additional risk factors had a 4-fold risk of death (95% CI, 1.57-9.96; p=0.004) compared with patients aged >65 years [25].

Another finding of the present study was that the body mass index may influence the presentation of SARS-CoV-2 infection, with a higher severity observed in overweight and obese patients. This result was consistent with that of other published studies [26-30]. A systematic review published by Peres et al., which was performed at the University of Sao Paolo and University of Campinas-Brazil, assessed the impact of being overweight and obese on the outcome of patients with SARS-CoV-2 infection. Obesity was found to be associated with a worse prognosis, due to the association between restrictive lung ventilatory defects accompanied by dysfunctional adipocytes, which produce huge volumes of pro-inflammatory cytokines, and an increased risk of developing cardiovascular complications [31].

In terms of laboratory findings, multiple parameters, which had been closely associated with disease severity in previous studies, were investigated in the present study [32,33]. Acute phase proteins (CRP, fibrinogen, and serum ferritin) were found to be correlated with an increased risk of lung damage and ICU admission. Our findings were similar to those of several other studies published between 2019 and 2020 in China and other countries affected by SARS-CoV-2 infection [4-8,34-42].

In the current study, elevated plasma values of an emerging biomarker (LDH) present in the lung tissue (as isoenzyme 3) were correlated with features of pneumonia on chest X-ray scans in patients with COVID-19. Several researches also compared elevated LDH values in different forms of COVID-19 and identified an association with unfavourable disease progression in these patients [4,21,41,43]. The present study confirmed that increased LDH values were significantly correlated with ICU admission and mortality.

It was reported that NLR and PLR can be used as inflammatory markers in SARS-CoV-2 infection [12]. The simple and inexpensive method of measuring these two parameters using CBC, a widely available investigation, renders them useful tools for predicting the course of viral pneumonia. We demonstrated, when NLR and PLR were independently compared with other inflammatory markers, patients with high levels of CRP also exhibited high values of the two ratios. Elevated NLR values were present in the COVID-19 cases with hyperfibrinogenemia. Based on these results, NLR and PLR can be used as markers of lung changes during COVID-19.

The present study had certain limitations. First, it was based exclusively on an Eastern European population, and therefore further confirmation is mandatory in other populations. Secondly, it was a single-centre study, and its conclusions may therefore differ from those of large studies, due to the relatively small sample size. Further research should be conducted on a larger patient sample from different geographic locations.

CONCLUSION

It is essential to have a knowledge of factors aggravating SARS-CoV-2 infection to perform a careful triage of patients with mild, moderate, and severe forms of

the disease. At the beginning of the pandemic, an abundance of material and human resources was mobilised in Romania, where all patients testing positive for COVID-19, including asymptomatic individuals, were hospitalised in an attempt to effectively control the spread of the virus. Scaling back this extensive use of resources and preventing the complications of COVID-19 disease using well-defined indicators of poor outcome is preferred. The results of the present study confirmed that middle-aged patients with a high body mass index and increased values of acute phase proteins, CRP, serum ferritin and fibrinogen, and the biomarker LDH, were associated with a more severe form of COVID-19 and a poor outcome. In addition, the present study proposed that NLR and PLR may represent potential useful indicators of disease severity; however, a future evaluation on a larger number of patients should be conducted to determine their predictive role in SARS-COV-2 infection.

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