sciendo

COVID-19 associated pulmonary embolism: clinical, biochemical and CT imaging findings

EDUARD DUMEA[1], MIHAI LAZĂR[1,2,*], CRISTINA EMILIA CHIŢU-TISU[1], ECATERINA CONSTANŢA BARBU[1], DANIELA ADRIANA ION[1]

[1] Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, No. 37, Dionisie Lupu Street, Sector 2, 020021 Bucharest, Romania
[2] "Prof. Dr. Matei Balş" National Institute for Infectious Diseases, No. 1, Calistrat Grozovici Street, Sector 2, 021105 Bucharest, Romania

Abstract

Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection represented a disruptive pathology that emerged in late 2019 with profound implications ranging from individual health to health systems and world economy. Our study aimed to evaluate clinical, biochemical and computerized tomography (CT) parameters values in determining the severity of pulmonary embolism (PE) associated with COVID-19.

Methods: We performed an observational cohort study evaluating demographic, clinical, biochemical, coagulation markers, as well as CT imaging parameters.

Results: In our study on 186 patients with COVID-19, we found that 31 patients (16,66%) had pulmonary embolism. Significant correlations for the patients with PE were detected in C-reactive protein, lactate dehydrogenase, serum ferritin, IL-6, serum myoglobin, NT-proBNP, D-dimers, serum proteins, transaminases as well as white cell blood counts. Patients with pulmonary embolism had a more severe lung involvement, with thrombi distribution mainly involving the lower lobes.

Conclusion: Early identification of PE is an important step for timely and efficient treatment in the intensive care management of COVID-19 patients. Our study showed that high plasmatic values of lactate dehydrogenase, ferritin, IL-6, white blood cells and D-dimers and low proteins serum levels are strongly linked with COVID-19-associated pulmonary embolism.

Keywords: pulmonary embolism; thrombosis; thromboinflammation; COVID-19; SARS-CoV-2 infection; risk factors.

What is new? What is important?

The patients with PE were older and mostly male, with a higher length of hospitalization and more severe lung involvement.
Thrombi distribution mainly involved the lower lobes, with a slight predominance of the right lower lobe, corresponding to a more severe lung involvement in the lower lung lobes.
High plasmatic values of LDH, ferritin, IL-6, WBC counts and D-dimers were strongly associated with PE developed in COVID-19 patients, as well as low protein serum levels.
Early identification of COVID-19-associated-PE patients is an important step for timely and efficient treatment in the intensive care management of these patients.

INTRODUCTION

Acute pulmonary embolism (PE) is a severe complication in COVID-19 patients, caused due to a pro-coagulant pattern observed in SARS-CoV-2 infections, with a higher risk of thrombus formation in both arterial and venous vascular compartments [1, 2]. General recommendations have been issued for dealing with this particular type of complication, especially in patients with severe forms of the disease [3, 4].

Published data suggested that males, obesity, mechanical ventilation, severe forms of pneumonia, ICU admission, elevated D-Dimers levels and high blood values for white blood cells are associated with a higher risk for PE in COVID-19 patients [5]. For the COVID-19 non-ICU patients, the risk factors for PE include rather independent clinical

 DOI: 10.2478/rjim-2024-0017

and biological findings at admission, such as the presence of chest pain and dyspnea; a longer delay from symptoms onset to hospitalization; and high inflammatory markers (leucocyte and platelets counts, and C-reactive protein level) [6].

The incidence of thrombo-embolic events is difficult to precisely estimate, as a significant number of patients could not be diagnosed with contrast-enhanced computerized tomography (CT), due to the severity of the disease and their inability to be transported to the radiology department, which led to heterogeneous data.

Furthermore, coagulopathy has been proven to be a prognostic factor for poor outcomes in COVID-19 patients [7, 8]. An aggressive inflammatory response seems to be one of the key pathologic mechanisms leading to thrombi formation, via complement activation and endothelium inflammation, along with the cited cytokine storm [9, 10]. Myocardial injury has also been cited as a complication within the COVID-19 cohort, with an incidence of up to 12% [11], with similar mechanisms.

The patients with COVID-19 and significant D-dimers elevations also exhibited increased mortality [7] with a high incidence of thrombotic complications despite the administration of prophylactic anticoagulants [12]. The communicated mortality for intensive care units (ICU) patients was higher in patients with PE compared to that of patients without PE (69% vs. 20%; $p = 0.04$) [13].

PE is an important complication in moderate and severe forms of COVID-19, with increased morbidity and mortality, the hospitalized patients with a critical state of the disease having a higher risk [3, 14, 15, 16]. Only a few studies have assessed risk factors for poor outcomes in COVID-19-associated PE patients. These patients may present a higher risk of needing mechanical ventilation, dialysis and ECMO (extracorporeal membrane oxygenation), intensive care unit admission and a longer hospitalization period compared to the patients without PE; patients with COVID-19 and PE also carry a higher risk of developing right ventricular dysfunction and shock [14, 17, 18, 19]. Furthermore, a high simplified Pulmonary Embolism Severity Index score (sPESI) is correlated with a high risk of mortality in both patients with COVID-19-associated PE (over 3-fold increased mortality) and those having PE without COVID-19 [18, 20]. Therefore the timely diagnosis of PE and the appropriate management of the patients at risk of developing PE are of the essence in COVID-19 patients.

Endothelial injury is proposed as one of the main mechanisms through which pathologic coagulation develops. Endothelial cells have a significant ACE2 receptor expression [20], making them prone to direct viral infection and local injury, shifting the balance to a pro-coagulant tendency.

PE in COVID-19 may occur also as in situ thrombosis in pulmonary arteries, especially in situ distal pulmonary thrombosis and this mechanism was revealed in histopathological research [21].

In specific studies, elevated D-dimers and white blood cell values (at both hospital admission and closest to CT pulmonary angiography) have been proven as risk factors for PE in COVID-19, suggesting that the reason may be that they are closely related to excessive inflammation and severe form of COVID-19. This connection advocates the more severe evolution of the disease when PE is present and the demand to adjust the treatment for such cases with potentially severe evolution. Using preventive anticoagulants in the management of COVID-19 has always been a debated topic. While some studies recommend the use of preventive anticoagulants in higher doses than the conventional ones for potential reduction of thrombotic events in patients with severe COVID-19 or those at high risk of thrombosis, the usage of prophylactic anticoagulation on all COVID-19 patients remains controversial. Therefore, original studies are still needed to improve the assessment of the risk factors for PE in COVID-19 patients and the management of this condition [5].

The von Willebrand Factor (vWF) plays an important role in hemostasis and it is solely produced by thrombocyes and endothelial cells. Related to local hemostasis, vWF also plays a role in inflammation mediation, recruiting leukocytes once activated [22]. The vWF protease, ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) enzyme is an important balacing factor in the vWF activity, it's main function being cleaving highly active vWF multimers into less thrombogenic and inflammatory ones [23]. Besides expressing a systemic inflammation in COVID-19 patients, a raised white blood cell count may also indicate an increased vWF activity and a higher risk of thrombus formation, especially in at-risk territories. Deficient ADAMTS13 is also communicated in patients with acute liver injury [24, 25], and thus, reduced serum proteins levels may relate to a reduced ADAMTS13 level, further emphasizing the thrombogenic and inflammatory imbalance. In

conditions of reduced serum protein levels, the level of ADAMTS13 may be reduced, resulting in a low rate of cleaving the highly active vWF multimers and a high risk of thrombosis.

Furthermore, platelet-leukocyte complexes have frequently been observed in COVID-19 and linked to disease progression and poor outcomes [26]. The formation of neutrophil extracellular traps (NET) around platelets once again sustains the procoagulant state, having been identified in lung, cardiac and renal thrombi [27, 28]. NET formation has been a key focus of COVID-19 therapy research from the beginning, showing how NET inhibitors such as dexamethasone and colchicine reduced mortality in SARS-CoV-2 infected patients [29, 30].

Our study aimed to identify and further characterize clinical, biochemical and CT parameters in COVID-19 patients, leading to faster identification of patients at risk of developing PE and allowing timely patient management in and diagnosis of COVID-19-associated PE.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

Our study is an observational retrospective cohort study of 186 patients admitted between January 2021 and August 2021 to our department in the "Prof. Dr. Matei Balș" National Institute of Infectious Diseases, Bucharest, Romania. The patients were divided into two groups: Group A (155 patients without imaging-proven PE) and Group B (31 patients with imaging proven PE).

Acute PE was defined as a filling defect in the pulmonary arterial tree, ranging from the pulmonary artery trunk to the subsegmental pulmonary arterial branches. The thrombus disposition inside the vessel had to be centered, with or without surrounding contrast around it, and without any signs of chronic PE (lateral disposition, calcified components, and old pulmonary infarction lesions in the distal portion).

The data recorded in the study (clinical, biochemical and CT imaging) were taken in the first two days after hospital admission, to reduce potential modifiers (such as medical treatment, intubation and/or other medical procedures).

Inclusion criteria were adult age (over 18 years old), positive rt-PCR COVID-19 test and contrast-enhanced CT in the first two days following hospital admission. Exclusion criteria were pediatric age; patients with known chronic PE; known chronic heart and/or kidney disease/renal dysfunction; antiphospholipid syndrome; patients undergoing anticoagulation treatment for other prior pathologies; and pregnant or breastfeeding women.

For the calculation of the minimum sample size we considered a confidence level of 95%, a margin of error of 5% and a population proportion of 5.4% (representing the prevalence of COVID-19 in the general population in our country at the time of the study, according to the data communicated by World Health Organization). We calculated the minimum sample size using the following formula: $n=[z^2 \times \hat{p} \times (1- \hat{p})]/\varepsilon^2$, where n=sample size, z = z score, $\hat{p}$ = population proportion, ε=margin of error, resulting in a minimum population of 79 patients [11].

DEFINITIONS

All patients in our study received prophylactic treatment with low-molecular-weight heparin (LMWH) upon arrival at the hospital. The anticoagulant treatment was escalated to therapeutic doses after the diagnosis of PE. In accordance with the Ministry of Health protocol and with our hospital protocol, LMWH was administered as prophylactic treatment in doses of 40 mg enoxaparin subcutaneously once daily (or twice daily if BMI ≥ 40 kg/m^2) or 5000 units of dalteparin subcutaneously once daily (or 7500 units once daily if BMI ≥ 40 kg/m^2). After PE was revealed, the therapeutic doses were 1 mg/kg of enoxaparin subcutaneously at every 12 hours or 100 units/kg of dalteparin subcutaneously at every 12 hours.

All patients in our study received steroid therapy with dexamethasone upon arrival at the hospital. The patients received Dexamethasone 6mg orally daily or Dexamethasone phosphate 8mg (equivalent to dexamethasone 6.6 mg) intravenously daily for a minimum duration of 3 days. In the first 2 days when or data were recorded all patients received the same steroid dose.

National Institutes of Health (NIH) defines a severe form of COVID-19 in patients who present one or more of the following criteria: peripheral oxygen saturation (SpO2) < 94% in ambient air, respiratory rate (RR) > 30/min, arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2 ratio) < 300mmHg, or lung infiltrates > 50% of lung parenchyma [31].

DEMOGRAPHIC, CLINICAL AND BIOCHEMICAL PARAMETERS

We registered the following data for each patient: the following data: age; sex; duration of hospitalization; status at the end of hospitalization (survivors or deceased) or survival rate; peripheral oxygen saturation in ambient air; markers of cardiac dysfunction (Troponin I - Tn I); N terminal pro B type natriuretic peptide (NT-proBNP); creatine kinase muscle brain (isoenzyme, CK-MB); serum myoglobin; lactate dehydrogenase (LDH); C reactive protein (CRP); serum fibrinogen; serum ferritin; interleukin 6 (IL-6); tumor necrosis factor alpha (TNF alpha); lymphocyte and white blood cell counts; coagulation markers (prothrombin time [PT]; activated partial thromboplastin time [aPTT]); D-dimers high sensitivity (HS); liver disfunction markers (alanine transaminase [ALT[; aspartate transaminase [AST]; gamma-glutamyl transferase [GGT], total bilirubin [TB]; direct bilirubin [DB]); serum albumin; and serum total proteins (TSP).

The biological parameters were determined on the following systems: ADVIA2120 Hematology Analyzer, ACL Top Coagulation Analyzer, Vitros_FS3, RAMP Analyzer and BNII System; the measurement of cytokines was performed using specific ELISA kits.

RADIO-IMAGING PARAMETERS

Chest contrast-enhanced CT scans were obtained in the first two days of admission, with contrast bolus timing to optimize the visualization of pulmonary arterial branches on a Somatom Sensation 64, Siemens AG, Erlangen, Germany.

The hospital protocol included CT scan with contrast only for the patients with clinical suspicion of PE or for the patients with D-dimers ≥500ng/mL.

Two radiologists (ML and ED) with 20 and 6 years of experience in chest radiology, respectively, read the scans, blinded to the clinical and biochemical parameters of the patients.

Subsequently, they scored the extent of the ground glass opacities (GGO), crazy-paving pattern, alveolar consolidation and fibro-atelectatic changes from 0 to 3, depending on the number of segments involved, where 0 required no segments with the before-mentioned lesions, grade 1 required up to 5 segments, grade 2 required up to 11 segments, while grade 3 required equal or more than 12 segments. Vascular ectasia was graded from 0 to 2, where 0 meant no vascular ectasia could be observed, 1 meant less than half of pulmonary segments with GGO presented vascular ectasia, where as 2 meant more than half of GGO segments presented vascular ectasia (Fig.1, Fig. 2a, Fig. 2b); pleural and pericardial effusion were scored as 0 and 1, depending on its presence or absence.

The number of segments affected by PE was also established, as well as PE extension in the main pulmonary artery or the pulmonary artery trunk.

Lung parenchyma density (on the Hounsfield unit scale) was measured next to the embolized arterial vessel and graded as follows: greater than -100 HU (consolidation), between -100 HU and -799 HU (interstitial involvement), and between -800 HU and -1000 HU (normal lung densities).

STATISTICAL EVALUATION

Statistical Package for Social Sciences (SPSS version 25, IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous variables were presented as medians and quartiles, while categorical variables were presented as percentanges. A significant correlation between variables was established through Spearman's equation.

Receiver operating characteristics (ROC) curve were calculated for all measured parameters. Additional data analysis was conducted using multivariable logistic regression. The independent variables were excluded based on the individual parameter results obtained during logistic regression analysis using the Wald test. The least significant effect with a p-value higher than 0.2 was removed from the prognostic model. The Omnibus test of model coefficients was used to estimate the statistical significance of the logistic regression. A p value of less than 0.05 was considered of statistical significance.

ETHICS STATEMENT

The study has been approved by the local ethics committee (C10218/15.09.2021) and is in line with the Declaration of Helsinki.

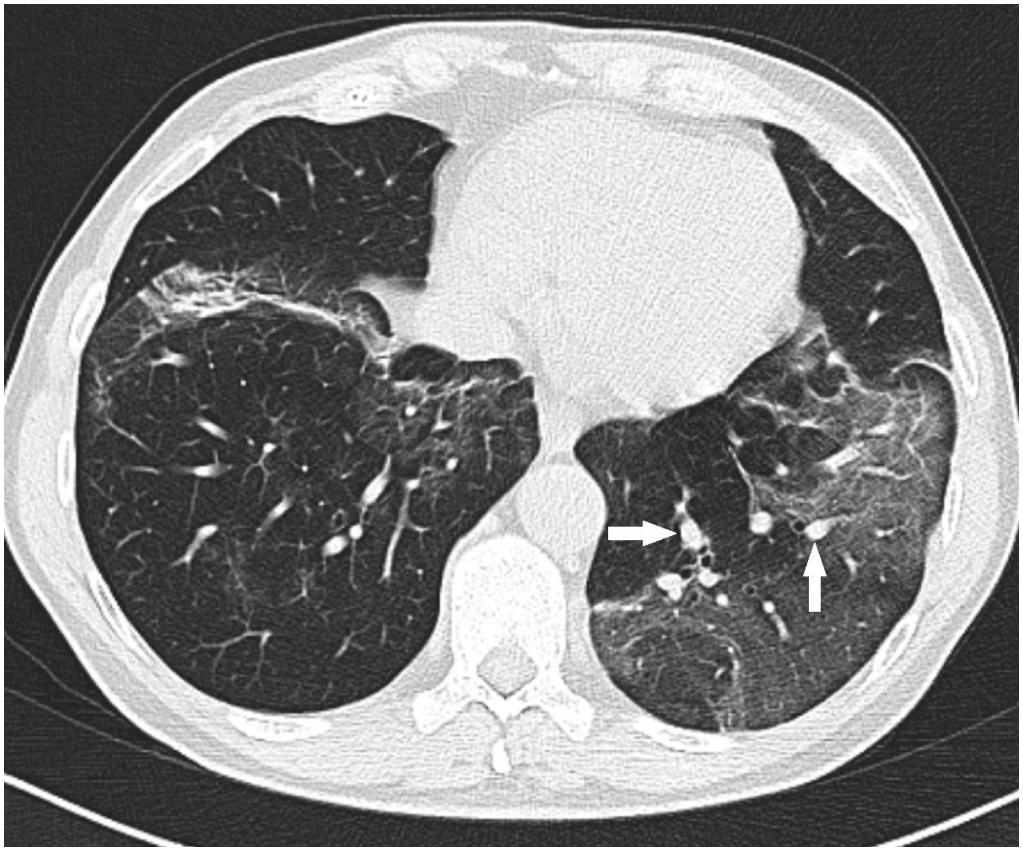

Fig. 1. Focal vascular ectasia can be observed associated with ground glass opacities in left lower lobe (white arrows), and smaller vessels on the opposed side (axial view).

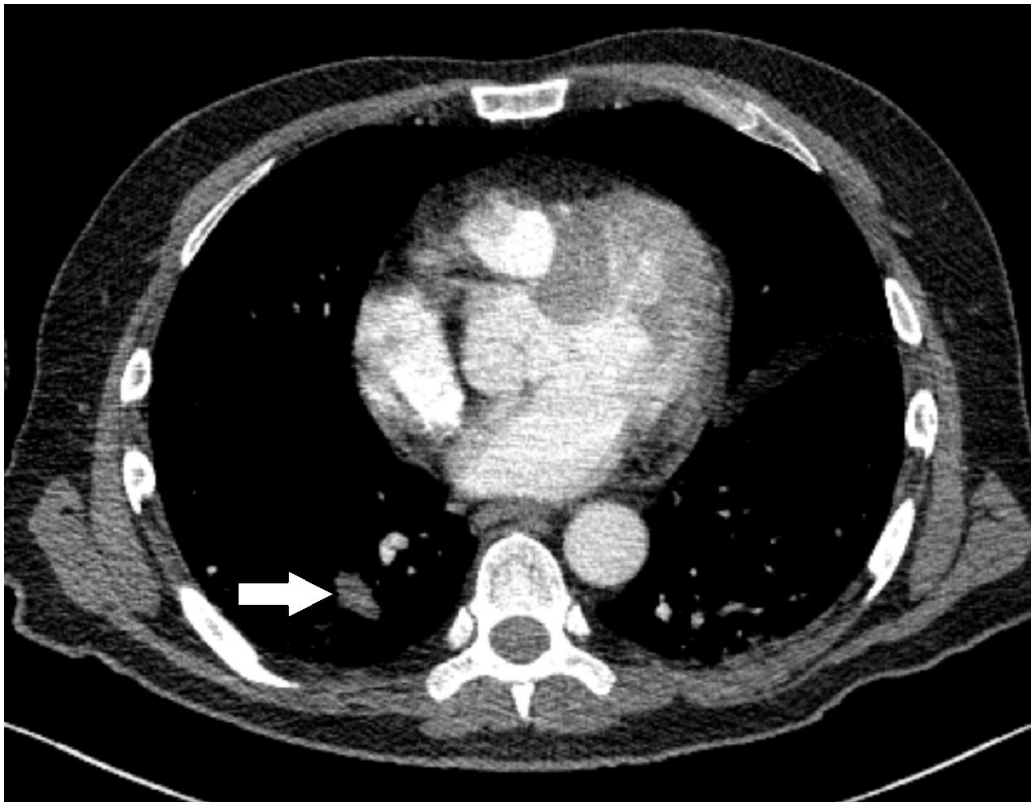

Fig. 2a. Enlarged posterior segmental branch of inferior lobar pulmonary artery with complete thrombosis (white arrow).

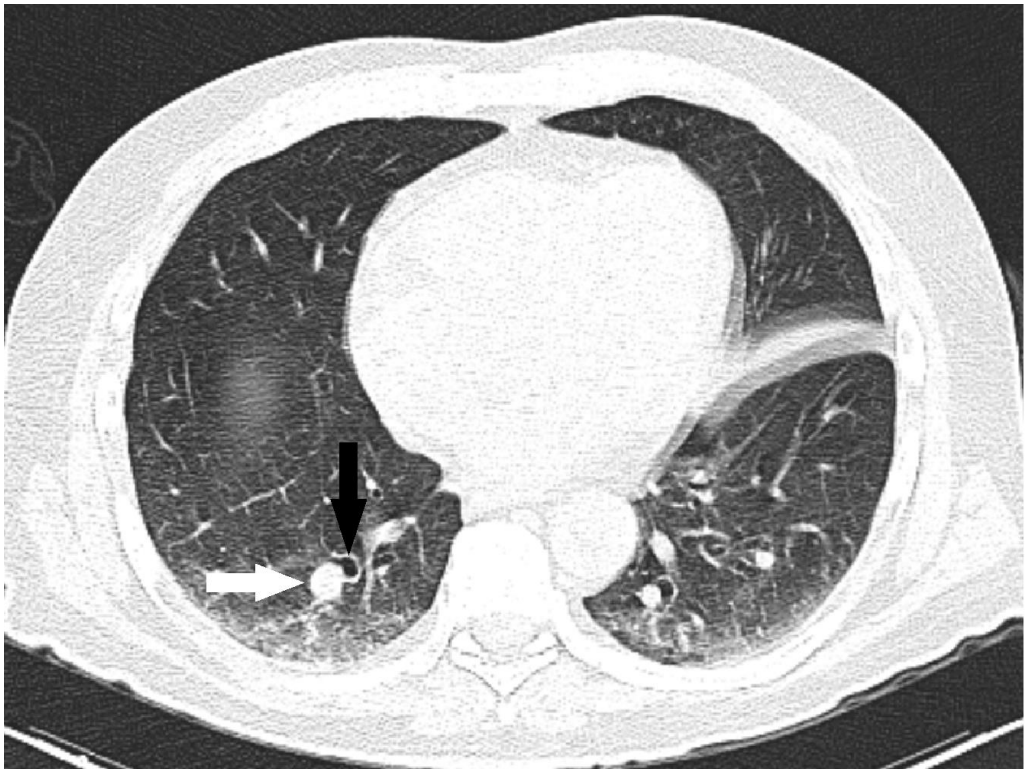

Fig. 2b. Vascular ectasia in inferior right lobe; please notice the difference between the calibre of the thrombosed arterial branch (white arrow) and the bronchial calibre (black arrow) in the right lower lobe and their similar dimensions in the left lower lobe.

RESULTS

The cohort of patients was divided into two groups: Group A consisted of in patients without PE and included 155 patients (83%) and Group B consisted of patients that presented at least one filling defect in the pulmonary arterial tree as evidenced by contrast-enhanced CT and included 31 patients (17%). Group A included 84 males (54%) and 71 females (46%), with a male-to-female sex ratio of 1.18:1, while Group B included 23 males (74%) and 8 females (26%), with a male-to-female sex ratio of 2.87:1.

Considering the criteria for severe form of COVID-19 defined by National Institutes of Health (NIH), 94 patients (60.6%) from Group A and 31patients (100%) in Group B had severe forms of COVID-19 at presentation.

Patients with CT-proven PE were older, mainly comprised males, had a longer hospitalization period and registered a mortality rate higher than that of the patients in the non-PE group (Table 1).

Ferritin levels, myoglobin, LDH, CRP and IL-6 were higher in Group B (PE group) with a p value of less than 0.05. Albumin and TSP levels, as well as lymphocyte counts, were lower in group B. Statistical differences were also seen in white blood cell counts, with the counts being higher in group B, slightly above the upper normal limit (10.0).

Admission contrast-enhanced CT scans revealed statistically significant differences in almost all imaging characteristics and scales used, with a greater extension of GGO; alveolar consolidation; interstitial thickening with crazy-paving pattern; and vascular ectasia, bronchiectasis and fibro-atelectatic changes (Table 2). Pleural and pericardial effusion did not show statistically significant differences between the two groups. Patients with PE had bilateral modifications consistent with pneumonia, and almost all of them had all 5 lung lobes affected (96.8%).

None of the patients required mechanical ventilation or hemodynamic support at admission. During the hospital stay 4 patients needed mechanical ventilation: 1 patient in Group A (0.6%) and 3 patients in Group B (9.7%), and 13 patients presented hemodynamic instability with shock (7 patients in Group A representing 2.6% and 6 patients in Group B representing 19.4%).

Thrombus formation was found mostly in segments of the lower lobes rather than in the middle or upper lobes, with a slight favour towards the right side (43%). Only 6% (2) of the patients presented with main pulmonary artery thrombus,

and none of them had main arterial trunk involvement. Most patients presented with unilateral PE (61.3%).

We found PE images in 102 segments in Group B patients, representing 17.31% of the total lung segments, with a mean density of nearby lung tissue ranging between -100HU to -799HU for the majority of patients (84%) (Table 3), suggesting that the PE occurred mostly in lung segments with densitometric changes of interstitial pneumonia.

Table 1

General characteristics of the cohort patients

Parameter	Group A (without PE)	Group B (with PE)	p-value
Age (years)	58 [46; 68]	64 [55; 76]	0.017
Sex (male:female)	84:71	23:8	0.044
Duration of hospitalization (days)	11 [7;14]	18.5[12; 24.2]	<0.001
Deceased patients (n, %)	8 (5.16%)	7 (22.6%)	0.003
Saturation O_2 (%)	93 [89; 97]	85 [79; 91]	<0.001
Tn I (ng/mL)	0.03 [0.03; 0.03]	0.3 [0.3; 0.35]	0.378
NT-proBNP (ng/L)	72 [14.5; 256]	176.5 [51; 1434.5]	0.221
CK-MB (UI/L)	12 [8; 16.5]	13 [8.25; 17]	0.381
LDH (UI/L)	268 [217; 349.5]	556 [392.2; 704]	<0.001
Myoglobin (ng/mL)	102.2 [67.8; 142]	184.6[115.8; 207.6]	0.018
CRP (mg/L)	12.4 [4.3; 48.7]	69.9 [6.1; 114]	0.05
Fibrinogen (mg/dL)	399 [312; 524.5]	425 [287.7; 549.5]	0.701
Ferritin (ng/mL)	446.6 [209.8; 890.6]	1341 [724.7; 1650]	<0.001
IL-6 (pg/ml)	17.4 [3.1; 123.3]	399 [49.4; 833.7]	0.006
TNF-alpha (pg/ml)	3.5 [0.62; 10]	8.3 [1.6; 55.8]	0.352
D-dimers HS (ng/ml)	181 [106; 375]	1878 [866.7; 7623.2]	<0.001
ALT (UI/L)	48.5 [26; 93.2]	76 [38.5; 124.5]	0,123
AST (UI/L)	40 [30; 59.5]	64[43;82]	0,753
TB (mg/dL)	0.7 [0.5; 0.9]	0.7[0.5; 0.95]	0,138
DB (mg/dL)	0.2 [0.2; 0.3]	0.3[0.1;0.4]	0,266
GGT (UI/L)	57 [36; 117.2]	71[51.5;119]	0,141
Albumin (g/dL)	3.7 [3.4; 4.2]	3.3[3.1;3.9]	0,015
TSP (g/dL)	7.1 [6.6; 7.4]	6.2[5.85;6.7]	0,003
PT (sec)	12.2 [11.5; 13.6]	13.6 [12.2; 15.8]	0.102
aPTT (sec)	30.2 [27.7; 34.4]	28.1 [23.7; 31.2]	0.786
Lymphocytes (*10^3/μL)	1.02 [0.7; 1.7]	0.8[0.4; 1.2]	0.025
WBC (*10^3/μL)	7.7 [5.7; 10.6]	11.7[7.7; 16.5]	<0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK-MB, creatine kinase MB isoform; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, interleukin-6; TNF alpha, tumor necrosis factor alpha; D-dimers HS, D-dimers high sensitivity, ALT, alanine transaminase; AST, aspartate transaminase; TB, total bilirubin; DB, direct bilirubin; GGT, gamma-glutamyl transaminase; TSP, total serum proteins; PT, prothrombin time; aPTT, activated partial thromboplastin time; WBC, white blood cells
Reference ranges: Saturation O2:95-100%;Tn-I: 0 - 0.16ng/mL; NT-proBNP: 0-125 ng/L; CK-MB:1-16 UI/L; LDH:120-246 UI/L; myoglobin:0-99.3 ng/mL; CRP: 0-3mg/L; IL-6: 0-9.7 pg/mL; TNF alpha: 0-1.9pg/mL; D-dimers HS:50-230ng/mL; ALT:4-50UI/L; AST:17-59UI/L; TB:0.2-1.3mg/dL; DB:0-0.4mg/dL; GGT:15-73UI/L; albumin:3.5-5g/dL; TSP:6.5-8.5g/dL; PT:10.5-13 sec; aPTT:24-38sec; lymphocytes:1-4*10^3/μL; WBC:4-10*10^3/μL

Table 2

CT imaging characteristics and scaling of the cohort patients

Parameter		**Group A (without PE)**	**Group B (with PE)**	**p-value (Omnibus test)**
Number of patients with pneumonia (n, %)	0	20 (12.9)	0 (0)	<0.001
	1 lobe	4 (2.58)	0 (0)	
	2 lobes	10 (6.4)	0 (0)	
	3 lobes	6 (3.87)	0 (0)	
	4 lobes	10 (6.4)	1 (3.2)	
	5 lobes	105 (67.7)	30 (96.8)	
Type of involvement (n, %)	one lung	26 (16.7)	0	0.001
	both lungs	129 (83.3)	31 (100)	
Number of patients with GGO (n, %)	0	24 (15.5)	0	<0.001
	1	63 (40.6)	0	
	2	45 (29)	2 (6.4)	
	3	23 (14.8)	29 (93.6)	
Number of patients with crazy paving (n,%)	0	51 (32.9)	0 (0)	<0.001
	1	62 (40)	10 (32.2)	
	2	42 (27.1)	21 (67.8)	
Number of patients with vascular ectasia (n, %)	0	88 (56.8)	0 (0)	<0.001
	1	34(21.9)	12 (38.7)	
	2	33 (21.3)	19 (61.3)	
Bronchiectasis (n, %)	0	90 (58)	12 (38.7)	0.020
	1	48 (30.9)	11 (35.5)	
	2	17 (11.1)	8 (25.8)	
Number of patients with fibro-atelectatic lesion (n,%)	0	67 (43.2)	10 (32.2)	0.003
	1	46 (29.6)	6 (19.5)	
	2	35 (22.6)	5 (16.1)	
	3	7 (4.5)	10 (32.2)	
Number of patients with alveolar consolidation (n, %)	0	99 (63.9)	0 (0)	<0.001
	1 lobe	17 (10.9)	2 (6.4)	
	2 lobes	25 (16.1)	10 (32.2)	
	3 lobes	7 (4.5)	6 (19.5)	
	4 lobes	1 (0.6)	10 (32.2)	
	5 lobes	6 (3.9)	3 (9.7)	
Pericardial fluid (n, %)		33 (21.3)	7 (22.5)	0.887
Pleural fluid (n, %)		17 (10.9)	7 (22.5)	0.102

Table 3

Pulmonary embolism distribution

Parameter		n (% of total segments with PTE)
Segments of LLL with PTE (n,%)		32 (31.37)
Segments of LUL with PTE (n,%)		7 (6,86)
Segments of RLL with PTE (n,%)		44 (43.13)
Segments of RML with PTE (n,%)		6 (5.88)
Segments of RUL with PTE (n,%)		13 (12.74)
Total segments with PTE(n,%)		102 (17.31)
Patients with PTE extension in lobar arteries (n, %)		10 (32.2)
Patients with PTE extension in left/right pulmonary arteries (n, %)		2 (6.4)
Patients with PTE extension in pulmonary trunk (n, %)		0 (0)
Unilateral PTE (n, %)		19 (61.3)
Bilateral PTE (n, %)		12 (38.7)
Lung density adjacent to PTE vessel (n, %)	-800UH to -1000UH	2 (6.4)
	-100UH to -799UH	26 (84)
	>-100 UH	3 (9.6)

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right medium lobe; RUL, right upper lobe.

Parameters that were proportional significantly correlated with the presence of acute thrombus within the arterial pulmonary tree included days of hospitalization, LDH, ferritin, IL-6, white blood cell count and D-dimer levels ($p < 0.001$). Survivability, serum albumin and TSP registered inversely proportional correlations ($p < 0.05$) (Table 4).

We performed a ROC curve analysis to evaluate the relation between the measured parameters and the presence of COVID-19-associated-PE. Considering the area under curve, we found a good ability to predict COVID-19-associated-PE for D-Dimers HS, LDH, IL-6, TSP, ferritin, duration of hospitalization, WBC, and myoglobin. The extent of GGO, crazy paving, alveolar consolidation, and the presence of vascular ectasia also showed significant correlation with COVID-19-associated-PE. We found the largest area under the curve (AUC) for the D-dimers HS (0.921), followed by the extent of GGO involvement (0.919) (Table 5).

LDH, ferritin, IL-6 and the extent of alveolar consolidation are important parameters in predicting COVID-19-associated-PE, as presented in the multivariable logistic regression model depicted in Table 6, which had an overall prediction percentage of 90.7% and *p*-value < 0.001. Since elevated levels of D-dimers were a criterion for contrast administration and indirectly, patient enrolment in the study, we excluded this parameter from the regression model.

Based on the values in Table 6 we can calculate the probability of COVID-19-associated-PE using the formula: EXP (Constant + 0.006 x LDH + 0.003 x Ferritin + 0.002 x IL-6 + 0.554 x alveolar consolidation)/[1+ EXP (Constant + 0.006 x LDH + 0.003 x Ferritin + 0.002 x IL-6 + 0.554 x alveolar consolidation)].

Table 4

Correlations of clinical and biochemical markers with PE associated COVID-19

Parameter	Pearson/Spearman	p-value
Age (years)	0.176	0.017
Sex (male:female)	-0.151	0.04
Duration of hospitalization (days)	0.343	<0,001
Deceased patients (n, %)	0.238	0.001
Saturation O_2 (%)	0.358	<0.001
Tn I (ng/mL)	0.91	0.252
NT-proBNP (ng/L)	0.212	0.009
CK-MB (UI/L)	0.064	0.394
LDH (UI/L)	0.450	<0,001
Mioglobin (ng/mL)	0.243	0.003
CRP (mg/L)	0.182	0.015
Fibrinogen (mg/dL)	-0.022	0.769
Ferritin (ng/mL)	0.344	<0.001
IL-6 (pg/ml)	0.374	<0.001
TNF-alpha (pg/ml)	0.160	0.198
D-dimers HS (ng/ml)	0.552	<0.001
ALT (UI/L)	0.138	0.083
AST (UI/L)	0.244	0.002
TB (mg/dL)	0.065	0.426
DB (mg/dL)	0.094	0.262
GGT (UI/L)	0.109	0.187
Albumin (g/dL)	-0.262	0.009
TSP (g/dL)	-0.358	0.001
PT (sec)	0.211	0.008
aPTT (sec)	-0.164	0.076
Lymfocytes (n, %)	-0.2	0.012
WBC (*10^3/µL)	0.304	<0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK-MB, creatine kinase MB isoform; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, interleukin-6; TNF alpha, tumor necrosis factor alpha; D-dimers HS, D-dimers high sensitivity, ALT, alanine transaminase; AST, aspartate transaminase; TB, total bilirubin; DB, direct bilirubin; GGT, gamma-glutamyl transaminase; TSP, total serum proteins; PT, prothrombin time; aPTT, activated partial thromboplastin time; WBC, white blood cells.

Table 5

Receiver operating characteristics (ROC) curve for the ability to predict COVID-19-associated-PE

Parameter	AUC	Std. Error [a]	Asymptotic sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Age (years)	0.636	0.501	0.017	0.536	0.736
Sex (male:female)	0.400	0.54	0.79	0.295	0.505
Duration of hospitalization (days)	0.768	0.05	<0.001	0.668	0.967
Tn I (ng/mL)	0.546	0.065	0.462	0.419	0.672
NT-proBNP (ng/L)	0.666	0.056	0.01	0.556	0.776
CK-MB (UI/L)	0.551	0.061	0.393	0.432	0.670
LDH (UI/L)	0.856	0.035	<0.001	0.788	0.924
Myoglobin (ng/mL)	0.708	0,067	0.004	0.577	0.839

Table 5 (continued)

Parameter	AUC	Std. Error [a]	Asymptotic sig. [b]	Asymptotic 95% Confidence Interval	
				Upper Bound	Upper Bound
CRP (mg/L)	0.643	0.057	0.015	0.531	0.754
Fibrinogen (mg/dL)	0.483	0.062	0.768	0.362	0.604
Ferritin (ng/mL)	0.771	0.057	<0.001	0.659	0.884
IL-6 (pg/ml)	0.813	0.052	<0.001	0.711	0.915
TNF-alpha (pg/ml)	0.635	0.111	0.197	0.417	0.852
D-dimers HS (ng/ml)	0.921	0.027	<0.001	0.867	0.974
ALT (UI/L)	0.603	0.056	0.084	0.492	0.713
AST (UI/L)	0.682	0.050	0.002	0.585	0.780
TB (mg/dL)	0.550	0.067	0.428	0.419	0.682
DB (mg/dL)	0.570	0.068	0.274	0.436	0.703
GGT (UI/L)	0.584	0.056	0.186	0.475	0.693
Albumin (g/dL)	0.691	0.065	0.010	0.564	0.819
TSP (g/dL)	0.780	0.079	0.001	0.624	0.935
PT (sec)	0.653	0.056	0.008	0.544	0.763
aPTT (sec)	0.613	0.066	0.076	0.482	0.743
Lymphocytes (*10³/µL)	0.649	0.060	0.012	0.532	0.766
WBC (*10³/µL)	0.725	0.058	<0.001	0.612	0.838
Extent of lobe involvement	0.649	0.045	0.009	0.560	0.738
Type of lung involvement (one/both lungs)	0.584	0.051	0.141	0.485	0.683
Extent of GGO involvement	0.919	0.020	<0.001	0.879	0.958
Extent of the crazy paving	0.756	0.040	<0.001	0.677	0.835
Vascular ectasia	0.810	0.032	<0.001	0.747	0.873
Fibro-atelectatic changes	0.632	0.062	0.021	0.510	0.753
Alveolar consolidation	0.897	0.023	<0.001	0.851	0.943
Pericardial effusion	0.506	0.057	0.910	0.394	0.619
Pleural effusion	0.558	0.059	0.308	0.442	0.675

a.Under the nonparametric assumption
b.Null hypothesis: true area=0.5
AUC – area under the curve

Table 6

Multivariable logistic regression model for patients with COVID-19-associated-PE

Regression Model Type	B	S.E.	Wald	p	OR	95% CI for OR	
						Lower	Upper
LDH (UI/L)	0.006	0.003	5.341	0.021	1.006	1.001	1.012
Ferritin (ng/mL)	0.003	0.001	5.403	0.020	1.003	1.000	1.005
IL-6 (pg/mL)	0.002	0.001	4.453	0.035	1.002	1.000	1.004
Alveolar consolidation	0.554	0.335	2.738	0.098	1.739	0.903	3.351
Constant	-9.470	2.637	12.896	<0.001	0.000		

DISCUSSION

Patients with PE in our study were older and mostly male, with a higher length of hospitalization and increased mortality. Significant differences between PE and non-PE groups were found in CRP, LDH, serum ferritin, IL-6, serum myoglobin, NT-proBNP, D-dimers, PT, albumin, TSP and AST parameters as well as lymphocyte and white cell blood counts.

Patients with PE had a more severe lung involvement (inflammation involving more lung segments, higher percentage of crazy paving pattern, vascular ectasia and higher extent of fibro-atelectatic changes).

The lung injury found in COVID-19 patients mainly involves the lower lobes and has frequent bilateral distribution [32, 33], inducing an asymmetric inflammation process in the lungs (basal segments >> apical segments). According to our data the mean density of the lung parenchyma adjacent to the thrombosed vessel ranged between -100 HU and -799 HU for 84% of the patients, corresponding to areas whith interstitial pneumonia. This can explain the distribution of the thrombi being mainly in the lower lobes in our study, where the inflammation process is more important.

Recent literature data indicates that substantial alterations in iron metabolism can be utilized for predicting mortality in patients admitted to intensive care units, and serum ferritin has been newly recognized as one of the indicators for predicting mortality in COVID-19 patients [34]. Serum ferritin is an iron storage protein responsible for regulating cellular oxygen metabolism; it is composed of two subunits, H and L. Studies have has demonstrated that H-ferritin serves as an immune modulator, exhibiting both pro-inflammatory and immunosuppressive properties. Elevated ferritin levels may serve as an indicator of a pronounced inflammatory response triggered by the entry of a virus into the human body, affecting iron metabolism [35].

The significance of IL-6 in COVID patients has gained prominence, and the conventional sepsis score parameters do not comprehensively address or resolve all the issues arising from the cytokine storm. While iron parameters are not currently considered standard biomarkers for monitoring septic progression, the association between IL-6 and iron metabolism is widely acknowledged [36].

Gul *et al.* [37], using the National Collaborative COVID-19 retrospective cohort, compared PE vs non-PE 90-day mortality and intubation outcomes, as well as the value of testing for D-dimer, LDH, ferritin and other biochemical markers in COVID-19 patients. PE patients had a higher 90-day mortality rate (23.6% vs 12.8%), in keeping with our results (22.6% vs 5.16%, p=0.003). Similarly, older and male patients were more likely to develop pulmonary embolism, as well as having a longer hospital stay (18.5 vs 11 days in our study). Although, they measured presence of deep vein thrombosis or prior pulmonary embolism, and they showed a correlation with PE presence, we have excluded these patients from our cohorts so as to limit possible confounders with immunothrombosis in pulmonary vessels. In light of this, both studies showed higher levels of D-Dimers in patients with PE, reaching statistical significance (p<0.001). LDH and CRP were both higher in PE cohort, similar to our study.

Interstingly, ferritin was not found to have significant differences between the cohorts, while as we have found it to have a higher value in PE patients (1341 ng/mL vs 446 ng/mL, p=0.003) and have positive correlation with presence of PE.

Yousaf *et al.* [38] found no significant differences between demographics, inflammatory markers or coagulation parameters and presence of PE, including CRP, IL-6, ferritin, LDH and lymphopenia. However, cohort selection is different between studies, males consisting of 95% of the studied population, with a 67% cohort of critically unwell patients (undefined by the authors), as well as a higher incidence of PE (almost 22% vs. our 16%). D-Dimers levels were the only biomarker that was clearly associated with PE, reaching statistical significance, similar to ours. Older age and longer hospital stay were also not correlated with pulmonary embolism presence.

Although, Riyahi *et al.* [39] tried to identify the incidence and mortality of PE in COVID-19 patients, they found associations with male sex (p=0.02), increased D-dimers (p<.001), increased LDH (p<.001), ferritin (p=.001) and IL-6 (p=0.02), matching our findings. However, excess mortality was not recorded within the PE group. In contrast, Scudiero *et al.* [40] found a longer hospital stay (11 vs 6 days), higher D-dimers (p<.001) and higher prevalence of myocardial injury (47% vs. 28%, p=0.033) within the PE group. What is

more, mortality rates and cardiogenic shock were significantly higher in the pulmonary embolism group. As such, there is a great heterogenicity in assessment of mortality within this sublot of COVID-19 patients, partly owing to different inclusion criteria, as well as different strain and period assessment.

In our study, both IL-6 and serum ferritin levels have been positively correlated with PE and severe form of COVID-19.

In our study, D-dimers were found to have the most important correlation with the presence of COVID-19-associated-PE. D-dimers, products of fibrin degradation, were firmly established as an indirect indicator of thrombotic activity, particularly in risk assessment for venous thromboembolism within the population [41]. Elevated D-dimers levels upon admission were frequent and correlated with high disease severity and in-hospital mortality [42], irrespective of whether thrombus formation was evidenced or not.

An elevated LDH activity suggests an insufficiency of oxygen in biochemical processes, tissue oxygen deficiency, or multi-organ failure [43]. Elevated LDH levels can signify cellular damage, hypoxia or cell death. It's important to note that high LDH activity may also be linked to other conditions, including those related to cardiac ischemia (these patients were excluded from our study) and pathological processes in the lungs, renal cortex, liver, muscles and red blood cells. Due to the clinical advantages associated with early identification of patients at risk of severe COVID-19, the recognition of markers indicating severe disease holds significant practical importance. Even though, as previously mentioned, it is a vague and general bio-marker, LDH has earned a place next to D-dimers, IL-6, ferritin and PCR in predicting COVID-19 severity, according to Fialek's meta-analysis [44]. LDH is released from cells following cell injury and death, a frequent situation in PE and severe COVID-19 infections; in our study, it was the biomarker second most with the presence of PE, shortly after D-dimers. Additionally, high LDH and CRP levels were found to also represent risk factors for post-COVID-19 pulmonary fibrosis, along with the duration of hospitalization and severity of pneumonia [45].

In the present study, significant differences between PE and non-PE groups were also found regarding age, LDH,serum myoglobin, albumin levels as well as lymphocyte count. Similarly, parameters such as age, lymphocyte count, LDH, serum albumin and serum myoglobin levels were significantly associated with mortality in SARS-CoV-2 infection in one of our previous studies [46].

Study strengths: In our study we described, identified and characterized the demographic, clinical and biological parameters, indicating the most valuable risk factors in COVID19-associated-PE. We also approached the COVID19-associated-PE from the imaging perspective – we performed a characterization of the most useful parameters to consider in the case of COVID19-associated-PE; we demonstrated on CT images the importance of local inflammatory changes in the occurrence of vascular thrombosis, the correlation between the PE and the severity of lung involvement, and the most likely pulmonary areas to consider when searching for PE.

Study limitations: The results presented are descriptive; the identified PE markers need further validation on additional studies. Our study aimed to evaluate the value of clinical, biochemical and CT imaging in patients with COVID-19, to determine the severity of PE and the distribution pattern of thrombi with impact on morbidity and mortality, without demonstrating specific pathways for pulmonary thrombi. CT scans may underdiagnose PE as not all cases of peripheral PE can be detected. Echocardiography was not included in the standard protocol for evaluation of COVID-19 patients; therefore, no patient underwent echocardiography at admission in hospital.

CONCLUSIONS

In our study, patients with PE were older and mostly male, with a higher length of hospitalization and more severe lung involvement.

Thrombi distribution mainly involved the lower lobes, with a slight predominance of the right lower lobe, corresponding to a more severe lung involvement in the lower lung lobes.

High plasmatic values of LDH, ferritin, IL-6, WBC counts and D-dimers were strongly associated with PE developed in COVID-19 patients, as well as low protein serum levels.

Early identification of COVID-19-associated-PE patients is an important step for timely and efficient treatment in the intensive care management of these patients.

Introducere*: Infecția cu coronavirusul sindromului respirator acut sever (SARS-CoV-2) reprezintă o patologie apărută la sfârșitul anului 2019, cu implicații semnificative nu numai asupra sănătății individuale, ci și asupra sistemelor de sănătate și economiei mondiale. Scopul studiului este evaluarea rolului parametrilor clinici, biochimici și computer-tomografici în determinarea apariției trombemboliei pulmonare asociate cu COVID-19.*

Metoda*: Am efectuat un studiu de cohortă observațional, evaluând markeri demografici, clinici, biochimici, de coagulare și computer-tomografici.*

Rezultate*: În studiul nostru, efectuat pe 186 de pacienți cu COVID-19, am identificat trombembolie pulmonară la 31 pacienți (16.66%). La pacienții cu trombembolie pulmonară am găsit corelații cu semnificație statistică pentru proteina C reactivă, lactat dehidrogenaza, feritina serică, IL-6, mioglobina serică, NT-proBNP, D-dimeri, proteinele serice totale, transaminaze și numărul de leucocite. Pacienții cu trombembolie pulmonară au avut un grad mai sever de afectare pulmonară cu o distribuție a trombilor preponderent în lobii pulmonari inferiori.*

Concluzie*: Identificarea precoce a trombemboliei pulmonare este importantă în stabilirea precoce a managementului terapeutic al pacienților cu COVID-19. Studiul nostru arată ca valorile plasmatice ridicate ale lactat dehidrogenazei, feritinei, IL-6, leucocitelor și D-dimerilor, precum și valorile plasmatice reduse ale proteinelor totale serice sunt corelate cu trombembolia pulmonară la pacienții cu COVID-19.*

Correpsondence to: Mihai Lazăr, M.D, Ph.D, „Prof. Dr. Matei Balş" National Institute for Infectious Diseases, No. 1, Calistrat Grozovici Street, Sector 2, 021105 Bucharest, Romania
E-mail: mihai.lazar@umfcd.ro
phone: +021 201 09 80 (ext. 4078)

Declaration of interest: The authors declare that there are not conflicts of interest.

REFERENCES

1. LODIGIANI C., IAPICHINO G., CARENZO L., CECCONI M., FERRAZZI P., SEBASTIAN T., *et al.*, Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020 Jul;191:9-14.
2. KOLLIAS A., KYRIAKOULIS KG., DIMAKAKOS E., POULAKOU G., STERGIOU GS., SYRIGOS K., Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020 Jun;189(5):846-847.
3. BIKDELI B., MADHAVAN MV., JIMENEZ D., CHUICH T., DREYFUS I., DRIGGIN E., *et al.*, Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 16;75(23):2950-2973
4. KLOK FA., KRUIP MJHA., VAN DER MEER NJM., ARBOUS MS., GOMMERS DAMP.J, KANT KM., *et al.*, Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020 Jul;191:145-147.
5. CUI LY., CHENG WW., MOU ZW., XIAO D., LI YY., LI YJ., *et al.*, Risk factors for pulmonary embolism in patients with COVID-19: a systemic review and meta-analysis. Int J Infect Dis. 2021 Oct;111:154-163.
6. FAUVEL C., WEIZMAN O., TRIMAILLE A., MIKA D., POMMIER T., PACE N., *et al.*, Critical Covid-19 France Investigators. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. Eur Heart J. 2020 Jul 1;41(32):3058-3068.
7. TANG N., LI D., WANG X., SUN Z., Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844-847
8. LLITJOS JF., LECLERC M., CHOCHOIS C., MONSALLIER JM., RAMAKERS M., AUVRAY M., *et al.*, High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020 Jul;18(7):1743-1746.
9. HUANG C., WANG Y., LI X., REN L., ZHAO J., HU Y., *et al.*, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
10. GUAN WJ., NI ZY., HU Y., LIANG WH., OU CQ., HE JX., *et al*., China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720.
11. DUMEA E., LAZAR M., BARBU EC., CHITU CE., ION DA., Pulmonary Involvement in SARS-CoV-2 Infection Estimates Myocardial Injury Risk. Medicina (Kaunas). 2022 Oct 11;58(10):1436.

12. ACKERMANN M., VERLEDEN SE., KUEHNEL M., HAVERICH A., WELTE T., LAENGER F., *et al.*, Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120–128
13. CONTOU D., PAJOT O., CALLY R., LOGRE E., FRAISSÉ M., MENTEC H., *et al.*, Pulmonary embolism or thrombosis in ARDS COVID-19 patients: A French monocenter retrospective study. PLoS One. 2020 Aug 27;15(8):e0238413.
14. ORTEGA-PAZ L., TALASAZ AH., SADEGHIPOUR P., POTPARA TS., ARONOW HD., JARA-PALOMARES L., *et al.*, COVID-19-Associated Pulmonary Embolism: Review of the Pathophysiology, Epidemiology, Prevention, Diagnosis, and Treatment. SeminThrombHemost. 2023 Nov;49(8):816-832.
15. SCHULMAN S., HU Y., KONSTANTINIDES S. Venous thromboembolism in COVID-19. ThrombHaemost 2020;120(12):1642–1653).
16. EDLER C., SCHRÖDER AS., AEPFELBACHER M., FITZEK A., HEINEMANN A., HEINRICH F., *et al.*, Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med. 2020 Jul;134(4):1275-1284.
17. GOMEZ CA., SUN CK., TSAI IT., CHANG YP., LIN MC., HUNG IY., *et al.*,Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. Sci Rep 2021;11(01):16025.
18. MIRO O., JIMENEZ S., MEBAZAA A., FREUND Y., BURILLO-PUTZE G., MARTIN A., *et al.*, Spanish Investigators on Emergency Situations TeAm (SIESTA) network. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. Eur Heart J 2021;42(33):3127–3142)
19. HOBOHM L., SAGOSCHEN I., BARCO S., FARMAKIS IT., FEDELI U., KOELMEL S., *et al.*, COVID-19 infection and its impact on case fatality in patients with pulmonary embolism. Eur Respir J. 2023 Jan 27;61(1):2200619.
20. MONTEIL V., KWON H., PRADO P., HAGELKRÜYS A., WIMMER RA., STAHL M., *et al.*, Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell. 2020 May 14;181(4):905-913.e7.
21. CARSANA L., SONZOGNI A., NASR A., ROSSI RS., PELLEGRINELLI A., ZERBI P., *et al.*, Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two centre descriptive study. Lancet Infect Dis 2020;20(10): 1135–1140
22. DENORME F., VANHOORELBEKE K., DE MEYER SF., von Willebrand Factor and Platelet Glycoprotein Ib: A Thromboinflammatory Axis in Stroke. Front Immunol. 2019 Dec 17;10:2884.
23. CHAUHAN AK., MOTTO DG., LAMB CB., BERGMEIER W., DOCKAL M., PLAIMAUER B., *et al.*, Systemic antithrombotic effects of ADAMTS13. J Exp Med. 2006 Mar 20;203(3):767-76.
24. TAKAYA H., YOSHIJI H., KAWARATANI H., SAKAI K., MATSUMOTO M., FUJIMURA Y., *et al.*, Decreased activity of plasma ADAMTS13 are related to enhanced cytokinemia and endotoxemia in patients with acute liver failure. Biomed Rep. 2017 Sep;7(3):277-285.
25. UEMURA M., FUJIMURA Y., KO S., MATSUMOTO M., NAKAJIMA Y., FUKUI H., Pivotal role of ADAMTS13 function in liver diseases. Int J Hematol. 2010 Jan;91(1):20-9.
26. NICOLAI L., LEUNIG A., BRAMBS S., KAISER R., WEINBERGER T., WEIGAND M., *et al.*, Immunothrombotic Dysregulation in COVID-19 Pneumonia Is Associated With Respiratory Failure and Coagulopathy. Circulation. 2020 Sep 22;142(12):1176-1189.
27. SCHURINK B., ROOS E., RADONIC T., BARBE E., BOUMAN CSC., DE BOER HH., *et al.*, Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe. 2020 Nov;1(7): e290-e299.
28. VERAS FP., PONTELLI MC., SILVA CM., TOLLER-KAWAHISA JE., DE LIMA M., NASCIMENTO DC., *et al.*, SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology. J Exp Med. 2020 Dec 7;217(12): e20201129.
29. TOMAZINI BM., MAIA IS., CAVALCANTI AB., BERWANGER O., ROSA RG., VEIGA VC., *et al.*, COALITION COVID-19 Brazil III Investigators. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020 Oct 6;324(13): 1307-1316.
30. DEFTEREOS SG., GIANNOPOULOS G., VRACHATIS DA., SIASOS GD., GIOTAKI SG., GARGALIANOS P., *et al.*, GRECCO-19 investigators. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Netw Open. 2020 Jun 1;3(6):e2013136.
31. National Institutes of Health (NIH). COVID-19 Treatment Guidelines, Clinical Spectrum of SARS-CoV-2 Infection. 2021. Available online: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed on 15 March 2024)
32. HASELI S., KHALILI N., BAKHSHAYESHKARAM M., SANEI TAHERI M., MOHARRAMZAD Y. Lobar Distribution of COVID-19 Pneumonia Based on Chest Computed Tomography Findings; A Retrospective Study. Arch Acad Emerg Med. 2020 Apr 18;8(1):e55
33. TARBOX AK., SWAROOP M. Pulmonary embolism. Int J CritIllnInj Sci. 2013 Jan;3(1):69-72.
34. KERNAN KF., CARCILLO JA. Hyperferritinemia and inflammation. Int Immunol. 2017 Nov 1;29(9):401-409.
35. LEVY MM., FINK MP., MARSHALL JC., ABRAHAM E., ANGUS D., COOK D., *et al.*, SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003 Apr;31(4):1250-6.
36. NARAZAKI M., KISHIMOTO T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. Int J Mol Sci. 2018 Nov 9;19(11):3528.
37. GUL MH., HTUN ZM., DE JESUS PEREZ V., SULEMAN M., ARSHAD S., IMRAN M. *et al.*, Predictors and outcomes of acute pulmonary embolism in COVID-19; insights from US National COVID cohort collaborative. Respir Res 24, 59 (2023).
38. YOUSAF M., THOMAS MM., ALMUGHALLES S., HAMEED MA., ALHARAFSHEH A., VARIKKODAN I., *et al.*, Pulmonary embolism in COVID-19, risk factors and association with inflammatory biomarkers. Medicine 102(7):p e32887, February 17, 2023.

39. RIYAHI S., DEV H., BEHZADI A., KIM J., ATTARI H., RAZA SI., *et al.*, Pulmonary Embolism in Hospitalized Patients with COVID-19: A Multicenter Study. Radiology. 2021 Dec;301(3):E426-E433. doi: 10.1148/radiol.2021210777. Epub 2021 Jul 13. PMID: 34254850; PMCID: PMC8294351.
40. SCUDIERO F., SILVERIO A., DI MAIO M., RUSSO V., CITRO R., PERSONENI D. *et al.*, Pulmonary embolism in COVID-19 patients: prevalence, predictors and clinical outcome, Thrombosis Research, Volume 198, 2021, ISSN 0049-3848.
41. WEITZ JI., FREDENBURGH JC., EIKELBOOM JW. A Test in Context: D-Dimer. J Am Coll Cardiol. 2017 Nov 7;70(19):2411-2420.
42. YAO Y., CAO J., WANG Q., SHI Q., LIU K., LUO Z., *et al.*, D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020 Jul 10;8:49.
43. LI X., XU S., YU M., WANG K., TAO Y., ZHOU Y., *et al.*, Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020 Jul;146(1):110-118.
44. FIALEK B., PRUC M., SMEREKA J., JAS R., RAHNAMA-HEZAVAH M., DENEGRI A., *et al.*, Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis. Cardiol J. 2022;29(5):751-758.
45. LAZAR M., BARBU EC., CHITU CE., TILISCAN C., STRATAN L., ARAMA SS., *et al.*, Interstitial Lung Fibrosis Following COVID-19 Pneumonia. Diagnostics (Basel). 2022 Aug 22;12(8):2028.
46. LAZAR M., BARBU EC., CHITU CE., ANGHEL AM., NICULAE CM., MANEA ED., *et al.*, Mortality Predictors in Severe SARS-CoV-2 Infection. Medicina (Kaunas). 2022 Jul 18;58(7):945.

Received 20th January 2024