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Independent risk factors for COVID-19-associated coagulopathy

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Abstract. – OBJECTIVE: Past three years since the beginning of the outbreak, we have obtained satisfactory data on COVID-19. However, data on risk factors of COVID-19-associated coagulopathy (CAC) are extremely limited. Prediction of CAC might be a game changer since it is related to poor prognosis. Seeking independent risk factors for CAC was the main aim of the study.

PATIENTS AND METHODS: 510 hospitalized COVID-19 patients were retrospectively screened. Forty-eight of them were excluded due to irrelevant D-dimer or ferritin elevation. The remaining patients were stratified into three groups as overt coagulopathy, significant pulmonary microthrombosis, and patients without coagulopathy. The overt coagulopathy group included cases with macrothrombosis or disseminated intravascular coagulation (DIC). The significant pulmonary microthrombosis group covered the cases that had clinical deterioration with simultaneous marked D-dimer elevation. The group of patients without coagulopathy included the asymptomatic patients with normal or elevated D-dimer levels.

RESULTS: Overt coagulopathy developed in 3.2% and significant pulmonary microthrombosis in 10.1% of the patients. In the multivariate analysis, not receiving low molecular weight heparin (LMWH) (p=0.002) and a level of D-dimer >15,000 U/ml (p=0.013) were associated with overt coagulopathy. In addition, levels of initial LDH >480 IU/L (p=0.022), initial ferritin >1,000 ng/ml (p=0.036) were associated with significant pulmonary microthrombosis. Not receiving LMWH (p=0.001) was also associated with significant pulmonary microthrombosis, when multivariate analysis was performed by the parameters with a p-value <0.1 in the univariate analysis. Furthermore, all cases with DIC had Gram-negative bacterial sepsis.

CONCLUSIONS: Not receiving LMWH, high levels of D-dimer, initial LDH, and initial ferritin are independent risk factors for CAC. DIC does not appear to develop based on COVID-19.

Key Words:
COVID-19, Inflammation, Lactate dehydrogenase, Low molecular weight heparin, Thrombosis.

Introduction

Data provided by initial studies[1,2] even before the announcement of the pandemic pointed to a strange COVID-19-associated coagulopathy (CAC). In retrospective documentation[2] of the first experience in Wuhan, it was found that abnormal coagulation parameters were present in 71.4% of non-survivors and 0.6% of recovered patients. These parameters included increased D-dimer and fibrin degradation products, mild prolongation of prothrombin and activated partial thromboplastin time, and sometimes moderate thrombocytopenia[2]. Emerging data revealed that CAC had unique features mostly present as pulmonary micro-macrothrombosis and less frequently as systemic venous and/or arterial macrothrombosis[3-5].

With the flowing time, studies[6] defined some acquired, environmental, and epigenetic factors that increase the risk of severe COVID-19 for some populations (primarily older people, individuals with obesity, and individuals with diabetes). Additional experiences and research gave the start for the recognition of underlying mechanisms for CAC. As studies[3,5,7-11] on Alpha or Delta variants deepened, the pathogenesis of SARS-CoV-2-dependent throm-

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boinflammation was clarified. This process includes endothelial dysfunction, hyperinflammation, cytokine storm, formation of neutrophil-extracellular traps, complement system activation, imbalance of renin-angiotensin-aldosterone system, hypofibrinolysis, and hypoxia. As a result, antithrombotic therapies became a part of the global management program as a logical next step over the usual care.

We met trials that yield the effect of antithrombotic treatment on the COVID-19 outcome[12,13]. Here, we share our experience with antithrombotic treatment in COVID-19 that we shaped to ameliorate the course by considering thromboinflammatory mechanisms. We also report the results of the intensively collected data of our cohort.

Patients and Methods

We retrospectively screened the medical records, patients' files, and the hospital's electronic data system of hospitalized COVID-19 patients. Laboratory confirmation was performed with reverse transcriptase-polymerase chain reaction (RT-PCR) assays. The ones who have a negative result of RT-PCR but have typical clinical, laboratory, and thoracic computed tomography (CT) findings for COVID-19 were also included in the analysis.

Definitions

COVID-19 severity was categorized as moderate, severe, or critically severe. Moderate disease defines patients with lymphocytopenia, increased serum C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer levels, and bilateral infiltration on thorax CT, and additionally a pulse oxygen saturation greater than 93% in room air or with low-flow nasal oxygen support. The severe disease refers to patients with PaO2/FiO2 ratio below 300 who need reservoir bag oxygen masks or high-flow nasal oxygen. Critically severe disease defines the cases that need intensive care unit (ICU) support.

Patients were also classified into three groups according to their COVID-19-associated coagulopathy (CAC) status; patients with overt coagulopathy, patients with significant pulmonary microthrombosis, and patients without coagulopathy, respectively. Overt coagulopathy arm included the radiologically demonstrated cases [except non-ST-elevated myocardial infarction (MI)] arterial and/or venous macrothrombosis or patients with disseminated intravascular coagulation (DIC). The condition of significant pulmonary microthrombosis was a marked increase in serum D-dimer level accompanied by clinical worsening. Criteria of clinical worsening consisted of a striking increase in oxygen demand, intubation need or death. Also, patients with a D-dimer level above 20,000 U/mL at any time were included in the significant pulmonary microthrombosis arm in the absence of macrothrombosis. In some cases, macrothrombosis was highly suspected but could not be proven radiologically, or radiologic studies could not be performed due to the patient's poor clinical status. Patients without coagulopathy had normal serum D-dimer levels or mild to moderate elevations without apparent clinical worsening.

Serum CRP, D-dimer, and ferritin levels were assessed on admission when they arrived at the peak level, and finally when the patients were discharged or died.

Treatment Strategies

The treatment protocol was based on the national health authority protocol, which included hydroxychloroquine and azithromycin in the early period of the pandemic and favipiravir, which was added shortly to them. Patients with cytokine storm received anti-cytokine drugs, either tocilizumab or anakinra. Antithrombotic treatment consisted of dipyridamole 75 mg peroral twice daily, accompanied shortly by enoxaparin subcutaneously at a dose of 40 mg/day in all hospitalized patients. Enoxaparin dose was increased to a therapeutic dose of 1 mg/kg twice daily in patients with D-dimer levels above 1,000 U/mL.

Statistical Analysis

Continuous variables were presented as medians, and the number of categorical variables was presented. Differences between groups were analyzed with the χ^2 test. Risk factors were evaluated in univariate and multivariate logistic regression models. Variables found to be significant in the univariate analysis were included in the logistic regression analysis. A bilateral α lower than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to determine the best cut-off value reflecting the relationship of the variable to the endpoint. The propensity score matching method was applied to find the most appropriate cohort for patients not taking low-molecular-weight heparin (LMWH) and, similarly, for not taking dipyridamole. LMWH and dipyridamole variables were included in the Cox regression model following propensity score matching. Statistical analysis was performed in STATA 13 software (Stata Corp LLC, College Station, TX, USA).

Results

The data collection encompassed the three-month periods of the first wave. A total of 510 COVID-19 patients were evaluated. Patients with comorbidities that may intervene in assessing the clinical and laboratory parameters (malignancy, pregnancy, hemorrhagic diathesis, etc.) for COVID-19-associated clinical courses were excluded from the analysis. The exclusion reasons were in order of frequency as follows; sixteen patients due to insufficient data, eleven patients due to active malignancy, six patients due to pregnancy, five patients due to uncertain COVID-19 diagnosis, three patients with multiple reasons for having elevated serum D-dimer level other than COVID-19, three patients having already thrombosis, two patients due to non-COVID-19 related high ferritin level and two patients due to being in the postoperative period (Figure 1).

The median age of the remaining 462 patients was 56 (23-98). The majority of the cohort was male (61.5%). Fatigue and myalgia were the most common symptoms, with a rate of 94% (n=432). Other common symptoms were cough (84%, n=389), fever (72%, n=224), and dyspnea (43%, n=198). Nausea (15%, n=71), diarrhea (12%, n=54), anosmia (8%, n=38), and sputum (3%, n = 14) were relatively uncommon symptoms. RT-PCR was positive in 61.7% of the patients (n=285). Demographic characteristics, initial signs and symptoms, and comorbidities of the patients are summarized in Table I.

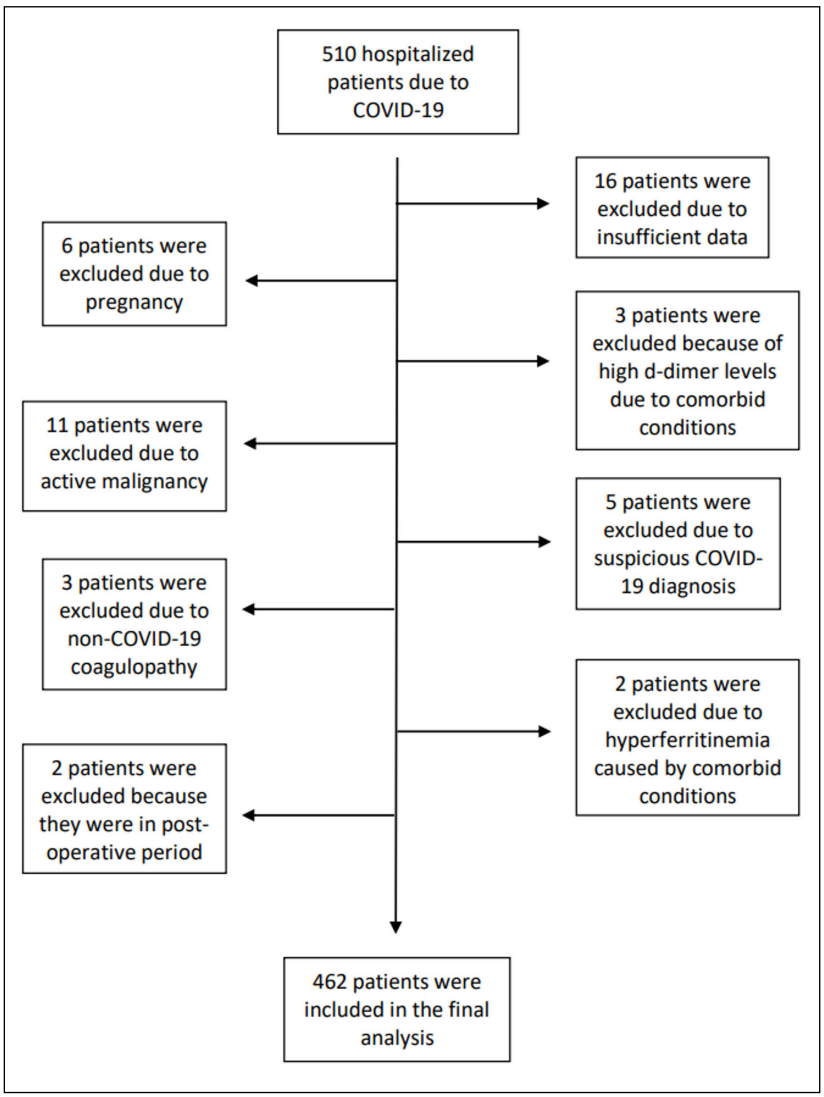

Figure 1. Flow chart of exclusion and enrollment of the patients.

Table I. Demographic characteristics, initial signs and symptomatology.

	n=462
Median Age (range)	56 (23-98)
Sex	
Female (%)	178 (38.5%)
Male (%)	284 (61.5%)
Initial symptoms	
Fatigue and myalgia	432 (94%)
Cough	389 (84%)
Fever	224 (72%)
Dyspnea	198 (43%)
Nausea	71 (15%)
Diarrhea	54 (12%)
Anosmia	38 (8%)
Sputum	14 (3%)
Initial vital signs	
Median saturation on pulse oximetry (range)	96% (70-100)
Median systolic blood pressure (range)	130 (80-250)
Median diastolic blood pressure (range)	75 (50-136)
Median pulse rate (range)	93 (66-190)
Median respiratory rate (range)	18 (12-36)
COVID RT-PCR positive vs negative	285 vs 177
Median number of comorbidities (range)	1 (0-6)
Initial computerized tomography feature	
Mild pneumonia	218 (49%)
Moderate to severe pneumonia	230 (51%)
Comorbid conditions	
Hypertension	182 (40%)
Diabetes mellitus	100 (22%)
COPD or Asthma	56 (12%)
Coronary artery disease	51 (11%)
Congestive heart failure	30 (6.5%)
Solid malignancy	22 (5)
Hematologic malignancy	13 (3%)
Anti-hypertensive exposure	177 (38%)
ACE inh	35 (8%)
ARB	83 (18%)
Acute conditions at the time of admission	
Acut kidney injury	10
Acute myocardial infarction	1
Deep venous thrombosis	1
Hypertensive pulmonary edema	1
Cerebrovascular accident	1
Peritonsillar abscess	1

COPD: chronic obstructive pulmonary disease, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

Patients with overt coagulopathy represent 3.2% of the cohort (n=15) with a mean age of 64.8 (40-86 years) and male predominance. Most (n=7/15) of the patients had arterial thrombosis. Venous thrombosis and DIC evolved in four patients each. Time to thrombotic events ranged from 1 to 33 days after COVID-19 diagnosis. The type of arterial thromboses manifested as MI in five patients, in one patient as cerebrovascular accident, and in one patient as arterial thrombosis of the lower extremi-

ty. Venous thrombosis developed as lower extremity deep venous thrombosis (DVT) in one patient and the other as an upper extremity DVT. One patient experienced catheter-related thrombosis and pulmonary embolism. Another patient had severe thrombotic occlusion of extracorporeal membrane oxygenation cannulas, preventing membrane oxygenation. All patients with DIC had Gram-negative sepsis, proven by cultures. In all these cases, serum procalcitonin levels were significantly elevated (0.54-4.83 ng/mL). Two of the DIC cases survived and were discharged.

Univariate Analyses

The parameters significantly associated with overt coagulopathy and significant pulmonary microthrombosis are summarized in Table II. Patients progressing to anti-cytokine treatment requirement developed pulmonary microthrombosis significantly ($p<0.001$).

Table II. Parameters significantly associated with overt coagulopathy and/or significant pulmonary microthrombosis in univariate analyzes.

		Overt coagulopathy (n=15)		Significant pulmonary microthrombosis (n=47)	
Factor		**positive/total**	***p***	**positive/total**	***p***
Age	≥65	9/138	**0.01**	27/138	**<0.001**
	<65	6/324		20/324	
Dyspnea	present	12/198	**0.003**	34/198	**<0.001**
	absent	3/263		13/263	
CAD	present	5/51	**0.005**	12/51	**0.001**
	absent	10/409		35/409	
CHF	present	2/30	0.277	8/30	**0.002**
	absent	13/430		39/430	
Comorbidity	≥3	4/ 69	0.202	12/69	**0.034**
	<3	11/389		35/389	
Respiratory rate	≥32/min	3/9	**<0.001**	3/9	**0.019**
	<32/min	11/448		43/448	
Initial room air Oxygen Saturation	≤85%	3/20	**0.002**	8/20	**<0.001**
	>85%	11/438		38/438	
Initial disease severity	severe	8/137	**0.041**	28/137	**<0.001**
	moderate	7/325		19/325	
Initial lymphocyte count	<500/mcl	5/32	**<0.001**	8/32	**0.004**
	≥500/mcl	10/430		39/430	
Initial monocyte count	≤300/mcl	5/70	**0.046**	12/70	**0.036**
	>300/mcl	10/392		35/392	
Initial LDH level	>480 IU/L	4/23	**<0.001**	8/23	**<0.001**
	≤480 IU/L	10/435		36/435	
Initial CRP level	>115 mg/L	2/81	0.656	14/81	**0.021**
	≤115 mg/L	13/378		33/378	
Initial ferritin level	>1,000 ng/ml	1/68	0.406	14/68	**0.001**
	≤1,000 ng/ml	13/387		31/387	
Initial D-dimer level	>3,600 U/ml	2/3	0.255	8/31	**0.002**
	≤3,600 U/ml	12/427		38/427	
Leukocyte count in the peak period	>15,000/mcl	1/17	0.492	7/17	**<0.001**
	≤15,000/mcl	13/440		39/440	
Neutrophil count in the peak period	>13,500/mcl	1/16	0.453	7/16	**<0.001**
	≤13,500/mcl	13/440		39/440	
Lymphocyte count in the peak period	<500/mcl	5/63	**0.024**	14/63	**0.001**
	≥500/mcl	10/399		33/399	
NLR in the peak period	>30	0/21	0.404	5/21	**0.033**
	≤30	14/435		41/435	

Continued

Table II (continued). Parameters significantly associated with overt coagulopathy and/or significant pulmonary microthrombosis in univariate analyzes.

Factor		Overt coagulopathy (n=15)		Significant pulmonary microthrombosis (n=47)	
		positive/total	p	positive/total	p
Monocyte count in the peak period	<150/mcl	3/16	**<0.001**	4/16	**0.044**
	≥150/mcl	11/440		42/440	
Hemoglobin level in the peak period	<8.5g/dl	2/21	0.079	7/21	**<0.001**
	≥8.5 g/dl	12/436		39/436	
Peak D-dimer level	>15,000 U/ml	6/29	**<0.001**	20/29	**<0.001**
	≤15,000 U/ml	9/429		27/429	
AST level in the peak period	>200 U/L	2/19	0.055	7/19	**<0.001**
	≤200 U/L	12/435		38/435	
ALT levelin the peak period	>200 U/L	2/29	0.218	9/29	**<0.001**
	≤200 U/L	12/426		37/426	
Direct bilirubin level in the peak period	>1.3 mg/dl	2/7	**0.001**	3/7	**0.011**
	≤1.3 mg/dl	12/361		41/361	
Total bilirubin level in the peak period	>1.8 mg/dl	1/8	0.193	3/8	**0.024**
	≤1.8 mg/dl	13/361		41/361	
LDH level in the peak period	>5,000 IU/L	0/3	0.755	3/3	**<0.001**
	≤5,000 IU/L	14/447		42/447	
Peak ferritin level	>20,000 ng/ml	2/8	**<0.001**	6/8	**<0.001**
	≤20,000 ng/ml	12/449		39/449	
SOFA score in the peak period	>10	8/68	**<0.001**	25/68	**<0.001**
	≤10	7/394		22/394	
SIC score in the peak period	≥4	7/27	**<0.001**	10/27	**<0.001**
	<4	7/410		29/410	
LMWH administration	present	10/413	**0.004**	40/413	0.314
	absent	5/49		7/49	
Anti-cytokine treatment	present	6/127	0.197	29/127	**<0.001**
	absent	8/332		17/331	
Intubation	present	8/53	**<0.001**	27/53	**<0.001**
	absent	6/408		19/408	
Disease severity in the peak period	severe and critically severe	11/177	**0.005**	39/177	**<0.001**
	moderate	4/285		8/285	
Intensive care need	present	10/67	**<0.001**	30/67	**<0.001**
	absent	4/386		16/386	
Progressively worsening disease severity	present	9/82	**<0.001**	33/82	**<0.001**
	absent	6/380		14/380	

CAD: coronary artery disease, CHF: congestive heart failure, LDH: lactate dehydrogenase,CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, AST: aspartate aminotransferase, ALT: alanin aminotransferase, SOFA: sequential organ failure assessment, SIC:sepsis-induced coagulopathy, LMWH: low-molecular-weight heparin.

Multivariate Analyses

Patients with overt coagulopathy

All parameters with a p-value <0.05 in the univariate analysis were included in the multivariate analysis. Not receiving LMWH (p=0.002), peak D-dimer level above 15,000 U/ml (p=0.013), and peak sepsis-induced coagulopathy (SIC) score of 4 or higher (p=0.022) were found to be statistically significant and independent risk factors for overt coagulopathy (Table III). Although they were not statistically significant, absolute monocyte count ≤300/μl on admission (p=0.062) and direct bilirubin level above 1.3 mg/dl in the peak period (p=0.058) had a statistical tendency for overt coagulopathy development (Table III).

Table III. Independent risk factors or the parameters which has tendency to be an independent risk factor in multivariate analysis of the parameters with $p < 0.05$ in univariate analysis for Overt Coagulopathy group.

	Overt Coagulopathy (n=15)		
Factor	**positive/total**	***p***	**HR**
Initial monocyte count			
≤300/mcl	5/70	**0.062**	**35.327**
>300/mcl	10/392		
Direct bilirubin on the peak period			
>1.3 mg/dl	2/7	**0.058**	**39.049**
≤1.3 mg/dl	12/361		
Peak D-dimer level			
>15,000 U/ml	6/29	**0.013**	**1,360.964**
≤15,000 U/ml	9/429		
SIC score in the peak period			
≥4	7/27	**0.022**	**1,270.538**
<4	7/410		
LMWH administration			
present	10/413	**0.002**	**5,376.383**
absent	5/49		

LMWH: low-molecular-weight heparin, SIC: sepsis-induced coagulopathy, HR: hazard ratio.

Patients with significant pulmonary microthrombosis

All parameters with a p-value <0.05 in the univariate analysis were included in the multivariate analysis. LDH levels over 480 IU/L (p=0.022) and ferritin levels over 1,000 ng/ml on admission (p=0.036) were found to be statistically significant and independent risk factors for significant pulmonary microthrombosis. Including the parameters with a p-value <0.1 in the univariate analysis, not receiving LMWH (p=0.001) was also found to be statistically significant and an independent risk factor for significant pulmonary microthrombosis (Table IV). In addition, having coronary artery disease (CAD) (p=0.093), three or more comorbidities (p=0.058), presence of dyspnea on admission (p=0.087), and severe disease at the time of presentation (p=0.054) had a statistical tendency for significant pulmonary microthrombosis development (Table IV).

Discussion

The SARS-CoV-2 outbreak induced physician collaboration as all specialists and even interns in some countries became responsible for COVID-19 care. It was obligatory when most of the health workers fell into COVID-19. On the other hand, COVID-19 showed multiple faces of dysfunction, such as inflammation, endothelial dysfunction, and coagulopathy. This created a need for multidisciplinary working, developing research projects, rapidly evolved trials, workshops, and guidelines.

We were especially interested in CAC, which involves inflammatory, immune, coagulation, fibrinolytic, complement, and kallikrein-kinin system where the story begins with SARS-CoV-2 infection of type II pneumocytes via angiotensin-converting enzyme 2 (ACE2)[14-16]. Although it has been shown that SARS-CoV-2 can also infect extra-pulmonary tissues, there are conflicting reports on whether SARS-CoV-2 infects endothelial cells directly[17,18]. Pneumocytes' position with the alveolar vascular network might explain the damage of microvascular endothelium beyond the alveoli. However, endothelial damage in COVID-19 is not limited to the pulmonary vascular bed, and systemic endothelial damage and distant thrombotic events may be related to severe systemic hyperinflammation[18].

The severity and mortality of COVID-19 pointed to the so-called "cytokine storm[19]". Cytokine storm defines the vicious circle of progressive severe systemic inflammation. We already have been familiar with this term from the etiologies of macrophage activation syndrome. We all clini-

Table IV. Independent risk factors or the parameters which has tendency to be an independent risk factor in multivariate analysis of the parameters with $p < 0.05$ in univariate analysis for significant pulmonary microthrombosis group.

	Significant pulmonary microthrombosis (n=47)		
Factor	**positive/total**	***p***	**HR**
Dyspnea on admission			
present	34/198	**0.087**	**3.931**
absent	13/263		
Initial disease severity			
severe	8/137	**0.054**	**0.176**
moderate	7/325		
Number of comorbidities			
≥3	12/69	**0.058**	**0.120**
<3	35/389		
Coronary artery disease			
present	12/51	**0.093**	**4.174**
absent	35/409		
LDH level on admission			
>480 IU/L	8/23	**0.022**	**91.948**
≤480 IU/L	36/435		
Ferritin level on admission			
>1,000 ng/ml	14/68	**0.036**	**0.010**
≤1,000 ng/ml	31/387		
LMWH administration			
present	40/413	*__0.001__	*__34.565__
absent	7/49		

*These statistical results belong to the Multivariate analysis of the parameters with $p < 0.1$ in univariate analysis. LDH: lactate dehydrogenase, LMWH: low-molecular-weight heparin, HR: hazard ratio.

cians pursued the best-reflecting biomarker of this picture, and finally, criteria for COVID-19-associated hyperinflammation were defined[20]. Indeed, CAC, endothelial dysfunction, and hyperinflammation were found to be closely related to the disease severity and death in COVID-19[7,21,22]. On the other hand, Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)[23] demonstrated that successful suppression of inflammation protects the endothelium and reduces thrombotic complications. Consistently with the relationship between endotheliopathy, inflammation, and thrombosis revealed in CANTOS, our data demonstrated that serum ferritin levels above 1,000 ng/ml on admission were an independent risk factor for CAC. In addition, our study revealed that prior CAD might contribute to the development of CAC. This result indicates that prior endothelial dysfunction build-up a risk factor for CAC.

We also observed that serum LDH over 480 IU/L was associated with significant pulmonary microthrombosis (p=0.022) and was an independent risk factor for CAC development. Consistent with that, patients with dyspnea and severe COVID-19 on admission were at risk for CAC development in multivariate analysis (p=0.087 and p=0.054, respectively).

Another point that has to be emphasized is that DIC is not a form of CAC. In our study, all patients with DIC among COVID-19 had Gram-negative bacteremia with sepsis. Therefore, we strongly suggest that in the case of DIC during the COVID-19 course, an underlying precipitating factor should be sought.

With our observation and findings as clinical and laboratory data assessment, we can also suggest that CAC may represent a clinical spectrum. A negligible pulmonary microthrombus formation may progress to a diffuse pulmonary microthrombus causing clinical respiratory failure. Each COVID-19 patient's management should be individualized with carried risk factors. Therefore, the discovery of well-defined and reliable

risk factors for hyperinflammation, endothelial dysfunction, and CAC is a need for individualized treatment.

Our study is worthy from several different points. Firstly, the concept of the study is unique. For the best and most accurate prognostic evaluation, we distinguished the patients with asymptomatic D-dimer elevation, representing negligible pulmonary microthrombosis that does not progress to CAC. Our findings will contribute to the literature and help clinicians make risk analyses for CAC since our analysis uncovered some independent risk factors. Secondly, strict criteria were applied to exclude the cases with other comorbidities causing increased D-dimer and ferritin levels and to get reliable results from the analysis.

Limitations

The main limitations of our study are the retrospective design and the fact that the treatment data provided do not belong to randomized groups. Initiation of anticoagulation after a certain date resulted in two patient groups that received LMWH and did not receive it. Although our study included RT-PCR negative patients, we consider this as real-life data, not a major limitation, since all patients were clinically, biochemically and radiologically examined, and patients were excluded if there was any suspicion of COVID-19 diagnosis. Besides, we did not detect any difference in statistical analysis between RT-PCR positive and negative patients.

Conclusions

We highly recommend that patients with initial LDH >480 IU/L and initial ferritin >1,000 ng/ml receive high-dose anticoagulant therapy if they do not have a high risk of bleeding. In addition, we recommend close monitoring of patients with dyspnea and severe disease on admission, a history of CAD, three or more comorbidities, and monocytopenia (<300/mcl). These cases should be evaluated for preemptive high-dose anticoagulation therapy. In case of an increase in direct bilirubin and a SIC score of 4 and above, it would be appropriate to evaluate for septic shock and DIC and to reorganize anticoagulant therapy.

Conflicts of Interest

The authors have no conflict of interest to declare.

Ethics Approval

This study was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (No.: 27/05/2020-85499).

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Availability of Data and Materials

The data of the study is available upon request from the corresponding author.

Informed Consent

Informed consent was obtained from all patients to be included in the study.

Authors' Contributions

All authors made critical contributions to the multidisciplinary follow-up and management of patients in the cohort and the drafting of the study. YBT and SKB designed the details of the study. YBT, EA, NS, and AM provided the data. YBT and EA investigated the data and ensured accurate and strict exclusions according to the study criteria. The analysis was carried out by MO. YBT, SKB, and MO interpreted the analysis and wrote the paper. AAC, AG, ME, MK, and TT contributed to the critical evaluation and revision of the manuscript. YBT and SKB shaped the final version, and all authors approved the final version of the article.

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