ORIGINAL ARTICLE

COVID-19 associated coagulopathy in septic critically ill patients - a retrospective cohort study

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ABSTRACT

Aim To determine the relationship between coagulation disorders and septic condition in COVID-19 critically ill patients.

Methods Data from 99 patients who presented with COVID-19 acute hypoxemic respiratory failure (CAHRF) were divided into two groups: Group 1- patients who developed sepsis, and Group 2 - patients who developed septic shock. Age, sex, comorbidities, quick Sequential Organ Failure Assessment (qSOFA) score, vasopressor and inotrope requirement, laboratory findings (platelets, neutrophils, lymphocytes, procalcitonin - PCT, C-reactive protein, fibrinogen, D-dimer, sepsis-induced coagulopathy – SIC, and disseminated intravascular coagulation - DIC score) were recorded on the day of admission and on the day of starting invasive mechanical ventilation. The primary outcome was to establish COVID-19 associated coagulopathy with sepsis and septic shock; the secondary outcome measure was incidence of coagulopathy in septic COVID-19 critically ill patients.

Results The most common coagulation abnormality was international normalized ratio (INR) (p=0.019) for Group 2, followed by the values of inflammatory parameters PCT (p=0.002) and lymphocytes (p=0.011) also for Group 2. The statistical significance of SIC score was observed for both groups (p=0.007) and p=0.012, respectively. Norepinephrine (p=0.000) and dobutamine (p=0.000) for Group 2, qSOFA for both groups (p = 0.000) were statistically significant.

Conclusion The observed coagulation abnormalities met the criteria for a SIC diagnosis, therefore, the management of coagulation disorders at this stage of the disease should follow the management of a septic condition.

Key words: coagulation disorders, incidence, sepsis

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INTRODUCTION

Despite the decline in the number of COVID-19 critically ill patients, it has re-emerged in many parts of the world, prompting the need for new approaches to this disease, especially for its most significant complications. COVID-19 associated coagulopathy (CAC) is one of the most common conditions in patients with COVID-19, especially in critically ill patients (1). Severe COVID-19 acute hypoxemic respiratory failure (CAHRF) leads to a systemic inflammatory response and imbalance between procoagulants and anticoagulants (2). As a result of this, T cell activation and cytokine production occur with subsequent damage to internal organs, primarily the lungs (3). About 40% of COVID-19 patients have a high risk of developing thromboembolism (4). The viral vascular injury of COVID-19 causes a decrease in the expression of the fibrinolytic system, reducing blood flow and consequently causing vasoconstriction (5). In addition to this phenomenon, increased Von Willebrand factor secretion enhances platelet aggregation and recruitment, which activates the coagulation cascade and platelet plug formation (6). Autopsies of patients suffering from COVID-19 confirmed clots in the small vessels of vital organs (7).

It has already been established that COVID-19 infection and sepsis are associated with endogenous activation of coagulation events, but with different effects on the anticoagulant and procoagulant ability of the serum. Therefore, this dysregulation particularly contributes to the pathophysiology of the disease (8).

The most common form of coagulopathy is reflected in increased levels of fibrinogen, D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombocytopenia (9). New disease severity prediction scores and coagulopathy markers, which are direct indicators of the severity and outcome of the COVID-19 disease, among others, are sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) scores (10). The cause of coagulation disorders is very worrying and requires finding the causes, and therefore timely treatment approach. There is an urgent need to understand the etiology of bleeding and thrombotic manifestations associated with coagulopathy of COVID-19, as well as the clinical utility of coagulation testing to predict the risk of coagulopathy.

The aim of this study was to establish the development of CAC in relation to the development of a septic condition in critically ill patients with COVID-19. Also, given the previously demonstrated association between coagulation disorders and mortality in patients with COVID-19, to establish the frequency of these disorders.

PATIENTS and METHODS

Patients and study design

This retrospective cohort study was conducted in the COVID-19 Intensive Care Unit in the Department of Anaesthesiology, Resuscitation and Intensive Care, Cantonal Hospital Zenica. Data from the electronic database were retrospectively analysed for the period of 2021. Inclusion criteria were all adult critically ill patients tested positive for reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swabs to coronavirus 2 (SARS-CoV-2) presented with CAHRF. Exclusion criteria were: patients younger than 18, immunodeficient patients, patients with history of malignancies and septic state before admission, coagulopathy, liver and platelet disease.

The patients were divided into two groups: Group 1 patients who developed sepsis, and Group 2 patients who developed septic shock.

The CAHRF was defined as COVID-19 acute respiratory failure with severe arterial hypoxemia refractory to supplemental oxygen. Sepsis was defined as a life-threatening reaction of the organism caused by an unregulated response of the host to infection. Clinical criteria for sepsis included suspected or documented infection and an increase of two or more points of quick sequential assessment of organ failure (qSOFA) as an indicator of organ failure. For high-risk patients, the qSOFA score was used to assess and predict mortality in septic patients. The qSOFA includes 1 point for each of 3 following criteria: respiratory rate $\geq$ 22 breaths/min, altered mental status, or systolic blood pressure $\leq$ 100 mmHg. The qSOFA score $\geq$ 2 is suggestive of sepsis (11). Septic shock was defined by the clinical criteria of sepsis and vasopressor therapy necessary to elevate mean arterial pressure >65mmHg and lactate values >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation.

An approval of the Ethics Committee of Cantonal Hospital Zenica was obtained.

Methods

All patients admitted to the Intensive Care Unit (ICU) with the clinical presentation of CAHRF were treated in accordance with the treatment protocol for new coronavirus infection (12). Therapy included corticosteroids, low molecular weight heparin, proton pump inhibitors, and vitamins. Antibiotics and immunomodulatory therapy were determined in consultation with an infectious diseases specialist according to laboratory findings.

Data were extracted from electronic medical records. The data included demographic parameters, comorbidities, vasopressors requirement, laboratory findings, in-hospital mortality scoring and diagnostic coagulation scores. Demographic parameters were taken on the day of admission, all other variables were taken on the day of admission to the ICU and on the day of initiation of invasive mechanical ventilation or on the day of discharge from the ICU.

Demographic parameters included age and sex of the patient, followed by comorbidities which was marked with Yes or No on the day of admission at the ICU.

Coagulation incidents were defined as widespread microvascular thrombosis in small and medium-sized vessels or profuse bleeding from various sites associated with sepsis. These incidents were noted during the patient's stay in the ICU. Mortality was assessed according to the qSOFA score and vasopressors requirement (norepinephrine and dobutamine) on the day of admission (T1) and on the day of initiation of invasive mechanical ventilation or on the day of discharge (T2). Laboratory analysis included the analysis of platelets, neutrophils, lymphocytes, procalcitonin (PCT), C-reactive protein (CRP), fibrinogen, D-dimer, international normalized ratio (INR) on the day of admission (T1) and on the day of initiation of invasive mechanical ventilation or on the day of discharge (T2).

The SIC and DIC scores were determined at the same time intervals as laboratory parameters.

Statistical analysis

The analyses of continuous variables were performed using Student's t-test or Mann Whitney U test, and the comparison of categorical variables was performed using the $\chi 2$ or Fisher's test. The numerical, continuous values were represented as mean and standard deviation (SD), and categorical variables were presented as numerical values and percentages. All hypotheses were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Hospitalized patients with severe type of CAHRF in both groups had statistical significance according to age (p=0.003) and arterial hypertension (p=0.002), while there was no statistically significant difference for other data (gender, length of hospitalization and other comorbidities) (p>0.05) (Table 1, 2). The results of laboratory parameters showed statistical significance between the groups for PCT T2 (p=0.002), lymphocytes T2 (p=0.011) and INR T2 (p=0.019). Further analysis of inotropes requirement, coagulation scores and qSOFA score showed statistical significance for norepinephrine T2 (p=0.000) and dobutamine T2 (p=0.000), followed by SIC T1 (p=0.007), SIC T2 (p=0.012) and qSOFA T1 (p=0.000) and T2 (p=0.000) (Table 3.).

Table 1. Demographic parameters, Intensive Care Unit length of stay (ICU LOS), comorbidities and coagulation incident

Parameter	Group 1 N=49	Group 2 N=50	p
Gender female/male (No, %)	23/26 (46.9/53.1)	22/28 (44.0/56.0)	0.769
Age (Mean±SD) (years)	61.02±12.59	67.80±9.54	0.003
ICU LOS (Mean±SD) (days)	10.47±6.16	10.76±7.14	0.258
Comorbidities with coagulation incident (NO/YES)	No (%) of patients		
Arterial hypertension	28/21 (57.1/42.9)	13/37 (26.0/74.0)	0.002
Diabetes	39/10 (79.6/20.4)	42/8 (84.0/16.0)	0.960
Coronary disease	40/9 (81.6/18.4)	5/25 (16.7/83.3)	0.755
Neurological disease	46/3 (93.3/6.7)	49/1 (83.3/16.7)	0.298
Thyroid disease	46/3 (93.9/6.1)	47/3 (94.0/6.0)	0.980
Renal disease	48/1 (98.0/2.0)	48/2 (96.0/4.0)	0.570
COPD	47/2 (95.9/4.1)	46/4 (92.0/8.0)	0.414
Joint disease	48/1 (98.0/2.0)	50/0 (100.0/0.0)	0.310
Coagulation incident	47/2 (95.9/4.1)	49/1 (92.0/3.0)	0.546

COPD, chronic obstructive pulmonary disease; Group 1, patients who developed sepsis; Group 2, patients who developed septic shock

DISCUSSION

This retrospective cohort study investigated the occurrence of coagulopathy in COVID-19 septic critically ill patients. Demographic parameters, comorbidities, qSOFA, SIC and DIC scores,

Table 2. Laboratory parameters on the day of admission (T1) and on the day of initiation of invasive mechanical ventilation or on the day of discharge (T2) according to groups

Parameter		Mean±SD		p
		Group 1 N=49	Group 2 N=50	
PCT (ng/mL)	T1	1.27± 2.96	1.27±3.49	0.435
	T2	2.81±10.47	5.24± 11.53	0.002
CRP (g/L)	T1	74.33±24.21	67.31±26.75	0.156
	T2	83.37±70.68	116.57±149.23	0.095
Lactate (mmol/L)	T1	2.30±0.96	2.75±1.47	0.077
	T2	2.68±1.04	3.20±1.67	0.066
Platelets (x10^9/L)	T1	233.73±83.63	251.68±98.94	0.333
	T2	237.32±102.92	214.88±102.06	0.281
Neutrophils (1)	T1	0.85±0.07	0.86±0.07	0.626
	T2	0.85±0.10	0.87±0.12	0.130
Lymphocytes (1)	T1	0.85±0.07	0.08±0.04	0.768
	T2	0.85±0.10	0.06±0.03	0.011
INR	T1	1.10±0.18	1.21±0.48	0.254
	T2	1.14±0.17	1.36±0.51	0.019
Fibrinogen (g/L)	T1	4.19±1.98	4.62±1.77	0.254
	T2	3.99±1.97	4.24±1.93	0.520
D dimer (mg/L)	T1	7.03±8.60	10.16±12.61	0.693
	T2	34.84±175.58	9.03± 9.25	0.495

PCT, procalcitonin; CRP, C-reactive protein; INR, international normalized ratio; Group 1, patients who developed sepsis; Group 2, patients who developed septic shock

Table 3. Vasopressors, coagulation scores and qSOFA score on the day of admission (T1) and on the day of initiation of invasive mechanical ventilation or on the day of discharge (T2) in the study groups

Parameter		Group 1 N=49	Group 2 N=50	p
Vasopressors NO/YES		N (%)		
Norepinephrine	T1	49/0 (100/0)	50/0 (100/0)	A
	T2	49/0 (100/0)	0/50 (0/100)	0.000
Dobutamine	T1	48/1 (98/2)	50/0 (100/0)	0.310
	T2	46/3 (93.8/6.2)	21/29 (42/58)	0.000
Score (Mean±SD)				
DIC	T1	3.08±0.93	3.10±0.97	0.924
	T2	3.18±0.755	3.52±0.99	0.163
SIC	T1	0.80±1.04	1.32±1.11	0.007
	T2	1.90±1.05	2.64±1.60	0.012
qSOFA	T1	0.20±0.41	1.18±0.39	0.000
	T2	1.18±0.39	2.66±0.48	0.000

A, statistical constant; DIC, disseminated intravascular coagulation; SIC, sepsis induced coagulopathy; qSOFA, quick sequential organ failure assessment; Group 1, patients who developed sepsis; Group 2, patients who developed septic shock

vasopressors requirement, laboratory findings were compared between patients who developed sepsis or septic shock. The results of this study showed that the highest abnormality in laboratory parameters were values of INR, PCT and lymphocytes. SIC in contrast to DIC score was observed for both groups.

Earlier studies have shown that elderly people are more prone to thromboembolism due to a "prethrombotic state" caused by a more sensitive activation of coagulation and a weaker fibrinolysis system (13), with a septic state which significantly increases the risk of coagulation disorders (14). However, the impact of this inflammatory response on coagulation outcomes in COVID-19 is unknown.

In accordance with previous studies, our study showed that coagulation disorders of COVID-19 were present equally in patients of both genders, and according to the study by Wilcox et al., more pronounced in younger patients (15). Length of ICU stay of 10 days in our study corresponds with results of Bourguignon et al. analysing thrombotic incidents in the ICU and after discharge (16). Of the present comorbidities, only arterial hypertension was statistically significant between the two analysed groups in our study, compared to other studies in which significance was found for chronic kidney disease, atrial fibrillation, COPD, and arterial hypertension (17,18). This can be partially explained by the imbalance of angiotensin-converting enzyme 2, especially in patients with comorbidities, such as hypertension, diabetes mellitus and cardiovascular diseases (19).

Laboratory findings of examined patients disclose that the main coagulation disorder were high levels of INR and indicators of inflammation, namely, lymphocytes and PCT for group 2 (septic shock), respectively, which is consistent with other literature data describing coagulopathies in septic COVID-19 critically ill patients (20,21). During intensive care hospitalization, slightly elevated CRP values were found, which is not in accordance with the reported findings of Smilowitz et al. who analysed 2782 patients with COVID-19 in the American population (22). Other laboratory parameters in our study including lactate and inflammatory and coagulation parameters were in agreement with the results of other studies (23,24). It is difficult to explain the described deviations. One possible hypothesis is that it is sepsis-associated immunosuppression with delayed immune system activity (25). Another reason could be clustering of immune reaction (26).

The use of vasopressors and inotropes is associated with increased mortality due to the severity of critical illness, catecholamines also affect other systems including the haematological system, which may have a detrimental effect on survival (27). Our results showed that the requirement for vasopressors and inotropes administration is si-

milar to that in non-Covid patients. Progressive hypoxemia and the use of vasopressors can alter vascular control, and therefore, hemodynamic support should be focused on optimizing perfusion (28). Given that low platelet count, elevated D-dimer concentration, decreased fibrinogen concentration, and prolongation of clotting times such as prothrombin time (PT) were not observed in the groups analysed in the presented study, the hypothesis of the existence of DIC as a coagulopathy was not confirmed.

Our results are more in favour of SIC in both groups (sepsis and septic shock), while a study by Pluta et al. showed different elements of coagulopathy that are more in favour of a special pattern (29). Considering all the deviations found, it is more likely that the SIC coagulopathy pattern will develop in septic patients than DIC.

Our study has limitations, including its retrospective nature and a relatively small group of patients with a lack of a control group.

In conclusion, hospitalized patients with COVID-19 in intensive care are more prone to septic coagulation disorders. Coagulation changes in septic COVID-19 patients have a specific pattern. Although the pathophysiology of coagulopathies in these patients is still not sufficiently investigated, according to our results coagulopathy in the terminal phase of the COVID-19 disease is sepsis-induced coagulopathy.

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TRANSPARENCY DECLARATIONS

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