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Coagulopathy in hospitalized COVID-19 patients: A single-center experience

Marwa Kasim Ahmed, Ali Muhammed Jawad Almothaffar[1]

Abstract:

BACKGROUND: The coronavirus disease pandemic had spread across all countries. SARS-COV-2 infected up to date millions of people and the threat remains there for others. A lot of SARS-19-infected people with critically ill symptoms admitted to intensive care facilities had developed respiratory failure, coagulopathy, and organ failure.

AIMS: The aims of this study were to investigate the prevalence and risk factors associated with coagulopathy in COVID-19 patients who were admitted to the Private Nursing Home Hospital in Baghdad/Iraq.

PATIENTS AND METHODS: A case series study was conducted in the Nursing Home Hospital in Baghdad, Iraq, from October 2020 to December 2021. A total of 150 cases were included in this study with confirmed COVID-19 infection by polymerase chain reaction of throat or nose swab. These patients were admitted to two isolation wards (isolation intensive care unit for critical cases and medical ward isolation unit for moderately severe cases). Baseline and follow-up characteristics and laboratory parameters of coagulopathy (blood counts, prothrombin time [PT], partial thromboplastin time, D-dimers, and plasma fibrinogen) were obtained for each patient. The ISARIC 4C has been used for risk stratification (4C Mortality Score is a prognostic model for clinical deterioration among hospitalized adults with community-acquired or hospital-acquired COVID-19, it is used for stratifying and predicting mortality in COVID-19 patients on arrival in hospital).

RESULTS: The mean age across patients was 56.6 ± 15.7 years (range: 14–90 years). Males were representing the majority of cases (63.3%) with a male-to-female ratio of 2:1. The mean 4C score of patients was 10.3 ± 4.9 (range: 0–20 points). The risk group stratification showed that many patients had high risk (42.7%), and only 10.7% of patients had low scores. There were 86 (57.3%) patients who developed coagulopathy during the follow-up period and 46.7% of total patients died. There was a significant association between developing coagulopathy with higher risk group and death in COVID-19 patients ($P < 0.05$), while age and gender did not demonstrate a significant association. Furthermore, there was a significant association between respiratory failure, patients with cancer, patients with stroke, higher computed tomography lung involvement, lower SPO_2, the presence of shock, and pulmonary embolism with the development of coagulopathy ($P < 0.05$). There were significant higher baseline levels of the neutrophil count, PT, D-dimer, and ferritin among patients who developed coagulopathy, while there were significant lower baseline levels of platelet count and serum albumin among patients who developed coagulopathy.

CONCLUSIONS: The development of coagulopathy in the course of severe SARS-COV-2 infection is associated with different severity biomarkers and is associated with excessive mortality.

Keywords:

Coagulopathy, COVID-19, respiratory failure

Department of Haematology, Baghdad Teaching Hospital, Medical City, [1]Department of Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq

Address for correspondence:
Dr. Marwa Kasim Ahmed, Department of Haematology, Baghdad Teaching Hospital Medical City, Baghdad, Iraq.
E-mail: marwakasim.1988@yahoo.com

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Introduction

COVID-19 virus is number seventh member of the coronavirus family. This family is divided into four generations, of which the alpha and beta subfamilies contain those relevant in human disease.[1,2] SARS-COV-2 virus has high contagiousness and unusual potential lethality.[3,4]

The pathogenesis of the COVID-19-induced coagulopathy has not yet been fully elucidated, but the mechanisms may overlap in some parts to those including[2-5]

1. Bacteria-induced septic coagulopathy/disseminated intravascular coagulation (DIC)
2. The excess production of pro-inflammatory cytokines
3. Increased levels of damage-associated molecular patterns (DAMPs)
4. The stimulation of cell death mechanisms and vascular endothelial damage are the major causes of coagulation disorder in any severe infection
5. Activation of fibrinolysis and elevated levels of fibrin-related biomarkers, prolonged prothrombin time (PT), and partial thromboplastin time (PTT) are often recognized in COVID-19, but the degree is less prominent compared to the bacterial sepsis-induced coagulopathy/DIC
6. Viral pathogenesis and viral virulence with host reaction determine the clinical symptoms and outcomes both direct virus-induced cytotoxic effect and indirect injury mediated by host responses collaboratively damage the host and consumptive coagulopathy further worsens the condition
7. Complement-mediated microangiopathy, dysregulated complement system activation may be a major contributor to cytokine storm, particularly through the pro-inflammatory effects of anaphylatoxins C3a and C5a, these effects are likely to become more detrimental in patients with a genetic predisposition for decreased complement regulation and may contributed to findings of thrombotic microangiopathy and subsequent organ dysfunction
8. Dysregulated renin–angiotensin system.

The ISARIC 4C has been used for risk stratification (4C Mortality Score is a prognostic model for clinical deterioration among hospitalized adults with community-acquired or hospital-acquired COVID-19, it is used for stratifying and predicting mortality in COVID-19 patients on arrival in hospital).[6]

Hence, the aim of this study was to investigate the prevalence and risk factors associated with coagulopathy in COVID-19 patients who were admitted to the Private Nursing Home Hospital in Baghdad/Iraq.

Patients and Methods

A case series study was conducted in Baghdad, Iraq, from October 2020 to December 2021. With 150 cases were included in this study confirmed infected by COVID-19. These patients were admitted to two isolation wards (isolation intensive care unit [ICU] for critical cases and medical ward/isolation unit) in Private Nursing Home Hospital in Medical City Complex, then each admitted patient was assessed clinically, and full laboratory reading including complete blood count, PT, PTT, fibrinogen level, renal function test, liver function test, ferritin, D-dimer, C-reactive protein, and albumin were tested at admission then on weekly basis till discharge or death.

The diagnostic criteria are proposed as follows:[4,5]
(A)Confirmed COVID-19 patients
(B)Two or more of the following criteria:
(1) Low platelet count (<150 × 10^9/L)
(2) High D-dimer (>2 times the of normal limit)
(3) Prolonged PTT or INR.
(4) Low in fibrinogen level
(5) The presence of thrombosis.

This study was approved by the Ethical Committee of Iraqi Ministry of Health, and written informed consent was waived because of the nature of the study. The privacy was protected to all patients.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software (version 23) (IBM SPSS Statistics 23, USA) had been used for data entry and analysis. In the descriptive statistics for sociodemographic characteristics, the means, standard deviations, min, and max values were used for continuous data. Numbers and percentage values were used for countable data. In analyzing the differences between the groups, the Chi-square test was used for categorical variables and the independent sample *t*-test for continuous variables. Independent *t*-test and paired sample *t*-test were used for continuous variable comparison. Pearson correlation has been used to assess the correlation between continuous variables. $P < 0.05$ was used as the threshold for statistical significance.

Results

The mean age across patients was 56.6 ± 15.7 years (range: 14–90 years). Males were representing the majority of cases (63.3%) with a male-to-female ratio of 2:1. Majority of patients were presented with cough (87.3%), followed by fever (75.3%). The most common comorbidities were hypertension (50%), followed by diabetes mellitus (37%), and there were 32 (21.3%) patients smokers [Table 1]. The mean 4C score of patients

was 10.3 ± 4.9 (range: 0–20 points). The risk group stratification showed that the majority of patients had high risk (42.7%) and only 10.7% of patients had low scores [Table 2]. There were 65 (43.3%) patients who developed respiratory failure and 10 (6.7%) patients who developed cytokine storm. There were 86 (57.3%) patients who developed coagulopathy during follow-up and 70 (46.7% of total) patients died [Table 3].

Factors associated with coagulopathy

There was a significant association between developing coagulopathy with higher risk group and death in COVID-19 patients ($P < 0.05$), while age and gender did not demonstrate significant difference. Furthermore, there was a significant association between respiratory failures, patients with cancer, patients with cerebrovascular accident (CVA), higher computed tomography (CT) scan involvement, lower SPO_2, the presence of shock, and PE with the development of coagulopathy ($P < 0.05$) [Table 4].

There were significantly higher baseline levels of neutrophil, PT, D-dimer, and ferritin among patients who developed coagulopathy, while there were significantly lower baseline levels of platelet and albumin among patients who developed coagulopathy [Table 5].

Table 1: Demographic characteristics of patients

Variable	*n* (%)
Gender	
Male	95 (63.3)
Female	55 (36.7)
Fever	113 (75.3)
Cough	131 (87.3)
Rash	9 (6)
CVA	15 (10)
Hematuria	9 (6)
Arterial ischemia	3 (2)
Bleeding spots	7 (4.6)
Chest pain	15 (10)
Comorbidities	
DM	56 (37)
HT	75 (50)
IHD	21 (14)
AF	9 (6.0)
History of stroke	7 (4.7)
Smoking	32 (21.3)
Cancer	8 (5.3)

CVA=Cerebrovascular accident, DM=Diabetes mellitus, IHD=Ischemic heart disease, AF=Atrial fibrillation, HT=Hypertension

Table 2: 4C Mortality Score stratification

4C score	Frequency (%)
Low	16 (10.7)
Intermediate	35 (23.3)
High	64 (42.7)
Very high	35 (23.3)

Discussion

Coagulopathy and COVID-19

The prevalence of coagulopathy in COVID-19 Iraqi patients with moderate-to-severe symptoms was 57%. Other studies showed lower prevalence, the prevalence of systemic coagulopathy was 7.1% in a large meta-analysis study.[7] Another three studies reported the prevalence of DIC ranging from 4% to 8%.[8-10] While two studies reported the prevalence of sepsis-induced coagulopathy ranging from 1% to 14%.[11] The difference was due to the nature of the patients sample in this study which included patients with moderate and severe cases mainly.

Factors associated with coagulopathy

In this study, age did not show a significant association with the development of coagulopathy, this was against Yuan's *et al*.'s[10] study which demonstrated a significant higher rate of coagulopathy among elderly patients (>65 years).[12] Furthermore, it has been shown by previous studies that elderly is being a risk factor in the development of venous thromboembolism (VTE).[13,14]

There was a significant association between developing coagulopathy with higher risk group in COVID-19 patients. This was in line with Klok FA *et al*.'s[13] study which reported the rate of VTE was 27% in patients with severe COVID-19 infection.[15] Furthermore, another study reported that coagulopathy results from severe cases of COVID-19 infection.[16]

Llitjos *et al*.[15] reported an overall rate of 69% VTE in severe COVID-19 patients admitted to ICU. In this study, VTE incidence was found to be significantly higher in patients treated with prophylactic anticoagulation compared with those treated with therapeutic anticoagulation.[17] Thus, COVID patients with severe disease status need special attention to overcome coagulopathy development. Furthermore, Tang *et al*. interestingly found that more than 70% of dead patients met the criteria for DIC, with only <1% of survivals had DIC.[5]

There was a significant association between respiratory failure and the development of coagulopathy and this was in line with another study that showed thrombotic dysregulation in COVID-19 is associated with respiratory failure and coagulopathy and severe acute respiratory syndrome coronavirus 2 pneumonia is linked to both acute respiratory distress syndrome and development of systemic hypercoagulability.[18]

A variety of disorders, including infectious conditions or malignant disease, can lead to activation of coagulation.[19] Moreover, in this study, there was a significant association between the development of coagulopathy and cancer in

Table 3: Serious events

Variable	Frequency (%)
Respiratory failure	65 (43.3)
Cytokine storm	10 (6.7)
Pneumothorax	9 (6.0)
Shock	32 (21.3)
Lung fibrosis	3 (2)
Serious thrombotic event	21 (14)
DVT	1 (0.6)
Pulmonary embolism	9 (6.0)
Coagulopathy (at any point)	86 (57.3)
Death	70 (46.7)

DVT=Deep vein thrombosis

patients with COVID-19 infection. This might relate to the synergistic effect of cancer and COVID-19 to increase the incidence of coagulopathy. However, a study by Patell *et al*.[18] showed that similarly high incidence of thrombosis and bleeding among patients admitted with COVID-19 with or without active cancer.[20]

In this study, there was a significant association between coagulopathy and CVA, in which COVID-19 is also associated with inflammatory coagulopathy that causes disseminated vascular obstructions, including but not limited to CVA.[21]

Both CT involvement and Spo_2 saturation showed a significant association in developing coagulopathy in this study and this relates to the fact that both CT involvement and Spo_2 saturation have been associated with increased severity of COVID-19 infection and the severity by turn is associated significantly with coagulopathy development.

Furthermore, pulmonary embolism during illness showed to be associated significantly with coagulopathy. In a study showed that acute pulmonary embolism was observed in 81% of all acute thrombotic complications in patients with COVID-19 infection.[22] Out of 12 autopsies, 4 of them were found that PE is the cause of death.[23]

Laboratory results and development of coagulopathy

In hospitalized patients for suspected or confirmed COVID-19, a coagulation profile should be performed, including D-dimer, PT, PTT, platelet count, and fibrinogen, repeating these coagulopathy parameters are recommended in patients with severe COVID-19, at least every 2–3 days.[24]

In this study, a higher neutrophil count showed to be associated with coagulopathy. This is related to the fact that DIC releases DAMPs and neutrophil extracellular traps that promote thrombosis, which lead to increase neutrophil count.[25]

Table 4: Factors associated with developing coagulopathy

	Coagulopathy, count (%)		*P*
	Yes	No	
Age (years)			
<40	13 (65)	7 (35)	0.09
40-65	35 (40.2)	52 (59.8)	
>65	16 (37.2)	27 (62.8)	
Gender			
Female	27 (49.1)	28 (50.9)	0.22
Male	37 (38.9)	58 (61.1)	
Risk group of COVID			
Low	15 (42.9)	20 (57.1)	0.001**
Intermediate	14 (87.5)	2 (12.5)	
High	25 (39.1)	39 (60.9)	
Very high	10 (28.6)	25 (71.4)	
Death	16 (22.9)	54 (77.1)	
HT			
No	33 (44.0)	42 (56.0)	0.74
Yes	31 (41.3)	44 (58.7)	
DM			
No	42 (44.7)	52 (55.3)	0.51
Yes	22 (39.3)	34 (60.7)	
Respiratory failure			
No	50 (58.8)	35 (41.2)	0.0001**
Yes	14 (21.5)	51 (78.5)	
Cancer			
No	64 (45.1)	78 (54.9)	0.012**
Yes	0	8 (100)	
Smoking			
No	51 (43.2)	67 (56.8)	0.79
Yes	13 (40.6)	19 (59.4)	
AF			
No	61 (95.3)	3 (4.7)	0.55
Yes	80 (93)	6 (7)	
History of stroke			
No	63 (98.5)	1 (1.5)	0.29
Yes	80 (93)	6 (7)	
CVA during illness			
No	63 (46.7)	72 (53.3)	0.003**
Yes	1 (6.7)	14 (93.3)	
Arterial ischemia			
No	64 (43.5)	83 (56.5)	0.13
Yes	0	3 (100)	
Chest CT% involvement on admission			
1	19 (63.3)	11 (36.7)	0.02**
2	32 (45.7)	38 (54.3)	
3	12 (34.3)	23 (65.7)	
4	1 (6.7)	14 (93.3)	
SpO_2% on admission			
≤93	44 (38.2)	71 (61.7)	0.048**
>93	20 (57.1)	15 (42.9)	
Shock			
No	58 (49.1)	60 (50.9)	0.009**
Yes	6 (18.8)	26 (81.2)	
Cytokine storm			

Contd...

Table 4: Contd...

	Coagulopathy, count (%)		*P*
	Yes	No	
No	62 (44.3)	78 (55.7)	0.134
Yes	2 (20)	8 (80)	
Pulmonary embolism during illness			
No	64 (45.4)	77 (54.6)	0.008**
Yes	0	9 (100)	

**Significant *P* value. CVA=Cerebrovascular accident, DM=Diabetes mellitus, AF=Atrial fibrillation, HT=Hypertension, CT=Computed tomography

Furthermore, there was a significant lower platelet level among patients who developed coagulopathy. Although thrombocytopenia is considered the most sensitive indicator in sepsis-induced coagulopathy/DIC, the platelet was significantly lower among patients who developed coagulopathy; however, the mean was above 200×10^9/L.

Lippi *et al.*[24] showed in a meta-analysis study that increased risk of disease severity and mortality was associated with low platelet in a patient with COVID-19.

Huang *et al.*[26] showed that admission in ICU patients had higher D-dimers and prolonged PT at the time of admission. Similarly, Wang *et al.*[27] reported elevated PT in ICU patients, as well as for D-dimers.

Furthermore, Han *et al.*[12] compared COVID-19 patients with healthy controls reported lower antithrombin and higher D-dimers, fibrinogen degradation product, and fibrinogen.

Overall, apart from elevated PT, increased D-dimer and fibrinogen levels, and thrombocytopenia in COVID-19 patients, bleeding events requiring therapeutic intervention are not reported.

Several other studies have shown D-dimer levels and fibrinogen levels as good indices for identifying patients at high risk for VTE and in predicting disease severity.[28,29]

Albumin levels showed to be significantly lower in patients who develop coagulopathy and this was in line with Ronit *et al.*[28] showed that hypoalbuminemia enhanced the risk of artery and venous thrombosis.[30] Furthermore, many studies demonstrate the role of low albumin in bad prognosis of COVID-19 patients.[31,32] However, data regarding coagulopathy and vascular disease in COVID-19 are unknown.

In this study, the ferritin level showed a significant association with the development of coagulopathy, in which a higher ferritin level was associated with the development of coagulopathy. This was in line with

Table 5: Initial laboratory results association with developing coagulopathy

	Coagulopathy (mean±SD)		*P*
	No	Yes	
WBC count ($\times 10^9$/L)	10.91±5.41	12.54±5.71	0.079
Neutrophils count ($\times 10^9$/L)	9.1±5.2	11.1±5.5	0.027*
Lymphocytes count ($\times 10^9$/L)	1.11±0.79	0.90±0.65	0.076
Hemoglobin (mg/dl)	13.2±1.9	12.6±2.3	0.068
Platelet count ($\times 10^9$/L)	272.8±101.2	221.1±99.1	0.002*
PT (s)	14.4±1.8	15.6±3.0	0.007*
PTT (s)	28.3±4.0	29.5±11.1	0.41
INR	1.15±0.17	2.50±11.09	0.33
D-dimer (ng/dl)	493.1±415.1	810.3±501.7	0.0001*
Fibrinogen (mg/dl)	482.6±107.5	522.2±130.7	0.05
Serum creatinine (mg/dl)	1.00±0.52	1.12±0.93	0.37
CRP (mg/dl)	99.3±100.5	136.2±97.0	0.26
AST (U/L)	55.8±114.8	59.1±61.2	0.81
ALT (U/L)	59.1±118.5	59.7±66.7	0.97
ALP (IU/L)	75.2±26.0	91.4±56.1	0.33
Serum ferritin (mg/l)	604.0±565.5	1099.2±664.1	0.0001*
Serum albumin (g/dl)	3.71±0.68	3.33±0.60	0.0001*
Blood urea (mg/dl)	51.3±36.7	59.3±48.2	0.29

*Significant *P* value. WBC=White blood cell, PT=Prothrombin time, PTT=Partial thromboplastin time, INR=International normalized ratio, CRP=C-reactive protein, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, ALP=Alkaline phosphatase, SD=Standard deviation

Long *et al.*'s[31] study that showed higher ferritin levels associated with the development of coagulopathy, and interestingly, they reported that serum ferritin is closely related to the coagulopathy severity of patients with COVID-19.[32]

Conclusions

There is a high incidence of hypercoagulability in critically ill patients with COVID-19 infection and a significant higher mortality rate in patients with hypercoagulability. There is a significant association between coagulopathy and higher 4 CM score, development of respiratory failure, lower SPO_2, the presence of cancer, higher CT involvement, higher neutrophil count, lower platelet count, higher serum ferritin, higher D-dimer, and lower serum albumin.

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Conflicts of interest
There are no conflicts of interest.

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