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ORIGINAL ARTICLE

Pattern of Coagulopathy and Their Association with Mortality in COVID-19 Patients in Makkah, KSA

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ABSTRACT

Objective: To determine the pattern of coagulation profile and their association with mortality in COVID-19 patients.
Study Design: Retrospective descriptive study
Place and Duration of Study: Makkah, Saudi Arabia from 2nd March 2020, to 2nd July 2020.
Methodology: One thousand, nine hundred and twenty three conceded COVID-19 patients affirmed with polymerase chain response testing were included.
Results: Patients' average age was 58.7±2.75 years. Patients drop was observed 6.4% in the survivor group as compared to 0.8% in the non-survivor group with a significant (p=0.000) association with mortality. Prolonged PT/INR was observed in 16% of patients, having a significant association (P=0.003) with mortality. APTT was prolonged in 29.4% of patients, and a comparison of APTT levels between the survivor and non-survivor groups showed a significant difference (p=0.002. A higher fibrinogen level was seen in 23.2% of patients with a significant (p=0.001).
Conclusion: Severe COVID-19 infection is related to coagulopathy that is related to the destitute condition of hospitalized patients. Early and consistent evaluation of the coagulation profile along the disease course can help to treat and prevent disease morbidity and mortality in the hospital setting.
Keywords: COVID-19, thrombosis, coagulation profile

INTRODUCTION

On January 30, 2020, the World Health Organization designated COVID-19 (corona viral illness) as a "Public Health Emergency''.[1] This pandemic is spreading across the whole world at an alarming rate. This viral infection can cause the host's immune system to overreact, resulting in a "cytokine storm". There are multiple risk factors documented that might have a role in causing severe illness.[2]

Initially, an inflammatory response occurs, which leads to thrombo-inflammation through different mechanisms like cytokine storm, complement activation, and endothelitis.[3-5] SARS-CoV-2 infects the alveolar epithelium by way of the ACE2 receptor. Inflammation and thrombosis begin in the pulmonary alveoli.

COVID-19's coagulopathy pattern has recently been linked to a high rate of thrombosis because of prophylactic and therapeutic anticoagulation. This raises concerns about COVID-19's coagulopathy pattern.[6,7] A prothrombotic phase in this disease has been linked to high D-dimer, fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), and low antithrombin.[3,8-11] COVID-19 promotes hypercoagulability via processes that are special to SARS-CoV-2 and are involved in inflammation and thrombosis.[12,13] Wuhan investigations initially targeted COVID-19's high mortality rate and its link to thromboembolic events, particularly at the disease's most severe and critical phases.[14-16] Later the same observations were documented by different researchers globally.[17-19.]The pathogenesis of this life-threatening event is multifactorial and elucidated, but some mechanisms continue to be determined and elaborated.

COVID-19 causes coagulopathy, which is characterized by significant increases in D-dimer, fibrin, and plasminogen activator inhibitor (PAI-1) due to IL-6, as well as anomalies in prothrombin time, partial thromboplastin time, and platelet count for a variety of reasons.[20] These abnormalities are relatively uncommon in initial presentation but are seen in severe and critical stages of disease.[21]

So, blocking these responses could reduce the patient's mortality, especially when they are critically ill. Infections can evolve and change over time, affecting the success of interventions. In the late stages of the disease, the endothelium regulates hemostasis, fibrinolysis, vascular permeability, inflammation, and oxidative stress.[21]

COVID-19 associated coagulopathy (CAC) is a new subtype of coagulopathy with unique features.CAC looks like disseminated intravascular coagulopathy (DIC), antiphospholipid syndrome (APS), hemophagocytic syndrome (HPS), and thrombotic microangiopathy (TMA) in several ways.[22]

COVID-19 has been the subject of much recent literature, which has often provided ambiguous or contradictory results. That is, knowledge about its pathophysiology still needs to be discussed and interpreted. The treatment of the underlying cause is the general rule in the management of coagulopathy. COVID-19's definitive treatment, on the other hand, is still in its early stages of development. As a result, being able to effectively manage the consequences of COVID-19-associated coagulopathy is critical.

Saudi Arabia could be a hot zone for flare-ups of irresistible infections like COVID-19, particularly in the Makkah locale. Conducting such a study in this population with different genetics may give new insight into the COVID-19 associated coagulopathy dilemma. This may offer pivotal prognostic and preventive bits of knowledge which can likely direct modifications in the management of COVID-19.

MATERIALS AND METHODS

This retrospective descriptive study was conducted in Makkah, Saudi Arabia. This consideration was conducted after endorsement from the organization's ethical committee. The patients were affirmed as positive for COVID-19 by a real-time polymerase chain reaction test. It was done by nasal and throat swabs. According to the inclusion criteria, all admitted confirmed COVID-19 patients over the age of 14 were included in the study. At the time of admission, each patient's demographic information, hematological (CBC), inflammatory markers (CRP, ESR, Ferritin, D-dimer), and coagulation profile (PT, aPTT, fibrinogen, and platelet count) were extracted and documented from their medical records. Statistical Package for Social Sciences (SPSS) version 24 were used to analyze the data. The Chi-square test was connected

to a survey affiliation between coagulation markers and mortality. P-value less than 0.05 was considered significant.

RESULTS

There were 1035 (53.8%) males and 888 (46.2%) females. The average of the patients was 58.7±2.76 years and 95% C.I. (2.739, 2.78). The transcendent (74.6%) age group was more seasoned than 40 years of age, and only 25.4% were in the 21–41-year-old age group. Detailed demographic data, presenting symptoms and co-morbidities, and their correlation with the mortality of patients are documented in Table 1. Patients with a platelet count of less than 150,000/cu mm (thrombocytopenia) were seen 6.4% in the survivor group, as compared to 0.8% in the non-survivor group of patients. Normal platelets (150,000-400,000/cu mm) were observed 73.9% and 0.7% in survivor and non-survivor group patients, respectively. Platelets greater than 400,000/cu mm (thrombocytosis) were observed in 17.9% of survivor group patients only. Thrombocytopenia shows a significant (p .000) correlation with the mortality of COVID-19 patients. Prolonged PT/INR was observed in 16% of patients, with a significant correlation (P.003) to mortality. APTT was prolonged in 29.4% of patients. On comparison of APTT levels between the survivor and non-survivor groups, a significant difference was observed with a significant P-value of.002. A higher fibrinogen level was seen in 23.2% of patients. The fibrinogen levels in two patient groups (survivor and non-survivor) showed a significant {P=0.001) [Table 2). The other covariates (D. Dimer, LDH) and details of serological markers (ESR, CRP, ferritin, and procalcitonin) along with their mortality correlation are shown in Tables III and IV, respectively. There is a trend of elevated PT, aPTT, and fibrinogen with a decrease in platelets at the time of admission. Fibrinogen levels were higher than normal initially at the time of admission, then a decreasing trend of fibrinogen levels was observed in our patients, who succumbed to the disease.

Table 1: Demographic and clinical features frequencies and their correlation with mortality of COVID-19 patients (n=1923)

Variable	Total cases	Outcome		P value
		Survivor (n=1892)	Non-survivor (n=31)	
Age (years)				
21 – 40	490 (25.5%)	489 (25.4%)	1 (0.05%)	0.000
41 – 65	1406(73.1%)	1393 (72.4%)	13 (0.6%)	
> 65	1406(73.1%)	10 (0.5%)	17 (0.8%)	
Smoking	450 (23.4%)	435 (22.6%)	15 (0.7%)	.002
Hypertension	298 (15.5%)	298 (15.4%)	0 (0.0%)	.010
Hypertension	195 (10.1%)	165 (8.5	30 (1.5%)	.000
Hypertension	34 (1.7%)	30 (1.5%)	4 (0.2%)	.002
Lung diseases	30 (1.5%)	30 (1.5%)	0 (0.0%)	1.000
Stroke	30 (1.5%)	30 (1.5%)	0 (0.0%)	1.000
CKD	45 (2.3%)	44 (2.2%)	1 (0.05%)	.523
Liver disease	15 (0.8%)	15 (1.5%)	0 (0.0%)	1.000
Temperature (°C)				
< 38	447 (23.2%)	447 (23.2%)	-	.006
38 – 40	1446 (75.1%)	1415 (73.6%)	31 (1.6%)	
> 40	30 (1.5%)	30 (1.5%)	-	
Cough	1448 (75.3%)	1417 (73.7%)	31 (1.6%)	.000
SOB	921 (47.9%)	894 (46.5%)	27 (1.4%)	.000
Myalgia	701 (36.4%)	685 (35.6%)	16 (0.8%)	.000
Sore throat	626 (32.5%)	626 (32.5%)	0 (0.0%)	.000
GIT symptoms	194 (10%)	193 (10%)	1 (0.05%)	.360
Headache	477 (24.8%)	477 (24.8%)	0 (0.0%)	.002
Blood pressure (mmHg)				
<90/60	30 (1.5%)	-	30 (1.5%)	.000
91-140/61-90	1728 (89.8%)	1727 (89.8%)	1(0.05%)	
>140/90	165 (8.5%)	165 (8.5%)	-	
Pulse (/min)				
71 – 100	1889 (98.2%)	1888 (98.1%)	1 (0.05%)	.000
> 100	34 (1.7%)	4 (0.2%)	30 (1.5%)	
SPO2 % by pulse oximeter				
93 – 96	1876 (97.5%)	1860 (96.7%)	16(0.8%)	.000
< 93	47 (2.4%)	32 (1.6%)	15 (0.7%)	
Respiratory Rate/min				
16 – 20	1295 (67.3%)	1292 (67.1%)	3 (0.2%)	.000
21 – 30	604 (31.4%)	578 (30%)	26 (1.3%)	
> 30	24 (1.2%)	22 (1.1%)	2 (0.1%)	

COVID-19 is linked to a high rate of mortality, with 67 (3.5%) of cases requiring admission to an intensive care unit. Nearly 1606 (83.5%) of patients required supplementary oxygen, 492 (25.6%) required brief non-invasive ventilation and 58 (3.0%) required intrusive ventilation. Septic shock in 17 (0.9%) and disseminated intravascular coagulation (DIC) in 8 (0.4%) of cases are documented. During this four-month period, 31 (1.6%) of the participants were died. Mostly, 30 (96.8%) patients died due to respiratory arrest. Different variables' associations with mortality and their P-values are mentioned in Table 3.

Table 2: Covariates frequencies and their association with Mortality of Covid-19 Patients

Variable	Total cases	Outcome		P value
		Survivor (n=1892)	Non-survivor (n=31)	
Platelet count / cu mm				
<100000	48 (2.5%)	32 (1.6%)	16 (0.8%)	0.000
100000-150000	94 (4.9%)	94 (4.8%)	-	
151000-400000	1436 (74.6%)	1421 (73.9%)	15 (0.8%)	
>400000	345 (17.9%)	345 (17.9%)	-	
D-Dimer (mg/l)				
< 0.5	586 (30.5%)	583 (30.3%)	3 (0.1%)	0.000
0.5 – 1.0	653 (33.9%)	647 (33.6%)	6 (0.3%)	
1.1 – 1.5	552 (28.7%)	536 (27.8%)	16 (0.8%)	
5.1 – 10	132 (6.8%)	126 (6.5%)	6 (0.3%)	
Lactate dehydrogenase (LDH) u/l				
140 – 280	641 (33.3%)	640 (33.3%)	1 (0.05%)	0.000
281 – 400	950 (49.4%)	936 (48.6%)	14 (0.7%)	
401 – 500	332 (17.3%)	316 (16.4%)	16 (0.8%)	
Prothrombin Time/International Normalized Ratio (PT/INR)				
< 0.88	683 (35.5%)	678 (35.3%)	5 (0.3%)	0.003
0.89 – 1.1	932 (48.5%)	922 (47.9%)	10 (0.5%)	
1.12 – 1.4	308 (16.0%)	292 (15.1%)	16 (0.8%)	
Activated partial thrombin time (APTT) sec.				
23 – 40	1359 (70.7%)	1348 (70.0%)	11 (0.6%)	0.002
40.1 – 42	459 (23.9%)	447 (23.2%)	12 (0.6%)	
> 42	105 (5.5%)	97 (5.0%)	8 (0.4%)	
Fibrinogen level (mg/dl)				
200 – 400	1432 (74.5%)	1418 (73.7%)	14 (0.7%)	0.001
401 – 500	446 (23.2%)	430 (22.7%)	16 (0.8%)	
Parenteral Anticoagulation				
Enoxaparin	1657 (86.2%)	1642 (85.4%)	15 (0.8%)	0.008
Heparin	210 (10.9%)	194 (10.0%)	16 (0.8%)	
Fondaparinox	56 (2.9%)	56 (2.9%)	-	
Septic Shock				
Present	17 (0.9%)	17 (0.8%)	-	0.602
Absent	1906 (99.1%)	1875 (97.5%)	31 (1.6%)	
Intensive Care Unit (ICU) admission				
Yes	67 (3.5%)	37 (1.9%)	30 (1.5%)	0.000
No	1855 (96.5%)	1854 (96.4%)	1 (0.05%)	
Disseminated intravascular coagulopathy (DIC)				
Present	8 (0.4%)	8 (0.4%)	-	1.000
Absent	1915 (99.5%)	1884 (97.9%)	31 (1.6%)	

Table 3: Inflammatory Markers frequencies and their correlation with mortality of Covid-19 patients

Variable	Total cases	Outcome		P value
		Survivor (n=1892)	Non-survivor (n=31)	
ESR				
< 15	814 (42.3%)	806 (41.9%)	8 (0.4%)	0.001
15 – 30	745 (38.7%)	730 (37.9%)	15 (0.7%)	
31 - 40	140 (7.3%)	132 (6.8%)	8 (0.4%)	
> 40	224 (11.6%)	224 (11.6%)	-	
Procalcitonin (ug/ml)				
< 0.5	1271 (66.0%)	1259 (65.5%)	12 (0.6%)	0.008
0.51 – 1.0	440 (22.9%)	421 (21.8%)	19 (0.9%)	
1.1 – 1.5	139 (7.2%)	139 (7.2%)	-	
Ferritin (ug/ml)				
205 – 300	269 (13.9%)	268 (13.9%)	1 (0.05%)	0.000
301 – 500	1103 (57.3%)	1073 (55.7%)	30 (1.5%)	
501 – 700	313 (16.3%)	313 (16.2%)	-	
701 – 900	238 (12.4%)	238 (12.3%)	-	
Oxygen Therapy (by nasal cannula/face mask)				
Yes	1606 (83.5%)	1579 (82.1%)	27 (1.4%)	0.807
No	317 (16.5%)	313 (16.3%)	4 (0.2%)	
Non-Invasive Ventilation				
Yes	492 (25.6%)	477 (24.8%)	15 (0.7%)	0.006
No	1431 (74.4%)	1415 (73.6%)	16 (0.8%)	
Mechanical Ventilation				
Yes	58 (3.0%)	32 (1.7%)	26 (1.4%)	0.000
No	1865 (97.0%)	1860 (96.7%)	5 (0.2%)	

DISCUSSION

COVID-19 comes about in both systemic (arterial and venous) thrombosis within the disease, as well as a likely transcendent localized pulmonary microthrombosis coming about in extreme sickness and conceivably atypical ARDS. The advancement of an atypical pro-coagulant DIC is seen among non-survivors with a lack of bleeding diathesis, according to recent writing.[4]The activation of the coagulation cascade and the consumption of clotting factors are hallmarks of DIC. Up-regulation of plasminogen activator inhibitor 1 (PAI-1) causes hypercoagulability with concomitant suppression of fibrinolysis.[23]As coagulation factors and platelets are depleted, bleeding events occur. The International Society of Thrombosis and Haemostasis (ISTH) diagnostic system[24] is the only diagnostic tool that incorporates platelets,[25] prothrombin time, fibrinogen and D-dimer level.[26]

Our study found a measurably noteworthy distinction between the means, and frequencies of coagulation parameters (prothrombin time, aPTT, platelets, D-dimer, and fibrinogen) among the survival and non-survival groups. More so, the non-survivors (n=31) illustrated more derangements of coagulation parameters with diligently raised D-dimer levels and other intense acute inflammatory markers (Table 3). These laboratory findings were in accordance with recently published studies. Tang et al.[8] found raised D-dimer, fibrinogen, prolongation of prothrombin time, and activated partial thromboplastin time in non-survivors. In critical cases, Huang et al[2] described prolonged PT in the early hospital days. In a study conducted on 43 patients[27] and another on 140 patients,[28] fibrinogen and D-dimer values were significantly higher in the group with severe disease than in the mild disease group. In another study conducted in Wuhan, D-dimer was linked to 28-day mortality in 191 patients.[16] Wu et al[29] elevated PT and D-dimer were found to be related to higher risks for acute respiratory distress syndrome.

In the intensive care unit, thrombocytopenia is linked to the severity of sepsis and mortality. This is likely multifactorial, but it is due in part to the often pre-terminal massive platelet activation and consumption seen in DIC. In laboratory-confirmed COVID-19 patients in Wuhan,[3] 36.2% had thrombocytopenia, and thrombocytopenia was linked to a more than fivefold increased risk of severe illness, according to a later meta-analysis.[30]

In this study, elevated fibrinogen levels are observed in critical patients at the time of admission; this pattern is consistent with that in other recent studies.[13,31,32] Survivors have a 35% reduction in fibrinogen levels, while non-survivors have a 16% decrease.[31,32] One of the markers of fibrinolysis is D-dimer. In this situation, an increase in D-Dimer levels, which can be found in both survivors and (to a greater extent) non-survivors, is interpreted as a sign of increased fibrinolysis. It shows a significant correlation with the mortality of patients, as seen in other studies.[31,33] On the other hand, D-dimers, have no connection to fibrin synthesis. The cause of D-dimer elevation in COVID-19 patients is still unknown, but extravascular fibrin degradation (mostly in the interstitial and alveolar lung space) has been suggested.[33]

CONCLUSION

In critically ill COVID-19 patients, inappropriate coagulation indicators played a substantial influence in disease morbidity and mortality. Steady evaluation of the coagulation profile along with the malady course can aid in treating and avoiding infection dismalness and mortality in hospitalized patients.

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