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Coagulation and Comorbidity: Determining the Outcomes in Covid Patients

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Abstract:
INTRODUCTION: *Hypercoagulability due to severe viral pneumonia is not novel. Patients with COVID-19 pneumonia exhibit coagulation abnormalities, most commonly elevated levels of fibrinogen and D-dimer, often with mild thrombocytopenia. Three stages of COVID-19-associated coagulopathy have been proposed: stage 1 showing elevated D-dimer, stage 2 showing elevated D-dimer together with mildly prolonged PT/INR and aPTT and mild thrombocytopenia, and stage 3 with critical illness and laboratory studies progressing towards classic DIC.*
METHODOLOGY: *The present study is a prospective hospital based cross sectional study Conducted in patients admitted in Intensive care unit at Dr. Shankar Rao Chavan Government Medical College Nanded between April 1st 2021 to April 30th 2021. 312 patients were included in the study.*
RESULTS*: A total of 312 patients were admitted during the study period. The mean age of the patients was 46.43 ± 17.13 years, ranging from 19 to 89 years. patients had at least one chronic comorbidity. Hypertension (14.10%), diabetes (10.26%), and both hypertension and diabetes (10.26%). On bivariate analysis the decreased platelet counts and raised APTT and D-Dimer and the presence of co morbidity were statistically significant. Any co morbidity emerged as the independent risk factor for the mortality in multivariate analysis.*
CONCLUSION: *COVID-19 patients with low levels of PLT, high PT and INR that were associated with poor prognosis. The abnormal pattern of coagulation parameters was highly associated with comorbidities and mortality.*
Keywords: *COVID 19, COMORBIDITY, PT INR, APTT, D-DIMER, PLATELETS.*

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I. Introduction:

People are going through a battle against novel coronavirus pneumonia (COVID-19) all over the world. 80% of patients infected by SARS-CoV-2 may be asymptomatic or only mildly symptomatic, but around 10% develop severe respiratory symptoms that evolve to acute respiratory distress syndrome (ARDS) [1].

Men are well known to be infected more frequently than women, and the elderly and patients with comorbidities (such as cardiovascular disease, hypertension, diabetes, and obesity) are more likely to develop more severe disease [2,3,4]. However, severe disease can develop even in young people and those without comorbidities, and many points remain unclear regarding what factors contribute to the outcomes.

SARS-CoV-2 causes lung inflammation which progresses to cytokine storm in the most severe cases. The lungs of patients with COVID-19 show extensive alveolar and interstitial inflammation [5]. Severe pulmonary inflammation causes activation and damage of the pulmonary vasculature and may trigger pulmonary thrombosis early in the disease course [6].

Hypercoagulability due to severe viral pneumonia is not novel. This increased VTE incidence in COVID-19 patients is similar to that seen in patients with other epidemic coronavirus pneumonias, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS- CoV)[7.8]. The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself; rather, the coagulopathy is most likely the result of the profound COVID-19 inflammatory response and endothelial activation/damage [9].

Patients with COVID-19 pneumonia exhibit coagulation abnormalities, most commonly elevated levels of fibrinogen and D-dimer, often with mild thrombocytopenia [9,10]. In more severely affected patients, a disseminated intravascular coagulopathy (DIC)-like state can develop with relatively mild prolongation of the PT and aPTT (while fibrinogen tends to remain normal/elevated) [9]. However, D-dimer levels are elevated far out of proportion to any abnormalities detected in the PT/INR, aPTT, fibrinogen level, or platelet count; these findings are unusual for DIC, as defined by the criteria of the International Society of Thrombosis and Hemostasis (ISTH) [11]. Unlike the pattern seen in classic DIC from bacterial sepsis or trauma, in COVID-19

prolongation of the aPTT and/or PT is minimal[12], thrombocytopenia is mild (a platelet count of 100–150 $\times 10^9$/L), hypofibrinogenemia is rare, and laboratory results supporting hyperfibrinolysis are uncommon[13].

COVID-19-associated coagulopathy is the term used to describe this spectrum of coagulation changes. Three stages of COVID-19-associated coagulopathy have been proposed: stage 1 showing elevated D-dimer, stage 2 showing elevated D-dimer together with mildly prolonged PT/INR and aPTT and mild thrombocytopenia, and stage 3 with critical illness and laboratory studies progressing towards classic DIC [6].

Respiratory failure is the most common cause of death, but coagulation activation accompanied by excessive immune/infammatory reactions (representing the so-called cytokine storm), thrombosis and disseminated intravascular coagulation (DIC), and progression to multiple-organ failure are also causes of death [14-18]. In particular, thrombosis and DIC can lead to a rapid deterioration in condition.

II. Methodlogy:

The present study is a prospective hospital based cross sectional study. The study subjects for the present study included the patients admitted in Intensive care unit at Dr. Shankar Rao Chavan government medical college Nanded between April 1st 2021 to April 30th 2021.

STUDY TOOLS:

After obtaining the clearance from the institutional ethics committee the necessary data for the conduction of the study was collected from the central laboratory of the medical college.

The patient's consent was taken when conscious for the utilization of necessary data, when not possible the consent from the nearest possible was taken.

SAMPLE SIZE:

All the patients admitted to ICU during the prescribed study period were included in the study. A total of 312 samples were included in the study.

OUTCOME OF ILLNESS: According to clinical progression, outcomes in endpoints were divided into two types: hospital discharge, and death.

STATISTICAL ANALYSIS:

The master chart of the collected data was prepared in Excel Sheet. The data was analyzed using statistical software Epi info 07 software and was presented in the form of tables, figures, graphs and diagrams wherever necessary. Bivariate analysis and multivariate analysis tests were used for the analysis of the data.

III. Results

Clinical Characteristics

A total of 312 patients were admitted during the study period. The mean age of the patients was 46.43 $\pm$ 17.13 years, ranging from 19 to 89 years. Two hundred eight (208/312, 66.67%) patients were male, and 104 (104/312, 33.33%) patients had at least one chronic comorbidity. Hypertension (14.10%), diabetes (10.26%), and both hypertension and diabetes (10.26%) were the most common comorbidities, others included CHRONIC OBSTRUCTIVE PULMONARY DISEASE, CORONARY ARTERY DISEASE, CHRONIC KIDNEY DISEASE and LIVER DISEASES. Comparisons of the demographic and clinical characteristics of the survivors and non-survivors are shown in Table 1.

TABLE :1 Comparisons of the demographic and clinical characteristics of the survivors and non-survivors.

	All patients	Survivors	Non-survivors	*P*
Subjects, *n*	312	180	132	-
Age (years)	46.43 $\pm$ 17.13	41.57 $\pm$ 13.04	53.80 $\pm$ 19.98	0.105
Gender, male, *n* (%)	208 (66.67%)	128 (41.03%)	80 (25.64%)	1.000
Any comorbidity, *n* (%)	112 (35.90%)	32 (10.26%)	80(25.64%)	0.001
Hypertension, *n* (%)	44 (14.10%)	12 (32.88%)	32 (50.00%)	
Hypertension + Diabetes, *n(%)*	32(10.26%)	4(1.28%)	28(8.97%)	
Diabetes, *n* (%)	32 (10.26%)	16(5.13%)	16(5.13%)	
Others, *n* (%)	4 (1.28%)	00	4 (1.28%)	

Coagulation parameters of survivors and non- survivors:

The admission PT, INR, and levels of D-dimer were significantly higher in the non-survivors than in the survivors, while the reverse was true for PT-act (Table 2). Meanwhile, the percentages of those with PT > 13 s, PT-act < 75%, D- dimer > 0.55 mg/L, were significantly higher in non-survivors than in survivors (Table 2).

Bivariate and multivariate logistic regression analyses were performed to determine whether admission PT-act < 75% was independently associated with mortality (Table 3). Admission PT-act < 75% was not a risk factor for mortality when the other variables were controlled. Any co morbidity emerged as the independent risk factor for the mortality (adjusted odds ratio (OR) = 1.973; 95% confidence interval (CI): 1.10-3.530; *P* = 0.02).

On bivariate analysis the decreased platelet counts and raised APTT and D-Dimer and the presence of co morbidity were statistically significant.

Even though the odds ratio for the Raised D dimer and decreased platelets is higher, both the factors did not emerge as independent risk factors on Multivariate analysis.

Table 2 Comparison of coagulation parameters between survivors and non-survivors

Normal range		All patients	Survivors	Non-survivors	*P*
Subject	-	312	180	132	-
PT (s)	9–13	16.28 ± 3.406	16.14 ± 3.68	16.5 ± 3.0	1.00
9–13, *n* (%)		28 (8.97%)	16 (5.13%)	12 (3.85%)	
> 13, *n* (%)		284(91.03%)	164 (52.57%)	120(38.46%)	
INR	0.76–1.24	1.295 ± 0.300	1.03 (0.98, 1.07)	1.307 ± 0.257	0.490
0.76–1.24, *n* (%)		128 (41.03%)	80 (25.64%)	48 (15.38%)	
> 1.24, *n* (%)		184(58.97%)	100(32.05%)	84(26.92%)	
APTT (s)	25–31.3	41.244 ± 9.966	39.978 ± 10.053	43.161 ± 9.678	0.680
≤ 25, *n* (%)		136 (43.59%)	84 (26.92%)	52(16.67%)	
>25, *n* (%)		176(56.41%)	96 (30.77%)	80(25.64%)	
D-Dimer (mg/L)	0–500	1377.69 ± 622.01	1105 ± 475.29	1790.9 ± 594.78	0.036
0–500, *n* (%)		24(7.69%)	24 (7.69%)	0 (0.00%)	
> 500, *n* (%)		288(92.31%)	156 (50.00%)	132 (42.31%)	
Platelets (mg/L)	1.5-4.5l/mm^3	1.745 ± 0.67	1.840 ± 0.654	1.602 ± 0.671	0.002
1.5–4.5L, *n* (%)		176 (56.41%)	128 (41.03%)	48 (15.38%)	
<1.5L, *n* (%)		136 (43.59%)	52 (16.67%)	84 (26.92%)	

APTT activated partial thromboplastin time, *INR* international normalized ratio, *PT* prothrombin time,

Table:3 Multivariate logistic regression to identify risk factors at admission related to mortality:

Term	Odds Ratio	95%	C.I.	P-Value
AGE	1.0307	0.6362	1.6700	0.9022
Sex	1.2151	0.3944	3.7438	0.7343
Co morbidty	1.9730	1.1011	3.5353	0.0224
Raised APTT	1.1712	0.2228	6.1566	0.8519
Raised D Dimer	172603.8767	0.0000	>1.0E12	0.9685
Raised INR	1.2184	0.2211	6.7130	0.8205
Decreased Platelets	2.3963	0.7868	7.2983	0.1241
Raised PT	0.6311	0.0958	4.1560	0.6322

CI confidence interval, *OR* odds ratio.

IV. Discussion:

Coagulation dysfunction seems to be an important issue in patients with COVID-19. Recently, some researchers analyzed the clinical and laboratory findings of COVID-19 and found that severe patients often had prolonged PT, increased D-dimer levels, low fibrinogen, and DIC[8,1].

As one of the most important parameters, PT is widely used to assess coagulation function in the clinic.

Chen et al.[19] showed that the PT was not significantly different between severe cases and moderate cases with COVID-19. Han et al.[12] also reported that there was no significant difference in PT between patients

with different levels of severity of COVID-19 and healthy controls. Our study findings are consistent with the studies conducted by Han et al and Chen et al.

In addition, two studies on COVID-19 indicated that non-survivors had higher PT levels than survivors [3,14]. We also found that admission PT was significantly higher in non- survivors than in survivors, while the admission PT values of most patients were in the normal range (9 to 13 s) in the present study.

In the present study, we found that the INR values were significantly higher in non- survivors than in survivors; however, 42.3% of INR values at admission were within the normal range (0.76–1.24).

COVID−19 patients with D−dimer levels ≥ 2.0 μg /mL had a higher incidence of mortality than those with D−dimer levels < 2.0 μg /mL, and the authors argued that D−dimer could be an early and helpful marker to improve the management of COVID−19 patients[20]. A meta- analysis showed that approximately 37.2% of patients with COVID-19 had an elevated D-dimer level[21].

Our study showed that the levels of D- dimer in 92.30% of patients with COVID-19 were larger than the upper limit of normal (0.55 mg/L), and the non-survivors had significantly higher D-dimer levels than the survivors.

However, admission D-dimer > 0.55 mg/L was not an independent risk factor for mortality. Zhou et al.[3] reported that multivariable regression showed increasing odds of in- hospital death associated with D-dimer > 1 μg/mL on admission. Liu et al.[22] found that increased D-dimer levels at admission were closely related to death through multivariable logistic regression. Wu et al.[23] also reported that D-dimer was associated with progression from ARDS to death in bi- variate Cox regression analysis.

Of the patients affected by the 2003 SARS epidemic,20–55% had thrombocytopenia[24]. Subsequent rebound thrombocytosis was also reported[8,25]. The patients who developed thrombocytopenia during the epidemic experienced greater morbidity/mortality[26].

A meta-analysis of 7,613 COVID-19 patients revealed that patients with severe disease had a lower platelet count than those with non-severe disease. Additionally, the non-survivors had a much lower platelet count than the survivors[26,27]. These study findings were consistent with our study findings.

APTT prolongation was frequently seen in COVID-19, and the presence of lupus anticoagulant was identified at a high rate [17, 18]. It should be noted that APTT testing in patients with COVID-19 also provides information useful for screening for lupus anticoagulant as well as monitoring heparin. However our study did not include the search for lupus anticoagulant among the covid positive patients with prolonged APTT. There is scarcity of literature in comparing the APTT values and the outcomes in covid positive patients.

The abnormal pattern of coagulation parameters (higher PT, aPTT, INR, and D-dimer) observed in majority patients with comorbidities who died compared to non-survived patients without comorbidities

The overall rate of mortality in affected patients in this study was 42.03%. The high mortality rate among ICU-admitted patients from the present study was due increased age and a high rate of comorbidities. Two studies from Italy reported a difference in mortality rate; in one study the ICU and the hospital mortality rate of COVID-19 patients with a mean age of 61 years were 10% and 12.5%, respectively[30]. In a second study among patients with a mean age of 70 years the tracheal intubation rate was 8.5% and the overall mortality was 12.8%. All patients who died were on ventilation and had multiple comorbidities[31]. These findings were similar to our study.

V. Conclusion:

COVID-19 is often accompanied by abnormal coagulation. COVID -19 patients with low levels of PLT, high PT and INR that were associated with poor prognosis. The abnormal pattern of coagulation parameters was highly associated with comorbidities and mortality.

VI. Limitations:

This study has several limitations. This was a single-center study, and the results may not be generalized. However, it is the clinical study concerning the predictive value of presence of co morbidity with coagulation parameters at admission for mortality in patients with COVID-19. A multicenter study with a larger sample size is needed to verify our results. we only collected blood coagulation tests at admission , which may not accurately reflect the continuous dynamic changes of coagulation.

References:

[1]. Marietta M, Ageno W, Artoni A, De Candia E, Gresele P, Marchetti M, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. 2020 May;18(3): 167–9.

[2]. 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;395(10223):497–506.

[3]. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.

[4]. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20

[5]. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol. 2020 Jul;2(7):e437–45

[6]. Thachil J, Cushman M, Srivastava A. A Proposal for Staging COVID-19 Coagulopathy. Res Pract Thromb Haemost. 2020 Jul 6;4(5):731–6

[7]. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al.; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020 Aug;18(8):1859–65.

[8]. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020 Jun;127:104362.

[9]. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020 Jun;135(23):2033–40

[10]. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun;7(6):e438–40.

[11]. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JC, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020 Jul;136(4):489–500

[12]. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020 Jun;58(7):1116–20

[13]. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, et al. Hematological features of persons with COVID-19. Leukemia. 2020 Aug;34(8):2163–72

[14]. 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;18(4):844–7

[15]. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4

[16]. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between infammation and coagulation. Lancet Respir Med. 2020;8(6):e46–7

[17]. Wright DJM. Prevention of the cytokine storm in COVID19. Lancet Infect Dis. 2020. https://doi.org/10.1016/S1473 - 3099(20)30376-5.

[18]. . Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. Crit Care Med. 2020;48(9):1358–64

[19]. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q (2020) Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest 130(5):2620–2629. https://doi.org/10.1172/ JCI137244

[20]. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z (2020) D- dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 18(6):1324–1329. https://doi. org/10.1111/jth.14859

[21]. Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C (2020) Clinical characteristics of 3,062 COVID-19 patients: a meta-analy- sis. J Med Virol 92:1902–1914. https://doi.org/10.1002/jmv.25884

[22]. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, Ren H, Liu W, Wang Q, Wu Q (2020) D-dimer and prothrombin time are the significant indicators of severe COVID-19 and poor prognosis. Biomed Res Int 2020:6159720–6159710. https://doi.org/10.1155/ 2020/6159720

[23]. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y (2020) Risk factors associated with acute respiratory dis- tress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180(7):1–11. https://doi.org/10.1001/jamainternmed.2020.0994

[24]. Yang M, Ng MH, Li CK. Thrombocytopenia in patients with severe acute respiratory syndrome (review) [review]. Hematology. 2005 Apr; 10(2): 101–5.

[25]. Wong RS, Wu A, To KF, Lee N, Lam CW, Wong CK, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ. 2003 Jun; 326(7403): 1358–62.

[26]. Zou Z, Yang Y, Chen J, Xin S, Zhang W, Zhou X, et al. Prognostic factors for severe acute respiratory syndrome: a clinical analysis of 165 cases. Clin Infect Dis. 2004 Feb; 38(4):483–9.

[27]. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, et al. Hematological features of persons with COVID-19. Leukemia. 2020 Aug; 34(8): 2163–72.

[28]. Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with covid-19. J Thromb Haemost.2020;18(8):2064–5.

[29]. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al.Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med. 2020;383(3):288–90

[30]. Pavoni V, Gianesello L, Pazzi M , Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID- 19 pneumonia. J Thromb Thrombolysis. 2020 Aug;50(2):281-286 doi:10.1007/s11239-020-02130-7.

[31]. Annunziata A, Imitazione P, Polistina GE. Pulmonary embolism in Covid-19. coagulation parameters, close monitoring to prevent?Turk Thorac J. 2020;21:287-288. doi:10.5152/TurkThoracJ.2020.20067

Dr Mohammad A. Sameer, et. al. "Coagulation and Comorbidity: Determining the Outcomes in Covid Patients." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(07), 2021, pp. 09-13.