RESEARCH ARTICLE

Coagulation profile and D-dimer level in hospitalized COVID-19 patients: A cross-sectional study in a tertiary care hospital

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ABSTRACT

Background: Most of the patients of Coronavirus Disease-19 (COVID-19) presented with mild symptoms and recovered, but a considerable number of cases deteriorated and succumbed to death. They often present with hemostatic abnormalities mimicking disseminated intravascular coagulation with increased risk of thrombosis rather than bleeding. Hence, early prediction of disease severity by some easily available hematological parameters might be helpful to reduce mortality in COVID-19 cases. **Aim and Objectives:** The aim of the study was to determine whether values of Prothrombin Time (PT), International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT) and D-Dimer (DD) correlate with disease severity in COVID-19 and also to find out cutoff value of these parameters to predict disease severity. **Materials and Methods:** This observational cross-sectional study was done on total 400 hospitalized COVID-19 adult patients where patients were categorized into moderate and severe cases as per guideline of Government of India. Patients with pre-existing coagulation disorder or receiving anticoagulant drugs were excluded from the study. PT, INR, APTT, and DD values of these two groups were evaluated and compared statistically to determine their significance and the cutoff value to predict severity. **Results:** Among the measured blood parameters means of PT (P < 0.001), INR (P < 0.001) and DD (P < 0.001) found to be significantly higher in the severe group of patients compared to moderate ones and DD value ≥1.365 mg/L indicates severe disease. APTT showed no statistically significant association with severity. **Conclusion:** PT and INR can be used as severity marker in COVID-19 patients; however, DD is the most reliable marker correlating with disease severity.

KEY WORDS: Coronavirus Disease-19; D-Dimer; International Normalized Ratio

INTRODUCTION

Coronavirus Disease-19 (COVID-19) has emerged as a global health problem due to its pandemic nature since December 2019. Many countries including India have already experienced two waves of this pandemic. Though most of the patients presented with mild symptoms and recovered, a considerable number of cases deteriorated and succumbed to death both in first as well as in second wave. They developed severe pneumonia, acute respiratory distress syndrome, multi-organ failure, and death.¹ They present with hemostatic abnormalities mimicking disseminated intravascular coagulation (DIC) associated with sepsis, with the major difference being increased risk of thrombosis rather than bleeding. Hence, early prediction of disease severity by some cost effective routine hematological parameters might be helpful to reduce the mortality in COVID-19 cases.
Commonly used laboratory parameters for detecting coagulation abnormalities include Prothrombin Time (PT), International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), and D-dimer (DD). DD is the product of fibrinolytic solubilization of cross-linked fibrin, and the elevated level of DD indicates a hypercoagulable state with secondary fibrinolysis in the body, which can be seen in deep venous thrombosis, pulmonary embolism and DIC.[2][3] The previous studies during first wave mostly done in China and few other countries have already shown role of DD and PT as predictors of severity in COVID-19.[4] However, elevated DD level is also associated with disease activity correlating with C-reactive Protein (CRP) level rather than risk of thrombotic activity in inflammatory disease such as granulomatosis polyangiitis and inflammatory digestive diseases.[3][4][5][6] In COVID-19, role of CRP, Ferritin and LDH as inflammatory markers of disease severity has already been proved by different authors.[5][6]

In COVID-19 patients, dysregulated uncontrolled host immune response causes excessive production of many inflammatory mediators such as TNF-α, IL-6, and IL-8.[7] This results in a macrophage activation syndrome-like pictures triggering endothelial cells, macrophages, and neutrophils to express tissue factor within the lungs, which, in turn, initiates and augments pulmonary coagulopathy and microvascular thrombosis.[8] Articles on post-mortem series have shown widespread endothelial injury in COVID-19 patients.[9] This inflammatory endothelial cascade can directly cause microvascular dysfunction along with occlusion and able to induce hypercoagulable state, resulting in microvascular thrombosis. DIC was reported in 71.4% of fatal cases with a median time of development of DIC is 4 days from admission.[10][11]

Hence, early prediction of development of coagulopathy in COVID-19 patients can play a key role to improve the survival by prompt management. Accordingly, the current study has been carried out during second wave of COVID-19 in India with the aim to determine whether values of PT, INR, APTT, and DD correlates with disease severity in COVID-19 and also to find out cut-off value of these parameters to predict disease severity.

**MATERIALS AND METHODS**

This is a hospital-based cross-sectional study conducted with approval of Institutional Ethics Committee (Ref No.MC/KOL/IEC/NON-SPON/1078/05/2021 dated 18/05/2021) at the dedicated tertiary care COVID Hospital of Eastern India from 2nd week of June 2021 to 2nd week of July 2021. Patients of more than 18 years of age admitted at this COVID hospital (COVID ward/COVID ICU) with COVID-19 positive report (based on RT-PCR test) have been included but those having any hematological malignancy, existing coagulation or bleeding disorder or receiving chemotherapeutic or anticoagulant drug have been excluded from the study. Patients were categorized into moderate and severe disease based on the “Clinical Management Protocol For COVID-19 (in adults), version 6, dated 24.05.2021” by the Ministry of Health and Family Welfare, Govt. of India.[12] Adult patients with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90–94%) on room air, respiratory rate is more or equal to 24/min (24–30) were classified as moderate disease while patients with severe pneumonia having clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air or features of sepsis and septic shock were categorized as Severe disease.

Blood samples were collected on admission of the patients in trisodium citrate anticoagulant vial (citrate:blood, 1:9 ratio), centrifuged at 4000 rev/min for 15 min to produce platelet poor plasma and finally analyzed by Stago STA Compact Max fully automated coagulation analyzer at Pathology division of Central Laboratory. PT, INR, APTT, and DD of all the selected cases were recorded for further analysis.

**Statistical Analysis**

Results were tabulated and data were analyzed in Statistical packages for the Social Sciences software version 11. Unpaired t-test was done to determine significance of these coagulation parameters between moderate and severe disease while to determine the cut-off value for determination of severity of disease compared to moderate Receiver operating characteristic (ROC) curve was drawn.

**RESULTS**

Blood sample of 400 hospital admitted COVID19 patients was analyzed for the study. Among them 297 (74.2%) admitted patients were of moderate severity and 103 (25.8%) were suffering from severe form of disease. Patients were predominantly male (64.5%). Their mean age was 54.26 years with standard deviation of 16.23 years.

There is no significant correlation of age with severity ($P = 0.836$). Similarly there is no significant association of gender with the severity ($P = 0.124$).

Overall mean of PT, INR, and APTT was 16.55 s, 1.17, 44.69 s, respectively. Similarly overall mean of DD was 2.72 mg/L.

Unpaired t-test was conducted to find out difference of means of different blood parameters between severe and moderate group of disease. Among the measured blood parameters means of PT ($P < 0.001$), INR ($P < 0.001$), and DD ($P < 0.001$) found to be significantly higher in the severe
group of patients compared to moderate ones. Difference of APTT was found to be non-significant [Table 1].

To determine the cutoff value for determination of severity of disease compared to moderate form ROC curve was drawn [Figure 1]. Three variables, namely, PT, INR, and DD had more than 50% area under the curve denoting that they can be used to find out the cut-off value. Among these DD has 79.4%, INR has 78.7% area, and PT has 78.6% area under the curve making them important indices for use as cutoff value for severity determination [Figure 1].

Cutoff value of 14.85 s of PT can be used with 79.6% sensitivity and 64.3% specificity. It is interesting to note that the mean values of INR and PT of moderate and severe diseases vary significantly from the upper normal level of these two parameters (1.2 and 13 s, respectively). It can be concluded that for COVID-19 patients PT values increase for both groups but increased INR has more diagnostic value of severity as at the level of 1.2 it gives 85% specificity indicating that values below this are more likely to be from moderate patients. A value of DD at 1.365 mg/L or more gives 76.7% sensitivity and 70% specificity of diagnosis for severity. Conventionally, DD value of 1.00 mg/L is taken as a cutoff for severity. In the present study, it is found that though at this cutoff sensitivity increases a little (82.5%) but specificity falls below 60% (58.9%) giving rise to a considerable number of false positives [Table 2].

**DISCUSSION**

In the present study, on 400 COVID-19 patients, means of PT, INR, and DD were 15.19, 1.07, and 1.78, respectively, in moderate group of patients where as they were 20.47, 1.48, and 5.43, respectively, for severe group of patients. Thus, means of PT, INR, and DD were found to be significantly higher in the severe group of patients compared to moderate ones by unpaired t-test.

In COVID-19 cases, a higher DD level has been frequently encountered in critically ill patients compared to milder cases (mean level of 2.4 vs. 0.5 mg/L) and higher DD is inversely proportional with survival rate.[13-15] Zhou et al. showed that 81% of non-survivors have DD >1 mg/L compared to survivors where 24% of patients have DD >1 mg/L.[10] Similarly, Tang et al. showed that DD level of >3 mg/L in more than 85% of COVID-19 non survivors.[11] Zhang et al.[16] carried out a study on 343 COVID-19 cases where they found four fold increase of DD level is associated with significant mortality and they concluded that on admission >2.0 μg/mL (four-fold increase) of DD could effectively predict in-hospital mortality in patients with COVID-19. Guan et al.[13] analyzed 1099 patients with laboratory-confirmed COVID-19 from over 550 hospitals
in China and found the non-survivors had a significantly higher DD (median: 2.12 μg/ml) than that of survivors (median: 0.61 μg/ml). Our study findings are also in concordance with these previous study results where we found elevated level of DD has strong association with disease severity. However, the cutoff value to determine severity is slight different in our study where at the level of 1.365 mg/L, we found better sensitivity and specificity to determine severity. Regarding PT, most of the previous studies have reported mild prolongation of PT in severe disease.\cite{11,13} Study done by Martín-Rojas et al. showed statistically significant elevation of PT in non-survivors with median value of 14 s versus 12.7 s.\cite{17} Jin et al. also found similar results in their retrospective study on 147 COVID-19 patients of hospital in Wuhan, China where they concluded that parameters such as DD, PT, and INR are significantly higher in death group in comparison to survival group.\cite{18} In the current study, the authors found similar results with statistically significant prolongation of PT in severe cases with cut off value of 14.85 s. However, INR value at 1.2 has shown better specificity to categorize severe patients. In contradiction to these findings, Lin et al. concluded in their meta-analysis based review article that PT was higher in severe group compared to non-severe one but the difference was not statistically significant.\cite{19} Bashas et al. also revealed similar results where they concluded that though mean of PT values was higher in severe cases but that was not statistically significant in comparison to non-severe group.\cite{20} In this regard, Aggarwal et al. commented that this mild prolongation of PT may not be apparent if expressed as PT% or PT ratio rather than in seconds.\cite{21} Regarding APTT, most of the studies found no correlation with disease severity.\cite{21,22} Martín-Rojas et al. also found no significant difference of APTT in COVID-19 patients admitted in ICU versus admitted in normal ward.\cite{18} In this regard, authors of current study also found similar results where no statistically significant difference of APTT value was observed between severe and moderate category COVID-19 patients ($P = 0.728$). This mild prolongation of PT and insignificant change of APTT along with significant rise in DD in severe group supports the clinical scenario of thrombotic nature rather than bleeding tendency in severe COVID-19 group of patients.

The strength of the study lies in its attempt to validate very common coagulation parameters to be utilized as marker of severity in COVID-19 and also to set a cut-off value to define severity in population of Eastern India. However, there are a few limitations in the study. First, this is a cross sectional study where follow up of the patients could not be done and hence correlation of the study parameters with actual survival rate could not be calculated. Moreover, other important coagulation related parameters such as fibrinogen, thrombin time, thrombin-antithrombin complex, and thrombomodulin were not included in the study.

**CONCLUSION**

The authors conclude that APTT is not useful to predict severity while PT and INR can be used as severity marker with INR value ≥1.2 has 85% specificity to indicate severe disease. But DD is the most reliable marker among these coagulation related parameters that is associated with disease severity with value ≥1.365 mg/L indicates severe disease.

**REFERENCES**


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