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Coagulopathy biomarkers in mild to moderate CoVID-19 patients admitted in a tertiary care public hospital in eastern India

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Abstract: *Background:* The present study was undertaken to identify various prognostic biomarkers related to coagulation that may predict the outcome of mild to moderate CoVID-19 patients. *Objectives:* The biomarkers aPTT, PT, INR, D-Dimer, Procalcitonin, Ferritin were studied with their interdependence on each other and with their severity in the CoVID-19 patients. *Methods:* An analytical cross-sectional study was conducted at the department of Biochemistry, and Indoor medical wards of Medical College & Hospital, Kolkata from June 2020 to December 2020 among 120 adult consecutive consenting mild to moderate patients with documented history and diagnosis of CoVID-19. Statistical analysis was done to find association of these coagulation parameters and their significant correlation to prognosticate severity of CoVID-19. *Results:* Highest numbers of cases were from 51-60 years age group, followed by 21-30 and 31-40 years with almost equal gender distribution; unfavourable findings were more in males in all age groups except 31-40 years, not statistically significant. Activated partial thromboplastin time (aPTT), Prothrombin time (PT), Procalcitonin (PCT), D-dimer levels were significantly higher in mild and moderate CoVID-19 cases; gender-wise difference was significant only in PCT and D-dimer levels. Ferritin levels were higher, with no significant differences in age and gender. *Conclusions:* Procalcitonin and D-dimer were superior biomarkers to predict severity in COVID-19 patients. These observations need further evaluation with systems approach.
Keywords: aPTT, CoVID-19, D-Dimer, Ferritin, INR, Procalcitonin, PT.

Introduction

CoVID-19 is an unparalleled global public health problem and we need valid laboratory data to frame out foundation of Clinical Practice Guidelines from diagnosis, case management and to predict prognosis. Biomarkers of SARS-CoV-2 are being explored as integral part in emergency medical practice for the severity, evaluation, and outcomes [1]. Globally, 164,523,894 confirmed cases of COVID-19, including 3,412,032 deaths, reported to WHO affecting 219 countries and territories till middle of May 2021 [2].

It is important for the clinician to rapidly categorize the morbidities into different stages so as to carry out important investigations and interventions when required. Hence, as the most promising among all the non-invasive investigations, the role of blood biomarkers come into play here to halt this dreaded pandemic [3]. WHO provided riders regarding testing of clinical specimens from CoVID-19 patients in appropriately equipped laboratories by healthcare workers trained in the relevant technical and safety procedures [4].

Research groups have reported SARS-CoV-2 biomarkers viz. C-reactive protein, Serum amyloid A, Interleukin-6, Lactate dehydrogenase, D-dimer, Cardiac troponin, renal biomarkers etc. to derived markers viz. Neutrophil-to-lymphocyte ratio, Lymphocytes to platelet ratio etc. with different deflection from their normal [5]. Increased serum procalcitonin and ferritin levels were reported in patients with SARS COV-2 infection whereas dwindling time for coagulopathy parameters reported in several cases [6].

In the above scenario the present study was undertaken with the primary objective to assess blood biomarkers viz. aPTT, PT, INR, D-Dimer, Procalcitonin, Ferritin among mild and moderate CoVID-19 patients. The secondary objective was to identify interdependence of various laboratory test results with high index of suspicion of coagulopathy to predict the prognosis of mild and moderate CoVID-19 patients.

Material and Methods

It was an analytical cross-sectional non-interventional study conducted at the department of Biochemistry, and Indoor wards of Medical College & Hospital, Kolkata from June 2020 to December 2020 with the following selection criteria.

Inclusion criteria:

a) All consenting mild to moderate CoVID-19 adults with documented history & diagnosis
b) Adult mild to moderate CoVID-19 admitted cases in the tertiary care public hospital
c) Mild to moderate CoVID-19 cases without concurrent exacerbation of co-morbidities
d) Consenting competent mild to moderate CoVID-19 cases

Exclusion Criteria:

a) Children and adolescents below 19 years of age
b) Patients who did not provide written consent for participation in this study
c) Seriously ill and non-consenting, non-cooperating CoVID-19 patients
d) CoVID-19 cases undergoing treatment for other serious medical or surgical co-morbidity
e) CoVID-19 patients with known coagulopathy, bleeding disorder or hemoglobinipathies.

Primary Outcome Variable: To find significant coagulopathy among mild to moderate CoVID-19 cases admitted in a tertiary care public hospital.

Study Population: Consecutive 120 patients with documented history and diagnosis of mild to moderate CoVID-19 were recruited as participants in our study.

Data Collection Procedure: After approval from Institute research committee and Institute ethics committee, the study was initiated. Ethical principles were adhered to while gathering the information with strict confidentiality and Helsinki declaration was followed in letter and spirit. Data were collected by Principal and Co-Principal Investigators. The data have been strictly kept confidential with the investigators and will never be disclosed for the assessment, management, intervention or any other purposes.

Informed consent process was followed with best sincerity. Each patient was individually counseled regarding the objectives of the study and was ensured that the data will only be used for research purpose and will not hamper the course of treatment irrespective of their participation in the study or even if they leave the study for any reason after consent in the midway. Then written informed consent was obtained from each participant separately without any coercion.

This was followed by preparation and collection of samples from patients. Approximately 5 ml of blood sample was collected from the patients in single needle prick with universal precautions. The samples were aseptically stored in the primary containers which were transferred to secondary container at the central laboratory for further storage and analysis. All the collection procedures and tests were done under strict standard operative guidelines under direct supervision of the investigators.

To reduce risk of biohazards in this unprecedented second wave of CoVID-19 pandemic, all the additional precautions were strictly followed in the collection, transport, storage, biochemical testing, report writing and returning back report to the individual patient and their caregivers. ICMR and State government suggested highest form of precautions to prevent biohazards including use of protection mask, double gloves by the investigator, physical distancing, and all the sanitization measures of doning and doffing. Further, in our laboratory, there were dedicated infrastructure, instruments and

logistics for suspected/ confirmed SARS CoV-2 infected body fluid/ materials. All the logistics were sterile single use materials and will be disposed of using universal precaution and standard operative procedures on biomedical waste management.

Primary outcome variable: Biomarkers of coagulopathy in mild and moderate CoVID-19 cases.

Operational Definitions:

Activated partial thromboplastin time (aPTT): Involved recalcification of plasma in presence of standardized amount of Cephalins (Platelet substitute) and particulate activator (Silica);aPTT explores coagulation factors XII, XI, IX, VIII, X, V, II, I except platelets. Normal range 30-40 seconds [Critical values that should prompt a clinical alert: aPTT more than 70 seconds signifies spontaneous bleeding crisis in patients] [7-9].

Prothrombin time (PT): The reference range for PT is 11.0-12.5 seconds; 85%-100% (although the normal range depends on reagents used for PT) full anticoagulant therapy: >1.5-2 times control value; 20%-30% [9].

International Normalized Ratio (INR): INR = (Patient's PT/ Mean normal PT) ^{ISI}. The reference range (not on anticoagulation): 0.8-1.1 regardless of the ISI or particular performing laboratory; above 4.9-5.5 considered possible critical values to predict increase risk of bleeding at 20 seconds [9-10].

D-dimer: D-dimer produced in human body by the degradation of cross-linked (by factor XIII) fibrin showing ongoing activation of hemostatic system. Done by immunoturbidimetric assay, the reference concentration of D-dimer is < 250 ng/mL, or < 0.4 mcg/mL. Elevated D-dimer levels reflect ongoing activation of the hemostatic and thrombolytic system, providing clinical utility in: a) Evaluation of thrombus formation, b) Ruling out Deep Vein Thrombosis, c) Disseminated intravascular coagulation (DIC) [9].

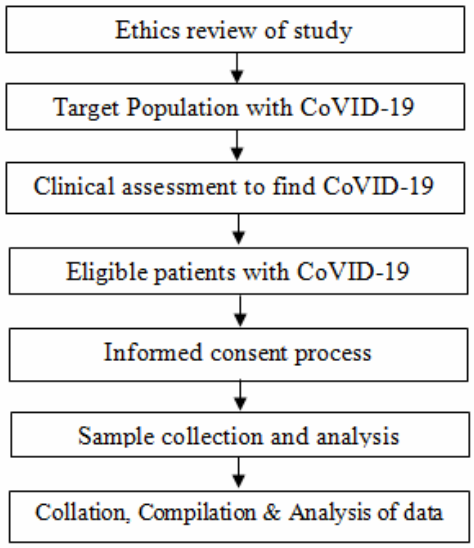
Procalcitonin (PCT): Procalcitonin (from endopeptidase-cleaved preprocalcitonin) is the peptide precursor of calcitonin, synthesized by thyroid parafollicular C-cells promotes calcium homeostasis. Reference value of PCT in adults and children older than 72 hours is 0.15 ng/mL or less (may be below the level of detection) [11].

Ferritin: Normal ferritin levels: 12-300 ng/mL of blood (males) and 12-150 ng/mL for females. Higher-than-normal levels of ferritin is indicative of an iron accumulation in the organs; prognotically leads to destruction and loss of normal function. Higher values reported in CoVID and other chronic inflammatory medical conditions [12].

Instrument Used: Fully automated Hemostasis Analyzer (STA Compact Max) with regular quality control following NABL guidelines.

Data Analysis: After data collection, data was tabulated in the 'Master table' followed by analysis by Statistical analysis was done using EpiInfo software. Z test and Chi-square test was used to find significant correlation between study variables with alpha level of five percent was considered significant in all analysis.

Flow diagram of the entire experimental process will be as follows:



Results

The predictability of the coagulation parameters regarding prognosis of CoVID-19 was explored among 120 adult consecutive consenting mild and moderate patients with documented history and diagnosis. Among the

age groups of patients in our case series, highest number of cases were reported from 51-60 years (Male 21, Female 12) age group, followed by 21-30 years (Male 20, Female 12), then 31-40 (Male 13, Female 14), while cases were almost equal in gender distribution (male 63, female 57). The unfavourable finding were more in males in all age groups except 31-40 years, yet this difference was not statistically significant [Table 1].

Table-1: Age and gender distribution of coagulation markers in patients diagnosed as mild and moderate CoVID-19

Age distribution of markers in mild and moderate CoVID-19 patients						
Age	**21-30 years (n=32)**	**31 - 40 years (n=27)**	**41 - 50 years (n=20)**	**51 - 60 years (n=33)**	**61 years and above (n=08)**	**Chi Square test (n=120)**
Male n= 67	20	13	10	21	03	3.4046 d.f. 4 p=0.4925
Female n= 53	12	14	10	12	05	
Activated partial thromboplastin time (aPTT) > 70 Seconds						
No	02	01	00	01	00	1.8312 d.f.: 4 p: 0.7668
Yes	30	26	20	32	08	
D-dimer ≥ 0.4 mcg/mL						
No	02	02	00	03	01	2.2105 d.f.: 4 p: 0.6971
Yes	30	25	20	30	07	
Ferritin > 300 ng/mL (male) and >150 ng/mL (female)						
No	11	08	11	08	04	6.3341 d.f.: 4 p: 0.1755
Yes	21	19	09	25	04	
Procalcitonin > 0.15 ng/mL						
No	07	07	04	05	01	1.429 d.f.: 4 p: 8391
Yes	25	20	16	28	07	
Prothrombin time (PT) ≤12.5 seconds						
No	28	26	17	29	06	3.2851 d.f.: 4 p: 0.5113
Yes	04	01	03	04	02	

Gender distribution of markers in mild and moderate CoVID-19 patients with unwelcome findings						
	aPTT	**D-dimer**	**Ferritin**	**Procalcitonin**	**PT**	**Remarks**
Male	66	63	40	53	62	Minority of both genders had favorable coagulation markers
Female	50	49	38	43	44	
Chi-square test corrected (Yates)	0.5640	0.0000	1.3818	0.0021	1.7599	
2-tailed p	0.4526	1.0000	0.2398	0.9633	0.1846	

Activated partial thromboplastin time (aPTT): In our study it was observed that aPTT levels were significantly higher in mild and moderate CoVID-19 cases. However, gender-wise this elevation was not significant [Table 2].

PT and INR: PT was significantly higher in our CoVID-19 cases; no gender difference noted. It was observed that though INR levels were prolonged in many, yet were below critical levels [Table 2].

D-dimer: D-dimer values were was significantly higher in our series of CoVID-19 cases. Further, the gender-wise positivity was highly significant [Table 2].

Procalcitonin (PCT): PCT was significantly higher in our series of CoVID-19 cases; significant diference was noted among gender-wise positivity [Table 2].

Ferritin: In our study higher levels of ferritin was reported among mild and moderate CoVID-19 cases, yet there was no significantly difference in age and gender [Table 2].

Table-2: Analysis of individual coagulation marker in mild and moderate CoVID-19 patients

Parameters	p Value	Statistically significance	CI at 95%
aPTT > 70 sec 4 out of 120	<.0001	Statistically significant, z= 10.3	0.0004 - 0.0605
INR >4.9 nil			
D - dimer <0.4 8 out of 120	<.0001	Statistically significant, z= 9.6	0.0175 - 0.1025
Procalcitonin <0.15 24 out of 120	<.0001	Statistically significant, z= 6.6	0.1284 - 0.2716
Ferritin >300 67 out of 120	0.1887	not significant z = 1.3	0.4712 - 0.6488
PT (11- 12.5 sec) 104 out of 120 are beyond the normal range	<.0001	Statistically significant, z= 7.9	0.7979 - 0.9221

Discussion

The search for critical care CoVID-19 biomarkers especially point-of-care test (POCT) is challenging because the symptoms and progression of disease varies from person to person in different parts of the world since WHO declared CoVID-19 pandemic on March 11, 2020 [1]. Structural mutations of spike glycoprotein in SARS-CoV-2 virus devastate human cells [13] and rapidly transmitted to exposed persons [14]. CoVID-19 cases present with variety of symptoms from asymptomatic carrier to affliction of almost all organ-systems of human body. The clinical features include fever, cough, myalgia, dry cough with or without sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and in very severe cases, acute respiratory distress syndrome [15].

CoVID-19 cases are categorized as per clinical severity into mild, moderate and severe. Mild cases present with uncomplicated upper respiratory tract infection with fever, cough, sore throat, nasal congestion, malaise, headache without breathlessness or hypoxia. Moderate cases are associated with dyspnea and/or hypoxia, fever, cough, including SpO2< 94% on room air; respiratory rate ≥ 24/ minute. Severe CoVID-19 is defined by significant respiratory distress; in adults tachypnea (30 breaths/ minute), oxygen saturation <93%, PaO2/FiO2 ratio < 300 mmHg, lung infiltrates > 50% within 24–48 hours, or clinical assessment of severe distress [16].

Risk of severe or fatal CoVID-19 is associated with three key categories of risk factors: patient characteristics, disease characteristics, and biomarkers; age is consistently associated as non-modifiable risk factor multispectral morbidities; elderly folks with or without co-morbidities had increased likelihood of severe form with higher admission rates, and longer stretch of hospital stay, increased risk of mortality and long term complications [17-19]. Several disease characteristics at presentation have additionally been identified as markers of progression from mild/moderate to severe disease; include fever, dyspnea, tachypnea, and chest tightness [20-21].

It has been postulated that laboratory investigations are central to early diagnosis and prompt treatment to interrupt the chain of transmission from primary health care level

onwards. To optimize the best possible outcomes of CoVID-19 cases, all the healthcare workers are working round the clock in spite of high risks to play the role of front-level worriers [22-23]. Clinicians in the whole world are unanimous regarding their role from primary level laboratory medicine to stop the unending flow of cases from SARS CoV-2 virus which has been mutated in different parts of the world [24-26]. It has been noted that critically ill CoVID-19 cases have high plasma levels of inflammatory biomarkers suggesting potential immune dysregulation [27]. Coagulopathy is an alarming signal in stage-1 with elevated D-dimer, in stage-2 with high D-dimer with mildly prolonged PT/INR and aPTT and mild thrombocytopenia, in stage-3 with critical progression towards classic disseminated intravascular coagulation (DIC) [28]. Several mechanisms including coagulopathy have been incriminated in higher fatality in CoVID-19 cases [29].

Activated partial thromboplastin time (aPTT): In our study it was observed that aPTT levels were was significantly higher in mild and moderate CoVID-19 cases which were also observed by other researchers [28]. Research group suggested that the markers of activated coagulation, impaired fibrinolysis and haemostasis viz. aPTT, prothrombin time, and D-Dimers should be monitored routinely to save capillaries of vital organs [30]; especially mildly prolonged aPTT with waveforms was noted in ICU admitted cases [31].

Prothrombin time (PT): PT was significantly higher in our CoVID-19 case series like others [28]; significantly prolonged prothrombin time were reported to be prognostically bad for capillary homeostasis [30, 32].

International normalized ratio (INR): In our study, however, it was observed that INR was prolonged, yet below critical levels similar to other reported studies [28]. Researches thus focused on changes in hemostasis laboratory values among CoVID-19 cases and severe cases are associated with thrombotic and bleeding events comparable to other hemorrhagic infections [33].

D-dimer: D-dimer values were was significantly higher in our series of CoVID-19 cases in line with other studies with elevated (3-4 fold) to predict thrombosis [28, 30, 32]; degree of elevation positively correlated with mortality in other studies [33], and the cut-off > 0.5 [34] or >1 μg/mL [35] has been proposed to stratify higher risk of worst outcomes. Others reported higher levels of D-dimers to be associated with poor outcome in adult hospitalized cases [30, 36-37].

D-Dimers quantify activated coagulation, a prominent feature in COVID-19 and emerged as strong predictors of death. Due to the central role of endotheliitis and venous thrombo-embolism in COVID-19, D-dimers serial measurements help treating physicians to select patients for further evaluations and interventions [38]; also earlier reported in pre-pandemics time related with thrombin formation, non-specific acute phase post-infection/ inflammation response, DIC associated with shock [39].

Procalcitonin (PCT): PCT was significantly higher in our series of CoVID-19 cases. Other research group reported that PCT levels may be normal on admission, yet became higher among ICU admitted cases [36]. In initial phases of CoVID-19 pandemic, the role of PCT as the sepsis biomarker was uncertain in interventions as it does not significantly increase in all cases. Later on it was comprehended that PCT assay can support clinical diagnosis to rule out superimposed bacterial infection as PCT synthesis is greatly upregulated in multiple tissues by bacterial endotoxin and decide on aggressive antimicrobial initiation or cessation. Yet, the severity of the viral infection can be incriminated for higher PCT levels (>0.5 or >1.0 ng/mL) up to 30% of CoVID-19 cases observed in Chinese research groups [40-41].

Indian research group from Mumbai noted a positive association with CoVID-19 severity with elevated PCT levels (upto 5-fold), suggesting associated bacteremia; additional biomarker for intervention by optimum antibiotic stewardship [42].

Ferritin: In our study significant hyperferritinemia was noted among mild and moderate CoVID-19 cases. Acute

hyperferritinemia mediates immune dysregulation via direct immune-suppression and pro-inflammation leading to the cytokine storm of CoVID-19 cases, especially noted among fatal severe diabetics [43]. Others also noted high serum ferritin levels associated with critical and life-threatening CoVID-19 illness with cytokine storm [30, 36, 44] with mortality. Zhou et al. reported higher serum ferritin level with severe and very severe COVID-19 cases, significantly elevated in very severe cases than severe CoVID-19 group [45]. Two Chinese studies reported sustained non-stop increased ferritin levels in severe and fatal CoVID-19 cases [46-47] while other research group proposed that cytokine storm syndrome may be evaluated by serum ferritin levels [48]. New Orleans autopsy reports showed high ferritin levels in SARS-CoV-2 infected patients [49].

Strengths of the study: We found suitability of coagulation biomarkers as the user-friendly and cost-effective tool for mild and moderate cases of CoVID-19 cases inpatients of our CoVID hospital. These data were compared with those of the previous published literatures on comparable researches to find where we stand among our peers working in the same field of research as well as disparity between present and past works.

Limitations of the study: We had several limitations. Firstly, this was a single centre study. Secondly, in the scary environment of CoVID-19 pandemic the patients did hardly participate leading to small sample. Lastly, in this self-funded study in the overburdened infrastructure poor setting, burnt-out manpower and logistics-crunch system, we could not initiate our study early to help imbibe our observation in the clinical practice guidelines earlier.

Future directions of the study: Unique observations found in the present work, would be attempted to be explained, whenever possible, implemented. Further robust multicentric randomized controlled studies are needed to guide optimum diagnostic and intervention algorithm for CoVID-19 patients and better elucidate the role that platelets play in CoVID-19 pathophysiology to reach at conclusions drawn carefully avoiding the biases and considering reliability and validity.

Conclusions

The research group concluded that lab medicine has huge role from the pre-pathogenesis through early phases in CoVID-19 case management with high index of suspicion for early evaluation and interventions. There is urgent need of incorporation of predictable laboratory coagulation profile parameters and suitable biomarkers of the clinical practice guidelines of CoVID-19 patients for best possible outcomes.

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