Original Research Article

D-Dimer: a primer biomarker in COVID-19

Abstract

Aim & Objective: To explore risk factors associated with mortality in COVID-19 patients and assess the use of D-dimer as a first line biomarker for disease severity and clinical outcome.

Materials & Methods: We retrospectively analysed the pathological and radiological characteristics of 2087 consecutive cases of COVID-19 in PSH, Vadodara, Gujarat, from March 2021 to July 2022. Graphically, MS-Excel with median values were used. Correlations of D-dimer upon admission with disease severity and in-hospital mortality were analysed accordingly. Data were collected in MS-Excel with median values.

Results: 2087 patients having positive RT-PCR and confirm diagnosis of Covid-19 were included upon hospital admission. Whereas, 65.78% (n= 1373) were male and 34.21% (n= 714) were female. Mean age was 52± 4 year. D-dimer level > 250 ng/mL at the time of hospital admission was the only fluctuating value accompanying with increased mortality [(95% CI), P = 0.025]. D-dimer elevation (≥250 ng/mL) was seen in 81.31% patients. Pericardial effusion and Deep vein thrombosis were ruled out in probability of thrombosis based on 2-D echo, X-ray chest and USG. This recommend that hyper-coagulopathy of the fibrin plays a significant role in the occurrence of thromboembolic complications with COVID-19 patients. D-dimer levels was crucially escalated with increasing severity of COVID-19 as determined by clinical improvement (within 5 days of hospital stay) and chest CT staging (CO-RADS score out of 25, $P = 0.000$). 319 patient were died during above said period and overall in-hospital mortality rate was 15.28%. Additionally, 6.08 % (n=127) patient were on BIPEP and all are died with 100% death ratio. Median D-dimer level in non-survivors (15.29%) was significantly higher than in survivors (84.71%, $n = 1768$, RR 24.69%). Median elevated D-dimer level was 600.5 ng/ml. Furthermore, the disease activity were higher in the overhead D-dimer level group demonstrated to have anticipating value in differentiating disease severity along with high ESR level and hs-CRP and the fibrinogen level was also upraised indicated seriousness of disease.

Conclusion: We concluded that D-dimer level was routinely uplifted in patients with COVID-19 disease. D-dimer levels match up with severity of the disease and are a significant definitive prognostic first line marker for in-hospital mortality for COVID-19 disease. Furthermore, a significant association between the high D-dimer level and severity of COVID-19 disease was noted among comorbid patients. Additionally, raced D-dimer level demonstrated with high ESR level and hs-CRP and the fibrinogen level indicated seriousness of disease in comorbid patients.

Keywords: Biomarker, COVID-19, Mortality, Pandemics and Severity.

INTRODUCTION

"Coronavirus disease-19 (COVID-19) is the life-threatening disease emergence in 2019-nCoV/SARS-CoV-2, a novel β coronavirus of group 2B. The affliction ranges from asymptomatic or mild infection to severe respiratory tract infections in humans such as those seen in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)".[1] "Demonstrations of COVID-19 encompasses (but not limited to) fever, coughing, dyspnoea, watery diarrhoea, myalgia, severe lymphopenia, prolonged coagulation profiles, cardiac disease, and in some cases lead to sudden death".[2] "Therefore the emergence in Wuhan, Hubei province of China in December 2019, COVID-19 has increased expeditiously in Wuhan as well other province in China and progressed worldwide. On January 30, 2020, WHO announced the outbreak as a Public Health Emergency. As of April 2022, approx. 50 Crore cases have been confirmed globally and approx. 60 Lacs deaths have been reported".[3]

"Based on WHO epidemiology report, globally, nearly 2.9 million new cases and over 11000 deaths were reported in the week of 2 to 8 January 2023. This represents a reduction in weekly cases and deaths of 9% and 12%, respectively. In the last 28 days (12 December 2022 to 8 January 2023), over 13.9 million cases and over 49000 new deaths were reported globally- an increase of 10% and 22% respectively, compared to the previous 28 days. The weekly epidemiological update on COVID-19 on **02-July-2023, over 767 million confirmed cases and over 6.9 million deaths have been reported globally"**.[4]

"The more worrying omicron sub variant and one to watch closely is XBB1.5, which has rapidly spread in the USA, where it comprised 40·5% of cases at the end of December, 2022, and had a doubling time of 1 week, according to the Centers for Disease Control and Prevention".[5] "The expansion in the value of D-dimer is the most companionate change in coagulation parameters in COVID-19 and preferably a greater risk for the evolution of thrombosis. Additionally, ago the D-dimer is well-known to be a mixture of fragments of different weight, and tests may report results in terms of weight for units of volume or as fibrinogen equivalent units (FEU). So, it may be not correct to compare results between different tests". [6] Additionally, in a retrospective cohort study conducted in 2 French centres[7]**,** "consecutive patients hospitalized in medical wards non-ICU with confirmed COVID-19 and adequate thromboprophylaxis were enrolled. D-dimers at baseline were crucially elevated in patients with deep venous thrombosis (DVT)". Furthermore, In another prospective study "of 165 consecutive patients hospitalized in non-intensive care units with diagnosis of COVID- 19 pneumonia and D-dimer >1000 ng/ml were screened for asymptomatic DVT with complete compression Doppler ultrasound and suggested D-dimer association as a marker of disease severity".[8]

Considering a respiratory disease the coagulopathy was disclosed and D-dimer elevations were seen in 3.75- 68.0% of the COVID-19 positive patients.[9] "Due to lack of studies in COVID-19 few previous studies in Community-Acquired Pneumonia (CAP) and Chronic Obstructive Pulmonary Disease (COPD) patients have shown that D-dimer level is higher in severe cases and can be used as a prognostic biomarker, and D-dimer > 1 μg/ml is one of the risk factors for mortality in adult inpatients with COVID-19 positive" [10].

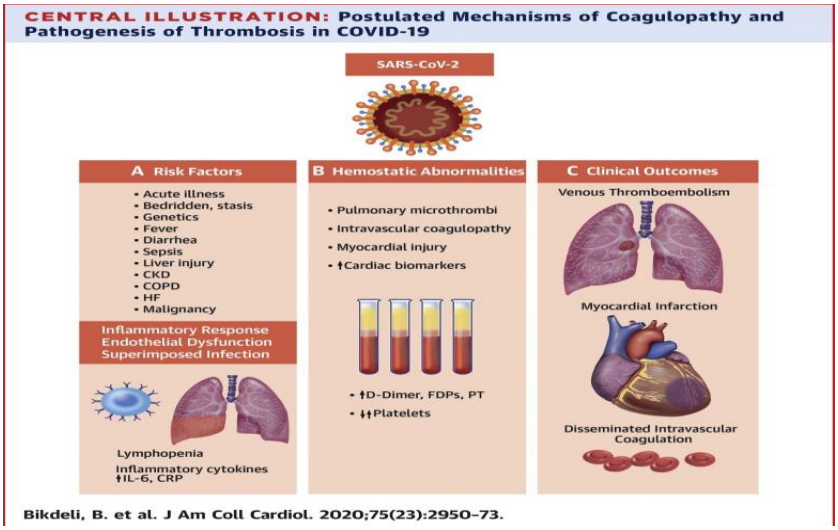

Figure 01: Postulated Mechanism of Coagulopathy and Pathogenesis of Thrombosis in COVID-19

"Clinical studies found correlations between the severity of COVID-19 and its unfavourable evolution and the degree of liver damage".[11-12] "Coagulation disorders and microthrombus formation are also responsible for some of the dermatological lesions in the COVID-19".[13-14] Another study of "critically ill patients with COVID-19 showed dermatological manifestations of hypercoagulability such as significant ischemia of the limbs with plantar plaques and acral cyanosis".[15]

However, the characteristic role of D-dimer in COVID-19 patients has not been fully investigated and confirmed. In this study, we showed D-dimer levels in patient groups stratified by clinical severities, imaging staging, in-hospital death, and assessed the role of D-dimer as a primary biomarker for disease severity and clinical out-come**.**

MATERIAL AND METHODS

An retrospectively study was carried out in **2087 patients** of Parul Sevashram hospital during the period from March 2021 to July 2022 after obtaining an approval from Institutional Ethics Committee. The data's were collected in the Patient Profile Form (PPF) for complete duration of therapy, the analysis made from the data was reported in predesigned forms which includes information such as patient demographic details (BP, all vitals, weight, medical & medication history, physical examination etc.) and required laboratory information were performed and documented.
Graphically, MS-Excel with median values were used to explore risk factors associated with in-hospital mortality. Correlations of D-dimer upon admission with disease severity and in-hospital mortality were analyzed. Excel curve was used to determine the optimal cut off level for D-dimer that discriminated those survivors versus non-survivors during hospitalization.

- Observation was carried out to find out the scope of the study in the Parul Sevashram hospital
- Relevant literatures were reviewed.
- Data collection form was designed.
- Data of the patients was recorded in Patient Profile Form and analysed for the role of D-Dimer (Study title given after confirmation)

❖ **Study Criteria**

- **Inclusion criteria**
  1. Age about ≥16 years
  2. Subjects having confirm diagnosis of Covid-19 along with comorbid condition.
  3. Patients without microangioma
  4. Absence of ocular disease.
- **Exclusion criteria**
  1. Pregnant, lactating women
  2. Mentally ill or other psychological subjects
  3. Subject who are on antineoplastic medication
  4. Other comorbid disease or condition which can interfere with study as per investigators discretion.
- **Biochemical estimations**

  Physical examination, all vitals, RBS, HbA1c, Hematology, D-dimer, CRP, Trop-I, Serum electrolyte, IL6 and lipid profile and echocardiography. Coagulation profile, renal and liver function, creatinine kinase, myocardial enzymes, C-reactive protein, and procalcitonin were collected routinely on admission.
- **Radiological estimation**

  HRCT and X-ray chest. Doppler ultrasound and CT pulmonary angiography were done for any patients with high clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/ DVT). Chest CT scan was done for all inpatients.
- **Statistical analysis**

  The data was represented graphically in MS-Excel with median values.

RESULT

A total of 2087 patients were randomly selected after having positive RTPCR result and confirm diagnosis of Covid-19 were included upon hospital admission, out of them 65.78% (n= 1373/2087) were male and 34.21% (n= 714) were female. Median age was 52± 4 years. D-dimer > 250 ng/mL at admission was the only fluctuating value accompanying with increased mortality [(95% CI), P = 0.025].

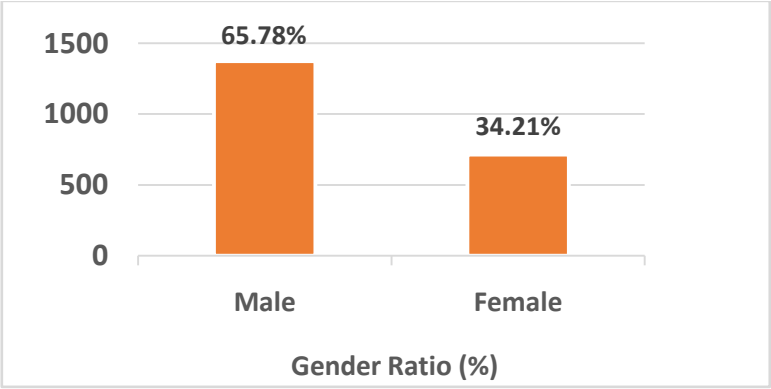

Figure 02: Gender Ratio Presentation

D-dimer elevation (≥250 ng/mL) was seen in 81.31% (n= 1697/2087) of the patients. Pulmonary embolism and deep vein thrombosis were ruled out in patients with higher probability of thrombosis

based on 2-D echo, X-ray chest and USG. This recommend that hyper-coagulopathy of the fibrin plays a significant role in the occurrence of thromboembolic complications with COVID-19 patients.

D-dimer levels was crucially escalated with increasing severity of COVID-19 as determined by clinical improvement (within 5 days of hospital stay) and chest CT staging (CO-RADS score out of 25, P = 0.000). 319 patient were died during above said period and overall in-hospital mortality rate was 15.28%. Additionally, 6.08 % (n=127) patient were on BIPEP and all are died with 100% death ratio. Median D-dimer level in non-survivors (15.29%) was significantly higher than in survivors (84.71%, n = 1768, RR 24.69%). Median Spo2 level was 96%

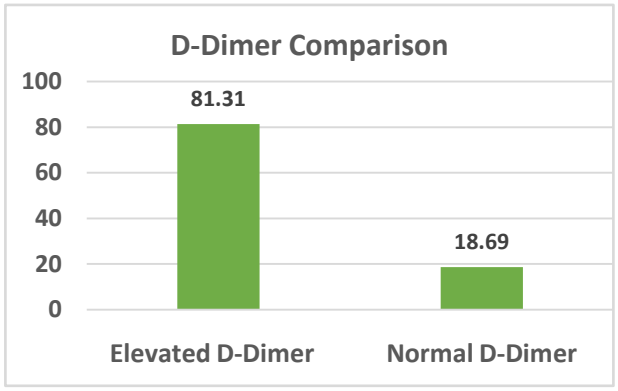

Figure 03: Comparison of D-Dimer

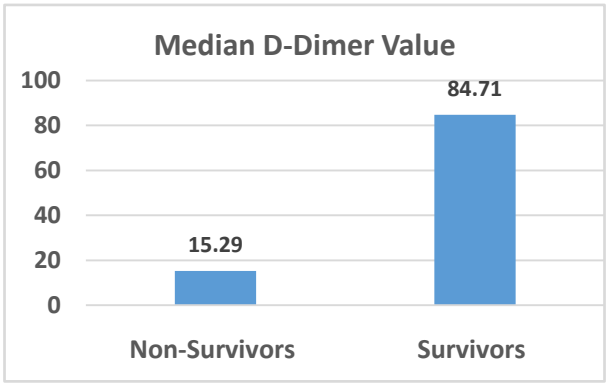

Figure 04: Survivor Vs Non- Survivors

Median elevated D-dimer level was 600.5 ng/ml. Furthermore, the disease activity were higher in the overhead D-dimer level group demonstrated to have anticipating value in differentiating disease severity along with high ESR level and hs-CRP and the fibrinogen level was also upraised indicated seriousness of disease.

DISCUSSION

The interconnection between D-Dimer and COVID-19 was elucidated in different published literatures and it was commonly observed that D-dimer level is one of the measures used in patients to detect thrombosis. **Elkhalifa AM**[16] concluded that "the D-dimer mean values climb up remarkably in COVID-19 and in hospitalized intensive care unit wards patients, indicating a potential predictive and prognostic severity marker, particularly among COVID-19 patients in the ICU". **Rostami M et al.** [17] reported "an increase in D-dimer and fibrinogen concentrations in the early stages of COVID-19 disease with a 3 to 4-fold rise in D-dimer levels is linked to poor prognosis". "D-dimer is the negligible bifurcated product of fibrin humiliation, demonstrating unique aspect and same can be usable tool to quantify the activation state infective aetiology".[18] Similarly, **Yao Y et al.**[10] also concluded that "D-dimer is commonly elevated in patients with COVID-19. D-dimer levels correlate with disease severity and are a reliable prognostic marker". Furthermore, few investigators, **I Martinelli et al., J S Barger et al** [19-20] have also concluded that "the upregulated levels of D-dimer in individuals with severe novel coronavirus infection might be associated with severe illness, higher rates of thrombotic activity, and higher mortality rates of such patients and in hospital mortality".

Bilian Y et al[21] who delineate "a significant correlation of the levels of D-dimer with the levels of hsCRP, a marker of inflammation, in COVID-19 patients". In another study, **Chen N et al**[22] concluded that how the levels of D-dimer could imaginably be used as a marker to predict the in hospital mortality

rate of COVID-19 patients. Based on their research & results, they were able to establish a cut-off D-dimer value of more than 2.14 mg/L to predict the outcome of COVID-19 patients at the time of admission to the hospital which was very similar to our study.

As stated above, the levels of D-dimer straight correlate with COVID-19. It is perceptible by the findings of several previous studies that showed that levels of D-dimer were crucially higher in COVID-19 patients, especially those who were either severely ill or had deceased.

CONCLUSION

Our study concluded that D-dimer level was routinely uplifted in patients with COVID-19 disease. D-dimer levels match up with severity of the disease and are a significant definitive prognostic first line marker for in-hospital mortality for COVID-19 disease. Furthermore, a significant association between the high D-dimer level and severity of COVID-19 disease was noted among comorbid patients. Additionally, raced D-dimer level demonstrated with high ESR level and hs-CRP and the fibrinogen level indicated seriousness of disease in comorbid patients.

LIMITATION

The only limitation of this study was a single centre study Indeed it needs multicentre study to evaluate the same. Our study used comorbid subject along with Covid-19 Infected patients that was probably interfere with D-dimer level reveals long standing inflammatory status, comorbid disease condition and other medical conditions in the human body which might interfere with the study result.

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ABBREVIATION

BIPEP	Bi-Level Positive Airway Pressure
CI	Confidence Interval
CO-RADS	COVID-19 Reporting and Data System
COVID-19	Corona Virus Disease-19
CRP	C-Reactive Protein
CT	Computerized Tomography
DVT	Deep Venous Thrombosis
ESR	Erythrocyte Sedimentation Rate
FEU	Fibrinogen Equivalent Units
HbA1c	Haemoglobin A1c
HRCT	High Resolution Chest Tomography
ICU	Intensive Care Unit
MERS	Middle East Respiratory Syndrome
nCOV	Novel Corona Virus
PPF	Patient Profile Form
RBS	Random Blood Sugar
RTPCR	Real-Time Reverse Transcription – Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome

VTE	Venous Thromboembolism
WHO	Word Health Organization

DECLARATIONS

Conflict of Interest: No conflict

Financial support & Sponsorship: No (Self-Funded)

Ethical approval: Yes (Institutional Ethics Committee)

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

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