*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*
*e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 10 Ser. 10 (October. 2024), PP 79-85*
*www.iosrjournals.org*

# D-dimer as a Biomarker for Disease Severity and Mortality in COVID-19 Positive Pregnant Women

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***Abstract***
***Background:** The COVID-19 pandemic presents unique challenges in managing pregnant women, especially in predicting disease severity and adverse clinical outcomes. D-dimer, a fibrin degradation product, is a well-known biomarker for thrombosis and disseminated intravascular coagulation (DIC). Its significance in assessing the severity of COVID-19 infection in pregnant women is critical. This study aimed to evaluate the role of D-dimer as a biomarker for disease severity and morbidity in third-trimester COVID-19 positive pregnant women.*
***Methods:** A prospective observational study was conducted from March 2019 to February 2020 at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, involving 62 third-trimester pregnant women diagnosed with COVID-19. Plasma D-dimer levels were measured on Days 1, 7, and 14. Clinical outcomes were recorded, and statistical analysis was performed using SPSS v22.0, with a significance level of $p < 0.05$.*
***Results:** Severe to critical illness developed in 45.2% of the participants. A significant association was found between elevated D-dimer levels (≥1.5 mg/L) and severe COVID-19 illness ($p < 0.05$), with respondents having D-dimer levels ≥1.5 mg/L being 2.048 times more likely to develop severe illness. The sensitivity, specificity, and accuracy of D-dimer in predicting severe COVID-19 illness were 64.29%, 67.55%, and 66.13%, respectively. Common adverse outcomes included ICU admission, preterm delivery, and complications such as preeclampsia and venous thrombosis.*
***Conclusion:** Elevated D-dimer levels are strongly associated with severe disease in COVID-19 positive third-trimester pregnant women and may be utilized as a predictive biomarker for morbidity and mortality.*
***Keywords:** COVID-19, D-dimer, pregnant women, disease severity, biomarker, morbidity.*

Date of Submission: 16-10-2024 Date of Acceptance: 26-10-2024

## I. Introduction

Pregnant women represent a potentially high-risk population in the COVID-19 pandemic. The most recent data from the Centers for Disease Control and Prevention (CDC) showed the pregnant women with COVID-19 are more likely to be hospitalized, admitted to the intensive care unit, and intubated.[1] The overall risk of COVID-19 infection to pregnant women is similar to nonpregnant women. However, pregnancy increases the risk for severe illness with COVID-19. Pregnant women who have COVID-19 appear more likely to develop respiratory complications requiring intensive care than women who aren't pregnant. Pneumonia arising from disease is an important cause of morbidity and mortality. Coagulopathy & oxidative stress are mainstay of COVID-19 pathogenesis. Pregnancy itself also a hypercoagulable state. Therefore, COVID-19 in pregnancy can accelerate the several adverse event like toxaemia in pregnancy, hypertensive disorder or HELLP syndrome.

However, women who are pregnant or were recently pregnant are at increased risk of severe illness with COVID-19. Severe illness means that you might need to be hospitalized, have intensive care or be placed on a ventilator to help with breathing. Pregnant women with COVID-19 are also more likely to deliver a baby before the start of the 37th week of pregnancy (premature birth). Pregnant women with COVID-19 might also be at increased risk of problems such as stillbirth and pregnancy loss.[2] This SARS-CoV-2 virus can spread from an infected person's mouth or nose in respiratory droplet particles when they cough, sneeze, speak, sing or breathe heavily.

Therefore, the associated hyper-inflammation and coagulopathy is in turn associated with a wide derangement in various hemostasis parameters, including serum D-dimer, prothrombin time (PT), and thrombocytopenia, with these also serving as potential prognostic markers of severe disease and/or mortality in COVID-19.[3] Examples include deep vein thrombosis/ pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, and conditions such as pregnancy, inflammation, cancer, chronic liver diseases, post-trauma and surgery status, vasculitis.[4] Hyper-inflammation and hypoxia-induced injury caused by SARS-CoV-2 infection could cause the dysfunction of endothelial cells and stimulate thrombosis and elevation of serum D-dimer.[5] This elevated serum D-dimer could reflect excessive inflammation, platelet activation, endothelial dysfunction, and stasis, which play a significant role in developing thrombotic complications often associated with poor prognosis. Previous studies demonstrated that serum D-dimer was associated with the severity of COVID-19.[4,6,7] Several other studies have shown that serum D-dimer level is higher in severe cases and may be used as a prognostic biomarker for COVID-19 mortality.[5,8,9]It has been reported that about 50% of the patients had increased serum D-dimer levels, and abnormal serum D-dimer levels are associated with poor prognosis.[10] Serum D-dimer >2.5ug/ml is one of the risk factors for critical illness in hospitalized adult inpatients with COVID–19.[11,12] According to American Society of Hematology, elevated serum D-dimer at admission and markedly increasing serum Ddimer levels (3- to 4-fold) over time are associated with high mortality, likely reflecting coagulation activation from sepsis, cytokine storm and impending organ failure.[13] In-hospital mortality among patients with COVID-19 was high early in the pandemic and was reported to range from 12% to 28%.[14] As infection-induced coagulopathy and secondary hyper-fibrinolysis have been perceived in COVID-19 patients[15], the sequential estimation of serum Ddimer level at admission and then subsequently on the third and seventh day might help to assess the prognosis of the disease in hospitalized patients.

## II. Objectives

This study was aims to evaluate the role of D-dimer as a biomarker for disease severity and morbidity in third-trimester COVID-19 positive pregnant women.

## III. Methodology & Materials

This prospective observational analytical study was conducted in the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from March 2019 to February 2020. Estimation of plasma serum D-dimer was done in the Department of Hematology of BSMMU. Total 62 COVID-19 positive pregnant women was selected purposively upon obtaining their informed written consent.

**Selection criteria:**

**Inclusion criteria**

• Pregnant women in their third trimester of pregnancy admitted with moderate to severe symptoms of COVID-19 (respiratory tract or blood specimen positive for SARS-CoV-2 by RTPCR assay).

• Patients with percent saturation of oxygen in the blood ≤92% in room air and fulfilling other hospital admission criteria

• Patients those was agreed to give informed consent to take part in this study

**Exclusion criteria:**

• Patients requiring immediate ICU/CCU at hospital admission (critically ill patients at admission)
• Patients on previous oral anticoagulants or intravenous heparin
• Diagnosed case of chronic liver disease, peripheral vascular disease, cancer, hematologic malignancy, thyroid disorder, autoimmune diseases
• History of recent surgery or trauma

**Data collection**

Data collection involved a structured, semi-structured questionnaire, which was used to obtain socio-demographic information, clinical history, and laboratory results from each participant. The clinical history included details of comorbidities such as gestational diabetes mellitus (GDM), chronic obstructive pulmonary disease (COPD), asthma, and hypothyroidism, along with a record of any previous COVID-19 vaccinations. Obstetric history, including parity and gestational age, was also noted.

Participants' serum D-dimer levels were measured on Day 1, Day 7, and Day 14 of admission. Blood samples were collected from the ante-cubital vein under aseptic conditions, and 5 ml of venous blood was drawn for each test. The samples were analyzed at the Department of Hematology, BSMMU, using the CTM D-dimer Latex Kit, which is widely used for detecting D-dimer levels. The normal reference range for serum D-dimer was considered to be <250 ng/mL, or <0.4 mcg/mL. A serum D-dimer level of 1.5 mg/L was selected as the threshold for further analysis based on its known association with severe outcomes in COVID-19 patients.

In addition to D-dimer levels, other laboratory investigations such as C-reactive protein (CRP) levels, complete blood count (CBC), and lymphocyte counts were conducted. Pulse oximetry was used to monitor the oxygen saturation levels of all participants, and the need for supplemental oxygen, high-flow nasal oxygen (HFNO), or admission to the intensive care unit (ICU) was recorded.

**Ethical consideration:**

All participants provided informed written consent before enrollment in the study. Patients were informed about the nature of the study, its objectives, and any potential risks or benefits. Confidentiality was strictly maintained, and participants were assured of their right to withdraw from the study at any time without any consequence to their medical care. The study did not involve the administration of any experimental drugs or treatments. The collection of blood samples adhered to standard medical procedures to minimize discomfort and risk to the participants.

**Statistical analysis of data:**

The data were analyzed using SPSS statistical software, version 27.0. Descriptive statistics were generated for socio-demographic and clinical characteristics, and results were expressed as frequencies, percentages, means, and standard deviations. Continuous variables were compared between the two groups using an unpaired t-test, while categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the association between elevated serum D-dimer levels (≥1.5 mg/L) and severe COVID-19 illness. A p-value of <0.05 was considered statistically significant for all analyses.

## IV. Results

**Table-1: Distribution of the respondents according to their socio-demographic and obstetrics characteristics (n = 112)**

| Parameters | | Number of patients | Percentage(%) |
|---|---|---|---|
| Age (Years) | 18-30 | 44 | 71.0 |
| | 30-40 | 15 | 24.2 |
| | >40 | 3 | 4.8 |
| Occupation | Housewife | 45 | 72.6 |
| | Job Holder | 17 | 27.3 |
| Residence | Urban | 40 | 64.5 |
| | Rural | 22 | 35.5 |
| Education | Illiterate | 3 | 4.8 |
| | Primary | 7 | 11.2 |
| | Secondary | 13 | 21.0 |

| | | | |
|---|---|---|---|
| | Higher-secondary | 31 | 50.0 |
| | Graduate/Post-graduate | 8 | 13.0 |

Table-1 shows the distribution of the respondents according to their sociodemographic characteristics, where majorities (71%) were within the 18 to 30 years of age group. Majority of the patients are housewife (72.6%). Above three-fifths (64.5%) were urban dwellers and 50% of the patient's educational qualification was higher secondary.

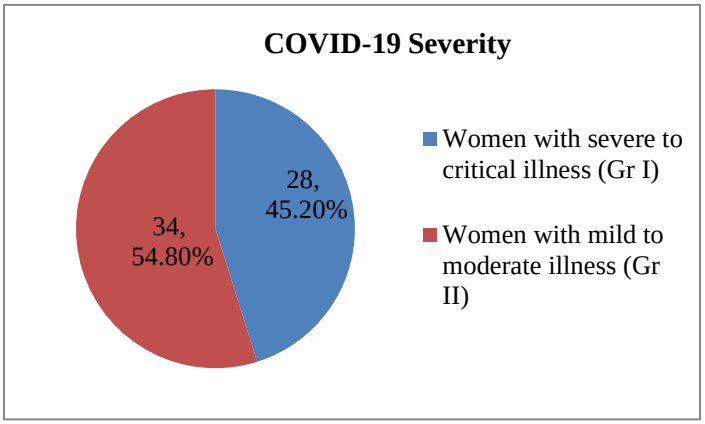


**Figure 2: Distribution of the respondents according to the severity of COVID-19 infection (n=62)**

Figure 2 shows, severe to critical illness developed in 45.2% of the respondents. Whereas 54.8% of the hospitalized pregnant women with COVID-19 infection had mild to moderate illness.

**Table-2: Distribution of the respondents according to their obstetric parameters by severity group (n = 62)**

| Obstetric parameters | | Group 1 (n=28) | Group 2 (n=34) | P value |
|---|---|---|---|---|
| Gestational age (weeks) | | | | 0.123[a] |
| Mean ± SD | | 33.68 ± 3.04 | 34.91 ± 3.13 | |
| Parity | Nulliparous | 8 (28.6%) | 8 (23.5%) | 0.652[b] |
| | Parous | 20 (71.4%) | 26 (76.5%) | |
| BMI (kg/m$^2$) | | | | 0.056[a] |
| Mean ± SD | | 29.86 ± 3.27 | 28.36 ± 2.81 | |
| Delivery time | <37 weeks | 5(17.9%) | 2 (5.9%) | 0.652[c] |
| | ≥37 weeks | 23(82.1%) | 32 (94.1%) | |

a = unpaired t-test, b = chi-square test, c = fisher's exact test

Table.2 states, there was no significant association found between obstetric parameters and severity of the disease (COVID-19) ($p>0.05$).

**Table-3: Distribution of the respondents according to their comorbidities by severity group (n = 62)**

| Comorbidities | | Group 1 (n=28) | Group2 (n=34) | P Value |
|---|---|---|---|---|
| GDM | Present | 6(21.4%) | 2(5.9%) | 0.125c |
| | Absent | 22(78.6%) | 32(94.1%) | |
| COPD/Br.Asthma | Present | 1(3.6%) | 0 | 0.452c |
| | Absent | 27(96.4%) | 34(100%) | |
| Hypothyrodism | Present | 1(3.6%) | 2(5.9%) | 1.000c |
| | Absent | 27(96.4%) | 32(94.1%) | |

[c] = fisher's exact test

In table 3 no significant association was found between comorbidities of respondents and severity of the disease (COVID-19) ($p>0.05$).

**Table -4: Association of the risk of severe to critical COVID-19 illness according to predicted level by maternal serum CRP (n = 62)**

| S. CRP level (mg/g) | Group 1 (n=28) | Group 2 (n=34) | P value | RR 95%CI |
|---|---|---|---|---|
| ≥47 | 15 (53.6%) | 10(29.4%) | 0.054[b] | 1.708 (0.993-2.937) |
| <47 | 13 (46.4%) | 24(70.6%) | | |

b = chi-square test
CI = Confidence Interval

Table -4 says, no significant association was found between the risk of severe to critical COVID-19 illness and maternal serum CRP ($p\geq0.05$).

**Table-5: Association of the risk of severe to critical COVID-19 illness according to predicted level by maternal serum D-dimer (n = 62)**

| S. D-dimer level (mg/l) | Group 1 (n=28) | Group 2 (n=34) | P value | RR (95%CI) |
|---|---|---|---|---|
| ≥1.5 | 18(64.3%) | 11(32.4%) | 0.012[b] | 2.048(1.135-3.697) |
| <1.5 | 10(35.7%) | 23(67.6%) | | |

b = chi-square test
CI = Confidence Interval

A significant association was observed between the risk of severe to critical COVID19 illness and maternal serum D-dimer level where more than half of respondents having D-dimer level ≥1.5 mg/l were in higher to critical group and only 32.4% were in mild to moderate group ($p<0.05$). Respondents having D-dimer level ≥1.5 mg/l had 2.048 times more risk of severe to critical COVID-19 illness.

## V. Discussion

This study was aimes to determine the association of serum D-dimer level with disease severity and mortality in hospitalized COVID-19 positive pregnant women. A total of 62 pregnant women with COVID-19 infection in their third trimester of pregnancy fulfilling the selection criteria were enrolled for the study. The severity of COVID-19 was assessed through the severity index score. Pregnant women, who subsequently developed severe to critical illness was categorized into Group I, and who developed mild to moderate illness were enlisted into Group II.

Pregnancy is a hypercoagulable state that predisposes women to thrombotic complications, which may be exacerbated by COVID-19. This study observed a strong association between elevated D-dimer levels and adverse maternal outcomes, including ICU admission, preterm delivery, and venous sinus thrombosis. These findings are consistent with existing literature that highlights the elevated risk of thrombosis in COVID-19 patients, particularly among pregnant women. Previous research reported that elevated D-dimer levels reflect an ongoing coagulation process and are associated with a poor prognosis in COVID-19 patients.[5] Another research demonstrated that increased D-dimer levels in pregnant women are linked to adverse pregnancy outcomes, including preterm delivery, similar to the present study's findings.[7]

Majority of the respondents (71.0%) were within the 18 to 30 years of age group, above three-fifths (64.5%) were urban dwellers, half (50.0%) of the patient's level of education was higher secondary and above, 72.6% were housewives and majorities (96.8%) belonged from the middle-class families. Nearly three-quarters (74.2%) of the participants were multigravida, while only 25.8% COVID-19 infected hospitalized pregnant women were primigravida. In this study, severe to critical illness developed in 45.2% of the respondents, whereas 54.8% of the hospitalized pregnant women with COVID-19 infection had mild to moderate illness. The high rate of severe cases in the study population may be attributed to the hypercoagulable nature of pregnancy, which exacerbates the inflammatory and thrombotic effects of COVID-19. A similar study revealed 2.7% to 6.9% incidence rate of severe infection requiring ICU admission with no maternal deaths.[16] Another study reported, women presenting in the third trimester with fever (68%) and coughing (34%) and 91% of the women were delivered by cesarean section. Three maternal intensive care unit admissions were noted but no maternal

deaths. One neonatal death and one intrauterine death were also reported which did not support the findings of present study and this dissimilarity might be due to geographical variation and individual immunity response.[17] Additionally, the study explored the role of comorbidities such as gestational diabetes mellitus (GDM), chronic obstructive pulmonary disease (COPD), and hypothyroidism. Although the presence of GDM was more frequent in the severe group (21.4% vs. 5.9%), no statistically significant association was found between these comorbidities and disease severity ($p>0.05$). These findings contrast with reports which suggested that pre-existing comorbidities significantly impact the severity of COVID-19 in the general population.[12] The lack of association in this study may be due to the relatively small sample size or differences in the population characteristics. Larger, multicenter studies are needed to clarify the role of comorbidities in COVID-19 severity among pregnant women.

This study shows no significant association between maternal serum CRP levels and severe COVID-19 illness ($p=0.054$), suggesting that CRP may not be a strong predictor of severity in pregnant women. This contrasts with studies which identified CRP as a key marker of severe disease.[18] Pregnancy's unique inflammatory response may affect the utility of CRP as a biomarker in this population. A significant association between elevated D-dimer levels (≥1.5 mg/L) and severe illness ($p=0.012$) was demonstrated at table 5. Pregnant women with high D-dimer levels had a two-fold increased risk of severe disease,which link elevated D-dimer to poor COVID-19 outcomes.[5,7] Monitoring D-dimer in pregnant women can help identify those at higher risk and guide early interventions.

## VI. Conclusion

The study found that elevated serum D-dimer levels were significantly associated with severe to critical illness in COVID-19 positive third-trimester pregnant women. Patients with higher serum D-dimer levels faced greater risks of adverse outcomes, including ICU admission, preterm delivery, and maternal complications like preeclampsia. The findings suggest that maternal serum D-dimer can serve as a predictive biomarker for assessing disease severity and guiding clinical management in hospitalized COVID-19 positive pregnant women.

## VII. Limitations of the study

This study was conducted in a single tertiary hospital, which may limit the generalizability of the findings. Additionally, the sample size was relatively small, and only third-trimester pregnant women were included, restricting the applicability of the results to earlier stages of pregnancy. Moreover, the study did not account for long-term maternal or neonatal outcomes.

## VIII. Recommendations

Based on the results, routine measurement of serum D-dimer levels in COVID-19 positive pregnant women could be useful for early detection of disease severity and timely intervention. Further multicentric studies with larger populations are recommended to validate these findings and expand the understanding of D-dimer's role in predicting COVID-19 severity across all trimesters.

**Financial support and sponsorship**
No funding sources.

**Conflicts of interest**
There are no conflicts of interest.

**Ethical approval**
The study was approved by the Institutional Ethics Committee.

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