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Original Research Article

Comparative Study of the Relation of D-Dimer Levels of COVID-19 Patients with Diabetes Mellitus

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Abstract:

Background: The coronavirus belongs to the Coronaviridae family and is characterized by enveloped, positive-sense, single-stranded RNA structure. COVID-19 has been shown to exhibit greater disease severity in individuals with diabetes. In healthy individuals, circulating D-dimer levels remain low. Conversely, conditions marked by hypercoagulation and heightened fibrinolytic activity often result in elevated D-dimer levels. This study seeks to investigate and compare D-dimer levels among COVID-19 patients with diabetes and those without diabetes.

Methods: This current research is designed as a prospective cohort study with a predetermined sample size of 60 participants. COVID-19 diagnosis was confirmed through either RT-PCR (Real Time Reverse Transcription Polymerase Chain Reaction) or RAT (Rapid Antigen Test). Participants with a prior medical history of diabetes and HbA1c levels exceeding 6.5 were included in the study. To assess variations among various groups, statistical comparisons were carried out employing the ANOVA test, and further examination of significant differences between pairs of means was conducted using Scheffe's test.

Results: One-third of cases (33.3%) were from the 55-64 years' age group, followed by 45-54 (23.3%), and the least (3.3%) cases were from the 75-84 years' age group. Random Blood Sugar (RBS) and mean D-dimer levels were 248.9±139.83 mg/dl and 878.62±860.74, respectively. In the present study, there was a statistically significant correlation of D-dimer with Random Blood sugar (spearman's Rho coefficient-0.752), and a 43.6% change in D-dimer can be explained by the change in RBS.

Conclusion: A significant increase in D-dimer levels is observed in patients with diabetes compared to those without the condition. This suggests that D-dimer could be a dependable indicator for assessing prognosis and predicting mortality outcomes.

Keywords: D-Dimer, COVID-19, Diabetes, Random blood glucose, RT-PCR.

Introduction

In December 2019, a novel beta coronavirus associated with acute respiratory syndrome emerged in Wuhan, China. Subsequent genetic analysis of samples collected from the respiratory tracts of infected individuals allowed for the identification and characterization of this novel virus, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In 2020, the World Health Organization (WHO) officially abbreviated the disease caused by this virus as COVID-19 [1]. Viruses enter through ACE2 (angiotensin converting enzyme2) receptors and affect the host's cell membrane. In the cell, the virus begins its replication through various mechanisms and then exocytosis and finally necrosis of the cell due to stress caused by the virus [2]. These elevated D-dimer levels can trigger an inflammatory cascade and activate proinflammatory cytokines. This can subsequently lead to the development of a "Cytokine Storm" characterized by an increased number of cytokines, ultimately culminating in multi-organ collapse and hyperinflammation [3,4]. Coronavirus disease 2019 (COVID-19) results in a profound inflammatory response and leads to a coagulation cascade [5]. As coagulation activation progresses toward a hypercoagulable state, it can lead to adverse clinical outcomes and potentially fatal consequences. Monitoring hemostatic laboratory parameters becomes crucial in this context, enabling better assessment and management of therapeutic interventions to address these critical

issues. Currently, D-dimer is the best marker for COVID-19-associated hemostatic abnormality (CAHA) [6]. D-dimer is a fibrin degradation product found raised in hypercoagulation and elevated fibrinolytic activity. Coagulopathy and pulmonary inflammation develop concomitantly and can overlap in the second stage. In this stage, raised levels of inflammatory markers, like D-dimer, interleukin 6&1, and CRP, are utilized to predict severity and prognosis.

This progression can ultimately lead to the third stage, characterized by fibrosis. It's important to note that the severity of COVID-19 appears to be closely associated with diabetes mellitus. Uncontrolled hyperglycemia is strongly linked to a poor prognosis and increased mortality due to the dysregulation of both innate and adaptive immune responses.

Chronic low-grade inflammation results in cytokine storm and imbalance between clotting factors and fibrinolysis, which results in recurrent thrombotic events [7]. D-dimer is famously known as a thromboembolic marker and prognosis marker in Acute respiratory distress syndrome (ARDS) and critically ill patients. Progressively increasing D-dimer levels associated with high mortality may be due to cytokine storms, impending organ failure, and infection/sepsis resulting in coagulation activation [8].

The objective of this study was to examine the relationship between D-dimer levels in COVID-19 patients and their diabetes mellitus status. The aim was to assess the association between D-dimer levels and the presence of both COVID-19 and type 2 diabetes at the time of presentation. This research seeks to enable early prevention and treatment of thrombotic events and their associated adverse outcomes in cardiovascular, central nervous system, and peripheral vascular disease.

Materials and Methods:

In April 2021, a prospective cohort study was conducted at the Department of Medicine, SMS Medical College, spanning duration of one year. The study aimed to investigate a sample size of 60 cases, specifically focusing on patients with moderate and severe COVID-19 illness who were admitted to SMS Hospital's Medicine Department. Based on the previous studies, the prevalence of diabetes mellitus is 55%, for 80% power and 0.5 α error with 5% absolute error. Patients were triaged as per severity based on national guidelines-asymptomatic, mild (respiratory rate <24/min, SpO2>94% at room air), moderate (respiratory rate: 24 to 30/min, SpO2 90 to 94 % at room air), severe (respiratory rate>30/min SpO2<90%), ARDS and septic shock. Only moderate and severe patients with laboratory-confirmed COVID-19 cases by RT-PCR (Real Time Reverse Transcription Polymerase Chain Reaction) or RAT (Rapid Antigen Test) were included in this study. This study included participants aged between 18 to 80 years who expressed their willingness to participate. Individuals with known cases of diabetes mellitus and an HbA1c level greater than 6.5 were included in the study.

On the other hand, exclusion criteria encompassed pregnant females, patients taking antidepressants, antipsychotics, or anticoagulants, those under the age of 18, individuals with HIV/AIDS or compromised immune systems, patients with a pre-existing history of venous thromboembolism, malignancy, or active pulmonary tuberculosis. The participants were categorized into two groups based on their diabetes status, and subsequent analysis was conducted.

Informed consent was obtained from all participants, and the study received approval from the Rajasthan University of Health Sciences (RUHS) Ethics Committee under reference number 435/MC/EC/2022.

Results:

In the present study, one-third of cases (33.3%, 20/60) were of the 55-64 years age group, followed by the 45-54 years of the age group of 14 (23.3%) cases and the least 2 (3.3%) cases were of 75-84 years age group. The mean age of cases was 54.7±12.6 years.

The gender distribution in this study was equal, with 30 males and 30 females. In the current study, the majority, 56 (93.3%) cases, were discharged after the treatment, and the rest, 4 (6.7%), expired. 33 (55%) cases had Diabetes Mellitus, and the rest, 27 (45%), were Non-diabetic. (Table 1)

Table 1: Relationship of Age, sex and diabetic status with patients with and without diabetes

Age group (Years)	Total	DM	NDM
25-34	6(100)	3(50)	3(50)
35-44	6(100)	3(50)	3(50)
45-54	14(100)	8(57.1)	6(42.9)
55-64	20(100)	13(65)	7(35)
65-74	12(100)	5(41.7)	7(58.3)
75-84	2(100)	1(50)	1(50)
Total	60(100)	33(55)	27(45)

Sex	Total	DM	NDM
Female	30(100)	17(56.7)	13(43.3)
Male	30(100)	16(53.3)	14(46.7)
Total	60(100)	33(55)	27(45)
Diabetic status	**Total**	**DM**	**NDM**
Discharged	56(93.3)	30(90.9)	26(96.3)
Expired	4(6.7)	3(9.1)	1(3.7)
Total	60(100)	33(100)	27(100)

The laboratory investigations that included hemoglobin (Hb), Total leucocyte counts (TLC), platelet count, Random blood sugar (RBS), D-Dimer, Urea, Creatinine, SGPT, SGOT, and Total bilirubin are mentioned in Table 2. In our study, mean Hemoglobin, Total leukocyte count, and platelet count were 11.66±2.33 gm/dl, 13.52±6.53 thousand per cubic mm, and 2.01±0.93 lacs/ml, respectively. Random blood sugar and meanD-dimer levels were 248.9±139.83 mg/dl and 878.62±860.74, respectively. Mean urea level, creatinine, SGOT, SGPT, and total bilirubin were 58.53±34.82 mg/dl, 1.3±1.03 mg/dl, 57.45±31.09 U/L, 58.12±55.77 U/L and 0.81±0.32 respectively in the present study. The laboratory values had a statistically insignificant correlation between patients with diabetes and patients without diabetes, which can be seen in Table 2.

Table 2: Laboratory investigations

	Overall	DM	NDM	Test of significance
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Hb (gm/dl)	11.66(2.33)	11.45(2.17)	11.91(2.53)	t=0.762, Df=58, p value=0.449
TLC(*1000/cumm)	13.52(6.53)	12.62(4.51)	14.62(8.34)	t=1.185, Df=58, p value=0.241
Platelet Count(lakhs/ml)	2.01(0.93)	1.89(0.93)	2.16(0.92)	t=1.123, Df=58, p value=0.266
RBS® (mg/dl)	248.9(139.83)	356.58(96.3)	117.3(15.94)	t=12.750, Df=58, pvalue<0.001
D Dimer	878.62(860.74)	1291.33(972.3)	374.19(193.03)	t=4.817, Df=58, p value<0.001
Urea (mg/dl)	58.53(34.82)	58.09(35.67)	59.07(34.41)	t=0.108, Df=58, p value=0.914
Creatinine(mg/dl)	1.3(1.03)	1.25(0.95)	1.36(1.14)	t=0.409, Df=58, p value=0.684
SGOT (U/L)	57.45(31.09)	54.03(27.38)	61.63(35.18)	t=0.941, Df=58, p value=0.351
SGPT (U/L)	58.12(55.77)	53.09(46.1)	64.26(66.11)	t=0.769, Df=58, p value=0.445
TotalBillirubin(mg/dl)	0.81(0.32)	0.79(0.31)	0.83(0.35)	t=0.469, Df=58, p value=0.641

Half of patients aged 25-44 and 75-84 were diabetic, and the rest were non-diabetic. Most of the other age groups were diagnosed with diabetes mellitus. In this study, there is almost a similar proportion of diabetic cases with different age groups. In the present study, more than half of both genders (56.7% females and 53.3% males) had diabetes. In the current study, among diabetic cases, three (9.1%) cases expired, and among patients without diabetes, one (3.7%) case expired.

The mean RBS of diabetic cases was 356.58±96.30, higher than that of patients without diabetes cases (117.30±15.94 mg/dl). This difference in Random blood sugar of patients with diabetes and without diabetes was statistically significant (p value<0.05). The mean D-dimer level of patients with diabetes was 1291.33±972.30, which was higher than patients without diabetes (374.19±193.03) and was statistically significant (p value<0.05). The mean D-dimer level in female cases (1399.35±1174.4) with diabetes was higher compared to male (1176.56±719.96) patients with diabetes.

In our study, there was a statistically significant correlation of D-Dimer with Random Blood sugar (spearman's Rho coefficient-0.752), and a 43.6% change in D-Dimer can be explained by a change in RBS. (Table 3) (Figure 1)

Table 3: Correlation of D-Dimer with Random Blood Sugar in Covid Cases

Variables	Spearman's Rho	$R2$	p value
RBS with D-Dimer	0.752	0.436	<0.001

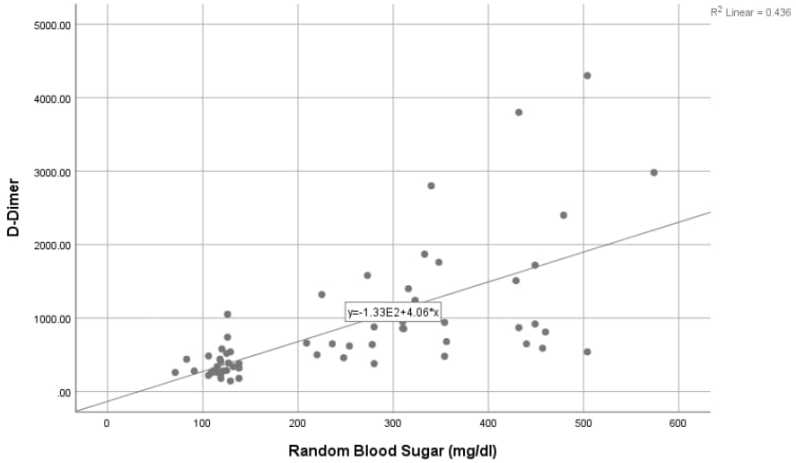

Figure 1: Correlation of D-Dimer with Random Blood Sugar in Covid Cases

Discussion:

This is a single-center, prospective study focusing on cases who presented to a tertiary hospital and were diagnosed with SARS-CoV-2 by means of RT-PCR and with a history of diabetes mellitus. This cohort study aims to assess the effectiveness of D-dimer levels as a biomarker for gauging disease severity and predicting prognosis in individuals with COVID-19 who also have diabetes. Under usual circumstances, the formation of fibrin clots in response to vascular damage and the regulation of coagulation mechanisms maintain a delicate balance in the process of hemostasis. However, when infections trigger endothelial dysfunction, this equilibrium is disrupted, leading to a hypercoagulable state characterized by an overproduction of thrombin and a shutdown of the fibrinolysis process [9,10]. Moreover, hypoxia can further exacerbate thrombosis by increasing blood viscosity and initiating a hypoxia-inducible transcription factor-dependent signaling pathway in cases of severe pneumonia [11]. Consequently, coagulopathy may manifest in many individuals experiencing severe pneumonia. Meanwhile, the increase in D-dimer levels can have physiological or pathological origins, as seen in conditions like malignancies, chronic liver disorders, postoperative scenarios, pregnancy, inflammation, and infections. Notably, our study unveiled a prevalent elevation in D-dimer among patients diagnosed with COVID-19 with a history of diabetes, which correlated with the severity of the disease.

In COVID-19 patients, various significant alterations have been observed within the lung vasculature. These changes encompass extensive pulmonary interstitial fibrosis, varying levels of hemorrhagic pulmonary infarction, severe damage to the endothelial lining, widespread vascular thrombosis resulting in nearly complete blockage of alveolar capillaries, structural abnormalities in capillaries, and the development of new blood vessels through an intussusceptive angiogenesis mechanism [12]. Furthermore, in severe COVID-19, intravascular disseminated coagulation can be fatal, and anticoagulant medication appears to enhance prognosis. A retrospective study conducted in China observed that non-survivors among diabetic patients admitted to the hospital for COVID-19 had prolonged prothrombin times and elevated D-dimer levels [13].It's worth noting that patients with COVID-19 who also have diabetes often present with additional risk factors such as obesity, advanced age, and hospitalization. These additional risk factors can further contribute to the procoagulative state and increase the likelihood of experiencing thrombotic complications.

In a model that took into account sociodemographic factors and comorbidities, the hazard ratio (HR) for in-hospital mortality was notably elevated among patients with an HbA1c level of 58 mmol/mol (7.5%) or higher (HR 3.36, 95% CI 2.18-2.56) when compared to those with lower HbA1c levels (HR 1.50, 95% CI 1.40-1.60) or individuals who did not have a recent HbA1c measurement (HR 1.87, 95% CI 1.63-2.16) [14]. Another study [15] reported an increased risk of COVID-19-related mortality in individuals with either type 1 or type 2 diabetes who had an HbA1c level exceeding 86 mmol/mol (10%), compared to those with HbA1c levels below 48 mmol/mol (6.5%). Interestingly, the CORONADO study16 did not identify any significant association between HbA1c levels and the primary composite outcome (mortality and the need for tracheal intubation for mechanical ventilation within the initial 7 days following hospital admission) in patients with diabetes who were hospitalized with COVID-19.

High blood sugar levels upon hospital admission were the most significant predictor of unfavorable chest radiographic findings in a retrospective study of 85 COVID-19 patients [17]. In another study [18], mortality was significantly higher in

uncontrolled hyperglycemic patients, with 41.7% of them succumbing to the disease compared to 14.8% in diabetic patients ($p<0.001$). These findings underscore the importance of enhancing glycemic control in all patients with elevated blood sugar levels, regardless of their diabetes status. In-hospital glycaemic control random hyperglycemia during treatment in the hospital contributed to a worse prognosis for patients with COVID-19 in Wuhan [19]. Many COVID-19 patients have experienced diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome20, with severe cases documented in two clinical instances [21]. A study [22] revealed that ketosis occurred in 6.4% of COVID-19 patients, rising to 11.6% in those with diabetes, resulting in a significant mortality rate (33.3%). In the initial stages of the CORONADO trial [16], 11.1% of participants had diabetes-related conditions, including 132 individuals with severe hyperglycemia and 40 with ketosis, of which 19 had diabetic ketoacidosis. Additionally, new-onset diabetes has been observed in COVID-19 patients receiving hospital care [18,23].

D-dimer elevation was observed in 61.7% of these cases. Huang et al. conducted a study involving 41 COVID-19 patients and discovered that those with severe symptoms had D-dimer levels approximately five times higher than patients with milder symptoms [24]. In another study involving 183 COVID-19 patients, Tang et al. found that patients with severe symptoms had D-dimer levels roughly 3.5 times higher than those with non-severe symptoms [25]. Similarly, in a retrospective analysis of clinical and radiological data from 248 COVID-19 patients at a Wuhan hospital, Yao et al. observed significantly higher D-dimer levels in patients with severe symptoms than others [26].

The pathology associated with COVID-19 involves several key features, including alveolar destruction, pneumocyte desquamation, the development of hyaline membranes, pulmonary edema, and leakage of mononuclear inflammatory cells into the interstitial space. Elevated D-dimer levels and increased lung involvement result from disruptions in the hemostasis cascade, heightened inflammatory responses, and hyperfibrinolysis [27,28]. Patients with high D-dimer levels tend to have longer hospital stays and require intensive care unit (ICU) admission [27].In COVID-19 individuals who exhibit significant clinical and radiological symptoms with lung abnormalities, there is typically a decrease in lymphocyte counts and an elevation in neutrophil levels. This immune response is linked to increased serum cytokines and chemokines [12,27]. Recent research has suggested that D-dimer could be a valuable predictor of outcomes in COVID-19 patients. However, many of these studies have limitations, such as small sample sizes and questionable methodology, and they have primarily focused on static D-dimer values without investigating D-dimer trends [19,27].We acknowledge some limitations in this study. This was a single-center, prospective study and thus might have a selection bias. The study findings need to be corroborated with a larger, multicentric study. The dynamic measurement of D-dimer could be more informative in assessing the value of D-dimer as a predictor of mortality. PT and APTT were not measured in all patients, and serial evaluation of the two was not performed, limiting the assessment of their role as predictors of the disease outcome. Since there was no follow-up, post-discharge clinical status is not available.

Conclusion

The available evidence suggests that hyperglycemia can lead to a pro-thrombotic state, characterized by an imbalance between pro-coagulation, anti-coagulation, and fibrinolysis. Given that thrombosis significantly impacts the prognosis of COVID-19 patients, it is crucial to comprehend the factors contributing to an increased risk of thrombotic events in this disease. Consequently, investigating the potential connection between hyperglycemia and thrombosis through dedicated studies could offer valuable insights for enhancing the management of COVID-19.

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