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Correlation of Hyperglycaemia with Inflammatory Marker and Biomarker of Thromboembolism in Patients with Covid 19

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KEYWORDS

hyperglycaemia, neutrophil lymphocyte ratio, D-dimer, covid 19

ABSTRACT:

Introduction: COVID-19 constitutes a significant global public health challenge. New mutants areon the rise and sufficient information is not available for the management of infection by the same. Studies suggest that the combination of elevated glucose possessed high risk formortality from COVID-19.

Objective: 1. To Study the correlation between hyperglycaemia and inflammatory markers in Covid-19.

2. To Study the correlation between hyperglycaemia and biomarker of thromboembolismin Covid-19

Methodology: Between August and September 2021, a study was carried out on 40 adult patients whotested positive for COVID-19 using RT-PCR. Among the participants, 20 had diabetes, and the other 20 did not have diabetes. The glucose levels were assessed by Hexokinase methods. Severity ofCovid 19 was assessed by Neutrophil Lymphocyte ratio (NLR) detected by Flowcytometry and D-dimer measured by Turbidimetric Immunoassay. The study commenced after obtaining approval from the Institutional Ethical Committee, and informed consent was obtained from every patient before the study initiation.

Results: The median age of patients included in this study is 43. Analysis of COVID-positivepatients revealed that diabetic individuals had higher mean WBC and Neutrophil counts, while their mean Lymphocyte count was lower compared to non-diabetic patients. Consequently, theNeutrophil Lymphocyte Ratio (NLR) was significantly higher in COVID-positive patients withdiabetes (Mean NLR 6.8380 versus 3.3050). Moreover, D-dimer levels were notably higher inCOVID-positive diabetic patients in comparison to COVID-positive non-diabetic patients (P =0.048). Additionally, a positive correlation was observed through Pearson correlation between random blood sugar levels and inflammatory markers like NLR (P = 0.015, r = 0.194) and D- dimer (P = 0.048, r = 0.474).

Conclusion: A positive correlation was observed between hyperglycaemia and elevated inflammation levels, as well as a hypercoagulable state associated with more severe illness. Consequently, hyperglycaemia poses as a risk factor for the increased severity

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of COVID-19. Monitoring plasma glucose levels upon hospitalization could potentially aid in identifying a subset of patients predisposed to a worse clinical course.

INTRODUCTION

The COVID-19 (coronavirus disease 2019) outbreak initially emerged in Wuhan, Hubei Province, China, towards the end of 2019[1, 2]. Classified as an infectious disease by the WHO,COVID-19 is caused by a novel coronavirus. Advanced age is a contributing factor to the severity of the disease, particularly affecting older individuals. Additionally, individuals with comorbidities like cardiovascular disease, diabetes, chronic respiratory disease, and cancer areat a higher risk of developing severe illness. Of particular interest in this study are diabetes andhyperglycaemia, as they have been associated with adverse outcomes in hospitalized patients with acute medical conditions, including COVID-19. The primary objective of this study is to explore the correlation between poorly controlled diabetes and inflammatory markers in COVID-19.

Hyperglycaemia, which is high blood glucose seen in patients with diabetes mellitus, is an important factor in this study.

The WHO diagnostic criteria for diabetes are:

- Fasting plasma glucose > 126 mg/dL, or
- 2-hour postprandial plasma glucose > 200 mg/dL

Various biomarkers have been utilized to predict severe disease in COVID-19 patients, such as C-reactive protein, ferritin, lactate dehydrogenase, D-dimer, interleukin 6, and fibrinogen [3]. Complementing these biomarkers, chest computed tomography (CT) has been recognizedas a crucial tool for assessing the severity of COVID-19 [4]. Notably, the neutrophil- lymphocyte ratio (NLR) has emerged as an independent risk factor for severe COVID-19 pneumonia, offering an early warning signal for worsening infections. This ratio serves as an objective basis for early identification [5].

The study conducted by Zhu et al. [6] revealed that individuals with Type II DM necessitated more medical interventions and faced significantly higher mortality rates and multiple organ injuries compared to non-diabetic individuals. Similarly, AY Mazori et al. [7] found that elevated levels of both glucose and lactate could identify a high-risk group vulnerable to mortality from COVID-19, irrespective of diabetic status. Regardless of diabetic status, maintaining controlled blood glucose levels and regular glucose testing have been shown to becrucial. These practices have been associated with lower mortality rates in comparison to individuals with inadequately controlled blood glucose levels.

According to Ceriello [8], there is a plausible hypothesis that the SARS-CoV-2 virus could potentially reduce insulin secretion by affecting the pancreatic β-cells. This, in turn, may lead to insulin resistance due to the cytokines produced during the infection. Research conducted by Cheng et al. [9] demonstrated that the severity of COVID-19 in patients with Type II DM is dependent on the levels of HbA1C, IL-6, and lymphocyte count. Additionally, Zhang et al. [10] found that diabetic patients experienced a higher proportion of critical cases and longer hospitalization durations compared to non-diabetic patients. Furthermore, Yang et al. [11] conducted a study showing that high blood glucose levels in COVID-19 patients at the time ofhospital admission can serve as a strong predictor of mortality and complications. Moreover, Sardu et al. [12] conducted a study that provided evidence suggesting that hyperglycaemic patients treated with insulin infusion had a lower risk of severe disease when compared to patients without insulin infusion.

Previous studies have shown that diabetic patients are more susceptible to the cytokine storm,resulting in an imbalance between coagulation factors and fibrinolysis. This imbalance increases their vulnerability to thrombotic events, which can have fatal consequences [13]. In both diabetics and non-diabetics with COVID-19, D-dimer, a biomarker of thromboembolism,has been identified as a predictor of disease severity.

The objective of our study is to determine the correlation between hyperglycaemia and the severity of COVID-19 infection. To assess disease severity, we will be using two parameters: the Neutrophil-Lymphocyte Ratio (NLR), an inflammatory marker, and D-dimer, a biomarker of thromboembolism. The study will involve patients above 18 years of age with confirmed COVID-19 through RT-PCR testing, who are visiting our tertiary care hospital in India.

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OBJECTIVES

1. To Study the correlation between hyperglycaemia and inflammatory markers inCovid-19.
2. To Study the correlation between hyperglycaemia and biomarker ofthromboembolism in Covid-19.

METHODOLOGY

Between August and September 2021, we conducted a study involving 40 patients who tested positive for Covid-19 through RT-PCR. Out of these, 20 patients were diabetic, and the other 20 were non-diabetic individuals. All patients included in the study were above 18 years of ageand had visited our tertiary care hospital. The severity of Covid-19 in both groups of patients was assessed using lab values of Neutrophil Lymphocyte Ratio (NLR) detected by Flowcytometry and D-dimer measured by Turbidimetric Immunoassay. To assess random blood glucose levels, the Hexokinase method was utilized. Before the study commenced, we obtained approval from the Institutional Ethics Committee, and informed consent was obtained from each patient participating in the study.

STATISTICAL METHODS

The data analysis for this study was performed using the Statistical Package for Social Service (SPSS 22.0) software. To analyse the report, Student's t-test and Pearson correlation tests wereemployed. A p-value of less than 0.05 was considered statistically significant in the analysis.

RESULTS

This study included 40 COVID-positive patients who were confirmed by the Real-Time Polymerase Chain Reaction test. Among these patients, 20 had Type 2 Diabetes mellitus, while the other 20 had no comorbidities. The median age of all patients in the study was 43.

Upon admission, it was observed that diabetic patients had higher random blood sugar levelscompared to non-diabetic patients (refer to table 1). Additionally, the study found that the mean White Blood Cell (WBC) count and mean Neutrophil count were higher, while the mean Lymphocyte count was lower in diabetic patients compared to non-diabetic patients (refer to table 2 and table 3).

As a result, the Neutrophil Lymphocyte Ratio (NLR) was significantly higher in COVID- positive patients with diabetes (Mean NLR 6.8380 versus 3.3050) (refer to table 4). This finding aligns with the study conducted by Jingyuan et al [14], which demonstrated that NLR had high predictive value and was the most critical factor influencing the incidence of severedisease.

Furthermore, based on NLR and age stratification, the study by Jingyuan et al [14] found thatthe incidence of severe cases in patients aged ≥ 50 years old with NLR ≥ 3.13 was 50%, while it was 9.1% in patients aged ≥ 50 with NLR < 3.13.

Table 1: Random blood sugar (RBS) in diabetes and Non diabetes

RBS	N	Mean	Std. Deviation	p
Diabetes	20	284.65	157.262	0.000*
Non Diabetes	20	108.30	14.535	

In this study, it was observed that D-dimer levels were significantly higher in COVID- positive diabetic patients compared to COVID-positive non-diabetic patients (P = 0.048) (refer to table 5). This finding aligns with the results of a study conducted by Chaymae Miri [15], which also indicated a significant association between diabetes and D-dimer and C- reactive protein (CRP) levels. In Chaymae Miri's study, a D-dimer value greater than 2885 ng/mL was identified as a predictor of mortality in COVID-19 patients with diabetes.

Furthermore, the study revealed a significant positive correlation, as determined by Pearson correlation, between random blood sugar levels and inflammatory markers such as the Neutrophil Lymphocyte Ratio (NLR) (P = 0.015, r = 0.194) (refer to Fig 1), as well as D- dimer (P = 0.048, r = 0.474) (refer to Fig 2). These correlations suggest that elevated randomblood sugar levels are associated with increased inflammatory response markers like NLR and D-dimer in COVID-positive patients.

Table 2: Neutrophil in diabetes and Non diabetes

Neutrophil	N	Mean	Std. Deviation	p
Diabetes	20	78.315	10.3913	0.002*
Non Diabetes	20	67.500	12.0558	

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Table 3: Lymphocyte in diabetes and Non diabetes

Lymphocyte	N	Mean	Std. Deviation	p
Diabetes	20	16.830	8.0935	0.035*
Non Diabetes	20	27.420	11.2952	

Table 4: Neutrophil/lymphocyte ratio in diabetes and Non diabetes

Neutrophil/lymphocyte ratio	N	Mean	Std. Deviation	p
Diabetes	20	6.8380	4.56936	0.015*
Non Diabetes	20	3.3050	2.46147	

Table 5: Dimer in diabetes and Non diabetes

D dimer	N	Mean	Std. Deviation	p
Diabetes	20	439.500	322.2726	0.048*
Non Diabetes	20	320.400	132.0532	

Fig 1: Correlation of RBS and NLR

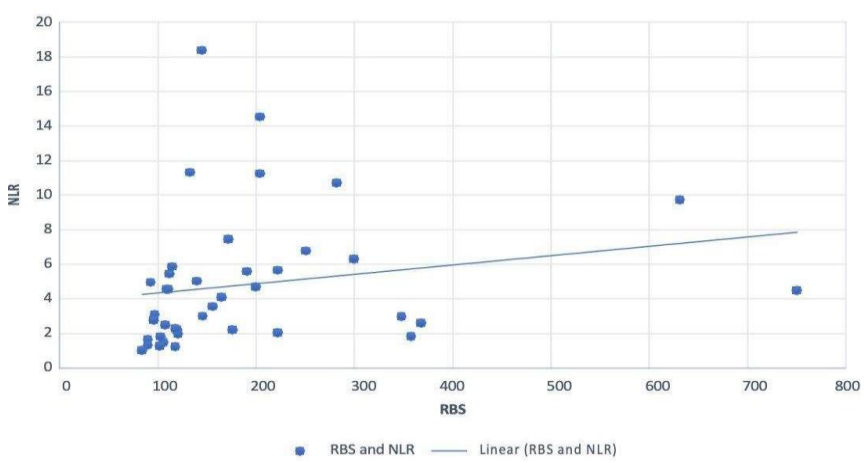
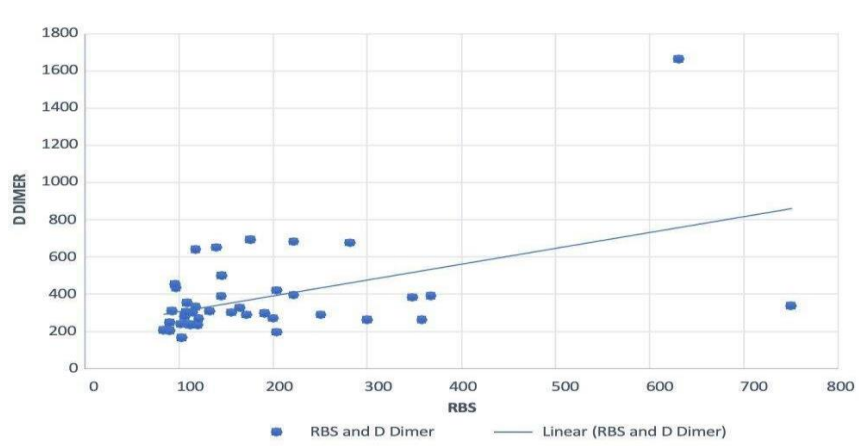


Fig 2: Correlation of RBS and D dimer



DISCUSSION

COVID-19 is a novel disease with varying degrees of severity, ranging from asymptomatic cases to severe illness leading to death. As a result, conducting studies to predict the severity of the disease in patients with or without comorbidities is crucial to provide appropriate medical management and save lives. Notably, uncontrolled diabetes with hyperglycemia upon admission has been linked to poor outcomes in hospitalized patients, including those with COVID-19. Recent studies have shown that COVID-19 patients with comorbidities, includingdiabetes, are at higher risk

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of mortality. Given that diabetes is one of the most common comorbidities in COVID-19 patients, hyperglycemia has emerged as an independent predictor of inflammation level and disease severity in COVID-19.

Both patients with established diabetes and those with hyperglycemia, regardless of diabetes diagnosis, face a significantly higher risk of experiencing severe COVID-19 and a more pronounced inflammatory response compared to patients with normal blood sugar levels. Furthermore, elevated random blood sugar (RBS) levels have been strongly associated with disease severity in both diabetic and non-diabetic patients. These findings underscore the importance of monitoring and managing blood sugar levels in COVID-19 patients, as hyperglycemia can exacerbate the severity of the disease and contribute to poorer outcomes. Effective control of hyperglycemia may play a crucial role in mitigating the impact of COVID-19 in both diabetic and non-diabetic individuals.

In our study, we enrolled 20 diabetic patients and 20 non-diabetic patients. Upon admission, we observed that the random blood sugar (RBS) levels were significantly higher in the diabeticgroup compared to the non-diabetic group. This finding suggests that patients with diabetes may be more prone to fluctuations in blood glucose levels or poorly controlled blood glucose when exposed to a viral infection [20].

Consistent with other studies, we also found a significant association between RBS levels anddisease severity in our study. This association implies that hyperglycaemia could be a contributing factor to poor outcomes in COVID-19 patients [22]. Numerous studies have reported a two-fold increase in the severity of COVID-19 among patients with diabetes [21].

Furthermore, it has been well-documented that COVID-19 patients exhibit elevated plasma levels of inflammatory cytokines [23, 24]. Moreover, changes in the neutrophil count and lymphocyte count, represented by the neutrophil-lymphocyte ratio (NLR), have emerged as reliable indicators of severe COVID-19 [25, 26]. These findings collectively highlight the importance of monitoring blood glucose levels, particularly in diabetic patients, as hyperglycaemia appears to play a role in disease severity. Additionally, the assessment of inflammatory markers like NLR could provide valuable insights into the severity of COVID- 19 and aid in patient management.

In our study, we conducted a comparison of the Neutrophil-Lymphocyte Ratio (NLR) betweenCOVID-19 positive patients with and without diabetes. The results revealed significantly higher NLR levels in patients with diabetes mellitus. This finding suggests that NLR could bea valuable marker for early screening of COVID-19 patients [27].

Monitoring NLR from the point of hospitalization is crucial, as higher NLR concentrations have been correlated with more severe symptoms and increased mortality rates associated withCOVID-19. Therefore, NLR emerges as an important systemic inflammation marker for screening COVID-19 infected patients and may serve as a significant indicator of poor prognosis upon initial hospitalization [28]. One notable advantage of using NLR as a marker is its cost-effectiveness, as its measurement is already a routine part of clinical blood tests. Thisfurther strengthens the case for utilizing NLR as a practical and accessible marker for identifying COVID-19 patients with potential complications and adverse outcomes.

In our study, we made a noteworthy discovery regarding D-dimer levels, finding that diabeticpatients exhibited significantly higher levels compared to non-diabetics. This finding suggests that individuals with diabetes are more susceptible to a hypercoagulable state, possibly due tothe pro-thrombotic nature induced by hyperglycaemia [29]. The underlying mechanisms leading to this state involve two distinct pathways: firstly, oxidative stress during acute hyperglycaemia enhances thrombin production, and secondly, non-glycation processes lead toa reduction in the function of antithrombin III and heparin co-factor II through enzymatic reactions, contributing to inflammation and endothelial dysfunction, ultimately resulting in thrombus formation [30, 31].

As a marker of hypercoagulopathy, D-dimer levels rise when plasmin cleaves fibrin to break down clots, producing fragments known as D-dimers. Clinically, assays routinely use D-dimermeasurements as part of

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diagnostic algorithms to exclude thrombosis diagnosis. Increased plasma D-dimer levels may be indicative of any process, whether pathologic or non-pathologic,that affects fibrin production or breakdown [32].

Moreover, our study found that diabetic patients with higher D-dimer levels also exhibited more severe disease. The continuous hyperglycaemia experienced by individuals with diabetes can lead to endothelial dysfunction and inflammation, which, in turn, may trigger thrombus formation. Consequently, severe SARS-CoV-2 infection in the presence of diabetes is more likely to result in coagulopathy and poorer outcomes.

LIMITATIONS

In our study, we acknowledge that a larger sample size would have provided more precise anddetailed results. A multicentric study involving multiple centres would also be more ideal to enhance the generalizability of the findings.

It is important to note that we did not observe long-term prognoses in our study, and further research would be necessary to investigate the outcomes over an extended period.

Additionally, we recognize that there are other confounding factors that could influence the results, such as elderly age, hypertension, cardiovascular disease, and obesity. These factors were not taken into consideration in our study, and future research should aim to address these variables to gain a more comprehensive understanding of the relationship between diabetes, hyperglycaemia, and COVID-19 outcomes.

CONCLUSION

The findings from our study clearly indicate that diabetic patients have higher levels of inflammatory markers compared to non-diabetic patients. This suggests that the severity of the disease is more pronounced in individuals with diabetes. NLR emerges as a promising predictive factor for assessing the severity of the illness.

Moreover, in diabetic patients, we observed elevated levels of D-dimer, indicating a state of hypercoagulability and potentially contributing to a poorer prognosis. Taken together, these results emphasize the importance of monitoring inflammatory markers and D-dimer levels in diabetic patients to better understand disease progression and potentially improve patient outcomes.

Abbreviations:

COVID-19: Coronavirus disease 2019 BG: Blood glucose
RT PCR: Real-Time Polymerase Chain ReactionWHO: World Health Organisation
FBG: Fasting blood glucoseHbA1c: Haemoglobin Ac1
CT: Computed tomography
Type II DM: Type II Diabetes mellitusWBC: White blood cell
NLR: Neutrophil to lymphocyte ratioIL-6: Interleukin 6
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Conflicts of Interest:

No authors declare any conflicts of interest

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