Original Article

DOI: 10.7860/JCDR/2022/55998.16424

Markers of Coagulation Dysfunction and Inflammation in Diabetic and Non Diabetic COVID-19 Patients- A Retrospective Study

Biochemistry Section

FIRDUSHI BEGUM[1], MALAVIKA BARMAN[2], ELTEZA TAHJIBA JAHIR[3]

ABSTRACT

Introduction: Since the end of 2019, a novel Coronavirus Disease 2019 (COVID-19), declared a pandemic by World Health Organisation (WHO) has ravaged the world. Diabetic patients have been reported to be more susceptible to intensive care admissions, and deaths due to COVID-19. Diabetes Mellitus (DM) and COVID-19, both associated with chronic and acute inflammation respectively can impact each other in terms of clinical progression and outcome. Given the novelty of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pathogen, there is need to update and increase the limited evidence on the probability of DM acting as a risk factor and influencing disease severity and progression.

Aim: To compare the markers of inflammation and coagulation dysfunction between COVID-19 patients with and without DM as co-morbidity and thereby, to study the effect DM has on the prognosis of COVID-19.

Materials and Methods: This was a retrospective, observational, single-centre study, conducted Department of Biochemistry at Gauhati Medical College and Hospital, Guwahati, Assam, India, from January 2021 to June 2021. Clinical and laboratory data of 500 laboratory confirmed COVID-19 patients were reviewed in the present study. The patients were grouped as diabetic case group and non diabetic control group. Data was presented as percentages for categorical variables and median (interquartile range) for continuous variables. Chi-square test was used to see the association of different qualitative information and Mann-Whitney U test was used to see the association of quantitative data and all p-values were given for justification. A p-value <0.05 was considered statistically significant.

Results: The sample included 300 diabetic and 200 non diabetic COVID-19 patients. The mean age of non diabetic patients (47.5 years) was significantly less as compared to the diabetic group (54.5 years), p-value <0.001. The serum level of inflammatory biomarkers, C-Reactive Protein (CRP), ferritin, and markers of hypercoagulable state, D-dimer, was found to be significantly high (p-value <0.001) in diabetic patients as compared to non diabetic patients. Diabetics had a poor prognosis with 231 (77%) receiving oxygen as compared to 51 (25.5%) of non diabetic patients. Total 173 (57.7%) of diabetic COVID-19 patients had to be shifted to ICU, 201 (67%) suffered from post COVID-19 complications and the mortality rate was higher at 18% in diabetics as compared to 1.5% in non diabetic subjects.

Conclusion: Diabetic patients are at higher risk of uncontrolled inflammation and hypercoagulable state which eventually leads to deterioration of COVID-19 infection status.

Keywords: Co-morbidity, Coronavirus disease 2019, Glycaemic control, Hypercoagulable state, Prothrombin time

INTRODUCTION

Towards the end of 2019, a new virus named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first identified in Wuhan province of China [1]. The disease caused by infection with the virus was named Coronavirus Disease 2019 (COVID-19) and declared a pandemic by World Health Organisation (WHO) [2]. Since 2019, the virus has spread across continents and has affected 382.3 million people worldwide and resulted in the death of 5.7 million as of 2nd February 2022 [3]. Spread via respiratory droplets, the main clinical manifestation is lung injury [4,5]. SARS-CoV-2 pathophysiology remains incompletely understood, but research evidence has suggested that exaggerated inflammation play a critical role in its pathogenesis. Inflammatory responses triggered by a rapid viral replication and cellular destruction, can induce the release of cytokines by macrophages and monocytes leading to cytokine storm [6]. Inflammatory markers like ferritin, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Interleukin-6 (IL-6), have been reported to be significantly associated with a high risk of development of severe COVID-19. The increased likelihood of thromboembolic events in COVID-19 is another factor of grave concern as reflected by high levels of D-dimer, elevated activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT). The SARS-CoV-2 can enter the endothelial cells via the Angiotensin Converting Enzyme 2 (ACE2) receptor, with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis and microvascular prothrombotic effects [7,8].

Several factors like advanced age, male sex, presence of co-morbidities like Diabetes Mellitus (DM), hypertension, coronary vascular disease, chronic kidney disease, cancer, predisposes COVID-19 infected patients to more severe infection with long hospital stay and fatal outcome [9,10]. Mankind has been struggling with the diabetes mellitus pandemic, when it confronted this new COVID-19 pandemic [11]. The physiology of both DM and COVID-19 are quite similar though the inflammatory responses, hyperglycaemia and resultant tissue damage in COVID-19 is intensely acute as compared to DM, which is characterised by chronic low grade inflammation, impaired glycaemic control, and slowly progressive multi tissue injury [11]. With similar pathological injury inflicted by both these diseases on the body organs, it is highly likely that the acute inflammation brought about by COVID-19 adversely affects the glycaemic control in DM patients and aggravates the multi-tissue injury resulting in adverse outcomes.

Given the novelty of SARS-CoV-2 pathogen, there is need to update and increase the limited evidence on the probability of DM acting as a risk factor and influencing disease severity and progression [4,12]. This study was thus designed to compare the inflammatory and coagulability status of COVID-19 patients with and without diabetes and find out whether a diabetic patient was at a greater risk of adverse prognosis compared to a non diabetic patient.

MATERIALS AND METHODS

This retrospective observational study was conducted in Gauhati Medical College and Hospital, Guwahati, Assam, India. For the study purpose, the records of patients admitted to the COVID-19 wards from May 2020 to October 2020 were scanned. Analysis of collected data was done in the months of May 2021 and June 2021. Total patients enrolled for the study was 500 based on the inclusion and exclusion criteria, 300 diabetic patients (cases) and 200 non diabetic patients (controls). The study was done only after obtaining approval of Institutional Ethics Committee (Ref No: MC/190/2007/Pt-II/DEC-2020/10).

Inclusion criteria:

- COVID-19 positive patients admitted to the COVID-19 wards, irrespective of severity.
- Age ≥15 years
- Already diagnosed diabetic cases with COVID-19 were taken as case group and COVID-19 patients without any co-morbidity were taken as control group.

Exclusion criteria:

- Patients with liver disorders, coagulopathies, and other co-morbidities other than DM.
- Pregnant women
- Age <15 years.

Data Collection

Infection by SARS-CoV-2 was diagnosed either by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Test (RAT). The COVID-19 positive patients were either admitted to Corona Wards or Intensive Care Units (ICU) depending on the severity of the cases. The patients were classified into mild, moderate and severe based on WHO guidelines on clinical management of COVID-19 [13].

Mild disease: Symptomatic patients meeting the case definition for COVID-19 without evidence of pneumonia or hypoxia.

Moderate disease: Adults with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing), SpO_2 ≥90% on room air.

Severe disease: Adults with clinical signs of pneumonia and one of the following:

- Respiratory rate > 30 breaths/min;
- or SpO_2 < 90% on room air.

The COVID-19 patients who were categorised as mild and moderate at the time of admission and admitted to COVID-19 wards were chosen as study subjects.

- Diabetic case group (n=300): Has diabetic COVID-19 cases (223- mild and 77-moderate).
- Non diabetic patients group (n=200): Has non diabetic controls (149-mild and 51-moderate)

But 173 diabetic cases and 16 non diabetic controls progressively became severe after admission and had to be shifted to COVID-19 ICU.

Study Procedure

Demographic and clinical data as regards to signs and symptoms, duration of hospital stay, treatment protocol followed which included administration of medicines and oxygen, post COVID-19 complications transfer to ICU, and final prognosis records were collected from Medical Records Department and noted down in a proforma prepared for the purpose. Laboratory data was collected from the Central Clinical Laboratory. On admission of the patients, Random Blood Glucose (RBG), urea, creatinine, Liver Function tests (LFT), C-Reactive Protein (CRP), ferritin, Lactate Dehydrogenase (LDH), D-dimer, Complete Blood Count (CBC) were done to collect the baseline data. Urea, Creatinine, LFT, along with other parameters was estimated at the time of admission in all COVID-19 patients. For the purpose of the present study, Urea, Creatinine, LFT (except AST, ALT, TP, Albumin) were not compared. Data of AST, ALT, TP, Albumin, LDH, Lymphocyte, Neutrophil, CRP, Ferritin, D-Dimer, APTT, PT, was collected and compared.

The blood tests were repeated according to the clinical progression of the cases. For the purpose of the present study, CRP, ferritin, D-dimer, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total Protein (TP), albumin, Lactate Dehydrogenase (LDH) levels, neutrophil count, lymphocyte count, activated Partial Thromboplastin time (aPTT) and Prothrombin Time (PT) between diabetic case group and non diabetic control group were compared. The CRP, ferritin, D-dimer, AST, ALT, TP, albumin, LDH were done in the Vitros 5600 Integrated System (Ortho Clinical Diagnostics, New Jersey, USA). Neutrophil and lymphocyte count were done in Sysmex Haematology Analyser and aPTT and PT on ERBA ECL 105 Coagulation Analyser. For the parameters showing an increasing trend, the highest reported level was chosen for the purpose of the study.

STATISTICAL ANALYSIS

Data collected were scrutinised thoroughly and baseline information was presented by standard statistics. Categorical values were expressed as percentages (%) and continuous variables as median, Interquartile Range (IQR) as the data was found to be dispersed and did not follow normal distribution. All the statistics have been calculated and computed using IBM, Statistical Package for Social Sciences (SPSS), version 20.0 and graph prepared using Microsoft Excel. To see the association of different qualitative data Chi-square test was administered and all p-values were given for justification. Similarly to test the equality of medians for quantitative data Mann-Whitney's U test was used. A p-value <0.05 was considered statistically significant at 5% level.

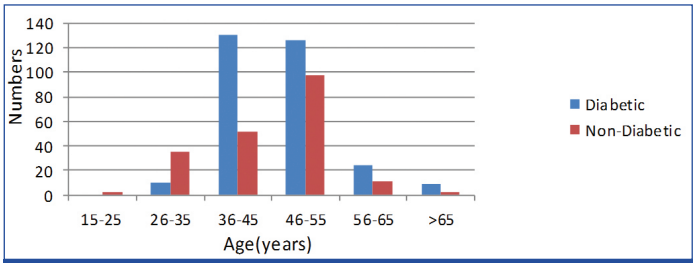
RESULTS

The median age of non diabetic patients (47.5 years) was significantly less as compared to the diabetic group (54.5 years), p-value <0.001. Males were two times more infected by SARS-CoV-2 than females. For all the patients the most common presenting symptoms were fever, chill, cough and fatigue [Table/Fig-1]. Maximum number of diabetic COVID-19 cases was in the age group of 36-45 years (131/300,

Parameters	Total (N, %)	Non diabetic group (n, %)	Diabetic group (n, %)	p-value
Age, Median (IQR)*, Years	52 (42-62)	47.5 (37-58)	54.5 (44.75-63)	<0.001
Duration of hospital stay† (Days)	10±4.1	7.58±3.9	14±5.13	<0.001
Gender				
Male	310 (62)	132 (66)	178 (59.3)	<0.001
Female	190 (38)	68 (34)	122 (40.67)	<0.001
Signs and symptoms				
Fever	405 (81)	158 (79)	247 (82.33)	0.001
Fatigue	150 (30)	54 (27)	96 (32)	0.001
Cough	175 (35)	64 (32)	91 (30.33)	0.03
Chill	301 (60.2)	124 (62)	177 (59)	0.002
Headache	40 (8)	24 (12)	26 (8.67)	0.777
Chest tightness	135 (27)	58 (29)	77 (25.67)	0.102
Chest pain	35 (7)	20 (10)	15 (5)	0.398
Shortness of breath	120 (24)	51 (25.5)	69 (23)	0.100
Myalgia	125 (25)	44 (22.5)	81 (27)	0.001
Nausea and vomiting	45 (9)	22 (11)	23 (7.67)	0.881
Diarrhoea	65 (13)	32 (16)	33 (11)	0.901

[Table/Fig-1]: Clinico-demographic data of COVID-19 patients (N=500).
Data are Median (IQR), Mean±SD or Number (percentage).
*Mann-Whitney U test was used; †Student's t-test was used to find p-values; The other variables are categorical values and Chi-square test was used; p-value <0.05 was considered statistically significant; IQR: Interquartile range

43.67%) [Table/Fig-2]. There was significant difference in CRP, ferritin, neutrophil and lymphocyte count and D-dimer levels between the diabetic case group and non diabetic control group [Table/Fig-3].



[Table/Fig-2]: Age-wise distribution of COVID-19 patients.

Parameters	Normal range	Total median (IQR)	Non diabetic median (IQR)	Diabetic (n=300)	p-value
Aspartate transaminase (U/L)	17-59	65 (42-108)	56 (41-101)	69.5 (44.75-116)	0.142
Alanine transaminase (U/L)	4-50	40 (25.75-78)	38.5 (25-81.5)	40 (27-77.25)	0.581
Total protein (gm/dL)	6.3-8.2	6.6 (5.9-7.1)	6.7 (6-7.3)	6.6 (5.9-7)	0.291
Albumin (gm/dL)	3.5-5	3.5 (3-4.1)	3.7 (3.1-4.2)	3.45 (3-4)	0.108
Lactate Dehydrogenase (U/L)	120-246	409 (289.5-700)	317.5 (221.75-513.25)	496 (306.25-792)	<0.001
Lymphocytes ($\times10^3$/µLL)	1-4.8	1.2 (0.5-2.2)	2.1 (1.3-3.3)	0.75 (0.38-1.4)	<0.001
Neutrophils ($\times10^3$/µL)	1.5-8	3.91 (3.09-5.13)	3.54 (3.05-4.22)	6 (4.3-8.52)	<0.001
C-reactive protein (mg/L)	0-10	56 (19.85-122.92)	29.7 (9.6-81.4)	58.75 (51.98-127.58)	<0.001
Ferritin (ng/mL)	11-306.8	514.75 (194-861.75)	206.5 (90.5-478.5)	546.75 (512.28-1002.6)	<0.001
D-dimer (µg/mL of FEU)	<0.5	0.84 (0.49-1.8)	0.56 (0.28-1.07)	1.16 (0.66-2.61)	<0.001
Activated partial thromboplastin time (sec)	28-44	35 (30.1-40.45)	32.5 (26.68-36.8)	37.6 (31.5-44.7)	<0.001
Prothrombin time (sec)	12-16	14.6 (12.9-16.6)	13.4 (12.1-14.5)	15.6 (13.88-18)	<0.001

[Table/Fig-3]: Comparison of inflammatory and coagulation markers between diabetic and non diabetic COVID-19 cases.
Mann-Whitney U test was used to find p-values; FEU: Fibrinogen equivalent unit

On comparison of the prognosis it was found that diabetics had a poor prognosis with 231 (77%) receiving oxygen as compared to 51 (25.5%) of non diabetics. Total 173 (57.7%) of diabetic COVID-19 patients and 16 (8%) non diabetic controls progressively became severe and had to be shifted to ICU, 201 (67%) suffered from post COVID-19 complications and the mortality rate was higher at 54 (18%) in diabetics as compared to 3 (1.5%) in non diabetics [Table/Fig-4].

Prognostic criteria	Non diabetic group (n, %)	Diabetic group (n,%)	p-value (Chi-square test)
Received steroid	83 (41.5)	263 (87.67)	<0.001
Received anticoagulants	65 (32.5)	251 (83.67)	<0.001
Received antiviral	34 (17)	241 (80.33)	<0.001
Received oxygen	51 (25.5)	231 (77)	<0.001
ICU admissions	16 (8)	173 (57.7)	<0.001
Post COVID-19 complications	19 (9.5)	201 (67)	<0.001
Hospital discharge	197 (98.5)	246 (82)	0.02
Deaths	3 (1.5)	54 (18)	<0.001

[Table/Fig-4]: Comparison of the prognosis of non diabetic (n=200) and Diabetic (n=300) COVID-19 groups.

Finally, high levels of the inflammatory markers and markers of coagulation dysfunction were found to be associated with a worse prognosis. There were 98 (54.75%) of patients with a D-dimer level between 0.5 to 2 µg/mL and 75 (88.24%) of patients with D-dimer level >2 µg/mL required to be shifted to ICU. The ICU admissions and mortality also rose with the rise in ferritin levels with 75 (78.13%) of patients with a ferritin level of more than 1000 ng/mL needing ICU admission. The CRP also showed a positive association with worse prognosis as reflected by the increasing percentages of ICU admissions and death with increasing CRP levels [Table/Fig-5]. Higher percentage of diabetic COVID-19 patients were found to suffer from Acute Respiratory Distress Syndrome (ARDS), 146 (48.7%) and acute kidney injury, 41 (13.7%) as compared to non diabetics [Table/Fig-6].

Parameters	Outcome, No (%)			
	Total (n=300)	ICU admissions	Discharge	Deaths
D-dimer (µg/mL of FEU), (Mean±SD=2.34±2.8)				
<0.5	36 (12)	0	36 (12)	0
0.5-2.0	179 (59.67)	98 (54.75)	150 (83.8)	29 (16.2)
>2.0	85 (28.3)	75 (88.24)	60 (70.59)	25 (29.41)
p-value		<0.001	0.001	
Ferritin (ng/mL) (Mean±SD=688.07±400.2)				
<500	32 (10.67)	11 (34.38)	28 (87.5)	4 (12.5)
500-1000	172 (57.33)	87 (50.58)	153 (88.95)	19 (11.05)
>1000	96 (32)	75 (78.13)	65 (67.71)	31 (32.29)
p-value		<0.001	<0.001	
C-Reactive protein (mg/L) (Mean±SD=115.2±116.8)				
<50	41 (13.67)	2 (4.88)	39 (95.12)	2 (4.88)
50-90	145 (48.33)	111 (76.55)	129 (88.97)	16 (11.03)
>90	114 (38)	60 (52.63)	77 (67.54)	37 (32.46)
p-value		<0.001	<0.001	

[Table/Fig-5]: Relation between D-dimer, ferritin, CRP levels and prognosis of COVID-19 in diabetic cases.
FEU: Fibrinogen equivalent unit. Chi-square test used for statistical analysis

Post COVID-19 complications	Total (N, %)	Non diabetic controls (n, %)	Diabetic cases (n, %)	p-value
Acute respiratory distress syndrome	162 (32.4)	16 (8)	146 (48.7)	<0.001
Acute cardiac injury	25 (5)	2 (1)	23 (7.7)	<0.001
Acute kidney injury	46 (9.2)	5 (2.5)	41 (13.7)	0.001
Acute liver injury	7 (1.4)	1 (0.5)	6 (2)	0.059
Secondary infection	7 (1.4)	0	7 (2.3)	-

[Table/Fig-6]: Comparison of post COVID-19 complications between diabetic (n=300) and non diabetic (n=200) group. Chi-square test used for p-value calculation.

DISCUSSION

Mankind has been trying hard to deal with DM, a chronic metabolic disorder that currently affects about 422 million persons worldwide particularly in the low and medium income countries [14]. With the emergence of COVID-19 infection, the diabetic population which is vulnerable to any infectious condition due to compromised immunity is exposed to another severe acute respiratory viral disease. Characterisation of COVID-19 patients in India showed that 28.6% of the patients have co-morbidities like Hypertension (HTN) or DM [15]. It became clear as COVID-19 evolved, that associated co-morbidities, most important being Cardiovascular Disease (CVD) and DM predisposed patients to adverse outcomes [16]. For a better understanding of this novel COVID-19 disease and its early diagnosis laboratory medicine plays a very important role [17]. Biochemical monitoring of COVID-19 patients through testing is critical for assessing disease severity and progression, as well as monitoring of therapeutic intervention [18]. The present study was planned to compare the inflammatory and coagulation markers between diabetic and non diabetic COVID-19 patients, to document that presence of

DM increased the risk of coagulation disorders in COVID-19 patients resulting in increased adverse outcomes.

During the course of the study while going through the case reports of the admitted patients retrospectively an important initial finding was that the admitted patients with co-morbidities outnumbered those without by 4:1 and three out of five admitted patients was diabetic. Kushwaha S et al., studied the age and gender variations in Indian COVID-19 cases and found that the male COVID-19 cases (65.39%) were more than females (34.16%) [19]. In another study by Mithal A et al., conducted in a COVID-19 facility in Delhi, India, it was found that people with DM were significantly older (mean age 59.9 vs 47.7 years), and had a higher proportion of men (74.6 vs 63.7 %). The mean duration of hospital stay was higher for the diabetes group (10.4 vs 9.1 days, p-value=0.016) [20]. Median Length Of Stay (LOS) was found to be longer in 184 patients with diabetes and/or uncontrolled hyperglycaemia compared with 386 patients without diabetes, in a study conducted by Bode B et al., in USA [21]. In the present study patients in the diabetic group was significantly older than in the non diabetic group (54.5 years vs 47.5 years, p-value <0.0001). In the diabetic case group males constituted 178 (59.3%) as compared to 122 (40.67%) females. The hospital stay of the diabetic cases were higher than non diabetic controls (14±5.13 days vs 7.58±3.9 days, p-value <0.001). The stronger immune response in females attributed to hormone estrogen being immune boosting and testosterone being considered immune suppressing may be the factor bringing in more males to the hospitals [22].

Statistical analysis of the biochemistry results showed that AST and LDH was elevated in the COVID-19 patients, whereas ALT was within range as was Total protein and Albumin levels. AST and ALT levels were high in the diabetic group as compared to non diabetic group, but the difference was not found to be significant, and as such cannot be taken as indicative of liver injury. Significantly high LDH and AST levels in diabetic COVID-19 group can be taken as indicative of tissue injury. On comparison of CRP and Ferritin levels between diabetic cases and non diabetic controls they have been found to be significantly raised in diabetic patients in this study. In a retrospective study conducted by Das B et al., involving COVID-19 patients admitted to Kokilaben Dhirubhai Ambani Hospital and Medical Research Centre, Mumbai a significant increase was found in mean values of AST, ALT, total billirubin, creatinine, CRP, Procalcitonin (PCT), LDH, IL6, ferritin, LDH, hsTroponin I, NT Pro BNP and decrease in mean values of albumin, oxygen saturation and partial pressure of oxygen in COVID-19 cases than control [23]. In a study by Malik SUF et al., blood biomarkers notably serum ferritin, CRP, D-dimer, ALT, troponin I, were significantly (p-value <0.05) higher in COVID-19 patients. Ferritin was significantly (p-value <0.05) higher in DM than non DM COVID-19 patients [24]. In a study by Guo W et al., in Wuhan Union hospital, inflammation-related markers, such as CRP {76.4 mg/L (IQR,12.4-93) vs 7.43 mg/L (3.14-13.45)}, and serum ferritin {764.8 ng/mL (IQR: 164-1496) vs 128.9 ng/mL (IQR:57.25-193.15)} was found to be significantly higher in COVID-19 patients with DM as compared to non diabetics in absence of other co-morbidities in both the groups [25].

Ferritin induces the activation of the monocyte-macrophage system which is a crucial part of the inflammatory storm [26]. In a pooled analysis aimed to compare inflammatory storm and hypercoagulability status between diabetic and non diabetic COVID-19 patients, Varikasuvu SR et al., found that the levels of serum ferritin, CRP, and D-dimer were significantly higher in diabetic COVID-19 cases as compared to non diabetic COVID-19 patients, suggesting more susceptibility of diabetic COVID-19 patients to coagulation dysfunction and inflammatory storm [27]. Along with the above markers, haematological markers also play an important role in the COVID-19 prognosis. Neutrophil to Lymphocyte ratio (NLR) is considered to be of great value in indicating a patient's inflammatory status [28]. Neutrophil count was found to be significantly raised and lymphocyte count was lower in diabetic cases. In a study by Celine et al., NLR was found to be markedly raised in COVID-19 symptomatic patients with DM [29]. With decreased immune response in diabetics [30], the raised levels of inflammatory markers along with uncontrolled hyperglycaemia signify exacerbation of the chronic inflammation, a characteristic pathology of DM progressing to cytokine storm and rapid deterioration of endothelial function, if left untreated.

D-dimer level was studied as a marker of severity in COVID-19 patients by Saravanan B et al., in Tirunelveli Medical College. It was noted that the odds of patients with high levels of D-dimer being clinically symptomatic was 5.5 times more than the odds of patients with D-dimer levels <500 ng/mL [31]. In the present study, the markers of coagulation, D-dimer, APTT, PT was found to be significantly raised in the diabetic group as compared to non diabetics. D-dimer level in COVID-19 patients with DM have been shown to be significantly high in studies by Varikasuvu SR et al., and Alguwaihes AM et al., [27,32]. Retrospective study by Chen X et al., conducted in Wuhan Jinyintan hospital showed that D-dimer levels in COVID-19 patients with DM were significantly increased in non survivors [33]. Elevated D-dimer levels are a direct consequence of increased fibrin formation and lysis and thus, an indicator of increased thrombotic activity [34]. This increased thrombotic activity signified by high D-dimer levels can result in Disseminated Intravascular Coagulation (DIC) or thromboembolism leading to the development of post COVID-19 complications. High D-dimer levels have been reported as one of the risk factors for occurrence of ARDS in COVID-19 patients [35]. In the present study, a higher percentage of diabetic COVID-19 patients were found to suffer from ARDS 146 (48.7%) and acute kidney injury 41 (13.7%) as compared to non diabetics.

Zhu L et al., in a study in Hubei province of China found that subjects with DM suffered from multiple organ injury and had a significantly higher mortality (7.8% versus 2.7%; adjusted hazard ratio: 1.49) as compared to non diabetic individuals [36]. In a study by Soni L et al., in a tertiary hospital in Chandigarh, India, significant association was found between severe COVID-19 disease and co-morbid conditions, DM and hypertension [37]. Studying the prognosis, DM patients were found to have more adverse outcomes, in terms of more percentage of diabetic patients required oxygen therapy, ICU admissions and suffered from post COVID-19 complications. Percentage of mortality was also high among diabetics as compared to non diabetics. Similar adverse outcomes have been reported in studies by Goyal P et al., [10]. Wang et al., found that patients with DM constituted 22.9% of ICU patients vs 5.9% of non ICU patients [12]. Guan WJ et al., showed that 26.9% of COVID-19 patients with DM as compared to 6.1% non diabetics suffered from severe infection and met the primary composite end point of ICU admission, mechanical ventilation and death [4].

Diabetes Mellitus or uncontrolled hyperglycaemia increased the length of hospital stay and mortality. However the study findings of Shi Q et al., DM (HR:1.58, 95% CI: 0.84-2.99) contradict this finding and rule out any association between DM and mortality or ICU admissions [38]. But DM still remains a major co-morbidity bringing about adverse prognosis. Increased risk of ICU admissions and in-hospital mortality in diabetic COVID-19 patients can be tried to be explained by advanced age, presence of diabetic complications, and inflammation further exaggerating the insulin resistance [39]. But taking into account the COVID-19 pathophysiology other factors like hyperglycaemia associated prothrombotic state should also be considered [40]. The common pathology of COVID-19 and DM suggest that acute COVID-19 induced adverse reactions may superimpose on pre-existing inflammation, glucose variability and multi-tissue injury in patients with DM to aggravate adverse outcomes.

Limitation(s)

The study did not take into consideration the complications of DM in the diabetic case group at the time of admission, which may have

individually contributed to the adverse outcomes in the diabetic case group. Duration of DM was also not taken into consideration.

CONCLUSION(S)

The present retrospective study provides direct evidence supporting the severity of COVID-19 infection in diabetic patients resulting in significantly higher mortality as compared to non diabetic patients. Keeping these findings under consideration the diabetic patients should be taken as a high risk group and vigorous monitoring as regards to glycaemic control, inflammatory markers and coagulation profile should be undertaken. This will help in early detection of cytokine storm and impending coagulation disorder so that preventive treatment can be initiated at the earliest to reduce risk of thromboembolism and DIC, thereby, decreasing the morbidity and mortality of diabetic COVID-19 infected patients.

REFERENCES

[1] Rothan HA, Byareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.
[2] Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91:157-60.
[3] COVID-19 dashboard by the center for Systems Science and Engineering (CSSE) at John Hopkins University (JHU) [Internet]. [Cited 2022 Feb 2]. Available from: https://coronavirus.jhu.edu/map.html.
[4] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
[5] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
[6] Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: Immunopathology in COVID-19. Arthritis Rheumatol. 2020;72(7):1059-63.
[7] Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-48.
[8] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8.
[9] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81.
[10] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372-74.
[11] Feldman EL, Savelieff MG, Hayek SS, Pennathur S, Kretzler M, Pop-Busui R. COVID-19 and diabetes: A collision and collusion of two diseases. Diabetes. 2020;69(12):2549-65.
[12] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-69.
[13] World Health Organization. Clinical Management of COVID-19. 2020. [Cited 2022 Feb 2]. Available from: https://apps.who.int/iris/rest/bitstreams/1278777/retrieve.
[14] World Health Organization. Global Report on Diabetes. 2021. [Cited 2022 Feb 2]. Available from: https://www.who.int/health-topics/diabetes.
[15] Gupta N, Agrawal S, Ish P, Mishra S, Gaind R, Usha G, et al. Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India. Monaldi Arch Chest Dis. 2020:90(1).
[16] Roy S, Mazumder T, Banik S. The association of cardiovascular diseases and diabetes mellitus with COVID-19 (SARS-CoV-2) and their possible mechanisms. SN Comprehensive Clinical Medicine. 2020;2(8):1077-82.
[17] Plebani M, Laposata M, Lippi G. A manifesto for the future of laboratory medicine professionals. Clin Chim Acta. 2019;489:49-52.
[18] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med (CCLM). 2020;58(7):1131-34.
[19] Kushwaha S, Khanna P, Rajagopal V, Kiran T. Biological attributes of age and gender variations in Indian COVID-19 cases: A retrospective data analysis. Clin Epidemiol Glob Health. 2021;11:100788.
[20] Mithal A, Jevalikar G, Sharma R, Singh A, Farooqui KJ, Mahendru S, et al. High prevalence of diabetes and other comorbidities in hospitalized patients with COVID-19 in Delhi, India, and their association with outcomes. Diabetes Metab Syndr. 2021;15(1):169-75.
[21] Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol. 2020;14(4):813-21.
[22] Ortona E, Pierdominci M, Rider V. Editorial: Sex hormones and gender differences in immune responses. Front Immunol. 2019;10:1076.
[23] Das B, Bhatia SY, Pal PM. Evaluation of the role of routine laboratory biomarkers in COVID-19 patients: Perspective from a tertiary care hospital in India. Indian J Clin Biochem. 2021;36(4):473-84.
[24] Malik SUF, Chowdhury PA, Hakim A, Islam MS, Alam MJ, Azad AK. Blood biochemical parameters for assessment of COVID-19 in diabetic and non-diabetic subjects: A cross-sectional study. Int J Environ Health Res. 2021:01-14.
[25] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020:e3319.
[26] Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol. 2019;10:119.
[27] Varikasuvu SR, Varshney S, Dutt N. Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. Journal of Thrombosis and Thrombolysis. 2021;51(4):941-46.
[28] Faria SS, Fernandes PC Jr, Silva MJB, Lima VC, Fontes W, Freitas-Junior R, et al. The neutrophil-to-lymphocyte ratio: A narrative review. Ecancermedicalscience. 2016;10:702.
[29] Celine, Vijayalakshmi TN, Chandini G. A Study on Neutrophil Lymphocyte Ratio in Covid 19 Patients in Tertiary Care Centre. International Journal of Physiology. 2021;9(4):16-22.
[30] Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736-E741.
[31] Saravanan B, Vasuki S, Pabithadevi BM, Saradha M, Erusan RR, Alagesan S, et al. D-Dimer: A marker of severity in COVID-19. J Clin Diagn Res. 2020;14(11):BC10-14.
[32] Alguwaihes AM, Al-Sofiani ME, Megdad M, Albader SS, Alsari MH, Alelayan A, et al. Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: A single-centre retrospective study. Cardiovasc Diabetol. 2020;19(1):205.
[33] Chen X, Chen Y, Wu C, Wei M, Xu J, Chao YC, et al. Coagulopathy is a major extrapulmonary risk factor for mortality in hospitalized patients with COVID-19 with type 2 diabetes. BMJ Open Diabetes Res Care. 2020;8(2):e001851.
[34] Soomro AY, Guerchicoff A, Nichols DJ, Suleman J, Dangas GD. The current role and future prospects of D-dimer biomarker. Eur Heart J Cardiovasc Pharmacother. 2016;2(3):175-84.
[35] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
[36] Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-1077.e3.
[37] Soni SL, Kamal K, Yaddanapudi LN, Malhotra P, Puri GD, Bhalla A, et al. Demographic & clinical profile of patients with COVID-19 at a tertiary care hospital in north India. Indian Journal of Medical Research. 2021;153(1-2):115-25.
[38] Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: A two-center, retrospective study. Diabetes Care. 2020;43(7):1382-91.
[39] Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: Understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020;8(9):782-92.
[40] Vazzana N, Ranalli P, Cuccurullo C, Davì G. Diabetes mellitus and thrombosis. Thromb Res. 2012;129(3):371-77.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam, India.
2. Associate Professor, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam, India.
3. Demonstrator, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Firdushi Begum,
Associate Professor, Department of Biochemistry, Gauhati Medical College and Hospital, Guwahati, Assam, India.
E-mail : firdushi72@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 08, 2022
- Manual Googling: Mar 12, 2022
- iThenticate Software: Apr 23, 2022 (16%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 03, 2022**
Date of Peer Review: **Mar 19, 2022**
Date of Acceptance: **May 16, 2022**
Date of Publishing: **Jun 01, 2022**