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ORIGINAL ARTICLE

Diabetes mellitus and Covid-19: the double trouble

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ABSTRACT

Objevtives: To evaluate the variations in inflammatory responses among COVID-19 patients with and without diabetes mellitus (DM) and to determine whether comorbid DM is associated with more severe outcomes during COVID-19 infection.

Methods: This cross-sectional, single-center study was conducted at Combined Military Hospital Malir, Karachi, Pakistan from July to December 2022. Ethical approval was obtained (ERC letter #78/2022/Trg/FCPS). Hospitalized COVID-19 patients with confirmed SARS-CoV-2 infection via PCR were included, while those with chronic inflammatory diseases, secondary diabetes, or pregnancy were excluded. Patients were classified into DM and non-DM (NDM) groups using American Diabetes Association criteria. COVID-19 severity was categorized based on national guidelines. Inflammatory biomarkers, including Interleukin-6 (IL-6), ferritin, and C-reactive protein (CRP), were measured within 48 hours of admission. Statistical analyses were performed using SPSS-23, with $p \leq 0.05$ considered significant.

Results: The study analyzed 483 COVID-19-positive patients with a mean age of 45.43±13.19 years, predominantly male (69.3%). Among these, 130 (27.0%) had severe disease, and 135 (28.0%) had comorbid DM. Severe COVID-19 was more prevalent in DM patients (43.7%) compared to non-diabetics (20.4%, $p<0.001$). Serum levels of CRP (Q1–Q3: 6.10–31.57 mg/L), Ferritin (Q1–Q3: 182–352 ηg), and IL-6 (Q1–Q3: 5.98–39.78 ρg/ml), were significantly higher in COVID-19 patients with DM compared to non-diabetic patients ($p <0.001$).

Conclusion: COVID-19 patients with comorbid DM exhibit heightened inflammatory responses and are at a greater risk of severe disease compared to non-diabetic patients. This highlights the importance of stringent monitoring and tailored management strategies for diabetic patients during COVID-19 infections.

Keywords: COVID-19 (MeSH); Diabetes Mellitus (MeSH); Hyperglycemia (MeSH); SARS-CoV-2 (MeSH); Cytokine Release Syndrome (MeSH); Interleukin-6 (MeSH); C-Reactive Protein (MeSH); Ferritins (MeSH); Biomarkers (MeSH); Patient Acuity (MeSH).

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INTRODUCTION

The novel Coronavirus disease 2019 (COVID-19), which originated in China, has caused unprecedented damage to healthcare systems worldwide. To date, over 771 million confirmed cases have been reported globally, with fatalities exceeding six million.[1] Beyond the health crisis, measures such as physical distancing and quarantine have disrupted the social fabric, significantly impacting mental health and well-being. Pakistan has also borne a heavy burden during the pandemic, experiencing substantial loss of lives, economic setbacks, and increased poverty rates. National statistics report, 1,580,631 confirmed cases and 30,656 deaths attributed to COVID-19, as communicated to the World Health Organization (WHO).[2]

The causative agent of COVID-19, designated as "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2), belongs to coronavirus family and is highly transmissible, primarily spreading through respiratory droplets, and leading to a spectrum of clinical manifestations, spanning from asymptomatic/ mild cases to severe pulmonary disease.[3] Evidence from the recent studies suggests a prevalent occurrence of COVID-19 in patients suffering with other comorbid conditions including hypertension, diabetes mellitus (DM) and cardiovascular disease. These underlying comorbid conditions also amplify the risk of death in addition to escalating the risk of sprouting severe illness among such patients.[4] Individuals with DM are notably vulnerable and more prone to experiencing severe complications when infected with this virus. This vulnerability has been consistently demonstrated in various viral pandemics, including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), spanning the past decades.[5] Extended hospital stay associated with severe COVID-19 disease is also observed among patients with pre-existing DM, thereby elevating the risk of mortality up to fourfold compared to individuals without diabetes.[6] Although further studies are required to validate these findings, it has been demonstrated that DM magnifies the susceptibility to complications associated with COVID-19 probably owing to the dysregulated or suppressed immune system caused by chronic hyperglycemia.[7]

The prevalence of diabetes among COVID-19 patients varies across studies and depends significantly on country-specific data.[8] According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021, over half a billion people worldwide are living with diabetes.[9] Alarmingly, Pakistan holds the highest global prevalence of diabetes.[10] The ongoing economic

instability and rising inflation in the country have exacerbated the situation, making diabetes a critical public health challenge akin to a death sentence for many.[11]

Considering the high prevalence of DM, it is imperative to comprehend the distinctive facets of COVID-19 disease in diabetic patients and the interrelationship between these two pandemics should be unveiled. Data from recent studies suggest that inflammation may play a crucial intermediary role in synergising the both diseases.[12] Evidence from literature states that DM inherently represents a chronic inflammatory state indicated by raised Ferritin and C-reactive protein (CRP) levels. Concurrently, patients with COVID-19 have been shown to undergo a cytokine storm characterized by heightened circulating levels of pro-inflammatory cytokines.[13] COVID-19 patients with DM often present with distinct clinical manifestations, laboratory findings, and prognoses compared to non-diabetic (NDM) patients.[14] Understanding the complex interplay between DM, inflammation, and COVID-19 in hospitalized individuals is crucial for developing targeted strategies to improve outcomes in this high-risk population. However, current data on the immune and inflammatory responses of COVID-19 patients with DM remains limited, highlighting a pressing need to address this knowledge gap.

This study was planned to explore the variations in inflammatory response of COVID-19 patients with and without DM and to ascertain whether comorbid DM is associated with more severe outcomes in COVID-19 infection.

METHODS

This cross-sectional, single-centred study was conducted at Combined Military Hospital, Malir Karachi from July to December 2022 after obtaining the ethical permission from institutional ethical review committee (letter # 78/2022/Trg/FCPS dated April 19, 2022).

All the hospitalised COVID-19 patients with positive SARS-CoV-2 nucleic acid detection through PCR were enrolled for this study. Their socio-demographic data including gender, age and pre-existing medical conditions was also collected. COVID-19 positive patients with history of any other chronic inflammatory disease, secondary diabetes or pregnancy were excluded out from this study.

The patients were classified according to American Diabetes Association (ADA) "Standards of Medical Care in Diabetes-2022" criteria into two categories, DM and NDM.[15] The severity of COVID-19 was categorised into mild/moderate and severe on the basis of national guidelines provided by Ministry of National Health Services.[16] To record the inflammatory and immune response of COVID-19 patients, the blood sample of each patient was collected within 48 hours of admission and analysed for the estimation of Interleukin 6 (IL-6), Ferritin and CRP levels. Values of IL-6 < 7ρg/ml, ferritin 20-250 ηg/ml and CRP <6 mg/l were taken as reference values.

The results of biochemical analysis were entered and analyzed on SPSS version 23.Categorical variables were expressed as percentages (%) and frequency rates. χ2 test was applied to find out whether the severe COVID-19 disease was associated with comorbid DM. The continuous variables in the study were expressed as mean ± standard deviation (SD) for normally distributed data, or as median (interquartile range, IQR) if not. Comparison of continuous variables between DM and NDM groups was conducted using either Student's t-test or Mann-Whitney U test as deemed appropriate. The $p \leq 0.05$ was considered as statistically significant

RESULTS

A total of 483 confirmed COVID-19 positive patients admitted to Combined Military Hospital, Malir were included in this study. Their mean age came out 45.43±13.19 years with higher proportion of male patients as compared to female patients (69.3% vs 30.6%). Diabetic patients with COVID-19 were older (57.1±7.7) than the COVID-19 patients without DM (40.8±12.0). Table I shows the other baseline characteristics of these patients.

Although the comorbid DM was present in lesser proportion (28%), its prevalence in severe COVID-19 disease was more than the twice of NDM (Table II).

As shown in Table III, COVID-19 positive patients had raised serum levels of CRP (Q1-Q3: 6.10-31.57 mg/L), Ferritin (Q1-Q3: 182-352 ηg/ml) and IL-6 (Q1-Q3: 5.98-39.78 ρg/ml) that

Table I: Baseline characteristics of a COVID-19 patients

Variables		Frequency (n=483)	Percentage (%)
Gender	Male	335	69.3
	Female	148	30.6
Glycaemic status	Diabetes Mellitus	135	28.0
	Non-Diabetes Mellitus	348	72.0
COVID-19 disease	Severe	130	27.0
	Mild to moderate	353	73.0

Table II: Comparison of COVID-19 Severity among diabetes mellitus (DM) and non-diabetes mellitus (NDM) patients

COVID-19 Disease	Glycaemic status of patients		Total (n=483)	p-value
	Diabetes Mellitus (n=135)	Non-Diabetes Mellitus patients (n=348)		
Severe	59 (43.7 %)	71 (20.4%)	130 (26.9%)	<0.001
Mild to moderate	76 (56.3%)	277 (79.6%)	353 (73.1%)	

Table III: Comparison of inflammatory biomarkers' levels among diabetes mellitus (DM) and non-diabetes mellitus (NDM) Covid-19 patients

Inflammatory Biomarkers	DM (n=135)	NDM (n=348)	Total (n=483)	p value
CRP (<6 mg/L) (IQR)	39.19 (53.9)	8.70 (7.3)	11.30 (25.5)	<0.001
Ferritin (20-250 ηg/ml) (IQR)	358.0 (337.0)	216.0 (145.3)	268.0 (170.0)	
IL-6 (<7 ρg/ml) (IQR)	30.65 (38.41)	7.54 (6.22)	9.76 (33.80)	

CRP: C-Reactive Protein, IQR: Interquartile range, IL-6: Interleukin-6

were significantly elevated in comorbidity group as compared to patients without DM (p <0.001). NDM patients with COVID-19 also had the elevated CRP and IL-6 levels (13.79±17.66 and 17.55±23.67 respectively). However; serum Ferritin levels among this study group were within the reference range (231.572±114.17 ηg/ml).

DISCUSSION

This study assessed inflammatory responses and disease severity in 483 hospitalized COVID-19 patients, 28% of whom had DM. Severe disease was more frequent in DM patients (43.7% vs. 20.4%, p<0.001). Inflammatory biomarkers were significantly higher in DM patients, with CRP at 39.19 mg/L vs. 8.70 mg/L, ferritin at 358.0 ηg/ml vs. 216.0 ηg/ml, and IL-6 at 30.65 ρg/ml vs. 7.54 ρg/ml (p<0.001). These results suggest a stronger inflammatory response in DM patients, correlating with increased disease severity.

DM, a chronic metabolic disorder, poses a significant global health challenge. Emerging evidence highlights its association with increased susceptibility to infections, as well as heightened morbidity and mortality. The coexistence of DM with COVID-19 presents a compounded burden on healthcare systems. In our study, prevalence of DM among confirmed cases of COVID-19 was 28%. Moreover, severe COVID-19 disease afflicted the 59 (43.7%) patients with DM compared to 71 (20.4%) patients with NDM. The inflammatory response to COVID-19 was also more marked in patients with DM (p<0.001) than the NDM (Table III).

The prevalence of DM in our study was considerably higher than that reported by some initial studies form China, a country that served as the epicentre for the global dissemination of COVID-19.[6] This difference can be well explained by the top rank of Pakistan in Diabetes prevalence (30.8 %).[17] Our findings are in agreement with a study that included 5,700 COVID-19 positive hospitalised patients from New York, and had reported 33.8% prevalence of DM in this cohort.[18] Another study conducted in India by Mittal et al. reported analogous findings, with a prevalence of DM at 45.8% among COVID-19 hospitalized patients.[19] Similarly, in a recent meta-analysis, Bradley reported that out of 10,648 COVID-19 confirmed cases, 3112 patients had DM, yielding a prevalence of 29.23%.[20] Albishi WK in his retrospective study also documented the 33% prevalent DM in COVID-19 patients of Saudi Arabia, a country with second highest DM prevalence in that region.[14]

Our study results indicated a strong association between severe COVID-19 disease and pre-existing DM (p<0.001). Our observation aligns with one of the most extensive meta-analyses, encompassing 40 research papers and analyzing 18,012 confirmed cases of COVID-19, in which Pititto et al. observed a discernible positive association between DM and the COVID-19 severity as well as mortality.[4] However, Zhang et al. presented a dissenting perspective in his study, suggesting that DM may not pose a significant risk for severe disease in the context of COVID-19. This difference can be attributed to small sample size (n=140) and lesser prevalence of DM (12.1%) in their study.[21]

Aligning with the broader trend, our study also revealed that a little higher proportion of DM patients exhibited mild to moderate manifestations of COVID-19, as opposed to severe forms of the disease (56.3% vs 43.7%). These findings are further supported by a retrospective study conducted in Indonesia which similarly demonstrated a lesser percentage of DM patients experiencing the severe COVID-19. The majority of the patients predominantly exhibited mild and asymptomatic manifestations of the disease (55.4% & 26.9% respectively).[22]

DM has also been identified as a significant risk factor for unfavourable outcomes in the two preceding coronavirus infections, "SARS" (Severe Acute Respiratory Syndrome) and "MERS" (Middle East Respiratory Syndrome), before the advent of the COVID-19 pandemic. A comprehensive meta-analysis assessing mortality risk factors across the spectrum of these three coronavirus diseases, revealed the existence of analogous laboratory indicators signalling unfavourable outcomes.[5] The bidirectional link between hyperglycemia and chronic inflammation renders DM susceptible to diverse changes in the immune system. These changes encompass alterations in the levels of specific proinflammatory cytokines, chemokines, and other inflammatory biomarkers, leading to insulin resistance and β-cell dysfunction. A parallel inflammatory response has also been reported in the literature concerning COVID-19 disease.[12] Understanding how DM intricately contributes to the severity of COVID-19 disease is critical. While the definitive causal link between diabetes and COVID-19 remains unexplored, the existing body of knowledge suggests that proinlammatory state along with immune dysregulation caused by chronic hyperglycemia observed in DM synergistically contribute to an increased susceptibility for COVID-19 disease and its adverse outcomes.[23]

We posit that in diabetic patients, the underlying chronic inflammatory state may set the background for additional elevations in the levels of inflammatory cytokines and other biomarkers in those suffering with COVID-19, thereby, leading to the development of cytokine storm resulting in widespread tissue injury and poor prognosis of such patients. CRP is an Acute Phase Reactant (APR) produced in liver by the

prompt of IL-6 in certain inflammatory conditions and is thought to mediate the association between DM and COVID-19 disease.[13] IL-6 itself a leading cause of inflammatory response in COVID-19 patients and is associated with high mortality due to virally driven hyperinflammation.[23] Similarly, although Ferritin is used to estimate the iron stores of our body, it also serves as inflammatory marker in both acute and chronic inflammatory states.[24]

In our study, we observed the elevated levels of inflammatory biomarkers in both groups with DM and NDM. However, the levels were significantly higher in COVID-19 hospitalized patients with DM compared to NDM patients (CRP: 39.19 vs 13.79, Ferritin: 358 vs 216, IL-6: 30.65 vs 7.54p<0.001). This observation indicates that individuals with COVID-19 and comorbid DM were more prone to have severe inflammatory response. Our study observations are supported by the similar findings of studies from India, China and Bangladesh.[19,25,26]

COVID-19 Variations observed among countries are more plausibly linked to diverse factors such as distinct healthcare systems and interventions implemented to mitigate the outbreak. Additionally, these differences may be influenced by variations in the prevalence and characteristics of conditions that could synergistically exacerbate health outcomes in the context of COVID-19, such as the average age of the population and the prevalence of other comorbidities.

Limitations of the study and future direction

This study has several limitations. The relatively small cohort size and single-centre design may limit the generalizability of the findings. Additionally, the unequal distribution of DM (28%) and NDM (72%) patients may have influenced the comparative analysis. The reliance on a single time point for biochemical assessments might not fully capture the dynamic inflammatory response. Furthermore, detailed historical data on DM patients, including treatment modalities, glycemic control status, and the prevalence of untreated or uncontrolled diabetes, were lacking.

Future research should focus on large-scale, multi-centre studies that include detailed risk factor analyses and extended follow-up periods. These efforts are crucial for advancing our understanding of the pathophysiological mechanisms linking COVID-19 and DM, ultimately aiding in the development of more effective clinical management strategies.

CONCLUSION

This study highlights the significant impact of diabetes mellitus on the inflammatory response and severity of COVID-19 infection. Hospitalized COVID-19 patients with DM demonstrated markedly elevated levels of inflammatory biomarkers, including CRP, ferritin, and IL-6, compared to non-diabetic patients. Additionally, severe disease was more prevalent in the diabetic cohort, underscoring the heightened vulnerability of this group. These findings emphasize the importance of vigilant monitoring and tailored management strategies for COVID-19 patients with DM to mitigate adverse outcomes and improve clinical care in this high-risk population.

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AUTHORS' CONTRIBUTIONS

Following authors have made substantial contributions to the manuscript as under:

AiA: Conception and study design, acquisition of data, drafting the manuscript, approval of the final version to be published

SY: Study design, critical review, approval of the final version to be published

AAK: Conception, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

AbA & RQ: Acquisition of data, critical review, approval of the final version to be published

MHA: Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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