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# Mortality of COVID-19 Patients at ICU with Diabetes Mellitus in Bangladesh: Role of Multimorbidity and Diagnostic Biomarkers

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## Abstract

***Background:*** Diabetes Mellitus (DM) is one of the major reasons for mortality of hospitalized COVID-19 patients. This study aimed to determine the role of multimorbidity anddiagnostic biomarkers in the mortality of diabetic COVID-19 patients in the intensive care unit (ICU).

***Methods:*** We conducted a cross-sectional study among ICU admitted COVID-19 patients with DM at two tertiary-level hospitals in Dhaka from May 2020 to April 2021. The role of multiple co-morbidities such as lung disease, cardiovascular diseases, hypertension, malignancy, hyperthyroidism, etc., including diagnostic biomarkers of COVID-19 severity were also assessed.

***Results:*** Overall, 40% of ICU admitted COVID-19 patients with DM died during the study period. With the increase in the number of co-morbidities, the proportion of death increases. The death rate was as high as 86% if COVID-19 patients had five or more selected chronic diseases. Moreover, smoking habit (AOR= 2.7, 95% CI: 1.6, 4.5), acute kidney infection (AOR=5.2,95% CI: 3.0, 8.9), anemia (AOR=1.7, 95%CI: 1.1, 2.8), lymphopenia (AOR=1.9, 95%CI: 1.2, 3.1), leukocytosis (AOR=1.9, 95%CI: 1.3, 2.9), abnormal D-Dimer (AOR=2.7, 95% CI: 1.7, 4.5), abnormal ALT level (AOR=1.5, 95%CI: 1.1, 2.9), and abnormal BUN (AOR=2.1, 95%CI: 1.2, 3.6) was identified as significant predictor of mortality.

***Conclusion:*** A highproportion of mortality was seen among patients with several comorbidities. Sincere attention should be given to COVID-19 patients with DM and early consideration of multimorbidity would decrease patients' death risk.


**Keywords:** COVID-19; Diabetes Mellitus; Mortality; Multimorbidity; ICU; Biomarkers.

# Introduction

Since the inception of the COVID-19 pandemic, scientists have emphasized the impact of multimorbidity on higher mortality risk of patients by using epidemiological data (1,2). Diabetes mellitus (DM) patients have a poor glucose control mechanism that makes them more vulnerable to developing severe COVID-19 infection, especially among poorly controlled patients(3,4). According to the International Diabetes Federation (IDF),there were around 465 million diabetes mellitus patients worldwide in 2019, comprising about 10% of the global population(5); predicted to be double by2045(6). Among those diagnosed cases, more than 75% of diabetic patients live in low-income or middle-income countries, especially from Asian regions(7). Diabetic patients have approximately 10 years less life expectancy than normal people, and 80% die from cardiovascular diseases (8).

Bangladesh is facing rapid growth in the prevalence of diabetes mellitus and other non-communicable diseases. According to IDF report of February 2022, there is more than 13 million adult case of diabetes mellitus in Bangladesh which is 12.5% of total adult population (6).This indicates a sharp increase in both the number and prevalence of DM when compared to estimates last few years (9,10). Moreover, DM is the reason of more than 3% of all death in Bangladesh (11).

There is also a potential pathogenetic relationship between uncontrolled blood glucose and COVID-19, which affect inflammation, immune system, and activation of the renin-angiotensin-aldosterone system (RAAS), etc.(12). Moreover, Cardiovascular disease, cancer, hypertension, lung disease, hypothyroidism and some other chronic diseases are also associated with severe form of COVID-19 infection(13). Treatments for chronic diseases like cancer weakens patients' ability to fight with other disease. As COVID-19 is associated with severe lung infection therefore, a preexisting of lung disease can make the condition worse. Similarly, having cardiovascular problems and hypertension can also increase the risk of life threatening COVID-19 infection (14).

After the inception of COVID 19 pandemic a vast number of studies have been conducted worldwide on available diagnostic biomarkers such as anemia value, D-dimer, platelet count, lymphocyte count, etc. showed a good predictive

value for severe infection (15,16). Study has also been conducted among ICU patients regarding the role of comorbidity in mortality and observed an association of severe progression and death(17). However, the research in Bangladesh is very much limited to various socio-demographic factors and mental health condition.

A high prevalence of DM among Bangladeshi adults urges special attention to COVID-19 patients with DM. However, study focusing on COVID 19 patients in ICU with DM have not been conducted in Bangladesh and very limited around the world yet though there is a potential pathogenetic relationship. Moreover, the impact of multiple co-morbidities has not been clearly demonstrated. Therefore, the aim of this study was to assess the role of multiple co-morbidities (selected chronic diseases) such as lung disease, cardiovascular diseases, hypertension, malignancy, hyperthyroidism etc. including available diagnostic biomarkers among ICU patients having diabetes mellitus.

# Methodology

## Study design

We conducted a cross-sectional study among COVID-19 patients with Diabetic Mellitus who were admitted to the intensive care unit (ICU) of two conveniently selected COVID-19 dedicated tertiary-level hospitals located inside Dhaka city. Data from ICU admitted patients were collected from August 2020 to July 2021. During the study period, complete set of demographic information and medical records of 564 diabetic patients were retrieved for analysis. Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay for COVID-19 infection was applied to each of the patients for confirmation.

## Tools and variables

Primarily we have recorded various socio-demographic characteristics of patients' which includes the age, gender, and smoking habit of the participants. In line with the aim, we have targeted the presence of various comorbidities, such as hypertension, lung disease, malignancy, cardiovascular disease and hypothyroidism. Multimorbidity was determined by the presence of any of the five selected chronic diseases (hypertension, lung disease, CVD, malignancy, hypothyroidism) with diabetes mellitus. For the presence of any of those disease the proportion of death increases compared to people those does not have. We have assessed diagnosis results related to severe COVID-19 infection such as acute kidney injury (AKI), blood group, acute respiratory distress syndrome (ARDS), bacterial co-infection, anemia, lymphocytopenia, leukocytosis, D-Dimer level, sodium level, ALT level, CRP, Ferritin, BUN. On the basis of severity, the presence of ARDS was divided into mild, moderate and severe.

## Statistical analysis

The descriptive statistics (mean, frequency, percentage) were used to describe the explanatory and dependent variables. The status of multimorbidity and its impact on mortality was described by bar diagram. To determine the association between various explanatory variables and death in ICU, Pearson's chi-square test, Mann-Whitney U test, Fisher's exact test were fitted when appropriate. Statistically significant variables were subjected to multiple logistic regression analyses to identify the predictors of ICU death in COVID-19 infection. Data were analyzed by IBM SPSS version 23 statistical package software. A p-value of $<0.05$ was considered statistically significant.

## Ethical consideration

The Ethical approval of this research was obtained from the Institutional Review Board (IRB) of North South University (NSU), Bangladesh (2020/OR-NSU /IRB-No-). The study was completed following the suggestion and guidelines of the IRB of NSU. Informed consent from patients was waived as it was a hospital-based retrospective cross-sectional study. All the patient's data were maintained confidential. The Helsinki Declaration (1964) was followed in the whole procedure of the research.

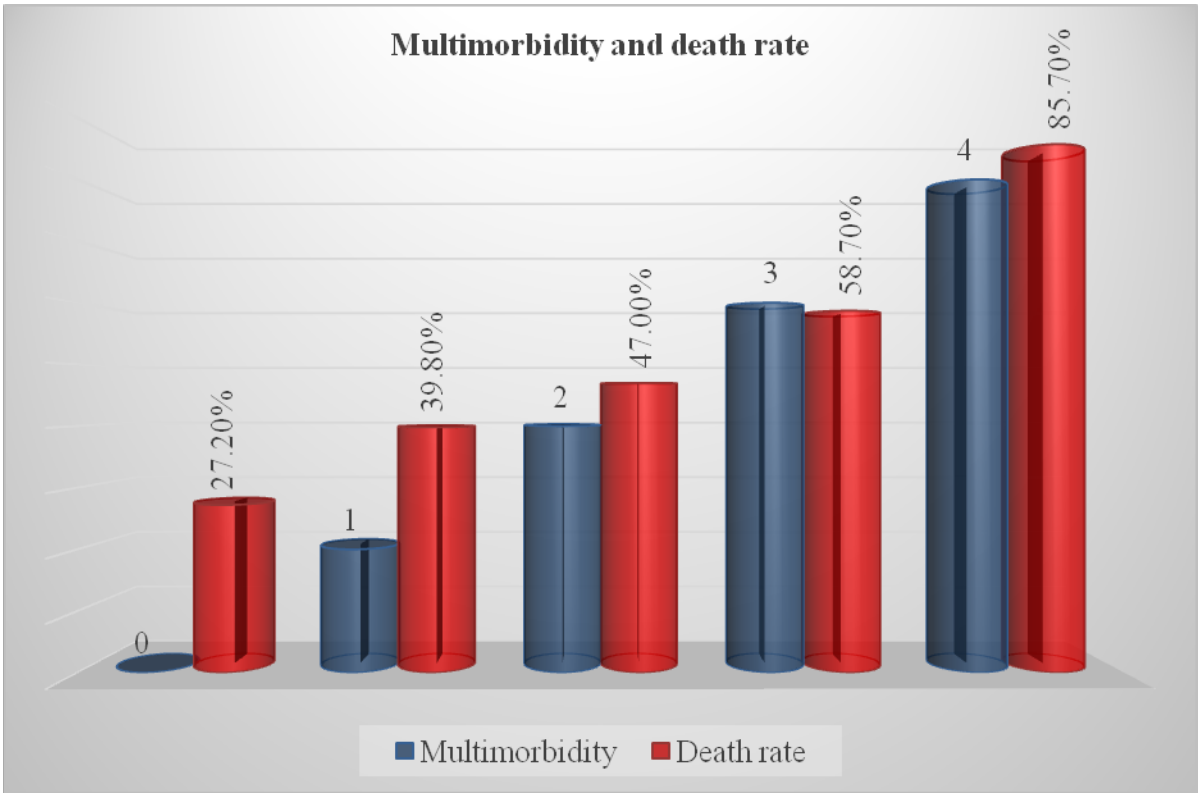
## Results

Overall, 564 ICU admitted COVID-19 patients with DM were included in the analysis, of them 226 (40%) patients died. The mean age of the diabetic COVID-19 patients was 58.6 years and the mean age of the non-survivor group was much lower (63 years) than the survivor/ discharged group (56 years). The death rate was much higher among patients aged 60 years or more (51.5%) and the association was statistically significant. Male also poses a higher death rate (43%) compared to female (33%) and smoking has a highly significant association with COVID-19 mortality in diabetic patients.

Table 1:Socio-demographic characteristics, comorbidities of COVID-19 patients

| Variables | Total N = 564 | Survivors N = 338 | Non-survivors N = 226 | P value |
|---|---|---|---|---|
| Age(years), Mean ± SD | 58.58 ± 11.33 | 55.86 ± 9.9 | 62.64 ± 12.1 | |
| < 60 years | 298 | 209 (70.1) | 89 (29.9) | <0.01* |
| ≥ 60 years | 266 | 129 (48.5) | 137 (51.5) | |
| Gender | | | | 0.03* |
| Male | 396 (70.2) | 226 (57.1) | 170 (42.9) | |
| Female | 168 (29.8) | 112 (66.7) | 56 (33.3) | |
| Smoking | | | | <0.01* |
| Yes | 136 (24.1) | 59 (43.4) | 77 (56.6) | |
| No | 428 (75.9) | 279 (65.2) | 149 (34.8) | |
| Hypertension | | | | 0.08 |
| Yes | 277 (49.1) | 156 (56.3) | 121 (43.7) | |
| No | 287 (50.9) | 182 (63.4) | 105 (36.6) | |
| Lung disease | | | | 0.03* |
| Yes | 112 (19.9) | 57 (50.9) | 55 (49.1) | |
| No | 452 (80.1) | 281 (62.2) | 171 (37.8) | |
| Malignancy | | | | 0.02* |
| Yes | 11 (2.0) | 3 (27.3) | 8 (72.7) | |
| No | 553 (98) | 335 (60.6) | 218 (39.4) | |
| Hypothyroidism | | | | 0.01* |
| Yes | 80 (14.2) | 38 (47.5) | 42 (52.5) | |
| No | 484 (85.8) | 300 (62.0) | 184 (38.0) | |
| Cardiovascular disease | | | | <0.01* |
| Yes | 171 (30.3) | 80 (46.8) | 91 (53.2) | |
| No | 393 (69.7) | 258 (65.6) | 135 (34.4) | |

Figure 1. Multimorbidity and deaths rate of COVID 19 Patients with diabetes mellitus at ICU




The figure 1 is a clear indicator of multimorbidity impact on the death rate of ICU admitted COVID-19 patients with DM. If the patients had no considered comorbidity other than DM, the death rate was around 27%. The death rate was drastically increased with the increase in comorbidity numbers. According to our observations, there were patients with five comorbidities, including DM, and in those cases, the death rate is very high at around 86%. The death rate was 59% when there were four comorbidities, including DM, and 47% when three comorbidities. Our chi-square analysis also identified a statistically significant association with the presence of all selected co-morbidities except hypertension ($p<0.05$).

We have also assessed the blood group of our patients, where group B followed by A was more common than the O or AB blood group. The death rate was higher among A and O blood group patients. The prevalence of acute kidney infection (AKI) was very high (31.6%) among COVID-19 patients with DM and associated with a high death rate in ICU patients. Moreover, 26.6% had moderate, and 13.1% had severe ARDS, which showed a statistical association with an increased death rate. We have also analyzed available diagnostic biomarkers, and the majority of them have a statistically significant association with the increased death rate in the Mann-Whitney U test (Table 2).

Table 2:Diagnostic biomarkers of COVID-19 patients

| Variables | Total N = 564 | Survivors N = 338 | Non-survivors N = 226 | P value |
|---|---|---|---|---|
| Blood Group | | | | 0.25 |
| A | 148 (26.2) | 82 (55.4) | 66 (44.6) | |
| AB | 56 (9.9) | 37 (66.1) | 19 (33.9) | |
| B | 257 (45.6) | 162 (63.0) | 95 (37.0) | |
| O | 103 (18.3) | 57 (55.3) | 46 (44.7) | |
| Rhesus (Rh) factor | | | | 0.88 |
| Positive | 528 (93.6) | 316 (59.8) | 212 (40.2) | |
| Negative | 36 (6.4) | 22 (61.1) | 14 (38.9) | |
| Acute kidney infection | | | | |
| Yes | 178 (31.6) | 77 (43.3) | 101 (56.7) | <0.01* |
| No | 386 (68.4) | 261 (67.6) | 125 (32.4) | |
| Acute respiratory distress syndrome | | | | <0.01* |
| No | 193 (34.2) | 134 (69.4) | 59 (30.6) | |
| Mild | 147 (26.1) | 98 (66.7) | 49 (33.3) | |
| Moderate | 150 (26.6) | 80 (53.3) | 70 (46.7) | |
| Severe | 74 (13.1) | 26 (35.1) | 48 (64.9) | |
| Hemoglobin, Mean ± SD | 12.32± 2.463 | 12.66± 2.4 | 11.82± 2.45 | <0.01* |
| WBC, Mean ± SD | 10.1 ± 2.9 | 9.72 ± 2.86 | 10.68 ± 2.88 | <0.01* |
| Lymphocyte, Mean ± SD | 1.33 ± 0.6 | 1.38 ± 0.63 | 1.25 ± 0.58 | 0.01* |
| Platelet, Mean ± SD | 206.2 ± 63.99 | 208.1 ± 66.63 | 203.4 ± 59.88 | 0.82 |
| D-dimer, Mean ± SD | 3.3 ± 1.62 | 3.14 ± 1.65 | 3.52 ± 1.54 | <0.01* |
| LDH, Mean ± SD | 484.19 ± 225.1 | 460.69 ± 187.1 | 519.34 ± 268.9 | 0.13 |
| CRP, Mean ± SD | 68.03 ± 64.8 | 59.1 ± 56.7 | 81.37 ± 73.53 | <0.01* |
| Ferritin, Mean ± SD | 637.19 ± 481.1 | 612.65 ± 427.4 | 673.88 ± 550.7 | 0.04* |
| Creatinine, Mean ± SD | 1.47 ± 1.51 | 1.44 ± 1.48 | 1.52 ± 1.56 | 0.51 |
| AST, Mean ± SD | 56.88 ± 31.86 | 52.27 ± 25.38 | 63.77 ± 38.67 | <0.01* |
| ALT, Mean ± SD | 69.13 ± 43.5 | 64.5 ± 40.24 | 76.05 ± 47.2 | <0.01* |
| BUN, Mean ± SD | 19.83 ± 8.9 | 19.08 ± 8.6 | 20.95 ± 9.25 | 0.01* |
| Sodium, Mean ± SD | 136.21 ± 6.48 | 136.57 ± 5.87 | 135.66 ± 7.28 | 0.04* |
| Potassium, Mean ± SD | 4.22 ± 0.78 | 4.25 ± 0.73 | 4.17 ± 0.86 | 0.07 |

We have also undergone a multiple logistic regression analysis to see the determinants of mortality among diabetic COVID-19 patients in the ICU. Our analysis revealed that, smoking habit (AOR= 2.7, 95% CI: 1.6, 4.5), acute kidney infection (AOR=5.2,95% CI: 3.0, 8.9), anemia (AOR=1.7, 95%CI: 1.1, 2.8), lymphocytopenia (AOR=1.9, 95%CI: 1.2, 3.1), leukocytosis (AOR=1.9, 95%CI: 1.3, 2.9), abnormal D-Dimer (AOR=2.7, 95% CI: 1.7, 4.5), abnormal ALT level (AOR=1.5, 95%CI: 1.1, 2.9), and abnormal BUN (AOR=2.1, 95%CI: 1.2, 3.6) was significant predictor of mortality(Table 3).

Table 3. Multiple logistic regression analysis of statistically significant factors of ICU mortality

| Associated factor | AOR | 95% CI | | P value |
|---|---|---|---|---|
| | | LCI | UCI | |
| Age (<60 years) | 0.12 | 0.07 | 0.21 | <0.01* |
| Gender (female) | 0.76 | 0.47 | 1.24 | 0.27 |
| Smoking (yes) | 2.68 | 1.61 | 4.46 | <0.01* |
| Lung disease (yes) | 1.12 | 0.63 | 1.92 | 0.73 |
| Malignancy (yes) | 2.29 | 0.52 | 1.57 | 0.27 |
| Hypothyroidism (yes) | 1.22 | 0.68 | 2.16 | 0.51 |
| Acute kidney disease (yes) | 5.18 | 3.01 | 8.94 | <0.01* |
| Preexisting CVD (yes) | 3.06 | 1.05 | 8.92 | 0.09 |
| Anemia (yes) | 1.74 | 1.11 | 2.76 | 0.02* |
| Lymphopenia (yes) | 1.92 | 1.21 | 3.08 | 0.01* |
| Leukocytosis (yes) | 1.93 | 1.26 | 2.95 | <0.01* |
| D-Dimer level (abnormal) | 2.74 | 1.71 | 4.48 | <0.01* |
| Sodium level (normal) | 0.77 | 0.50 | 1.18 | 0.23 |
| ALT level (abnormal) | 1.55 | 1.02 | 2.95 | 0.04* |
| CRP (Abnormal) | 1.04 | 0.56 | 1.93 | 0.91 |
| Ferritin (Abnormal) | 1.16 | 0.68 | 1.97 | 0.58 |
| BUN (Abnormal) | 2.08 | 1.20 | 3.61 | 0.01* |

## Discussion

A large number of studies have been conducted focusing on COVID-19 since the inception of the pandemic. However, a few studies have focused on ICU patients. The current study is focused on the multimorbidity of ICU patients with COVID-19 and DM, which has come up with some critical observations. According to our analysis, a high proportion (40%) of ICU patients with COVID-19 died, indicating coronavirus's potential pathogenetic relationship with uncontrolled blood glucose. The overall balance of ICU death was also much lower in previous studies conducted in Bangladesh and India (18,19). We have successfully assessed the impact of multimorbidity on the mortality of ICU admitted COVID-19 patients with DM. Where, the death rate of ICU patients was drastically increased with the increase of comorbidity numbers. A study conducted in Scotland identified a significant impact of multimorbidity on mortality, with 48% increase in death risk (20). Multimorbidity was also observed as an independent predictor of greater risk of severe infection and mortality in the United kingdom (21).

A recently conducted study has identified acute kidney disease, cardiovascular disease, respiratory disease, diabetes, hypertension, and cancer as independent determinants of COVID 19 mortality (22). We have also observed a statistically significant association between these comorbidities and the mortality of ICU patients. Another study also discussed the increase in the mortality risk, which concluded that having at least one of those comorbidities is associated with a significant increase in mortality (23). Abnormal BUN, an indicator of kidney infection, was also identified as a significant predictor of mortality. The BUN, BAR, and albumin levels were also described as reliable predictors of mortality of hospitalized covid 19 patients in several previously conducted studies (24,25). A study conducted in Iran identified anemia as an independent predictor of COVID-19 death, which corroborates our findings(26).

*Li Tan et al.* concluded that lymphopenia as a reliable indicator of the severity, hospitalization and increased death rate in COVID-19 patients. They also suggested to includeit in the diagnosis and therapeutic guidelines of COVID-19 patients (27).Our analysis has also identified lymphopenia as independent predictor of mortality of ICU admitted COVID-19 patients. A study conducted by *Babak et al.* observed a significant association between rate of mortality in patients with COVID-19and leukocytosis(28). Our analysis also identified leukocytosis as independent predictor for COVID-19 related mortality of ICU patients. Previous studies have identified liver dysfunction as independent predictor for COVID-19 infection(29,30). In our analysis, we have identified abnormal ALT level as an indicator for ICU mortality of diabetic COVID-19 patients. Therefore, liver dysfunction related indicators should be closely monitored among hospitalized patients.

We have also determined the statistical association between demographic factors with the mortality of ICU patients. According to this study, smokers with DM are at high risk of COVID-19-related mortality. A study conducted in the UK also identified that smoking is associated with a higher infection rate, increased severity of infection, and mortality (31).

**This was probably the first study in Bangladesh which specifically focused on** COVID-19 patients with DM and assessment of multimorbidity. It has successfully reveled the impact of multimorbidity in the mortality of COVID-19 patients and also identified some other critical determinants for ICU death of diabetic patients. Besides these important findings, the study has several limitations. The study was conducted in only two hospitals of Dhaka city, a confined geographic area that limits the generalizability of our findings. Collection of samples from each of the administrative division of Bangladesh would assure the significancy of findings. Moreover, inclusion of some other important variables such as patient's lifestyle, habit, BMI, qSOFA score would provide more reliable results. We did not follow the patients after discharge from the hospital, which was also important to identify some other crucial findings.

## Conclusion

Non-communicable disease specially diabetes mellitus has become a burden for Bangladesh health system and inception of COVID-19pandemic made the burden an enormous challenge. Our analysis has revealed a high proportion of death among COVID-19 patients with DM. Moreover, patients with several comorbidities increase the death risk to a very high level. Therefore, sincere attention should be given to COVID-19 patients with DM and an early consideration of those multimorbidity in treatment procedures is essential to decrease the death risk of patients.

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