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Type 2 diabetes is associated with increased risk of critical respiratory illness in patients COVID-19 in a community hospital

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ABSTRACT
Background: Type 2 diabetes (T2D) is the leading non-communicable disease worldwide and is associated with several microvascular and macrovascular complications. Individuals with T2D are more prone to acquiring selected types of infections and are more susceptible to complications due to these infections. This study aimed to evaluate the relationship between T2D and COVID-19 in the community setting.

Methods: This was a single-center retrospective analysis that included 147 adult patients with laboratory-confirmed COVID-19 admitted to a community hospital. Demographics, medical history, symptoms and signs, laboratory findings, complications during the hospital course, and treatments were collected and analyzed. The Kaplan-Meier method was used to describe the probability of intubation in patients with T2D as compared with patients without T2D. The hazard ratio for intubation in the survival analysis was estimated using a bivariable Cox proportional-hazards model.

Results: Of 147 patients, 73 (49.7%) had a history of T2D. Patients with T2D had higher requirement of ICU admission (31.5% vs 12.2%; p = .004), higher incidence of ARDS (35.6% vs 16.2%, p = .007), higher rates of intubation (32.9% vs 12.2%, p = .003), and higher use neuromuscular blocking agents (23.3% vs 9.5%, p = .02). In the survival analysis at 28 days of follow-up, patients with T2D showed an increased hazard for intubation (HR 3.00; 95% CI, 1.39 to 6.46).

Conclusion: In our patient population, patients with COVID-19 and T2D showed significantly higher ARDS incidence and intubation rates. The survival analysis also showed that after 28 days of follow-up, patients with T2D presented an increased risk for shorter time to intubation.

1. Introduction

Diabetes is a chronic disease characterized by abnormally high blood glucose levels resulting from an impairment in insulin action or secretion. Diabetes is the leading non-communicable, chronic pandemic disease worldwide and is associated with several complications. Over time, high blood glucose can damage the body's small and large blood vessels, causing an increased risk for microvascular and macrovascular complications (Beckman and Creager, 2016). Based on the epidemiological evidence, individuals with diabetes are more prone to acquiring selected types of infections, and they are also more susceptible to certain complications from these infections (Crichtley et al., 2018; Muller et al., 2005; Shah and Hux, 2003). SARS-CoV-2 is a novel coronavirus that causes COVID-19, which was declared a pandemic as of March 11, 2020, by the World Health Organization (WHO). As of July 1, 2020, 10.3 million cases have been reported, with an estimated fatality rate of 0.5%–3.5% (World Health Organization, 2020).

Diabetes is one of the most frequent comorbidities reported in patients with COVID-19. Among patients with confirmed COVID-19, the proportion with diabetes was 22% in one study of 191 patients (Zhou...
et al., 2020) and 16.2% in another cohort of 1099 patients (Guan et al., 2020). Notably, a report of 72,314 COVID-19 cases found higher mortality in patients with diabetes (7.3% vs. 2.3% overall) (Wu and McGoogan, 2019). There have been a plethora of publications since the pandemic breakout. At the same time, many of the studies have confirmed the association of diabetes with worse outcomes. However, most populations vary in their epidemiological characters and health system. This study investigates the association of diabetes with COVID-19 outcomes in patients admitted to a community hospital in Illinois, USA.

2. Methods

In this single-center, retrospective cohort study, we included patients subsequently admitted to AMITA Health Saint Francis Hospital from March 1 to April 30, 2020, with symptomatic COVID-19. Data were abstracted from Electronic Medical Records among all patients with laboratory-confirmed COVID-19 by RT-PCR (Abbott™ RealTime™ SARS-CoV-2 assay). Diabetes was defined as a diabetes history listed in the chart or newly documented glycohemoglobin of ≥ 6.5% on admission. We collected demographic data, symptoms, signs, lab results, treatments, hospital courses, and complications.

Descriptive statistics were used to summarize the data; categorical variables were described as frequency rates and percentages, and continuous variables were described using median and interquartile range values. We used the Mann-Whitney U test, Chi-squared test, or Fisher’s exact test to compare differences between patients with and without diabetes when appropriate. Given mortality findings, the primary analysis focused on invasive mechanical ventilation. We used a Kaplan-Meier curve to describe the probability of intubation in patients with diabetes compared to patients without diabetes. Patients without the event were right-censored at day 28 of follow-up. Survival curves were compared using the Log-Rank test, where a two-sided P value of less than 0.05 was considered statistically significant. The hazard ratio for intubation in the survival analysis was estimated using a bivariable Cox proportional-hazards model. All statistical analyses were performed using SPSS Version 23.0. (Armonk, NY: IBM Corp).

3. Results

A total of 147 patients were included. The median age was 69 years (interquartile range [IQR], 59–79 years), with 58 (40%) being female, and 73 (49.7%) had a history of diabetes. Among patients with diabetes, the median age was 73 years (IQR, 59–76 years), and 41.1% were female. The median BMI was 26.6 (IQR, 22–32), and the median glycated hemoglobin (HbA1c) was 6.3% (IQR, 5.7–7.7%). (Table 1.1)

The most common underlying comorbidities were hypertension (68.7%), followed by dementia (29.3%), chronic obstructive pulmonary disease (COPD) (20.4%), chronic kidney disease (CKD) (17.0%), congestive heart failure (CHF) (13.6%), coronary artery disease (CAD) (12.9%), history of cancer (9.5%), and asthma (8.2%). Compared with patients without diabetes, patients with diabetes had significantly higher hypertension rates (Table 1).

For all patients, the most common presentation was fever (76.1%) and shortness of breath (72.6%), followed by cough (57.1%). Other symptoms included altered mental status (15.0%), chest pain (4.1%), nausea or vomiting (9.6%), sore throat (6.8%), and anosmia (4.8%). Clinical presentations were similar between the two groups, except patients without diabetes had more nausea or vomiting (Table 1). Among patients with diabetes, the values of white blood cell count, the absolute neutrophils count, serum creatinine, and lactate were numerically significantly higher than those without diabetes. In contrast, patients with diabetes had numerically/significantly lower levels of as compared to those without diabetes. Other laboratory results are shown in Table 2.

Regarding inflammation-related markers, patients with diabetes presented significantly higher levels of D-dimer compared to patients without diabetes. Other inflammation-related markers are shown in Table 3.

Further, we analyzed the complications developed in our patients and compared their number and effects on patients with and without diabetes. Among the total COVID-19 patients analyzed, transaminitis was the most commonly observed complication (48.3%), followed by acute kidney injury (AKI) on admission (42.9%), ARDS (26.0%), myocardial ischemia (20.8%), prolonged corrected QT interval (15.6%), GI bleed (6.2%), new-onset arrhythmia (5.5%), venous thromboembolism (VTE) (4.1%) and stroke (1.4%). Patients with diabetes presented statistically significant higher ARDS rates and numerically higher transaminitis, AKI on admission, prolonged QTc, and stroke than patients without diabetes. On the other hand, patients without diabetes developed a significantly higher percentage of new-onset, GI bleed, and myocardial ischemia (Table 4).

Finally, we analyzed the outcome measures (Table 5). A significantly higher percentage of patients with diabetes required diuretics, invasive mechanical ventilation, intensive care unit (ICU) admission and neurovascular blocking agents compared to patients without diabetes. Likewise, a numerically higher percentage of patients with diabetes required pressor support on admission or later during the hospital course and required prone positioning compared to the patients without diabetes. Interestingly, mortality rates were higher among patients without diabetes compared with patients with diabetes. However, a Log Rank test showed a statistically significantly different intubation survival distribution between patients without and with diabetes (p = .002), with patients with diabetes having a 75% chance of sooner intubation (hazard ratio for intubation, 3.00; 95% CI, 1.39 to 6.46) (Fig. 1).

Table 1

Demographics and clinical presentation of patients with COVID-19 and with and without Type 2 Diabetes.

|                      | Total (n = 147) | With T2D (n = 73) | Without T2D (n = 74) | P value |
|----------------------|----------------|------------------|----------------------|---------|
| Age                  | 69 (59.7%)     | 73 (59.76%)     | 74 (58.80%)          | 0.878   |
| Female               | 58 (40%)       | 30 (41.10%)     | 28 (37.84%)          | 0.686   |
| BMI                  | 26.5           | 28.3            | 25 (20.9–30.6)       | 0.019   |
| LTCF                 | 78 (53%)       | 37 (50.70%)     | 32 (43.25%)          | 0.366   |
| Glycohemoglobin      | 6.3            | 7.3 (6.4–8.2)   | 5.7 (6.4–8.2)        | 0.001   |
| Hypertension         | 101 (68.7%)    | 60 (82.2%)      | 41 (55.4%)           | 0.001   |
| Dementia             | 43 (29.3%)     | 17 (23.3%)      | 26 (35.1%)           | 0.147   |
| COPD                 | 30 (20.4%)     | 12 (16.4%)      | 18 (24.3%)           | 0.307   |
| CKD                  | 25 (17.0%)     | 15 (20.5%)      | 10 (13.9%)           | 0.260   |
| CHF                  | 20 (13.6%)     | 9 (12.3%)       | 11 (14.9%)           | 0.811   |
| CAD                  | 19 (13.2%)     | 10 (13.7%)      | 9 (12.2%)            | 0.811   |
| Cancer history       | 14 (9.5%)      | 4 (5.5%)        | 10 (13.5%)           | 0.158   |
| Asthma               | 12 (8.2%)      | 8 (11.0%)       | 4 (5.5%)             | 0.177   |
| Mortality            | 41 (28.1%)     | 19 (26.0%)      | 2 (30.1%)            | 0.713   |
| Fever                | 113 (76.1%)    | 70 (92.2%)      | 43 (58.1%)           | 0.246   |
| SOB                  | 106 (49.8%)    | 48 (65.1%)      | 58 (77.0%)           | 0.267   |

a Continuous variables are presented as median (interquartile range). Categorical variables are presented as counts with percentages (%).

b P value less than 0.05 indicates statistically significant difference among patients with and without T2D.

c AMS: Altered mental status; BMI: Body mass index; CHF: Congestive Heart Failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LTCF: Long-term care facility; SOB: Shortness of breath; T2D: Type 2 Diabetes.
4. Discussion

In our patient population, patients with COVID-19 and diabetes showed significantly higher ICU admission requirements, higher ARDS incidence, and higher intubation rates. The survival analysis also showed that patients with diabetes presented a significantly shorter time to intubation. Our findings support previous reports where diabetes was a significant risk factor for worst presentation and outcomes in patients with COVID-19. Yan et al. (Yan et al., 2020) found that patients with diabetes were at more risk of ICU admission and mechanical ventilation. Zhu et al. (Zhu et al., 2020) found that patients with diabetes needed more medical interventions and had more frequent multiple organ injury events than patients without diabetes. Huahua et al. (Yi et al., 2020) found that patients with diabetes and COVID-19 developed more injury events than patients without diabetes. Huahua et al. (Yi et al., 2020) also support patients without diabetes. Sardu et al. (Sardu et al., 2020) also support patients without diabetes.

Table 2

| Variable                      | Total (n = 147) | With T2D (n = 73) | Without T2D (n = 74) | P value |
|-------------------------------|-----------------|-------------------|----------------------|---------|
| WBC                           | 1150 (601–2382.75) | 914.0 (445.25–1976.7) | 1296.50 (821–5075.25) | 0.033   |
| Ferritin                      | 426 (171–2103.50) | 412 (155–25–989) | 448 (175.75–1326) | 0.557   |
| CRP                           | 10 (4.90–15.90) | 10.25 (4.30–17.02) | 10.05 (5.10–13.95) | 0.392   |
| ESR                           | 65 (35.50–99.50) | 67.00 (36.00–47.90) | 64.00 (35.00–43.00) | 0.344   |
| CK                             | 138 (58.50–299.50) | 131 (51.75–345.75) | 295.95 (197.75–350.5) | 0.074   |
| PCT                           | 0.53 (0.26–2.53) | 0.59 (0.28–3.8) | 0.5 (0.24–2.1) | 0.935   |
| Transaminitis                 | 32 (19.9%) | 23 (12.9%) | 9 (12.2%) | 0.005   |
| AKI during admission          | 55 (14.3%) | 14 (9.5%) | 7 (9.5%) | 0.104   |
| Myocardial injury             | 24 (16.3%) | 17 (9.5%) | 7 (9.5%) | 0.027   |
| Prolonged QTC                 | 13 (8.9%) | 9 (5.5%) | 4 (5.5%) | 0.157   |
| New onset arrhythmia          | 17 (23.3%) | 12 (16.4%) | 12 (16.4%) | 0.300   |
| ICU stay (Days)               | 55 (37.9%) | 34 (24.7%) | 21 (28.2%) | 0.027   |
| Hospital stay (Days)          | 8 (5–14.25) | 9 (3–14) | 6 (2–17) | 0.791   |

Table 3

| Variable                      | Total (n = 147) | With T2D (n = 73) | Without T2D (n = 74) | P value |
|-------------------------------|-----------------|-------------------|----------------------|---------|
| WBC                           | 1150 (601–2382.75) | 914.0 (445.25–1976.7) | 1296.50 (821–5075.25) | 0.033   |
| Ferritin                      | 426 (171–2103.50) | 412 (155–25–989) | 448 (175.75–1326) | 0.557   |
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Table 4

| Variable                      | Total (n = 147) | With T2D (n = 73) | Without T2D (n = 74) | P value |
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| Transaminitis                 | 32 (19.9%) | 23 (12.9%) | 9 (12.2%) | 0.005   |
| AKI during admission          | 55 (14.3%) | 14 (9.5%) | 7 (9.5%) | 0.104   |
| Myocardial injury             | 24 (16.3%) | 17 (9.5%) | 7 (9.5%) | 0.027   |
| Prolonged QTC                 | 13 (8.9%) | 9 (5.5%) | 4 (5.5%) | 0.157   |
| New onset arrhythmia          | 17 (23.3%) | 12 (16.4%) | 12 (16.4%) | 0.300   |
| ICU stay (Days)               | 55 (37.9%) | 34 (24.7%) | 21 (28.2%) | 0.027   |
| Hospital stay (Days)          | 8 (5–14.25) | 9 (3–14) | 6 (2–17) | 0.791   |

4. Discussion

In our patient population, patients with COVID-19 and diabetes showed significantly higher ICU admission requirements, higher ARDS incidence, and higher intubation rates. The survival analysis also showed that patients with diabetes presented a significantly shorter time to intubation. Our findings support previous reports where diabetes was a significant risk factor for worse presentation and outcomes in patients with COVID-19. Yan et al. (Yan et al., 2020) found that patients with diabetes and COVID-19 developed more severe disease, had more complications (such as ARDS and AKI), required ICU admission more often, and had higher mortality than patients without diabetes. Sardu et al. (Sardu et al., 2020) also support similar findings. Roncon et al. (Roncon et al., 2020) demonstrated that patients with diabetes and COVID-19 had a higher ICU admission and mortality risk and found that diabetes was the second more common
comorbidity in their population. Finally, a meta-analysis of 30 studies (6452 patients) (Huang et al., 2020) showed higher mortality, severe COVID-19 disease, ARDS, and disease progression in the subgroup analysis, and diabetes was overall associated with poor composite outcomes.

Although diabetes did not have an evident impact on mortality in our study, this has been demonstrated by previous reports. In the study by Yang et al. (Yan et al., 2020), patients with severe COVID-19 and diabetes had worse survival rates than patients without diabetes. In their study, the median survival duration from hospital admission in patients with severe COVID-19 with and without diabetes was 10 days and 18 days, respectively. In our study, the median hospital stay for people with diabetes with COVID-19 was 8 days versus 7 days for patients without diabetes. Bode (Bode et al., 2020) et al. also found that patients with diabetes had higher mortality and more extended hospital stay. They also found that hyperglycemia (serum glucose >180 mg/dL, as set by American Diabetes Association guidelines [American Diabetes Association, 2020]) was also associated with these adverse events. The study by Alkundi et al. (Alkundi et al., 2020) also supports the same.

Inflammatory responses play a critical role in the progression of COVID-19 (Stebbing et al., 2020). The exact mechanism is not well understood. Accumulating data suggest direct virus endothelial injury and cytokine/complement mediated endothelial injury, and inflammation leading to hypercoagulability. Elevation of inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6), creatine kinase (CK), D-dimer has been reported to be significantly associated with the high risks of the development of severe COVID-19 and subsequent mortality (Cheng et al., 2020). In our patient population, the elevation of D-dimer in patients with diabetes and COVID-19 was significantly higher than in patients without diabetes. A D-dimer greater than four times the normal upper limit from baseline has been shown to predict in-hospital mortality in patients with COVID-19 (Zhang et al., 2020), which points that patients with diabetes and elevated D-dimer are at greater risk of mortality.

Patients with diabetes have been known to present more severe infections than patients without diabetes. This may be due to the cardiovascular or renal complications of diabetes. It may also be because diabetes is a chronic inflammatory condition that affects the body’s response to viral agents. Uncontrolled hyperglycemia has also been implicated in the severity of disease associated with different viruses such as the 2009 pandemic influenza A (H1N1), SARS-CoV, and MERS-CoV. Hyperglycemia promotes the synthesis of glycosylation end products and cytokines, leading to oxidative stress and tissue inflammation. It also causes blunting of the immune response as it affects lymphocyte, macrophage, neutrophil, and complement functions adversely (Hussain et al., 2020). Studies have shown that the SARS-CoV-2 enters endothelial cells through the angiotensin-converting enzyme 2 (ACE2) protein. ACE2 is highly expressed in endothelial tissue. Its consumption leads to a local increase of angiotensin-II, causing vasoconstriction and cytokines release through endothelial activation. Furthermore, endothelial cell dysfunction and microthrombi formation caused by COVID-19 is further worsened from pre-existing microangiopathy associated with poorly controlled diabetes (Whyte et al., 2020). Lastly, ACE2 pathway imbalances can also lead to β-cell dysfunction in the pancreas resulting in more hyperglycemia and worse vasculopathy and coagulopathy (Cuschieri and Grech, 2020).

On the other hand, diabetes can cause microvascular injury in the lung, leading to decreased diffusion capacity for carbon monoxide (DLCO). The injury is directly related to the levels of HbA1c and the presence of other microvascular complications such as diabetic neuropathy, retinopathy, and nephropathy. This entity has been described as a “diabetic lung” and can predispose to increased COVID-19 severity (Whyte et al., 2020).

Overall, the COVID-19 pandemic affected care-making, making glycemic control and close follow-up of patients with diabetes more
difficult. Glycemic control during acute illness and infection is also challenging to achieve. On top of the usual precautions to mitigate COVID-19 spread, these variables must also be considered to prevent the severity of COVID-19 in patients with diabetes effectively. (Peric and Stulnig, 2020).

Our study is not without limitations. This was a single-center study with patients from a community hospital, and generalizing data would not be appropriate. Additionally, our sample size was small, which may have contributed to the fact that we did not find any differences in mortality among patients with and without diabetes.

In conclusion, in our patient population from a community hospital setting, patients with COVID-19 and diabetes showed significantly higher ARDS incidence, intubation rates, and increased risk for shorter time to intubation. Our findings support previous reports where diabetes was shown to be a significant risk factor for worse presentation and outcomes in patients with COVID-19.

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Ethics approval

Approval for this work was obtained through AMITA Health Institutional Review Board and Ethics Committee.

Consent to participate

Informed consent was waived because of the retrospective nature of the study.

Availability of data and material

Data and materials used for this work are available upon reasonable request.

CRediT authorship contribution statement

Ekta Shrestha: Conceptualization, Project administration, Data curation, Writing - original draft, Formal analysis. Mariam Charkviani: Project administration, Data curation, Writing - review & editing. Clio Musurakis: Data curation, Writing - review & editing. Aswin Ratna Kansakar: Writing - review & editing. Amrit Devkota: Data curation, Writing - review & editing. Rabin Banjade: Data curation, Writing - review & editing. Prasun Pudasainie: Writing - review & editing. Solab Chitrakar: Data curation, Writing - review & editing. Alisha Sharma: Data curation, Writing - review & editing. Alisha Sharma: Data curation, Writing - review & editing. Hanika Subedi: Data curation, Writing - review & editing. Shanthya Padhamnanth: Data curation, Writing - review & editing. Harvey J. Friedman: Supervision. Guillermo Rodriguez Nava: Methodology, Formal analysis, Writing - original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ACE2 angiotensin-converting enzyme 2
AKI Acute kidney injury
ARDS Acute respiratory distress syndrome
CKD Chronic kidney disease
COPD Chronic obstructive pulmonary disease
CHF Congestive heart failure
CAD Coronary artery disease
COVID-19 Coronavirus disease 2019
CRP C-reactive protein
CK Creatinine kinase
DLCO Diffusion capacity for carbon monoxide
ESR Erythrocyte sedimentation rate
GI gastrointestinal
HbA1c Glycated hemoglobin
ICU Intensive Care Unit
IL-6 Interleukin-6
IQR Interquartile range
PCT Procalcitonin
SARS-CoV-2 Severe acute respiratory syndrome virus 2
VTE Venous thromboembolism
WHO World Health Organization

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