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The impact of impaired insulin regulation on severity of SARS-CoV-2 infection: a 2-year retrospective single-center analysis

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Background: The COVID-19 pandemic has caused an international healthcare crisis and produced a large healthcare burden. Diabetes mellitus (DM) is a common disease that can be controlled via pharmacologic agents; however, many patients have poor glycemic control, leading to disease-related complications. DM has been reported in the literature to be associated with increasing morbidity and mortality in COVID-19 patients. The authors aim to assess the associations between glucose homoeostasis and COVID-19 disease severity and mortality.

Methods: A retrospective chart review of patients ages 18–100 years of age admitted with COVID-19 between January 2020 and December 2021 was performed. The primary outcome was COVID-19 mortality with respect to haemoglobin A1C levels of less than 5.7%, 5.7–6.4%, and 6.5% and greater. Disease severity was determined by degree of supplemental oxygen requirements (ambient air, low-flow nasal cannula, high-flow nasal cannula, non-invasive mechanical ventilation, and invasive mechanical ventilation). COVID-19 mortality and severity were also compared to blood glucose levels on admission as grouped by less than 200 mg/dl and greater than or equal to 200 mg/dl.

Results: A total of 1156 patients were included in the final analysis. There was a statistically significant association between diabetic status and mortality ($P = 0.0002$). Statistical significance was also noted between admission blood glucose ≥ 200 mg/dl and mortality ($P = 0.0058$) and respiratory disease severity ($P = 0.0381$). A multivariate logistic regression for predicting mortality showed increasing haemoglobin A1C was associated with increased mortality (odds ratio 1.72 with 95% CI of 1.122–2.635).

Conclusions: In our 2-year retrospective analysis, there was an association between a diagnosis of DM and COVID-19-related mortality. Hyperglycaemia on admission was found to be statistically significant with mortality in patients diagnosed with COVID-19. Glucose homoeostasis and insulin dysregulation likely play a contributing factor to COVID-19 disease severity and mortality.

Keywords: blood glucose, COVID-19, diabetes mellitus, respiratory distress

Introduction

The (COVID-19 is caused by an infection from the SARS-CoV-2, and the first case in the United States was documented on 31 January 2020[1,2]. SARS-CoV-2 is an RNA virus that has 82% homology with SARS-CoV, which caused a pandemic in 2003[2]. SARS-CoV-2 enters cells via the angiotensin converting enzyme 2 receptor, which is primarily expressed in the lung[2]. COVID-19 has led to a worldwide pandemic, with over six million deaths attributed to the virus, according to the WHO. This emerging infection has caused an international healthcare crisis with a significant burden on healthcare workers.

Advanced age, male sex, cardiovascular disease, and diabetes mellitus (DM) are known to be associated with increasing risk for COVID-19 severity and mortality[2]. DM is a common disease that affects the general population by disrupting glucose homoeostasis[2–4]. Impaired glycemic control produces a state of hyperglycaemia, which leads to multi-organ injury via a chronic,

HIGHLIGHTS

- Haemoglobin A1C (HbA1C) levels 6.5 and greater were associated with 172% increase in COVID-19-related mortality.
- As HbA1C levels increased there was noted COVID-19 respiratory disease severity
- Blood glucose levels on admission did not influence mortality and respiratory disease severity as much as HbA1C.

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pathophysiologic inflammatory state[2–4]. Early retrospective studies demonstrated the association of insulin dysregulation with COVID-19 disease severity and mortality[5–11]. With more data availability and time, many studies have been conducted to better characterize the relationships between hyperglycaemia and elevated haemoglobin A1c (HbA1c) with COVID-19 disease susceptibility, severity, and mortality[2–11].

Through this 2-year retrospective analysis, we aimed to investigate the associations of HbA1c levels and hyperglycaemia with COVID-19 mortality and disease severity in a Southern California county hospital.

Methods

Study setting and design

An observational, retrospective cohort review of patients ages 18 years or older admitted to a community high-capacity Level 1 trauma centre with COVID-19 between January 2020 and December 2021 was performed. All patients admitted with a primary diagnosis of COVID-19 were gathered. Infection with SARS-CoV-2 was confirmed by nasal polymerase chain reaction analysis for all patients diagnosed with COVID-19. Exclusion criteria in our study included COVID-19 in pregnancy and age under 18. Amongst all the collected data there was 1993 identified patients. Retrospective chart review was performed to obtain emergency department records, admission records, and inpatient records. Patient demographics in this study were extracted from their electronic medical chart. The data collected included patient age, sex, ethnicity, medical comorbidities, medications, level of oxygen supplementation requirements, and mortality. The primary endpoints included COVID-19 illness severity as differentiated by patient haemoglobin A1C levels and blood glucose levels on admission. Mortality is defined as COVID-19-related mortality. All patients admitted with hyperglycaemia and/or diabetes mellitus were initiated on an insulin-based regimen with a target blood glucose goal of 140–180 mg/dl. All data that were collected were obtained from chart review. Informed consent was waived, and data were reported in an aggregated format. No patient data were included in this study. Consent, ethical approval, data gathering, and analysis were obtained from the local Institutional Review Board (IRB #21-35). This study was reported in accordance with the STROCSS criteria[12]. This project has been registered with ClinicalTrials.org.

Statistical analysis

The data were collected using Microsoft Excel and information was stored on a password-secured computer folder. All statistical analyses were conducted using the SAS software for Windows version 9.3. Descriptive statistics are presented as means and standard deviations for continuous variables, along with frequencies and proportions for categorical variables. An intense *t*-test was conducted to assess the difference in continuous outcomes. χ^2 tests were used to assess the association between categorical variables. Fisher's exact test was used if the expected cell count for each cell was less than 5. All statistical tests were performed on both sides. Analysis of variance (ANOVA) was utilized for any analysis with more than two variables. A multivariate analysis was performed to consider the variables associated with mortality. The binary logistic regression was utilized to determine the odds ratio with the confidence interval for predicting mortality based on significant predictors noted in the multivariate analysis. For all tests a P value less than 0.05 was considered statistically significant.

Results

A total of 1993 patients had a diagnosis of COVID-19 and 1156 had HbA1C levels and blood glucose levels documented on admission. Table 1 groups patients by 3 HbA1C levels; 1. HbA1C less than 5.7%, 2. HbA1C of 5.7–6.4%, 3. HbA1C greater than 6.4%. The average age for each respective group was 53.34 ± 19.39, 56.91 ± 16.64, and 56.21 ± 16.1 ($P = 0.0415$). The vast majority of patients was Hispanic at 64% in the overall population. Patients with COVID-19 and as grouped by HbA1C did not have any statically significant medical comorbidities. Similarly, patients' body mass indices were similar in the three groups respectively (30.12 ± 9.64, 31.55 ± 8.78, 32.48 ± 9.16, $P = 0.0065$). Notably, disease severity as defined by respiratory status showed a higher percentage of patients in the HbA1C greater than 6.4% having more intubated patients, 20.5% as compared to the 9.4% in the HbA1C less than 5.7% and 11.1% in the HbA1C of 5.7–6.4% ($P < 0.0001$). The remainder of the results are summarized in Table 1.

Table 2 focuses on patient groups by blood glucose on admission under 200 mg/dl and blood glucose on admission greater than or equal to 200 mg/dl. The average age for each respective group was 55.78 ± 17.16 and 56.09 ± 16.61 ($P = 0.7698$). Mortality for the group with blood glucose on admission under 200 mg/dl was 18.7% and blood glucose on admission greater than or equal to 200 mg/dl was 25.6% ($P = 0.0058$). Notably, disease severity as defined by respiratory status did show statistical significance, $P = 0.0381$. The patients who were intubated, 19.6%, belonged to the group with a blood glucose greater than or equal to 200 mg/dL as compared to 13.2% group with a blood glucose under 200 mg/dl. The remainder of the results are summarized in Table 2.

To determine predictors of mortality with COVID-19 positive patients, we analyzed the data utilizing binary logistic regression. Logistic regression was performed for the total set of patients ($N = 1156$). HbA1C greater than 6.4% and history of deep venous thrombosis (DVT) had increased statically significant association with mortality. Patients with a HbA1C greater than 6.4% had an odds ratio of 1.720 (95% CI 1.122–2.635) and history of DVT had an odds ratio of 3.157 (95% CI 1.668–5.978). The remainder of the results are in Table 3.

Discussion

It is known that diabetic patients with severe acute respiratory syndrome (SARS) or Middle Eastern Respiratory Syndrome (MERS) have worse outcomes[2,3]. As such, it is unsurprising that diabetic patients may have worse outcomes when infected with SARS-CoV-2. The current literature describes DM as an independent risk factor for COVID-19 disease severity, susceptibility, and mortality[2–11]. Disease susceptibility may be explained by several mechanisms. The first is through impaired innate and acquired immunity, providing an environment for the virus to replicate. Second, patients with DM have elevated levels of angiotensin converting enzyme 2, which may promote viral entry.

Table 1

Comparison of variables among three A1c groups

	A1c < 5.7 *N* = 215	A1c 5.7–6.5 *N* = 360	A1c 6.5 + *N* = 581	*P*
Demographics				
Age	53.34 ± 19.39	56.91 ± 16.64	56.21 ± 16.1	0.0415
BMI upon first admission	30.12 ± 9.64	31.55 ± 8.78	32.48 ± 9.16	0.0065
Ethnicity, *N* (%)				0.0134
African-American	28 (13.1)	45 (12.6)	66 (11.4)	
Caucasian	54 (25.2)	66 (18.4)	82 (14.2)	
Hispanic	124 (57.9)	227 (63.4)	402 (69.7)	
Other	8 (3.7)	20 (5.6)	27 (4.7)	
Male (%)	119 (55.4)	194 (53.9)	326 (56.1)	0.8008
Medical comorbidities, *N* (%)				
Deep venous thrombosis	3 (1.4)	9 (2.5)	29 (5)	0.0217
Pulmonary embolism	0	1 (0.3)	11 (1.9)	0.0133
Cerebral vascular accident	3 (1.4)	5 (1.4)	13 (2.3)	0.5550
Haemorrhagic stroke	4 (1.9)	1 (0.3)	3 (0.5)	0.1026
Disseminated intravascular coagulation	3 (1.4)	2 (0.6)	4 (0.7)	0.5458
Cancer	10 (4.7)	9 (2.5)	15 (2.6)	0.2579
Hypertension	26 (12.1)	72 (20)	126 (21.7)	0.0092
Obesity overweight—BMI > 30 (%)	38 (17.7)	81 (22.5)	120 (20.7)	0.3845
Chronic lung disease	10 (4.7)	18 (5)	26 (4.5)	0.9334
Cirrhosis	3 (1.4)	4 (1.1)	9 (1.6)	0.8936
Liver disease	13 (6.1)	14 (3.9)	14 (2.4)	0.0440
Myocardial Infarction	3 (1.4)	9 (2.5)	9 (1.6)	0.5022
Chronic kidney disease	13 (6.1)	33 (9.2)	50 (8.6)	0.3945
End stage renal disease	15 (7)	18 (5)	32 (5.5)	0.6004
Prior anticoagulation use	14 (6.6)	29 (8.1)	44 (7.6)	0.8195
Hospitalization outcomes, *N* (%)				
Limb ischemi	0	0	6 (1)	0.0503
Mortality	35 (16.3)	58 (16.1)	152 (26.2)	0.0002
Respiratory treatment				< 0.0001
Room air	80 (37.7)	73 (20.3)	134 (23.1)	
Low-flow oxygen	80 (37.7)	163 (45.3)	199 (34.3)	
High-flow oxygen	17 (8)	62 (17.2)	95 (16.4)	
NIMV	15 (7.1)	22 (6.1)	34 (5.9)	
Intubated	20 (9.4)	40 (11.1)	119 (20.5)	

NIMV, Non invasive mask ventilation.

Third, elevated serum glucose levels directly increase SARS-CoV-2 replication[4].

It has been previously described in numerous studies that DM is positively associated with COVID-19 disease severity and mortality[2–11]. The pathophysiological mechanisms for this are unclear and are likely multifactorial. DM is characterized by a hyperglycemic state, which increases oxidative stress and production of pro-inflammatory cytokines. This inflammatory environment may damage the vascular endothelium, leading to increased prevalence of venous thromboemboli, which are known to be associated with increased COVID-19 mortality. Additionally, inflammation causes interstitial lung damage and increases vascular permeability, both of which can contribute to the development of acute respiratory distress syndrome commonly seen in patients with COVID-19. Further, the common use of corticosteroids in the management of COVID-19 creates a vicious cycle, as corticosteroids impair glucose homoeostasis, leading to worsening hyperglycaemia. When combining the chronic inflammatory state of DM and acute inflammatory state of COVID-19, the host may produce a stronger immunologic and inflammatory response, known as cytokine storm[2,3]. Put together, these mechanisms may explain the propensity for worse outcomes in diabetic patients with COVID-19.

We identified 1156 patients with a HbA1c value reported during admission with 50.3% of patients meeting criteria for DM (DM), demonstrating that DM is a common comorbidity seen in patients admitted for COVID-19 (Table 1). We found that patients admitted for COVID-19 with DM had an increased risk of mortality ($P = 0.0002$, Table 1). Additionally, an elevated serum blood glucose greater than or equal to 200 mg/dl on admission was also positively correlated with COVID-19 disease mortality ($P = 0.0058$, Table 2). Regarding disease severity, we found that patients with DM had a positive correlation with COVID-19 disease severity, as evidenced by intubated patients ($P < 0.0001$, Table 1). We also found that elevated initial blood glucose greater than or equal to 200 mg/dl on admission was positively correlated with COVID-19 disease severity, as evidenced by intubated patients ($P = 0.0381$, Table 2). Next, we sought to further assess the risk of mortality in patients admitted for COVID-19 in this cohort. When compared to non-diabetic patients (HbA1c <5.7%), diabetic patients (HbA1c > 6.4%) had a 172% increased risk of mortality (odds ratio 1.72, Table 3). We also incidentally identified that patients in our cohort had a 316% increased risk of mortality when they suffered from a deep vein thrombosis during admission (odds ratio 3.157, Table 3). Overall, our univariate analyses and regression analysis support

Table 2

Comparison of variables among blood glucose levels on admission

	Blood glucose on admission <200 N = 738	Blood glucose on admission ≥200 N = 418	P
Demographics			
Age	55.78 ± 17.16	56.09 ± 16.61	0.7698
BMI upon first admission	32.32 ± 9.81	30.73 ± 7.78	0.0032
Ethnicity, *N* (%)			< 0.0001
African-American	91 (12.4)	48 (11.6)	
Caucasian	158 (21.5)	44 (10.6)	
Hispanic	444 (60.4)	309 (74.6)	
Other	42 (5.7)	13 (3.1)	
Male (%)	406 (55)	233 (55.7)	0.8109
Medical comorbidities, *N* (%)			
Deep venous thrombosis	22 (3)	19 (4.6)	0.1611
Pulmonary embolism	7 (1)	5 (1.2)	0.7649
Cerebral vascular accident	13 (1.8)	8 (1.9)	0.8419
Haemorrhagic stroke	7 (1)	1 (0.2)	0.2709
Disseminated intravascular coagulation	5 (0.7)	4 (1)	0.7302
Cancer	27 (3.7)	7 (1.7)	0.0551
Hypertension	140 (19)	84 (20.1)	0.6418
Obesity overweight—BMI > 30	164 (22.2)	75 (17.9)	0.0843
Chronic lung disease	37 (5)	17 (4.1)	0.4637
Cirrhosis	7 (1)	9 (2.2)	0.0921
Liver disease	30 (4.1)	11 (2.6)	0.2055
Myocardial infarction	11 (1.5)	10 (2.4)	
Chronic kidney disease	65 (8.8)	31 (7.4)	0.4101
End stage renal disease	47 (6.4)	18 (4.3)	0.1436
Prior anticoagulation use	55 (7.5)	32 (7.7)	0.9226
Hospitalization outcomes, *N* (%)			
Mortality	138 (18.7)	107 (25.6)	0.0058
Limb ischaemia	3 (0.4)	3 (0.7)	0.6731
Respiratory treatment			0.0381
Room air	181 (24.6)	106 (25.4)	
Low-flow oxygen	297 (40.4)	145 (34.7)	
High-flow Oxygen	116 (15.8)	58 (13.9)	
NIMV	44 (6)	27 (6.5)	
Intubated	97 (13.2)	82 (19.6)	

NIMV, Non invasive mask ventilation.

Table 3

Odds ratio with the confidence interval for predicting mortality

Characteristic	Odds ratio (n = 1156)	95% CI	P[a]
HbA1c 5.7–6.4	1.024	0.637–1.645	0.1728
HbA1c 6.5 +	1.720	1.122–2.635	0.0007
Have DVT	3.157	1.668–5.978	0.0004

Only significant predictors were shown. Variable for the model include BMI upon first admission, blood glucose on admission, HbA1c, ethnicity, DVT, PE, and limb ischaemia. Presented is only variables that approached significance and were significant.

DVT, deep venous thrombosis; HbA1c, haemoglobin A1c; PE, pulmonary embolism.

the hypothesis that patients with DM and impaired glucose homoeostasis tend to have poorer outcomes. Additionally, our results are consistent with the majority of the currently published data relating DM and COVID-19 mortality and severity.

When evaluating patients based on HbA1c values, we found that diabetic patients (HbA1c > 6.4%) had a statistically significant increased risk of developing deep vein thrombosis ($P = 0.0217$), pulmonary embolism ($P = 0.0133$), and gastrointestinal bleeding ($P = 0.0312$). There was no statistical association between diabetes and development of a stroke or disseminated intravascular coagulopathy. However, when we assessed the relationships between elevated blood glucose greater than200 mg/dl and development of stroke, DVT, and pulmonary embolism, there were no statistically significant associations. The significant associations of elevated HbA1c with pulmonary embolism and deep vein thrombosis may be explained by the fact that COVID-19 itself is a pro-thrombotic state, and DM may be contributing to a more severe inflammatory host response that increases the risk of venous thromboembolism development. We believe that the stratified analysis of blood glucose levels did not produce significant results because some patients included in the group of blood glucose greater than or equal to 200 mg/dl may not have been diabetic and that their serum glucose elevations were a result of the host response to viral stress via cortisol.

Limitations of the study

This study has two notable strengths. First, the laboratory samples collected on hospital admission were not confounded by prior anti-inflammatory therapy, meaning that our results truly reflect the inflammatory state the patients presented with. Second, the data collected were completed via manual chart review, rather than a collection from an automated dataset. This study also has its limitations. The first limitation being that it was a single-centre study, which may represent a cohort unique to this region. Though this limitation exists, our sample size was large enough to provide statistically significant data and can contribute to our centre's understanding of COVID-19 patients. As our centre is located in Southern California, future studies can join data from multiple Southwestern United States hospitals to assess for regional patterns in diabetic patients affected by COVID-19. Next, our study did not delineate between Type 1 DM and Type 2 DM and if patients had microvascular or macrovascular changes due to their diabetes. As such, we cannot provide differences between COVID-19 severity and mortality for these two groups. Future studies may compare COVID-19 complications in Type 1 and Type 2 DM. Another limitation of our study had an age range of 18–100. Previous studies have noted increased age had higher mortality, but we did not control for this as we aimed to include every patient regardless of age[13]. Finally, our study population was predominantly of Hispanic descent, but although this limitation exists, it may provide insight into the outcomes of this minority demographic. Regardless of these limitations, we believe that they are minor and do not change the overall findings of our study.

Conclusion

This 2-year retrospective analysis of 1993 patients demonstrates that insulin dysregulation and disruption in glucose homoeostasis increase COVID-19 disease severity and mortality. Hyperglycaemia on admission laboratory findings and elevated HBA1c levels were associated with increased mortality in patients diagnosed with COVID-19. We suggest that the combined pro-inflammatory states associated with SARS-CoV-2 infection and insulin dysregulation

are contributing factors to increasing COVID-19 severity and mortality.

Ethical approval

Ethics approval granted from Institutional Review Board (IRB #21-35).

Consent

All data anonymized and confidential.

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Author contribution

A.T.P., E.N., A.Q., C.K., and S.A. conceptualized and designed the study. A.U., A.T., A.M., J.P.T.N., A.K., A.M., and J.L. collected the data. F.D. conducted the statistical analysis of the data. A.T.P., A.U., A.M., A.T., E.N., A.Q., C.K., F.D., D.O., and S.A. interpreted the results. A.T.P., A.U., A.M., A.T., E.N., A.Q., F.D., D.O., and S.A. critically revised the manuscript. All authors gave approval of the final manuscript.

Conflicts of interest disclosure

The authors declare there is no conflict of interest.

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Data availability statement

All datasets generated and analyzed during the current study are included in this article.

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