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ORIGINAL ARTICLE

Association between glycemic control and the outcome in hospitalized patients with COVID-19

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Abstract

Purpose Coronavirus disease 2019 (COVID-19) clinical outcome and disease severity affected by several factors; deterioration of glycemic control is one of them. Therefore, achieving optimum blood glucose parameters is hypothesized for better consequences of COVID-19. However, varying data supporting this hypothesis is available in literature. The intention of this study was to investigate the role of glycemic management on the prognosis of hospitalized COVID-19 patients with varying degrees of severity.

Methods From April 2020 to January 2021, we carried this retrospective cohort in a clinical care facility in Pakistan.

Results Mortality was lowest in patients with HbA1c of less than 7% (53 mmol/mol) ($p < 0.001$). Similarly, mortality was found lowest in patients with fasting blood glucose less than 126 mg/dl and random blood glucose less than 160 mg/dl ($p < 0.001$ in each). In contrast, need for admission in critical care was found highest in patients with HbA1c between 7 and 10% (53–86 mmol/mol) (p 0.002). However, participants with blood glucose levels during fasting greater than 200 mg/dl and random blood glucose levels greater than 250 mg/dl were found to have a greater need for invasive mechanical ventilation. Cox regression hazard showed no difference in risk of death and invasive mechanical ventilation based on previous glycemic control.

Conclusion Effective diabetic management is correlated with a considerably lower risk of mortality and invasive mechanical ventilation in COVID-19 cases.

Keywords COVID-19 · diabetes mellitus · HbA1c · invasive mechanical ventilation · intensive care unit · mortality

Introduction

Coronaviruses are pathogens that cause significant diseases in humans and animals. Novel coronavirus was first identified in 2019 from China, resulting in a rapidly progressive global pandemic. Later on, it was named COVID-19, which means coronavirus disease 2019 [1]. Over 300,000 new cases and 56,000 new deaths were reported globally in the last week; the global COVID-related death toll exceeded 400,000 [2]. Whereas, in Pakistan, recent data has shown approximately 1 million total cases, with 40 thousand active cases reported and COVID related death score standing at 22 thousand [3]. China's early statistics indicated that the majority of deaths happened in persons who had underlying causes such as advanced age or chronic medical illnesses such as high blood glucose, high blood pressure, coronary heart disease, chronic renal disease, obesity, or malignancy [4–6]. The physiological receptor for COVID-19 disease has been revealed as a metallopeptidase known as angiotensin-converting enzyme 2 (ACE-2). It is expressed in all tissues, including endocrine organs contributes to the pathogenesis of the SARS-CoV-2 virus [7]. New-onset diabetes or deterioration of previous glycemic control thought to be battered by the entry of SARS-CoV-2 virus in islets cells by using ACE-2 receptors and cause pancreatic islet cell damage that results in impairment in beta cell insulin secretion [8]. Among several cytokines discovered to be significantly greater in diabetic patients than in non-diabetics, Interleukin-6 (IL-6) is already enhanced in states of chronic inflammation and may play a more detrimental effect in COVID-19 infection [9]. Diabetes presents in

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approximately 5–20% of in-patients having COVID pneumonia in Chinese studies [10]. Glycemic control over the last three months' gauge by glycated hemoglobin A1c (HbA1c) and its raised level associated with a higher chance of developing complications [11]. Diabetes and hyperglycemia have developed as a thread for hospital admission, disease severity, acute renal failure, acute respiratory failure, critical care unit admission, and increased mortality in cases with coronavirus disease 2019 (COVID-19). Maintaining glycemic control can influence the outcome of SARS-CoV-2 virus patients [12].We assessed the effect of glycemic management on the outcome in 1300 hospitalized COVID-19 positive patients with varying degrees of disease severity in this retrospective cohort study.

Material and method

From April 2020 to January 2021, this retrospective cohort research was carried at a tertiary care center Dr. Ziauddin hospital Karachi, Pakistan. We included all patients who were positive for PCR (polymerase chain reaction) using a reverse transcription technique, rapid antigen testing positive patients through nasal pharyngeal swabs, or patients with radiological findings consistent with COVID-19.

Patients previously treated with diabetes mellitus or those without a history of diabetes but with a HbA1c of 6.5% (48 mmol/mol) or above, fasting blood glucose of 126 mg/dl or greater, or random blood glucose of 200 mg/dl or greater on two or more occasions were the primary study population. Participants were excluded from the trial if they were on glucocorticoids for any chronic condition, had hemolytic anemia, or died within 24 hours of admission. The primary outcomes of interest are admission to an intensive care unit, the necessity for invasive respiratory support, and death. The number of patients who improved and were discharged was a secondary outcome of interest. Prior to conducting the study, institutional review board's approval was taken.

We sorted patients into three groups as per HbA1c levels, group-1 included patients with HbA1c less than 7% (<53 mmol/mol), group-2 included patients with HbA1c of 7% to 10% (53–86 mmol/mol), and group-3 included patients with HbA1c of greater than 10% (>86 mmol/mol). We also categorized patients based on their fasting and random blood glucose. First, we calculated patients' mean fasting blood glucose and divided them into three groups, i.e., those with fasting blood glucose of less than 126 mg/dl, 126–200 mg/dl, and greater than 200 mg/dl. Similarly, we calculated patients' mean pre-lunch and pre-dinner values for their random blood glucose and further categorized them into three groups, i.e., those with a blood glucose of less than 160 mg/dl, 161–250 mg/dl, and greater than 250 mg/dl.

Data collection

A complete list of patients diagnosed with COVID-19 was collected through the electronic record. Demographics, signs and symptoms, imaging findings, outcomes, co-morbidities, and investigations were extracted through chart review to ensure adequate data capture. We also manually reviewed patients' records. One thousand three hundred fifty patients' charts were reviewed, 638 patients were found to have history of diabetes which were included in this study, 15 were excluded because of chronic use of steroids, two had hemolytic anemia, and 15 expired within 24 hours of admission, while 23 patients were removed due to insufficient medical information.

Statistical analysis

We processed and gathered information utilizing SPSS software version 24; for categorical variables, we computed frequencies and percentages and compared them using the chi-square test. The median and interquartile range were computed for continuous variables and compared using a Kruskal—Wallis test. Kaplan–Meier analyses were performed to analyze survival. The Cox proportional hazards regression model was used to assess the importance of HbA1c levels in mortality and the need for invasive mechanical ventilation. We set statistical significance at a p value less than 0.05.

Results

Six hundred thirty-eight confirmed COVID-19 individuals with diabetes who met the inclusion criteria were included in this study (Fig. 1).

The demographic presentation is shown in Table 1

The mean age of the patient in HbA1c groups was not significantly different among groups (p value 0.21). Of 638 patients, 373 (58.46%) were males, and 265 (41.54%) were female, and there was no statistical difference among groups. Among co-existing comorbid conditions, hypertension was the most prevalent condition, followed by ischemic heart disease, chronic kidney disease, and asthma with no significant p values (0.329, 0.476, 0.404, and 0.669, respectively). Fever, cough, and shortness of breath were the most often seen presenting symptoms in our study. Apart from these features, runny nose, GI symptoms, and anosmia were other common presenting features. Baseline laboratory parameters are shown in Table 2.

White cell count and hemoglobin levels at the median were not significantly correlated. (p-0.302, p 0.740 respectively). We found lymphocyte count higher in group-1 compared to other groups (12 vs. 9 vs. 8 vs. 11, p 0.004).

Fig. 1 Flow chart

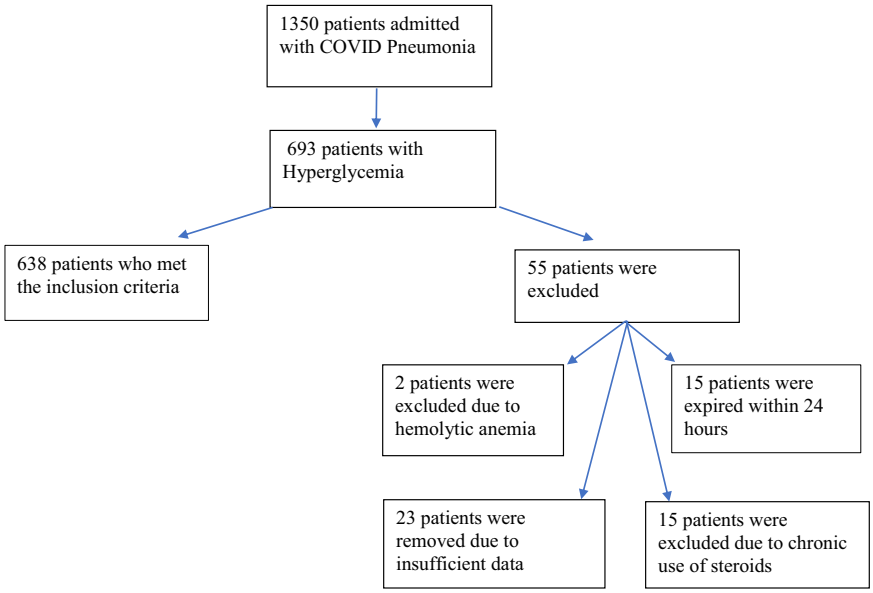

Table 1 Demographic characteristics

HbA1c	< 7.0% (53 mmol/mol) *N* (%)	7.0–10% (53–86 mmol/mol) *N* (%)	>10% (>86 mmol/mol) *N* (%)	*P* value
Age mean (SD)	60.76 (12.68)	62.30 (10.87)	60.28 (11.36)	0.21
Gender (Total)	107 (16.8%)	459 (71.9%)	72 (11.3%)	0.706
Male	60 (16.1%)	273 (73.2%)	40 (10.7%)	
Female	47 (17.7%)	186 (70.2%)	32 (12.1%)	
Smoking	8 (20.5%)	24 (61.5%)	7 (18%)	0.272
Hypertension	86 (17.8%)	346 (71.6%)	51 (10.6%)	0.329
Asthma	6 (15%)	31 (77.5%)	3 (7.5%)	0.669
Ischemic heart disease	27 (16.1%)	126 (75%)	15 (8.9%)	0.476
Chronic Kidney Disease	8 (20%)	30 (75%)	2 (5%)	0.404
Symptoms				
Fever	85 (17.1%)	348 (70.2%)	63 (12.7%)	0.077
Cough	64 (16.8%)	273 (71.4%)	45 (11.8%)	0.888
Shortness of breath	76 (15.5%)	360 (73.5)	54 (11%)	0.244
Runny nose	10 (28.6%)	21 (60%)	4 (11.4%)	0.149
GI symptoms	26 (16.9%)	111 (72.1%)	17 (11%)	0.994
Anosmia	20 (28.6%)	42 (60%)	8 (11.4%)	0.018
Medications				
Tocilizumab	24 (16.7%)	95 (66%)	25 (17.3%)	0.030
Remdesivir	26 (9.6%)	217 (79.8%)	29 (10.7%)	<0.001

SD standard deviation, *GI* gastrointestinal

We found neutrophil count lowest in group-1 (81 vs. 84.5 vs. 83.5 *p* 0.028). There was no statistically substantial change in inflammatory markers.

The outcome of COVID subjects according to HbA1c is seen in Table 3.

Group-3 patients had the lowest discharge rates compared to others, with a significant *p* value of 0.020. Mortality was seen as lowest in patients with HbA1c of less than 7% ($p < 0.001$). Interestingly, the need for ICU admission and mechanical ventilation was found highest in group-2 patients (p 0.002, p 0.090 respectively). The outcome of patients according to random and fasting blood glucose is shown in Tables 4, 5.

Most of the discharged patients had fasting blood glucose between 126 and 200 mg/dl and random blood glucose between 160–250 mg/dl, with statistically significant values

Table 2 Baseline blood counts and biochemical markers

HbA1c	< 7.0% (53 mmol/mol) Median (IQR)	7.0–10% (53–86 mmol/mol) Median (IQR)	>10% (>86 mmol/mol) Median (IQR)	*P* value
Hemoglobin (g/dl)	12.0 (10.5–13.0)	12.0 (10.6–13.1)	12.0 (10.7–13.0)	0.740
White cell count (x10^9 /L)	10.0 (7.0–13.0)	10.8 (7.9–14.7)	10.1 (7.5–15.7)	0.302
Neutrophils (%)	81.0 (70.0–88.0)	84.5 (77.0–90.0)	83.5 (75.0–90.0)	0.028
Lymphocytes (%)	12.0 (7.5–19.5)	9.0 (5.0–15.0)	11.0 (4.25–16.0)	0.004
ALT (U/L)	30.0 (19.0–39.5)	34.0 (22.0–60.0)	34.0 (22.0–50.5)	0.041
GGT (U/L)	50.0 (29.7–84.2)	45.0 (25.0–88.0)	47.0 (24.0–105.2)	0.707
Creatinine (mg/dl)	1.0 (0.95–1.15)	1.07 (0.96–2.0)	1.0 (0.89–1.63)	0.017
Urea (mg/dl)	34 (27–55)	46 (33–86)	42.5 (29–83)	<0.001
LDH(U/L)	404 (308–517)	408 (300–569)	392 (289–536)	0.724
D-Dimer (ng/ml FEU)	1251 (617–3086)	1507 (766–7248)	1728 (766–5736)	0.138
CRP (mg/dl)	100 (38–203)	108 (39.3–204)	103 (52–207)	0.779
Ferritin (ng/ml)	697 (288–1056)	739 (362–1436)	845 (450–1553)	0.206
Procalcitonin (ng/ml)	0.43 (0.19–1.0)	0.36 (0.14–1.12)	0.46 (0.18–1.10)	0.647

ALT alanine transaminase, *AST, GGT* Gamma-Glutamyl Transferase, *LDH* lactate dehydrogenase, *SD* standard deviation, *CRP* C-Reactive protein, *FEU* fibrinogen-equivalent units

Table 3 The outcome of patient according to HbA1c

HbA1c	<7.0% (53 mmol/mol) N (%)	7.0–10% (53–86 mmol/mol) N (%)	>10% (>86 mmol/mol) N (%)	*P* value
Discharged	79 (19.9%)	272 (68.7%)	45 (11.4%)	0.020
Expired	12 (7.1%)	134 (79.8%)	22 (13.1%)	<0.001
ICU admission	15 (9.9%)	126 (83.4%)	10 (6.6%)	0.002
Invasive mechanical ventilation	6 (9.1%)	55 (83.3%)	5 (7.6%)	0.090

ICU intensive care unit

compared to other groups ($p < 0.001$ in each). Conversely, lowest number of patients was discharged with fasting values more than 200 mg/dl. Mortality was lowest in patients with fasting blood glucose less than 126 and random blood glucose less than 160 mg/dl (p 0.001 in each). Similarly, need for ICU admission was found the lowest in patients with fasting and random blood glucose less than 126 mg/dl and 160 mg/dl ($p < 0.001$ in each). Conversely, utilization of invasive mechanical ventilation was higher in patients with fasting blood glucose of more than 200 mg/dl and random blood glucose of more than 250 mg/dl.

Survival is shown in Fig. 2.

Using Kaplan–Meier analysis, there was no noteworthy disparity in time from admission to death among groups, although survival was found slightly higher in Group-2 (Group-1 7.83 days vs. Group-2 9.19 days vs. Group-3 8.50 days; Log-Rank 0.984, respectively). Similarly, no consequential difference was found in time from admission to discharge in all groups (Group-1 8.20 vs. Group-2 9.74 vs. Group-3 7.89 days; Log-Rank 0.297, respectively). Time from admission to invasive mechanical ventilation was again not statistically meaningful (Group-1 3.0 days vs. Group-2 3.67 days vs. Group-3 4.60 days; Log-Rank 0.828 respectively).

According to the Unadjusted Cox Regression Model, using group-1 as the reference category, there was no significant difference in risk of death and need for invasive mechanical ventilation ($p = 0.904$, $p = 0.606$ respectively).

Discussion

This research investigated whether poorly controlled diabetes or in-patient glycemic control is associated with poor outcomes in COVID-19. It is postulated that diabetes may enhance the hazard of COVID-19 and result in poor outcomes in these patients [13]. There are many similarities between these diseases, including high blood glucose levels, raised cytokines, and oxidative stress [14–16]. Wang et al. [17] reported an association of hypercoagulability, low oxygen saturation, and inflammation with HbA1c levels with higher mortality in patients having higher levels of HbA1c.

Reduction in lymphocytes is associated with high viral load, ICU admission, the worsening of disease, and

Table 4 The outcome of the patient according to random blood glucose

Random blood glucose	<160 mg/dl (8.9 mmol/L) N (%)	160–250 mg/dl (8.9–13.9 mmol/L) N (%)	>250 mg/dl >13.9 mmol/L N (%)	*P* value
Cured	38 (9.6%)	319 (80.6%)	39 (9.8%)	<0.001
Expired	4 (2.4%)	97 (57.7%)	67 (39.9%)	<0.001
ICU admission	1 (0.7%)	94 (62.3%)	56 (37.1%)	<0.001
Invasive mechanical ventilation	0 (0.0%)	31 (47.0%)	35 (53.0%)	<0.001

ICU intensive care unit

Table 5 Outcome of the patient according to fasting blood glucose

Fasting blood glucose	<126 mg/dl (< 7 mmol/L) N (%)	126–200 mg/dl (7–11.1 mmol/L) N (%)	>200 mg/dl (>11.1 mmol/L) N (%)	*P* value
Cured	93 (23.5%)	278 (70.2%)	25 (6.3%)	<0.001
Expired	13 (7.7%)	92 (54.8%)	63 (37.5%)	<0.001
ICU admission	11 (7.3%)	88 (58.3%)	52 (34.4%)	<0.001
Invasive mechanical ventilation	2 (3.0%)	27 (40.9%)	37 (56.1%)	<0.001

ICU intensive care unit

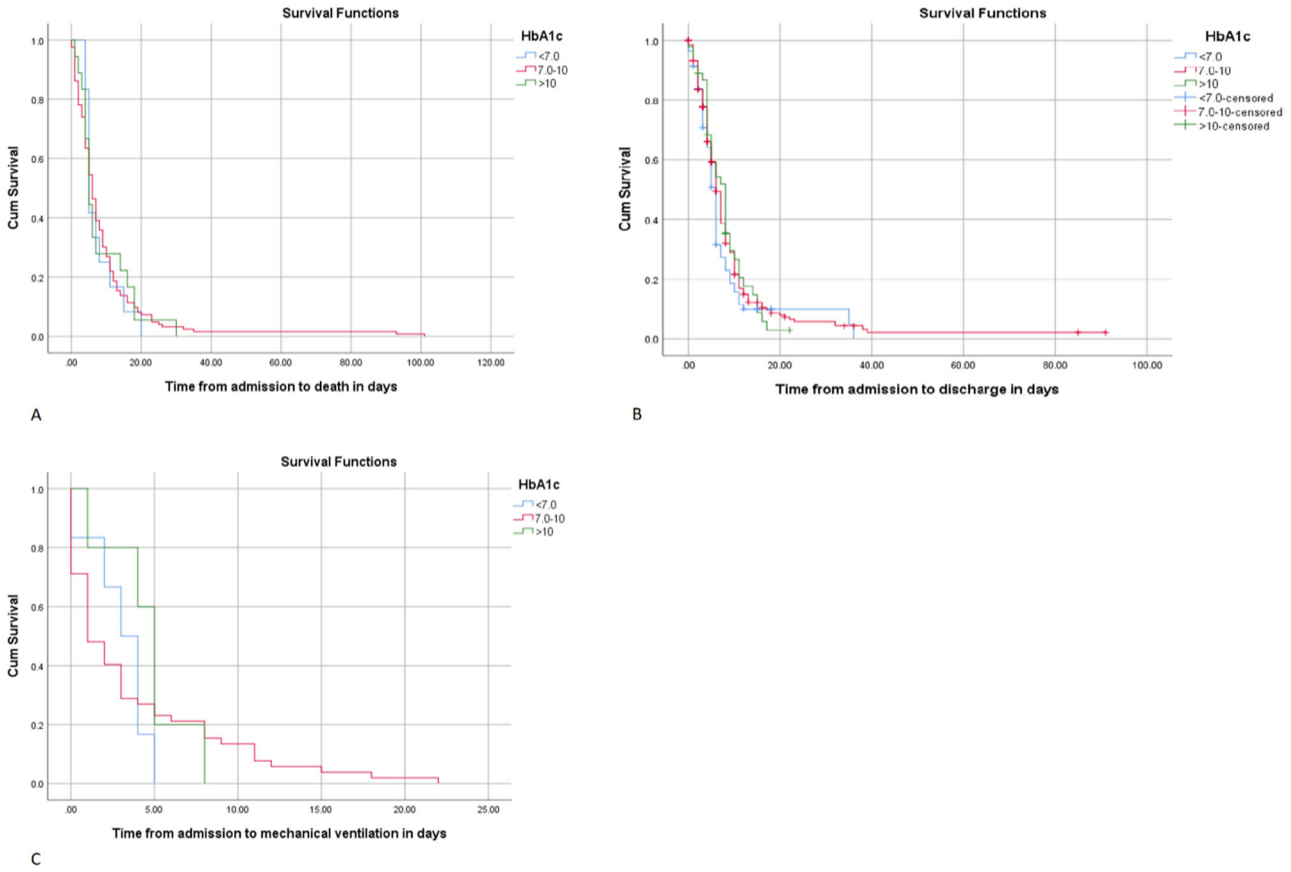

Fig. 2 Kaplan–Meier estimates of the cumulative probability of (**A**) Time from admission to discharge in days; (**B**) Time from admission to death in days; (**C**) Time from admission to intubation in days

mortality in COVID-19 patients. This study reported higher lymphocyte count in patients with reasonable glycemic control. Liu et al. reported similar findings [18]. who reported a significant difference between lymphocytes and reasonable glycemic control. Similarly, neutrophil counts were lower in patients with reasonable glycemic control, a finding similar to Liu et al. [18], who found higher neutrophil in patients with poor glycemic control. Liu et al. [18] also reported a significant elevation in C-reactive protein and serum ferritin in patients with poor glycemic control; finding contradicts this research, where we found no statistically significant difference among our study groups. The current study reports that D-dimer levels remained lowest with reasonable glycemic control, a finding consistent with finding seen by Sardu C et al. [19]. Sardu C et al. reported higher levels of D-dimer and IL-6 with hyperglycemia on presentation. Higher C-reactive protein, serum ferritin, and d-dimer levels were found at admission in patients requiring intensive care unit admission later on [20].

This research concluded that mortality was significantly lower in patients with reasonable glycemic control, a finding consistent with AK Singh et al. [21]. They reported a hazard ratio of 0.14 (p 0.008) in patients with well-controlled diabetes compared to those with uncontrolled diabetes with about 86% reduction in risk of death. In another study, a significantly higher proportion of deaths was seen in uncontrolled arms ($p < 0.001$) than in well-controlled arms [22]. Contrary to this, no difference in the outcome of patients was found according to HbA1c prior hospitalization, which suggests no association between risk stratification and glycemic control [23]. Similarly, the lack of this type of association is in line with multiple published studies in Hospitalized COVID-19 patients [10, 24, 25]. Another study concluded that well-controlled diabetes at the time of hospitalization was not associated with better outcomes [26]. A critical finding of this study is that poor outcomes do not correlate as diabetes advances; mortality was found lower in patients with HbA1c greater than 10% (>86 mmol/mol) than those with HbA1c between 7% and 10% (53–86 mmol/mol).

The need for admission in the intensive care unit was lowest in patients with poorest glycemic control, a finding contradicting published literature. Roncon L et al. [27]. found that diabetes was associated with a higher risk for ICU admission than non-diabetic patients were. However, this study did not classify patients based on their glycemic control before and after admission to the hospital. A higher risk of ICU admission in diabetics has been seen in other studies [4, 5, 28, 29]. One other study found that admission hyperglycemia was an essential predictor of the need for ICU admission and death [30]. This study also concluded lower intubation rates in patients with HbA1c of less than 7% (53 mmol/mol) or over 10% (86 mmol/mol) on admission, with no statistical significance. Similarly, Vamvini et al. reported higher rates of invasive mechanical ventilation, ICU admission, and death in patients with type-I diabetes mellitus and COVID-19 compared to the control group [31]. A multicenter French study reported that diabetes and glycated hemoglobin A1c did not affect rates of mechanical ventilation and death within one week of admission [32]. Significantly greater odds of intubation and death were observed in poorly controlled diabetics ($p < 0.05$) by Windham et al. [33]. A large-scale cohort found an association between risk of death and mechanical ventilation with poor glycemic control during hospitalization in COVID-19 [34].

This study also concluded that glycemic control during the hospital stay is directly related to poor outcomes in patients with COVID-19. Patients with poor glycemic control had higher rates for invasive mechanical ventilation. However, the need for ICU admission, death, and mechanical ventilation was found lowest in patients with reasonable glycemic control during hospitalization. Sardu et al. reported that reasonable glycemic control during hospital stay was linked with excellent outcomes in COVID-19 patients [19]. Similar findings were reported in a retrospective observational study, which concluded four times higher mortality in patients with poor glycemic control than those with optimal glycemic control [22]. Many studies have proved the association of hyperglycemia in admission with COVID-19 irrespective of the previous history of diabetes. Higher rates of invasive mechanical ventilation, death and need for ICU admission were higher in patients with new-onset hyperglycemia than in normoglycemic patients [35]. Copelli et al. reported hyperglycemia in presentation as an independent health threat for mortality in individuals without diabetes [36]. Our findings contradict P Mehta et al., who reported no association of HbA1c on admission, glycemic control during admission with the need for mechanical ventilation, ICU admission, and mortality [23]. Wang S et al. reported that fasting blood glucose of more than 126 mg/dl was an essential predictor of 28-day mortality [37]. Similarly, Zhang J et al. reported that patients with impaired fasting glucose and diabetes were associated with an increased risk of poor outcomes [38].

On cox-regression analysis, this study did not find a significant difference in risk of death and need for invasive mechanical ventilation, a finding contradicting findings of Sardu et al., who reported a higher risk of fatality in patients with poor glycemic control [19]. Similarly, Liu L et al. found a hazard ratio of 1.30 ($p = 0.019$) per 1 percent increase in HbA1c [18]. Finally, AR Saand also found that hyperglycemia, along with age greater than 60 years, was associated with increased ICU mortality [39].

This research has few limitations. First, its retrospective design, relying on medical records rather than a direct

patient interview and single-center experience. Second, critically ill patients received various modalities, which might have influenced glycemic control in these patients. Third, since our institutes are private and do not cater to underserved populations, results are not generalizable to this population cohort.

This study has few strengths. First, the study included many patients. Second, it validated the results of published literature, i.e., Liu et al., Sardu C et a., AK Singh et al. Third, we divided patients into three groups, as most studies divided these patients into only two groups based on HbA1c, which might have influenced the results. Finally, we also analyzed patients' outcomes based on their fasting and random blood glucose to assess their effects on outcomes.

Conclusion

This study concluded that reasonable glycemic control is associated with excellent outcomes in patients with COVID-19, although more advanced diabetes does not significantly affect outcomes. Poor fasting glucose and random glucose during admission are independent risk factors for poor outcomes. Further studies are needed for the validation of these results.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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