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ORIGINAL RESEARCH

Glycosylated hemoglobin as a predictor of mortality in severe pneumonia by COVID-19

Jesús Salvador Sánchez Díaz[a], Karla Gabriela Peniche Moguel[a], Eduardo Alberto González Escudero[b], Luis Del Carpio Orantes[c], Enrique Monares Zepeda[d], Orlando Rubén Perez Nieto[e], Eder Ivan Zamarron Lopez[f], Ernesto Deloya Tomas[e], Fernando Enrique Estrada Gonzalez[a], Jesús Díaz Torres[a], Diego Escarraman Martinez[g] and Manuel Alberto Guerrero Gutierrez [h]

[a]Department of Critical Care, Hospital General De PEMEX, Veracruz, México; [b]Department of Critical Care, Hospital De Especialidades, Monterrey, México; [c]Department of Critical Care, Hospital General De Zona No, México; [d]Department of Critical Care, Medical Center ABC, Mexico City; [e]Department of Critical Care, Hospital General San Juan Del Rio. San Juan Del Rio, Mexico; [f]Department of Critical Care, CEMAIN Hospital, Tampico, Mexico; [g]Department of Anesthesiology, National Medical Center IMSS "La Raza", Mexico City; [h]Department of Critical Care, Instituto Nacional De Cancerologia, Mexico City

ABSTRACT

Objective: Determine whether the levels of glycated hemoglobin (HbA1c) measured on admission to the intensive care unit (ICU) are associated with mortality in patients with severe SARS-CoV-2 pneumonia with invasive mechanical ventilation.
Design: Cohort study, retrospective, observational. A single center.
Place: ICU of a second-level care hospital.
Patients: Severe SARS-CoV-2 pneumonia confirmed with IMV since admission to the ICU.
Interventions: none.
Results: A total of 56 patients with severe pneumonia, confirmed with SARS-CoV-2, all with IMV. The group with HbA1c <6.5% included 32 (57.14%) patients and the group with HbA1c ≥6.5% included 24 (42.86%) patients and the mortality rate in ICU was 43.8% and 70.8%, respectively, with p = 0.04. Predictors of mortality at 28 days in ICU were DHL >500 U/L, OR 3.65 (95% CI 1.18–11.29), HbA1c ≥6.5%, OR 3.12 (95% CI 1.01–9.6), SAH, OR 3.12 (95% CI 1.01–9.5), use of vasopressor, OR 0.2 (95% CI 0.05–0.73), diabetes was not statistically significant.
Conclusion: The 28-day probability of survival in patients with severe SARS-CoV-2 pneumonia with IMV in the ICU is lower when the HbA1c level is ≥6.5% on admission.

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Severe pneumonia; SARS-CoV-2; COVID-19; mechanical ventilation; glycosylated hemoglobin; mortality

1. Introduction

Patients with diabetes who develop severe SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) pneumonia have a higher risk of dying compared to patients without diabetes. In fact, current data report a higher prevalence of diabetes (22% to 36%) in patients with coronavirus disease 2019 (COVID-19) [1]. Furthermore, the coexistence of diabetes and COVID-19 is associated with the development of critical illness in 32% of cases, increasing 2.34 times the risk of ARDS (Acute Respiratory Distress Syndrome) [2]. The outcome of severe acute infections in patients with diabetes has worse results due to the alteration of immune functions (chemotaxis of neutrophils and phagocytes) and due to its pro-inflammatory effect that favors an exaggerated inflammatory response ('cytokine storm') [1]. SARS-CoV-2 uses receptors for angiotensin converting enzyme 2 (ACE-2) to enter the cell. These receptors are located in the heart, lung, pancreas, intestine, and kidney, hence the different clinical presentations. The binding of glycoprotein S ('Spike') located on the surface of SARS-CoV-2 to the cellular receptor of ACE-2 is the main determinant of virulence [3]. In addition to the changes typical of diabetes, specific factors increase the risk of severe disease due to SARS-CoV-2 in this population. Such factors are as follows: longer time for viral elimination [4], higher expression of ACE-2 [5], higher levels of furin [6], poor T-cell function [7], and increased levels of interleukin 6 (IL-6) [8].

Acute or chronic hyperglycemia increases the permeability of the glycocalyx, causing endothelial dysfunction [9], which is characterized by alterations in the synthesis, release, diffusion, or degradation of the factors synthesized by the endothelium [10]. Also, chronic hyperglycemia is associated with increased oxidative stress, a determining phenomenon in the appearance of endothelial dysfunction [11]. The mean plasma glucose level of the last 3 months can be assessed with glycated hemoglobin (HbA1c). In fact, HbA1c is not affected by a critical illness, being a good marker of premorbid hyperglycemia [12]. Therefore, elevated HbA1c levels indicate chronic hyperglycemia, which is related to increased morbidity and mortality [13]. We consider elevated HbA1c levels are associated with

CONTACT Manuel Alberto Guerrero Gutierrez Manuelguerreromd@gmail.com Department of Critical Care, Instituto Nacional De Cancerologia. Mexico City, Mexico

mortality in patients with severe SARS-CoV-2 pneumonia who receive invasive mechanical ventilation (IMV).

2. Materials and methods

This study was approved by the research and ethics committee of the hospital, with registration, F-2020-3001-111. A retrospective, observational cohort study that included patients admitted to the intensive care unit (ICU) with confirmed IMV secondary to severe SARS-CoV-2 pneumonia. The study was carried out at a second-level hospital in the city of Veracruz, Mexico, during the period from March 18 to 2 October 2020. The inclusion criteria were confirmed infection by SARS-Cov-2 with reverse transcriptase polymerase chain reaction (RT-PCR), presence of severe pneumonia, which was defined by the use of IMV, and age equal to or greater than 18 years. Patients with any condition that affected HbA1c levels (e.g. stage 5 chronic kidney disease, erythropoiesis-stimulating drugs, blood transfusion in the 7 days prior to taking the sample, hemolysis, pregnant women) were excluded. Patients who concluded their treatment in another medical unit or with incomplete variables. We divided the sample into two groups: group 1: severe SARS-CoV -2 pneumonia with HbA1c <6.5% and group 2: severe SARS-CoV-2 pneumonia with HbA1c ≥6.5%. Data were collected through electronic medical record, demographic data, medical comorbidities, laboratory values, ventilatory parameters upon admission to the ICU, and hospital results were obtained (Figure 1). The SOFA (Sequential Organ Failure Assessment Score) and SAPS II (Simplified Acute Physiology Score II) scores were performed upon admission to the ICU to assess the initial severity of the disease and predict organ dysfunction and mortality. The primary outcome was mortality in the ICU. The patient was considered a survivor upon discharge from the unit. Secondary outcomes included in-hospital mortality.

3. Statistical analysis

Normality tests were performed, all the analyzed variables had free distribution, and they were represented as median and

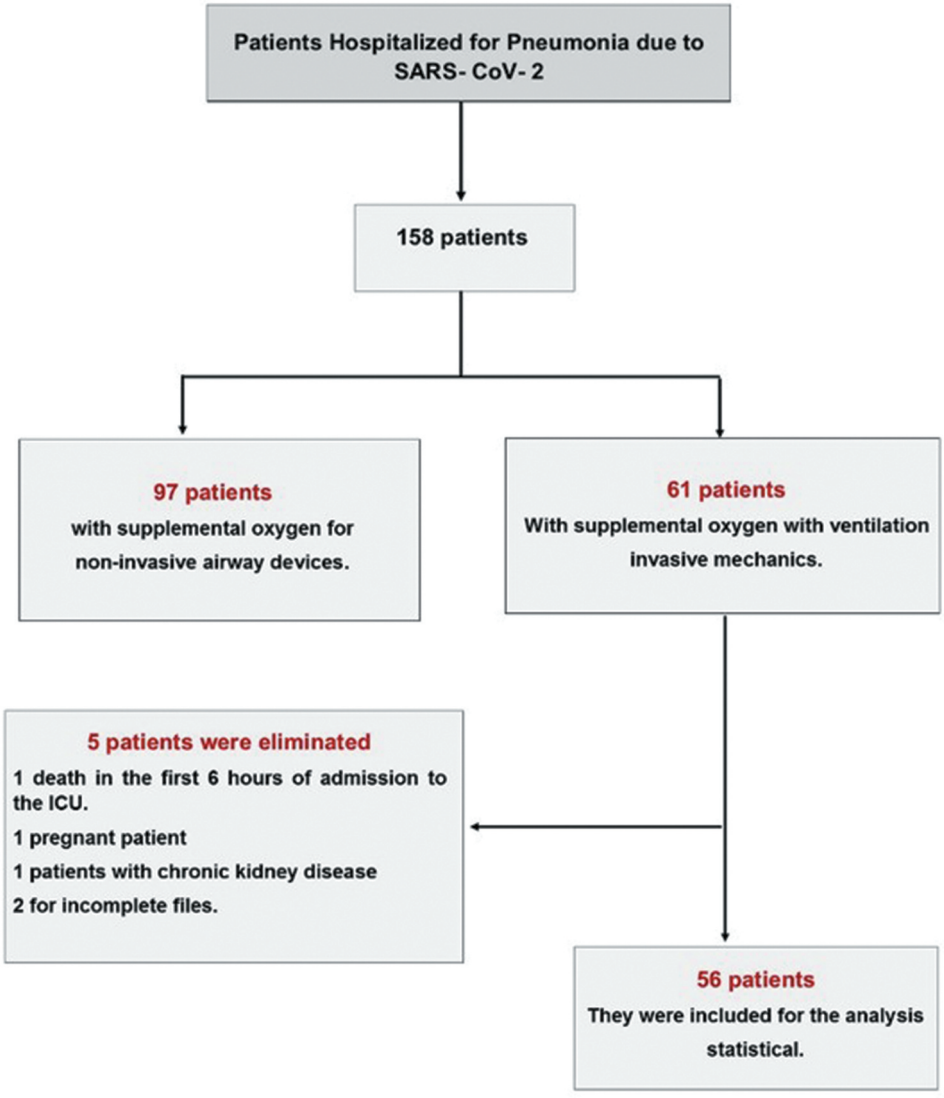

Figure 1. Enrollment flowchart.

interquartile ranges. Nonparametric statistics were performed, the Mann–Whitney U-test for the difference of means, and the Spearman test for correlations. Qualitative variables were represented as frequencies and percentages. Chi-square was used for qualitative variables. Associations are represented as odds ratio (OR) and their 95% confidence intervals (95% CI). Survival was assessed using Kaplan–Meier and log-rank tests. We consider p-values <0.05 to indicate significance. All statistical analyses were performed with SPSS version 22 software.

4. Results

A total of 56 patients with pneumonia, confirmed with SARS-CoV-2, were admitted, all with IMV since their admission. The group with HbA1c <6.5% included 32 (57.14%) patients and the group with HbA1c ≥6.5% included 24 (42.86%) patients. The median HbA1c was 6% and 7.6% (p = 0.00) for the group <6.5% and ≥6.5%, respectively. The median age was 66 (58–-76) years for the group <6.5% and 65 (60–74) years for the group ≥6.5%. Male sex was the most frequent in both groups. High blood pressure (HBP) was the most common comorbidity, followed by type 2 diabetes (DM2). Smoking was present in 25% of patients with HbA1c <6.5% and 41.7% of patients with HbA1c ≥6.5%. The body mass index (BMI) in the total population was 31.6 kg/m^2 (27.4–35.06) of which 37 patients (66.1%) presented obesity and 13 patients (23.2%) were overweight, finding no significant difference in both groups. In the pulmonary variables, peak pressure (PP), plateau pressure (PPl), PaO_2/FiO_2 (arterial oxygen pressure/fraction of inspired oxygen), positive end expiratory pressure (PEEP), compliance, driving pressure (DP), ventilatory efficiency (EV), and mechanical power (PM), there was no statistical significance. Patients in the group with HbA1c <6.5% used vasopressor less frequently (28.1%) compared to the group with HbA1c ≥6.5% (41.7%) with p = 0.29. Troponin and N-terminal probrain natriuretic peptide (NT-proBNP) were not statistically significant. The D dimer (DD) was 1210 ng/ml (624–3450) and 2818 (1520–5000) ng/ml for the group <6.5% and ≥6.5%, respectively, with p = 0.05. lactic dehydrogenase (DHL), ferritin, C-reactive protein (CRP), and fibrinogen were not statistically significant. There was no difference in the days of IMV, days of ICU stay, and reintubation. SAPS II was higher (82 points) in the group with HbA1c ≥6.5% compared to the group with HbA1c <6.5% (78 points), although without statistical significance. Mortality at 28 days in ICU was 43.8% and 70.8% for the group <6.5% and ≥6.5%, respectively, with p = 0.04; on the other hand, hospital mortality was 50% and 79% for the same groups with p = 0.04 (Table 1).

Of the variables that correlated with mortality at 28 days were lung compliance with a negative correlation of −0.44 (p = 0.001), APPS (Age, Plateau, PaO_2/FiO_2, Score) positive correlation of 0.40 (p = 0.003), the SAPS II positive correlation of 0.37 (p = 0.004), the use of vasopressor with a negative correlation of −0.34 (p = 0.01), the days of IMV with a correlation of 0.32 (p = 0.01), the PEEP with a positive correlation of 0.32 (p = 0.01), the HBP with a correlation of 0.30 (p = 00.04), and the level of sodium (Na +) with a positive correlation of 0.30 (p = 0.03), all with a moderate level of correlation (Table 2).

The predictors of mortality at 28 days in the ICU according to the univariate analysis with statistical significance were DHL> 500 U/L with OR 3.65 (95% CI 1.18–11.29), HbA1c ≥6.5% with OR 3.12 (95% CI 1.01–9.6), SAH with OR 3.12 (95% CI 1.01–9.5), use of vasopressor with OR 0.2 (95% CI 0.05–0.73), diabetes had OR 2.1 (0.68–6.5) although it was not statistically significant (Table 3). The Kaplan–Meier analysis estimates the probability of survival at 28 days in the ICU according to the HbA1c level on admission, which was significantly lower in patients with HbA1c ≥6.5% with p < 0.05 (Figure 2).

5. Discussion

The association between acute hyperglycemia and increased mortality in COVID-19 patients, even without a history of diabetes, is well documented. In fact, up to 50% of COVID-19 patients have hyperglycemia since admission to the ICU [14].

The association between premorbid glycemic status and the outcome of patients with COVID-19 is unclear, especially in the context of SARS-CoV-2 pneumonia with the need for IMV. As we mentioned, critical illness does not alter HbA1c levels, making it a good marker for chronic hyperglycemia [15]. Elevated HbA1c levels are related to chronic damage to the endothelial glucocalyx, the main mechanism responsible for complications in patients with diabetes [16]. In fact, patients with COVID-19 also present endothelial involvement in different degrees, which contributes to worse results [17]. Studies have shown a relationship between HbA1c level upon admission to ICU and mortality. Lee et al. [18] in a total of 90 patients diagnosed with septic shock, documented that HbA1c levels ≥6.5% are an independent predictor for progression of organ dysfunction (OR 2.98, 95% CI 1.033–8.567, p = 0.043) and for mortality (HR 3.49, 95% CI 1.802–6.760, p = <0.001). Su et al. [19] used the plasma glucose/HbA1c ratio measured upon admission to the emergency department in diabetic patients. HbA1c was found as a risk factor in the univariate analysis (HR 0.42, 95% CI, 0.33–0.55, p = <0.001) but not in the multivariate, plasma glucose (HR 0.89, 0.70–1.13, p = 0.328) it had no statistical significance. On the other hand, the plasma glucose/HbA1c index was an independent risk factor for mortality at 90 days (HR1.29, 95% CI, 1.05–1.57, p = 0.013). Therefore, measuring the HbA1c level upon admission to the ICU may be useful to predict mortality in patients with severe SARS-CoV-2 pneumonia with or without a diagnosis of diabetes. Our findings suggest that the probability of survival at 28 days in the ICU of patients with severe SARS-CoV-2 pneumonia with HbA1c level ≥6.5% measured upon admission is significantly lower.

Even HbA1c values ≥6.5% increase 3.12 (p = 0.04) times the risk of death in this population of patients according to the univariate analysis, but the statistical significance is not maintained in the multivariate analysis. Klein et al. [20] documented that patients with COVID-19 and HbA1c ≥6.5% have a greater need for IMV, in addition to presenting higher levels of CRP and IL-6. There was a trend toward higher hospital mortality. Wang et al. [21] reported greater hypercoagulability with higher fibrinogen and ferritin levels in patients with COVID-19 and diabetes with HbA1c ≥6.5%. They also associated elevated

Table 1. Patient demographics.

Variable	Total of patients n = 56	Severe pneumonia for SARS-Cov-2 with HbA1c <6.5% n = 32	Severe pneumonia for SARS-Cov-2 with HbA1c ≥6.5% n = 24	p
Gender				
• **Male**	38 (67.9%)	21 (65.6%)	17 (70.8%)	0.68
• **Female**	18 (22.1%)	11 (34.4%)	7 (29.2%)	
Age (years)	66 (59–74)	66 (58–76)	65 (60–74)	0.91
BMI (kg/m^2)	31.6 (27.4–35.06)	2 (6.3%)	4 (16.7%)	0.91
• **Normal**	6 (10.7%)	7 (21.95%)	6 (25%)	
• **Overweight**	13 (23.2%)	23 (32%)	14 (58.3%)	
• **Obesity**	37 (66.1%)			
Background:				
• **Smoking**	18 (32%)	8 (25%)	10 (41.7%)	0.18
• **DM2**	21 (37.5%)	3 (9.4%)	18 (75%)	0.005
• **HBP**	35 (62.5%)	15 (46.9%)	20 (83.3%)	0.001
HbA1c (%)	6.3 (6–7.57)	6 (5.8–6.2)	7.6 (7–10.4)	0.00
Vasopressor	19 (33.9%)	9 (28.1%)	10 (41.7%)	0.29
MSI	1.3 (1.1–1.15)	1.2 (1.04–1.47)	1.4 (1.21–1.59)	0.07
Troponina I (ng/ml)	0.3 (0.03–0.3)	0.03 (0.03–0.3)	0.03 (0.03–0.22)	0.68
NT-ProBNP (ng/L)	389 (142–1162)	373 (115–773)	440 (143–2930)	0.29
PaO_2/FiO_2 (mmHg)	83 (62–119)	78 (64–109)	86 (60–121)	0.48
PEEP (cmH_2O)	8 [7–9]	8 [7–9]	8 (8–9.5)	0.68
PP (cmH_2O)	27 (32–30)	26 (24–30)	27 (22–31)	0.90
PPI (cmH_2O)	24 (20–27)	22 (19–27)	24 (20–27)	0.77
DP (cm/H_2O)	15 [12–18]	14 [11–18]	16 [12–18]	0.77
VE (L/min)	1.84 (1.59–2.36)	2.04 (1.61–2.36)	1.77 (1.54–2.35)	0.61
MP (J/min)	19.2 (16.5–24.9)	19.8 (16.2–25)	19.8 (16.5–24.8)	0.93
Distensibility (ml/cmH_2O)	34.5 (26–41.25)	34 (26–38)	34 (24–42)	0.93
APPS	19 (33.9%)	10 (31%)	9 (37.5%)	0.39
<7 points	37 (66.1)	22 (69%)	15 (62.5%)	
≥7 points				
Days of MV	5 [1,3–7]	5 (3–8.7)	5 [3–7]	0.64
Reintubation	14 (25%)	10 (31.3%)	4 (16.7%)	0.21
Cr (mg/dl)	0.86 (0.65–1.2)	0.72 (0.6–0.96)	1.02 (0.78–1.6)	0.04
Na^+ (mEq/L)	137 (134–140)	137 (134–142)	137 (133–138)	0.42
Cl^- (mEq/L)	101.5 (98–106)	102 (98–106)	100 (97–106)	0.58
DD (ng/ml)	1862 (910–4960)	1210 (624–3450)	2818 (1520–5000)	0.05
DHL (U/L)	580 (433–945)	560 (413–907)	583 (433–974)	0.54
Ferritine (ng/L)	979 (656–1669)	836 (652–1571)	1137 (738–1815)	0.25
Fibrinogen (mg/L)	292 (275–319)	294 (275–320)	292 (272–303)	0.61
CRP (mg/L)	150 (92–234)	129 (90–187)	173 (111–278)	0.08
SAPS II (puntos)	79.5 (72–86)	78 (70–85)	82 (72–87)	0.32
ICU days	7 [3–7]	6 [3–8]	7 [4–7]	0.82
ICU mortality	31 (55.4%)	14 (43.8%)	17 (70.8%)	0.04
Days of stay in the hospital	35 (62.5%)	16 (50%)	19 (79%)	0.04

BMI: Body mass index, **DM2**: Diabetes mellitus 2, **HBP**: High blood pressure, **HbA1c**: Glycosylated hemoglobin, **MSI**: Modified shock index, **NT-ProBNP**: N-terminal probrain natriuretic peptide, **PaO_2/FiO_2**: Arterial pressure of oxygen/inspired fraction of oxygen, **PEEP**: Positive end expiratory pressure, **PP**: Peak pressure, **PPI**: Plateau pressure, **DP**: Driving pressure, **VE**: Ventilatory efficiency, **MP**: Mechanical power, **APPS**: Age, Plateau, PaO_2/FiO_2, Score, **MV**: Mechanical ventilation, **Cr**: Creatinine, **Na^+**: Sodium, **Cl^-**: Chlorine, **DD**: D-dimer D, **DHL**: Lactic dehydrogenase, **CRP**: C- reactive protein, **SAPS II**: Simplified acute physiology score II, **ICU**: Intensive care unit.

Table 2. Variables that correlate with mortality in the ICU.

Variable	r	p
Compliance	−0.44	0.001
APPS	0.40	0.003
SAPS II	0.37	0.004
Vasopressor	−0.34	0.01
Days of MV	0.32	0.01
PEEP	0.32	0.01
HBP	0.30	0.04
Na^+	0.30	0.03

APPS: Age, Plateau, PaO_2/FiO_2, Score, **SAPS II**: Simplified acute physiology score II, **MV**: Mechanical ventilation, **PEEP**: Positive End Expiratory Pressure, **HBP**: High blood pressure, **Na^+**: Sodium, **ICU**: Intensive care unit

Table 3. Predictors of mortality in the ICU.

Variable	OR	IC95%	p
DHL > 500	3.65	(1.18–11.29)	0.02
HbA1c ≥ 6.5	3.12	(1.01–9.6)	0.04
HBP	3.12	(1.01–9.5)	0.04
DM 2	2.1	(0.68–6.5)	0.18
Vasopressor	0.2	(0.05–0.73)	0.01

DHL: lactic dehydrogenase, **HbA1c**: Glycosylated hemoglobin, **HBP**: High blood pressure **DM2**: Diabetes mellitus 2

HbA1c levels with greater inflammation (higher levels of interleukins and CRP) and negative linear correlation between SaO_2 (arterial oxygen saturation) and HbA1c. We did not measure IL-6 levels but CRP was higher in the group with HbA1c ≥6.5%, with a median of 173 mg/L (111–278) compared to the group <6.5% with 129 mg/L (90–187). This difference was also observed in the DD with a median of 1210 ng/ml (624–3450) and 2818 ng/ml (1520–500) for the group with HbA1c <6.5% and ≥6.5%, respectively. Therefore, we consider that higher the

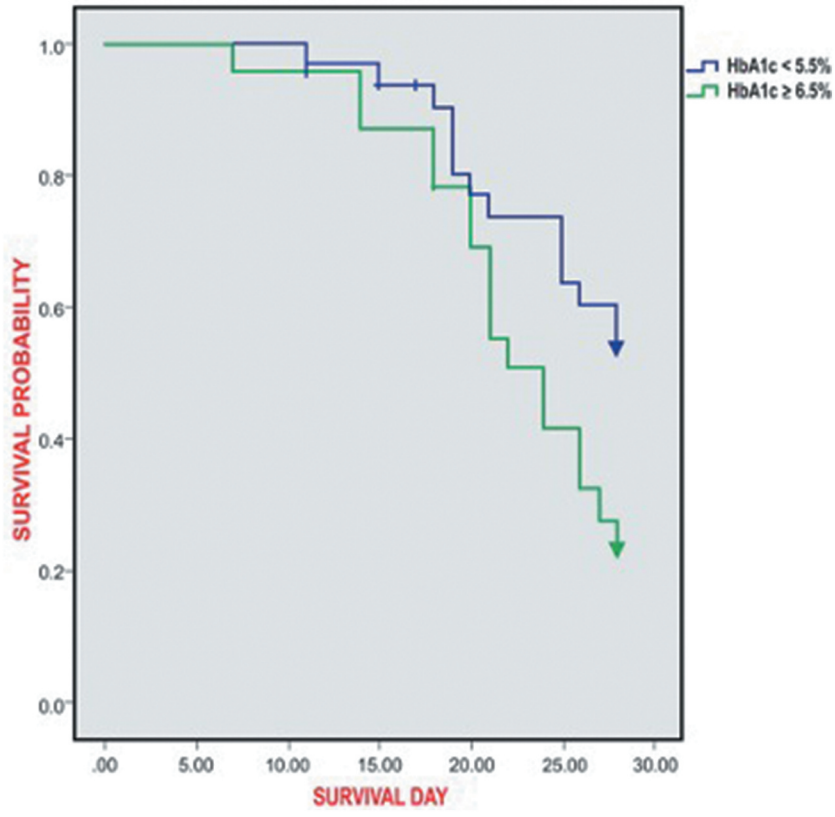

Figure 2. Kaplan–Meier survival to 28 days in the ICU according to HbA1c level.

HbA1c level, the greater the systemic inflammation and hypercoagulability. Merzon et al. [22] reported that HbA1c levels ≥9% increase the risk of hospitalization in patients with diabetes (OR 4.95, 95% CI, 1.55–15.76, p = <0.05) who acquire COVID-19. We consider that premorbid glycemic status is associated with outcomes in patients with severe SARS-CoV-2 pneumonia in need of IMV.

The present study has limitations. First, the sample size (n = 56) is small. Second, it is a retrospective cohort. Third, we do not have information on the quality of life of the survivors. Within the strengths, 100% of the patients were in the ICU with IMV. We carry out follow-up in hospitalization, so we report hospital mortality. These results support the idea that the HbA1c level together with other factors may be useful in clinical practice to predict outcomes in patients with severe SARS-CoV-2 pneumonia with IMV.

6. Conclusion

In patients with severe SARS-CoV-2 pneumonia with IMV admitted to the ICU, HbA1c level ≥6.5% measured on admission is associated with higher 28-day mortality.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors contributions

JSSD was responsible for the conceptualization of the study, and the revision and approval of this manuscript. KGPM drafted the manuscript, and was responsible for the accuracy and collection of the data. ORPN and MAGG critically reviewed the paper. All the authors read and approved the final version of the manuscript.

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ORCID

Manuel Alberto Guerrero Gutierrez http://orcid.org/0000-0002-0645-1836

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