Relationship between glycosylated hemoglobin levels and severe disease and mortality in patients hospitalized for COVID-19

JUAN DAVID PALOMAR-AVILÉS, LINA PAOLA FAJARDO-LATORRE, MARCELA GODOY-CORREDOR, MILCIADES IBÁÑEZ-PINILLA • BOGOTÁ, D.C. (COLOMBIA)

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Abstract

Objective: to determine the relationship between elevated glycosylated hemoglobin levels and severe disease and mortality from COVID-19 in patients hospitalized for SARS-CoV-2 disease at Clínica Universitaria Colombia between June 2020 and December 2021.

Materials and method: this was an observational, analytical, retrospective cohort study. Patients over the age of 18 who were admitted with a COVID-19 diagnosis confirmed by antigens or PCR were included. An association was sought between glycosylated hemoglobin (HbA1c) levels and the outcomes of severe disease and mortality. We performed a univariate analysis to describe the population, a bivariate analysis to determine the associations, and a predictive multivariate analysis, all with a 5% statistical significance level. Data was collected from electronic medical charts of patients hospitalized for COVID-19 at Clinica Universitaria Colombia between June 2020 and December 2021. Patients' sociodemographic variables, history, use of medications, hospital laboratory exams and hospital course were extracted. The glycosylated hemoglobin variable was classified as less than 7%, between 7 and 10%, and greater than 10%, in order to evaluate its relationship with severe disease, defined as patients who were admitted to the intensive care unit or required orotracheal intubation (OTI).

Results: the cohort consisted of 329 patients. The mean age was 62.1 years (SD=14 years). The patients' most common comorbidities were hypertension, diabetes mellitus and cardiovascular disease. The average glycosylated hemoglobin drawn on admission or in the three months prior to hospitalization was 7.08 ±1.86%. Those with an HbA1c of 7% and 10% had a 1.90 times greater risk of dying (95%CI 1.03-3.50) compared to those with an HbA1c less than 7%. They also had a 1.63 and 1.78 times greater risk of being admitted to the ICU or requiring OTI.

Conclusions: We found a cohort of patients with a high burden of comorbidities. The proportion of patients with an out-of-target HbA1c was high. Glycosylated hemoglobin behaved as a risk factor for severe disease and mortality. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.2853).**

Keywords: *HbA1c, COVID-19, mortality.*

Dr. Juan David Palomar-Avilés: Médico Internista; Dra. Lina Paola Fajardo-Latorre: Médica Internista, Nutrióloga Clínica. Coordinadora Semillero Diabetes y Metabolismo; Dra. Marcela Godoy-Corredor: Laboratorio Clínico y de Patología. Clínica Colsanitas. Grupo de Investigación INPAC. Grupo Keralty: Dr. Milciades Ibáñez-Pinilla: Epidemiólogo. **Fundación Universitaria Sanitas.** Bogotá, D.C. (Colombia).
Correspondencia. Dr. Juan David Palomar-Avilés. Bogotá, D.C. (Colombia).
E-mail: juanpalo9403@gmail.com
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Introduction

Beginning in late 2019, the SARS-CoV-2 pandemic increased mortality, with an estimated excess mortality of 120.3 deaths (113.1-129.3) per 100,000 inhabitants worldwide, and 201.2 deaths (191.5-209.4) per 100,000 inhabitants in Colombia (1). Furthermore, population groups with particular characteristics were found to be more susceptible to severe disease and death (2), mainly affecting older adults and people with comorbidities like cancer, obesity or diabetes mellitus (DM) (3).

These comorbidities cause immune pathway abnormalities that lead to increased inflammatory activity, which causes a cytokine imbalance and prothrombotic state (4). Patients with DM, especially, have a higher risk of dying from COVID-19 (5). This is due to a higher susceptibility to SARS-CoV-2 infection, due to decreased immune pathway activity triggered by insulin deficiency and hyperglycemia (6). This, in turn, inhibits leukocyte recruitment and triggers leukocyte, macrophage and complement system hypoactivity (7). As a result, this population has a 2.75 times greater risk of developing severe disease and a 1.90 times greater risk of dying (8).

Glycosylated hemoglobin (HbA1c) is a laboratory test that evaluates patients' glycemic control over the previous

three months (9). Therefore, various scientific societies recommend its use for follow-up of patients with DM or high cardiovascular risk (10). During the pandemic, some laboratory tests, including HbA1c, were proposed as prognostic factors in patients with COVID-19 (11).

However, studies have yielded inconsistent results (12). There have been contradictory results and conclusions, showing both an association between HbA1c and death (13) as well as no association between the two (14). Due to these results, no conclusion could be drawn regarding whether the glycemic control reflected in elevated HbA1c levels is related to severe disease and death in hospitalized patients (15). In Latin America, a study by Sanchez Diaz et al. on a retrospective cohort of 56 critically ill patients with COVID-19 at a secondary care hospital in Mexico reported that HbA1c levels over 6.5% were associated with higher 28-day mortality (16).

In Colombia, there have been no studies evaluating the association of HbA1c levels in patients hospitalized for COVID-19 to determine if patients with elevated HbA1c have a worse prognosis when admitted for SARS-CoV-2 infection. Therefore, the objective of this study was to establish the relationship between elevated glycosylated hemoglobin levels and severe COVID-19 and mortality in patients hospitalized for the disease caused by SARS-CoV-2 at Clínica Universitaria Colombia from June 2020 to December 2021.

Materials and method

An observational, analytical retrospective cohort study was carried out, enrolling patients over the age of 18 admitted to Clínica Universitaria Colombia due to moderate or severe SARS-CoV-2 infection, confirmed by a polymerase chain reaction (PCR) or viral antigen test, from June 2020 to December 2021. The selected patients had to have an HbA1c measurement on admission or up to three months prior to admission. Patients who were referred to home medical care were excluded.

Data was collected from Clínica Colombia's electronic charts. The sociodemographic variables, history, use of medications, inpatient laboratory tests and hospital course were extracted. The glycosylated hemoglobin variable was classified as less than 7%, 7 to 10% and over 10%. For patients with two or more HbA1c levels recorded, the measurement closest to the hospitalization date was used. Severe disease was defined as patients who were admitted to the intensive care unit or required orotracheal intubation (OTI).

The selected sample was consecutive or sequential, including patients who met the selection criteria from June 2020 to December 2021. The sample was calculated using 95% confidence, 80% power, and 42.1% mortality in patients with poor glycemic control versus 24.8% mortality in patients with target glycosylated hemoglobin (<6.5%). The sample size for the study was 116 exposed and 116 non-exposed patients to detect a relative risk (RR) of 1.6.

To control bias and ensure study validity, HbA1c was used as an objective and longitudinal measure of glycemic control. Only patients with a positive PCR or antigen test were considered to have a COVID-19 diagnosis, to control selection bias. To control classification bias, HbA1c was divided by cut-off points. Confounding bias was controlled through a multivariate analysis. Variables like the ROX or NEWS2 scores were not included in the analysis, given their significant individual variability over relatively short periods of time that makes them difficult to measure reliably in a retrospective study, and also considering that not all subjects involved received respiratory support with a high-flow nasal cannula. The detection of concomitant bacterial or fungal infections was not included either, due to their low prevalence in the study population.

Statistical analysis

Measures of absolute and relative frequency were calculated for qualitative variables; measures of central tendency and dispersion were calculated for quantitative variables, according to their distribution. Bivariate analysis was done using Person's Chi square or Fisher's exact test and the likelihood ratio (for expected values less than 5). The Mann-Whitney U test was used due to the distribution calculated by the Shapiro Wilk test. Finally, a multivariate analysis was constructed to obtain the adjusted RRs of the HbA1c levels and their relationship with severe disease and mortality. The statistical analysis was evaluated with a 5% level of significance.

Ethical considerations

The study was presented to and approved by the ethics committee at Fundación Universitaria Sanitas, with code 084-22 UNV. It was considered to be a "no risk" study, and therefore informed consent was not required.

Results

Characteristics of the study cohort

The cohort consisted of 329 patients who were admitted to Clínica Colombia with a confirmed SARS-CoV-2 infection diagnosis; the main characteristics of the population are presented in Table 1. The mean age was 62.1 years (SD=14 years), with a minimum age of 25 and a maximum age of 98 years, and the male sex predominated. On the other hand, the most common comorbidities recorded were hypertension, diabetes mellitus and cardiovascular disease. In patients with diabetes mellitus, metformin was ordered for 124 (37.7%) and insulin for 104 (31.6%).

Glycosylated hemoglobin levels

The average glycosylated hemoglobin level taken on admission or within the three months prior to hospitalization was 7.08 ± 1.86%, with a minimum of 4.60 and a maximum of 16.20. Figure 1 shows the frequency histogram. Altogether, 51.7% (n=170) of the cohort had HbA1c levels less than 7,

while 39.8% (n=131) and 8.5% (n=28) had levels between 7 and 10% and over 10%, respectively.

ICU admission, severe disease and mortality

During hospital follow-up, 266 patients were diagnosed with acute respiratory distress syndrome (ARDS). The frequency of intensive care unit admission was 43.5%; these patients required advanced support measures, including orotracheal intubation, which was ordered for 89 patients. The mean length of hospital and ICU stays are reported in Table 1. The mortality rate in the cohort was 20.5%.

Table 1. Sociodemographic characteristics of the cohort of patients admitted to Clínical Colombia for COVID-19 from June 2020 to December 2021.

Variable	n (%)
Sex, male	183 (55.6)
Age	62.1 (14.0)
20-29	4 (1.2)
30-39	16 (4.9)
40-49	38 (11.6)
50-59	82 (24.9)
60-69	86 (26.1)
70-79	62 (18.8)
80-89	34 (10.3)
90-99	7 (2.1)
CVD	78 (23.7)
Pulmonary disease	50 (15.2)
CKD	43 (13.1)
HTN	194 (59.0)
Obesity	64 (19.5)
Diabetes mellitus	170 (51.7)
Days of hospitalization, mean (SD)	10.2 (11.8)
ICU admission	135 (43.5)
Days in ICU, mean (SD)	5.4 (9.4)
OTI	89 (28.9)
Mortality	62 (20.5)

CVD= Cardiovascular disease. CKD= Chronic kidney disease. HTN= Hypertension. ICU= Intensive care unit. OTI= Orotracheal intubation.
n= Sample. SD= Standard deviation. %= Percentage

Association between HbA1c and severe disease

The association between glycosylated hemoglobin levels and the outcomes of interest showed statistically significant differences. There was a correlation between the HbA1c level and ICU admission, the need for OTI and mortality. Furthermore, the mean HbA1c was significantly higher in patients who died (Table 2).

Table 2. *Association between HbA1c levels and severe disease and mortality in patients admitted to Clínica Colombia for COVID-19 from June 2020 to December 2021.*

Variable %	ICU admission = YES	ICU admission = NO	0.003*
Less than 7	56 (36.4)	106 (65.4)	
Between 7 and 10	63 (52.1)	58 (47.9)	
Over 10	16 (59.3)	11 (40.7)	
	OTI = YES	**OTI= NO**	0.025*
Less than 7	36 (22.2)	126 (77.8)	
Between 7 and 10	43 (36.1)	76 (63.9)	
Over 10	10 (37.0)	17 (63.0)	
	Mortality= YES	**Mortality= NO**	
Less than 7	22 (13.7)	139 (86.3)	
Between 7 and 10	35 (30.2)	81 (69.8)	
Over 10	5 (20.0)	20 (80.0)	
HbA1c, mean (SD)	7.37 (1.56)	6.95 (1.93)	0.005**

HbA1c= Glycosylated hemoglobin. ICU= Intensive care unit. OTI= Orotracheal intubation.
SD= Standard deviation. *Chi square test ** Mann-Whitney U

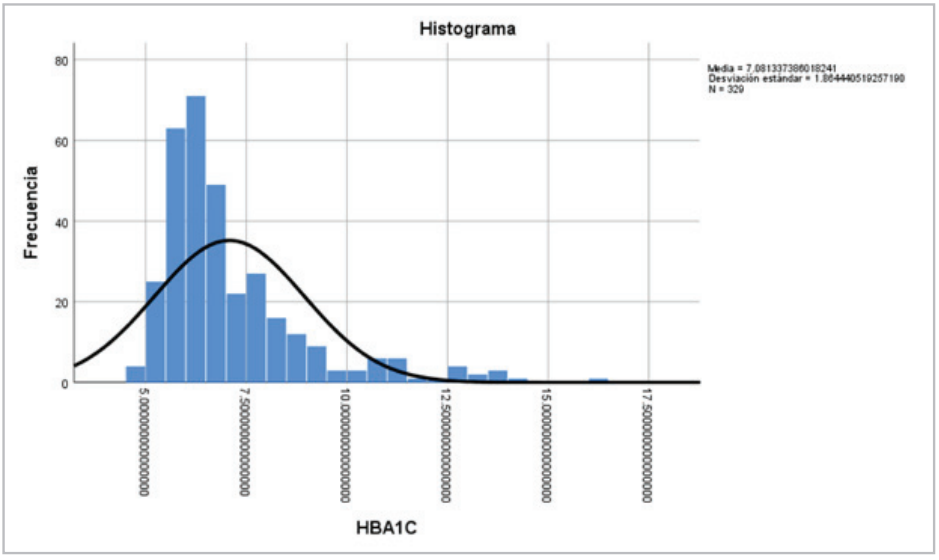

Figure 1. *Frequency histogram for the HbA1c variable.*

The ROC curve (Figure 2) showed a predictive area of 63.9% (95% CI 56.9-71.0) for the mortality outcome, with a cut-off point of 6.34% for a sensitivity of 77.4% and a specificity of 46.7%.

The multivariate analysis (Table 3), after adjusting the HbA1c variable for age and comorbidities, showed that patients with HbA1c levels between 7 and 10% had a 1.90 times greater risk of dying (95% CI 1.03-3.50) compared to those with HbA1c levels under 7%. Moreover, age was also identified as an independent risk factor for mortality, with an RR of 1.02. For each additional year, the patients were 0.02 times more likely to die.

An observation of the association between HbA1c levels and severe disease (ICU admission and OTI) indicated that glycosylated hemoglobin between 7 and 10% also behaved as a risk factor for these events. These patients had 1.63 and 1.78 times the risk of being admitted to the ICU or requiring OTI, compared with those who had HbA1c levels under 7%.

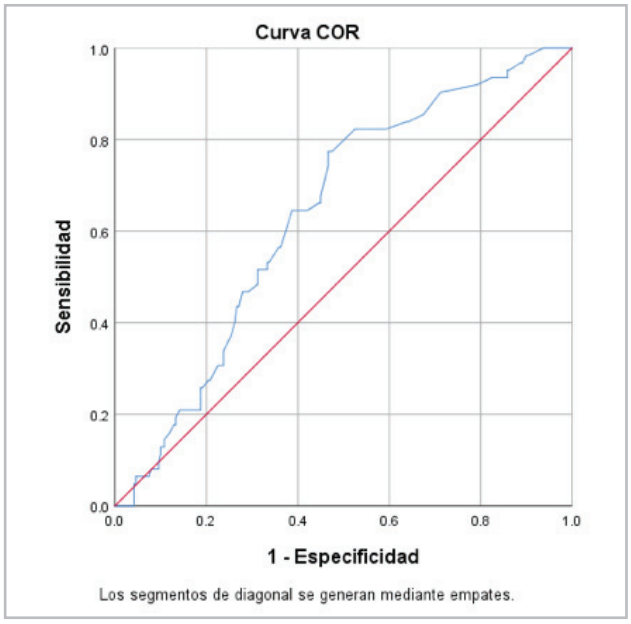

Figure 2. *HbA1c ROC curve for mortality in patients admitted for COVID-19.*

Discussion

Glycemic control is an important factor for preventing microvascular injury caused by immune disorders due to elevated blood glucose levels (6). These disorders cause patients with poor glycemic control to have a higher risk of infectious diseases (17). During the pandemic, an HbA1c outside of the target range was hypothesized to increase the risk of contracting and developing severe COVID-19 (18).

The population description showed a similar proportion of men and women. The average age was in the 50s, indicating an older population, similar to previous reports in which most of the people admitted for COVID-19 were over the age of 50. For example, in the district of New York, the average age of those hospitalized was 68 (19). The collected cohort showed a high burden of comorbidity, which may have led to their hospitalization. In the first studies, the patients who were hospitalized and died the most had a history of more diseases, which can be explained by immune and microvascular disorders and a lower physiological reserve (7, 20).

Hypertension (HTN) was one of the most prevalent chronic diseases in the cohort, a similar finding to the US registries, in which 49.7% of the hospitalized patients had hypertension (21). In the OpenSAFELY study, which gathered information from more than 17 million people, the prevalence of HTN was 34.3%, and it was also the most common comorbidity (13).

There was a high prevalence of DM in those who were hospitalized; in this study, more than half of the patients (51.7%) had been diagnosed with diabetes prior to being admitted for SARS-CoV-2 infection, a similar proportion to what was reported in the United States, where 62% of 184 patients admitted for hospital care had a history of DM (21). However, it is a disproportionate figure when compared to Klein et al.'s data, who reported 31.7% of patients having diabetes (22).

An analysis of the patients with high HbA1c (over 7%) showed that almost half had HbA1c levels out of the target range, indicating chronic poor glycemic control. Merzo et al. found a concordant figure in their study, in which more than half of the patients hospitalized for COVID-19 care had glycosylated hemoglobin levels outside of the target range (23).

During the pandemic, the onset of severe disease and, therefore, the site of care, were affected by glycemic control. A study in Israel found that patients with HbA1c > 9% had an almost five times greater risk of being hospitalized than those with lower HbA1c levels (23). In our case, severe disease was defined as intensive care unit admission and OTI.

The frequency of ICU admission and OTI was 43.5 and 28.9%, respectively. In the CORONADO study, 410 patients (31.1%; 95% CI: 28.6-33.7) were admitted to the ICU within seven days of hospital admission, and 267 people required tracheal intubation for mechanical ventilation (20.3%; 95% CI: 18.1-22.5) (14).

They found that a higher proportion of patients with HbA1c levels within the target range were not admitted to the intensive care unit: 56 (36.4%) compared to 106 (65.4%). Likewise, a higher proportion of patients with HbA1c levels above 10% were admitted to the ICU (16 [59.3%] versus 11 [40.7%]), with statistically significant differences (p=0.003). These results had already been reported by Bhandari et al., although their population was small. They found significant differences in ICU admission when patients with HbA1c levels under 8% (n = 2 [3.45%]) were compared to those with HbA1c levels over 8% (n = 3 [13.64%]) (p = 0.09) (24).

Altogether, 28.9% of the patients required OTI, a slightly higher percentage than the 23.9% reported by Smith et al.

Table 3. *Multivariate analysis. HbA1c as a risk factor for severe disease and mortality in patients admitted for COVID-19.*

Variable	B	P value	RR	95% CI for the RR	
For the mortality outcome					
HbA1c (7%-10%) *	**0.64**	**0.03**	**1.90**	**1.03**	**3.50**
HbA1c (>10%) *	0.51	0.35	1.67	0.56	4.95
Age	**0.02**	**0.02**	**1.02**	**1.003**	**1.05**
CVD	0.14	0.66	1.215	0.60	2.19
Pulmonary disease	0.18	0.61	1.20	0.58	2.50
CKD	0.57	0.11	1.77	0.87	3.57
HTN	-0.16	0.63	0.84	0.42	1.68
For the ICU admission outcome					
HbA1c (7%-10%) *	**0.48**	**0.03**	**1.63**	**1.03**	**2.56**
HbA1c (>10%) *	0.50	0.15	1.65	0.82	3.31
Age	-0.07	0.45	0.99	0.97	1.01
CVD	0.25	0.31	1.29	0.78	2.12
Pulmonary disease	-0.03	0.90	0.96	0.53	1.73
CKD	-0.40	0.25	0.67	0.33	1.32
HTN	-0.05	0.82	0.94	0.58	1.52
For the orotracheal intubation outcome					
HbA1c (7%-10%) *	**0.58**	**0.03**	**1.78**	**1.05**	**3.04**
HbA1c (>10%) *	0.52	0.20	1.69	0.74	3.83
Age	-0.002	0.82	0.99	0.97	1.01
CVD	-0.80	0.80	0.92	0.49	1.71
Pulmonary disease	0.11	0.74	1.11	0.57	2.18
CKD	0.09	0.79	1.10	0.53	2.26
HTN	-0.36	0.20	0.69	0.39	1.21

HbA1c= Glycosylated hemoglobin. CVD= Cardiovascular disease. CKD= Chronic kidney disease. HTN= Hypertension.
B= Beta coefficient. RR= Relative risk. 95% CI= 95% confidence interval.
Compared with HbA1c less than 7%*

(21). Like us, they found that higher levels of HbA1c were associated with OTI (average HbA1c 8.0 versus 7.2, p = 0.034).

On multivariate analysis, HbA1c levels between 7 and 10% functioned as risk factors for severe disease. After adjusting for confounding variables, these patients had a 1.63 and 1.78 times greater risk of ICU admission or needing OTI, compared to those with HbA1c levels below 7%.

Mortality in COVID-19 patients has been one of the outcomes of greatest interest for researchers, which has even facilitated the development of meta-analyses (12,15). The proportion of patients in our study who died was 20.5%. Previous cohorts found an inpatient mortality of up to 48.3% (2). After multivariate analysis, we found that age was an independent risk factor for death. In a Spanish cohort of patients admitted to the ICU, Ferrando et al. concluded that the risk of death for these people increased by 1% per year (OR 1.054 95% CI 1.01-1.09. p = 0.014) (25). This is explained by the greater frailty of elderly patients, which creates a higher risk of complications and a lower likelihood of achieving adequate recovery after overcoming the SARS-CoV-2 infection (26).

Moreover, HbA1c levels outside of the target range (over 7%) were an independent factor for death in hospitalized patients. These results were congruent with some reports (13, 27), but divergent from others (14, 24). Therefore, systematic reviews with meta-analyses were needed to reach conclusions with greater statistical power. The meta-analysis by Prattichizzo et al. concluded that HbA1c, as a dichotomous variable, functioned as a risk factor for dying (OR=1.12 95% CI 1.05-1.20. Chi^2 heterogeneity = 2.12. I^2 = 6%) (12). Zhu et al., also evaluated this association in a meta-analysis, concluding that HbA1c, as a dichotomous variable, triggered a greater risk of dying (OR 2.30; 95% CI, 1.67-3.15); however, when it was analyzed as a continuous variable, this association was not significant (OR 1.02; 95% CI, 0.95-1.09).

The higher risk associated with poor glycemic control reflected in an HbA1c level outside of the target range is explained by the immune imbalance that occurs in patients with DM and elevated HbA1c levels, where the inhibited leukocyte recruitment, and leukocyte, macrophage and complement system hypoactivity lead to a prothrombotic state that results in a higher risk of thrombotic events and ARDS (7).

Among the limitations of this study, we recognize that retrospective data collection may have caused information bias, although measures were taken to corroborate the information obtained from the medical charts, to control this bias. Another limitation may have been the HbA1c measurement; this measurement bias was controlled by taking the HbA1c closest to the date of hospitalization and measured by the same laboratory. Likewise, the relationship between the HbA1c levels and potentially longer hospital stays was not evaluated: however, in light of the statistically significant direct relationship with the major outcomes described, we believe it is plausible to infer that worse glycemic control is also associated with a longer hospital stay.

Conclusions

We found a patient cohort with a high burden of comorbidities, and a high proportion of patients had HbA1c levels outside of the target range. HbA1c functioned as a risk factor for severe disease and mortality, and therefore hospitalized patients with HbA1c levels should receive special attention from emergency room, floor and ICU physicians to reduce complications and mortality in these patients.

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