

Association between hyperglycemia treatment and mortality in patients with diabetes and COVID-19 in a Peruvian hospital: A retrospective cohort study

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ABSTRACT

Objective: To evaluate the association between hyperglycemia treatment and mortality in patients with diabetes and COVID-19 in a Peruvian hospital.

Methods: A retrospective cohort study was conducted between March and July 2020. Individual-level data were extracted from an implemented virtual platform. We included patients with type 2 diabetes hospitalized with COVID-19. The assessed outcome was in-hospital mortality. The Independent variable of interest was hyperglycemic treatment. We used Poisson regressions with robust variance to obtain crude and adjusted relative risks (RR) and their 95% confidence intervals (95% CI).

Results: Out of 1635 patients hospitalized for COVID-19 during the study period, 248 patients with diabetes mellitus were included. The majority were men (66.9%), the median age was 62 years. Ninety-seven patients died in the hospital (39.1%). The median glycemia on admission was 222.5 mg/dL. At 48 h after hospital admission, 125 patients (50.4%) received sliding scale insulin alone (SSI), 46 (18.5%) received a fixed-dose insulin regimen. In the adjusted analysis, the group with SSI at 48 h of hospitalization had higher mortality than those with fixed-dose insulin (adjusted RR: 1.69; 95% CI: 1.01 – 2.83), and those and who continued with SSI in the following days had higher mortality compared to the group that switched to fixed-dose insulin (adjusted RR: 1.64; 95% CI: 1.17 – 2.32).

Conclusion: Among assessed patients with diabetes and COVID-19, more than a third died during hospitalization. Early and continuous use of the sliding scale was associated with higher mortality compared to fixed-dose insulin regimens.

Introduction

In March 2020, the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) as a pandemic [1]. According to the Peruvian Ministry of Health about deaths related to COVID-19, diabetes mellitus is the second most reported comorbidity (8%), after arterial hypertension (8.7%) [2]. In October 2020, Peru became one of the countries with the highest mortality per million inhabitants in America [3].

The general prevalence of diabetes mellitus in adults is close to 8% [4]; but in cohorts of hospitalized patients with COVID-19, it fluctuates between 8 and 31% [5–8] and has been linked to an increased risk of complications and mortality [9,10] compared to the general population. Glycemic control is a fundamental pillar of treatment, despite this, the best treatment strategies are not yet well established in patients with COVID-19 [11], since a study found that the use of insulin was associated with higher mortality [12].

International guidelines for hospital management of diabetes have

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extrapolated their recommendations to patients with COVID-19, recommending the use of fixed-dose insulin regimens (basal, basal-plus, or basal-bolus insulin) [13–15] to achieve glycemic control quickly following admission. On the other hand, sliding scale insulin (SSI) alone is discouraged, but its use is still frequent in hospitals [14].

Very limited information about hyperglycemia treatment strategies is available from low- and middle-income countries (LMIC), such as Peru. In patients with diabetes and COVID-19, blood glucose monitoring and adequate hyperglycemia treatment may not be uniformly conducted throughout the hospital stay due to pandemic-related resource limitations, and further information is needed to evaluate any possible association with mortality.

Using a recently implemented platform for electronic health records, we extracted individual-level data to evaluate the association between hyperglycemia treatment with mortality in patients with type 2 diabetes hospitalized for COVID-19 in a Peruvian hospital.

Materials and methods

Study design and population

A retrospective cohort study was conducted during the first wave of the COVID-19 pandemic at *Hospital Nacional Alberto Sabogal Sologuren* (In Spanish), which is a regional referral hospital located in the constitutional province of Callao, Peru. The study period was between March 23 (first case hospitalized for COVID-19) and July 2020.

In our hospital, since the beginning of the pandemic, a differentiated emergency area was implemented for suspicious patients; there were 30 observation beds where confirmatory tests for COVID-19 and routine blood tests were carried out, and later they were hospitalized in a general hospitalization area, which had 276 beds or in the Intensive Care Unit (ICU), with 30 beds. The definition of the confirmed case of COVID-19 and the management of the patients were based on the clinical guidelines published by the WHO, which included the indications for corticosteroids and anticoagulants [16].

We included all patients with type 2 diabetes mellitus (previous history or debut) hospitalized for COVID-19 (confirmed by molecular or antigenic test) admitted to the general hospitalization area. Those under 18 years of age, pregnant, with a history of type 1 diabetes, with criteria compatible with diabetic ketoacidosis and/or hyperglycemic hyperosmolar state, who died in the first 24 h of hospitalization, and those without glycemia records on admission were excluded.

Data extraction

The clinical and laboratory data were extracted from the electronic medical records, which are available from a governmental virtual platform implemented in 2019 (*Servicio de Salud Inteligente del Seguro Social* in Spanish, <https://essi.pe/>). Among those hospitalized for COVID 19, we selected patients with ICD-10 diagnostic codes of diabetes (E10 to E14), then further reviewed electronic medical records to identify patients with pre-existing or newly-diagnosed type 2 diabetes mellitus; and any exclusion criteria. The variables of interest were registered in a Microsoft Excel database.

Variables and definition

The outcome was hospital discharge or death. The exposure was hyperglycemia treatment, which was categorized as: (a) fixed-dose insulin regimens (basal, basal-plus, or basal-bolus insulin), to the use of intermediate or long-acting insulin (NPH or glargine) alone or combined with rapid or ultra-rapid acting insulin (regular or lispro); (b) SSI alone regimens, (c) oral agents (metformin and/or glibenclamide) and (d) no anti-hyperglycemic treatment [17]. This variable was recorded according to the indication that appeared in the electronic medical records in the second (48 h after admission), fourth, and sixth day of

hospitalization.

Due to the lack of local protocols for the management of hyperglycemia and diabetes, the indication of the type of hyperglycemia treatment was according to the personal criteria of a general physician. Evaluation by an endocrinologist was generally performed after the second day of hospitalization, by teleconsultation.

Other variables recorded were demographic data (age, sex, and self-reported comorbidities), sick days before admission (time since onset of symptoms), partial oxygen saturation (SpO₂) on admission, and laboratory data on admission (serum glycemia, blood count, C-reactive protein, lactate dehydrogenase, ferritin, urea, and creatinine). Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) working group formula [18]. The capillary blood glucose values were not available in the electronic medical records, because they were only recorded in the physical medical records.

Statistical analysis

For the descriptive analysis, absolute and relative frequencies, measures of central tendency, and dispersion were used. Bivariate analysis was performed using the Chi-squared test or Fisher's exact test for categorical variables, and the Kruskal-Wallis test for continuous variables. To evaluate the association between the independent variables and mortality, relative risks (RR) and their respective 95% confidence intervals (95% CI) were obtained using Poisson regressions with robust variance.

Adjusted models were constructed including all the independent variables that presented a value of p less than 0.1 in their crude association with mortality and with hyperglycemia on admission. STATA software version 14 (StataCorp, College Station, TX, USA) was used for data processing.

Ethical aspects

The study protocol was evaluated and approved by the Ethics Committee of the *Instituto de Evaluación de Tecnologías en Salud e Investigación* (IETSI) of the Social Security of Peru.

Results

General characteristics of the sample

During the study period, 1635 patients were hospitalized as suspected or confirmed cases of COVID-19. Of these patients, 288 (17.6%) had a diagnosis of diabetes mellitus. From this group, 40 patients were excluded due to previously mentioned reasons (Fig. 1). Thus, 248 patients were included in the final analysis.

Of the 248 patients included, 166 (66.9%) were male, and the median age was 62 years (interquartile range [IQR]: 53–72). Hypertension was the most frequent comorbidity (52.4%), followed by chronic kidney disease (16.9%) and obesity (15.7%). 67.2% of patients reported seven or more days with symptoms of COVID-19 and 29% were admitted with SpO₂ less than 80%. More than 90% of patients in each anti-hyperglycemic treatment group received corticosteroids and anticoagulants as part of the COVID-19 treatment, so these variables were not included in the statistical analysis.

The median glycemia on admission was 222.5 mg/dL (IQR: 138.5–307), but when evaluated according to the hyperglycemia treatment indicated at 48 h of admission, we found that the median glycemic was 235 mg/dL (164–306) in the SSI group, 272 mg/dL (189–368) in those with fixed-dose insulin, 209 mg/dL (139.5–345.5) with oral agents, and 150 mg/dL (122–265) who did not receive anti-hyperglycemic treatment, this difference was statistically significant (p = 0.002). The other laboratory tests are found in Table 1.

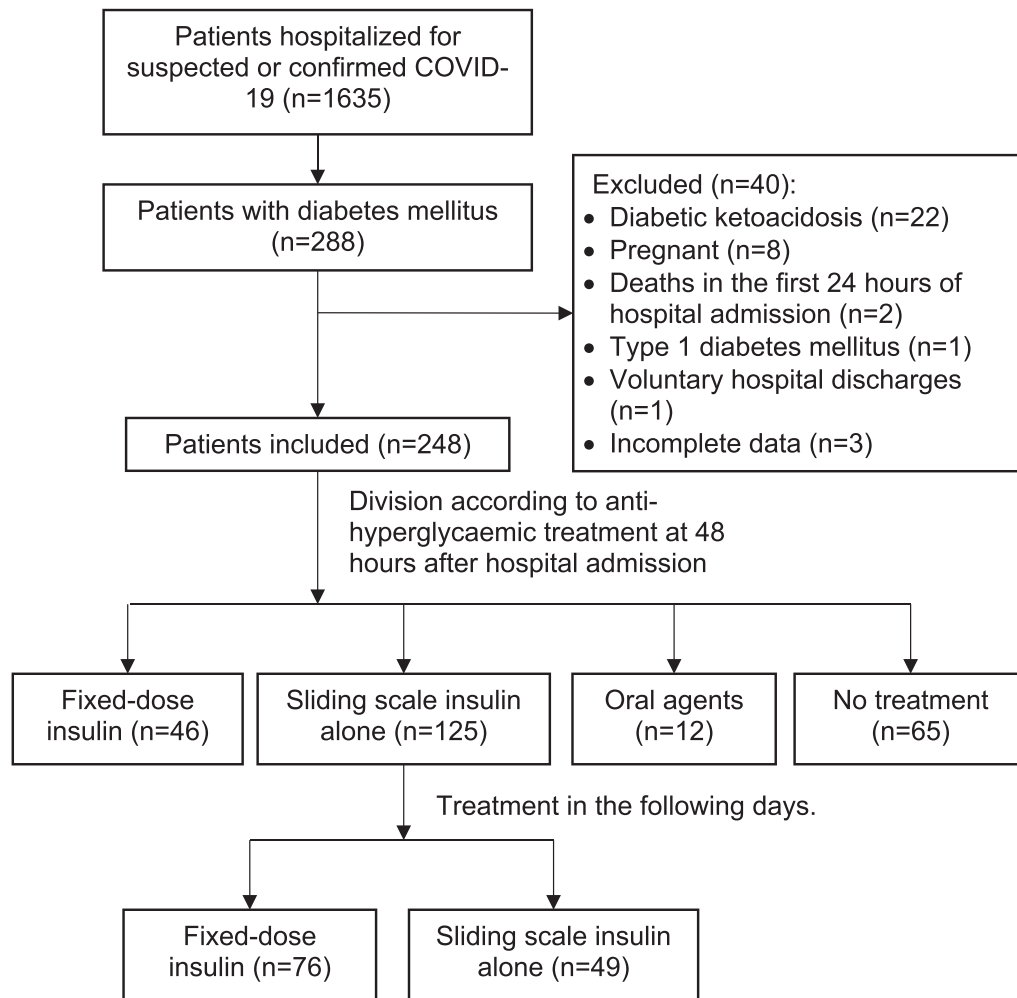


Fig. 1. Flow of patients included in the study.

Anti-hyperglycemic treatment and mortality

At 48 h after hospital admission, 125 patients (50.4%) received SSI alone, 46 (18.5%) received a fixed-dose insulin regimen. A small proportion of patients (4.8%) were treated with oral agents (metformin or glibenclamide) and 65 patients (26.2%) did not receive any anti-hyperglycemic treatment; mortality in the last two groups was higher compared to the fixed-dose insulin group, however, this difference was not statistically significant, in addition, these patients seemed to be less serious according to some parameters on admission (lower glycemia, ferritin level, and protein C-reactive and higher SpO₂) (Table 1).

During hospitalization, 97 patients died (mortality of 39.1%). Mortality in the group with SSI at 48 h of admission was 2.1 times higher than the group with fixed-dose insulin (95% CI: 1.22–3.63). After multivariate analysis, this association was slightly attenuated (RR: 1.69, 95% CI: 1.01–2.83) (Table 2).

On the sixth day of hospitalization, the proportion of patients with SSI decreased to 18.5%, while the use of fixed-dose insulin increased to 46.4% (Fig. 2). Among those who received SSI at 48 h of admission (n = 125), a secondary analysis was performed and we found that patients who continued with SSI had 70% higher mortality compared to those who switched to fixed-dose insulin (RR adjusted: 1.70; 95% CI: 1.21–2.39) (Table 2).

Glycemia on admission and other factors associated with mortality

Mortality in patients with glycemia on admission ≤ 140 mg/dL was 37.3%, lower compared to patients with glycemia between 141 and 179 mg/dL (42.9%) and those with values of 180 mg/dL or higher (39.2%), however, this difference was not statistically significant in the crude analysis (Table 2). Male sex (adjusted RR: 1.47; 95% CI: 1.01–2.13) and SpO₂ less than 80% at admission (adjusted RR: 1.74; 95% CI: 1.19–2.51) were associated with mortality, this result was statistically significant. Although age and number of comorbidities were associated with mortality in the crude analysis, this association was lost after adjusting for confounding variables (Table 2).

Discussion

In this context, limited data are available on management strategies for patients with diabetes and COVID-19 [19], glycemic control, and outcomes. In this observational study, we report high mortality; the majority of patients were treated with SSI 48 h after admission. Treatment with SSI appeared to increase mortality compared to fixed-dose insulin. Unfortunately, we were unable to assess glycemic control during hospitalization, because capillary blood glucose tests were recorded in the physical medical records.

These results contrast with the pre-pandemic studies in Peru. Gonzales-Grández et al. evaluated the results of 424 hospitalized patients with diabetes, mostly due to infectious diseases (69.6%); the mortality of

Table 1

Characteristics of patients with diabetes hospitalized for COVID-19, according to anti-hyperglycemic treatment in the first 48 h of admission.

Variables	Total N = 248 n (%)	Fixed-dose insulin N = 46 n (%)	Sliding scale insulin N = 125 n (%)	Oral treatment N = 12 n (%)	No treatment N = 65 n (%)	p-value*
Male gender	166 (66.9)	31 (67.4)	85 (68.0)	7 (58.3)	43 (66.1)	0.922
Age in years †	63 (53–72)	59 (52–67)	65 (54–72)	68 (61.5–72)	64 (52–73)	0.241
SpO2 on admission						0.586
91 to 100%	80 (32.3)	13 (28.3)	40 (32.0)	4 (33.3)	23 (35.4)	
85 to 90%	84 (33.9)	21 (45.7)	37 (29.6)	3 (25.0)	23 (35.4)	
80 to 84%	28 (11.3)	2 (4.3)	14 (11.2)	3 (25.0)	9 (13.9)	
<80%	56 (22.6)	10 (21.7)	34 (27.2)	2 (16.7)	10 (15.3)	
Comorbidities:						
Arterial hypertension	130 (52.4)	18 (39.1)	66 (52.8)	6 (50)	40 (61.5)	0.141
Chronic kidney disease	42 (16.9)	4 (8.7)	23 (18.4)	0	15 (23.1)	0.086
Obesity	39 (15.7)	10 (21.7)	17 (13.6)	2 (16.7)	10 (15.4)	0.638
Hypothyroidism	17 (6.9)	2 (4.3)	8 (6.4)	1 (8.3)	6 (9.2)	0.664
Cerebrovascular disease	13 (5.2)	3 (6.5)	10 (8.0)	0	0	0.071
Cancer	7 (2.8)	0	5 (4.0)	2 (3.1)	0	0.657
Sick days before admission						0.158
1 to 6 days	81 (32.8)	14 (30.4)	36 (29.0)	4 (33.3)	27 (41.5)	
7 to 9 days	95 (38.5)	14 (30.4)	50 (40.3)	6 (50.0)	25 (38.5)	
10 or more days	71 (28.7)	18 (38.2)	38 (30.7)	2 (16.7)	13 (20.0)	
Laboratory on admission						
Glucose in mg/dL †	223 (139–307)	272 (189–368)	235 (164–306)	209 (140–243)	150 (122–265)	0.002
Leukocytes in 10 ³ cells/uL †	9.9 (7.6 – 13.6)	10.1 (8.2–13.1)	10.8 (8.2–14.7)	9.2 (6.9–12.3)	8.2 (6.5–11.4)	0.011
Neutrophils in % †	85 (77–90)	84 (78–89)	86 (79–91)	88 (82–90)	84 (75–88)	0.123
Lymphocytes in cells/uL †	909 (634–1386)	1032 (742–1355)	894 (659–1412)	541 (450–873)	900 (556–1472)	0.051
Platelets in 10 ³ cells/uL †	290 (216–367)	290 (200–357)	294 (214–384)	292 (228–380)	288 (224–258)	0.947
C-reactive protein in mg/dL †	13 (5–24)	16 (4–26)	14 (6–24)	10 (6–24)	11 (4–23)	0.566
Glomerular filtration rate in ml/min /1.73 m ² †	92 (57–104)	99 (79–109)	92 (48–105)	94 (89–101)	90 (45–101)	0.122
Ferritin in ng/mL †	956 (640–1439)	906 (571–1510)	991 (683–1495)	1403 (879–1497)	897 (611–1330)	0.374
Lactate dehydrogenase in mg /dL †	654 (522–838)	608 (464–794)	694 (538–915)	572 (551–801)	652 (500–819)	0.141
Transference to intensive care unit	13 (5.2)	1 (2.2)	9 (7.2)	0	3 (4.6)	0.674
Mortality	97 (39.1)	11 (23.9)	63 (50.4)	5 (41.7)	18 (27.7)	0.002

† Median (interquartile range).

* p values were calculated by X² test, Fisher's exact test, or Kruskal-Wallis test, as appropriate.

the cohort was 8.6%. Regarding anti-hyperglycemic treatment, the majority used fixed insulin regimens (48.8%), 18.6% sliding scale insulin and 33.6% did not receive antihyperglycemic treatment, however, their association with mortality was not evaluated [20]. Similar mortality (8.25%) was found in a cohort of patients hospitalized for diabetic ketoacidosis in another Peruvian hospital [21].

Anti-hyperglycemic treatment and mortality

In-hospital mortality in patients with diabetes who received SSI at 48 h of admission was higher compared to the group with fixed-dose insulin (50.4% vs 23.9%) (adjusted RR: 1.69; 95 CI %: 1.01–2.83). Alike, those who continued with SSI alone also had higher mortality compared to those who switched to fixed-dose insulin (67.3% vs 39.5%) (adjusted RR: 1.7; 95% CI: 1.21–2.39). In 2007 Becker et al. [22] reported similar findings in patients hospitalized for pneumonia of any cause, the prescription of SSI was associated with in-hospital mortality and other complications (cardiovascular complications, sepsis, and ICU admissions).

During the COVID-19 pandemic, we found studies with ambiguous results regarding the association between insulin therapy and in-hospital mortality. In a cohort of patients in China, the use of insulin in a prandial regimen was associated with higher mortality compared to non-insulin users [12]. In contrast, Sardu et al. found that the intravenous insulin infusion in selected patients significantly reduced interleukin-6 and D-dimer levels and was associated with a lower frequency of adverse outcomes (death, ICU admission, or use of mechanical ventilation) [23].

Outpatients with type 2 diabetes who use insulin have higher mortality compared to those who do not; however, it is not accepted whether insulin is at fault [24]. Furthermore, experimental studies have shown that insulin can have immunomodulatory effects in patients with diabetes and chronic inflammation by reducing cytokine levels [25] and

can also stimulate the immune function of T lymphocytes from mice with severe viral infections [26].

According to our results, it appears that early and prolonged use of the sliding insulin scale may increase mortality in patients with diabetes and COVID-19. This suggests that its use in this context should be discouraged and fixed-dose insulin regimens should be chosen, as recommended by current diabetes management guidelines [6]. However, we believe that it is necessary to carry out controlled studies to compare the outcomes of different anti-hyperglycemic therapeutic strategies.

We observed that at 48 h of admission, more than half of the included patients used SSI alone, and less than a fifth used fixed-dose insulin. However, as days went by, these frequencies were reversed (Fig. 1). The use of SSI is a frequent practice in hospitals [14], possibly due to inexperience in the use of fixed-dose regimens and fear of hypoglycemia among general physicians [27].

Regarding patients with oral agents and those who did not receive anti-hyperglycemic treatment 48 h after hospital admission, they seemed to be less ill at presentation (lower blood glucose and inflammatory markers) and also had lower mortality, compared to patients with SSI. These results suggest the need for individualized regimens particularly among those with mild hyperglycemia to avoid iatrogenic hypoglycemia with complex insulin regimens.

Glycemia on admission and mortality

Hyperglycemia is a known marker of disease severity, even in patients without diabetes, and has been associated with increased mortality during the COVID-19 pandemic [28]. In our study, including only patients with type 2 diabetes, we found that hyperglycemia on admission (more than 140 and 180 mg/dL) was not associated with higher mortality after adjusting for relevant confounders (Table 2).

Despite this unexpected result, similar results were found in another

Table 2
Factors associated with mortality in patients with diabetes hospitalized for COVID-19, in a Peruvian hospital.

Variables	Outcome: mortality			
	No n (%)	Yes n (%)	Raw RR (95% CI)	Adjusted RR* (95% CI)
Sex				
Female	56 (68.3)	26 (31.7)	Ref	Ref
Male	95 (57.2)	71 (42.8)	1.35 (0.94–1.94)	1.47 (1.01–2.13)
Age (years)				
29 to 56	58 (69.9)	25 (30.1)	Ref	Ref
57 to 69	57 (64.0)	32 (36.0)	1.19 (0.78–1.84)	1.08 (0.71–1.65)
70 to 92	36 (47.4)	40 (52.6)	1.75 (1.18–2.59)	1.44 (0.97–2.13)
Number of prior comorbidities				
0	54 (71.1)	22 (28.9)	Ref	Ref
1	53 (57.6)	39 (42.4)	1.46 (0.96–2.24)	1.45 (0.96–2.22)
2 or more	44 (55.0)	36 (45.0)	1.55 (1.01–2.39)	1.49 (0.99–2.23)
Oxygen saturation on admission (%)				
91 to 100	56 (70.0)	24 (30.0)	Ref	Ref
85 to 90	60 (71.4)	24 (28.6)	0.95 (0.59–1.53)	0.87 (0.55–1.40)
80 to 84	14 (50.0)	14 (50.0)	1.67 (1.01–2.75)	1.56 (0.97–2.49)
Less than 80	21 (37.5)	35 (62.5)	2.08 (1.41–3.08)	1.74 (1.19–2.51)
Sick days before admission				
1 to 6	48 (59.3)	33 (40.7)	Ref	Ref
7 to 9	53 (55.8)	42 (44.2)	1.09 (0.77–1.54)	1.18 (0.85–1.62)
10 or more	50 (70.4)	21 (29.6)	0.73 (0.46–1.13)	0.76 (0.51–1.16)
Glycaemia on admission (mg/dL)				
≤140	42 (62.7)	25 (37.3)	Ref	Ref
141 to 179	16 (57.1)	12 (42.9)	1.14 (0.60–1.95)	0.93 (0.59–1.48)
≥180	93 (60.8)	60 (39.2)	1.05 (0.72–1.51)	0.98 (0.68–1.39)
Anti-hyperglycemic treatment at 48 h after admission				
Fixed-dose insulin regimen	35 (76.1)	11 (23.9)	Ref	Ref
Sliding scale insulin	62 (49.6)	63 (50.4)	2.10 (1.22–3.63)	1.69 (1.01–2.83)
Oral agents	7 (58.3)	5 (41.7)	1.74 (0.74–4.06)	1.35 (0.61–2.97)
No treatment	47 (72.3)	18 (27.7)	1.15 (0.60–2.21)	0.93 (0.50–1.73)
Subsequent management among those with SSI at 48 h of admission (n = 125)				
Change to fixed-dose insulin	46 (60.5)	30 (39.5)	Ref	Ref
Continue with SSI	16 (32.7)	33 (67.3)	1.70 (1.21–2.39)	1.64 (1.17–2.32)

RR: relative risk, SSI: Sliding Scale Insulin.

* Adjusted for sex, age, oxygen saturation level on admission, number of prior comorbidities, and hyperglycemia on admission.

small study carried out in Mexico [29]; and in the CORONADO study from France. In the CORONADO study, although hyperglycemia was associated with adverse composite outcomes (mortality and intubation), it was not significant for mortality alone [30]. However, more studies are needed in this regard to clarify these results.

Although we were unable to assess glycemic control due to data collection limitations, clinical trials in hospitalized patients with diabetes, conducted before the pandemic, have shown that basal or basal-bolus insulin regimens can lead to better glycemic control and a lower complication rate compared to SSI regimens [31,32,13–15].

Mortality and transference to ICU

Mortality in this cohort of patients was 39.1%, close to that reported by another Peruvian hospital (49.6%). These results are far superior to other studies conducted in patients with diabetes and COVID-19, where mortality fluctuated between 7 and 20% [5,9], and those with diabetes hospitalized before the pandemic [20–21]. We believe that there are other factors yet to be explored related to this high mortality, such as the impact of gaps in the health system (human resources and infrastructure), outpatient self-medication, among other factors.

It should be noted that the rate of admissions to ICU was lower (5.2%) compared to other cohorts; 31% for the CORONADO study [30], 17.6% for a cohort in China [5], and 10.2% for all patients from another Peruvian hospital [8]. This could be due to the immediate low availability of ICU beds in our hospital.

Study limitation

It is important to consider some limitations of our study: 1) the registration of capillary blood glucose tests was carried out by nurses and they were manually recorded in the physical medical history, unfortunately, we were unable to assess glycemic control in each treatment group; 2) it was not possible to assess glycemic control before hospitalization because only 17.7% of patients had a glycated hemoglobin result, and 3) even though we adjusted for relevant confounders identified during this pandemic, residual confounding is possible such as in-hospital glycemic control or underdiagnosis of obesity.

Conclusion

Among patients with diabetes and COVID-19 in a Peruvian hospital, more than a third died during hospitalization. The use of the insulin-only sliding scale was common and was associated with higher mortality compared to fixed-dose insulin regimens. More controlled studies are needed to evaluate this association with greater certainty.

Author Contributions

E.L-H. wrote the first draft of the manuscript and prepared the figures. E.L-H., D.D.G-C, and F.E-M conceived the research idea, designed the study, and collected the data. S.D-C, A.G-N, and E.S-M collected data and reviewed the manuscript. E.L-H. and A.T-R. analyzed the data and reviewed the manuscript. F.J.P. critically reviewed the analysis approach and successive versions of the manuscript. All authors participated in the writing of the article, and its final version approbation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial

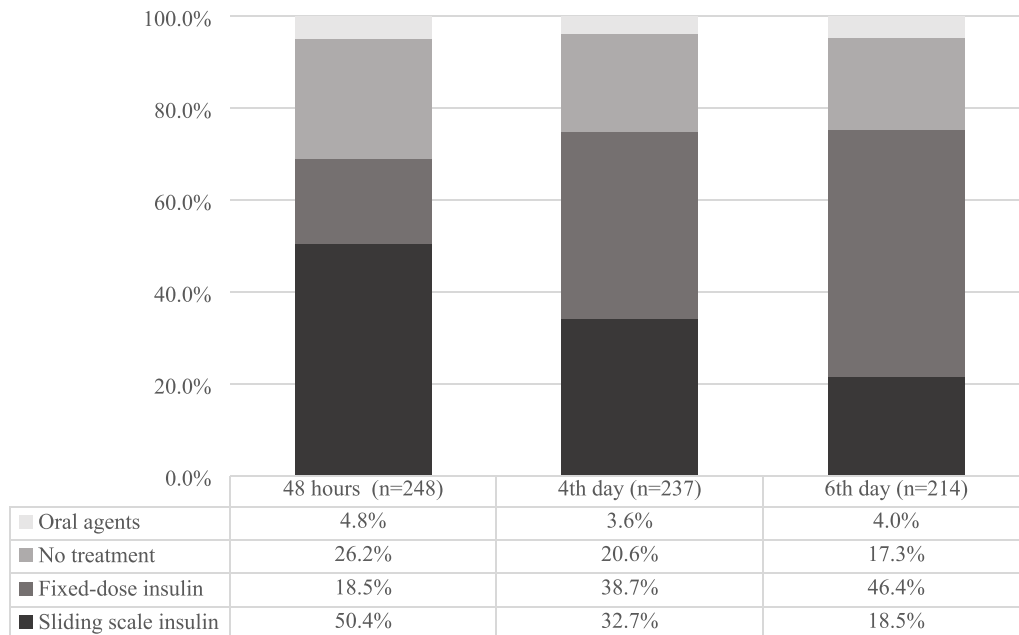


Fig. 2. Anti-hyperglycemic treatment during the first week of hospitalization in patients with type 2 diabetes mellitus and COVID-19.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- Pan American Health Organization. WHO characterizes COVID-19 as a pandemic [Internet]. 2020 [cited 2020 May 2]. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=15756:who-characterizes-covid-19-as-a-pandemic&Itemid=1926&lang=es.
- Ministerio de Salud de Peru. Análisis Epidemiológico de la Situación Actual de COVID-19 en el Perú, basado en la información de la Vigilancia Epidemiológica y la Investigación de Campo [Internet]. Lima; 2020 [cited 2020 Oct 19]. Available from: <https://www.dge.gob.pe/portal/docs/tools/coronavirus/analisiscoronavirus080520.pdf>.
- World Health Organization. Coronavirus disease (COVID-19) Global epidemiological situation [Internet]. Ginebra; 2020 [cited 2020 Dec 12]. Available from: <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201012-weekly-epi-update-9.pdf>.
- Seclen SN, Rosas ME, Arias AJ, Huayta E, Medina CA. Prevalence of diabetes and impaired fasting glucose in Peru: report from PERUDIAB, a national urban population-based longitudinal study. *BMJ Open Diabetes Res Care*. 2015;3(1):e000110. <https://doi.org/10.1136/bmjdr-2015-000110>.
- Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients with Diabetes in Wuhan, China: A Two-Center Retrospective Study. *Diabetes Care*. 2020;43(7):1382–91.
- Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(6):546–50.
- Tadic M, Cuspidi C, Sala C. COVID-19 and diabetes: Is there enough evidence? *J Clin Hypertens*. 2020;22(6):943–8.
- Mejía F, Medina C, Cornejo E, Morello E, Vásquez S, Alave J, et al. Oxygen saturation as a predictor of mortality in hospitalized adult patients with COVID-19 in a public hospital in Lima, Peru. *PLoS ONE* 2020;15(12):e0244171.
- Zhu L, She Z-G, Cheng Xu, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab*. 2020;31(6):1068–1077.e3.
- Xu Z, Wang Z, Wang S, Ye Y, Luo D, Wan L, et al. The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19. *J Diabetes*. 2020;12(12):909–18.
- Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. *Metabolism*. 2020;107:154216.
- Yu Bo, Li C, Sun Y, Wang DW. Insulin Treatment Is Associated with Increased Mortality in Patients with COVID-19 and Type 2 Diabetes. *Cell Metab*. 2021;33(1):65–77.e2.
- Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(1):16–38.
- Colunga-Lozano LE, Gonzalez Torres FJ, Delgado-Figueroa N, Gonzalez-Padilla DA, Hernandez A V., Roman Y, et al. Sliding scale insulin for non-critically ill hospitalized adults with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;11(11):CD011296.
- Zaman Huri H, Permalu V, Vethakkan SR, Pietropaolo M. Sliding-scale versus basal-bolus insulin in the management of severe or acute hyperglycemia in type 2 diabetes patients: A retrospective study. *PLoS ONE* 2014;9(9):e106505.
- World Health Organization. Clinical management of COVID-19: Interim guidance [Internet]. Geneva; 2020 [cited 2020 Oct 26]. Available from: <https://www.who.int/publications/i/item/clinical-management-of-covid-19>.
- Aljehani FA, Funke K, Hermayer KL. Inpatient Diabetes and Hyperglycemia Management Protocol in the COVID-19 Era. *Am J Med Sci*. 2020;360(4):423–6.
- National Kidney Foundation. GFR Calculator [Internet]. 2009 [cited 2020 Sep 24]. Available from: https://www.kidney.org/professionals/kdoqi/gfr_calculator.
- World Bank. World Bank Country and Lending Groups – World Bank Data Help Desk [Internet]. 2020 [cited 2020 Dec 13]. Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.
- Gonzales-Grández NN, Rodríguez-Lay EG, Manrique-Hurtado H. Características clínicas y factores asociados a morbilidad intrahospitalaria en los pacientes con diabetes mellitus tipo 2. *Rev Soc Peru Med Interna*. 2013;26(4):159–65.
- Tisce R, Alán-Peinado A, Baiocchi-Castro L. Características demográficas y epidemiológicas de pacientes con diabetes mellitus tipo 2 hospitalizados por cetoacidosis diabética en un hospital general de Lima-Perú. *Rev Medica Hered*. 2014;25(1):5.
- Becker T, Moldoveanu A, Cukierman T, Gerstein HC. Clinical outcomes associated with the use of subcutaneous insulin-by-glucose sliding scales to manage hyperglycemia in hospitalized patients with pneumonia. *Diabetes Res Clin Pract*. 2007;78(3):392–7.
- Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients with Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? *Diabetes Care* 2020;43(7):1408–15.
- Adler AI. Guilt, or guilt by association? Insulin therapy in type 2 diabetes and death. *Lancet Diabetes Endocrinol*. 2017;5(1):7–8.
- Goyal R, Faizy AF, Siddiqui SS, Singhai M. Evaluation of TNF- α and IL-6 levels in obese and non-obese diabetics: Pre- and postinsulin effects. *N Am J Med Sci*. 2012;4(4):180–4.
- Tsai S, Clemente-Casares X, Zhou AC, Lei H, Ahn JJ, Chan YT, et al. Insulin Receptor-Mediated Stimulation Boosts T Cell Immunity during Inflammation and Infection. *Cell Metab*. 2018;28(6):922–934.e4.
- Russell-Jones D, Pouwer F, Khunti K, Kamlesh KC. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab*. 2018;20:488–96.

- [28] Yang Y, Cai Z, Zhang J. Hyperglycaemia at admission is a strong predictor of mortality and severe/critical complications in COVID-19 patients: A meta-analysis. *Biosci Rep.* 2021;41(2):BSR2020358.
- [29] Gastélum-Cano JM, Islas-Osuna MA, Arízaga-Berber JA. Higher values of fasting blood glucose and glycated hemoglobin are not associated with mortality in Covid-19 Mexican patients. *Prim Care Diabetes.* 2021;15(1):1–3.
- [30] Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020;63(8):1500–15.
- [31] Umpierrez GE, Smiley D, Hermayer K, Khan A, Olson DE, Newton C, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: Basal plus trial. *Diabetes Care* 2013;36(8):2169–74.
- [32] Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al. Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial). *Diabetes Care* 2007;30(9):2181–6.