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At-admission HbA_{1c} levels in hospitalized COVID-19 participants with and without known diabetes

Andrea Valle [a], Javier Rodriguez [a,b], Félix Camiña [b], Miguel A Martínez-Olmos [c], Juan B Ortola [a], Santiago Rodriguez-Segade [a,b,*]

[a] Clinical Biochemistry Laboratory of University Hospital Complex, Santiago de Compostela. Travesía de la Choupana s/n. 15706-Santiago de Compostela (Spain)
[b] Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, Campus Vida. 15782-Santiago de Compostela (Spain)
[c] Endocrinology and Nutrition Service of University Hospital Complex, Santiago de Compostela. Travesía de la Choupana s/n. 15706-Santiago de Compostela (Spain)

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ABSTRACT

Background: To examine glycaemic status, and the impact of at-admission HbA1c levels on outcome, in a large group of participants hospitalized for COVID-19.
Methods: We inclued 515 participants with confirmed COVID-19 infection, with or without known diabetes, who met the following additional criteria: 1) age > 18 years, 2) HbA_{1c} was determined at admission; 3) fasting plasma glucose was determined in the week of admission, and 4) discharge or death was reached before the end of the study. We examined attributes of participants at admission and 3–6 months post-discharge. To assess the associations of pre-admission attributes with in-hospital mortality, logistic regression analyses were performed.
Results: Mean age was 70 years, 98.8% were of white race, 49% were female, 31% had known diabetes (KD), an additional 7% met the HbA1c criterion for diabetes, and 13.6% died. In participants with KD, FPG and HbA1c levels were not associated with mortality in adjusted analyses; however, in participants without KD, whereas FPG showed direct association with mortality, HbA1c showed slight inverse association.
Conclusions: There was a very high prevalence of people without KD with HbA1c levels above normal at-admission. This alteration does not seem to have been related to blood glucose levels.

Introduction

There is now considerable evidence that diabetes increases the likelihood of poor outcome among people with coronavirus disease 2019 (COVID-19), clinical studies in several countries having found that diabetes can increase the probability of a person hospitalized with COVID-19 progressing to intensive care and death [1–3]. In general, it is assumed that hyperglycaemia at the time of admission likewise increases the risk of poor outcome, regardless of prior diabetes status; indeed, tight glycaemic control significantly improves the prognosis of such peoples [4–6]. However, although this background suggests the advisability of checking glycosylated haemoglobin (HbA_{1c}) upon hospital admission for COVID-19, since HbA_{1c} reflects average glycaemia over the preceding 2 to 3 months, the significance of admission HbA_{1c} for the management of COVID-19 peoples remains unclear [7]: some studies have found significant association between admission HbA_{1c} and disease progression or mortality among COVID-19 people, whereas others have not [8–11]. Furthermore, there have in fact been rather few studies that have measured admission HbA_{1c} in all people (rather than only in those known to have diabetes), and most of them have been quite small, in which HbA_{1c} data taken from medical records were often collected long before admission for COVID-19, generally only from participants with diabetes or suspected diabetes [12–15], or for<10% of participants without known diabetes [15].

The initial aim of the present study was therefore to determine the impact of admission HbA_{1c} on outcome in a large sample of participants hospitalized consecutively for COVID-19.

Abbreviations: CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; KD, known diabetes; NG, normoglycemia; PD, prediabetes; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Corresponding author at: Bioquímica Clínica, Laboratorio Central. Complejo Hospitalario. Universidad de Santiago de Compostela. Travesía de la Choupana s/n, 15706-Santiago de Compostela, Spain.
E-mail address: santiago.rodriguez-segade@usc.es (S. Rodriguez-Segade).

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2. Methods

2.1. Participants and consent

The University Hospital Complex, Santiago de Compostela, Spain, is a tertiary centre serving an almost exclusively white population of approximately 450 000 people. This study concerned adult participants severely infected with acute respiratory syndrome coronavirus 2 (SARS-Cov-2, confirmed by polymerase chain reaction testing of nasopharyngeal specimens) who were admitted to the hospital between March 2020 and January 2021 and who met the following additional criteria: 1) age $>$ 18 years, 2) HbA_{1c} was determined at admission, after$<$3 days of corticosteroid treatment, 3) fasting plasma glucose (FPG) was determined in the week of admission, and 4) the endpoint (discharge or death) was reached before the end of the study (Fig. 1).

Anonymised information was entered on database hosted on secure server. Individual consent was not required for anonymous data. The study was reviewed and approved by the Clinical Research Ethics Committee of Consellería de Sanidade. Xunta de Galicia, Spain and in accordance with the current Declaration of Helsinki.

2.2. Study design

We retrospectively assessed the glycaemic status at admission and COVID-19-related mortality in participants with and without known diabetes (KD). Association of mortality with age, sex, comorbidities was also evaluated.

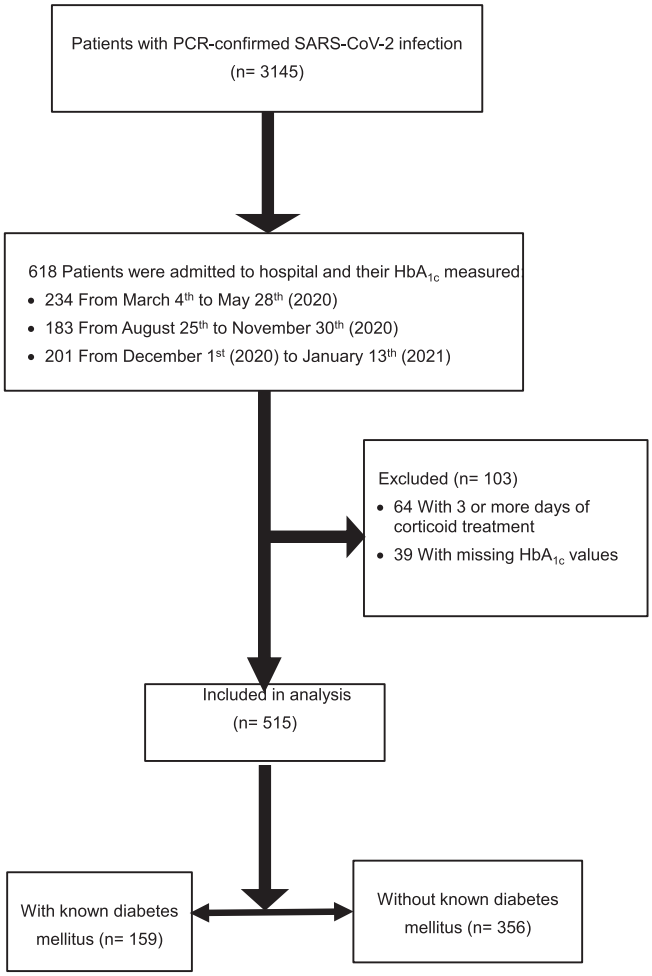

Fig. 1. Flowchart of the study population. PCR, polymerase chain reaction.

2.3. Data collection and laboratory procedures

We retrospectively collected data from medical records concerning HbA_{1c}, FPG, corticosteroid administration at admission, demographic characteristics, comorbidities, complications and clinical outcome (discharge or death while hospitalized). Comorbidities included hypertension, coronary artery disease, past or active cancer, chronic kidney disease (CKD) associated with stage 3–5 kidney failure (estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation), obesity (body mass index (BMI) $\geq$ 30 kg/m^2) and diabetes status. Following the American Diabetes Association (ADA) criteria, we defined prediabetes as an FPG level of 100–125 mg/dL (5.6–6.9 mmol/L) and/or HbA_{1c} of 39–47 mmol/mol (5.7–6.4%), and diabetes as $HbA_{1c} \geq$ 48 mmol/mol (6.5%), FPG level $\geq$ 126 mg/dL ($\geq$7 mmol/L), or current use of an antidiabetic drug [16]; normoglycaemia was indicated by FPG and HbA_{1c} values both being below the cutoff points for prediabetes. "Known diabetes" (KD) was attributed when the participant's medical record showed a diagnosis of diabetes, or the participant reported having diabetes and/or being treated with antidiabetic drugs.

The presence of SARS-CoV-2 in respiratory specimens was detected by real-time RT-PCR methods. HbA_{1C} was determined by high-performance liquid chromatography in a Menarini Diagnostics Arkray Adams HA-8180 T analyser; all HbA1c values were converted to Diabetes Control and Complications Trial (DCCT)-aligned units in accordance with the US National Glycohemoglobin Standardization Program (NGSP) [17]. Fasting plasma glucose was determined by the glucose hexokinase method in a Siemens Healthcare Diagnostics Advia 2400 autoanalyser; to limit distortion due to insufficient fasting (at least 8 h at-admission), participants with abnormal values were attributed the lowest morning blood glucose level during the first 3 days of hospitalization. All analyses were performed on the day of collection in the Clinical Biochemistry Laboratory of the University Hospital Complex, Santiago de Compostela.

2.4. Statistical analysis

Descriptive statistics were calculated for all variables, with mean $\pm$ SD or median and interquartile range reported for continuous variables, and number and percentage of total for categorical and integer variables. The baseline characteristics of the subjects with KD and without KD were compared using the Student t test for continuous variables (a two-tailed P value $\leq$ 0.05 was deemed statistically significant) and the Pearson χ^2 test for categorical variables. To investigate an observed discrepancy between the distributions of FPG and HbA_{1c} among non-KD participants, we used χ^2 tests to compare, for each HbA_{1c}-assigned diabetes status range and each FPG-assigned range, the proportions of non-KD participants in that range at admission and 3–6 months post-discharge; and we performed univariable analyses to compare HbA_{1c} range subgroups of the non-KD group in regard to demographic characteristics, non-KD comorbidities, FPG, and outcome. To assess the associations of preadmission attributes with in-hospital mortality, we performed logistic regression analyses with death as the outcome variable. In multivariable logistic regression analyses we used all variables as predictors simultaneously (age, sex, hypertension, dyslipidemia, current or former smoking, obesity, chronic kidney disease, coronary artery disease, cancer, fasting plasma glucose, and HbA_{1c}). The odds ratios from multivariable analyses are reported together with their 95% CIs. All calculations were performed using SPSS version 23 statistical software.

3. Results

During the study period, 3145 participants tested positive for SARS-CoV-2 in the hospital laboratory (Fig. 1); of these, 618 (19.7%) required hospitalization. Of these 618 participants, 103 were excluded from the

study because HbA_{1c} data were lacking or obtained after>3 days of steroid treatment; of the 515 participants included in the analysis, 413 (80.2%) had HbA_{1c} determined no later than the day on which steroid treatment started. The vast majority of participants were white (98.8%). Most participants (440 (85.4%)) had at least 1 comorbidity, KD in 159 cases (30.9%). The mean (SD) number of comorbidities other than KD was 4.1 (1.3) in the KD group as against 1.8 (1.4) in participants without KD (difference, 2.2; 95% CI, 2.0–2.5; $P < 0$ 0.001). More than half of all participants (57.4%) had known exposure to someone with COVID-19. Table 1 summarizes baseline demographic and clinical characteristics. Although KD participants, as well as having more non-KD comorbidities than participants without KD, were also significantly older, the KD and non-KD groups had similar proportions of participants older than 60 years. Suprisingly, although the third quartile of the FPG distribution of non-KD participants, 5.5 mmol/L, was in the normoglycaemic range, the whole of their HbA_{1c} interquartile range, 39–44 mmol/mol (5.7–6.2%), was in the prediabetic range.

Table 2 shows the glycaemic status of 215 non-KD participants (66.8% of survivors) for whom there were FPG and HbA_{1c} data not only at hospital admission but also 3–6 months after discharge. At admission, only 20.9% of these participants had $HbA_{1c} < 39$ mmol/mol (5.7%), but 3–6 months after discharge, 47.4% did ($P < 0.0001$). There was no such difference in regard to the proportion of participants with normoglycaemic FPG (75.8% at admission as against 68.4% 3–6 months after discharge; $P = 0.09$). Accordingly, only 39.1% of these participants were afforded the same glycaemic status by both ADA threshold criteria at admission, whereas 62.9% were 3–6 months after discharge. Similar results are observed if the at-admission data of all (356) non-KD participants are compared with the post-discharge data of the 215 (presented in Supplementary Table 1). The results with the WHO threshold criteria (presented in Supplementary Table 2) are numerically different, but qualitatively the same – or even more marked - as those obtained with the ADA criteria (Table 2).

At admission, approximately two-thirds of non-KD participants, 66.3%, had prediabetes (PD) on the basis of their HbA_{1c} levels. Univariable anlyses indicated that those with PD were more likely than those with normoglycaemia (NG) to be older than 60 years, and to suffer dyslipidemia (42.8 vs 31.0%, $P = 0.03$) and obesity (40.0 vs 28.8%, $P =$ 0.03), but less likely to suffer chronic kidney disease (6.8 vs 14.3%, $P =$

Table 1
Demographic and clinical characteristics, and outcomes, of participants hospitalized with COVID-19.

Characteristic	Total	With known	Without known	
	($n = 515$)	diabetes ($n = 159$)	diabetes ($n = 356$)	*P* value
Demographic characteristics				
Age (years)	70.4 ± 14.6	74.5 ± 10.8	68.6 ± 15.7	<0.001
>60 years	384 (74.6)	106 (66.8)	246 (69.1)	0.30
Female	254 (49.3)	87 (54.7)	167 (46.9)	0.05
White race	509 (98.8)	157 (98.7)	352 (98.9)	0.84
Comorbidities other than diabetes				
Hypertension	293 (56.9)	126 (79.2)	167 (46.9)	<0.001
Dyslipidemia	263 (51.1)	115 (72.3)	148 (41.6)	<0.001
Chronic kidney disease	74 (14.4)	39 (24.7)	35 (9.8)	<0.001
Coronary artery disease	66 (12.8)	29 (18.2)	37 (10.4)	0.007
Cancer	57 (11.1)	24 (15.1)	33 (9.5)	0.03
Current or former smoking	143 (27.8)	51 (32.1)	92 (25.8)	0.07
BMI (kg/m^2)	30.1 ± 5.3	31.7 ± 5.8	29.4 ± 4.8	<0.001
Obesity (BMI ≥ 30 kg/m^2)	242 (47.0)	100 (62.9)	142 (39.9)	<0.001
Severe obesity (BMI ≥ 40 kg/m^2)	21 (4.1)	12 (7.8)	9 (2.5)	0.001
Baseline glycemic values				
HbA_{1c} %	6.1 (5.8–6.7)	7.0 (6.5–7.9)	5.9 (5.7–6.2)	<0.001
HbA_{1c} (mmol/mol)	43 (40–50)	53 (48–63)	41 (39–44)	<0.001
Fasting plasma glucose (mmol/L)	5.3 (4.8–6.5)	7.7 (5.6–9.8)	5.1 (4.7–5.5)	<0.001
Outcomes				
Length of stay (days)	10 (7–17)	11 (8–20)	10 (7–16)	0.10
Requering intensive care unit	60 (11.7)	22 (13.8)	38 (10.7)	0.16
Mortality	70 (13.6)	36 (22.6)	34 (9.6)	<0.001

Data are *n* (%) or means ± SD or median (IQR). *P* value for comparison between groups with and without known diabetes.

Table 2
Glycaemic status of 215 COVID-19 participants without known diabetes by ADA threshold criteria, at hospital admission and 3–6 months after discharge.

Criterion	At admission	3–6 Months post-discharge	*P* value
HbA_{1c}			
< 5.7% (39 mmol/mol) (normoglycemia)	45 (20.9)	102 (47.4)	<0.001
5.7–6.4% (39–47 mmol/mol) (prediabetes)	148 (68.8)	98 (45.6)	<0.001
≥ 6.5% (48 mmol/mol) (diabetes)	22 (10.2)	15(7.0)	0.24
Fasting plasma glucose (mmol/L)			
<5.6 (normoglycemia)	163 (75.8)	147 (68.4)	0.09
5.6–6.9 (prediabetes)	40 (18.6)	56 (26.0)	0.07
≥7.0 (diabetes)	12 (5.6)	12 (5.6)	1
Participants who met both criterio			
Normal	43 (20.0)	90 (41.9)	<0.001
Prediabetes	31 (14.4)	38 (17.7)	0.35
Diabetes	10 (4.7)	7 (3.3)	0.46

Data are *n* (%).

Table 3
Univariable comparisons of COVID-19 participants without known diabetes mellitus in three groups defined by HbA_{1c} at admission.

Characteristic	HbA_{1c}, mmol/mol (%)				
	< 39 (5.7) (n = 84)	39–47 (5.7–6.4) (n = 236)	*P* value[a]	≥ 48 (6.5) (n = 36)	*P* value[a]
Female	37 (44.0)	112 (47.5)	0.29	18 (50.0)	0.27
Age (years)	65.0 ± 20.6)	69.2 ± 13.5)	0.04	73.2 ± 14.5)	0.03
>60 years	47 (56.0)	172 (72.9)	0.002	27 (75.0)	0.03
Hypertension	34 (40.5)	109 (46.2)	0.18	24 (66.7)	0.004
Dyslipidemia	26 (31.0)	101 (42.8)	0.03	21 (58.3)	0.003
Chronic kidney disease	12 (14.3)	16 (6.8)	0.02	7 (19.4)	0.24
Coronary artery disease	9 (10.7)	22 (9.3)	0.35	6 (16.7)	0.18
Cancer	7 (8.3)	23 (9.7)	0.35	3 (8.3)	0.50
Current or former smoking	26 (31.0)	53 (22.5)	0.06	13 (36.1)	0.29
BMI (kg/m^2)	28.6 ± 5.8	29.2 ± 4.2	0.26	31.9 ± 5.4	0.006
Obesity (BMI ≥ 30 kg/m^2)	24 (28.8)	94 (40.0)	0.03	23 (63.6)	<0.001
Severe obesity (BMI ≥ 40 kg/m^2)	2 (2.7)	3 (1.4)	0.22	2 (6.1)	0.18
FPG (mmol/L)	5.0 (4.4–5.3)	5.1 (4.7–5.5)	0.02	6.9 (5.7–10.7)	<0.001
Outcomes					
Length of stay (days)	10 (6–20)	9 (6–15)	0.16	14 (7–21)	0.37
Requering ICU care	11 (13.1)	22 (9.3)	0.15	5 (13.9)	0.45
Mortality	12 (14.3)	13 (5.5)	0.005	9 (25.0)	0.08

Data are *n* (%) or means ± SD or median (IQR). ICU, intensive care unit. [a]For comparison with $HbA_{1c} < 39$ mmol/mol (5.7%) group (normoglycaemia). FPG = Fasting plasma glucose.

0.02) (Table 3). Participants in the diabetic range (D) were more likely than NG participants to be older than 60 years (75 vs 56%, $P = 0.03$) and to have hypertension (66.7 vs 40.5%, $P = 0.004$), dyslipidemia (58.3 vs 31.0%, $P = 0.003$) and obesity (63.6 vs 28.8%, $P < 0.001$).

During the study period, 70 deaths occurred in the whole study group (13.6%). In univariable analysis the risk of death was 2.8 times greater among KD participants than among non-KD participants (95% CI, 1.7–4.6). However, in the non-KD group, the death rate among participants with HbA_{1c} in the PD range was 2.6 times smaller than that of the NG subgroup, 14.3%, as well as being 4.5 times lower than that of the D subgroup, 25% (Table 3). There were no significant differences among the NG, PD and D subgroups of the non-KD group as regards the duration of hospitalization (median 10 days (range 1–62) in the whole non-KD group) or the proportion requiring ICU care (10.7% in the whole non-KD group) (Table 3).

Table 4 lists the results of multivariable analyses for factors associated with COVID-19 mortality in the KD and non-KD groups. In the KD group, age (OR 1.05, 95% CI 1.00–1.11; $P = 0.04$), cancer (OR 9.18, 95% CI 2.82–29.93; $P < 0.001$) and chronic kidney disease (OR 5.02, 95% CI 1.99–12.66; $P = 0.001$) were significant independent predictors of mortality, but there was no significant association with FPG or HbA_{1c}. In the non-KD group, age (OR 1.12, 95% CI 1.07–1.18; $P < 0.001$) and FPG (OR 2.06, 95% CI 1.45–2.92; $P < 0.001$) were significantly associated with higher mortality, but HbA_{1c} was independently associated with significantly lower mortality (OR 0.27, 95% 0.12–0.63; $P = 0.002$).

4. Discussion

This study focused on SARS-CoV-2-positive participants admitted to a single hospital since March 2020 and before the start of general vaccination. The prevalence of known diabetes in this cohort was 30.9% (greater than previously reported for Europe but similar to U.S. data [12,18–20], and an additional 7% met ADA criteria for type 2 diabetes.

In keeping with the findings of previous studies [18,21–23], participants with known diabetes were 2.4 times more likely to die than participants without diabetes, the significant independent risk factors for KD participants, as identified by multivariate analysis, being age, cancer, and chronic kidney disease; no significant association with FPG, HbA_{1c}, sex, hypertension, coronary artery disease, smoking, or obesity was observed.

However, results of this study concern participants without KD, who had not been receiving any kind of hypoglycaemic treatment, only age and FPG were identified as positive risk factors for mortality, and surprisingly, admission HbA_{1c} emerged as a negative risk factor. In particular, non-KD participants with prediabetic admission HbA_{1c} (66.3% of non-KD participants) had a significantly lower death rate than those with normal HbA_{1c} levels, as well as with respect to those with diabetic HbA_{1c}. Furthermore, 3–6 months after discharge, this "prediabetic" subgroup made up only 45.6% of the 215 participants with follow-up data (66.8% of survivors), while the proportion of non-KD participants with normoglycaemic HbA_{1c} had risen from 23.6% at admission to 47.4% ($P < 0.001$ in both cases). By contrast, the proportions of non-KD participants with FPG in the normoglycaemic and prediabetic ranges did not change significantly (and such change as there was, was in the opposite direction to that observed for the HbA_{1c}-defined subgroups).

These results question the notions that elevated HbA_{1c} at admission in COVID-19 participants is 1) necessarily due to an increase in blood glucose levels, and 2) necessarily a predictor of poor outcome. Among people with diabetes, the relevance of HbA_{1c} to poor outcome has been questioned previously by studies that failed to find any association between them [10,13,24,25]. In this context (diabetes), in which it can indeed be assumed that high HbA_{1c} is probably due at least in great part to hyperglycaemia, questioning its relevance to outcome amounts to questioning whether the well-documented statistical association of diabetes with poor outcome is directly due to hyperglycaemia or reflects metabolic concomitants or clinical complications of diabetes; but it is also possible that the hyperglycaemia of these participants is in part due to metabolic stress due to COVID-19 [24]. In the present study, FPG was a predictor of mortality among non-KD participants, though whether as simply a marker of metabolic stress remains an open question.

In regard to the relationship between high HbA_{1c} and glycaemia (point 1 above), our findings suggest that the elevated HbA_{1c} levels observed in a large proportion of participants with COVID-19 may be due to a direct or indirect effect of SARS-CoV-2 infection on haemoglobin, rather than to *de novo* hyperglycaemia or, in participants with diabetes, a worsening of glycaemic control. Although interaction between the virus and haemoglobin through ACE2, CD147, CD26 and other receptors located on erythrocytes and/or blood cell precursors has been put forward as a possible cause of hypoxia [26], it is conceivable that conformational changes in hemoglobin due to binding of the virus [27] might promote glycosylation without leading to poor outcome. It should also be borne in mind that it is normal for a proportion of the population to have higher HbA_{1c} levels than those generally regarded as corresponding to their glycaemia [28].

Three-quarters of the non-KD participants in this study had normal FPG levels on admission. That considerably higher levels have been reported in some studies [5,18] may have been due to their not ensuring an 8-hour fast, possibly because of the difficulty of obtaining these samples. Studies in which the 8-hour fasting period was guaranteed have reported results similar to ours [29,30], not only in regard to the percentages of people with different glycaemic statuses, but also in that admission FPG was an independent predictor for mortality in non-KD participants.

The main strengths of this study are that, unlike most studies of the impact of HbA_{1c} on COVID-19 outcome, it only admitted participants whose HbA_{1c} was determined on admission to hospital before the start of general vaccination. Further, HbA_{1c} was determined in all cases by the same method in the same laboratory on the day the sample was obtained. There are also limitations to our work. Since HbA_{1c} was determined post-discharge only in 67% of the non-KD participants (and naturally not in those who died), bias may have occurred due to these participants having been prioritized for testing for reasons unknown to us. Also, the data are predominantly from Spanish whites, which may limit generalizability.

In conclusion, in a large sample of participants with COVID-19 at admission and without known diabetes, we found a large proportion of

Table 4
Multivariable analysis of factors associated with COVID-19 death.

	Participants with known diabetes mellitus ($n = 159$)		Participants without known diabetes mellitus ($n = 356$)	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (yares)	1.05 (1.00–1.10)	0.04	1.12 (1.07–1.18)	<0.001
Sex (female vs. male)	0.53 (0.20–1.36)	0.18	0.62 (0.25–1.52)	0.30
Hypertension	1.35 (0.38–4.79)	0.64	1.09 (0.40–3.01)	0.86
Dyslipidemia	1.90 (0.64–5.66)	0.25	0.94 (0.39–2.30)	0.89
Coronary artery disease	1.12 (0.39–3.26)	0.84	2.26 (0.76–6.73)	0.14
Current or former smoking	1.07 (0.41–2.79)	0.89	2.20 (0.79–6.14)	0.13
Cancer	9.18 (2.82–29.93)	<0.001	2.31 (0.77–6.91)	0.13
Obesity[a]	1.42 (0.54–3.73)	0.47	0.72 (0.26–1.98)	0.52
Chronic kidney disease	5.02 (1.99–12.66)	0.001	1.59 (0.56–4.49)	0.39
FPG (mmol/L)	1.13 (0.98–1.31)	0.09	2.06 (1.45–2.92)	<0.001
HbA_{1c} (%)	0.74 (0.49–1.12)	0.16	0.27 (0.12–0.63)	0.002

[a] Obesity was defined as having a body mass index>30. FPG = Fasting plasma glucose.

subjects, 76.4%, with HbA_{1c} levels above the ADA criterion for normoglycaemia. This alteration does not seem to be related to actual glycaemia, because only 24.4% of non-KD participants had non-normoglycaemic FPG levels at admission; and because 3–6 months after discharge the percentage of non-KD participants with HbA_{1c} in the normal range was more than double that observed at admission. These findings may explain, at least in part, the absence of an association between HbA_{1c} levels and in-hospital mortality observed in several studies. More research seems necessary to determine whether these findings generalize to other populations and to study the causes of this intriguing behavior. Determining the HbA_{1c} of COVID-19 participants at admission to hospital would allow better stratification of their risk, and guide the care of both participants with diabetes and those without.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contribution statement

Andrea Valle and Santiago Rodriguez-Segade conceived the study, developed the statistical analisis and drafted the manuscript. Both are the guarantors of this work, and as such, had full access to the data in the study and take responsibility for the integrity and the accuracy of the data analisis. Javier Rodriguez; Félix Camiña, Miguel A Martínez-Olmos and Juan B Ortola contributed to research data and critically reviewed the manuscript for important intellectual content. Félix Camiña and Santiago Rodriguez-Segade edited the final version of the manuscript and made artwork. The final version of the manuscript was approved by all authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2022.05.027.

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