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LETTER TO THE EDITOR

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Preinfection glycaemic control and disease severity among patients with type 2 diabetes and COVID-19: A retrospective, cohort study

Type 2 diabetes (T2D) is one of the most common and important risk factors for severe health outcomes related to coronavirus disease-2019 (COVID-19).[1–3]

Data from the French Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study in patients with COVID-19 infection showed that higher body mass index (BMI) and complications of diabetes were associated with disease severity and death, but they did not identify a link between glycaemic control and mortality.[4,5] However, other studies found an association between HbA1c level and COVID-19–related death,[6–8] suggesting poor glycaemic control as a potential risk factor for mortality.

Establishing the exact nature and magnitude of the association between glycaemic control and COVID-19 severity is critical to inform appropriate glucose management strategies in people with diabetes, such as selecting an appropriate HbA1c target to reduce the risk of severe COVID-19. Appropriate methodologies must be used to investigate the impact of preinfection HbA1c on COVID-19 severity. First, HbA1c should be measured before the onset of COVID-19 infection, so as not to confuse a risk factor (baseline glycaemic control) with a complication of the disease (infection-related hyperglycaemia). Second, preinfection HbA1c should be modelled as a continuous exposure. Models using preinfection HbA1c as a categorical variable prevent a detailed assessment of the dose-response relationship between HbA1c and COVID-19 risk, and furthermore, the use of discrete HbA1c categories may create artificial boundaries between normal and increased risk. Last, models should be adjusted for diabetes complications to separate the effect of longstanding uncontrolled T2D from the effect of current glycaemic control (Figure S1).

Here, we used a large, population-representative dataset to estimate the direct association between preinfection HbA1c levels and the risk of severe illness following COVID-19 infection in patients with T2D. In our analyses, adjusted for the effects of previous poor glycaemic control, we modelled HbA1c as both a continuous and a categorical variable.

This cohort study used data from members of Clalit Health Services (CHS), an Israeli integrated payer-provider healthcare organization, which includes an electronic health record (EHR) database with more than 4.7 million members (approximately 53% of the Israeli population). The database contains inpatient, outpatient and COVID-19 data, including PCR test results, which are collected by the Israeli Ministry of Health (MoH) and sent daily to healthcare providers.

Data were extracted from the CHS EHR database on 8 November 2020 for patients with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR test result from 22 February 2020 to 25 September 2020. Inclusion and exclusion criteria are presented in Table S1. The index date for patients was set to the date of their first positive PCR test.

The outcome of interest was severe COVID-19, defined as a composite outcome of death as a result of COVID-19 or severe COVID-19 illness diagnosed in the 45 days after the initial diagnosis. Severity was defined according to the Israeli MoH definition, which aligns with the definition of severe COVID-19 illness from the World Health Organization (Table S2).[9]

The primary exposure of interest was the most recent HbA1c value measured in the 6 months before the index date. Demographic and clinical variables such as disease diagnosis and medication use (Table 1) were extracted from EHRs up to 5 years prior to the index date. Full lists of the extracted diagnosis and treatment variables and definitions are provided in Table S3 (T2D and other conditions) and Table S4 (antidiabetic medications).

Missing data were imputed once using the R package MICE,[10] with the complete dataset used for the study.

The characteristics of the study population were described using summary statistics, and the two-sample *t*-test and the χ^2 test were used to compare characteristics between patients with severe and non-severe COVID-19.

To assess the association between HbA1c as a continuous variable and COVID-19 severity, we used a generalized additive model.[11] A thin-plate spline was used for the primary exposure to allow a non-linear relationship, which was postulated based on clinical reasoning.[12] We present the non-linear relationship on the linear predictor (log) scale with the standard error. The model was adjusted for age, sex, BMI, ethnicity, socioeconomic status, smoking, co-morbidities, diabetes complications and antidiabetic medications.

To obtain 'dose-response' estimates (with 95% confidence intervals [CIs]) for the relative risk (RR) when reducing HbA1c from a reference value of 8.0% to different target values from 7.8% to 6.0%, we performed 1000 bootstrap iterations. Each iteration consisted of the

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following: (a) sampling (with replacement) from the dataset; (b) fitting a generalized additive model with a Poisson distribution and a log link function; and (c) obtaining and storing the differences in the estimated (log) risk (i.e. the risk on the linear predictor scale) between the reference HbA1c and each of the possible target values.

We obtained 95% CIs using the percentile method for the RR associated with each HbA1c percentage reduction from the reference level to each of the HbA1c target levels (7.8%–6.0%).

To facilitate comparison with the existing literature, we stratified HbA1c into five categories (≤6.0%, 6.1%–7.0%, 7.1%–8.0%, 8.1%–10.0% and >10.0%) and presented the association between HbA1c as a categorical exposure and disease severity, expressed as RRs with 95% CIs. A generalized linear model with a Poisson outcome distribution and a log link function was used. The model was adjusted for the same variables as the continuous model, with an HbA1c of 6.0% or less used as the reference category. Furthermore, as part of our sensitivity analysis, a subgroup analysis of patients with an HbA1c value available in the 3 months before the index date was performed.

This study was approved by the Institutional Review Board of CHS and was exempt from the requirement for informed consent.

In total, 102,514 CHS members received a diagnosis of PCR-confirmed COVID-19 during 22 February–25 September 2020. Of this population, 5869 patients were eligible for enrolment (Figure S2).

Baseline demographic and clinical characteristics are shown in Table 1. Mean (standard deviation [SD]) HbA1c was 7.24% (1.55%); the distribution density of HbA1c is shown in Figure S3.

Most patients experienced non-severe COVID-19 (n = 4855; 82.7%). There were significant differences between the demographic and clinical characteristics of the two groups (Table 1). Compared with patients who experienced non-severe COVID-19, those with severe COVID-19 had higher preinfection HbA1c (mean [SD] 7.40% [1.60%] vs. 7.21% [1.53%]), were older (mean [SD] 72.9 [12.1] vs. 63.8 [13.0] years), were more probable to be men (56.7% vs. 48.4%) and were significantly more probable to report macrovascular and microvascular diabetes complications.

Additionally, of 1527 patients hospitalized for COVID-19, 39.75% had mild or intermediate COVID-19 (Table S5).

Results from the generalized additive model showed a positive, significant, sigmoidal, non-linear association between preinfection HbA1c and the risk of developing severe COVID-19 (Figure 1). The strongest positive association was observed between HbA1c values of 6% and 12%.

There was a gradual dose-response relationship between HbA1c level and risk: a difference in HbA1c from 8.0% to 6.0% was associated with a 29.0% decreased risk of developing severe COVID-19 (RR 0.71, 95% CI: 0.52–0.87; Table 2). The smallest HbA1c difference examined, from 8.0% to 7.8%, was associated with a statistically significant 4% lower risk of severe COVID-19 (RR 0.96; 95% CI: 0.92–0.99).

The sensitivity analysis using categorized HbA1c as the primary exposure confirmed the association between HbA1c and severe COVID-19 (Figure S4). Compared with patients who had an HbA1c of 6.0% or less, those with an HbA1c of 8% or higher had an increased

TABLE 1 Baseline characteristics of patients with type 2 diabetes (T2D) and a diagnosis of coronavirus disease-2019 (COVID-19), for the full cohort and by disease severity

	Test-positive COVID-19 with T2D (N = 5869)	Disease severity		*p* value*
		Non-severe (n = 4855)	Severe (n = 1014)	
HbA1c, %, mean (SD)	7.24 (1.55)	7.21 (1.53)	7.40 (1.60)	<.001
HbA1c categories, n (%)				
≤6.0%	1110 (18.9)	927 (19.1)	183 (18.0)	
6.1%–7.0%	2171 (37.0)	1855 (38.2)	316 (31.2)	
7.1%–8.0%	1302 (22.2)	1059 (21.8)	243 (24.0)	
8.1%–10.0%	920 (15.7)	720 (14.8)	200 (19.7)	
>10.0%	366 (6.2)	294 (6.1)	72 (7.1)	
Age, years, mean (SD)	65.3 (13.3)	63.8 (13.0)	72.9 (12.1)	<.001
Sex, n (%)				
Female	2945 (50.2)	2506 (51.6)	439 (43.3)	<.001
Male	2924 (49.8)	2349 (48.4)	575 (56.7)	
BMI, kg/m^2, mean (SD)	30.7 (5.8)	30.7 (5.7)	30.7 (6.4)	.76
BMI categories, n (%)				
Obese (BMI > 30 kg/m^2)	2960 (50.4)	2457 (50.6)	503 (49.6)	<.001
Overweight (25≤ BMI <30 kg/m^2)	2034 (34.7)	1719 (35.4)	315 (31.1)	
Non-obese/non-overweight(BMI ≤ 24.9 kg/m^2)	807 (13.8)	630 (12.9)	177 (17.4)	
Missing	68 (1.2)	49 (1.0)	19 (1.9)	

TABLE 1 (Continued)

	Test-positive COVID-19 with T2D (N = 5869)	Disease severity		*p* value*
		Non-severe (n = 4855)	Severe (n = 1014)	
Smoking status, n (%)				<.001
Current	504 (8.6)	420 (8.7)	84 (8.3)	
Past	1543 (26.3)	1224 (25.2)	319 (31.5)	
Never	3799 (64.7)	3197 (65.8)	602 (59.4)	
Missing	23 (0.4)	14 (0.3)	9 (0.9)	
Socioeconomic status, n (%)[a]				.087
High	1131 (19.3)	921 (19.0%)	210 (20.8%)	
Medium	1990 (34.0)	1630 (33.6%)	360 (35.6%)	
Low	2733 (46.7)	2293 (47.3%)	440 (43.6%)	
Missing	15			
Co-morbidities, n (%)				
Hypertension	4213 (71.8)	3337 (68.7)	867 (85.5)	<.001
Hyperlipidaemia	5282 (90.0)	4327 (89.1)	955 (94.2)	<.001
Ever malignancy	962 (16.4)	736 (15.2)	226 (22.3)	<.001
Pulmonary disease	794 (13.5)	599 (12.3)	195 (19.2)	<.001
Chronic kidney disease	986 (16.8)	635 (13.1)	351 (34.6)	<.001
T2D duration categories, n (%)				
≤5 years	1384 (23.6)	1254 (25.8)	130 (12.8)	<.001
6–10 years	1230 (21.0)	1042 (21.5)	188 (18.5)	
>10 years	3255 (55.5)	2559 (52.7)	696 (68.6)	
Medication, n (%)				
SGLT2 inhibitor	403 (6.9)	327 (6.7)	76 (7.5)	.43
GLP1 agonist	667 (11.4)	567 (11.7)	100 (9.9)	.10
Insulin	1328 (22.6)	1011 (20.8)	317 (31.3)	<.001
Metformin	3770 (64.2)	3172 (65.3)	598 (59.0)	<.001
DPP4 inhibitor	193 (3.3)	134 (2.8)	59 (5.8)	<.001
Thiazolidinedione	174 (3.0)	148 (3.0)	26 (2.6)	.47
Sulphonylurea	384 (6.5)	303 (6.2)	81 (8.0)	.05
Statin	3676 (62.6)	3017 (62.1)	659 (65.0)	.09
Renin-angiotensin system inhibitor	3180 (54.2)	2575 (53.0)	605 (59.7)	<.001
Diabetes complications, n (%)				
Diabetic retinopathy	1112 (18.9)	834 (17.2)	278 (27.4)	<.001
Diabetic nephropathy	653 (11.1)	460 (9.5)	193 (19.0)	<.001
Diabetic neuropathy	1257 (21.4)	933 (19.2)	324 (32.0)	<.001
Peripheral artery disease	696 (11.9)	482 (9.9)	214 (21.1)	<.001
Cardiovascular disease	1919 (32.7)	1400 (28.8)	519 (51.2)	<.001

Abbreviations: BMI, body mass index; DPP4, dipeptidyl peptidase-4; GLP1, glucose-like peptide-1; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2.

**p* value is for the difference between severe and non-severe COVID-19.

[a]Socioeconomic status is based on place of residence (at the level of a neighbourhood or a small town).

risk of severe COVID-19. Furthermore, the results from the subgroup analysis in patients with one HbA1c value available in the 3 months before the index date were consistent with the full analysis (Figures S5 and S6; Tables S6 and S7).

Among 5869 patients with T2D who had a diagnosis of COVID-19, patients with poor glycaemic control were much more probable to have severe outcomes from COVID-19. While these findings support conclusions from previous studies,[6,13] they also

TABLE 2 Preinfection HbA1c and the risk of developing severe coronavirus disease-2019 (COVID-19) among patients with type 2 diabetes

HbA1c (%)		Relative risk	95% CI
Baseline	Target		
8.0	6.0	0.71	0.52–0.87
8.0	6.2	0.71	0.52–0.88
8.0	6.4	0.72	0.52–0.89
8.0	6.6	0.73	0.53–0.89
8.0	6.8	0.76	0.56–0.90
8.0	7.0	0.79	0.61–0.92
8.0	7.2	0.83	0.67–0.93
8.0	7.4	0.87	0.75–0.95
8.0	7.6	0.91	0.83–0.97
8.0	7.8	0.96	0.92–0.99

Note: The estimates and confidence intervals (CIs) were derived using the bootstrap percentile method, with 1000 iterations. In each resample, the generalized additive model was refit using a log link function and a Poisson outcome distribution, and the change in risk going from the baseline to the target HbA1c was noted.

provide new insights into the relationship between T2D and COVID-19 disease severity. We found that incremental differences in HbA1c levels are associated with decreased likelihood of severe illness, suggesting that even small improvements in glycaemic control could lead to better outcomes in patients with T2D who contract COVID-19. Furthermore, we quantified the dose-response relationship between HbA1c levels and the risk of severe COVID-19 in specific ranges. This is the first study to show this kind of association between HbA1c and the risk of severe COVID-19, and to estimate the impact of incremental differences in HbA1c values.

By modelling HbA1c as a continuous exposure, we found a significant non-linear association between HbA1c preinfection and the risk of developing severe COVID-19, with the risk increasing between HbA1c values of 6%–12% but exhibiting floor and ceiling effects at values outside this range. Importantly, the association between HbA1c preinfection and the risk of severe COVID-19 persisted following adjustment for demographic characteristics, pre-existing chronic conditions, diabetes complications and diabetes treatment. This could indicate a course of action for frontline physicians: to focus efforts on reducing HbA1c in patients with T2D,

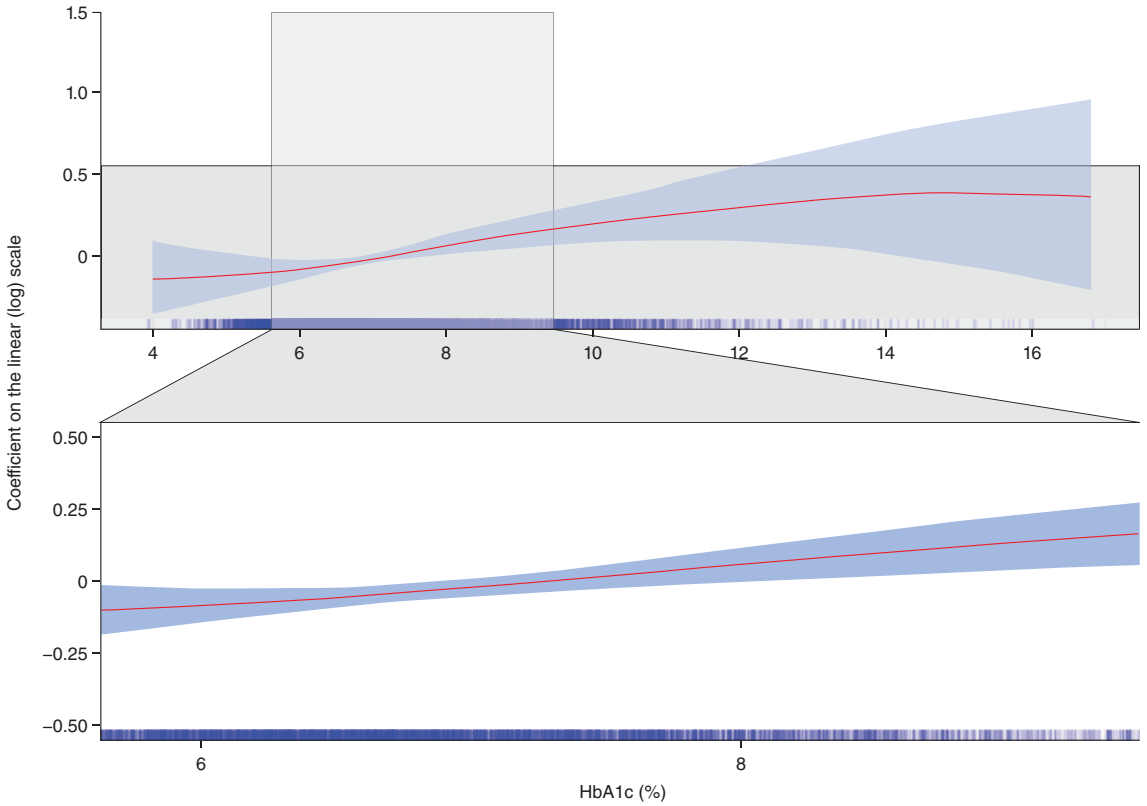

FIGURE 1 Results from a generalized additive model for the association between preinfection HbA1c level and the risk of developing severe coronavirus disease-2019 (COVID-19). The coefficient of HbA1c is shown. The exposure was modelled using a thin-plate spline in a generalized additive model. In the top panel, which shows the full range of HbA1c values, a sigmoidal shape is evident, showing the slope tapering at HbA1c values of less than 5% and higher than 10%. In the bottom panel, which shows a magnified view of the central part of the data (HbA1c values of 5.8%–9.3%), a consistently positive slope is seen, illustrating the dose-response effect detailed in the text. The ribbon around the line shows the standard error. The 'rug' at the bottom shows the actual distribution of HbA1c values in the sample. The model was adjusted for age, sex, body mass index, ethnicity, socioeconomic status, smoking, hypertension, cardiovascular disease, hyperlipidaemia, malignancy, chronic kidney disease, peripheral artery disease, pulmonary diseases, diabetes duration, diabetic neuropathy, diabetic retinopathy, diabetic nephropathy and antidiabetic medications (glucose-like peptide-1 agonists, sodium-glucose co-transporter-2 inhibitors, metformin, dipeptidyl peptidase-4 inhibitors, insulin, thiazolidinediones, sulphonylureas, statins and renin-angiotensin system inhibitors)

irrespective of co-morbidities, current medications or history of poor glycaemic control.

The results of our sensitivity analysis modelling HbA1c as a categorical exposure support and extend the findings of previous analyses. In a study of more than 17 million adults in the UK, an HbA1c of less than 7.5% was associated with an approximately 30% increased risk of COVID-19–related death compared with no T2D, but an HbA1c of 7.5% or higher was associated with a nearly twofold increase in risk (hazard ratio 1.95; 95% CI: 1.83–2.08).[7]

Research published prior to the COVID-19 pandemic provides a possible explanation for the relationship between HbA1c and severe COVID-19. These studies showed that hyperglycaemia can lead to impaired immune defences,[14–16] cytokine storms and elevated lactate levels, which are associated with COVID-19 severity in patients with diabetes.[17] Additionally, COVID-19 infections increase the production of mitochondrial reactive oxygen species, which induces hypoxia-inducible factor-1α stabilization and consequently promotes glycolysis.[16] Thus, people with diabetes may have a higher risk of serious infections compared with the general population.[18] Furthermore, hyperglycaemia is common in patients who are critically ill owing to stress-induced insulin resistance and enhanced glucose production. Hence, strict control of blood glucose levels is considered essential.[19] Moreover, diabetes medications, such as sodium-glucose co-transporter-2 inhibitors, increase angiotensin-converting enzyme 2 in the kidney, and osmotic diuresis, dehydration and euglycaemic diabetic ketoacidosis are known side effects limiting the use of these agents to control high blood glucose levels in patients with COVID-19, especially in those admitted to the intensive care unit.[20]

Our study used a comprehensive EHR database to include a large and representative sample of patients with T2D in Israel, with detailed data available on risk factors before COVID-19 infection. Furthermore, we adjusted our analyses for previous diabetes complications, which indicated previous poor glycaemic control and might confound the association between current glycaemic control and COVID-19 severity. Therefore, our results are generalizable to a wider population of patients with T2D, regardless of previous treatment, co-morbidities or diabetes complications.

The use of administrative data creates some limitations in study design. First, a large number of patients met all inclusion criteria except for an HbA1c measurement in the 6 months before COVID-19 infection and were excluded from the study. It is improbable that these data are randomly missing; therefore, selection bias in this study must be acknowledged. Although analyses are adjusted for multiple demographic characteristics, including age, sex, ethnicity and socioeconomic status, it is probable that some factors influencing patients' glycaemic control, risk of COVID-19 infection, severity of COVID-19 and mortality are not captured in this dataset. Confounders may remain owing to variables that are not directly measurable, such as health-conscious behaviour.

The identification of risk factors for severe COVID-19 is vital for the development of strategies to mitigate the impact of the pandemic and to aid in the efforts to prevent critical care capacity being overwhelmed. This study provides data that may help to identify patients most at risk of developing severe COVID-19; furthermore, it suggests a clear and achievable strategy for reducing this risk. Indeed, given the probability that COVID-19 will remain a significant concern for several months, clinicians must strive to optimize glycaemic control in patients with T2D to reduce the risk of progression of COVID-19.

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CONFLICT OF INTEREST

SH, YB-S, RB, MK, EK, ER and NB are employees of the Clalit Research Institute, which received funding from Novo Nordisk. KB and MZ are Novo Nordisk employees. IR received personal fees from Novo Nordisk.

AUTHOR CONTRIBUTIONS

SH, YB-S, RB, KB, MK, EK, MZ and NB participated in the study concept and design. SH, YB-S, EK and NB were involved in the acquisition, analysis and interpretation of data. All authors participated in preparing the manuscript, with the support of medical writing services. MK, IR and ER provided clinical consultation. All authors read and approved the submitted version of the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Due to data privacy regulations, the individual-level raw data of this study cannot be shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.