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RESEARCH ARTICLE

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Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes

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Abstract

Aim: Poor outcomes of coronavirus disease 2019 (COVID-19) have been linked to diabetes, but its relation to pre-infection glycaemic control is still unclear.

Materials and Methods: To address this question, we report here the association between pre-infection Haemoglobin A1c (HbA1c) levels and COVID-19 severity as assessed by need for hospitalization in a cohort of 2068 patients with diabetes tested for COVID-19 in Leumit Health Services (LHSs), Israel, between 1 February and 30 April 2020. Using the LHS-integrated electronic medical records system, we were able to collect a large amount of clinical information including age, sex, socio-economic status, weight, height, body mass index, HbA1c, prior diagnosis of ischaemic heart disease, depression/anxiety, schizophrenia, dementia, hypertension, cerebrovascular accident, congestive heart failure, smoking, and chronic lung disease.

Results: Of the patients included in the cohort, 183 (8.85%) were diagnosed with COVID-19 and 46 were admitted to hospital. More hospitalized patients were female, came from higher socio-economic background and had a higher baseline HbA1c. A prior diagnosis of cerebrovascular accident and chronic lung disease conferred an increased risk of hospitalization but not obesity or smoking status. In a multivariate analysis, controlling for multiple prior clinical conditions, the only parameter associated with a significantly increased risk for hospitalization was HbA1c $\geq$ 9%.

Conclusion: Using pre-infection glycaemic control data, we identify HbA1c as a clear predictor of COVID-19 severity. Pre-infection risk stratification is crucial to successfully manage this disease, efficiently allocate resources, and minimize the economic and social burden associated with an undiscriminating approach.

KEYWORDS
coronavirus infectious disease 2019 (COVID-19), pre-infection glycaemic control

1 | INTRODUCTION

Poor outcomes of coronavirus disease 2019 (COVID-19) have been linked to diabetes,[1-4] but its relation to pre-infection glycaemic control is still unclear. Glycaemic levels during hospitalization have been linked to poor outcomes of COVID-19. In a study of 28 patients with COVID-19 and diabetes in Wuhan, China, the Haemoglobin A1c (HbA1c) was similar between 14 patients who were admitted to the intensive care unit (ICU) and those who were not.[5] In another study of 269 patients with severe disease upon hospitalization, hyperglycaemia was not identified as associated with severity of disease upon admission but was associated with death.[6] In a retrospective study of 201 patients with COVID-19, pneumonia-increased glucose levels were identified as a risk factor for the development of acute respiratory distress syndrome (ARDS) but not for death.[7] A similar observation was noted in a study of 85 patients hospitalized due to COVID-19—admission glucose level was the strongest predictor of radiographic findings of ARDS.[8] In a large multi-centred retrospective study including 7337 cases of COVID-19 of which 952 patients had type 2 diabetes mellitus (T2DM), mean glycaemic levels between 70 and 180 mg/dl (3.9–10 mmol/L) during hospitalization were found to predict lower mortality.[9]

Despite this emerging evidence, the relation between pre-infection glycaemic control and COVID-19 severity is still unknown. To address this question, we report here the association between pre-infection HbA1c levels and COVID-19 severity as assessed by need for hospitalization in a cohort of 2068 patients with diabetes tested for COVID-19 in Leumit Health Services (LHSs), Israel, between 1 February and 30 April 2020.

2 | METHODS

2.1 | Population and clinical information

LHS is a large health maintenance organization (HMO) in Israel, which provides services to around 7,30,000 members nationwide. The comprehensive LHS electronic medical records (LHS-EMR) system integrates medical, pharmaceutical, and laboratory information and is continuously updated. Using the LHS-EMR, we identified patients with a prior diagnosis of diabetes (based on the Israeli diabetes registry[10]) who underwent at least one test for COVID-19 between 1 February and 30 April 2020. COVID-19 testing was done only by physician referral (based on clinical criteria of exposure to confirmed COVID-19 patients and/or symptoms suggesting COVID-19) using the Allplex™ 2019-nCoV Assay (Seegene Inc) until 10 March 2020, and since then—the COBAS SARS-Cov-2 6800/8800 (Roche Pharmaceuticals). Only patients with a positive COVID-19 test were considered as having COVID-19. Other information collected from LHS-EMR included age, sex, socio-economic status (SES—defined according to the patients home address, using the Israeli Central Bureau of Statistics classification[11]), weight, height, body mass index (BMI), HbA1c, prior diagnosis of ischaemic heart disease (IHD), depression/anxiety, schizophrenia, dementia, hypertension, cerebrovascular accident (CVA), congestive heart failure (CHF), smoking, and chronic lung disease. The validity of the diagnoses in the registry was previously examined and confirmed as high.[12] Among the selected population, we identified patients who contracted COVID-19 and those who were hospitalized due to COVID-19. In Israel, most COVID-19-positive patients were treated as outpatients in what is referred to as home hospitalization. This was done either in the patients' homes or converted hotels. LHS home-hospitalized patients received a pulse oxymeter and were followed twice daily by nurses via telemedicine or phone. Nurses were instructed to immediately refer a patient to a physician if his fever was ≥38°C, blood oxygen saturation was ≤95%, or shortness of breath developed. Hospitalization was at the discretion of the treating physician. The study protocol was approved by the Shamir Medical Center Review Board and the Research Committee of LHS.

2.2 | Statistical analysis

Statistical analysis was conducted using a STATA 12 software (StataCorp LP). Assumptions were two sided with an α of 0.05. Initial analysis compared demographic characteristics between the patients with positive or negative Covid-19 tests, using Student's *t*-test and Fischer's exact χ^2 test for continuous and categorical variables, respectively, based on normal distribution and variable characteristics. Categorical data are shown in counts and percentages. Data on continuous variables with normal distribution are presented as means with 95% confidence intervals (CI). Preliminary evaluation of risk estimates was conducted by stratified analyses. HbA1c was stratified as: <7% (53 mmol/mol); 7%–7.9% (53–62.8 mmol/mol); 8%–8.9% (63.9–73.8 mmol/mol); or ≥9% (74.9 mmol/mol), and obesity was defined as a BMI ≥ 30 kg/cm^2. Only patients who had at least one HbA1c test in the year prior to the COVID-19 test were included in the analysis. In patients who had more than one HbA1c measurement during the year prior to COVID-19 testing, the most recent measurement was used. Subsequently, multivariate logistic regression was used to estimate the odds ratios (OR) and 95% CI for the independent association between the following clinical characteristics—age, HbA1c ≥ 9%, sex, SES, smoking, IHD, depression/anxiety, schizophrenia, dementia, hypertension, CVA, CHF, smoking, chronic lung disease, obesity, and COVID-19 disease severity has assessed by the need for hospitalization.

3 | RESULTS

3.1 | Clinical characteristics of patients with diabetes and COVID-19

We identified 2068 patients with diabetes who were tested for COVID-19 (ages 14–103 years) of which 183 (8.85 %) patients were diagnosed with the disease. In a primary univariate analysis, patients with COVID-19 were younger, more likely to be male, had a higher

TABLE 1 Clinical characteristics of patients with diabetes and COVID-19

Variable	COVID-19 $n = 183$ (8.9%)	Control $n = 1885$ (91.2%)	p value
Mean age, years (CI)	61.82 (59.9–63.7)	65.53 (64.8–66.3)	<0.001
Age (years) *n* (%)			
0–20	0 (0.0)	3 (0.2)	<0.001
20–40	7 (3.8)	120 (6.4)	<0.001
40–60	77 (42.1)	515 (27.3)	<0.001
60–80	81 (44.3)	818 (43.4)	<0.05
80+	18 (9.8)	429 (22.8)	<0.001
Low-medium SES *n* (%)	135 (78.5)	1,131 (62.0)	<0.05
Male *n* (%)	109 (59.6)	934 (49.6)	<0.05
Mean BMI (CI)	31.4 (30.6–32.2)	30.1 (29.8–30.5)	<0.05
Mean HbA1c % (CI)	7.12 (6.81–7.57)	6.59 (6.52–6.65)	<0.05
Smoking *n* (%)	33 (19.3)	348 (21.4)	0.52
Depression/anxiety *n* (%)	27 (14.8)	370 (19.6)	0.055
Schizophrenia *n* (%)	8 (4.4)	57 (3)	0.15
Dementia *n* (%)	14 (7.7)	261 (13.9)	<0.05
Hypertension *n* (%)	98 (53.55)	1228 (65.15)	<0.005
Ischaemic heart disease *n* (%)	39 (21.3)	648 (34.4)	<0.005
CVA *n* (%)	11 (6.0)	187 (9.9)	0.0431
CHF *n* (%)	16 (8.7)	257 (13.6)	0.0620
Chronic lung disease *n* (%)	24 (13.1)	405 (21.5)	0.0077
Obesity *n* (%)	101 (58.1)	833 (46.9)	0.0052

Abbreviations: BMI, body mass index; CI, confidence interval; CHF, congestive heart failure; CVA, cerebrovascular accident; SES, socio-economic status.

TABLE 2 HbA1c and OR for COVID-19 in patients with diabetes

Variable	COVID-19 $n = 183$ (8.9%)	Control $n = 1{,}885$ (91.2%)	Crude OR (95% CI) for COVID-19	p value
HbA1c categories				
<7%	118 (64.5)	1351 (71.7)	1.00	-
7%–7.9%	24 (13.1)	258 (13.7)	1.065 (0.67–1.69)	0.79
8%–8.9%	19 (10.4)	139 (7.4)	1.56 (0.93–2.62)	0.09
≥9%	22 (12.0)	137 (7.3)	1.84 (1.13–2.99)	< 0.05

Abbreviations: CI, confidence interval; OR, odds ratio.

HbA1c and BMI, belonged to a lower SES and had fewer pre-existing medical conditions (Table 1). Furthermore, among COVID-19 patients, more patients had an HbA1c ≥ 9% (12.02% vs. 7.27%; $p < 0.05$; crude OR of 1.84; 95% CI 1.13–2.99; Table 2). These differences may reflect infection 'clusters' which were characteristic of the spread of COVID-19 in Israel—the major outbreak cluster was among the ultra-orthodox Jewish population which is characterized by a younger mean age (leading to fewer prior co-morbidities) and a lower SES.

We conducted a complementary analysis among patients who were COVID-19 negative. Patients who were found negative to COVID-19 but with an HbA1c ≥ 9% were younger (mean age 59.9 [95% CI 57.5–62.4] vs. 65.9 [95% CI 65.2–66.7]), male (82 [59.9%] vs 852 [48.8%]) and from a lower SES (103 [77.4%] vs. 1028 [60.8%]). No differences were observed in BMI or prevalence of pre-existing medical conditions (depression, dementia, HTN, CVA, IHD, and chronic lung disease) in these patients.

TABLE 3 Clinical characteristics of patients with diabetes hospitalized due to COVID-19

Variable *N* (%)	Hospitalized $n = 46$ (25.1%)	Not hospitalized $n = 137$ (74.9%)	*p* value
Mean age, years (CI)	67.0 (63.0–71.1)	60.0 (58.0–62.2)	-
Age (years) *n* (%)			<0.001
0–20	0 (0.0)	0 (0.0)	-
20–40	1 (2.2)	6 (4.4)	<0.001
40–60	14 (30.4)	63 (46.0)	<0.01
60–80	21 (45.7)	60 (43.8)	0.124
80+	10 (21.7)	8 (5.8)	<0.05
Low-medium SES *n* (%)	28 (63.6)	107 (83.6)	0.05
Male *n* (%)	25 (54.3)	84 (61.3)	0.05
Mean BMI (CI)	31.8 (30.2–33.4)	30.6 (29.7–31.5)	0.195
Mean HbA1c % (CI)	7.75 (7.17–8.32)	6.83 (6.54–7.13)	<0.005
Smoking *n* (%)	10 (24.4)	23 (17.7)	0.20
Depression/anxiety *n* (%)	9 (19.6)	18 (13.1)	0.34
Schizophrenia *n* (%)	5 (10.9)	9 (6.6)	0.40
Dementia *n* (%)	1 (2.2)	7 (5.1)	0.34
Hypertension *n* (%)	28 (60.9)	70 (51.1)	0.25
Ischaemic heart disease *n* (%)	13 (28.3)	26 (19.0)	0.18
CVA *n* (%)	4 (8.7)	7 (5.1)	<0.05
CHF *n* (%)	8 (17.4)	8 (5.8)	0.38
Chronic lung disease *n* (%)	13 (28.3)	11 (8.0)	<0.001
Obesity *n* (%)	25 (56.8)	76 (58.5)	0.85

Abbreviations: BMI, body mass index; CI, confidence interval; CHF, congestive heart failure; CVA, cerebrovascular accident; SES, socio-economic status.

TABLE 4 HbA1c and OR for hospitalization in patients with diabetes and COVID-19

Variable	Hospitalized $n = 46$ (25.1%)	Not hospitalized $n = 137$ (74.9%)	Crude OR (95% CI) for being hospitalized	*p* value
Haemoglobin HbA1c categories				
<7%	20 (43.5)	95 (69.3)	1.00	-
7%–7.9%	8 (17.4)	16 (11.7)	2.38 (0.88–6.39)	0.08
8%–8.9%	8 (17.4)	12 (8.8)	3.17 (1.11–8.97)	<0.05
≥9%	10 (21.7)	14 (10.2)	3.391 (1.28–9.28)	<0.01

Abbreviations: CI, confidence interval; OR, odds ratio.

3.2 | Clinical characteristics of diabetic patients hospitalized due to COVID-19

Of the 183 patients with COVID-19, 46 were admitted to hospital. The mean HbA1c in hospitalized patients was higher than patients who were not hospitalized. More hospitalized patients had an HbA1c between 8% and 8.9% or ≥9% when compared to patients who were not hospitalized (Tables 3 and 4). Other factors significantly associated with hospitalization were older age, female sex, higher SES, CVA, and chronic lung disease. In our cohort, obesity and smoking status were not associated with an increased risk for hospitalization. In a multivariate analysis, controlling for multiple prior clinical conditions, the only parameter associated with a significantly increased risk for hospitalization was HbA1c ≥ 9% (adjusted OR 4.95; 95% CI 1.55–15.76; $p < 0.05$). Other variables had no significant impact on the risk for hospitalization due to COVID-19 (Table 5).

We repeated the multivariate analysis with an HbA1c cutoff of >7% or with HbA1c as a continuous variable. In the former analysis,

TABLE 5 Multivariate logistic regression analysis, controlling for multiple clinical conditions assessing the OR for hospitalization in patients with diabetes and COVID-19

Variable	Adjusted OR (95% CI)*	*p* value
HbA1c ≥ 9	4.95 (1.55–15.76)	<0.01
Age	1.05 (0.99–1.10)	0.09
Male sex	0.70 (0.31–2.07)	0.64
Low-medium SES	0.53 (0.12–1.00)	0.06
Smoking	2.29 (0.73–7.19)	0.15
Depression/anxiety	2.07 (0.63–6.79)	0.23
Schizophrenia	0.41 (0.03–5.19)	0.49
Dementia	0.16 (0.01–1.34)	0.09
Hypertension	0.71 (0.24–2.06)	0.53
Ischaemic heart disease	0.43 (0.20–2.34)	0.55
CVA	0.73 (0.13–3.89)	0.71
CHF	5.41 (0.99–27.36)	0.05
Chronic lung disease	2.6 (0.77–8.76)	0.12
Obesity	0.96 (0.39–2.45)	0.98

Abbreviations: BMI, body mass index; CI, confidence interval; CHF, congestive heart failure; CVA, cerebrovascular accident; OR, odds ratio; SES, socio-economic status.

*Adjusted for age, sex, SES and co-morbidities.

the OR for hospitalization in patients with an HbA1c > 7% was 6.07 (95%CI 2.36–15.62; $p < 0.005$). Furthermore, an increased risk for hospitalization was observed in patients with prior congestive heart failure and a reduced risk for hospitalization in patients with low SES (Table S1). In the latter analysis, any increase in HbA1c by 1% above a 5% baseline was associated with an OR for hospitalization of 1.46 (95% CI 1.14–1.85; $p = 0.002$). In this model, low SES was protective and age was a risk factor for hospitalization (Table S2).

4 | DISCUSSION

Using pre-infection glycaemic control data, we identify HbA1c as a clear predictor of COVID-19 severity (as assessed by the need for hospitalization). Other clinical characteristics which were significantly linked to hospitalization included female gender, low SES, a prior CVA, and chronic lung disease. Surprisingly, obesity and smoking status and male sex were not associated with hospitalization despite being suggested as risk factors in prior publications.[13–15] In a multivariate logistic regression model adjusting for multiple potential risk factors and chronic conditions which may have a deleterious effect on disease outcomes (including age, sex, smoking, IHD, SES, depression/anxiety, schizophrenia, dementia, hypertension, CVA, CHF, chronic lung disease, and obesity), only HbA1c ≥ 9% remained a significant predictor for hospitalization. In fact, HbA1c remained a strong predictor of hospitalization due to COVID-19 when the model was repeated with an HbA1c cutoff of >7% or when addressing HbA1c as a continuous variable.

Prior studies linking glycaemic control and COVID-19 have suggested an association between in hospital glucose levels and disease severity. The link between hyperglycaemia during hospitalization and disease severity has been previously reported in numerous studies covering multiple disease conditions.[16–18] However, tight glycaemic control failed to lead to improved outcomes in hospitalized patients in conditions other than COVID-19.[19] This may suggest that hyperglycaemia is a biomarker for the severity of the disease and poor overall health status rather than having an actual causative effect. To our knowledge, our study is the first to identify pre-infection glycaemic control as a risk factor for COVID-19 severity.

The weaknesses of our study are its relatively small number of hospitalized patients, retrospective design, and lack of information regarding disease severity beyond the need for hospitalization. It would be interesting to learn whether HbA1c predicts COVID-19 mortality, need for ICU stay, or need for artificial ventilation. Moreover, our study does not prove that pre-infection glycaemic control has a causative role in COVID-19 severity. Similar to hyperglycaemia during hospitalization, HbA1c may be a biomarker of poor health. Future mechanistic studies are needed to determine this relationship. However, the multivariate logistic regression statistical model identifying HbA1c as the only predictor of COVID-19 hospitalization among numerous other severe and chronic health conditions (including prior cardiovascular disease, mental illness, chronic lung disease, etc.) and the observation that risk for hospitalization increases already at HbA1c ≥ 8% may suggest its pathogenic importance and clinical utility in risk stratification. Other strengths of our study are the large and comprehensive cohort (including all COVID-19-tested patients with diabetes in a large HMO) and the large amount of pre-COVID-19 clinical background information which we could access and present.

As many countries continue to battle with the COVID-19 pandemic while others begin to release strict measures of social distancing, identifying high-risk populations is key to successfully overcome this disease. Paying special attention to patients with diabetes and an HbA1c ≥ 9 while allowing a more lenient approach to patients with well controlled disease may prove to be beneficial in minimizing the economic and social burden associated with an undiscriminating approach. Moreover, once a vaccine is available, prioritizing those who are at highest risk for severe COVID-19 will be crucial to efficiently overcome this disease.

CONFLICT OF INTEREST

All the authors declared that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Eugene Merzon, Roy Eldor, Ilan Green, Avivit Golan-Cohen, Miriam Shpigelman, Shlomo Vinker, and Itamar Raz contributed the research question; Eugene Merzon and Ilan Green performed data mining; and Eugene Merzon performed statistical analysis. Roy Eldor, Eugene

Merzon, Ilan Green, and Miriam Shpigelman wrote the final draft of the manuscript. Shlomo Vinker, Itamar Raz, and Avivit Golan-Cohen contributed to editing of the manuscript. No honorarium, grant, or other form of payment was given to any of the authors to produce the manuscript.

ETHICAL STATEMENT

This is a data-based study, and as such, has no clinical trial registration number. The study received IRB approval from the Shamir Medical Centre IRB.

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SUPPORTING INFORMATION

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

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