Can HbA1c levels be used as an independent marker of mortality and morbidity risk in patients with COVID-19 positive swabs? – a retrospective observational study

Mansoor Zafar, MBBS, MRCP[1,3,7]; Ratan Singh Randhawa, MBBS, iBSc, PGDip, FY2[2]; Johannes Hegner, MBBS, FY1[2,3]; Saba Alam, MBBS[3]; Mariya Farooq, MBBS[1]; Reem Eldebri, MBBCh[2]; Bipin Pun, MBBS[4]; Muhammad Shahbaz, MBBS, MD, SHO[5]; Opeyemi Adebayo Makanjuola, MBBS, SHO[6]; Frederic Cuison, MD, MRCP[3]; Dana Safarova, MD, FY2[5]; Kamal Lawrence, MD, FY2[3]; Amr Elyasaky, MBBS, MSc, MD, MRCP[1,3,12]; Hesam Ahmadi Nooredinvand, MBBS, MRCP[7]; Manivannan Periasamy, MD[3]; Lucinda Barry, MBChB, FY1[5]; Alisha Khanna, MBChB, BMedSci, FY1[5]; Karuna Subba, MBBS[3]; Bolurin Adekunle Adekunle, MBChB[3]; Oluwamayowa Ojofeitimi, MBChB, FY1[6]; Mohamed Abdelbagi, MUDr, SHO[8]; Andreia Esteves Morete, MD, SHO[5]; Gjulio Ciroi, MD, FY1[3]; Mangala Milind Karkhanis, MD, SHO[2]; Bao Khuu, MD, SHO[2]; Zahra Maryam, MD[2]; Mirej Patel, MD Candidate[9]; Maaryah J. Zafar, MD Candidate[10]; Nadiyah Zafar, MD Candidate[10]; Ubaid ur Rehman, MBBS, IMT[3]; Steve Moran, MSc, FIBMS[11]; William Alfred O'Neill, MSc, FIIBMS[11]; Abubakr Hadid, MBChB[2]; Raphael Golez, MD[3,12]; Tila Muhammad, MBBS, MRCP[3,7]; Mark Whitehead, MBBS, FRCP[1,3,7]; Umesh Dashora, MBBS, MRCP, MD[2,13]

[1] General Internal Medicine and Gastroenterology Specialty Registrar, East Sussex Healthcare NHS Trust. United Kingdom, TN37 7RD
[2] General Internal Medicine, Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[3] Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[4] Cardiology, Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[5] General Medicine, Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[6] Acute Medicine, Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[7] Gastroenterology, Conquest Hospital, East Sussex Healthcare NHS Trust, TN37 7RD
[8] Emergency Department, Conquest Hospital, East Sussex Healthcare, NHS Trust, UK
[9] University of Debrecen, Hungary
[10] Universitatea din Oradea. Strada Universitatii nr. 1, 410087. Romania
[11] Microbiology Department, Eastbourne District General Hospital, East Sussex Healthcare NHS Trust
[12] Department of Elderly Medicine-Geriatrics
[13] Department of Endocrinology and Diabetes

Introduction

Coronavirus disease 2019 (COVID-19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as it is now called, has rapidly spread from its origin in Wuhan City of Hubei Province of China to the rest of the world.[1] By 12th of August 2020, 20,525,152 cases of COVID-19, 745,960 deaths and 13,445,997 recovered cases had been reported worldwide. As of 2nd of April 2021 this count has gone up to 130,174,617 cases of COVID-19, 2,840,184 deaths and 104,894,047 recovered cases. As of the 9th of August 2020, the number of deaths reported in the UK with a positive SARS-CoV 2 test was 46,526 and by 2nd of April 2021 this has increased to 126,764.[2,3] The number of expected UK deaths by 31st of July 2020 exceeded estimation by 63,810.[3]

Studies have shown that the severity with COVID-19 is related to age and comorbidities including diabetes, hypertension, cardiovascular, and cerebrovascular diseases.[4,5]

Recent studies have revealed that underweight or normal-weight patients have poor pancreatic β-cell function, and higher mean amplitude of glycaemic excursions (MAGE) than overweight or obese patients and more fluctuations.[6] However, hemoglobin A1c (HbA1c) remains endorsed in many countries as a diagnostic test for (type 2) diabetes as well as for monitoring.[7]

Studies towards association of COVID-19 and Diabetes mellitus, suggest increased risk of mortality in patients with type 1 diabetes mellitus, and association of syndromic nature of the diabetes association with COVID-19 infection.[8,9] There are also studies showing increased severity of Covid-19 infection in patients with higher HbA1c.[10-12] Nevertheless, studies have suggested higher HbA1c levels are related to increased risk of complications in patients with diabetes.[12,13]

In a resource strapped healthcare system, it is important to be able to identify which patients are more likely to require higher level of support from medical professionals and therefore independent markers of mortality and morbidity would be useful to help allocate healthcare resources more effectively.

We explored to see whether there was an association between HbA1c level and mortality in COVID-19 patients. This was achieved by conducting a retrospective study to evaluate the difference in mortality in patients with a positive swab (COVID-19 infection) and recent HbA1c level.

Corresponding Author:
Mansoor Zafar
1mansoorzafar@gmail.com

Materials and Methods

This was a retrospective observational study. The data pertaining to patient characteristics was collected from an electronic medical record system for analysis. COVID-19 swab results from 10th of February 2020 to the 1st of May 2020 were provided by the Department of Microbiology for East Sussex Healthcare NHS Trust. These results included patients being tested of whom some were admitted to Conquest Hospital and Eastbourne Hospital. A team of Junior Doctors were recruited to retrieve the blood test results including Full Blood Count (FBC), Liver Functions Tests (LFTs), Stool culture results, CXR-imaging reports, comorbidity history, summary care records, clinic letters, and notes from previous and current hospital admissions. Frailty scores were included for any patient with Rockwood Frailty (Dalhousie University Frailty Score) of 4 or more.[14]

1226 patients had SARS-CoV-2 RNA identification swabs between 10th February 2020 to 1st May 2020. Within this, a cohort of 120 patients were admitted to the hospital with COVID-19 swab positive and 516 patients with COVID-19 swab negative results with a recent HbA1c test. The recent HbA1c dated anytime during admission going back to a maximum of 3 months prior to admission. All patients with HbA1c levels done prior to more than 3 months were excluded. This was based on Diabetes UK criteria for indications for repeat HbA1c levels within 2 to 3 months of initial HbA1c test.[15] 35 patients had HbA1c repeated, and for such patients the most recent HbA1c levels were included, although since within shorter interval time, the repeat values were not significantly different from the prior values. These patients were grouped into three subsets as per WHO diagnostic criteria for pre-diabetes and diabetes by HbA1c; <42 mmol/mol (Group 1 - normal), 42 to 47 mmol/mol (Group 2 -pre-diabetics), and ≥48 mmol/mol (Group 3 – diabetic range).[16] There were 68 patients in the first group, 26 patients in second group, and 26 patients in third group. 19 patients (15.83%) were receiving insulin therapy before admission. The most common diabetic therapy received prior to admission was metformin. Mortality rates for non-survivors were adjusted to the first thirty days from the day of hospital admission. The chest x-ray infiltrates and complaints of diarrhoea that led to utilisation of extra NHS resources (allocation to side rooms) were assessed. Studies have suggested 70% sensitivity of the Covid 19 swab test. With a pre-test probability of 50% the post-test probability with a negative test appears to be 23% which would be far too high to assume someone is not infected.[17] Since a significant number of patients with negative swab results, were clinically noticed with number of symptoms, including fever, diarrhoea, cough with chest x-ray infiltrates reported as Covid pneumonitis, these patients were classified as 'Treat as Positive'(TAP).

Hence, all the patients with positive COVID-19 swab results and negative COVID-19 swab results but treated as COVID-19 were managed as per the British Thoracic Society (BTS) guidelines dated as of 5th of March 2020.[18] All patients clinically symptomatic with COVID-19 infection irrespective of swab status (either positive swab results or negative swab results) were treated with steroids namely dexamethasone or prednisolone as per the WHO guidance and recommendations of the UK-based RECOVERY trial of dexamethasone.[19-21] The study was approved by the Clinical effectiveness and Ethics committee at the East Sussex Healthcare NHS Trust.

Table 1. Patient characteristics and co-morbidities in swab positive patients

Variable	Alive N=84	Deceased N=36	Total	P value
Age, years	73.3 (15.9)	79.9 (12.6)	75.3 (15.2)	0.03
Sex, % male (N)	59.5% (50/84)	50.0% (18/36)	56.7% (68/120)	0.42
BMI, kg/m^2	24.2 (3.4)	25.3 (4.4)	24.5 (3.8)	0.14
Ever smoker, % (N)	10.7% (9/84)	11.1% (4/36)	10.8% (13/120)	1.00
CXR infiltrates, % (N)	16.7% (14/84)	66.7% (24/36)	31.7% (38/120)	<0.001
Co-morbidities				
Diarrhoea, % (N)	3.6% (3/84)	22.2% (8/36)	9.2% (11/120)	0.003
IHD, % (N)	7.1% (6/84)	25.0% (9/36)	12.5% (15/120)	0.01
Asthma/COPD/ILD, % (N)	7.1% (6/84)	19.4% (7/36)	10.8% (13/120)	0.06
Hypertension, % (N)	16.7% (14/84)	36.1% (13/36)	22.5% (27/120)	0.03
Dementia, % (N)	22.6% (19/84)	22.2% (8/36)	22.5% (27/120)	1.00
Frailty, % (N)	7.1% (6/84)	44.4% (16/36)	18.3% (22/120)	<0.001
ALD-CLD, % (N)	2.4% (2/84)	2.8% (1/36)	2.5% (3)	1.00
Malignancy, % (N)	8.3% (7/84)	16.7% (6/36)	10.8% (13/120)	0.21
PE, % (N)	2.4% (2)	0 (0/36)	1.7% (2/120)	1.00
DMx2	100% (84)	94.4% (34)	98.3% (118)	
DMx1	0% (0)	5.6% (2)	1.7% (2)	0.09

IHD; Ischaemic Heart Disease, COPD; Chronic Obstructive Pulmonary Disease, ILD; Interstitial Lung Disease, ALD; Alcohol Liver Disease, CLD; Chronic Liver Disease, PE; Pulmonary Embolism, DMx2; Diabetes mellitus type 2, DMx1; Diabetes mellitus type 1. Dementia Hx; history of Dementia. Frailty Hx; history of Frailty (As per any patient with Dalhousie Frailty [Rockwood] score of 4 or more classified as frail).

Statistical Analyses

The categorical variables were expressed in terms of frequency and percentages. They were compared between groups using Fisher's exact test. Continuous variables were assessed with mean (SD), median and range and compared by analysis of variance. Odds ratios for mortality by HbA1c category were obtained using logistic regression. As the number of events was small, we used a penalised model (Firth logistic regression) to deal with any possible bias due to sparse data.[22] HbA1c was also analysed as a continuous variable using restricted cubic splines to assess non-linearity of the association with mortality. A lasso model was fitted to obtain a model suitable for making predictions outside the estimation sample. All characteristics and co-morbidities were included and variable selection was made using cross-validation. A second model was fitted adding HbA1c as a predictor. The second model was selected as the best performing model. The predictive accuracy of each model was assessed using the area under the ROC curve. The p value < 0.05 was considered statistically significant. All statistical analysis was done using Stata Version 16 (StataCorp Texas).

Results

A total of 1226 patients were tested for SARS-CoV-2 with an RNA swab test. The median age of patients was 73 years, ranging from 18 years to 101 years.

HbA1c data was available for 120 swab positive and 516 swab negative patients. Patients were stratified into normal (HbA1c <42 mmol/mol), pre-diabetes (42-47) and diabetes (>=48 mmol/mol). The distribution of patients among these groups did not differ significantly between swab negative (66.7% (344), 14.3% (74), 19.0% (98)) and swab positive (56.7% (68), 21.7% (26), 21.7% (26)) patients p=0.08.

Positive patients were 57% male, with median [range] age 75 [44-100]. Hypertension, dementia and frailty were the most commonly occurring co-morbidities (Table 1). Patients who died were older, and significantly more likely to have co-morbidities including diarrhoea, IHD, hypertension and frailty (Table 1).

Increased HbA1c was significantly associated with diarrhoea (p<0.001), while no other comorbidities showed a significant association (Table 2).

Among the patients with a HbA1C >=48 53.9% of patients died compared to 15.4% with HbA1c 42-47 and 26.5% of patients with HbA1c <42 (p=0.005) (Table 1). After adjustment for age, sex, BMI and co-morbidities there were significant differences between the three categories (p=0.002). Mortality was significantly increased for HbA1c >=48 (OR (95% CI) = 3.46 (1.02-11.65) p=0.05) compared to the group with HbA1c <42 (table 3). For mortality assessed by HbA1c as a continuous variable there was significant non-linearity(p=0.001 unadjusted, p=0.029 adjusted for age, sex, BMI and co-morbidities) and a j-shaped relationship was identified (Figure 1) confirming the result seen in the analysis by category.

Other variables significantly associated with mortality in the multivariable model are diarrhoea (OR (95% CI) =19.01 (2.39-150.97)) p=0.0003 and frailty 19.74 (3.66-106.48) p=0.001.

Predictive models selected using lasso technique (Table 4) showed an increase in area under the ROC curve from 0.878 (0.814-0.943) to 0.915 (0.861-0.969) when including HbA1c in the model (figure 2).

Conclusion

This study suggests that HbA1c is an independent risk factor for mortality in COVID-19 positive patients (Table 2). Adjustment for co-morbidities increased the effect of HbA1c. Including HbA1c in predictive models increased the predictive accuracy from 0.878 to 0.915, suggesting that the use of Hba1C alongside other markers may lead to increased accuracy in the risk stratification of patients.

There are some limitations in this study. Firstly, this is a small study and does not allow us to assess how HbA1c interacts with co-morbidities. Secondly, the data only included outcomes for patients who were swabbed and hence does not include outcomes for patients who may have been infected with coronavirus but not have presented to hospital. As the analysis is restricted to patients with a positive test there is the possibility of selection bias (collider bias) which may result in non-causal associations with outcome. Additionally, there were outliers who were tested by swab by the local lab, but no further information was available about them, this way they were excluded as no information was available for them, and no HbA1c was done. With statistically significant results we can suggest with confidence that HbA1c is an independent risk factor for the patients with COVID-19 and may have utility for risk stratification of patients.

Table 2. Co-morbidities by HbA1c groups in swab positive patients

Variable	HbA1c less than 42 mmol/mol N=68	HbA1c 42-47 mmol/mol N=26	HbA1c=48 mmol/mol and higher N=26	P value
Age, years	76.1 (13.8)	74 (20.4)	74.5 (13.1)	0.81
Sex, % male (N)	58.8% (40)	38.5% (10)	69.2% (18)	0.08
BMI, kg/m^2	24.8 (3.1)	23.2 (4.1)	25.2 (4.7)	0.12
Ever smoker, % (N)	10.2% (7)	15.4% (4)	7.7% (2)	0.72
CXR infiltrates, % (N)	32.4% (22)	15.4% (4)	46.2% (12)	0.06
Co-morbidities				
Diarrhoea, % (N)	0% (0)	15.4% (4)	26.9% (7)	<0.001
IHD, % (N)	10.3% (7)	23.1% (6)	7.7% (2)	0.21
Asthma, % (N)	13.2% (9)	11.5% (3)	3.9% (1)	0.52
Hypertension, % (N)	25.0% (17)	19.2% (5)	19.2% (5)	0.87
Dementia, % (N)	23.5 (16)	26.9% (7)	15.4% (4)	0.63
Frailty, % (N)	19.1% (13)	26.9% (7)	7.7% (2)	0.18
ALD-CLD, % (N)	4.4% (3)	0% (0)	0% (0)	0.58
Malignancy, % (N)	13.2% (9)	7.7% (2)	7.7% (2)	0.78
PE, % (N)	2.9% (2)	0% (0)	0% (0)	1.00

Table 3. Mortality by hbA1c group

	Swab positive patients			
	Group 1: HbA1c less than 42 mmol/mol (N=68)	Group 2: HbA1c 42-47 mmol/mol (N=26)	Group 3: HbA1c=48 mmol/mol and higher (N=26)	Total (N=120)
Alive	50 (73.5%)	22 (84.6%)	12 (47.2%)	84 (70%)
Deceased	18 (26.5%)	4 (15.4%)	14 (53.9%)	36 (30%)
Odds ratio (95% CI)[1]	1.00	0.51 (0.11-1.80) P=0.39	3.20 (1.14 – 9.22) P=0.03	P=0.005
Odds ratio (95% CI)[2]	1.00	0.35 (0.09-1.38) P=0.14	4.06 (1.51-10.90) P=0.005	P=0.001
Odds ratio (95% CI)[3]	1.00	0.19 (0.03-1.37) P=0.10	3.46 (1.02-11.65) P=0.05	P=0.002

[1]unadjusted; [2]adjusted for age, sex; [3]adjusted for age, sex, hypertension and IHD
[3]adjusted for age, sex, bmi, all co-morbidities; Note: Group 3 vs. Group 2, p=0.0063.

Table 4. Lasso Models for predicting death

	Model 1	Model 2
Variable	Model coefficients	Model coefficients
Age	0.026	0.022
BMI	0.080	0.035
Diarrhoea	2.265	2.599
IHD	0.122	0.576
Hypertension	0.527	0.7708
Dementia	-0.923	-0.1.045
Frailty	2.239	3.022
Malignancy	0.602	0.929
Hba1c<42	-	-1.535
Hba1c>=48	-	1.167
ROC area (95% CI)	0.878 (0.814-0.943)	0.915 (0.861-0.969)

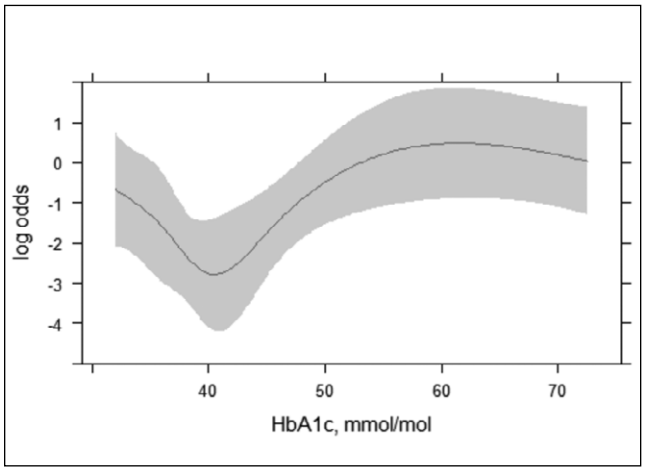

Figure 1. Log odds for mortality by Hba1c after adjustment for age, sex, BMI and co-morbidities. Restricted cubic spline model for the association of HbA1c with mortality risk: log odds (solid line) and 95% CI (shaded area).

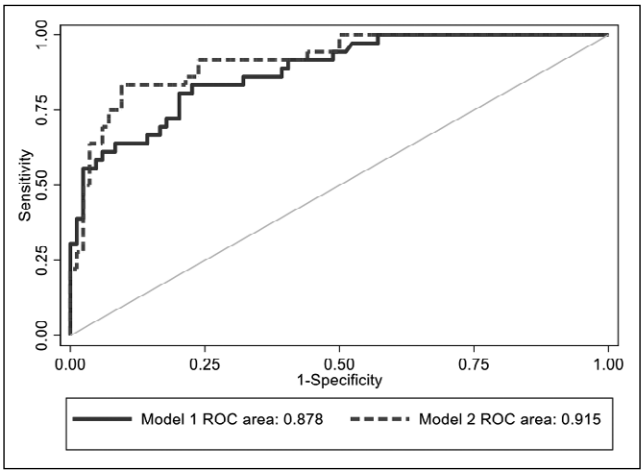

Figure 2. Area under the ROC curve for predictive lasso models with and without HbA1c as a predictor.

Discussion

Different studies have postulated different associations towards increase infection in diabetic patients with Covid 19 and hence mortality. Previous studies have reported that coronaviruses can cause pancreatic β-cell damage.[23] Recently it has been shown that cellular entry of SARS-COV-19 is thought to occur via binding of viral spike S1 protein to Angiotensin Converting Enzyme 2 (ACE 2).[24] The ACE 2 has also been found to be expressed more in diabetics as compared to non-diabetics, although it is not clear whether variations in expression of HbA1c could related to infection related severity of symptoms between diabetics and non-diabetics.[24] Polymerase chain reaction following autopsy did not however find SARS-CoV-2 in pancreatic islet cells.[25] Wang et al. have recently submitted a study suggesting an association between high HbA1c and mortality, and decreased association with normal and pre-diabetic range HbA1c.[13] Our study had a higher mortality rate (30% vs. 16.7%) and we observed a non-linear association with the lowest risk for HbA1c 42-47 mmol/mol, whereas Wang et al. observed a trend across the groups.[13] The trend observed by Wang et al. was an unadjusted association and does not take account of their observed trends in factors including hypertension, gender and age which may explain the difference observed between the studies. As well as adjusting for co-morbidities, we modelled HbA1c as a continuous variable which suggested risk is only increasing after a threshold is reached. There is evidence of a complex relationship between Hba1c and other outcomes, with non-linear associations being reported for lung function, vascular complications, and respiratory infections.[26-28] A systematic review of 46 published studies found higher all-cause mortality for low and high HbA1c and recommended optimal levels of HbA1c between 42 and 64 mmol/mol in those with diabetes.[29]

There are multiple COVID-19 studies done with most recent HbA1c levels tested.[10,11,13] However, the WHO report towards use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus and Diabetes UK previously have had laid down contraindications towards checking of HbA1c level testing, including acute severe illness, or use of steroids.[15,30,31] It is debatable then, would it be relevant to have HbA1c levels during acute admissions alone or inclusion of recent past HbA1c levels from 2-3 months, and its association with COVID-19 related mortality will be relevant as well, especially when the world is grasping with the third wave of pandemic.

With the resurgence of COVID-19 cases in multiple countries across the globe, it is imperative that we use as much information as possible collated during the first wave to help inform medical decision making and public health policy during the future. This includes identifying at risk populations who have contracted the virus and anticipating whether they will require more intensive medical therapy, closer observation and longer hospital stay.

This study may offer to solve a small piece of this puzzle. Additionally, with regards to public health policy, many previously identified risk factors include co-morbidities which are non-modifiable. This study suggests that a modifiable risk factor has a correlation with mortality and morbidity in COVID-19 and future studies may be useful in assessing whether factors which help reduce HbA1c such as diet and exercise are protective in COVID-19 patients. We recommend HbA1c testing to be considered for all SARS-COV2 positive patients without a recent HbA1c test, irrespective of pre-existing diagnosis of diabetes mellitus.

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Authors' contribution

Dr. Mansoor Zafar designed the study and wrote the manuscript. Ms. Jackie Cooper for assistance in the statistical analysis of the study. Dr. Johannes Hegner was involved in summing the data tables. Dr. Ratan Singh Randhawa helped proof read. Dr. Umesh Dashora reviewed the manuscript. 29+ contributors helped in collecting the data and cross-checking data entry.

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