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Predictors of readmission and mortality in adults with diabetes or stress hyperglycemia after initial hospitalization for COVID-19

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ABSTRACT

Introduction We previously reported predictors of mortality in 1786 adults with diabetes or stress hyperglycemia (glucose>180 mg/dL twice in 24 hours) admitted with COVID-19 from March 2020 to February 2021 to five university hospitals. Here, we examine predictors of readmission.

Research design and methods Data were collected locally through retrospective reviews of electronic medical records from 1786 adults with diabetes or stress hyperglycemia who had a hemoglobin A1c (HbA1c) test on initial admission with COVID-19 infection or within 3 months prior to initial admission. Data were entered into a Research Electronic Data Capture (REDCap) web-based repository, and de-identified. Descriptive data are shown as mean±SD, per cent (%) or median (IQR). Student's t-test was used for comparing continuous variables with normal distribution and Mann-Whitney U test was used for data not normally distributed. X^2 test was used for categorical variable.

Results Of 1502 patients who were alive after initial hospitalization, 19.4% were readmitted; 90.3% within 30 days (median (IQR) 4 (0–14) days). Older age, lower estimated glomerular filtration rate (eGFR), comorbidities, intensive care unit (ICU) admission, mechanical ventilation, diabetic ketoacidosis (DKA), and longer length of stay (LOS) during the initial hospitalization were associated with readmission. Higher HbA1c, glycemic gap, or body mass index (BMI) were not associated with readmission. Mortality during readmission was 8.0% (n=23). Those who died were older than those who survived (74.9±9.5 vs 65.2±14.4 years, p=0.002) and more likely had DKA during the first hospitalization (p<0.001). Shorter LOS during the initial admission was associated with ICU stay during readmission, suggesting that a subset of patients may have been initially discharged prematurely.

Conclusions Understanding predictors of readmission after initial hospitalization for COVID-19, including older age, lower eGFR, comorbidities, ICU admission, mechanical ventilation, statin use and DKA but not HbA1c, glycemic gap or BMI, can help guide treatment approaches and future research in adults with diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To our knowledge, there have been no studies of predictors of readmission in adults with diabetes or stress hyperglycemia who were initially admitted with COVID-19.

WHAT THIS STUDY ADDS

⇒ We found that older age, lower estimated glomerular filtration rate, history of intensive care unit admission, mechanical ventilation, diabetic ketoacidosis, statin use, and longer length of stay on initial admission but not HbA1c, glycemic gap or body mass index predicted readmission.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our data contribute to our understanding of predictors for readmission, which is needed to guide treatment and future research to help improve outcomes for adults with diabetes who were hospitalized with COVID-19 infection.

INTRODUCTION

Our consortium previously reported that older age, elevated glycemic gap, higher body mass index (BMI), and diabetic ketoacidosis (DKA) were associated with higher mortality in adults with diabetes or stress hyperglycemia (SH) admitted with COVID-19.[1] Little is known, however, about predictors of readmission after an initial admission due to COVID-19 in adults with diabetes. Our primary objective was to determine predictors of 30-day readmission in our cohort of adults with diabetes or SH initially hospitalized with COVID-19.

RESEARCH DESIGN AND METHODS

We examined data from 1786 adults with diabetes or SH who had a hemoglobin A1c (HbA1c) test on initial admission with COVID-19 infection or within 3 months prior to initial admission (March 1, 2020 through

February 28, 2021) from five university hospitals. Data were collected locally through retrospective reviews of electronic medical records, entered into a Research Electronic Data Capture (REDCap) web-based repository, and de-identified data were analyzed as previously described.[1] Data coordination was performed by investigators at Brigham and Women's Hospital.[1] The Institutional Review Boards for the Protection of Human Subjects at each institution considered this study "exempt" and not requiring informed consent.

We compared patients who were readmitted to those who were not based on characteristics identified during the initial hospitalization. Data used in the current analyses included age, race, sex, BMI, intensive care unit (ICU) stay, mechanical ventilation, use of statins and diabetes medications, length of stay (LOS), DKA, comorbidities, mortality during the first or second admission, estimated glomerular filtration rate (eGFR), admission glucose, and HbA1c. An individual was considered to have diabetes during their initial admission if they had an International Classification of Diseases, Tenth Revision (ICD-10) code E08.00 to E13.9 or HbA1c≥6.5% at any time between 3 months prior to the initial admission to the day of initial admission, or SH if they had glucose>180 mg/dL twice in 24 hours. The glycemic gap was calculated as admission glucose minus estimated average glucose (eAG=28.7 × HbA1c − 46.7 mg/dL). Excluded in the current analysis were 186 adults who died during their initial hospitalization and 98 individuals who died after the initial admission but were not readmitted to any of the above institutions while still alive.

Descriptive data are shown as mean±SD, per cent (%) or median (IQR). Student's t-test was used for comparing continuous variables with normal distribution and Mann-Whitney U test was used for data not normally distributed. X^2 test was used for categorical variable. A p value of<0.05 was considered statistically significant. Analyses were performed using Stata V.15.1 (College Station, Texas, USA).

RESULTS

The analysis cohort comprised 1502 adults from the original cohort, of whom 292 (19.4%) were readmitted after their initial discharge and 1210 (80.6%) were either not readmitted, readmitted to a different hospital, or lost to follow-up. Of those readmitted, 90.3% were readmitted within 30 days. The mean±SD days from initial admission to readmission was 8±30; the median (IQR) was 4 (0–14).

Characteristics during the initial hospitalization that were associated with readmission included older age (66.0±14.2 vs 63.8±14.5 years, p=0.018), lower eGFR (52.6±29.4 vs 59.8±29.1 mL/1.73 m^2/min), ICU admission (36.3% vs 30.2%), mechanical ventilation (26.7% vs 12.5%), DKA during hospitalization (19.1% vs 12.8%), statin use (44.8% vs 37.0%), and longer LOS (median (IQR) 8 (4, 13) vs 6 (4, 11) days); all p<0.05 (table 1).

ICU admission and mechanical ventilation during the first admission were associated with readmission (p<0.05) and predicted need for mechanical ventilation in the subsequent hospitalization; 17% of patients (n=50) required ICU admission but only 6.3% (n=18) required mechanical ventilation during readmission.

Mortality during readmission was 8.0% (n=23). Those who died were older than those who survived (74.9±9.5 vs 65.2±14.4 years, p=0.002) and were more likely to have had DKA during the first hospitalization (p<0.001). Mortality analyses were limited by the small number of deaths (n=23).

Adults with diagnosed diabetes were less likely to be readmitted (88.0% readmitted compared with 92.8% not readmitted, p=0.007) and readmitted adults had a lower HbA1c (7.7% vs 8.2%, p<0.001) as well as lower admission glucose during the initial admission compared with the second hospitalization (table 1).

A longer LOS during the initial admission was associated with readmission. However, LOS was negatively associated with requiring ICU care on readmission, indicating that a shorter LOS at initial hospitalization (8.0±7.4 vs 14.3±15.0 days) predicted a subsequent ICU admission. Glucocorticoid use during the first admission did not predict readmission (p=0.628), and among readmitted patients, the use of glucocorticoids during the first hospitalization was not associated with a shorter time to readmission. Median (IQR) time to readmission was 4 (0, 13) days among those who received glucocorticoids versus 4 (0, 16) days among those who did not receive glucocorticoids (p=0.655 by Mann-Whitney U test).

Age, gender, race, BMI, glycemic gap, HbA1c, diagnosed diabetes, and DKA at admission were not statistically significant predictors of ICU admission, mechanical ventilation, or mortality during readmission.

CONCLUSIONS

To our knowledge, there have been no studies of predictors of readmission in adults with diabetes or SH who were initially admitted with COVID-19. We found that older age, lower eGFR, history of ICU admission, mechanical ventilation, DKA, statin use, and longer LOS on initial admission predicted readmission.

Prior to the COVID-19 pandemic, studies of 30-day unplanned readmissions in adults with diabetes suggested that older age, longer LOS, renal disease, heart failure, depression, low health literacy, insulin therapy, and being white and female predicted readmission.[2] During the COVID-19 pandemic, the most common predictors of readmission after an index hospitalization with COVID-19 infection were the presence of comorbidities, age>65 years, need for ICU admission and mechanical ventilation, as well as an immunocompromised state during initial hospitalization,[3–6] but these reports did not focus on people with diabetes. Readmission rates were highest within 10 days post-discharge, similar to our findings.

Table 1 Patient characteristics during the initial admission and readmission

Variable	Total	Readmitted	Not readmitted	P value*
N	1502	292	1210	
Age (years)	64.2 (14.5)	66.0 (14.2)	63.8 (14.5)	**0.018**
Sex (% male)	51.5	46.9	52.6	0.083
Race				0.221
White	51.8%	56.9%	50.6%	
Black	19.0%	15.8%	19.8%	
Asian	3.0%	2.7%	3.1%	
Other†	23.6%	21.2%	24.1%	
Missing	2.6%	3.4%	2.4%	
Hispanic	29.8%	22.0%	31.7%	**0.001**
BMI (kg/m^2)	31.5 (7.9)	31.0 (7.6)	31.7 (7.9)	0.181
ICU stay	31.4%	36.3%	30.2%	**0.045**
Mechanical ventilation	15.4%	26.7%	12.5%	**<0.001**
Diagnosed diabetes	91.9%	88.0%	92.8%	**0.007**
Any diabetes medication	50.2%	54.5%	49.2%	0.105
HbA1c (%)	8.12 (2.24)	7.70 (1.96)	8.22 (2.30)	**<0.001**
DKA at admission	2.0%	2.2%	1.9%	0.812
DKA during hospitalization	14.1%	19.1%	12.8%	**0.019**
Glucose (mg/dL)	212.0 (129.1)	191.2 (106.1)	217.2 (133.7)	**0.002**
Glycemic gap (mg/dL)	25.3 (107.3)	16.5 (89.7)	27.5 (111.2)	0.123
Any comorbidity	76.4%	80.5%	75.5%	0.069
Use of statin	38.5%	44.8%	37.0%	**0.018**
Length of stay – median (IQR)	7 (4,12)	8 (4,13)	6 (4,11)	**0.005**
eGFR (mL/1.73m^2/min)	58.3 (29.3)	52.6 (29.4)	59.8 (29.1)	**0.001**

Continuous data presented as mean (SD) unless specified.
*P value of comparison of "Readmitted" vs "Not readmitted" using t-test for all continuous variables except Mann-Whitney U test for length of stay; χ^2 for categorical variables. p<0.05 indicated in bold type.
†American Indian, Alaskan Native, Hawaiian or Pacific Islander, multiracial.
BMI, body mass index; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ICU, intensive care unit.

Risk scores have been developed to predict readmissions in adults with diabetes. A Singapore-based retrospective study used pre-COVID-19 data from adults with diabetes and a diabetes-related initial admission diagnosis to develop a prediction model for readmission within 30 days called LIPiD.[7] This incorporates LOS (>4days), the presence of ischemic heart disease and peripheral vascular disease, and the number of drugs used. It was a better tool than previously reported models that were not diabetes-specific, such as the LACE index (LOS (L), acuity of the admission (A), comorbidity measured with the Charlson Comorbidity Index score (C), and visits to the emergency department within 6 months of admission (E)) or the PCi model (polypharmacy and high Charlson Index score).[7–9] The Diabetes Early Readmission Risk Indicator (DERRI) tool, also developed pre-COVID-19 includes 10 predictors of 30-day readmission in adults with diabetes (employment status, living within 5 miles of the medical center, preadmission insulin use, macrovascular disease, anemia, admission hematocrit, creatinine and sodium, hospital discharge within 90 days preadmission, and most recent discharge within a year of admission).[10]

Our study, limited to those with diabetes (91.9% of cohort) or SH and an initial admission with COVID-19, found some similar predictors to LIPiD and DERRI (eg, longer LOS and renal disease) as well as several additional factors. Our finding that statin use was associated with readmission may reflect the presence of more cardiovascular disease in statin-users, or greater engagement with the healthcare system. This possible association requires further study. A study of 30-day readmissions in adults initially hospitalized with COVID-19 reports that 44.3% are related to cardiovascular disease.[11] There is conflicting evidence that statins may reduce mortality in adults hospitalized with COVID-19, but further study is needed.[12 13] The unexpected relatively low readmission rate could be related to high post-discharge mortality, but this will require confirmation in future studies. The lower readmission rate in our cohort among Hispanics (compared with

non-Hispanic whites and non-Hispanic blacks) could be related to higher mortality during the initial admission (the admission rate to the ICU during the first hospitalization was higher in the Hispanic population but overall mortality numbers were too low for further analyses).

Surprisingly, elevated glycemic gap, diagnosed diabetes, and higher HbA1c were not predictors of readmission, perhaps related to the identification of diabetes during the first admission and initiation of medical therapy including metformin.[14] Larger studies are needed to study the use of specific medications as risk factors for readmission in adults with diabetes initially hospitalized with COVID-19.

Our consortium previously reported a mortality rate of 10.6% during initial hospitalization in this cohort, with advanced age and elevated glycemic gap being predictors of mortality.[1] Use of any diabetes medications was associated with lower mortality.[1] Our readmission cohort had a mortality rate of 8.0%. The small number of deaths in the readmission sample, however, limited our ability to reliably identify risk factors for mortality on readmission.

Although we found that a longer LOS during the initial admission was associated with having a second admission within 30 days, for those readmitted, a shorter LOS during the initial admission was associated with ICU admission during the second hospitalization. It is conceivable that some patients were discharged prematurely. This possibility will require further exploration including comparison with non-diabetes populations.

Readmissions cause physical and mental stress, relate to the development of frailty, and add to the cost burden for the healthcare system.[11 15] Our data contribute to our understanding of predictors for readmission, which is needed to guide treatment and improve outcomes for adults with diabetes and COVID-19 infection.

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Contributors DCS, MEM, and RSW are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AC contributed to the conception, design, interpretation of data, drafting and revising the work. KH contributed to data analysis, data interpretation and revising the work. DCS contributed to the conception, design, data analysis, data interpretation and revising the work. MEM contributed to the conception, design, data acquisition, data analysis, data interpretation, and revising the work. RG, GG and JM contributed to the conception, design, data acquisition, interpretation, and revising the work. JL, NEP, and GW contributed to data acquisition, interpretation, and revising the work. RSW contributed to the conception, design, data acquisition, interpretation, drafting, and revising the work.

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Competing interests DCS is a stockholder/shareholder of GI Windows (not related to current study). MEM participated in clinical trials, through her institution sponsored by DexCom Inc. JM was a consultant for Novo Nordisk and Eli Lilly and is an employee of Sequel. GG participated in clinical trials, through her institution, sponsored by Spruce Bioscience and Sparrow Pharmaceuticals. NEP participated in a clinical trial through her institution sponsored by Dexcom Inc. RSW participated in clinical trials, through her institution, sponsored by Insulet, Tandem, Eli Lilly, Novo Nordisk, Amgen, Diasome and Mannkind. DexCom Inc. provided devices, at reduced cost, for research studies.

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