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Glucometabolic changes influence hospitalization and outcome in patients with COVID-19: An observational cohort study

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ABSTRACT

Aims: The aim was to report the prevalence of diabetes status in patients hospitalized with COVID-19 and assess the association between the glucometabolic status at admission and 90-day mortality.
Methods: Consecutive patients hospitalized with COVID-19 were included in the study. All participants included had an HbA_{1c} measurement 60 days prior to or within 7 days after admission. We studied the association between diabetes status, the glycemic gap (difference between admission and habitual status), admission plasma-glucose, and mortality using Cox proportional hazards regression.
Results: Of 674 patients included, 114 (17%) had normal glucose level, 287 (43%) had pre-diabetes, 74 (11%) had new-onset, and 199 (30%) had diagnosed diabetes. No association between diabetes status, plasma-glucose at admission, and mortality was found. Compared to the 2nd quartile (reference) of glycemic-gap, those with the highest glycemic gap had increased mortality (3rd (HR 2.38 [1.29–4.38], $p = 0.005$) and 4th quartile (HR 2.48 [1.37–4.52], $p = 0.002$).
Conclusion: Abnormal glucose metabolism was highly prevalent among patients hospitalized with COVID-19. Diabetes status *per se* or admission plasma-glucose was not associated with a poorer outcome. However, a high glycemic gap was associated with increased risk of mortality, suggesting that, irrespective of diabetes status, glycemic stress serves as an important prognostic marker for mortality.

1. Introduction

Diabetes mellitus is associated with an increased risk of severe airway infections [1]. Prediabetes and diabetes (unknown- or known) have been associated with an increased risk of hospitalization due to coronavirus disease 2019 (COVID-19) [2–9]. Similarly, hyperglycemia is common among hospitalized patients with community acquired pneumonia (CAP) with other etiology than COVID-19 [10]. Hyperglycemia is seen in most cases of severe acute illness in patients with and without diabetes and has been linked to a poorer outcome of COVID-19 [11–15]. However, findings are inconsistent and mostly reported in patients with diabetes at time of COVID-19 infection [16]. As the individual habitual glucose level varies depending on diabetes status and glycemic control, the glycemic gap may be an appropriate biomarker for the glycemic stress caused by the acute disease. The glycemic gap is the difference between the average blood glucose level

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estimated from glycated hemoglobin (HbA_{1c}) [17] and the plasma glucose level. The glycemic gap has been identified as a predictor of poor outcome in several different settings; e.g. the intensive care unit (ICU), among patients with necrotizing fasciitis, acute heart failure, intracerebral hemorrhage and CAP [18–23]. Recently, a small study including patients with diabetes hospitalized with COVID-19 suggested that the glycemic gap could be of predictive value for in-hospital mortality in this population [24].

In this perspective, we report the prevalence of non-diabetes, prediabetes, unknown and known diabetes in an unselected consecutive cohort of patients hospitalized with moderate to severe COVID-19. Further, we report the association between glucometabolic status at admission measured by glycemic gap, admission plasma glucose and HbA_{1c} and mortality within 90 days.

2. Methods

This was a multicenter cohort study including consecutive patients hospitalized for COVID-19 at four Copenhagen University Hospitals (Amager, Glostrup, Hvidovre and Rigshospitalet) between 1 October 2020 and 31 March 2021 during the second wave of COVID-19 in Denmark.

Inclusion criteria for this study were 1) presence of SARS-CoV-2 confirmed by reverse transcription polymerase chain-reaction from either naso-/oropharyngeal swab, sputum, or endotracheal aspirate, 2) age $\geq$ 18 years, 3) COVID-19 illness requiring hospitalization for at least 24 h, and 4) a HbA_{1c} measurement within 60 days prior to admission or 7 days of admission.

2.1. Data collection

Evaluation and treatment of patients followed a predefined guideline enabling a prospective collection of a uniform dataset from health records. Data included demographic variables, comorbidities (i.e. hypertension, cardio-vascular diseases (CVD), chronic obstructive pulmonary disorder (COPD), asthma, prior or current cancer diagnosis), biochemical parameters on admission day (i.e. HbA_{1c}, estimated glomerular infiltration rate, plasma glucose, and C-reactive protein), glucose lowering treatment in patients with diabetes, and clinical outcome defined as 90-day mortality and requirement of intensive care. Baseline oxygen requirements were ascertained as the highest level of respiratory support within 24 h of admission and vital parameters were ascertained as the worst value within 24 h of admission and included temperature, respiratory rate, and peripheral oxygen saturation. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

Data collection was nearly 100% in all variables except for BMI (10% missing) and plasma glucose (2% missing). Missing values are provided in Table 1.

Table 1
Baseline demographics, usage of diabetes treatment, admission samples and clinical status in 674 adult patients hospitalized with COVID-19 grouped by diabetes status.

	Total (n = 674)	Non-diabetes (n = 114)	Prediabetes (n = 287)	Diabetes mellitus (unknown) (n = 74)	Diabetes mellitus (known) (n = 199)
Demographics					
Age, years [a]	*68 [55–78]*	64 [46–76]	66 [55–78]	68 [52–76]	72 [61–79]
Sex, n (%)					
Females	*270 (40)*	50 (44)	118 (41)	34 (43)	70 (35)
BMI, kg/m^2 [b]	*28 (7)*	26 (6)	28 (6)	30 (6)	30 (7)
Missing, n	*69*	*12*	*31*	*6*	*20*
Comorbidities, n (%)					
Hypertension	*271 (40)*	27 (24)	108 (38)	26 (35)	110 (55)
CVD	*289 (43)*	36 (32)	107 (37)	27 (37)	119 (60)
COPD	*105 (16)*	16 (14)	35 (12)	14 (19)	40 (20)
Astma	*82 (12)*	13 (11)	38 (13)	12 (16)	19 (10)
Cancer	*92 (14)*	23 (20)	35 (12)	15 (20)	19 (10)
Number of comorbidities, n (%)					
One	*197 (29)*	46 (40)	96 (33)	20 (27)	35 (18)
Two	*208 (31)*	35 (31)	91 (32)	25 (34)	57 (29)
Three	*188 (28)*	20 (18)	73 (25)	22 (30)	73 (37)
Four	*12 (2)*	1 (1)	5 (2)	4 (5)	2 (1)
Diabetes treatment, n (%)					
None	*505 (75)*	114 (100)	287 (100)	74 (100)	30 (15)
Metformin only	*50 (7)*	0 (0)	0 (0)	0 (0)	50 (25)
Other diabetes treatment with or without metformin	*54 (8)*	0 (0)	0 (0)	0 (0)	54 (27)
Insulin-regime	*65 (10)*	0 (0)	0 (0)	0 (0)	65 (33)
Baseline oxygen requirement, n (%)					
Ambient air	*146 (22)*	49 (43)	50 (17)	4 (5)	43 (22)
Low flow oxygen	*333 (49)*	43 (38)	146 (51)	41 (55)	103 (52)
High flow oxygen	*185 (27)*	21 (18)	85 (30)	28 (38)	51 (26)
Mechanical ventilation	*9 (1)*	1 (1)	5 (2)	1 (1)	2 (1)
Blood samples upon admission					
HbA_{1c},% [a]	*6.2 [5.8–7]*	5.4 [5.2–5.5]	6 [5.8–6.2]	6.7 [6.6–7.2]	7.6 [6.9–8.8]
HbA_{1c}, mmol/mol [a]	*44 [40–53]*	36 [33–37]	42 [40–44]	50 [49–55]	60 [52–73]
Plasma glucose, [a]	*7.0 [6.2–9.1]*	6.4 [5.6–7.0]	6.7 [6.1–7.5]	7.8 [6.8–9.5]	9.7 [7.0–12.9]
Missing, n	*16*	*5*	*9*	*0*	*2*
CRP, mg/l [a]	*77 [38–140]*	58 [19–122]	78 [44–130]	79 [46–160]	84 [38–130]

Non-diabetes: HbA_{1c} < 39 mmol/mol (<5.7%).
Prediabetes: HbA_{1c} 39–47 mmol/mol (5.7–6.5%).
Diabetes mellitus (unknown): $HbA_{1c} \geq$ 48 mmol/mol (>6.5%) w/o treatment.
Diabetes mellitus (known): Known diagnosis of diabetes mellitus or in diabetes treatment.
Abbreviations: HbA_{1c}: hemoglobin A1c, BMI: body-mass-index, CVD: cardio-vascular disease, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein.
[a]Median [IQR].
[b]Mean (SD).

2.2. Definitions

Patients were stratified into groups according to the American Diabetes Association guidelines using HbA_{1c} levels [25]: "Non-diabetes" with $HbA_{1c} < 5.7\%$ (<39 mmol/mol), "Prediabetes" with $5.7\% \leq HbA_{1c} \leq 6.5\%$ ($39 \leq HbA_{1c} \leq 47$ mmol/mol), "Unknown diabetes" with $HbA_{1c} \geq 6.5\%$ (≥48 mmol/mol) and no known diagnosis of diabetes prior to admission. "Known diabetes" was defined as a known diagnosis of diabetes or use of diabetes treatment prior to admission.

The glycemic gap was calculated as (admittance plasma-glucose – estimated average glucose from HbA_{1c}). The estimated average glucose was calculated as $(0.145 \times HbA_{1c}$ mmol/mol$) + 0.825$ [17].

2.3. Statistics

Data processing and statistical analysis were performed using R version 1.2.5001 (R Foundation for Statistical Computing, Vienna, Austria). The study population was characterized using descriptive statistics: categorical variables were reported as counts (%) and continuous variables were summarized using means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Comparison of baseline characteristics, antiviral treatment, hospitalization, 90-day mortality and admittance to ICU between diabetes status groups were performed using χ^2-test, Fisher's exact test, or Mann-Whitney *U* test, as appropriate. Non-normally distributed variables were log2-transformed to achieve normal distribution prior to analysis. The glycemic gap was categorized using quartiles constituting a categorial variable. The quartile with the lowest mortality was chosen as the reference group. Quartiles of the glycemic gap was as follows: 1st quartile: −14.33 to −1.04 mM, 2nd quartile: −1.04 to −0.08 mM (reference group), 3rd quartile: −0.08 to 1.14 mM, 4th quartile: 1.14 to 21.41 mM. Kaplan-Meier curves were performed to illustrate 90-day mortality within the glycemic gap (categorical variable). Cox proportional hazards regression was used to evaluate the association between diabetes status, glycemic gap, 90-day mortality, and ICU admittance, and Schoenfeld residuals were applied to test proportional hazards assumptions. Both univariate and multivariate models were fitted; the multivariate models included sex, age, CVD, BMI, and hypertension. To account for missing data among the covariates, we performed the analysis with and without BMI. Additionally, the interaction between diabetes status and glycemic gap was investigated.

We compared baseline characteristics of the excluded and included individuals to account for selection bias due to missing HbA_{1c}.

3. Ethics

This study was approved by the Danish Board of Health (record no. 31–1522–84 and 31–1521–309), the Capital Regional Data Protection Center (record no. P-2020–492). Register-based studies are exempted from ethical committee approval by Danish legislation.

4. Results

A total of 923 patients hospitalized for COVID-19 were identified within the four study sites. 182 patients were excluded due to missing HbA_{1c}, and 67 patients were excluded due to an HbA_{1c} measured > 60 days prior to admission or > 7 days after admission (Fig. 1) yielding a total of 674 participants. Sex and age did not differ between the excluded and included patients.

Baseline demographics, clinical and biochemical characteristics, and diabetes treatment of the total population and patients stratified according to diabetes status are provided in Table 1. The population were mostly older (>65 years), the majority males, and had a median BMI of 28 kg/m^2 (SD [7]). Participants were moderate to severely ill at admission as indicated by the frequent use of low- or high-flow oxygen (77%). Vital parameters suggested respiratory distress as indicated by the mean peripheral oxygen saturation of 92% (SD [6]) and respiratory rate of 22 breaths per minute (IQR [20–26]). The participants had frequent comorbidities (90% of the participants) with CVD being the most frequent followed by hypertension, COPD, and asthma.

Of 674 participants, 114 (17%) had normal glucose level, 287 (43%) had prediabetes, 74 (11%) had unknown diabetes, and 199 (30%) had a known diagnosis of diabetes. Of the participants with diabetes, the vast majority had type 2 diabetes (193 participants [97%]), three (1.5%) had

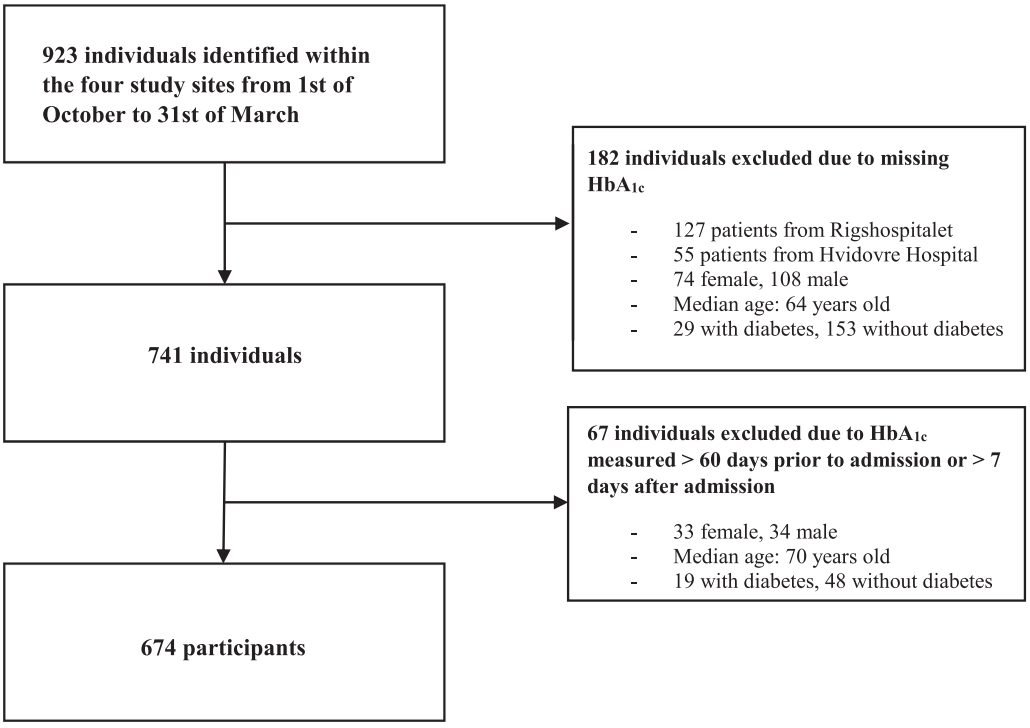

Fig. 1. Flowchart of included and excluded participants.

type 1 diabetes, two (1%) had secondary diabetes due to steroid therapy, and one participant (0.5%) had secondary diabetes due to pancreatitis. Participants with newly diagnosed diabetes were more ill at admission as indicated by a significantly higher requirement of high flow oxygen at baseline ($p = 0.010$) compared to the other groups.

4.1. Hospitalization, treatment and mortality according to diabetes status

Antiviral and anti-inflammatory treatment during hospitalization, requirement of intensive care including need of extra-corporal-membrane-oxygenation, and 30- and 90-day mortality are provided in Table 2. Participants were hospitalized for a median of 7 days (IQR [4–11]) with no differences across groups. More participants with unknown diabetes were admitted to ICU (18% vs. 6–9% across the other groups, $p = 0.022$). No difference in 30- nor 90-day mortality was found between the groups. Baseline characteristics stratified for 90-day mortality are provided in Supplementary Table 2. Participants who died were older ($p = 0.001$), had higher rate of comorbidities (two or higher) ($p = 0.001$), lower BMI ($p = 0.001$), and a higher rate of high flow oxygen requirement at baseline ($p = 0.009$). The glycemic gap was higher among those who died ($p = 0.017$).

In crude proportional hazard ratio analysis (Tables 3 and 4), no association between diabetes status and 90-day mortality or ICU admittance was found (Fig. 2c). However, compared to non-diabetes, participants with unknown diabetes seemed to be at higher risk of ICU admittance (OR: 2.09 95% CI [0.92–4.77], $p = 0.079$). In the multivariate analysis participants with prediabetes were less likely to die within 90 days compared to non-diabetes (HR 0.58, 95% CI [0.35–0.98], $p = 0.042$). Lastly, we found no association between admission plasma-glucose and ICU admittance or death within 90 days in crude and adjusted analysis (Fig. 2b).

A total of 76% of participants received treatment with remdesivir. Patients with non-diabetes and known diabetes had the lowest treatment rates (61% and 69%, respectively) compared to patients with unknown diabetes and prediabetes ([87% and 83%, respectively], $p = < 0.001$). A quarter of the patients in the non-diabetes group and 15% of patients with diabetes did not fulfill the treatment criteria of oxygen support to receive remdesivir and dexamethasone. Eighty-two percent of the population received dexamethasone. Participants with non-diabetes had a lower treatment rate compared to the other groups (73 individuals (64%), $p = < 0.001$). Only 5 patients (0.7%) were treated with tocilizumab in the given study period. Out of 502 patients at Amager, Hvidovre and Glostrup hospital 95.4% of patients were treated with anti-coagulative, and 3.4% were vaccinated prior to admission. Data collection on use of anticoagulative or vaccination status was not uniformly collected at Rigshospitalet, but as anticoagulative treatment was standard treatment for all patients hospitalized with COVID-19, and vaccinations were out-rolled nationally in late December 2020, we expect similar rates for the whole cohort. There was still no association between diabetes status and mortality once anticoagulative treatment was included in the multivariable model.

4.2. The glycemic gap

Among the four quartiles, no differences in sex, age, BMI, nor comorbidities were found. Participants in the 2nd quartile had higher

Table 2
Antiviral and anti-inflammatory treatment, hospitalization and outcome in 674 adult patients hospitalized with COVID-19 grouped by diabetes status.

	Total (n = 674)	Non-diabetes (n = 114)	Prediabetes (n = 287)	Diabetes mellitus (unknown) (n = 74)	Diabetes mellitus (known) (n = 199)
Antiviral and anti-inflammatory treatment					
Remdesivir, n (%)	*510 (76)*	70 (61)	238 (83)	64 (87)	138 (69)
Days of treatment [a]	*4* [3–4]	4 [3–4]	4 [3–4]	4 [3–4]	4 [3–4]
Reasons for missing treatment, n (%)					
eGFR < 30 ml/min/1,73 m²	*33 (5)*	5 (4)	8 (3)	3 (4)	17 (9)
ALAT > 300 U/l	*0*	0	0	0	0
Symptoms > 10 days	*37 (6)*	5 (4)	6 (8)	13 (7)	37 (6)
ICU admission	*1 (0.1)*	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
No oxygen requirement	*80 (12)*	28 (25)	22 (8)	0 (0)	30 (15)
Other	*9 (1)*	5 (4)	1 (0.3)	1 (0.5)	9 (1.3)
Dexamethasone, n (%)	*550 (82)*	73 (64)	248 (86)	68 (92)	161 (81)
Days of treatment, median [IQR]	*6* [3–9]	5 [3–9]	6 [3–8]	6 [3–9]	6 [4–9]
Hospitalization					
Days of hospitalization [a]	*7* [4–11]	6 [3–10]	7 [4–10]	7 [4–11]	7 [5–13]
ICU, n (%)	*60 (9)*	10 (9)	26 (9)	13 (18)	11 (6)
Days of hospitalization at ICU [a]	*13* [7–24]	14 [10–24]	13 [5–19]	14 [9–27]	17 [9–42]
ECMO, n (%)	*7 (1)*	1 (1)	2 (1)	2 (3)	1 (1)
Mortality, n (%)					
In-hospital mortality	*89 (13)*	14 (12)	30 (11)	15 (20)	30 (15)
30-day mortality	*101 (15)*	19 (17)	34 (12)	15 (20)	33 (17)
90-day mortality	*128 (19)*	23 (20)	44 (15)	18 (24)	43 (22)

Non-diabetes: $HbA_{1c} < 5.7\%$ (<39 mmol/mol).
Prediabetes: HbA_{1c} 5.7–6.5% (39–47 mmol/mol).
Diabetes mellitus (unknown): $HbA_{1c} > 6.5\%$ (≥48 mmol/mol) w/o treatment.
Diabetes mellitus (known): Known diagnosis of diabetes mellitus or in diabetes treatment.
Abbreviations: HbA_{1c}: hemoglobin A_{1c}, COVID-19: coronavirus disease-2019, IQR: interquartile range, ICU: intensive care unit, ECMO: extra corporal membrane oxygenation, ALAT: alanine aminotransferase, eGFR: estimated glomerular filtration rate.
Non-diabetes: $HbA_{1c} < 5.7\%$ (<39 mmol/mol).
Prediabetes: HbA_{1c} 5.7–6.5% (39–47 mmol/mol).
Diabetes mellitus (unknown): $HbA_{1c} > 6.5\%$ (≥48 mmol/mol) w/o treatment.
Diabetes mellitus (known): Known diagnosis of diabetes mellitus or in diabetes treatment.
Abbreviations: IQR: interquartile-range, CVD: cardio-vascular disease, COPD: chronic obstructive pulmonary disease, BMI: body-mass-index, HbA_{1c}: hemoglobin A_{1c}.
[a]Median [IQR].
[a]Statistics were performed using χ^2-test, Fisher's exact test, or Mann-Whitney *U* test, as appropriate.
[b]Median [IQR].
[c]Mean (SD).

Table 3
The association between diabetes status, glycemic control and death within 90 days in the study population.[a]

	Hazards ratio, unadjusted (95% CI)	p-value	Hazards ratio, adjusted[b] (95% CI)	p-value
Diabetes status				
Non-diabetes (reference)	1		1	
Prediabetes	0.72 (0.44–1.21)	0.22	0.58 (0.35–0.98)	**0.042**
Diabetes mellitus (unknown)	1.23 (0.66–2.28)	0.51	1.14 (0.59–2.19)	0.70
Diabetes (known)	1.08 (0.65–1.79)	0.77	0.69 (0.40–1.20)	0.191
Plasma glucose at admission				
< 6 mmol/l (reference)	1		1	
6–11 mmol/l	0.72 (0.32–1.66)	0.45	0.51 (0.22–1.17)	0.11
> 11 mmol/l	1.00 (0.41–2.44)	1.00	0.73 (0.30–1.81)	0.50
Glycemic gap (continuous)				
1 mM increment	1.07 (1.01–1.12)	**0.018**	1.06 (1.00–1.12)	0.05
Glycemic gap (categorical)				
1st quartile	1.71 (0.95–3.07)	0.07	1.82 (0.97–3.41)	0.06
2nd quartile (reference)	1		1	
3rd quartile	2.13 (1.21–3.76)	**0.009**	2.38 (1.29–4.38)	**0.005**
4th quartile	2.37 (1.36–4.14)	**0.002**	2.48 (1.37–4.52)	**0.003**

Non-diabetes: HbA_{1c} < 5.7% (<39 mmol/mol).
Prediabetes: HbA_{1c} 5.7–6.5% (39–47 mmol/mol).
Diabetes mellitus (unknown): HbA_{1c} > 6.5% (≥48 mmol/mol) w/o treatment.
Diabetes mellitus (known): Known diagnosis of diabetes mellitus or in diabetes treatment.
1st quartile: −14.33 to −1.04 mM.
2nd quartile: −1.04 to −0.08 mM.
3rd quartile: −0.08 to 1.14 mM.
4th quartile: 1.14 to 21.41 mM.
[a]Statistics were performed using Cox proportional hazards regression.
[b]Adjusted for age, sex, BMI, hypertension, and CVD.

Table 4
The association between diabetes status, glycemic control and admission to the intensive care unit in the study population.[a]

	Hazard ratio, unadjusted (95% CI)	p-value	Hazard ratio, adjusted[b] (95% CI)	p-value
Diabetes status				
Non-diabetes (reference)	1		1	
Prediabetes	1.05 (0.50–2.17)	0.90	0.93 (0.44–1.95)	0.84
Diabetes mellitus (unknown)	2.09 (0.92–4.77)	0.08	1.79 (0.77–4.18)	0.18
Diabetes mellitus (known)	0.62 (0.26–1.46)	0.27	0.43 (0.18–1.08)	0.07
Plasma glucose at admission				
< 6 mmol/l (reference)	1		1	
6–11 mmol/l	0.72 (0.32–1.66)	0.45	0.51 (0.22–1.16)	0.11
> 11 mmol/l	1.00 (0.41–2.44)	1.00	0.73 (0.30–1.82)	0.50
Glycemic gap (continuous)				
1 mM increment	1.08 (1.01–1.16)	**0.021**	1.09 (1.01–1.17)	**0.029**
Glycemic gap (categorical)				
1st quartile	1.58 (0.61–4.08)	0.34	1.46 (0.56–3.78)	0.44
2nd quartile (reference)	1		1	
3rd quartile	2.97 (1.26–7.02)	**0.013**	2.72 (1.15–6.45)	**0.023**
4th quartile	3.26 (1.39–7.62)	**0.006**	2.98 (1.27–7.00)	**0.012**

Non-diabetes: HbA_{1c} < 5.7% (<39 mmol/mol).
Prediabetes: HbA_{1c} 5.7–6.5% (39–47 mmol/mol).
Diabetes mellitus (unknown): HbA_{1c} > 6.5% (≥48 mmol/mol) w/o treatment.
Diabetes mellitus (known): Known diagnosis of diabetes mellitus or in diabetes treatment.
1st quartile: −14.33 to −1.04 mM.
2nd quartile: −1.04 to −0.08 mM.
3rd quartile: −0.08 to 1.14 mM.
4th quartile: 1.14 to 21.41 mM.
[a]Statistics were performed using Cox proportional hazards regression.
[b]Adjusted for age, sex, BMI, hypertension, and CVD.

eGFR, were more often treated with remdesivir, and had less use of diabetes treatment compared to the other quartiles. Of hospitalization and outcome, the 2nd quartile had shortest length of hospital stay, lowest admittance to ICU, in-hospital and 90-day mortality (Supplementary Table 2).

For each 1 mmol/L increase of the glycemic gap, the adjusted HR for mortality was 1.06 (95% CI [1.00–1.12], $p = 0.050$). Participants from the 2nd quartile had the lowest mortality risk and served as the reference (Fig. 2a). In the adjusted model, participants from the 3rd (HR 2.38 [1.29–4.38], $p = 0.005$) and 4th quartile (HR 2.48 [1.37–4.52], $p = 0.003$) all had increased 90-day mortality compared to the 2nd quartile. Participants from the 1st quartile tended to have increased mortality (HR 1.82 [0.97–3.41], $p = 0.06$) (Table 3). No interactions between diabetes status and glycemic gap in 90-day mortality was found.

The 3rd (HR 2.72 [1.15–6.45], $p = 0.023$) and 4th quartile (HR 2.98 [1.27–7.00], $p = 0.012$) were associated with a higher hazard of ICU admission (Table 4), but only the 4th quartile was associated with an increased hazard of mechanical ventilation during hospitalization (HR 2.61 [1.02–6.68], $p = 0.046$).

5. Discussion

We studied abnormalities in glucose metabolism and the influence on ICU admission and mortality among Danish patients hospitalized with COVID-19. We found that >80% of patients had abnormal glucose levels and that plasma glucose at admission and HbA_{1c} were of no predictive value, whereas a positive glycemic gap was associated with increased risk of 90-day mortality.

All participants included in this study had an HbA_{1c} measurement that made it possible to place them into diabetes status groups and determine their glycemic gap. A similar high prevalence of prediabetes and unknown diabetes has been reported in a previous study among patients with CAP [10], where the reported prevalence of prediabetes was 37.5% and of unknown diabetes 5%. As our study show even higher rates, we suggest that compared to non-COVID-related CAP, elevated HbA_{1c} might even further increase severity and risk of hospitalization in people with COVID-19. However, it cannot be ruled out that the stress of the infection itself could have increased glucose sufficiently to increase HbA_{1c} above 5.7% (39 mmol/mol) in some participants, and thereby explain the observed high prevalence of prediabetes. Most studies in patients with COVID-19 have reported prevalence of prediabetes ranging from 8.8% to 28% [26–29]. Only one study by Vargas-Vázquez *et al.* showed comparable rates to those of our study with a prevalence of prediabetes of 39.4% and unknown diabetes of 20% [30]. The study population in Vargas-Vásquez *et al.* was from an area known for the large rate of undiagnosed diabetes. In our study population, the known prevalence of type 2 diabetes is also relatively high (2.9–6.4% [31]), partly due to a large population of citizens of middle East origin at increased risk of type 2 diabetes [32] and a population of low socio-economic status. No current data are available on prediabetes in the studied area, but a recent study from a socio-economic comparable part of Denmark reported a prevalence of prediabetes of 5.8% and unknown diabetes of 0.8% [33]. As the prevalence of dysglycemia is high in our study compared to the background population, we find it of importance to screen patients with COVID-19 with HbA_{1c} at admission. Follow-up studies on the progression of HbA_{1c} after discharge and benefits of diabetes treatment during hospitalization in prediabetes and unknown

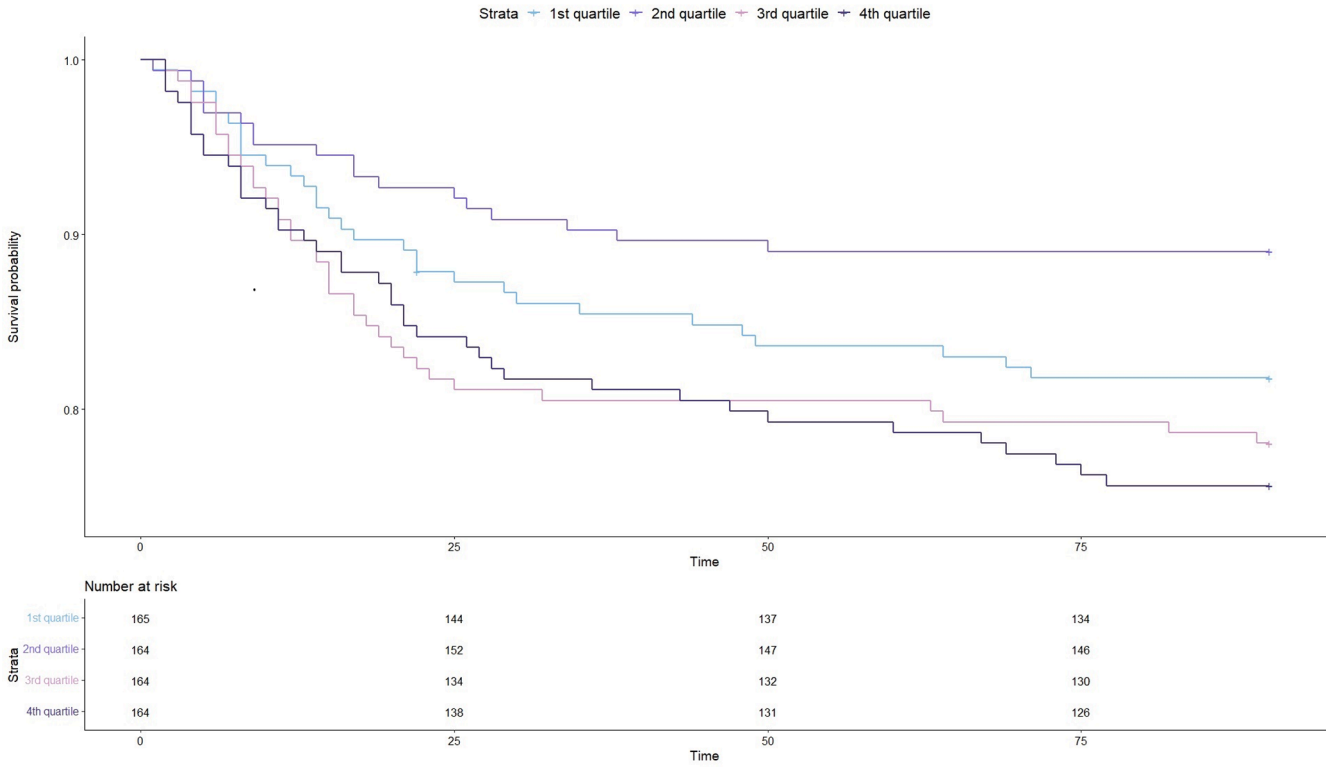

Fig. 2a. Kaplan Meier survival curve for the glycemic gap quartiles. p-value = 0.014.

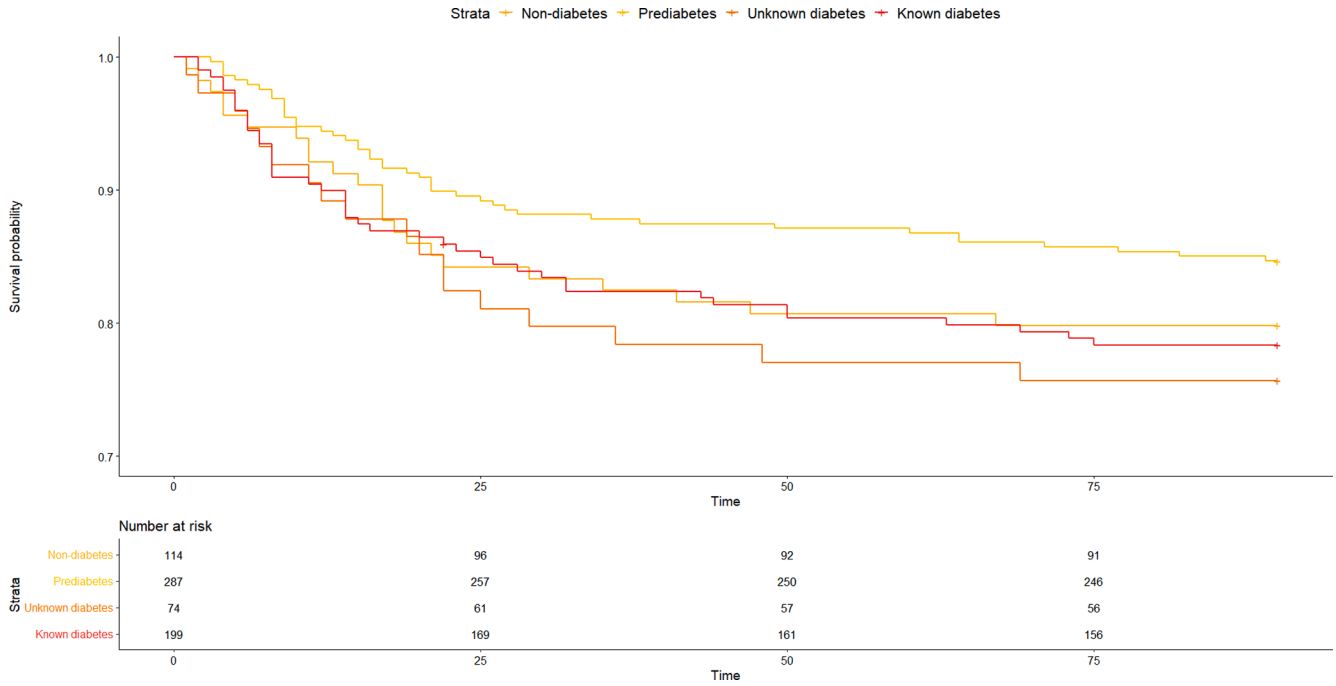

Fig. 2b. Kaplan Meier survival curve for admission glucose groups. p-value = 0.30.

diabetes are furthermore warranted.

In the adjusted mortality analysis, we did not find that individual admission plasma glucose or HbA_{1c} predicted ICU admission or 90-day mortality. However, we did find that patients with the highest glycemic gap had the highest hazard of 90-day mortality with a 2.5-fold increase compared to the reference, who had an admission plasma glucose similar to their habitual glucose level. Comparable to previous studies, our results indicate that irrespective of habitual diabetes status, the level of glycemic stress at admission, and thereby the relationship between the two, could be an important predictor of poorer outcome in patients hospitalized with COVID-19 [18–22,34]. It seems that imbalances with severe hyperglycemia at admission is linked to the poorest outcome. Hyperglycemia in severe disease is in general caused by a combination of insulin resistance and beta-cell failure. Insulin resistance in the

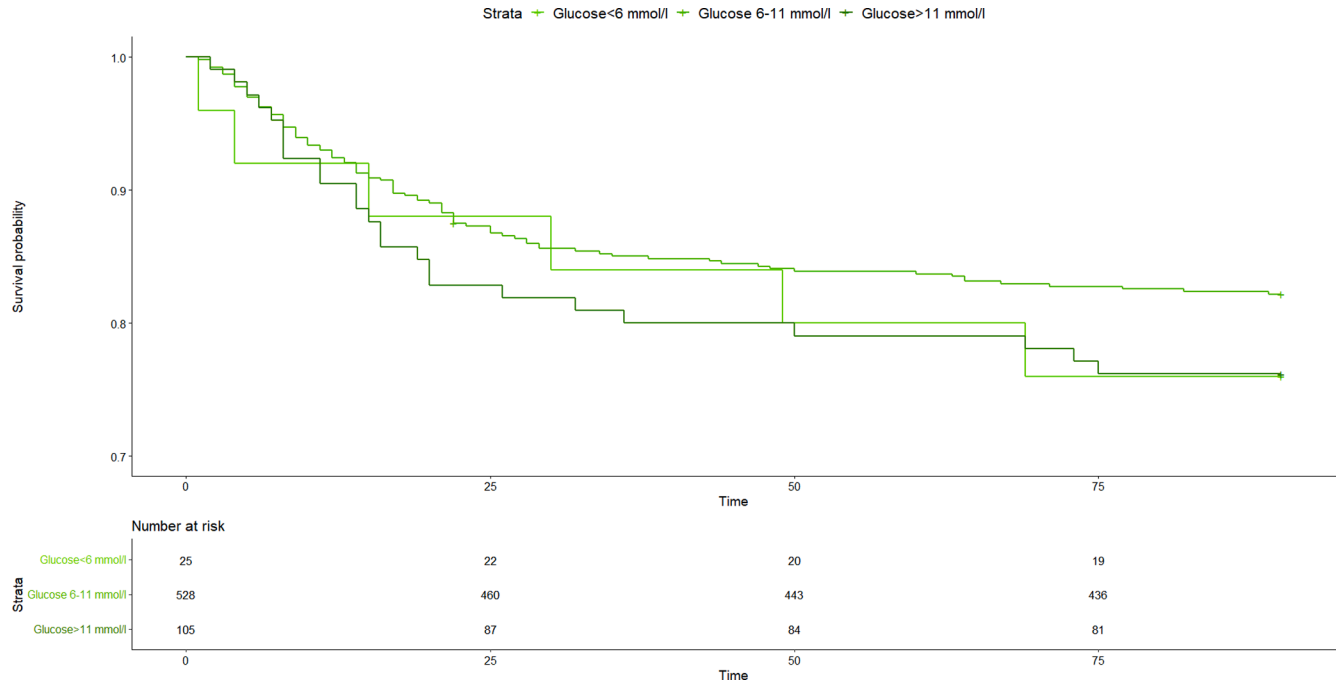

Fig. 2c. Kaplan Meier survival curve for diabetes status groups. p-value = 0.16.

peripheral tissue results in hyperglycemia and hyperinsulinemia, the latter because the beta-cell overproduce insulin in response to hyperglycemia. Beta-cell failure, on the other hand, results in failure of insulin production and thereby hyperglycemia. For patients with COVID-19, hyperglycemia has been reported to be mostly driven by insulin resistance, which have further been linked to inflammation of adipose tissue and reduced adiponectin-levels [35]. Until now, the glycemic gap as a predictor of severity and mortality in COVID-19 has only been reported in a study of 91 patients with type 2 diabetes [24]. They too reported increased hazards of hyperglycemia in the glycemic gap (levels ≥ 1.22) among patients with COVID-19. Our study results expand the use of the glycemic gap by including all patients irrespective of diabetes status.

We expected that known and unknown diabetes (and to some extent prediabetes) would be associated with 90-days mortality, since prior studies of diabetes and mortality have shown increased mortality among these patient groups. Additionally, studies have reported that angiotensin-converting-enzyme receptor 2 and transmembrane-protease-serin 2 are upregulated in patients with diabetes, which SARS-CoV-2 uses as cellular entrance-receptors. Upregulated expression of these receptors could, theoretically, enhance viral load and disease severity, and thereby cause enhanced disease progression among patients with diabetes. Regardless, in the present study unknown and known diabetes were not associated with increased mortality compared to non-diabetes; on the contrary, prediabetes seemed to be associated with reduced 90-day mortality. As a high proportion of patients included in this study were treated with dexamethasone, the clinicians' focus on the following hyperglycemia and treatment hereof may well have improved the outcome of patients with dysglycemia, as have been reported in a prior study [36]. Despite this, there is no obvious explanation of the reduced hazard of prediabetes compared to non-diabetes in this study, and it seems unlikely that prediabetes has protective properties in COVID-19.

5.1. Strengths and limitations

Strengths of the study include the cohort study design with prospective enrollment and complete follow-up of a large population of consecutive, unselected patients. Bias at data collection was avoided by doing assembled training for data collection. Furthermore, the 4th of December 2020 measurement of HbA_{1c} became a part of standard laboratory analysis upon admission of patients with COVID-19 yielding a large sample size without notable selection bias. Despite this, limitations include lack of HbA_{1c} measurement in 182 patients. However, the group characteristics in the excluded patients did not differ significantly from the included, suggesting that our population is representative. Given that some patients may have been sick days before hospitalization, some of the HbA_{1c} levels measured after admission may have been falsely high due to the acute infection and thereby overestimate the prevalence of prediabetes and unknown diabetes. Lastly, unmeasured variables could create residual confounding.

6. Conclusion

In conclusion, we report that among adults admitted with COVID-19, the individual hyperglycemic deviation from a habitual average glucose, but not the admission glucose levels, predict a fatal outcome from COVID-19. Furthermore, we conclude that hyperglycemia is very prevalent among hospitalized patients with COVID-19, and that diabetes status is not associated with a poorer outcome of COVID-19.

Authorship contributions

CLC contributed to the design of the study, collected and researched data, and wrote the manuscript. CLH contributed to the design of the study, collected and researched data, contributed to the introduction, and reviewed/edited the manuscript. DFJ, RKM, OK contributed to the design of the study and reviewed/edited the manuscript. CR reviewed the statistics. HLJ collected data and reviewed/edited the manuscript. TB reviewed/edited the manuscript. TPA, OS contributed to the design of the study, the introduction, discussion and reviewed/edited the manuscript. TPA and OS contributed to the study equally and should be regarded as joint senior authors.

All authors read and approved the final version of the manuscript.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109880.

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