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Glycated haemoglobin (HbA1c) levels among 3,295 hospitalised COVID-19 patients with and without diabetes and risk of severe infection, admission to an intensive care unit, and all-cause mortality

Running title: HbA1c in COVID-19 patients and adverse outcomes

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Abstract

Aims: Diabetes and hyperglycaemia have been associated with a more severe disease course in COVID-19 patients. However, less is known regarding the risk of adverse outcomes across the spectrum of glycated haemoglobin(HbA1c) levels among COVID-19 patients with and without diabetes.

Materials and methods: Danish nationwide registries were used to study the association between HbA1c levels and 30-day risk of all-cause mortality and the composite of severe COVID-19 infection, intensive care unit(ICU)admission, or all-cause mortality. The study population comprised patients hospitalised with COVID-19(3rd March-31st December 2020)with a positive PCR-test and an available HbA1c≤6 months before the first positive PCR-test. All patients had at least 30 days of follow-up. Among patients with diabetes,HbA1c was categorised as<48, 48-53, 54-58, 59-64(reference),and>64mmol/mol. Among patients without diabetes,HbA1c was stratified into<31, 31-36(reference), 37-41,and 42-47mmol/mol. 30-day standardised absolute risks and standardised absolute risk differences are reported.

Results: We identified 3,295 hospitalised COVID-19 patients with an available HbA1c(56.2% males and median age 73.9 years),of whom 35.8% had diabetes. The median HbA1c was 54mmol/mol and 37mmol/mol among patients with and without diabetes, respectively. Among patients with diabetes, the standardised absolute risk difference of the composite outcome was higher with HbA1c<48mmol/mol(12.0%[3.3-20.8%]) and HbA1c>64mmol/mol(15.1%[6.2-24.0%]), compared with HbA1c 59-64mmol/mol(reference). Among patients without diabetes, the standardised absolute risk difference of the composite outcome was greater with HbA1c<31mmol/mol(8.5%[0.5-16.5%]) and HbA1c 42-47mmol/mol(6.7%[1.3-12.1%]), compared with HbA1c 31-36mmol/mol(reference).

Conclusions: Patients with COVID-19 and HbA1c<48mmol/mol or HbA1c>64mmol/mol had a

higher associated risk of the composite outcome. Similarly, among patients without diabetes, varying HbA1c levels were associated with higher risk of the composite outcome.

Introduction

Coronavirus disease-2019(COVID-19)infection, caused by the Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2), was declared a global pandemic by WHO on 11th March 2020.(1, 2)

In previous studies, in a non-COVID-19 setting, HbA1c has been shown as a clinically useful marker for predicting all-cause mortality both among patients with and without diabetes.(3-6)In a COVID-19 setting, many studies have demonstrated that diabetes mellitus is a substantial risk factor for increased severity of COVID-19 infection, admission to intensive care unit(ICU), and COVID-19 related mortality.(7-10)Patients with diabetes and higher levels of HbA1c or hyperglycaemia also have higher levels of inflammatory markers, which could indicate a more severe inflammatory response than those without diabetes or with normoglycaemia.(11-16)However, to date, few studies have examined the relationship between varying glycated haemoglobin(HbA1c)levels and the associated risk of mortality and adverse outcomes among COVID-19 patients, with conflicting results.(17-19)The studies focused primarily on the association between HbA1c and mortality among COVID-19 patients with diabetes. Previously, Holman et al. identified an independent association between high HbA1c levels and COVID-19-related mortality among over 3 million people with type 1 diabetes and type 2 diabetes.(18)However, the absolute risk of mortality according to HbA1c levels following COVID-19 infection was not reported, only patients with diabetes were included, and important outcomes such as severe COVID-19 infection or ICU admission were also not examined.

In a COVID-19 setting, more information is needed on the association between varying HbA1c testing levels prior to a positive SARS-CoV-2 Polymerase chain reaction(PCR)test and risk of mortality and particularly adverse outcomes among patients with and without diabetes. Thus, the purpose of this Danish registry-based cohort study was to determine the risk of severe COVID-

19 infection, ICU admission, or all-cause mortality among COVID-19 patients, with and without diabetes, associated with varying levels of HbA1c.

Materials and methods

Data sources

All Danish residents are assigned a unique and personal civil registration number, which allows individual linkage of nationwide administrative registries. The data used in the present study were obtained from the Danish National Patient Registry, the Danish Microbiology Database, the Clinical Laboratory Information System, the Danish National Prescription Registry, and the Danish population Registry. The Danish National Patient Registry provides data on all hospital admissions and outpatient contacts since 1977 according to the International Classification of Diseases(8th Revision[ICD-8]until 1993 and 10th Revision[ICD-10]thereafter)as well as surgical procedures, registered based on the Nordic Medico-Statistical Committee(NOMESCO)Classification of Surgical Procedures(NCSP).(20)SARS-CoV-2 PCR data were obtained from the Danish Microbiology Database, which provides nationwide, complete reports from all Danish Departments of Clinical microbiology.(21)Information on HbA1c measurements was gathered from the Clinical Laboratory Information System, which holds information on all blood samples obtained from hospitals and medical practices in two Danish regions, representing one-third of the Danish population. In Denmark, the HbA1c measurement is reported in mmol/mol according to The International Federation of Clinical Chemistry and Laboratory Medicine(IFCC)Reference Measurement Procedure since 2010. The blood samples are coded according to the international Nomenclature, Properties and Units(NPU)coding system.(22)The Danish National Prescription Registry provides detailed information on all dispensed drug prescriptions from Danish pharmacies according to the Anatomic Therapeutic Chemical(ATC)Classification System since 1995.(23)The Danish Civil Registration

System holds information on birth date, sex, and vital status(i.e. whether a person is alive and citizen in Denmark, emigrated, or dead, along with the date of these events).(24)The Danish registries are of high quality and complete, and the definitions and codes obtained from the registries have been previously validated.(20, 25, 26)

Study population

The study population included all Danish citizens with a positive SARS-CoV-2 PCR test and a COVID-19-related hospitalisation between 26th February 2020 and 31st December 2020. The index date was defined as the first positive PCR test result. A COVID-19-related hospitalisation was defined as a hospital admission within 14 days after the first positive PCR test result with a length of stay of at least 12 hours. Information on the most recent HbA1c for each patient was identified from blood samples≤6 months before index date. Only patients with information on HbA1c were eligible for inclusion.

Patient characteristics, comorbidity, and pharmacotherapy

Patients with diabetes were identified according to diabetes-related hospital admissions or outpatient contacts(ICD-10 codes:E10-E14)any time before index date or by dispensed prescriptions for an antidiabetic drug(ATC-code:A10)or HbA1c≥48mmol/mol(6.5%)≤6 months before index date.

Patient comorbidity was determined from the Danish National Patient Registry using hospital admissions or outpatient contacts(i.e., primary or secondary diagnosis codes)any time prior to index date(see the Supplementary Appendix(Table S1)). Concomitant pharmacotherapy was identified from the Danish Prescription Registry as a dispensed prescription within 6 months prior to index date(Table S2). Patients with hypertension were identified from combination treatment with at least two dispensed antihypertensive drug prescriptions, as described previously.(27)

Follow-up and outcomes

The primary study outcome was a composite of COVID-19 severe acute respiratory syndrome(i.e., severe COVID-19 infection[ICD-10 code:B972A]), ICU admission(NCSP codes:NABE, NABB, and BGDA), or all-cause mortality. The secondary study outcome was all-cause mortality. All patients included had at least 30 days of potential follow-up from the first positive PCR test result. Patients were followed from the day of the first positive PCR test until the occurrence of a study outcome, death, or end of study(31st January 2021), whichever came first.

Statistical methods

Continuous variables are presented as medians with interquartile ranges(IQRs), and differences were assessed by the Kruskal-Wallis test. Categorical variables are presented as numbers with proportions, and differences were assessed by the Chi-square test.

To test the association of varying HbA1c levels among patients with and without diabetes separately, we performed stratified analyses according to diabetes status. Patients with diabetes were grouped according to the HbA1c cut-offs by the International Diabetes Federation(IDF)and American Diabetes association(ADA).(28-31):<48mmol/mol(6.5%), 48-53mmol/mol(6.5-7.0%), 54-58mmol/mol(7.1-7.5%), 59-64mmol/mol(7.5-8.0%), and>64mmol/mol(8.0%). For this analysis, HbA1c 59-64mmol/mol(7.5-8.0%)was used as the comparative reference as the IDF recommended this HbA1c target among patients using multiple medications including glucose-lowering drugs with a reduced life expectancy(e.g.,<10 years)and multiple comorbidities.(31)Among patients without diabetes, HbA1c was stratified into<31mmol/mol(5.0%), 31-36mmol/mol(5.0-5.4%)(reference), 37-41mmol/mol(5.5-5.9%), and 42-47mmol/mol(6.0-6.5%), as done previously.(4, 32)

Using working Cox regression models, we standardised the 30-day risks of all-cause mortality and the composite outcome in the aforementioned HbA1c groups among patients with and

without diabetes, according to the distribution of sex, age as continuous variable, history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, hypertension, chronic obstructive pulmonary disease(COPD), cancer, chronic renal disease, and use of cholesterol-lowering drugs, beta-blockers, calcium channel blockers, renin-angiotensin system inhibitors, aspirin, and anticoagulants in the study population. We report 30-day standardised absolute outcome risks(SAR)and differences thereof with 95% confidence intervals(CIs)of outcomes.(33)

In order to test the robustness of our results, we performed several sensitivity analyses. First, the model assumptions of the working Cox regression model(proportional hazards, linearity of effects, and absence of interactions)were tested estimating standardised 30-day outcome risks based on a random survival forest model among patients with and without diabetes, respectively.(34)Second, we report hazard ratios(HRs)with 95% CIs during complete follow-up among patients with and without diabetes, respectively. Third, in order to visualise the association between continuous HbA1c and the rates of the study outcomes, we fitted a Cox regression model, which used restricted cubic splines with 3 knots to illustrate the association between HbA1c and the outcome rates adjusted for all other variables of the main analysis.

Fourth, in order to assess if HbA1c per se has a significant biologic effect, we compared patients with and without diabetes but with the same range of HbA1c levels. The combined population was stratified in the following groups:HbA1c<39mmol/mol(5.7%)without diabetes, HbA1c<39mmol/mol with diabetes, HbA1c 39-47mmol/mol(5.7-6.5%)without diabetes, HbA1c 39-47mmol/mol with diabetes, 48-53mmol/mol, 54-58mmol/mol, 59-64mmol/mol, and>64mmol/mol(Table S7).

Fifth, a sensitivity analysis was conducted to assess if random blood glucose(BG)at the time of admission plays a critical role in prognosis of COVID-19 patients in terms of all-cause

mortality or the composite outcome. Sixth, to determine possible generalisability of the present study findings, we compared patient characteristics for the included study patients with COVID-19 patients with no information on HbA1c levels according to diabetes status.

Seventh, to test if time of diagnosis influenced our findings, the populations with and without diabetes were stratified in two periods before and after 1st August 2020, and the main analyses were repeated. Eighth, to test if time of HbA1c measurements prior to index date would influence our results, sensitivity analyses using HbA1c obtained 3 months before index date instead of 6 months were performed for both study outcomes among patients with and without diabetes as the main analyses.

The main statistical coding was conducted using the SAS(version 9.4,Cary,NC, USA), and all statistical analyses were obtained using R(version 4.0.3). The level of statistical significance was set at 5%.

Ethics

In Denmark, registry-based studies using de-identifiable data do not require ethical approval. The present study was approved by the data responsible institute(the Capital Region of Denmark-Approval number:P-2019-191)in accordance with the General Data Protection Regulation. Danish law prohibits reporting of low group numbers below 3, which were replaced with'≤3' throughout the paper. The exact numbers are known to the investigators.

Results

Of the 4,198,450 individuals in Denmark who underwent a PCR test, 163,908 Danish citizens had a positive test for SARS-CoV-2 from 26th February to 31st December 2020, of whom 7,865(4.8%)had a COVID-19-related hospitalisation. Among these, 3,295(41.9%)individuals had a HbA1c value≤6 months prior to index date and comprised the study population in the present study. A total of 1,178(35.8%)patients had diabetes. The first patient was included 3rd March 2020, and the last patient was included 31st December 2020. Among patients with diabetes, the median follow-up time to all-cause mortality and the composite outcome was 50.5 days[IQR:32-118 days] and 36 days[IQR:6-89 days], respectively. Among patients without diabetes, the median follow-up time to all-cause mortality and the composite outcome was 54 days[IQR:35-187 days] and 43 days[IQR:9-107 days], respectively.

Patient characteristics according to diabetes status are listed in Table 1. Compared with patients without diabetes, patients with diabetes were more likely to be male(62.7%)and suffer from comorbidities. Patient characteristics according to HbA1c groups among patients with and without diabetes are listed in Table 2 and Table 3, respectively.

Risk of mortality

Among patients with diabetes, 272(23.1%)died within 30 days of follow-up; 94(29.7%)with HbA1c<48mmol/mol, 55(20.2%)with HbA1c 48-53mmol/mol, 29(20.6%)with HbA1c 54-58mmol/mol, 23(16.9%)with HbA1c 59-64mmol/mol, and 71(22.8%)with HbA1c>64mmol/mol. Among patients with diabetes, HbA1c<48mmol/mol, 54-58mmol/mol, and>64mmol/mol were associated with significantly higher 30-day SAR differences of all-cause mortality, compared with HbA1c 59-64mmol/mol, (9.8%[3.5-16.0%]), (9.7%[1.7-17.8%]), and (8.8%[2.3-15.3%]), respectively(Fig.1). Furthermore, Figure S1 shows the adjusted HRs from the Cox regression analysis for

all-cause mortality among patients with diabetes. Illustrated in Figure S2 is a restricted cubic spline reporting the continuous association between HbA1c and the mortality rate among patients with diabetes.

In total, 401(18.9%)patients without diabetes died during 30 days of follow-up; 40(28.2%)with HbA1c<31mmol/mol, 122(15.8%)with HbA1c 31-36mmol/mol, 160(19.3%)with HbA1c 37-41mmol/mol, and 79(21.3%)with HbA1c 42-47mmol/mol. Among patients without diabetes, HbA1c<31mmol/mol was associated with higher 30-day SAR difference of all-cause mortality(11.2%[5.0-17.5%]), compared with HbA1c 31-36mmol/mol(Fig.2). Adjusted HRs from the Cox regression analysis and a restricted cubic spline for mortality among patients without diabetes are depicted in Figure S3 and Figure S4, respectively.

Risk of severe COVID-19 infection, intensive care unit admission, or all-cause mortality

Among patients with diabetes, the composite outcome of severe COVID-19 infection, ICU admission, or all-cause mortality appeared in 512(43.5%)within 30 days of follow-up;148(46.7%)with HbA1c<48mmol/mol, 109(40.1%)with HbA1c 48-53mmol/mol, 55(39.0%)with HbA1c 54-58mmol/mol, 48(35.3%)with HbA1c 59-64mmol/mol, and 152(48.7%)with HbA1c>64mmol/mol. Among patients with diabetes, HbA1c<48mmol/mol and HbA1c>64mmol/mol were associated with significantly increased 30-day SAR differences of the composite outcome, compared with HbA1c 59-64mmol/mol, (12.0%[3.3-20.8%])and (15.1%[6.2-24.0%]), respectively(Fig.1). Depicted in Figure S5 are HRs from the Cox regression analysis for the composite outcome among patients with diabetes. A restricted cubic spline reporting the continuous association between HbA1c and the rate of the composite outcome among patients with diabetes is illustrated in Figure S6.

The composite outcome occurred in 757(35.8%)patients without diabetes during 30 days of follow-up; 56(39.4%)with HbA1c<31mmol/mol, 246(31.8%)with HbA1c 31-36mmol/mol,

298(35.9%)with HbA1c 37-41mmol/mol, and 157(42.3%)with HbA1c 42-47mmol/mol. Compared with HbA1c 31-36mmol/mol, HbA1c<31mmol/mol and 42-47mmol/mol were associated with higher 30-day SAR differences of the composite outcome, (8.5%[0.5-16.5%]) and(6.7%[1.3-12.1%]), respectively(Fig.2). Finally, Figure S7 and Figure S8 depict HRs from the Cox regression analysis and a restricted cubic spline for the composite outcome among patients without diabetes, respectively.

Sensitivity analyses

The model assumptions of the Cox regression analysis, based on a random survival forest model, were fulfilled for both study outcomes among COVID-19 patients with and without diabetes(Table S3 and Table S4, respectively).

The comparison between patients with and without diabetes with the same range of HbA1c levels in a pooled population showed that patients with diabetes and HbA1c 39-47mmol/mol or HbA1c>64mmol/mol were associated with a higher risk of the composite outcome(Figure S9). However, patients without diabetes were not associated with an increased risk of the composite outcome.

According to baseline characteristics, a dose-response relationship was identified between increasing levels of HbA1c groups and median levels of BG among patients with and without diabetes(Table 2 and 3). Among patients with diabetes, BG 11.1-13.0mmol/l and BG>13.0mmol/l were associated with a higher risk of the composite outcome(Figure S10). A dose-response relationship was identified between increasing BG levels and the composite outcome among patients without diabetes(Figure S11).

Overall, few differences were observed in baseline characteristics in hospitalised COVID-19 patients with diabetes according to available HbA1c value(Table S5). Baseline differences among hospitalised COVID-19 patients but without diabetes are listed in Table S6.

In order to test if time affected our findings, we performed sensitivity analyses for the period from 3rd March to 1st August 2020 and from 1st August to 31st December 2020 according to diabetes status for both study outcomes, which all yielded similar results as the main analyses(data not shown). To test if time of HbA1c collection affected our findings, we performed sensitivity analyses using HbA1c measurements collected at<3 months prior to index date according to diabetes status. These analyses yielded the same results as the main analyses for both study outcomes, respectively(data not shown).

Discussion

In this Danish registry-based cohort study, we examined the association between varying HbA1c levels and the risk of severe COVID-19 infection, ICU admission, or all-cause mortality among COVID-19 patients with and without diabetes. This study yielded two principal findings. First, among COVID-19 patients with diabetes, both high HbA1c levels>64mmol/mol and low HbA1c levels<48mmol/mol were associated with increased risk of all-cause mortality and the composite of severe COVID-19 infection, ICU admission, or all-cause mortality, compared with HbA1c 59-64mmol/mol. Second, among COVID-19 patients without diabetes, HbA1c<31mmol/mol and HbA1c 42-47mmol/mol were associated with elevated risk of the composite outcome, compared with HbA1c 31-36mmol/mol.

A meta-analysis by Mantovani et al. showed that COVID-19 patients with pre-existing diabetes were associated with two-fold increased risk of critical COVID-19 illness requiring admission to an ICU(n=22 studies)and threefold increased risk of in-hospital mortality(n=15 studies), compared with patients without diabetes.(10)In accordance with the findings of Mantovani et al., the current study highlights that patients with dysregulated diabetes(i.e.,>64mmol/mol)are also more likely to experience adverse outcomes in a COVID-19 setting, compared with patients with well-regulated diabetes or without diabetes. In agreement with our study findings, hyperglycaemia was also independently associated with COVID-19-related mortality in a population-based cohort study by Holman et al. that examined risk factors for COVID-19-related mortality among people with diabetes.(18)Among 264,390 people with type 1 diabetes, only HbA1c≥86mmol/mol(10.0%)was associated with an increased mortality rate, compared with HbA1c 48-53mmol/mol. Notably, among 2,874,020 people with type 2 diabetes, a graded relationship was identified between increasing HbA1c≥59mmol/mol and mortality.(18)Collectively, both the present study and the study by Holman et al. showed that hyperglycaemia measured by HbA1c

is a strong predictor of mortality, which may partly be due to the fact that people with poor glycaemic control are at greater risk of many serious infections.(35, 36)Moreover, in line with previous COVID-19 studies, patients with diabetes and poorly regulated HbA1c or hyperglycaemia have higher levels of inflammatory markers, compared with patients without diabetes or with normoglycaemia.(11-16)Similarly, we also found higher CRP values to be correlated with higher HbA1c, although not statistically significant, which could suggest a more severe course of infection among patients with diabetes and high HbA1c levels.

In the current study, HbA1c levels>64mmol/mol were associated with both increased risk of all-cause mortality and the composite of severe COVID-19 infection, ICU admission, or all-cause mortality among COVID-19 patients with diabetes. Conversely, a nationwide observational study by Cariou et al.(CORONADO study)of 1,317 hospitalised COVID-19 patients with diabetes demonstrated no association between HbA1c and mortality or the composite of tracheal intubation for mechanical ventilation and mortality within 7 days of admission, even with the highest values of HbA1c>75mmol/mol(9.0%).(17)Correspondingly, a study by Myers et al. of 4413 COVID-19 patients with type 2 diabetes reported no difference in mortality between those with HbA1c≥75mmol/mol and HbA1c<75mmol/mol.(37)The findings of the CORONADO study conflict with the present study and could be attributed to missing HbA1c measurements among one-third of patients as well as a very short 7-day observation period. The findings of the current study suggest that poorly regulated HbA1c among patients with diabetes may affect the severity of COVID-19, leading to ICU admission and mortality. In support of the latter notion, a small study by Smith et al. demonstrated a higher prevalence of intubation among hospitalised COVID-19 patients with HbA1c≥58mmol/mol, compared with HbA1c<58mmol/mol.(38)Furthermore, a recent meta-analysis by Prattichizzo et al. demonstrated that HbA1c was linearly associated with a higher

COVID-19-related-mortality or worsening.(39)However, the small number and the large heterogenicity of the studies performed to date should be taken into consideration. The meta-analysis calls for more studies as no definitive conclusions can be drawn concerning the role of glycaemic control in providing COVID-19 prognosis or mortality among patients with diabetes.

In the present study, COVID-19 patients with diabetes and HbA1c<48mmol/mol had increased risk of all-cause mortality and the composite outcome. Similarly, a study by Holman et al. reported a significantly higher COVID-19-related mortality among patients with type 2 diabetes and HbA1c<48mmol/mol, compared with HbA1c 48-53mmol/mol, but outcomes other than mortality were not examined, as done in the current study.(18)A retrospective study by Yuan et al. concluded on that both lower HbA1c levels 10-30mmol/mol(3.0-4.9%)and higher HbA1c levels≥42mmol/mol were associated with increased all-cause mortality, compared with HbA1c 31-41mmol/mol, in a pooled population of 922 COVID-19 patients with and without diabetes.(19)Notably, both the present study and the study by Yuan et al. demonstrated that while lower HbA1c levels were associated with greater mortality, lower BG levels were associated with decreased mortality. However, patients with HbA1c 10-30mmol/mol had higher fasting BG in the study by Yuan et al., which may be due to power issue as the HbA1c group only included 14 patients. In the present study, BG increased with increasing HbA1c indicating that HbA1c is a sensitive and plausible marker of hyperglycaemia. Importantly, the study by Yuan et al. did not investigate varying HbA1c levels in a stratified analysis according to diabetes status, and outcomes such as severe COVID-19 infection and ICU admission were not examined. In the current study, a low HbA1c level as a risk factor for severe outcomes among COVID-19 patients with diabetes adds to the growing literature suggesting that tight glycaemic control or hypoglycaemia may lead to more severe outcomes. As investigated in previous studies in non-COVID-19 settings,(40, 41)a randomised clinical trial by Gerstein et al. reported a greater mortality among patients with type 2 diabetes randomised to receive intensive

therapy targeting HbA1c<42mmol/mol, compared with patients with type 2 diabetes receiving standard therapy(58-63mmol/mol)(7.5-7.9%)for 3.5 years.(40)Notably, the intensive-therapy group had significantly elevated rates of hypoglycaemia requiring assistance, compared with the standard-therapy group. Taken together, HbA1c may play an important role in predicting the prognosis of COVID-19 patients with and without diabetes.

Among patients without diabetes, we demonstrated that HbA1c levels<31mmol/mol, compared with HbA1c levels 31-36mmol/mol, were associated with increased risk of both all-cause mortality and the composite outcome. However, HbA1c 42-47mmol/mol was only associated with the composite outcome. In conformity with the HbA1c groups of the present study, a non-COVID-19 study by Selvin et al. reported a greater risk of all-cause mortality among patients with HbA1c<31mmol/mol, HbA1c 37-41mmol/mol, HbA1c 42-47mmol/mol, and HbA1c>48mmol/mol, compared with HbA1c 31-36mmol/mol.(4).Overall, HbA1c levels 39-47mmol/mol (5.7-6.5%)could be indicative of a prediabetic state according to ADA diagnostic criteria(28), who are susceptible to more adverse outcomes, or normoglycemia among patients without diabetes. In the current study, patients with HbA1c 42-47mmol/mol tended to be more comorbid and had a higher median age, which could also imply more severe clinical outcomes. A study by Vargas-Vásquez et al. of 317 hospitalised COVID-19 patients concluded that prediabetes(39-47mmol/mol)was associated with higher odds of severe COVID-19 infection, compared with patients with normoglycae-mia(<39mmol/mol).(42)Notably, other previous studies, in non-COVID-19 settings among patients without diabetes, have demonstrated that HbA1c levels in the range of 39-47mmol/mol or 42-47mmol/mol were associated with increased risk of all-cause mortality.(4, 6, 32, 43-45)Collectively, both low and high HbA1c levels may help identify hospitalised COVID-19 patients at greater risk for mortality and adverse outcomes. Accordingly, we recommend to measure the HbA1c level in all patients who get admitted to a hospital with a positive SARS-CoV-2 PCR test in

order to optimise treatment and improve patient outcomes. More studies are needed in order to elucidate the potential effect of varying HbA1c levels among COVID-19 patients with and without diabetes and the risk of severe COVID-19 infection, ICU admission, or all-cause mortality.

Study strengths and limitations

To the best of our knowledge, the current study is the first to provide large data on the association between varying HbA1c levels and adverse outcomes among hospitalised COVID-19 patients with and without diabetes. Due to the observational study design, no causal inference should be made from the findings in the present study, but rather interpreted as associations. Thus, we acknowledge the risk of residual confounding, although we tried to eliminate the effect of these. The risk of confounding by indication cannot be excluded as HbA1c is an independent risk factor for mortality regardless of COVID-19 infection. Moreover, we are also unable to determine why physicians decided to examine HbA1c levels in patients, which may have influenced the study findings.

The Danish National Health Service system ensures equal access for all Danish citizens irrespective of socioeconomic status, funded by taxes. Moreover, the study is based on large Danish nationwide registries of high quality and completeness. However, risk of selection bias cannot be excluded based on available HbA1c measurements gathered from the Clinical Laboratory Information System. Thus, caution needs to be taken when extrapolating the present findings to other populations with COVID-19. The median age of admission for the current study population was 73.9 years, which is slightly older than the remainder of the Danish population(median age:71.2 years)hospitalised with COVID-19 during the same time period. Thus, overall, according to Danish Health Authority, patients aged 70-79 years comprised the largest age group of hospitalised patients with confirmed COVID-19.(46)

HbA1c measurements were obtained up to 6 months prior to index date, which may have influenced our findings, although sensitivity analyses using HbA1c levels gathered up to 3 months before index date yielded the same results as the main analyses. Finally, we were not able to confidently distinguish type 1 and type 2 diabetes, which may have influenced our study findings.

Conclusion

In this registry-based observational study, we demonstrated that tightly regulated diabetes(HbA1c<48mmol/mol)and severely dysregulated diabetes(HbA1c>64mmol/mol)were associated with both increased risk of all-cause mortality and the composite outcome of severe COVID-19 infection, ICU admission, or all-cause mortality, compared with HbA1c levels 59-64mmol/mol among patients with COVID-19. Among patients without diabetes, HbA1c levels<31mmol/mol and 42-47mmol/mol were associated with greater risk of the composite outcome. Collectively, in a COVID-19 setting, HbA1c is an important marker to identify patients at risk of all-cause mortality and adverse outcomes among patients with and without diabetes.

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Conflict of Interest: none declared

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Data availability: The data that support the findings of this study are available from Statistics Denmark but are not publicly available due to Danish legislation on data protection.

Contribution statement: A.A. performed the main statistical coding, analysed the data, interpreted the results, and wrote the manuscript. P.E.W, L.K. and C.T.P contributed to the primary study conception, design and interpretation of the results. J.H.B and T.A.G contributed to the statistical analyses and interpretation of results. The manuscript is reviewed and revised critically for important intellectual content by all authors. The final version of the manuscript is approved by all authors. A.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline characteristics according to diabetes status

		Total, N(%) (n=3295)	**Patients without diabetes, N(%) (N=2117)**	**Patients with diabetes, N(%) (N=1178)**	**p-value**
Sex (male)		1,853 (56.2)	1114 (52.6)	739 (62.7)	<0.001
Age median [IQR]†(years)		73.9 [62.0, 81.8]	73.6 [59.9, 82.7]	74.3 [64.9, 80.8]	0.26
HbA1c median [IQR]† (mmol/mol)		40 [36, 48]	37 [34, 40]	54 [47, 65]	<0.001
Blood glucose median [IQR]† (mmol/l)		6.9 [5.9,8.8]	6.3 [5.7,7.4]	9.3 [7.0,12.1]	<0.001
	Missing	999	620	379	
C-reactive protein median [IQR]†		25 [4.3,72.0]	21 [4,66]	30 [6.7, 86.0]	<0.001
	Missing	468	256	212	
Leukocytes median [IQR]†		6.8 [5.2,9.0]	6.7 [5.0,8.7]	7.2[5.5,9.2]	<0.001
	Missing	340	159	181	
Comorbidity, N(%)					
Ischaemic heart disease		759 (23.0)	404 (19.1)	355 (30.1)	<0.001
Heart failure		338 (10.3)	183 (8.6)	155 (13.2)	<0.001
Previous myocardial infarction		300 (9.1)	172 (8.1)	128 (10.9)	0.01
Atrial fibrillation		562 (17.1)	346 (16.3)	216 (18.3)	0.16
Stroke		316 (9.6)	190 (9.0)	126 (10.7)	0.12
Peripheral artery disease		136 (4.1)	72 (3.4)	64 (5.4)	0.007

Hypertension		1,444 (43.8)	770 (36.4)	674 (57.2)	<0.001
Chronic obstructive pulmonary disease		344 (10.4)	207 (9.8)	137 (11.6)	0.11
Cancer		646 (19.6)	427 (20.2)	219 (18.6)	0.29
Liver disease		128 (3.9)	72 (3.4)	56 (4.8)	0.067
Rheumatic disease		258 (7.8)	163 (7.7)	95 (8.1)	0.76
Chronic renal disease		385 (11.7)	150 (7.1)	235 (19.9)	<0.001
Lipidaemia		470 (14.3)	290 (13.7)	180 (15.3)	0.23
Concomitant pharmacotherapy, N(%)					
Antidiabetics		951 (28.9)	0 (0.0)	951 (80.7)	<0.001
Insulin		395 (12.0)	0 (0.0)	395 (33.5)	<0.001
Oral glucose-lowering drugs		801 (24.3)	0 (0.0)	801 (68.0)	<0.001
Cholesterol-lowering drugs		1,344 (40.8)	628 (29.7)	716 (60.8)	<0.001
Beta-blockers		927 (28.1)	494 (23.3)	433 (36.8)	<0.001
Calcium channel blockers		786 (23.9)	440 (20.8)	346 (29.4)	<0.001
Renin angiotensin system inhibitors		1,375 (41.7)	738 (34.9)	637 (54.1)	<0.001
Thiazide		319 (9.7)	204 (9.6)	115 (9.8)	0.96
Loop diuretics		776 (23.6)	393 (18.6)	383 (32.5)	<0.001
Spironolactone		181 (5.5)	94 (4.4)	87 (7.4)	<0.001
Digoxin		144 (4.4)	83 (3.9)	61 (5.2)	0.11
Aspirin		542 (16.4)	280 (13.2)	262 (22.2)	<0.001
Adenosine diphosphate receptor inhibitors		407 (12.4)	245 (11.6)	162 (13.8)	0.077
Anticoagulants		683 (20.7)	407 (19.2)	276 (23.4)	0.005

†IQR, interquartile range

Table 2. Baseline characteristics according to HbA1c groups among COVID-19 patients with diabetes

		Total, N(%) (N=1178)	**HbA1c <48 mmol/mol, N(%) (N=317)**	**HbA1c 48-53 mmol/mol, N(%) (N=272)**	**HbA1c 54-58 mmol/mol, N(%) (N=141)**	**HbA1c 59-64 mmol/mol, N(%) (N=136)**	**HbA1c >64 mmol/mol, N(%) (N=312)**	**p-value**
			HbA1c <6.5%	**HbA1c 6.5-7.0%**	**HbA1c 7.1-7.5%**	**HbA1c 7.5-8.0%**	**HbA1c >8.0%**	
Sex (Male)		739 (62.7)	191 (60.3)	185 (68.0)	79 (56.0)	86 (63.2)	198 (63.5)	0.14
Age median [IQR]†(years)		74.3 [64.9, 80.8]	75.5 [68.0, 81.4]	75.3 [65.3, 80.3]	73.4 [64.6, 80.7]	74.1 [67.2, 81.2]	72.8 [60.6, 79.9]	0.01
HbA1c median [IQR]† (mmol/mol)		54 [47, 65]	43 [39, 45]	50 [49, 52]	55 [55, 57]	61 [60, 63]	75 [69, 84]	<0.001
Blood glucose median [IQR]† (mmol/l)		9.3 [7.0, 12.1]	7.6 [6.4, 9.5]	8.7 [7.1, 11.3]	9 [7.2, 11.8]	9.9 [8.3, 11.9]	11.6 [8.8, 15.4]	<0.001
	Missing	379	108	102	44	42	83	
C-reactive protein median [IQR]†		30 [6.7, 86.0]	25 [6, 80]	39 [7, 95]	24.5 [6.5, 63.0]	24.5 [6.2, 77.2]	30.5 [7.8, 89.0]	0.50
	Missing	212	48	53	35	24	52	

Leukocytes median [IQR]†		7.2 [5.5, 9.2]	7.3 [5.3, 9.7]	7 [5.4, 9.2]	7.2 [5.6, 9.1]	6.7 [5.5, 9.3]	7.2 [5.8, 9.1]	0.81
	Missing	181	35	54	29	19	44	
Comorbidity, N(%)								
Ischaemic heart disease		355 (30.1)	106 (33.4)	75 (27.6)	39 (27.7)	47 (34.6)	88 (28.2)	0.32
Heart failure		155 (13.2)	43 (13.6)	29 (10.7)	17 (12.1)	19 (14.0)	47 (15.1)	0.60
Previous myocardial infarction		128 (10.9)	34 (10.7)	31 (11.4)	13 (9.2)	15 (11.0)	35 (11.2)	0.97
Atrial fibrillation		216 (18.3)	72 (22.7)	44 (16.2)	20 (14.2)	23 (16.9)	57 (18.3)	0.15
Stroke		126 (10.7)	37 (11.7)	37 (13.6)	11 (7.8)	14 (10.3)	27 (8.7)	0.25
Peripheral artery disease		-	15 (4.7)	15 (5.5)	≤3	14 (10.3)	17 (5.4)	-
Hypertension		674 (57.2)	180 (56.8)	155 (57.0)	80 (56.7)	82 (60.3)	177 (56.7)	0.96
Chronic obstructive pulmonary disease		137 (11.6)	45 (14.2)	31 (11.4)	10 (7.1)	20 (14.7)	31 (9.9)	0.14

Cancer		219 (18.6)	71 (22.4)	50 (18.4)	25 (17.7)	26 (19.1)	47 (15.1)	0.22
Liver disease		-	18 (5.7)	11 (4.0)	7 (5.0)	≤3	17 (5.4)	-
Rheumatic disease		95 (8.1)	35 (11.0)	16 (5.9)	14 (9.9)	7 (5.1)	23 (7.4)	0.093
Chronic renal disease		235 (19.9)	67 (21.1)	32 (11.8)	22 (15.6)	31 (22.8)	83 (26.6)	<0.001
Lipidaemia		180 (15.3)	55 (17.4)	36 (13.2)	23 (16.3)	28 (20.6)	38 (12.2)	0.12
Concomitant pharmacotherapy, N(%)								
Antidiabetics		951 (80.7)	226 (71.3)	185 (68.0)	129 (91.5)	122 (89.7)	289 (92.6)	<0.001
Insulin		395 (33.5)	48 (15.1)	49 (18.0)	52 (36.9)	66 (48.5)	180 (57.7)	<0.001
Oral glucose-lowering drugs		801 (68.0)	206 (65.0)	161 (59.2)	109 (77.3)	101 (74.3)	224 (71.8)	<0.001
Cholesterol-lowering drugs		716 (60.8)	186 (58.7)	162 (59.6)	89 (63.1)	92 (67.6)	187 (59.9)	0.42
Beta-blockers		433 (36.8)	128 (40.4)	105 (38.6)	47 (33.3)	53 (39.0)	100 (32.1)	0.19

Calcium channel blockers		346 (29.4)	92 (29.0)	76 (27.9)	39 (27.7)	48 (35.3)	91 (29.2)	0.59
Renin angiotensin system inhibitors		637 (54.1)	159 (50.2)	149 (54.8)	75 (53.2)	85 (62.5)	169 (54.2)	0.20
Thiazide		115 (9.8)	26 (8.2)	33 (12.1)	18 (12.8)	14 (10.3)	24 (7.7)	0.23
Loop diuretics		383 (32.5)	105 (33.1)	83 (30.5)	45 (31.9)	45 (33.1)	105 (33.7)	0.94
Spironolactone		87 (7.4)	33 (10.4)	15 (5.5)	10 (7.1)	8 (5.9)	21 (6.7)	0.18
Digoxin		-	20 (6.3)	13 (4.8)	10 (7.1)	≤3	16 (5.1)	-
Aspirin		262 (22.2)	65 (20.5)	57 (21.0)	31 (22.0)	38 (27.9)	71 (22.8)	0.49
Adenosine diphosphate receptor inhibitors		162 (13.8)	42 (13.2)	42 (15.4)	16 (11.3)	20 (14.7)	42 (13.5)	0.82
Anticoagulants		276 (23.4)	90 (28.4)	60 (22.1)	31 (22.0)	32 (23.5)	63 (20.2)	0.16

[†]IQR, interquartile range

Table 3. Baseline characteristics according to HbA1c groups among COVID-19 patients without diabetes

		Total, N(%) (N=2117)	**HbA1c <31 mmol/mol, N(%) (N=142)**	**HbA1c 31-36 mmol/mol, N(%) (N=773)**	**HbA1c 37-41 mmol/mol, N(%) (N=831)**	**HbA1c 42-47 mmol/mol, N(%) (N=371)**	**p-value**
			HbA1c <5.0%	**HbA1c 5.0-5.4%**	**HbA1c 5.5-5.9%**	**HbA1c 6.0-6.5%**	
Sex (Male)		1,114 (52.6)	71 (50.0)	380 (49.2)	462 (55.6)	201 (54.2)	0.060
Age median [IQR]†(years)		73.6 [59.9, 82.7]	69 [52.2, 82.9]	71 [55.1, 81.3]	74.5 [62.5, 83.0]	75 [67.2, 83.2]	<0.001
HbA1c median [IQR]† (mmol/mol)		37 [34, 40]	29 [27, 30]	34 [33, 35]	39 [38, 40]	44 [42, 45]	<0.001
Blood glucose median [IQR]† (mmol/l)		6.3 [5.7, 7.4]	6 [5.2, 6.8]	6.1 [5.5, 7.0]	6.5 [5.7, 7.5]	6.9 [6, 8]	<0.001
	Missing	620	48	225	238	109	
C-reactive protein median [IQR]†		21 [4, 66]	13 [4, 44]	14 [4.0, 60.5]	23 [4, 69]	34 [6.0, 80.8]	<0.001
	Missing	256	13	93	117	33	

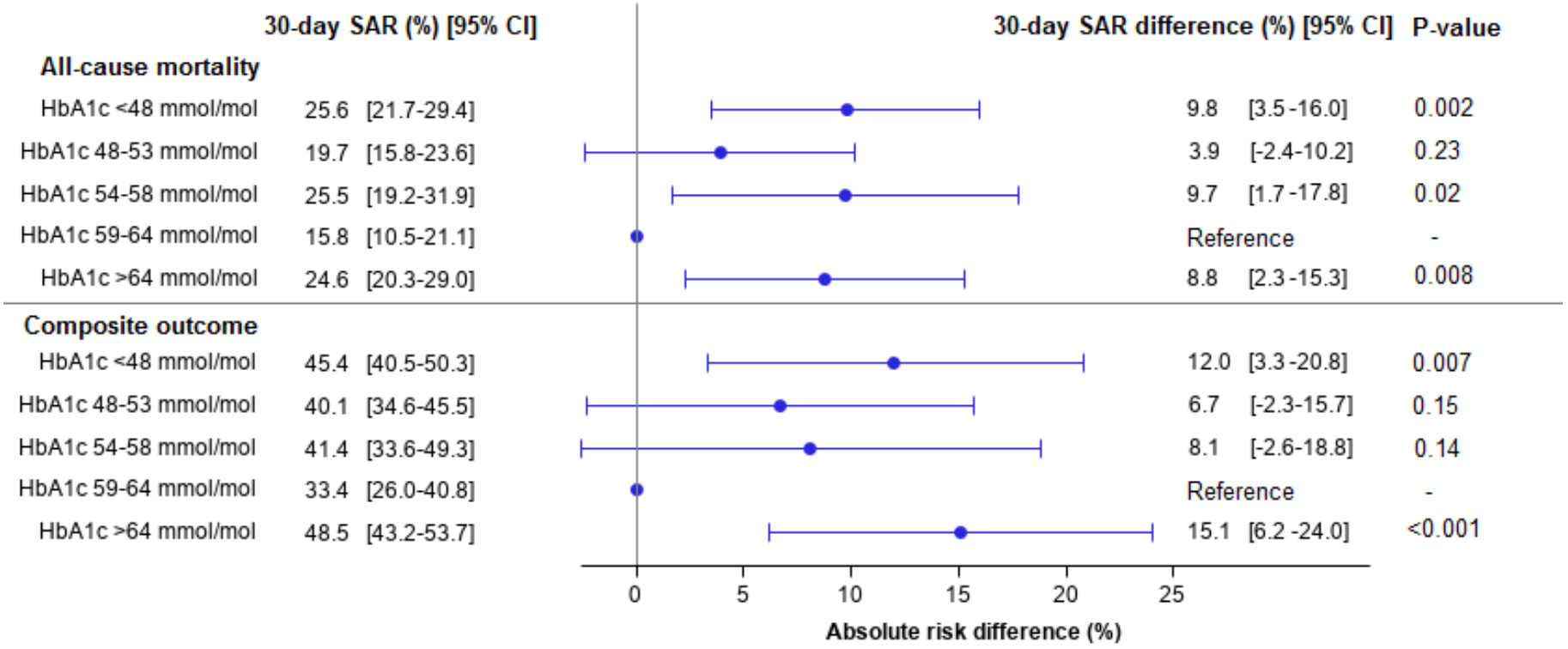
Leukocytes median [IQR]†		6.7 [5.0, 8.7]	6.7 [4.7, 8.1]	6.4 [4.9, 8.4]	6.8 [5.1, 8.9]	7.1 [5.4, 9.0]	0.03
	Missing	159	9	51	81	18	
Comorbidity, N(%)							
Ischaemic heart disease		404 (19.1)	18 (12.7)	107 (13.8)	183 (22.0)	96 (25.9)	<0.001
Heart failure		183 (8.6)	11 (7.7)	54 (7.0)	72 (8.7)	46 (12.4)	0.02
Previous myocardial infarction		172 (8.1)	10 (7.0)	42 (5.4)	73 (8.8)	47 (12.7)	<0.001
Atrial fibrillation		346 (16.3)	26 (18.3)	108 (14.0)	152 (18.3)	60 (16.2)	0.12
Stroke		190 (9.0)	13 (9.2)	63 (8.2)	86 (10.3)	28 (7.5)	0.32
Peripheral artery disease		72 (3.4)	10 (7.0)	24 (3.1)	22 (2.6)	16 (4.3)	0.04
Hypertension		770 (36.4)	41 (28.9)	230 (29.8)	315 (37.9)	184 (49.6)	<0.001
Chronic obstructive pulmonary disease		207 (9.8)	16 (11.3)	56 (7.2)	85 (10.2)	50 (13.5)	0.008
Cancer		427 (20.2)	36 (25.4)	139 (18.0)	170 (20.5)	82 (22.1)	0.15

Liver disease		72 (3.4)	12 (8.5)	30 (3.9)	16 (1.9)	14 (3.8)	<0.001
Rheumatic disease		163 (7.7)	9 (6.3)	62 (8.0)	57 (6.9)	35 (9.4)	0.41
Chronic renal disease		150 (7.1)	10 (7.0)	53 (6.9)	63 (7.6)	24 (6.5)	0.90
Lipidaemia		290 (13.7)	12 (8.5)	77 (10.0)	135 (16.2)	66 (17.8)	<0.001
Concomitant pharma-cotherapy, N(%)							
Cholesterol-lowering drugs		628 (29.7)	24 (16.9)	170 (22.0)	284 (34.2)	150 (40.4)	<0.001
Beta-blockers		494 (23.3)	34 (23.9)	143 (18.5)	203 (24.4)	114 (30.7)	<0.001
Calcium channel block-ers		440 (20.8)	19 (13.4)	142 (18.4)	195 (23.5)	84 (22.6)	0.008
Renin angiotensin sys-tem inhibitors		738 (34.9)	38 (26.8)	227 (29.4)	297 (35.7)	176 (47.4)	<0.001
Thiazide		204 (9.6)	6 (4.2)	66 (8.5)	89 (10.7)	43 (11.6)	0.04
Loop diuretics		393 (18.6)	36 (25.4)	104 (13.5)	149 (17.9)	104 (28.0)	<0.001
Spironolactone		94 (4.4)	7 (4.9)	28 (3.6)	36 (4.3)	23 (6.2)	0.26
Digoxin		83 (3.9)	5 (3.5)	26 (3.4)	34 (4.1)	18 (4.9)	0.66

Aspirin		280 (13.2)	17 (12.0)	82 (10.6)	109 (13.1)	72 (19.4)	<0.001
Adenosine diphosphate receptor inhibitors		245 (11.6)	20 (14.1)	78 (10.1)	96 (11.6)	51 (13.7)	0.24
Anticoagulants		407 (19.2)	27 (19.0)	127 (16.4)	171 (20.6)	82 (22.1)	0.077

[†]IQR, interquartile range

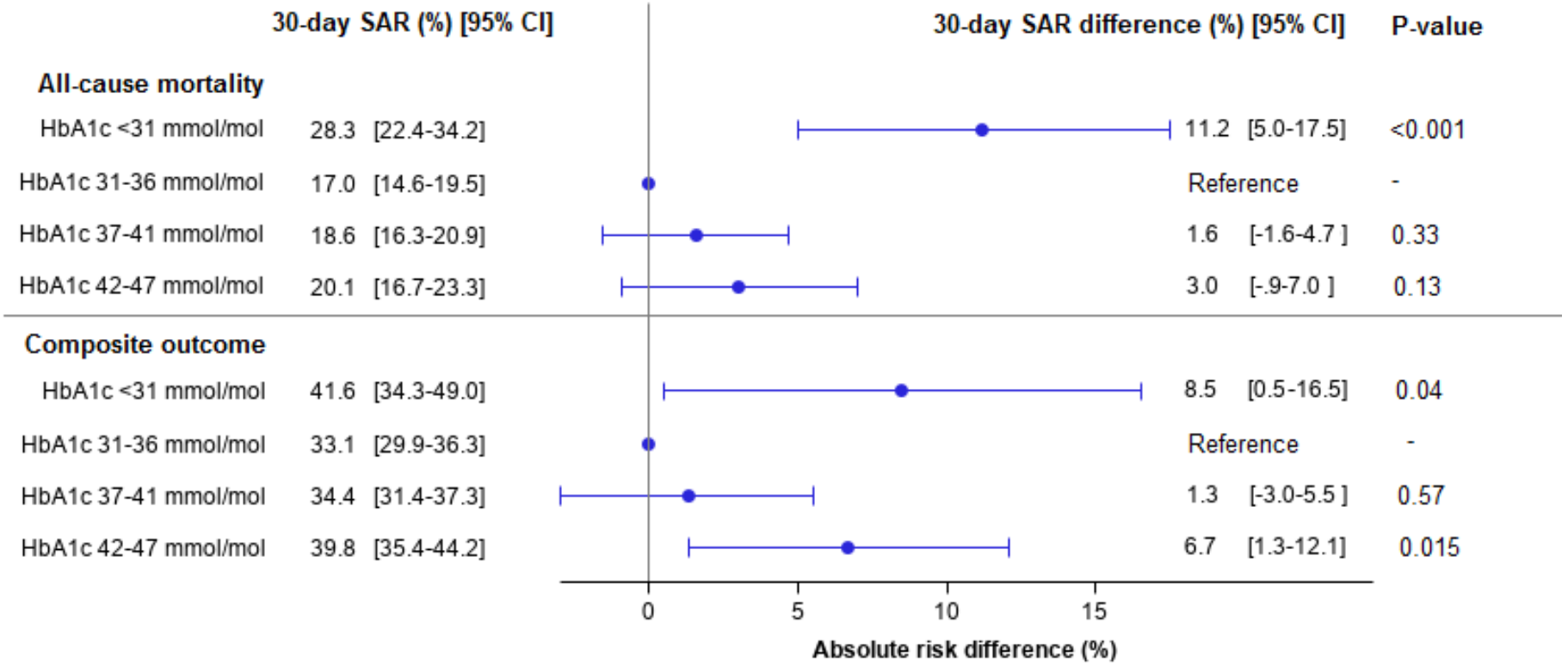
Fig. 1. Standardised 30-day absolute risks and standardised 30-day absolute risk differences for all-cause mortality and a composite of severe COVID-19 infection, admission to intensive care unit, or all-cause mortality according to HbA1c level among patients with diabetes



SAR, Standardised absolute risk

Standardised to age, sex, history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, hypertension, chronic obstructive pulmonary disease, cancer, chronic renal disease, and use of cholesterol-lowering drugs, beta-blockers, calcium channel blockers, renin-angiotensin system inhibitors, aspirin, and anticoagulants.

Fig. 2. Standardised 30-day absolute risks and standardised 30-day absolute risk differences for all-cause mortality and a composite of severe COVID-19 infection, admission to intensive care unit, or all-cause mortality according to HbA1c level among patients without diabetes



SAR, Standardised absolute risk

Standardised to age, sex, history of ischaemic heart disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, hypertension, chronic obstructive pulmonary disease, cancer, chronic renal disease, and use of cholesterol-lowering drugs, beta-blockers, calcium channel blockers, renin-angiotensin system inhibitors, aspirin, and anticoagulants.