Admission Blood Glucose Level and Its Association With Cardiovascular and Renal Complications in Patients Hospitalized With COVID-19

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Abstract

Objective: Investigate the association between admission blood glucose levels and risk of in-hospital cardiovascular and renal complications.

Research Design and Methods: A multicentre, prospective study of 36269 adults hospitalised with COVID-19 between 06.02.2020–16.03.2011 (total n before exclusions:143266). Logistic regression models explored associations between admission glucose level (mmol/l and mg/dL) and odds of in-hospital complications including heart failure, arrhythmia, cardiac ischaemia, cardiac arrest, coagulation complications, stroke and renal injury. Non-linearity was investigated using restricted cubic splines. Interaction models explored whether associations between glucose levels and complications were modified by clinically relevant factors.

Results*:* Cardiovascular and renal complications occurred in 10421 (28.7%) patients; median admission glucose level was 6.7mmol/l (IQR:5.8,8.7; 120.6mg/dL(104.4,156.6)). Accounting for confounders, for all complications except cardiac ischaemia and stroke there was a non-linear association between glucose and cardiovascular and renal complications. For example, odds of heart failure, arrhythmia, coagulation complications and renal injury decreased to a nadir at 6.4(115mg/dL), 4.9(88.2mg/dL), 4.7(84.6mg/dL) and 5.8(104.4mg/dL) mmol/l, respectively and increased thereafter until 26.0(468mg/dL), 50.0(900mg/dL), 8.5(153mg/dL) and 32.4(583.2mg/dL) mmol/l. Compared to 5 mmol/l (90mg/dL), odds ratios at these glucose levels were 1.28 (95%CI: 0.96,1.69) for heart failure, 2.23 (95%CI: 1.03,4.81) for arrhythmia, 1.59 (95%CI: 1.36,1.86) for coagulation complications and 2.42 (95%CI: 2.01,2.92) for renal injury. For most complications, a modifying effect of age was observed, with higher odds of complications at higher glucose levels for patients

younger than 69 years. Pre-existing diabetes status had a similar modifying effect on odds of complications, but evidence was strongest for renal injury, cardiac ischaemia and ‘any cardiovascular/renal complication’.

Conclusions: Increased odds of cardiovascular or renal complications were observed for admission glucose levels indicative of both hypo- and hyperglycaemia. Admission glucose could be used as a marker for risk stratification of high-risk patients. Further research should evaluate interventions to optimize admission glucose on improving COVID-19 outcomes.

As of December 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 267 million people and claimed over 5.2 million lives worldwide. After infection, the course of the disease (COVID-19) varies, ranging from asymptomatic mild infection to severe complications and death. People who require hospital admission have the worse outcomes, with a mortality risk of 10-26% in the USA and the UK.(1; 2)

Individuals with certain chronic comorbidities, e.g., obesity, hypertension, cardiovascular disease and diabetes, have increased susceptibility to severe COVID-19(3; 4), with over 25% of patients hospitalised with COVID-19 having at least one of these comorbidities. Diabetes in particular has been shown to increase the risk of adverse outcomes in individuals with COVID-19(4-6). A study of over 61 million people in England reported that both type 1 and 2 diabetes were associated with a more than three- and twofold increase in the odds of COVID-19 related in-hospital mortality, respectively(7). Another study also showed that pre-admission HbA1c was associated with an increased risk of in-hospital COVID-19-related mortality(8), while a positive relationship between plasma glucose on admission and in-hospital COVID-19 mortality has also been observed (9). These findings of heightened risks of adverse outcomes in individuals with high glucose levels are expected given the hyperglycaemia-induced disruptions to the immune system which have been observed(11). Conversely, an overly intensive glycaemic control may lead to severe hypoglycemia, which has also been associated with an increased risk of mortality in non-COVID-19 illness(12; 13). As such, it is vital to understand how the risk for adverse COVID-19-related outcomes changes across the range of the glucose spectrum.

In addition to the baseline risk associated with cardio-metabolic conditions such as diabetes, recent studies have shown that COVID-19 can cause acute cardiovascular injury including arrhythmias, cardiac arrest, myocardial infarction and heart failure(14; 15). These insults can in turn lead to chronic cardiovascular damage or death, even in those without existing cardiovascular disease(16; 17). The mechanisms linking COVID-19 with cardiovascular complications are multiple and include the release of cytokines (“cytokine storm”), dysregulation of the renin-angiotensin-aldosterone-system (RAAS) and coagulation systems and plaque rupture during the acute infection phase(18). However it has been suggested that the diabetes-related changes to the immune system and RAAS, namely an imbalanced expression of angiotensin-converting enzyme 2 (ACE2), paired with inflammation, oxidative stress and endothelial dysfunction may contribute to an increased vascular permeability and/or cytokine storm (22; 23), thus providing a mechanism underpinning the increased risk of cardiovascular dysfunction observed in these patient groups.

Because people with hyperglycaemia often have a combination of high risk characteristics, e.g., older age, obesity, ethnic minority status, it is important to understand how these characteristics interact to modify the risk of COVID-19 complications in people with hyperglycaemia . In order to unpick the relative importance of the various factors contributing to adverse COVID-19 prognosis, large, well-phenotyped samples are required, with good coverage of these contributing factors. Accordingly, this study investigated the association between glucose levels on admission and the risk of in-hospital cardiovascular and renal complications, in a large nationally representative sample of people hospitalised with COVID-19. Furthermore, we investigated whether the associations between glucose levels and

complications were different by age, sex, ethnicity, obesity and pre-existing diabetes diagnoses.

Research Design and Methods

Population

We used data from ISARIC WHO Clinical Characterisation Protocol UK (CCP-UK) for Severe Emerging Infection. Developed by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) and the World Health Organisation in 2009, the protocol was reactivated on 17th January 2020 in response to SARS-CoV-2 pandemic. The protocol and all study materials for this actively recruiting prospective cohort can be accessed online (https://isaric4c.net). The study was approved by the South Central - Oxford C Research Ethics Committee in England (Ref: 13/SC/0149), and by the Scotland Research Ethics Committee (Ref: 20/SS/0028). The ISARIC WHO CCP-UK study was registered at https://www.isrctn.com/ISRCTN66726260 and designated as an Urgent Public Health Research Study by NIHR.

Sample

Patients aged ≥ 18 years who were admitted to hospital between 6th February 2020 and 16th March 2021 with a confirmed COVID-19 diagnosis were included. Patients were excluded if they had missing outcome or sex data or were recipients of an organ transplant, immunosuppression therapies or had rare diseases likely to significantly increase the risk of infections (such as severe combined immunodeficiency). As of 16th March 2021, 143 266 patients were included in the CCP-UK study of which 140 685 (98.2%) had a confirmed diagnosis of COVID-19. Of these, 35 601 (25.3%) had the relevant outcome, exposure and covariate data for analysis (total n excluded= 107 665 (75.2%). Supplementary Figure 1 shows how the

final sample was derived. Differences in key clinical characteristics between those included and excluded are provided in Supplementary Table 1.

Data were directly transcribed from routine healthcare into case report forms hosted on a REDCap database (Research Electronic Data Capture, https://projectredcap.org). Data collection was undertaken by research nurses, administrators and medical students. Detailed demographic and clinical data were collected on admission, with follow-up data on clinical care collected at day 3, 6, and 9 and discharge or status at 28 days if not discharged.

Exposures

Blood glucose levels were assessed via a random venous glucose sample collected from patients on hospital admission by a healthcare professional. Blood samples were analysed in NHS clinical laboratories and usual processing standard operating procedures were followed. Blood glucose was available as continuous variable and measured in mmol/l. For descriptive purposes, individuals were classified as having hypo- (≤3.9 mmol/l; <70.2 mg/dL), normo-(4-11 mmol/l; 72-198 mg/dL) or hyperglycaemia (≥11.1 mmol/l; 199.8 mg/dL) based on their random admission glucose(24).

Covariates

Sex as recorded at birth, was coded as female/ male. Age was measured to the nearest year using the difference between date of birth and the admission date. For this analysis and due to low numbers, ethnicity was coded into four distinct groups, reflecting the most prevalent ethnic groups in the 2011 census in England and Wales (25), as follows: White, South Asian, Black and Other (East and West Asian, Arab, Latin American, Aboriginal/First Nations, Other). Obesity was coded as yes/no based

on clinical assessment from the attending clinician. This assessment was based on an objective measurement of obesity, such as body mass index (≥BMI of 30kg/m^2) or abdominal girth, or on subjective clinical judgment. Pre-existing diabetes status (yes/no) was based on an existing clinician diagnosis of the condition in patient records.

Outcomes

In-hospital cardiovascular complications were extracted from routine clinical records by local investigators and included stroke, heart failure, arrhythmia, cardiac ischaemia, cardiac arrest and coagulation disorders (abnormal coagulation identified by abnormal prothrombin time or activated partial thromboplastin time). Due to the intrinsic nature of cardiovascular and kidney dysfunction we also included 'acute renal injury' in the list of complications. A dichotomous variable representing *'any'* cardiovascular/renal complication was derived to identify patients with at least one of the in-hospital complications listed. Further information regarding how these variables were defined can be found in the Supplementary Material.

Statistical analysis

Descriptive statistics are presented as number (%) and median (25^{th} and 75^{th} centiles) for categorical and continuous data, respectively.

We used logistic regression models to investigate whether the odds of in-hospital complications and mortality differed across admission glucose levels. Nonlinear associations were investigated using restricted cubic splines, which were developed specific to each outcome and unadjusted for covariates (model 1). We tested spline models with 2, 3, 4 and 5 knots, located at equally spaced centiles across the glucose distribution. The Bayesian Information Criterion (BIC) was used to select

between models with a different number of knots, with a lower BIC indicative of improved fit. To aid interpretation, splines were centered on a reference value 5 mmol/l. In subsequent models we progressively adjusted for key demographic variables including age (entered as a restricted cubic spline), sex and ethnicity (model 2); obesity status (model 3); and diabetes status (model 4). In a final model, we adjusted for oxygen saturation at admission as a proxy for COVID-19 severity (model 5).

Using model 5, we then explored interactions to identify whether the association between admission glucose and each outcome was modified by clinically relevant factors, namely sex, ethnicity, age, obesity and pre-existing diabetes status. To aid interpretation, interactions with age were performed with a dichotomised age variable (based on the mean of the sample, 69 years). Interactions were formally tested using the likelihood ratio test for nested models, comparing models with and without the interaction term; $p<0.05$ indicated whether the interaction terms should be retained.

As supplementary analyses, we investigated the associations using the categorical hypo-/normo-/hyperglycaemia variable in logistic regression models, with patients categorised as having normoglycaemia as the reference. We also repeated the analyses using a variable representing ‘any cardiovascular/renal complication or all-cause death’ to account for the competing risk of death in assessing in-hospital complications.

All analyses were conducted in Stata version 16 (StataCorp. 2017. Stata Statistical Software: Release 16 College Station, TX: StataCorp). The statistical code for the analyses in this paper is publicly available at GitHub (repository URL: TBC).

Results

Descriptive statistics of the sample (n=35 601) are shown in Table 1. The sample comprised 20 591 males (56.8%), had a median age of 71 years (IQR: 57, 82) and 29 580 (81.6 %) of individuals were of 'White' ethnicity (Table 1). Median glucose level on admission was 6.7 mmol/l (IQR: 5.8, 8.7; 120.6 mg/dL (104.4, 156.6)). More than a quarter of the sample experienced a cardiovascular or renal complication whilst in hospital (n=10 421, 28.7%), of which 5 729 (55.0%) patients survived and 4 691 (45.0%) died. Patient characteristics of the sample included vs excluded from the analysis are shown in Supplementary Table 1. Imbalances between the samples were observed, with the included sample being younger (68.6 years vs 70.8 years), more likely to be from a Black or minority ethnic group (18.4% vs 14.4%) and have a pre-existing diabetes diagnosis (25.4% vs 19.1%). Patient characteristics of those who, at 28 days after admission, had been discharged vs remained in hospital or transferred to another facility are provided in Supplementary Table 2. Imbalances were observed in age and number of cardiovascular/renal complications, with the group remaining in hospital/transferred to another facility being older (70.0 years vs 65.0 years) and experiencing a higher proportion of cardiovascular/renal complications (41.0% vs 19.5%) than those who had been discharged within 28 days.

Admission glucose and cardiovascular and renal complications

For all complications except cardiac ischaemia and stroke, there was a non-linear association between admission glucose and cardiovascular and renal complications (Figure 1). For heart failure, arrhythmia, coagulation complications and renal injury, the pattern of association with glucose, adjusted for all covariates (i.e., model 5), was

such that odds of experiencing the outcome decreased to a nadir at 6.4 (115 mg/dL), 4.9 (88.2 mg/dL), 4.7 (84.6 mg/dL) and 5.8 (104.4 mg/dL) mmol/l, respectively and increased thereafter. For heart failure, coagulation complications and renal injury, odds increased until 26.0 (468 mg/dL), 8.5 (153 mg/dL) and 32.4 (583.2 mg/dL) mmol/l, respectively, with a subsequent plateau, while odds of arrhythmia continued to increase until 50 mmol/l (900 mg/dL) Compared to 5 mmol/l (90 mg/dL), the odds ratios at these glucose levels were 1.28 (95% CI: 0.96, 1.69) for heart failure, 2.23 (95% CI: 1.03, 4.81) for arrhythmia, 1.59 (95% CI: 1.36, 1.86) for coagulation complications and 2.42 (95% CI: 2.01, 2.92) for renal injury. The association between glucose and the odds of experiencing cardiac arrest, cardiac ischaemia and stroke was characterised by increasing odds of the outcome with increasing admission glucose. For cardiac ischaemia and stroke, the increase in odds was linear across the glucose distribution, whereas for cardiac arrest, the rate of increase diminished at higher glucose values. Accordingly the odds of experiencing cardiac arrest, cardiac ischaemia and stroke at the 95th centile of admission glucose levels (i.e., 16.5 mmol/l or 297 mg/dL) were 2.06 (95% CI: 1.63, 2.59)), 1.51 (95% CI: 1.25, 1.82) and 1.35 (95% CI: 1.09, 1.68) times higher, respectively, compared to 5 mmol/l.

Effect modification by ethnicity, age, sex, obesity and diabetes status

Evidence for a modifying effect of age was observed consistently across all complications except heart failure and cardiac ischaemia(Figure 2). In general, this manifested in a greater effect size for the association between higher admission glucose levels and the complications, in those younger than 69 years of age, however at the very highest glucose levels, this association reversed for heart failure, cardiac arrest and coagulation complications, though confidence intervals at

these extreme values are wide and overlapping. At lower glucose levels (<5 mmol/l; 90 mg/dL), the pattern of effect modification across the complications was less consistent. There was also a consistent pattern of effect modification by diabetes status, though the strength of evidence varied across the complications. This pattern of modification was broadly characterised as, in all but the very high glucose values (i.e. >97.5th centile; 20.1 mmol/l; 361.6 mg/dL), a greater effect size for the association between higher admission glucose levels and the complications in those without a previous diagnosis of diabetes (Figure 3). Evidence was strongest for renal injury, cardiac ischaemia and the 'any cardiovascular/renal complication' variable. At the very highest glucose levels (i.e., >97.5th centile) and for heart failure, cardiac arrest, coagulation complications, renal injury and the 'any cardiovascular/renal complication' variable, the pattern of association between admission glucose and diabetes status reversed, however. The pattern of effect modification across the complications was less consistent at lower glucose levels (e.g., <5 mmol/l; 90 mg/dL). Evidence for a modifying effect of ethnicity was only found for heart failure and cardiac arrest, though a consistent pattern of modification was not observed across these complications (Supplementary Figure 2). We observed no evidence of a modifying effect of sex (Supplementary Figure 3) or obesity status (Supplementary Figure 4) on the relationship between admission glucose levels and any of the complications.

Supplementary analyses

Patient characteristics of individuals stratified by glycaemia status are provided in Supplementary Table 3 and the results of the analyses comparing the odds of each outcome in patients classified as having hypo- and hyperglycaemia (vs normoglycaemia) are shown in Supplementary Figure 5. Increased odds of

experiencing the complications were observed in patients classified as having hyperglycaemia and this finding was consistent across all of the complications. In addition, while point estimates for five of the eight complications (any cardiovascular/renal complication, cardiac arrest, heart failure, cardiac ischaemia and renal injury) suggested an increased likelihood of the outcome in those with hypoglycaemia (vs normoglycaemia), the small numbers in this group resulted in imprecise confidence intervals.

We observed a consistent pattern of results to the main findings when re-running the analyses on a composite outcome representing ‘any cardiovascular/renal complication or all-cause death’, i.e., a non-linear association with admission glucose levels characterised by increased odds of the outcome at both high and low admission glucose levels (Supplementary Figure 6). In addition, and as per the main analysis, there was evidence that this association was modified by age and diabetes status (Supplementary Figure 7). Furthermore, increased odds of this outcome were observed in patients classified as having either hypo- or hyperglycaemia (Supplementary Figure 8).

Conclusions

Summary of findings

Using one of the largest in-hospital COVID-19 patient samples to date, we have investigated the relationship between glucose levels on admission to hospital and a diverse range of in-hospital cardiovascular and renal complications and death. In 35 601 hospitalised patients with COVID-19, 29% experienced an in-hospital cardiovascular or renal complication. For most complications, we observed a non-linear relationship between admission glucose and the likelihood of experiencing the outcome. However, the nature of the non-linear relationship was outcome specific, with the greatest likelihood of experiencing heart failure, arrhythmia and coagulation complications associated with glucose levels in the hypoglycaemic range while for the other complications, the greatest likelihood was observed at much higher glucose levels. Furthermore, for stroke and cardiac ischaemia, a linear relationship between the odds of experiencing either of these complications and admission glucose was observed, with increasing odds for higher glucose levels. We have also found that a number of these associations may be modified by age and diabetes status, with stronger effects observed in those of younger age and without a pre-existing diagnosis of diabetes.

Interpretation of findings

Blood glucose levels and a previous diagnosis of diabetes are now established risk factors for COVID-19 severity and mortality(7; 8; 26-29). However, there is much less evidence regarding the associations between admission blood glucose and the complications which are indicative of severe COVID-19 and which may ultimately result in death. We are aware of only three studies which have investigated

associations between admission blood glucose and cardiovascular and renal complications (e.g., cardiac and renal injury and coagulation complications)(19-21). In a study of 7 337 patients with COVID-19 in China, Zhu et al (2020)(19) observed that patients with well-controlled blood glucose (3.9-10.0 mmol/l) experienced less frequent occurrences of acute heart (1.4% vs 9.9%) and kidney injury (0.7% vs 3.8%) and disseminated intravascular coagulation (DIC; 0.0% vs 0.6%) than patients with poorly-controlled blood glucose(19). Klonoff et al (2021)(20), in a study of 1 544 patients with COVID-19 in the US, observed that the greatest risk of kidney injury occurred, conversely, in those with hypoglycaemia (<3.9 mmol/l) on admission(20). Finally, Li and colleagues (2020) in a much smaller sample of 132 patients observed that patients with admission glucose >11 mmol/l were more likely to experience acute cardiac injury than those with admission glucose <11 mmol/l(21). Our study, using a substantially larger sample, provides support for these findings by highlighting the heterogeneous relationship between blood glucose and complications, which demonstrated not only inter-complication variability, but also a varying association across the distribution of blood glucose levels.

We also provide evidence that associations between admission glucose and some cardiovascular and renal complications may be modified by age and pre-existing diabetes status. While we are not aware of other studies which have explicitly investigated this, a modifying role of age on the relationship between diabetes status and COVID-19 mortality and severity has been reported elsewhere and is in agreement with our findings, i.e., a stronger association in younger age groups(30; 31). Furthermore, in patients with COVID-19 and type 2 diabetes, the relationship between the underlying level of hyperglycaemia and COVID-19 mortality was modified by age, with a steeper gradient of risk in patients below 70 years(8). Our

finding of an attenuated risk of elevated glucose levels in older patients may reflect the absolute higher level of risk of complications in this age group, relative to younger adults, so that in elderly individuals, elevated glucose levels may not meaningfully affect the already higher rates of complications associated with older age, where other factors are likely to be more important. This is similar to findings relating to the risk of mortality in covid-19 patients with obesity, which was lower in those aged over 70 years (vs younger)'(32). Additionally, our finding of a potential modifying effect of pre-existing diabetes status, with higher likelihood of a poor prognosis observed in patients without a pre-existing diagnosis of diabetes, has been reported elsewhere(33). This may reflect heightened glucose monitoring and a more timely implementation of specific admission treatment protocols (i.e., insulin) in patients with a pre-existing diabetes diagnosis(34), resulting in improved glucose control in these patients compared to patients with high glucose levels but without a previous diabetes diagnosis. Strict glucose control has been shown to improve prognosis in both non-COVID19(35) and COVID-19 illness(36).

The mechanisms via which hyperglycaemia may contribute to COVID-19-related cardiovascular and renal complications include dysregulation of the immune response, affecting the production of cytokines such as interleukin-6 (IL-6), as well as altering the function of immune cells (36; 37). Hyperglycaemia also promotes glycosylation of the ACE2 receptor, which enables the binding of the SARS-CoV-2 virus to the host and therefore magnifies the extent of infection by SARS-CoV-2 (38). Hyperglycaemia is also known to induce oxidative stress(39) and have pro-inflammatory and pro-thrombotic effects (40; 41). The consequences of the pro-inflammatory and oxidative stress effects of hyperglycaemia and diabetes on the immune response, in the context of COVID-19, have been discussed

comprehensively in a recent review(43). In terms of hypoglycaemia, this has also been shown to induce pro-inflammatory and pro-thrombotic states(44; 45) and thus also having the potential to affect the immune response due to a similar background of chronic inflammation as per hyperglycaemia (43). It has been shown that acute hypoglycaemia can result in an increased expression of the CD40 receptor which is involved in the inflammatory response(44) and may also increase hormonal adrenergic activity(46), further increasing the inflammatory response and the risk of arrhythmia(47). As such, it has been speculated that hypoglycaemia may represent a trigger mechanism for the 'cytokine storm' during infection with COVID-19(48) and heart conduction abnormalities(49).

There may also be a bi-directional relationship between COVID-19 severity and hyperglycaemia, with the resultant cytokine production following COVID-19 infection exacerbating insulin resistance or impair insulin secretion(50; 51). Furthermore, the binding of SARS-CoV-2 to ACE2 receptors, which are found to be expressed in pancreatic beta-cells, makes it a target for the virus to bind. Upon binding, the virus is able to enter and damage the pancreatic islets, resulting in defective insulin production(52). We tested this possibility by adjusting for oxygen saturation levels at admission as a proxy for COVID-19 severity. Upon adjustment, only a small degree of attenuation in the associations between admission glucose and the complications was observed, suggesting a potentially independent role of glucose levels on admission to the likelihood of experiencing an in-hospital cardiovascular or renal complication.

Strengths and limitations

These data were collected prospectively across 302 facilities and represent a large heterogeneous proportion of people hospitalised with COVID-19 in the UK, thus increasing the generalisability of our findings to the underlying population, which is important to provide robust estimates of short-term morbidity for healthcare planners and policy makers. Other smaller, or single centre studies have typically focussed either exclusively on patients who received critical care, or on one type of complication and lack systematic approaches to data collection(53). This study includes all patients hospitalised with COVID-19. The large sample size enabled the testing of interactions by age, sex, ethnicity, obesity and pre-existing diabetes status, which, given the relatively low prevalence of some of the ethnic groups/conditions, may have been more difficult in a smaller sample. We acknowledge a number of limitations. Despite the relatively large sample size, a substantial proportion of the sample had missing glucose data. Possible explanations as to why only some individuals had glucose measured include the selective blood sampling of patients with risk factors for diabetes (e.g., patients with obesity or of certain ethnic groups, i.e., South Asian) or in those with a history of previous diabetes diagnosis or other related pre-existing disease. We compared the included and excluded samples across a number of key demographic variables and observed a greater number of patients with obesity, pre-existing diabetes and of South Asian origin. As such, there may be some evidence that our sample overly-represents individuals more likely to exhibit poor glucose control, compared to the full cohort and thus reduces the generalisability of the findings. Conversely, when comparing actual admission glucose levels in those included vs excluded, the mean of those included was lower than those excluded (8.1 mmol/l vs 8.7 mmol/l). Another explanation is that obtaining admission blood glucose could be driven by local protocols, which if random across

hospitals and patients, is unlikely to introduce bias. Furthermore, due to a lack of data relating to chronic glycaemic control (i.e., HbA1c), we were also unable to investigate the impact of a change in glucose control during admission and thus the role of stress hyperglycaemia. It has been demonstrated, in non-COVID-19 illness, that stress hyperglycaemia ratio may be a better predictor of acute kidney injury and in-hospital mortality and morbidity than admission glucose level(54). Due to a low prevalence of pre-existing type 1 diabetes (2%), we combined type 1 and type 2 diabetes into a single diabetes variable. To explore whether this may have masked heterogeneous effect modification by type of diabetes, we excluded those with type 1 diabetes from the definition of pre-existing diabetes and the results of the effect modification with glucose were almost identical across each of the complications. However, as both types of diabetes were based on a previous clinician diagnosis, our findings may still be obscured by cases of undiagnosed diabetes. Another limitation is that the dataset focusses on in-hospital complications during 28 days after the index admission for COVID-19 and does not contain longer-term outcome data. As we have shown that prevalence of in-hospital complications was twice as high in the group who remained in hospital vs those discharged within 28 days, the omission of longer term follow-up and outcome data in this group who are likely to be at higher risk of subsequent complications and longer term morbidity is a limitation. In addition, the complications that were captured were predefined by a pragmatic outbreak preparedness study protocol which was developed prior to the emergence of COVID-19 and which may lack the granular details for certain aspects which could be instead collected in ad-hoc cohort studies or trials. For example, we were unable differentiate between resuscitated and non-resuscitated cardiac arrest, which may have heterogeneous associations with admission glucose levels. All medical

conditions, which were clinically-defined following the diagnostic procedures deemed relevant by the healthcare professional, were extracted from clinical records and inputted from the local health professionals in charge of each individual's care. Local investigators were able to enter other complications as free text but this approach may have missed some important complications which were otherwise unexpected. Obesity was defined by the ISARIC protocol using objective measures (e.g. BMI) but also subjective clinical judgement, which is likely to vary between clinicians and thus introduces bias into the definition of obesity. In addition a lack of sociodemographic and lifestyle factors (e.g., smoking habits and physical activity) included in the study protocol means that the possibility of residual confounding biasing our estimates cannot be excluded. Finally, these data were collected from clinical practice and patients did not undergo any additional tests to detect the presence of complications. Therefore, the estimates presented here are likely to be a conservative estimate of the true burden of complications. However our estimates of in-hospital cardiovascular complications are higher than those reported in 3011 COVID-19 patients admitted to hospital at the beginning of the pandemic(55). Given the exploratory nature of the study, we did not adjust for multiple comparisons and we recommend that additional dedicated studies are conducted to confirm our findings.

Implications

Our study describes the increased risk of in-hospital cardiovascular and renal complications at both high and low glucose levels and in patients with and without diabetes. These findings highlight the importance of routine glucose screening on admission in order to implement individual treatment plans aimed at modifying any deleterious glucose levels.

It is likely that hospitalised COVID-19 patients who survive after cardiovascular and renal complications will experience long-term morbidity. Given the prevalence of these complications in our study (30%), this indicates a potentially large future burden placed on the healthcare system. This is in addition to the substantial burden expected as a result of post-covid syndrome ('long covid'), which has been associated with increased risks of morbidity, hospital readmission and mortality(56; 57). As such, governments, policy-makers, healthcare planners and frontline healthcare workers should anticipate an increased burden placed on health and social care resources, which will be critical to support those who survive COVID-19.

Conclusion

More than a quarter of patients hospitalised with COVID-19 experienced a cardiovascular or renal complication. Increased odds of experiencing a cardiovascular or renal complication were observed at admission glucose levels indicative of both hypo- and hyperglycaemia. For a number of complications, these associations were strengthened in younger patients and in patients without a pre-existing diagnosis of diabetes. In light of findings of increased odds of complications at both high and low glucose levels, admission glucose could be used as a marker for risk stratification of high risk patients. Future research should evaluate interventions to determine optimal glycaemic control by avoiding both hypo- and hyperglycaemia in people with COVID-19.

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Guarantor statement

Professor Kamlesh Khunti and Dr Claire Lawson 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.

Author contributions

T.N and C.R analysed the data. T.N wrote the first draft of the manuscript. K.K, C.L, T.N and C.R conceived of the study. T.Y, F.Z, C.L.G, Y.V.C, A.R, M.J.D, G.P.M, A.B, A.B.D, P.J.M.P, J.K.B, M.G.S, K.K and C.L all reviewed the manuscript and provided important edits to the manuscript.

Ethics

The study was approved by the South Central - Oxford C Research Ethics Committee in England (Ref: 13/SC/0149), and by the Scotland Research Ethics Committee (Ref: 20/SS/0028). The ISARIC WHO CCP-UK study was registered at https://www.isrctn.com/ISRCTN66726260 and designated an Urgent Public Health Research Study by NIHR.

Conflict of interests

KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and TY by the NIHR Leicester Biomedical Research Centre (BRC). KK is Director for the University of Leicester Centre for BME Health, Trustee of the South Asian Health Foundation, national NIHR ARC lead for Ethnicity and Diversity and a member of Independent SAGE and Chair of the SAGE subgroup on ethnicity and COVID-19. GPM is supported by a NIHR Research Professorship (2017-08-ST2-007). MGS is a member of HMG SAGE COVID-19. MGS reports grants from DHSC NIHR UK, grants from MRC UK, grants from HPRU in Emerging and Zoonotic Infections, University of Liverpool, during the conduct of the study, other from Integrum Scientific LLC, Greensboro, NC, USA, outside the submitted work. Other authors declare no conflicts of interests.

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Role of the funder/sponsor

The funder/sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1. Patient characteristics, stratified by presence of cardiovascular/renal complications

	Total sample (n=36 269)	**Patients not experiencing a cardiovascular/renal complication (n=25 848)**	**Patients experiencing a cardiovascular/renal complication (n=10 421)**
Sex			
Male	20 591 (56.8)	14 147 (54.7)	6 444 (61.8)
Female	15 678 (43.2)	11 701 (45.3)	3 977 (38.2)
Age on admission (years)	71 (57, 82)	69 (55, 81)	75 (63, 84)
Ethnicity			
White	29 580 (81.6)	21 069 (81.5)	8 511 (81.7)
South Asian	2 637 (7.3)	1 917 (7.4)	720 (6.9)
Black	1 285 (3.5)	833 (3.2)	452 (4.3)
Other	2 767 (7.6)	2 029 (7.9)	738 (7.1)
Glucose on admission (mmol/l)	6.7 (5.8, 8.7)	6.6 (5.7, 8.3)	7.2 (6.0, 9.5)
(mg/dL)	120.6 (104.4, 156.6)	118.8 (102.6, 149.4)	129.6 (108.0, 171.0)
Obesity	5 680 (15.7)	3 710 (14.4)	1 970 (18.9)
Pre-existing diabetes	9 202 (25.37)	5 933 (23.0)	3 269 (31.4)
In-hospital cardiovascular/renal complications			
Arrhythmia	2 967 (28.5)	-	2 967 (28.5)
Cardiac ischaemia	551 (5.3)	-	551 (5.3)
Cardiac arrest	920 (8.8)	-	920 (8.8)
Coagulation complications	1 625 (15.6)	-	1 625 (15.6)
Stroke	470 (4.5)	-	470 (4.5)
Heart failure	1 282 (12.3)	-	1 282 (12.3)
Renal injury	6 458 (62.0)	-	6 458 (62.0)
Outcome status at 28 days post admission			
Discharged alive	23 275 (65.4)	19 123 (74.0)	4 539 (43.6)
Remaining in hospital	837 (2.4)	424 (1.6)	435 (4.2)
Transferred to another facility	1 601 (4.5)	1 046 (4.1)	586 (5.6)
Palliative discharge	482 (1.4)	321 (1.2)	169 (1.6)
Died	9 398 (26.4)	4 927 (19.1)	4 691 (45.0)

Data are reported as n(%) for categorical variables and median(IQR) for continuous variables

Figure legends:

Figure 1. Associations between admission glucose level (mmol/l and mg/dL) at admission and odds of in-hospital cardiovascular and renal complications

Figure 2. Associations between admission glucose level (mmol/l and mg/dL) and odds of in-hospital cardiovascular and renal complications in those younger than 69 years vs those 69 years or above.

Figure 3. Associations between admission glucose level (mmol/l and mg/dL) and odds of in-hospital cardiovascular and renal complications, by pre-existing diabetes status