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SHORT COMMUNICATION

High glycaemic variability is associated with progression of COVID-19

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Introduction

Diabetes mellitus (DM) has unequivocally been linked to poorer COVID-19 prognosis. Although admission hyperglycaemia is an adverse prognostic marker, longer-term levels of glycaemia measured by HbA1c have not been consistently associated with poorer COVID-19 outcomes. Hyperglycaemia may not be the only factor leading to increased complications from DM. Oscillating blood glucose (BG) incites greater oxidative stress and endothelial dysfunction than sustained hyperglycaemia [1], increasing pro-inflammatory cytokines and endothelial permeability. In the intensive care, patients with higher GV had higher 30-day mortality [2]. To date, few studies have evaluated if GV may be an underlying risk factor for severe COVID-19, independent of the presence of DM.

Our aim was to evaluate the association between GV and risk of COVID-19 progression. Primary outcome of COVID-19 progression was defined as development of any of the following events > 24 h after initial presentation with mild illness: (1) intensive care unit (ICU) admission, (2) death, (3) respiratory rate > 30, (4) SpO2 < 93% on room air and (5) C-reactive protein (CRP) rise > 10 mg/l above a baseline > 20 mg/l. Evidence indicates that both an elevated baseline and rise in CRP are strong predictors for progressive respiratory failure in COVID-19 [3].

Methods

We performed a retrospective cohort of COVID-19 patients, diagnosed via RT-PCR on nasopharyngeal swabs, admitted to the general wards of Khoo Teck Puat Hospital Singapore from February to May 2020 primarily for monitoring and isolation purposes. Those without > 2 BG readings or with missing data on the primary outcome were excluded.

Clinical characteristics and biochemistry including HbA1c in the current admission were collected. Baseline CRP was measured within the first 48 h. BG is routinely measured pre-meals in our hospital. As difference between venous and capillary glucose in the pre-prandial state is small, they were interpreted together. GV was expressed as coefficient of variation (CV), calculated as the intrapersonal standard deviation (SD) divided by mean BG. Patients with an ICD code of "DM" or use of glucose-lowering medications were classified as having DM. In addition, to avoid missing newly diagnosed DM, patients with DM, prediabetes and normoglycaemia were additionally classified by HbA1c according to ADA criteria of HbA1c > 6.5% (48 mmol/mol), 5.7–6.4% (39–46 mmol/mol) or < 5.6% (38 mmol/mol) if they had no ICD code of "DM" or use of glucose-lowering medications. Glucose criteria were not incorporated as stress-induced hyperglycaemia in this inpatient cohort would overestimate DM prevalence.

Patients were stratified by GV tertiles. A two-tailed p-value < 0.05 was considered statistically significant. Continuous data were presented as mean (standard deviation,

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SD) if normally distributed and median (interquartile range, IQR) otherwise. Multivariable cox proportional hazards regression model was used to estimate hazard ratios (HR) for progression adjusting for age, gender, cardiovascular disease (CVD), hypertension, DM, HbA1c and mean intrapersonal glucose. Statistical analyses were performed using STATA v13.0 (STATA Corp., College Station, TX).

Results

Of 1042 patients admitted, 458 were analysed after excluding those without > 2 BG readings. There were 5634 glucose measurements in total; majority (87.1%) were capillary glucose measurements; the remainder were venous samples. 55.1% of glucose measurements were taken within the first 5 days of admission. Mean of 12 (SD 25, median 3, IQR 2–159) glucose measurements were taken per patient, and mean of 2.65 readings per patient per day (SD 2.34, median 2, IQR 1–3). Clinical characteristics are represented in Supplementary Table 1. The predominantly male cohort was due to Singapore's outbreak of COVID-19 among foreign worker dormitories and low community-transmission rates. 30.1% had DM distributed 1.3%, 8.5% and 20.3% into each GV tertile, respectively, 27.1% were on glucose-lowering agents, and 4.6% were on insulin. Two hundred and thirty-five patients (51.3%) had HbA1c measured. Among patients with DM, mean HbA1c was 8.5 ± 2.0%. Over a median follow-up of 4 (IQR 4–11) days, progression occurred in 83 (18.1%) subjects.

Median GV in each tertile was 3.5 (IQR 2.1–5.9), 13.6 (IQR 10.4–17.2) and 28.2 (IQR 23.8–33.7), respectively. Patients in glucose-CV tertiles-2 and 3 were older and had higher prevalence of diabetes, admission glucose and HbA1c. They had higher incidence of adverse clinical events, i.e. progression of disease, hypoglycaemia, ICU admission, death and longer length of stay.

Patients in tertile 3 had poorer progression-free survival compared to tertile 1 (Fig. 1). There was a step-wise increase in HR for progression in tertile 2 and tertile 3 on univariate analysis (Table 1), with the highest HR of progression 4.30 (95% CI 2.22–8.33; $p < 0.001$) in tertile 3. The association persisted in the multivariate analysis with the corresponding HR 2.98 (95%CI 1.50–5.91; $p = 0.002$) in tertile 3 compared to tertile 1 after correction for age, sex, CVD and hypertension, but lost significance in tertile 2. As diabetes could be a significant confounder for the effect of GV on COVID-19 progression, a multivariate analysis was additionally performed to correct for the presence of diabetes. HR attenuated slightly, but remained significant at 2.46 (95%CI 1.15–5.27; $p = 0.021$). Adjustment for HbA1c and mean intra-personal glucose resulted in a similar finding of an increased risk of progression in the highest tertile of GV (Model 4: HR 5.62, 95%CI 1.26–24.99, $p = 0.023$; model 5: HR 3.03, 95%CI 1.45–6.32, $p = 0.003$, Supplementary Table 2).

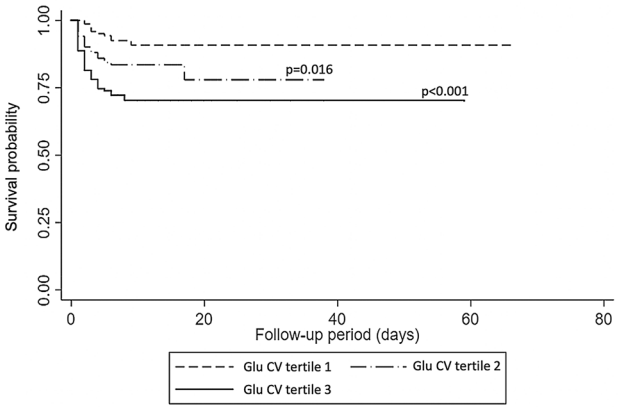

Fig. 1 Kaplan–Meier survival curve for progression of disease stratified by glucose coefficient of variant (Glu CV) tertiles 1, 2 and 3. *p*-values compare tertiles 2 and 3 with tertile 1

In patients without DM ($N = 320$), this relationship remained significant, with a greater risk of progression observed in tertile 3 compared to tertile 1 (HR 2.61, 95% CI 1.09–6.25, $p = 0.032$, Supplementary Table 3).

Discussion

This study supports previous studies demonstrating improved COVID-19 outcomes for patients who maintained euglycaemia as compared to hyperglycaemia. In addition, we demonstrate that GV is also an important prognostic marker for progression of COVID-19, independent of demographics, pre-existing diabetes or levels of glycaemia, and comorbidities of CVD and hypertension.

GV may be associated with adverse COVID-19 outcomes via several mechanisms. Firstly, increased oxidative stress and inflammatory cascade triggered may play a role in SARS-CoV-2 infection and progression, as described in the pathogenesis of several respiratory viruses [4]. In rodents, GV resulted in overproduction of reactive oxygen species, endothelial activation and influenza complications [4]. Secondly, high GV increases risk of hypoglycaemia, which correlates with cardiovascular events and mortality in both inpatient and outpatient settings.

Viral entry via ACE2 receptor on pancreatic islet cells may incite islet-cell damage. Large glycaemic excursions resulting from pancreatic insufficiency may induce more oxidative stress [1], driving beta-cell apoptosis in a vicious cycle, in addition to systemic inflammation.

Hence, beyond hyperglycaemia, high GV may explain previous observations of elevated risk for COVID-19 mortality in type 1 compared to type 2 diabetes [5]. Although

Table 1 Cox regression analysis of glucose variability associated with progression of COVID ($N=458$)

	Hazards ratio (95% confidence interval) *p*-value			
Variables	Model 1 (univariate)	Model 2 (multivariate)	Model 3 (multivariate)	Model 4 (multivariate)
Glucose CV				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	2.39 (1.17–4.85) $p=0.016$	1.91 (0.94–3.91) $p=0.075$	1.76 (0.85–3.66) $p=0.130$	4.09 (0.91–18.42) $p=0.067$
Tertile 3	4.30 (2.22–8.33) $p<0.001$	2.98 (1.50–5.91) $p=0.002$	2.46 (1.15–5.27) $p=0.021$	5.62 (1.26–24.99) $p=0.023$

Model 1: Unadjusted

Model 2: Adjusted for age, sex, cardiovascular disease, hypertension

Model 3: Model 2 adjusted for DM status

Model 4: Model 2 adjusted for HbA1c

CV coefficient of variation, *DM* diabetes, *HR* hazards ratio

they were not analysed separately, our findings of an elevated risk of progression associated with high GV would suggest need for heightened monitoring, particularly among patients with pancreatic insufficiency or labile BG. In addition, high GV is an adverse prognostic marker for progression of COVID-19 independent of diabetes status, HbA1c or mean glucose. This study conducted in a low-risk cohort implies that intensive glucose monitoring should extend beyond the ICU setting.

One limitation is measurement of only a few pre-meal BG readings. Nonetheless, based on previous studies, minimally 3–5 glucose readings to calculate GV are needed to translate to meaningful results [6] and predict macrovascular complications [7]. Continuous glucose monitoring which assesses GV more accurately could be utilized in future. Secondly, CT chest was not routinely performed as most patients were clinically well and chest radiograph with biochemistry was sufficient to guide management. Thirdly, the male predominance may limit generalizability. However, there is no evidence to suggest gender-specific differences of GV on diabetes complications.

Conclusion

Current recommendations are largely focused on avoidance of hyperglycaemia. High GV may also explain the poorer prognosis observed in diabetes, beyond hyperglycaemia alone. This study highlights the importance of minimizing BG fluctuations, as high GV is associated with two–threefold increased risk of COVID-19 progression, independent of diabetes status or levels of glycaemia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-021-01779-7.

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Authors' contribution CWSH, STO and EY designed the study. LY collected the data. XEY performed the statistical analysis. CWSH wrote the first draft of the manuscript. EY revised the manuscript. All authors approved the final version of the manuscript.

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Data availability The data that support the findings of this study are available on reasonable request from the corresponding author.

Declarations

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval Approval by the Institutional Review Board (DSRB2020/00750) was obtained, in accordance with the ethical standards of the Declaration of Helsinki.

Informed consent Each patient was assigned a unique identifier that was destroyed at study completion. This identifier did not allow the disclosure of patient identity hence the data was anonymous and informed consent was not needed for this study.

References

1. Ceriello A, Esposito K, Piconi L et al (2008) Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 57(5):1349–1354. https://doi.org/10.2337/db08-0063
2. Chao W-C, Tseng C-H, Wu C-L, Shih S-J, Yi C-Y, Chan M-C (2020) Higher glycemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. Ann Intensive Care 10(1):17. https://doi.org/10.1186/s13613-020-0635-3
3. Mueller AA, Tamura T, Crowley CP et al (2020) Inflammatory biomarker trends predict respiratory decline in COVID-19 patients. Cell Rep Med 1(8):100144. https://doi.org/10.1016/j.xcrm.2020.100144
4. Marshall RJ, Armart P, Hulme KD et al (2020) Glycemic variability in diabetes increases the severity of influenza. mBio 11(2):e02841-19. https://doi.org/10.1128/mBio.02841-19

5. Barron E, Bakhai C, Kar P et al (2020) Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 8(10):813–822. https://doi.org/10.1016/S2213-8587(20)30272-2
6. Hirakawa Y, Arima H, Zoungas S et al (2014) Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. Diabetes Care 37(8):2359–2365. https://doi.org/10.2337/dc14-0199
7. Echouffo-Tcheugui JB, Zhao S, Brock G, Matsouaka RA, Kline D, Joseph JJ (2019) Visit-to-visit glycemic variability and risks of cardiovascular events and all-cause mortality: the ALLHAT study. Diabetes Care 42(3):486–493. https://doi.org/10.2337/dc18-1430