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## High admission blood glucose is an independent risk factor of poor prognosis in COVID-19: A systematic review and dose-response meta-analysis

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#### ABSTRACT

**Aims** To investigate the prognostic value of admission blood glucose (BG) in predicting COVID-19 outcomes, including poor composite outcomes (mortality/severity), mortality, and severity.

**Materials and methods** Eligible studies evaluating the prognostic value of fasting BG (FBG) and random BG (RBG) levels in predicting COVID-19 outcomes were included and assessed for risk of bias with the Quality in Prognosis Studies tool. Random-effects high-vs-low meta-analysis followed by dose-response analysis using generalized least squares model in a two-stage random-effects meta-analysis were conducted. Potential non-linear association was explored using restricted cubic splines and pooled using restricted maximum likelihood model in a multivariate meta-analysis.

**Results** The search yielded 35 studies involving a total of 14,502 patients. We discovered independent association between admission FBG and poor prognosis in COVID-19 patients. Furthermore, we demonstrated non-linear relationship between admission FBG and severity (P<sub>non-linearity</sub><0.001), where each 1 mmol/L increase augmented the risk of COVID-19 severity by 33% (risk ratio 1.33 [95% CI: 1.26-1.40]). Albeit exhibiting similar trends, study scarcity limited the strength of evidence on the independent prognostic value of admission RBG. GRADE assessment yielded high-quality evidence for the association between admission FBG and COVID-19 severity, and moderate-quality evidence for its association with mortality and poor outcomes, while the other assessments yielded very low-to-low quality.

**Conclusion** High level of FBG at admission was independently associated with poor prognosis in COVID-19 patients. Further researches to confirm the observed prognostic value of admission RBG and to ascertain the estimated dose-response risk between admission FBG and on COVID-19 severity are required.

Keywords: blood glucose, COVID-19, fasting, patient admission, prognosis

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#### INTRODUCTION

The rapidly spreading coronavirus disease 2019 (COVID-19) has placed significant burdens on healthcare systems worldwide, with millions of cases and hundred-thousands of deaths.<sup>1</sup> Despite significant efforts in comprehending the disease, its diagnosis and prognostication remain challenging, attributing to the prevalent non-specific and atypical symptoms.<sup>2</sup> In light of this, recent reports have indicated that admission blood glucose (BG) may yield prognostic values in predicting COVID-19 outcomes.<sup>3,4</sup> Nevertheless, to the best of our knowledge, no meta-analysis has evaluated the prognostic value of admission BG level in predicting the outcomes of COVID-19 patients. Hence, this review intends to summarize the current knowledge regarding the role of admission BG level in determining the prognosis of COVID-19 patients.

#### MATERIALS AND METHODS

This systematic review was conducted in accordance with the guideline recommended by the Cochrane Prognosis Methods Group<sup>5</sup> and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>6</sup>. A detailed protocol has been previously registered in PROSPERO (CRD42020154772<sup>7</sup>).

### Search strategy

Two independent investigators performed thorough literature searches, with discrepancies resolved by a third investigator in a blinded fashion. Searches were conducted through PubMed, Ovid EMBASE, CENTRAL, EBSCO MEDLINE, CINAHL, Scopus, and WHO COVID-19 database for studies published up to 8 September 2020. Grey literature (e.g., preprints) search and literature snowballing of references were also performed. No language restrictions were applied. Details on databases and keywords are further elaborated in **Appendix Table S1**.

### Study eligibility criteria

Inclusion criteria were set to filter primary studies investigating the association between admission BG level and poor outcomes among COVID-19 patients (see **Appendix Table S2**). Admission BG level was determined from the first BG measurement following patients'

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admission to hospital prior to any intervention, while poor outcomes were further dichotomized into mortality and severity.<sup>8</sup> Conversely, studies were excluded if any of the following criteria were met: (1) case reports, case series, or letter to editors; (2) irretrievable full-text articles; or (3) non-English articles.

#### Data extraction and risk of bias assessment

Data extraction and risk of bias assessment were performed by two independent reviewers using a pre-specified form, with discrepancies resolved by the consensus with an independent third investigator. Details on the data items and handling are further discussed in **Appendix pg. 7.** The main outcome of interest in this review was the risk of poor composite outcomes (i.e. mortality/severity), mortality, and severity among COVID-19 patients. Whenever possible, outcomes on severity were further investigated per following criterion, including invasive ventilation, intensive care unit (ICU) admission, acute respiratory distress syndrome (ARDS), and shock.<sup>8</sup> Included studies were further assessed for methodological quality by using the Quality in Prognosis Studies tool<sup>9</sup> and subsequently judged to be yielding low, moderate, or high risk of bias (**Appendix Table S3**). Lastly, the certainty of the evidence was evaluated using the modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, where the quality of evidence was regarded as high, moderate, low, or very low.<sup>10</sup>

#### **Statistical analysis**

Analyses were performed for both adjusted and unadjusted estimates; however, adjusted estimates were primarily utilized for reporting and interpretation of results.<sup>11</sup> Pooled effects were converted to and presented in risk ratios (RRs; see **Appendix pg. 11**). Quantitative synthesis was first conducted by comparing the highest vs lowest categories of exposures by using the generic inverse variance method with the DerSimonian-Laird random-effects model<sup>12</sup>. Whenever appropriate ( $n \ge 10$ ), potential publication bias was evaluated visually by contour-enhanced funnel plot<sup>13</sup> and quantitatively by Egger's<sup>14</sup> and Begg's<sup>15</sup> tests. Statistical heterogeneity was investigated with Cochran's Q test and I<sup>2</sup> statistics. Dose-response meta-analysis (DRMA) was conducted only for adjusted outcomes. Study-specific linear trend was estimated using the generalized least squares method and pooled using the two-stage random effects meta-analysis. Meanwhile, potential non-linear dose-response trend was evaluated using restricted cubic splines with three-knots model at the 10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup> percentiles, and subsequently pooled using the

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restricted maximum likelihood method in a multivariate random-effects meta-analysis. The Wald test was used to assess for non-linearity.

A priori, we determined subgroup and sensitivity analyses only for adjusted results. Whenever available, subgroup analyses were carried out based on study design, location, sample size, risk of bias, number of categories, effect size type, and diabetic status. On the other hand, sensitivity analyses were conducted by leave-one-out analysis and the exclusion of studies with high-risk of bias. For DRMA, subset analysis was performed according to diabetic subgroups, while sensitivity analyses were conducted by assigning alternative approaches for open-ended categories (for linear trends) and alternative knots locations (for non-linear trends). Meta-analysis was conducted with R ver. 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria)<sup>16</sup>, and additional analyses with MetaXL software ver.5.3. (EpiGear International, Queensland, Australia)<sup>17</sup>. The significance level was set at 5% for all analyses. Further details on DRMA and additional analyses are discussed in **Appendix pg. 12-13**.

#### RESULTS

#### **Study selection and characteristics**

The details on the literature search process are summarized on **Figure 1**. The initial search yielded 1177 articles, of which 636 were deduplicated and 482 were excluded following title and abstracts screening, resulting in the retrieval of 59 records for full-text assessments–among which 13 inappropriate design, five inappropriate settings, four incompatible language, two irretrievable full-text articles, and one unidentifiable setting (**see Appendix pg. 12-13** for further details) were excluded. Consequently, a total of 35 studies with 14,502 patients were included in this systematic review, where 7918 patients were male (54.6%), and hypertension (4940 [34.1%]) as well as diabetes (4540 [31.3%]) were the most reported comorbidities (**Appendix Table S4**). In quantitative analysis, 10 studies were excluded as seven<sup>18–24</sup> only reported P-value and three<sup>25–27</sup> reported different effect measures.

From 35 included studies, more than half were conducted in China (23 studies), while the others were five each in America<sup>18,21,27–29</sup> and Europe<sup>20,25,30–32</sup>, and one each in Hong Kong<sup>33</sup> and South Korea<sup>34</sup>. FBG was utilized in 23 studies, while RBG in 13 studies. Bias assessment

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revealed a predominant low-to-moderate risk of bias (16 and 12 studies, respectively). Most of the studies yielded unclear risk of bias in study participation and confounding domains (**Figure 2** and **Appendix Figure S1**), which may partly be explained by the fact that all but two studies<sup>21,29</sup> were conducted retrospectively.

#### Outcomes

The summary of adjusted and unadjusted pooled effects of high vs low meta-analysis are consecutively listed in **Table 1** and **Appendix Table S5**; and the certainty of evidence as assessed with the GRADE approach is summarized in **Appendix Table S6**. GRADE assessments of the prognostic value of FBG resulted in high-quality evidence for severity and moderate-quality evidence for mortality and poor outcome, whereas the remaining domains yielded very low-to-low-quality evidence. Overlapping populations were observed in four studies<sup>35–38</sup> (**Appendix Table S7**), and analyses were prioritized to Wang et al.<sup>35</sup> due to larger sample size.

#### Fasting blood glucose

We demonstrated that FBG was independently associated with poor prognosis in COVID-19 patients (**Table 1** and **Figure 3A-C**), although all models yielded substantial heterogeneity ( $I^2$ =84% for poor outcome;  $I^2$ =87% for mortality,  $I^2$ =78% for severity; all with P<sub>heterogeneity</sub><0.001). Subgroup analyses based on study design and location were not possible as all studies were retrospective and conducted in China. Furthermore, publication bias assessment was only eligible for mortality outcome.

We discovered that high admission FBG increased the risk of poor outcomes by 20% (RR 1.20 [95% CI: 1.04-1.39]; **Figure 3A**). However, we were unable to establish firm evidence as the observed heterogeneity remained unexplained (see footnote in **Table 1**) and the observed effects were diminished following the exclusion of Fadini et al.<sup>32</sup> or Li et al.<sup>38</sup> (**Appendix Figure S2A**). In DRMA comprising of two studies<sup>32,39</sup>, we failed to observe exposure-response gradient (RR 1.23 [95% CI: 0.90-1.68]; P<sub>heterogeneity</sub>=0.008; **Figure 4A**), although study-specific slopes indicated that such trend exists. Considering this, we deemed the quality of evidence to be moderate for qualitative assessment and low for quantitative assessment.

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For outcomes on mortality, we found a relatively consistent result (RR 1.81 [95% CI: 1.41-2.33]; **Figure 3B**); although the observed heterogeneity remained unexplained following subgroup analysis, except when the analysis was stratified according to its category (i.e.  $I^2=2\%$ for studies reporting two categories). Furthermore, we discovered that the smaller-sized studies yielded excessively wide CIs as compared to larger studies (**Table 1**). Nonetheless, sensitivity analysis suggested that these small studies did not contribute much to the pooled estimate as our findings remained consistent, except when Fadini et al.<sup>32</sup> or Chang et al.<sup>34</sup> were excluded, which exaggerated the pooled estimates (**Appendix Figure S2B**). We detected asymmetry in the funnel plot which was further ascertained by Egger's test (P<0.001; **Appendix Figure S3**), although Begg's test indicated otherwise (P=0.245), suggesting the presence of publication bias. Nevertheless, we did not downgrade the outcome for publication bias upon qualitative assessment as most studies adequately adjusted for potential confounders (**Appendix Table S8**).

DRMA for mortality outcome included three studies<sup>32,35,39</sup> as overlapping populations were detected in two studies.<sup>35,38</sup> We were also unable to observe any exposure-response gradients although most studies reported otherwise<sup>35,38,39</sup>. However, when analysis was conducted only for non-diabetic patients, we observed an elevated mortality risk of about 38% per 1 mmol/L increase (RR 1.38 [95% CI: 1.21-1.57]; **Appendix Figure S4**). Despite this, we decided to upgrade the certainty of evidence for exposure-response gradient only for qualitative summary, resulting in the judgment of evidence quality for qualitative and quantitative analysis to be moderate and very low, respectively. This implied that we were confident that admission FBG was independently associated with mortality in COVID-19 patients, but the interpretation of the pooled estimate should be made with caution. Non-linear DRMA for poor outcome and mortality were not conducted since only one study reported three or more categories for each outcome.<sup>35,39</sup>

With regards to outcomes on severity, we revealed that high admission FBG level increased the patient's risk of developing severe COVID-19 infection by more than three-folds (RR 3.65 [95% CI: 2.31-5.75]). Although considerable heterogeneity was observed ( $I^2=78\%$ ,  $P_{heterogeneity}<0.001$ ), subgroup analysis according to risk of bias explained all heterogeneity (**Table 1**), suggesting that studies with moderate-to-high risk of bias exaggerated the estimates. Nevertheless, sensitivity analysis revealed similar estimates (**Appendix Figure S2C**), suggesting that the pooled effects were mainly derived from studies with low bias risk.

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DRMA for severity outcome consisted of three studies<sup>35,40,41</sup> cumulating a total of 1077 patients. We discovered that each 1 mmol/L increase in admission FBG level increased the risks of developing severe COVID-19 infection by 33% (RR 1.33 [95% CI: 1.26-1.40]; Figure 4B). Moreover, we observed a non-linear relationship ( $P_{non-linearity} < 0.001$ ), where the risks of progression to severe COVID-19 cases decelerated starting from 6.6 mmol/L and re-exponentiated starting from admission FBG level of 8.1 mmol/L (Figure 4C). Both linear and non-linear trends remained consistent following sensitivity analyses (Appendix Table S8 and Figure S5). When dose-response analysis was conducted only for non-diabetic patients, we observed a slightly higher risk (RR 1.36 [95% CI: 1.28-1.44]; Appendix Table S9).

The observed effects were more accentuated in patients without history of diabetes, where high admission FBG level increased the risk of poor outcome for diabetic patients by 10% and non-diabetic patients by a whopping 75% (diabetic vs non-diabetic; RR 1.10 [95% CI: 1.03-1.17] vs 1.75 [1.02-2.99]). Furthermore, diabetes-stratified analyses for mortality and severity outcomes revealed that the observed trends were non-significant for diabetic subgroup, whereas the models for non-diabetic subgroups remained robust (**Table 1**).

Due to the paucity of studies reporting specific criteria of COVID-19 severity (i.e. ICU admission, invasive ventilation, ARDS, shock), we were unable to ascertain the independent effects to the respective outcomes. Nonetheless, the results were coherent to the main outcomes as the pooled unadjusted effects showed similar trends in predicting ICU admission, invasive ventilation, ARDS, and shock (**Appendix Table S5**). However, as our findings were limited, we judged the certainty of evidence to be low for ICU admission and invasive ventilation, and very low for ARDS and shock (**Appendix Table S6**).

#### Random blood glucose

Similar to FBG, we discovered that COVID-19 patients with high RBG level at admission were more susceptible to poor prognosis (**Appendix Table S5**). Nevertheless, we were unable to establish a strong evidence on the independent prognostic value of admission RBG due to paucity of studies and equivocal trends. High vs low meta-analysis for adjusted effects was only eligible for outcomes on ICU admission, which resulted in non-significant estimate (RR 1.25

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[95% CI: 0.84-1.84]; **Figure 4D**), although study-specific estimates suggested otherwise. Considering this, we judged the quality of evidence to be low for mortality, and very low for the remaining outcomes (**Appendix Table S6**).

With regards to mortality, we found that the prognostic value of admission RBG was independent of age and sex.<sup>25,31</sup>. However, Cariou et al. reported that the observed effect diminished following adjustments for clinical and biological features (odds ratio 1.30 [95% CI: 0.94-1.82]),<sup>25</sup> while Coppelli et al. stated otherwise,<sup>31</sup> Moreover, exposure-response trend were also observed in two studies,<sup>31,42</sup> where Coppelli et al. reported that risk of mortality increased across quintiles of admission RBG (Q4 vs Q1, hazard ratios [HR] 5.91 [95% CI: 1.73-20.19]) and reached threshold effect at the highest quintile (Q5 vs Q1, HR 1.70 [95% CI: 0.49-5.90]; **Appendix Table S10**).<sup>31</sup> However, we were unable to perform a formal dose-response analysis due to insufficient information. In addition, two studies also reported that the risk of mortality was more accentuated in patients without history of diabetes<sup>30,31</sup>, as ascertained by Coppelli et al.– reporting that the hazard of mortality was more robust in non-diabetic than in diabetic patients. (vs. normoglycemia; hyperglycemia: HR 2.39 [95% CI: 1.10-5.19], diabetes: HR 0.78 [95% CI: 0.29-2.09]).<sup>31</sup> Subgroup and sensitivity analyses, as well as publication bias assessment and DRMA was not conducted due to insufficient number of studies.

#### DISCUSSION

This meta-analysis showed that high admission BG level was associated with poor prognosis in COVID-19 patients. Although we were unable to establish a firm evidence on the independent prognostic value of admission RBG, our results on admission FBG level was consistent and robust. Furthermore, we also demonstrated dose-response trend between admission FBG level and COVID-19 severity. Although the potential non-linear association between admission FBG level with poor composite and mortality outcomes remained unexplored due to paucity of studies, we were able to establish non-linear relationship between admission FBG level and severity. However, in contrast with Zhu et al.<sup>37</sup>, we did not observe a J-shaped association between admission FBG and COVID-19 severity, which may be explained by the fact that all but one study<sup>37</sup> reported only three categories.

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Further analysis indicated that the observed effects were more accentuated in patients without prior history of diabetes; which was intriguing, considering the fact that there was as increasing proportion of COVID-19 patients presenting with hyperglycemia despite having no prior diabetic history.<sup>32,35,43</sup> Furthermore, our findings indicated that at-admission hyperglycemia was associated with poorer outcomes regardless of prior diabetes status, suggesting the existence of a more direct link between glycemic status and poor COVID-19 outcomes.

The relationship between COVID-19 severity and hyperglycemia is possibly bidirectional, wherein infection might bring about state of stress and trigger an enhanced release of proinflammatory cytokines which may lead to insulin resistance.<sup>44</sup> Stress may also induce the release of stress hormones which trigger liver glycogenolysis, aggravating the effects.<sup>45</sup> Furthermore, SARS-CoV-2 is known to bind to angiotensin-converting enzyme 2 (ACE2) receptors, which are found to be expressed in pancreatic beta-cells, thus rendering it a target for the viral attack. Such binding provides a route for the virus to enter and damage the pancreatic islets, resulting in a defect of insulin production, as indicated in previous study with its SARS virus counterpart.<sup>46</sup> Together, these factors may contribute to the development of acute hyperglycemia in COVID-19 patients.

The mechanism by which acute hyperglycemia drives the progression of COVID-19 remains largely unexplored. A study by Fadini et al. found that a decline in respiratory parameters was most responsible for mediating the effects of hyperglycemia on the outcome.<sup>32</sup> Diabetes and hyperglycemia were previously known to induce structural changes in the lungs, giving rise to pulmonary remodelling and the subsequent restrictive respiratory pattern.<sup>47</sup> Moreover, hyperglycemia is also known to generate reactive oxygen species and induces oxidative stress<sup>44</sup>, leading to endothelial dysfunction which may cause further hyperglycemic pulmonary microangiopathy.<sup>48</sup> This is in line with the findings of a study by Lampasona et al. which demonstrated that inflammation and coagulopathy, rather than impaired antibody response as such present in individuals with diabetes, were more responsible in aggravating the outcomes.<sup>49</sup> Therefore, this explains the poorer prognosis found in hyperglycemic patients without prior diabetic history, and again supporting the direct link between glucose level and disease progression.

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Altogether, these findings illustrate the potential utility of admission BG as a predictor for poor prognosis in COVID-19 patients. Considering that BG measurement is relatively practical and instant, its quantification upon admission would be beneficial in predicting the likelihood of progression to severe COVID-19 cases. Therefore, we encourage clinicians to routinely obtain FBG values of each COVID-19 suspected case at admission, thus providing a simple method of risk stratification for management of patients in clinical settings, which would be particularly helpful in streamlining the limited number of medical resources during the current pandemic. Although our findings also favored over the use of admission RBG, future researches are required as we were unable to comprehensively explore the independent prognostic value of admission RBG due to paucity of studies. Furthermore, the current evidence indicated that the cut-off values to predict poor prognosis in COVID-19 patients are still equivocal<sup>31,34,50,51</sup>, suggesting that future large multicenter studies are required to obtain the most optimum cut-off value.

Despite the fact that our findings favored over the prognostic value of high admission BG, the observed unexplained heterogeneity and the fact that all studies were retrospective and conducted in China may limit the generalizability of our findings. Furthermore, most of the studies included in the DRMA on severity outcome yielded moderate risk of bias, thus indicating potential overestimation of the observed effects due to imprecision. These indicated that the observed effects should be interpreted cautiously, and future studies with higher quality of evidence are required to confirm the estimated risks. Nonetheless, our results were consistent with the independent prognostic value of admission FBG, thus we judged the certainty of evidence for severity to be high, and for mortality and poor outcome to be moderate. To the best of our knowledge, this is the first meta-analysis conducted to show the potential use of admission BG as a predictor of poor prognosis in COVID-19 patients. Although our eligibility criteria may introduce language bias, our study included a relatively large number of cohorts and only four non-English articles were excluded<sup>52–55</sup>, suggesting that any potential bias was negligible. We hope that our findings may enhance the current knowledge on the management of COVID-19, thus contributing to the alleviation of the devastating disease burden.

#### CONCLUSION

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In conclusion, this meta-analysis adds to the growing body of evidence corroborating the potential utility of admission BG as a predictor of poor prognosis in COVID-19 patients. There is a high-quality evidence on the prognostic value of admission FBG towards severity, and moderate-quality evidence on its prognostic value towards mortality and poor outcome, while the other outcomes yielded very low-to-low quality evidence. In addition, we demonstrated non-linear dose-response relationship between admission FBG and COVID-19 severity. Further studies to ascertain the estimated risk in the DRMA and to confirm the observed prognostic value of admission RBG are required.

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#### AUTHOR CONTRIBUTIONS

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GL and DLT conceptualized the idea for the project and designed the methodology. GL, JA, VKW, and AT performed the literature search, study screening, and data abstraction. GL administered the study protocol, undertook the formal analysis, and visualized the results. GL, JA, and VKW developed the risk of bias tool and drafted the manuscript, and risk of bias assessment was conducted by JA and VKW. GL, VKW, AT, and DLT reviewed and edited the manuscript for final submission. DLT validated and supervised the project. All authors have approved of the final manuscript for publication.

#### **CONFLICT OF INTERESTS**

The authors declare no conflict of interest.

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## TABLES

Table 1. Summary of high versus low meta-analysis and subgroup analyses

Outcomes	Studios	Evonts/N	DD (05% CI)	Heterogeneity		
Outcomes	Studies	Evenus/in	KK (95% CI)	$\mathbf{I}^2$	P value	
Fasting blood glucose <sup>†,‡</sup>						
Poor composite outcome	4	429/1184	1.20 (1.04-1.39)	84%	< 0.001	
Diabetic status				-		
Diabetic	2	108/184	1.10 (1.03-1.17)	0%	0.562	
Non-diabetic	3	367/848	1.75 (1.02-2.99)	95%	< 0.001	
Mortality <sup>§</sup>	10	827/3814	1.81 (1.41-2.33)	87%	< 0.001	
Subgroup analysis <sup>‡</sup>						
Categories						
Two categories	6	602/2494	2.26 (1.75-2.91)	2%	0.404	
11.1 mmol/L	1	19/132	5.66 (1.36-12.89)	NA	NA	
7.0 mmol/L	3	167/1284	2.60 (1.72-3.93)	0%	0.608	
6.1 mmol/L	2	416/1078	1.68 (1.25-2.26)	0%	0.640	
More than two categories	2	147/917	3.24 (1.28-8.19)	58%	0.121	
Continuous	2	78/403	1.02 (1.01-1.02)	0%	0.842	
Sample size						
<200 patients	3	65/307	2.52 (0.73-8.66)	86%	0.001	
$\geq$ 200 patients	7	762/3507	2.05 (1.34-3.15)	85%	< 0.001	
Risk of bias						
Low	8	700/2767	2.38 (1.50-3.78)	85%	< 0.001	
Moderate/High	2	127/1047	1.37 (0.68-2.77)	82%	0.019	
ES type						
RR	4	386/1225	2.10 (1.08-4.10)	87%	< 0.001	
HR	6	441/2589	2.13 (1.25-3.61)	87%	< 0.001	
Diabetes status						
Diabetic	4	245/586	1.70 (0.91-3.19)	70%	0.018	
Non-diabetic	6	605/2018	2.10 (1.16-3.79)	90%	< 0.001	
Severity <sup>§</sup>	7	824/3280	3.65 (2.31-5.75)	78%	< 0.001	
Subgroup analysis $^{\ddagger}$						
Categories						
Two categories	3	423/1891	2.31 (1.55-3.46)	21%	0.281	
More than two categories	4	401/1389	5.64 (2.35-13.54)	88%	< 0.001	
Sample size						
<200 patients	2	77/201	2.85 (1.63-4.98)	13%	0.284	
$\geq$ 200 patients	5	747/3079	4.08 (2.21-7.52)	85%	< 0.001	
Risk of bias						
Low	5	707/2808	2.30 (1.98-2.68)	3%	0.391	
Moderate/High	2	117/472	15.04 (7.03-32.19)	0%	0.368	
ES type						
RR	5	431/1278	4.99 (2.41-10.34)	84%	< 0.001	

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HR	2	393/2002	2.40 (1.37-4.20)	56%	0.131
Diabetes status					
Diabetic	2	112/230	1.58 (0.74-3.37)	87%	0.005
Non-diabetic	5	963/2936	2.67 (1.52-4.71)	97%	< 0.001
Random blood glucose					
ICU admission	2	120/423	1.25 (0.84-1.84)	86%	0.008

<sup>†</sup>Subgroup analyses to explore potential source of heterogeneity was not possible as no subgroup yielded a minimum of two studies. <sup>‡</sup>Subgroup analysis based on study design and location were not possible as all included studies were retrospective and conducted in China. <sup>§</sup>Overlapping populations were observed between Li et al.<sup>38</sup>, Wang et al.<sup>35</sup>, Zhang et al.<sup>36</sup>, and Zhu et al.<sup>37</sup>, of which Wang et al.<sup>35</sup> was prioritized for analysis due to larger sample size.

COVID-19, Coronavirus disease 2019; ICU, intensive care unit

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#### FIGURE LEGENDS

**Figure 1.** Diagram flow illustrating the literature search process and results. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature. WHO, World Health Organization.

**Figure 2.** Risk of bias graph summarizing the results of each risk of bias item in percentages across all studies.

**Figure 3.** Pooled adjusted effects of high vs low meta-analysis comparing the association between (A) admission FBG and poor composite outcome, (B) admission FBG and mortality, (C) admission FBG and severity, and (D) admission RBG and ICU admission. **FBG**, fasting blood glucose; **ICU**, intensive care unit; **RBG**, random blood glucose.

**Figure 4.** Results of dose-response meta-analysis illustrating linear trend between admission FBG and (A) poor outcome, (B) mortality, and (C) severity; and (D) non-linear trend between admission FBG and severity. In Figure C, darker area represents 95% confidence interval of non-linear trend, while lighter area represents 95% confidence interval of linear trend. **FBG**, fasting blood glucose.

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### **FIGURES**



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Study participation: description of baseline study sample Study attrition: adequate response rate for study participants Study attrition: description of attempts to collect information on participants who dropped out Study attrition: reasons for loss to follow-up provided Study attrition: adequate description of participants lost to follow-up Study attrition: no important differences between participants who completed the study and those who did not Blood glucose measurement: a clear definition or description of blood glucose measured is provided Blood glucose measurement: a clear definition or description of blood glucose measured is provided Blood glucose measurement: continuous variables reported or appropriate cut points used Blood glucose measurement continuous variables reported or appropriate cut points used Blood glucose measurement of the study sample has complete data for blood glucose variable Outcome measurement used is adequately valid and reliable Outcome measurement used is adequately valid and reliable Outcome measurement used is adequately valid and reliable Study confounding: clear definitions of the important confounders are measured Study confounding: clear definitions of the important confounders measured are Study confounding: appropriate methods are used if important confounders is adequately valid and reliable Study confounding: appropriate methods are used if important confounders is adequately valid and reliable Study confounding: appropriate methods are used if important confounders are measured Study confounding: appropriate methods are used if important confounders is adequately valid and reliable Study confounding: important potential confounders are accounted for in the study design Study confounding: important potential confounders are accounted for in the analysis Statistical analysis and reporting: the selected statistical model is adequate for the design of the study <b>b</b>	25%	50%	75%	
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Study participation: description of baseline study sample				
Study participation: description of baseline study earspla				
Study participation, adequate participation in the study by engible individuals				
Study participation: adequate description of inclusion and exclusion criteria				
Study participation: adequate description of place of recruitment				
Study participation: adequate description of recruitment period				
Study participation: adequate description of sampling frame and recruitment				
Study participation: description of source of population or population of interest				

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#### (A) Fasting blood glucose: Poor outcome

	Study	TE	seTE		Risk Ratio		RR	95%-CI	Weight
	Fadini GP; 2020 (/2)	0.14	1 0.0355			9	1.15	[1.07; 1.23]	44.9%
	Li H; 2020 (≥7.0 vs <7.0)	0.09	0.0143		· ·		1.09	[1.06; 1.13]	49.1%
	Zhang J; 2020 (≥7.0 vs <5.6)	1.26	6 0.4429				3.53	[1.48; 8.41]	2.7%
	Zhang Y(1); 2020 (≥7.0 vs <7.0	) 1.31	0.3890			• :	3.70	[1.73; 7.93]	3.4%
	Random effects model				$\diamond$		1.20	[1.04; 1.39]	100.0%
	Heterogeneity: $I^2 = 84\%$ , $\tau^2 = 0.0$	)110, p	< 0.01			1			
				0.2	0.5 1 2	5			
(B) F	asting blood glucose: M	ortal	ity						
	Study	TE	seTE		Risk Ratio	F	RR	95%-CI	Weight
	Cai Y: 2020 (≥7.0 vs <7.0)	0.75	0.3111		- <u>ia</u>	2	11	[1.15: 3.88]	8.9%
	Chang MC: 2020	0.01	0.0033			1.	01	[1.01: 1.02]	18.7%
	Fadini GP: 2020 (/2)	0.03	0.0636			1.	03	0.91: 1.16	17.9%
	Han M: 2020 (≥7 0 vs <7 0)	1 07	0 3335		T	2	90	[1 51: 5 58]	82%
	Li Y 2020	173	0 5732			5	1 66	1 84 17 391	3.9%
	L  ond  Q 2020 (>6.1 vs <6.1)	0.67	0 2292		<u> </u>	1	96	[1 25: 3 07]	11.7%
	Wang S: 2020 (≥7 0 vs <6 1)	0.83	0 2215			2	30	[1 49: 3 55]	12.0%
	Wu I 2020 (>6 1 vs <6 1)	0.61	0 2451			1	84	[1 14 2 97]	11 1%
		0.01					~		

#### Random effects model

Heterogeneity:  $l^2 = 87\%$ ,  $\tau^2 = 0.0874$ , p < 0.01

Yang JK; 2020 (≥7.0 vs <7.0) 1.32 0.5562

Zhang J; 2020 (≥7.0 vs <5.6) 1.83 0.6048

6.25 [1.91; 20.45] 1.81 [1.41; 2.33] 100.0% < Т 0.1 0.5 1 2 10

3.75 [1.26; 11.16]

4.1%

3.6%

#### (C) Fasting blood glucose: Severity

Study	TE	seTE	Risk Ratio	RR	95%-CI	Weight
Li Y; 2020 (≥6.1 vs <6.1)	0.89	0.2744		2.44	[1.43; 4.18]	16.6%
Liu S; 2020 (≥11.1 vs <7.0)	2.45	0.4867		11.55	[4.45; 29.98]	11.1%
Wang S; 2020 (≥7.0 vs <6.1)	0.81	0.0821		2.24	[1.91; 2.63]	21.1%
Wu J; 2020 (≥6.1 vs <6.1)	0.61	0.2451		1.84	[1.14; 2.97]	17.4%
Yang JK 2020 (≥7.0 vs <7.0)	1.57	0.5717		4.82	[1.57; 14.78]	9.4%
Zhang J; 2020 (≥7.0 vs <5.6)	1.18	0.2895		3.26	[1.85; 5.75]	16.2%
Zhu B(1); 2020 (>7.05 vs 4.74-5.2	1) 3.17	0.6427		- 23.85	[6.77; 84.07]	8.2%
Random effects model				3.65	[2.31; 5.75]	100. <b>0</b> %
Heterogeneity: $I^2 = 78\%$ , $\tau^2 = 0.249$	5, p < 0.0	1				
			0.1 0.51 2 10			
		Committee and a second second second				

Г

#### (D) Random blood glucose: ICU admission

TE	seTE	Risk Ratio	RR	95%-CI	Weight
0.05 0.45	0.0047 0.1513		1.05 - 1.57	[1.04; 1.06] [1.16; 2.11]	57.1% 42.9%
el τ <sup>2</sup> = 0.069	1, p < 0.01		1.25	[0.84; 1.84]	100.0%
	<b>TE</b> 0.05 0.45 $\tau^2 = 0.069$	TE seTE 0.05  0.0047 0.45  0.1513 st $\tau^2 = 0.0691, p < 0.01$	TE seTE Risk Ratio 0.05 0.0047 0.45 0.1513 $\tau^2 = 0.0691, p < 0.01$	TE     seTE     Risk Ratio     RR $0.05$ $0.0047$ 1.05 $0.45$ $0.1513$ 1.57 $t^2 = 0.0691, p < 0.01$ 1.25	TE     seTE     Risk Ratio     RR     95%-Cl $0.05$ $0.0047$ $1.05$ $[1.04; 1.06]$ $0.45$ $0.1513$ $1.57$ $[1.16; 2.11]$ el $1.25$ $[0.84; 1.84]$ $\tau^2 = 0.0691, p < 0.01$ $0.5$ $1$ $2$

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#### (A) Linear dose-response: Poor outcome



224 records identified from 11 similar systematic reviews/metaanalyses

# Records after duplicates removed (n = 541)

Titles and abstracts screened (n = 541)

Full-text articles assessed for eligibility (n = 59)

Studies included (n = 34)

Additional records identified from Reference lists : 44 Similar articles algorithm : 801

Studies included in qualitative synthesis (n = 35)

Studies included in quantitative synthesis (n = 25) Records excluded (n = 482)

Full-text articles excluded (n =25)

- 13 studies with inappropriate designs (7 letters to editor, 6 case series/reports)
- 5 studies with inappropriate settings (i.e. BG obtained during hospitalization and not at admission)
- 4 studies not in English
- 2 irretrievable full-text articles (i.e. conference abstracts)
- 1 studies with unidentifiable settings (i.e. unknown BG marker)

Studies excluded (n=10)

- 7 studies only reported p value
- 3 studies reported different outcome measures



Study participation: description of source of population or population of interest Study participation: adequate description of sampling frame and recruitment Study participation: adequate description of recruitment period Study participation: adequate description of place of recruitment Study participation: adequate description of inclusion and exclusion criteria Study participation: adequate participation in the study by eligible individuals Study participation: description of baseline study sample Study attrition: adequate response rate for study participants Study attrition: description of participants who dropped out Study attrition: reasons for loss to follow-up provided Study attrition: no important differences between participants who completed the study and those who did not Blood glucose measurement: a clear definition or description of blood glucose measured is provided

Blood glucose measurement: continuous variables reported or appropriate cut points used

Blood glucose measurement: method and setting of measurement of blood glucose is the same for all study participants Blood glucose measurement: adequate proportion of the study sample has complete data for blood glucose variable Outcome measurement: clear definition of the outcome provided

Outcome measurement: method of outcome measurement used is adequately valid and reliable Outcome measurement: method and setting of outcome measurement is the same for all study participants Study confounding: important confounders are measured

Study confounding: clear definitions of the important confounders measured are provided Study confounding: measurement of confounders is adequately valid and reliable Study confounding: same method and setting of confounding measurement in all study participants Study confounding: appropriate methods are used if imputation is used for missing confounder data Study confounding: important potential confounders are accounted for in the study design Study confounding: important potential confounders are accounted for in the analysis Statistical analysis and reporting: sufficient presentation of data to assess the adequacy of the analysis

Statistical analysis and reporting: the selected statistical model is adequate for the design of the study

## (A) Fasting blood glucose: Poor outcome

Study Rxiv preprint doi: https://doi.org/10.1101/10/20.0958 1/200774; this versio Riska Ration ber 27, 2020. The RR right holes 1/2 Weight preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC 4.0 International license . Fadini GP; 2020 (/2) 44.9% 1.15 [1.07; 1.23] Li H: 2020 (≥7.0 vs <7.0) 0.09 0.0143 1.09 [1.06; 1.13] 49.1% Zhang J: 2020 (≥7.0 vs <5.6) 3.53 [1.48: 8.41] 2.7% 1.26 0.4429 Zhang Y(1): 2020 (≥7.0 vs <7.0) 1.31 0.3890 3.70 [1.73: 7.93] 3.4% Random effects model 1.20 [1.04; 1.39] 100.0% Heterogeneity:  $I^2 = 84\%$ ,  $\tau^2 = 0.0110$ , p < 0.010.2 0.5 2 5 1

## (B) Fasting blood glucose: Mortality

Study

Study

Ctudy

Cai Y; 2020 (≥7.0 vs <7.0) 0.75 0.3111 Chang MC: 2020 0.01 0.0033 Fadini GP; 2020 (/2) 0.03 0.0636 Han M; 2020 (≥7.0 vs <7.0) 1.07 0.3335 Li Y; 2020 1.73 0.5732 Long Q: 2020 (≥6.1 vs <6.1) 0.67 0.2292 Wang S; 2020 (≥7.0 vs <6.1) 0.83 0.2215 Wu J; 2020 (≥6.1 vs <6.1) 0.61 0.2451 Yang JK; 2020 (≥7.0 vs <7.0) 1.32 0.5562 Zhang J: 2020 (≥7.0 vs <5.6) 1.83 0.6048

TE seTE

Random effects model

Heterogeneity:  $I^2 = 87\%$ ,  $\tau^2 = 0.0874$ , p < 0.01



## (C) Fasting blood glucose: Severity

Study	TE	seTE
Li Y; 2020 (≥6.1 vs <6.1)	0.89	0.2744
Liu S; 2020 (≥11.1 vs <7.0)	2.45	0.4867
Wang S; 2020 (≥7.0 vs <6.1)	0.81	0.0821
Wu J; 2020 (≥6.1 vs <6.1)	0.61	0.2451
Yang JK 2020 (≥7.0 vs <7.0)	1.57	0.5717
Zhang J; 2020 (≥7.0 vs <5.6)	1.18	0.2895
Zhu B(1); 2020 (>7.05 vs 4.74-5.21)	3.17	0.6427

## Random effects model

Heterogeneity:  $l^2 = 78\%$ ,  $\tau^2 = 0.2495$ , p < 0.01

## (D) Random blood glucose: ICU admission

Study	16	SEIL
Zhou J; 2020	0.05	0.0047
Mejía-Vilet JM; 2020	0.45	0.1513

Random effects model

Heterogeneity:  $I^2 = 86\%$ ,  $\tau^2 = 0.0691$ , p < 0.01

0.5



R	95%-CI	Weight	

2.44	[1.43; 4.18]	16.6%
11.55	[4.45; 29.98]	11.1%
2.24	[1.91; 2.63]	21.1%
1.84	[1.14; 2.97]	17.4%
4.82	[1.57; 14.78]	9.4%
3.26	[1.85; 5.75]	16.2%
- 23.85	[6.77; 84.07]	8.2%

3.65 [2.31; 5.75] 100.0%

Risk Ratio	RR	95%-CI	Weight
	1.05 1.57	[1.04; 1.06] [1.16; 2.11]	57.1% 42.9%
	1.25	[0.84; 1.84]	100.0%
1 2			



### Random effects model

Heterogeneity:  $I^2 = 11\%$ ,  $\tau^2 = 0.0003$ , p = 0.33

0.75

1

1.5

1.33 [1.26; 1.40] 100.0%

## (D) Non-linear dose-response: Severity



Admission FBG level, mmol/L