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CERTIFICATE OF ACCEPTANCE

Certificate of acceptance for the manuscript (**pathophysiology-2086484**) titled:

Are HbA1c and random blood glucose associated with mortality of diabetic COVID-19 patients? – A retrospective study in Indonesia

Authored by:

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Basel, April 2023

Dear reviewers,

Thank you for your invaluable comments and suggestions. Our responses related to your questions or comments are given below:

Reviewer 2			
Comments	**Reply by the authors**	**The first line indicates when the Track-changes function is set as "All Markup & Show Revision Inline" mode**	**Changes done in the manuscript.**
The majority of the comments were implemented as suggested by the authors. However, some minor changes are still needed in the conclusion section. Instead of beginning, "We did.....like that...", I would suggest beginning with novel findings.	Thank you for your suggestion. We have revised our conclusion and omitted "We did …" and begin with novel findings	L221-223	*HbA1c level has no association with mortality of COVID-19 patients with T2DM. In contrast, RBG level was an independent risk factor of mortality among individuals with SARS-CoV-2 infection and T2DM*

Faculty of Medicine
Universitas Airlangga
INDONESIA

14 February 2023

Editor-in-Chief
Pathophysiology

Re: Revised manuscript "**Random Blood Glucose but not HbA1c was Associated with Mortality in COVID-19 patients with Type 2 Diabetes Mellitus – A Retrospective Study**"

We would like to thank you for your email on 6 February 2023 and for giving us the opportunity to revise our manuscript. We have carefully revised our manuscript in response to the extensive and insightful comments from all reviewers.

In particular, we have provided:
1. The title has been revised as suggested by the editor
2. We have updated the statistical analysis based on reviewer #1 recommendation. Therefore, we have updated the Table 2 and 3.
3. Some major and minor revisions have been made based on reviewer #1 and #2 recommendations.

Our manuscript has been re-proofread to ensure the clarity of the meaning. The details can be seen in Responses to Reviewer file.

Sincerely yours,
Corresponding author

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Comments	Reply by the authors	The first line indicates when the Track-changes function is set as "All Markup & Show Revision Inline" mode	Changes done in the manuscript.
Editor			
The title should not include references to Indonesia	Thank you for the suggestion. We have omitted the word "Indonesia" in the title	Title	*Random Blood Glucose but not HbA1c was Associated with Mortality in COVID-19 patients with Type 2 Diabetes Mellitus – A Retrospective Study*
The title shod be more like "Random blood glucose but not HbA1c was associated with mortality in COVID-19 patients with T2DM"	Thank you for pointing this out. We have revised the title to "Random Blood Glucose but not HbA1c was Associated with Mortality in COVID-19 patients with Type 2 Diabetes Mellitus – A Retrospective Study"	Title	*Random Blood Glucose but not HbA1c was Associated with Mortality in COVID-19 patients with Type 2 Diabetes Mellitus – A Retrospective Study*
The English construction needs complete review- don't say 'A study... either say our study or whose study" Many examples like this. The study cannot be accepted for publication until the English	The manuscript has been proofread and edited. All the edits have been tracked changes.	The entire manuscript	The entire manuscript

construction and grammar are adjusted.			
Reviewer 1			
Major Points			
1. This is quite a small study, which probably explains the lack of statistical significant associations for well-established risk factors such as presence of cardiovascular disease, hypertension and male sex.	Thank you for the suggestions. We found that, for sex in particular, the result was diverse in several studies including the bigger study. Our study was single-centered, indeed it was a small study, which is one of our limitations.	NA	NA
2. Males are under-represented suggesting patient selection was biased.	We thank you for your opinion. But in our study, males made up 52.7% (125 subjects) of the subjects. Furthermore, we matched age, sex, and disease severity in our analysis between survival and non-survival groups to reduce confounding factors. We decided to match sex because previous studies revealed different conclusions regarding the relationships between sex and mortality.	See Table 1.	Table 1.
3. The small number of males also makes it difficult to make any definitive conclusions on sex differences.	We appreciate your opinion. Our study consisted of 125 males and 112 females indicating that the ratio of males/females is quite balanced. Males slightly dominated the subjects (52.7%). Therefore, we believe statistics are acceptable.	NA	NA

4. Rather than dichomotise most continuous variables, it would be more appropriate to compare means/medians of these variables between survivors and non-survivors and to perform logistic regression with mortality as the dependent variable and the variables of interest entered as (continuous) co-variates.	We deeply thank you for pointing this out. We realized that it would be more suitable to analyze the variables as continuous variables (ratio) as suggested. We have run the logistic regression and results are presented in Table 2 and Table 3	Table 2 and Table 3	Table 2 and Table 3
5. It is not clear why the authors chose a cut-off for serum ferritin of 2144.2.	We initially chose a cut-off for ferritin of 2144.2 based on Youden's J statistic and AUC which bring the best sensitivity and specificity. But it is no longer relevant because we have changed it to a ratio (continuous) variable.	NA	NA
6. In the Discussion, authors should mention a possible explanation of high blood glucose with mortality could be that high glucose is marker of a stress hormone response and therefore, of a more severe infection	Thank you for the suggestion. We have provided some possible explanations of how RBG could increase the mortality of COVID-19 in T2DM patients.	L264	*There are some possible explanations of how RBG could be an independent risk factor for COVID-19 mortality in T2DM individuals: (1) high blood glucose in T2DM patients could modulate inflammatory responses leading to severe COVID-19 and predispose cytokine storm-associated death [8]; (2) increased glucose level could promote the replication of SARS-CoV-2 via mitochondrial ROS and hypoxia-inducible factor 1-alpha [26]; (3) high blood glucose might cause glucotoxicity that could lead to interstitial lung*

			damage and therefore increase the risk of ARDS and death [8]; and (4) elevated blood glucose also could cause endothelial damages and this associates with risk of thromboembolic events such as pulmonary embolism [8].
Minor Points			
7. Can the authors confirm that they measured blood glucose rather than plasma glucose.	We measured plasma glucose rather than whole blood glucose, based on national and international recommendations. We have added this statement in the method section.	L105	*"Random blood glucose was measured as venous plasma glucose in mg/dL"*
8. There is a typographical error in the sentence, 'Based on HbA1c level, patients were grouped into good glycemic 73 control (HbA1c level < 7% for <65 years old patients and HbA1c level < 8% for < 65 years 74 old patients)' (Section 2.2).co-variates.	Thank you for pointing this out. We have omitted this sentence because we have changed it to continuous variable.	L108	Deleted: *"Based on HbA1c level, patients were grouped into good glycemic control (HbA1c level < 7% for <65 years old patients and HbA1c level < 8% for < 65 years old patients) and poor glycemic control (HbA1c level > 7% for < 65 years old patients and HbA1c level < 8% for > 65 years old patients)."*
9. The percentages of survivors and non survivors do not add up (Table 1).	We've checked percentages in the survival and non-survival group. 71.3 % + 28.7% = 100%. For the percentage in each category, a total of 100% will be met in each column. For instance, gender in the total column is 52.7% male + 47.3 % female = 100%). Gender in Survivor group: 49.7%+50.3%=100%.	See Table 1	Table 1

	Severity in Non-survivors: 22.1% + 77.9=100%. It is not Survivor + Non-survivor group will be 100% because each group has different denominators (169 vs 68 for the survivors and non-survivors).		

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Title: Are HbA1c and random blood glucose associated with mortality of diabetic COVID-19 patients? – A retrospective study in Indonesia Although study looks interesting there are issues with this manuscript.	Thank you for reviewing our manuscript. The comments and suggestions have improved the quality of our current manuscript significantly. Your suggestions have been addressed as below.	NA	NA
1. Introduction: -This section requires more details, mostly about type 2 diabetes, obesity, insulin resistance, and diabetes complications, and the authors should clarify the link between diabetes and COVID-19.	Thank you for your suggestions. We have added more detailed about type 2 diabetes, insulin resistance and its complication.	L60	*T2DM is associated insulin resistance, a compensatory state due to continuous increase of insulin production [9]. Elevated insulin will cause obesity and this will lead to insulin resistance – making continuous cycle until pancreatic beta-cells inadequately meet the insulin demand [9]. This condition results long-term hyperglycemia that leads to diabetes complications: macrovascular complications (cardiovascular disease, peripheral artery disease or stroke), microvascular complications (nephropathy, neuropathy, or*

			retinopathy) or miscellaneous complications such as thyroid dysfunction [9].
	We also have provided the clear link between diabetes and COVID-19.	L46	*SARS-CoV-2 infection in T2DM could cause severe disease and higher mortality because some of close interactions: (1) hyperglycemia state in T2DM patients could modulate inflammatory responses and therefore predisposing to severe COVID-19; (2) SARS-CoV-2 infection in T2DM individuals could increase the reactive oxygen species (ROS) and inflammatory cytokines such as interleukin 6 and interferon gamma and this could increase the chance for acute lung damage and acute respiratory distress syndrome (ARDS); (3) SARS-CoV-2 infection in T2DM individuals could induce insulin resistance and this could induce hyperglycemia and vascular endothelial damages leading to disseminated intravascular coagulation, thromboembolism or cardiovascular events; and (4) in diabetic patients, ACE-2 receptors, receptors for SARS-CoV-2 entry into host cells, are expressed more prevalent causing higher SARS-CoV-2 and therefore increased severity of pneumonia [8].*
-The authors should clarify the novelty of this article in the 'Introduction' and 'Conclusion' section.	Thank you. We have provided the novelty both in Introduction and Conclusion.	L76	*Furthermore, a study evaluating the association between HbA1C or RBG and mortality has never been done in Indonesia to this date to the best of our knowledge*
		L291	*We did the first retrospective study assessing the role of both HbA1c and RBG as predictors of COVID-19 mortality among T2DM individuals in Indonesia.*

2. Materials and methods: -The following sentence is unclear. It makes no difference and is instead repeated. "Based on HbA1c level, patients were grouped into good glycemic control (HbA1c level < 7% for <65 years old patients and HbA1c level < 8% for < 65 years old patients)"	This sentence has been removed because now the HbA1c level has been removed because now it is treated as continuous variable as recommended by another reviewer.	L108	Deleted text: "*Based on HbA1c level, patients were grouped into good glycemic control (HbA1c level < 7% for <65 years old patients and HbA1c level < 8% for < 65 years old patients) and poor glycemic control (HbA1c level > 7% for < 65 years old patients and HbA1c level < 8% for > 65 years old patients).*"
3. Results: -Why there is so many variations in the results of various parameters of patients. Justify it.	We have revised the results in Table 3 to make it simpler and the analysis has been changed based on the recommendation of another reviewer.	Table 3	Table 3
4. Discussion: -How is this article more informative than the previously published ones? Justify it.	Thank you for your question. To the best of our knowledge, this is the first study assessing both HbA1c and RBG as mortality predictors of T2DM patients infected with COVID-19. Furthermore, previous studies yielded different results regarding HbA1c as a mortality predictor	L71; L76	*A systematic review conducted to assess whether HbA1c and RBG are associated with mortality of COVID-19 patients with T2DM [14] yielded inconsistent results. Furthermore, a study evaluating the association between HbA1C or RBG and mortality has never been done in Indonesia to this date to the best of our knowledge.*
5. Conclusion: - This section is unclear to the reader. Authors should write in a	Thank you. Now we have revised our conclusion to be more concise focusing	L292	*Our study found that HbA1c level has no association with mortality of COVID-19 patients with T2DM. In contrast, we have proven that RBG level was an*

concise manner, emphasizing on their outcomes and future prospects.	on our study results and future prospects.		*independent risk factor of mortality among individuals with SARS-CoV-2 infection and T2DM. Therefore, RBG level needs to be measured as early as possible in COVID-19-confirmed individuals with T2DM in order to establish early management to prevent mortality.*