

Review report

Final title: Admission glycemic gap and other glycemic indices in assessing the need for mechanical ventilation among neurocritical patients with diabetes mellitus

Title at submission: Effect and predictive value of admission glycemic gap and other glycemic parameters on the need for mechanical ventilation and renal replacement therapy among diabetic neurocritical patient



OPEN ACCESS

Round 1

Reviewer: Tapati Basak, ORCID: 0000-0001-8052-061X

Overview

The authors conducted this study to explore the relationship between the admission glycemic gap and other glycemic parameters at ICU admission and their predictive value for the need for mechanical ventilation and renal replacement therapy in neurocritical patients with DM. Admission glucose and AGG potentially predicted the need for MV but not the need for RRT. They also established a cut-off value of 3.2125 mmol/L for AGG,

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Keywords

neurocritical care, diabetes mellitus, admission glycemic gap, glycemic parameters, mechanical ventilation.

Funding

None

Ethical approval

Approved by IRB of Bangabandhu Sheikh Mujib Medical University (BSMMU/2022/2412, Registration No - 4132).

Trail registration number

Not obtained

Declaration

This article encompasses MD thesis of Kazi Tuba-E Mozaffia

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|---|-----------------|---|
| 1 | Comment | Please use 'person-first language' (e.g., patient with diabetes, instead of diabetic patient) throughout the manuscript. |
| | Response | Thank you for your suggestions. We have revised and corrected it throughout the manuscript. |
| 2 | Comment | Were those with previously diagnosed respiratory illness (e.g., COPD, bronchial asthma) included in this study? |
| | Response | Thank you for the question. Those with previously diagnosed respiratory illnesses were not ruled out of the study. However, we analyzed whether respiratory illness (e.g., COPD, bronchial asthma) has any statistical association with (MV and RRT) as these can confound MV. There was no statistically significant association between h/o respiratory illness and the |
| 3 | Comment | Please mention the instruments with manufacturer and country of origin used for HbA1c |
| | Response | Thank you for your suggestions. We have clarified the name and origin of the instruments in our revised manuscript (Page 8, Lines 178-186). |
| 4 | Comment | Capillary blood glucose may be misleading in ICU settings for many reasons. The authors have acknowledged this as a limitation of the study. |
| | Response | Thank you for your comment and we agree with your observation. Therefore, we have acknowledged this limitation. However, before collecting data glucometer and laboratory oxidase methods were compared in the pre-test, and the variation was less than 0.5 mmol. |
| 5 | Comment | How was the sample size (60) determined? Does it give adequate power to the study? |
| | Response | Thank you for the quarry. We calculated the sample size with the sample size calculation method using the area under the receiver operating curve (AUROC) value in the Medcalc software (MedCalc - version 23.1.1). We used the AUROC of AGG for respiratory failure among ICU patients with DM failure in the work of Donagaon and Dharmalingam, 2018. Sample size calculation considered acceptable error as 5% and 80% strength. Our calculated minimum sample size was 54. We included a summary of the calculation in the revised manuscript. (Page 7, Lines 143-148). Donagaon, S. & Dharmalingam, M., 2018. Association between Glycemic Gap and Adverse Outcomes in Critically Ill Patients with Diabetes. Indian |
| 6 | Comment | Were the data in normal distribution? Was it tested for normality? |
| | Response | Thank you for the question. Normality tests were performed for all continuous variables in the data set. Tests were chosen according to the data's distribution. For normally distributed data, T-tests were performed, and for non-normally distributed data or skewed data, the Mann-Whitney U test was performed. In the Tables, we mentioned all the tests done for each |

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It's a good paper. Objectives were fair. Justification of the study was time demanding. Methodology was rational. Description and analysis were clear. Few things should be addressed which have been mentioned before publication.

7 **Comment** It's not clear Whether any patient needs both MV and RRT.

Response Thank you for your observation. We have added the number of patients who needed both MV and RRT in our result section. (Page 10, Line 225).

8 **Comment** Were those with previously diagnosed respiratory illness (e.g., COPD, bronchial asthma) included in this study?

Response Thank you for the question. Those with previously diagnosed respiratory illnesses were not ruled out of the study. However, we analyzed whether respiratory illness (e.g., COPD, bronchial asthma) has any statistical association with (MV and RRT) as these can confound MV. There was no statistically significant association between h/o respiratory illness and the need for MV/RRT (The findings shown in Table 1).

Responsible editor: Tahniyah Haq, ORCID: 0000-0002-0863-0619

9 **Comment** Reference 26 "Mozazfia KT-E, Mondol MK, Mazumder MK, Kader MA, Roy GC, Habibullah 406 AKM, Sultana S, Ahmed M. Association of Admission Glycemic Gap on Short407 term Outcome of Neuro-critical Patients with Diabetes. My-mensingh Med J. 2024;33(3):868–75. <https://pubmed.ncbi.nlm.nih.gov/38944734/>" is a similar publication by similar authors. Has this study been done on the same population? If so, is there any overlap in the method and result? May I request a copy of the article?

Response Thank you for the observation. The study includes the same samples. However, we ensured sample size was adequate for both methods. Sample size calculation summary for current work added in the revision (Page 7, Lines 143-148). However, except for the study place and selection criteria: data collection tools, analysis, and results differ in the two studies. There is no overlap in the results except in the demography. We added a scanned copy of that article as an additional file in the submission of the revision.

10 **Comment** The main objective and analysis focuses on the prediction of mechanical ventilation and RRT. Therefore, I think a more suited title would be "Predictive value of admission glycemic gap and other glycemic parameters on the need for mechanical ventilation and renal replacement therapy among neurocritical patients with diabetes mellitus", omitting "effect", as this was not really seen in the study.

Response Thank you for the suggestion. We also agree with your observation and edited the title accordingly.

11 **Comment** In the highlights, I think that it is important to mention that AGG and other glycaemic parameters did not predict RRT. This negative finding is also important. Is there a need for the first point?

Response Thank you for your observation. The negative finding regarding RRT is added in the highlights with the previous first point removed (Page 4, Lines 84-91).

12 **Comment** In the introduction, please talk more about AGG and why it is important among the glycaemic parameters. Are there any other recent studies on AGG use in ICU?

Response Thank you for your comment. We have revised the introduction and added information per your suggestions (Page 6, Lines 120-133).

13 **Comment** In the methods, please mention the glucometer used, along with its precision. Was the same glucometer used for all the patients?

Response Thank you for your suggestion. The same glucometer was used for all sixty patients. In our revised manuscript, we have clarified the names and origins of the instruments (Page 8, Lines 178-186).

14 **Comment** In the results, It would be good to give a description of the overall population in the beginning

Response Thank you for your suggestion. We have added an overall population description at the beginning (Pages 9-10, Lines 215-220).

15 **Comment** Please give a more meaningful interpretation in lines 183-184 and 192-19. For example, which group was significantly higher or had more cases? Just saying that there was a significant difference is not enough.

Response Thank you for the suggestions. We have revised and rephrased (Page 10, Lines 225-227)/ corrected with stating the groups (Page 10, Lines 234-236).

16 **Comment** In line 203, correlation should not be used as it specifies a test which was not done.

Response Thank you for the guidance. 'Correlation' was replaced with 'association' (Page 11, Line 245).

17 **Comment** In line 210, please do not say strongly significant. P value being very low does not imply that. The data is simply significant. The value of the OR is more important. The finding here is important. It can be written like this "All 4 glycaemic parameters (.....AGG, HbA1c....) significantly increased the risk of MV, but not RRT in neurocritical ICU pts with DM. HbA1c showed the greatest risk. Then give the interpretation of OR in each case as you have described."

Response Thank you for the guidance. Revised, removed, rephrased/ corrected as per the suggestions (Page 11, Line 250-252).

18 **Comment** In line 216, please omit the word "moreover".

Response Thank you. We revised and omitted.

Round 2

Reviewer: Tapati Basak, ORCID: 0000-0001-8052-061X

Thank you for your suggestions. We have revised and corrected it throughout the manuscript. Please consider the following point by point responses.

- 1 **Comment** Is the title appropriate? No
Estimation/prediction of predictive value...the meaning of the title is not clearly specifying the objective of the study. Moreover, it should be a "CASE STUDY among the patients of BSMMU for a specific duration".
- Response** Thank you for your suggestions. We have revised and corrected the title to 'Admission glycemic gap and other glycemic parameters in assessing the need for mechanical ventilation and renal replacement therapy among neurocritical patients with diabetes mellitus: A year-long case study on a medical university of Bangladesh.'
- 2 **Comment** Are the study objective(s) clearly stated and logical? No
No objectives are there in specific. It should be written very clearly--research objective, specific objectives
- Response** We revised this and corrected/elaborated/ specified the objectives in the last para of the introduction section.
- 3 **Comment** Is the rationale/justification for conducting the study clear? No
As the study objective is not clearly defined, it is hard to have the right direction about the structure of the research.
- Response** We revised this and corrected/elaborated/ specified the objectives in the last para of the introduction section, and thus, we hope clearly defined the objectives which would give the study a right direction.
- 4 **Comment** Are the methods described in sufficient detail so that the study could be reproduced? No
This is a case study which does not include all the variations from all over the country. But, the title is saying this study was conducted in general. What type of sampling methodology was used here? How the sample size was calculated for estimating the cut-off-value according to the selected sampling? How the relevant variables were selected for this study as well as for the logistic regression? No clear idea is there. More specifically, the Table 2 is showing 6 variables are significant. But only 4 variables were selected for the logistic regression. Why?
- Response** Thank you for the suggestions. We revised the title. We used the purposive sampling technique, which is mentioned in the design, place, population section.
We calculated the sample size with the sample size calculation method using the area under the receiver operating curve (AUROC) value in the Medcalc software (MedCalc - version 23.1.1). We used the AUROC of AGG for respiratory failure among ICU patients with DM in the work of Donagaon and Dharmalingam, 2018. Sample size calculation considered acceptable error as 5% and 80% strength. Our calculated minimum sample size was 54. We included a summary of the calculation in the design, place, population section of the revised manuscript.
Ref: Donagaon, S. & Dharmalingam, M., 2018. Association between Glycemic Gap and Adverse Outcomes in Critically Ill Patients with Diabetes. Indian journal of endocrinology and metabolism, 22(2), 208–211.
Thank you for the suggestions. We revised the title. We used the purposive sampling technique, which is mentioned in the design, place, population section.
We calculated the sample size with the sample size calculation method using the area under the receiver operating curve (AUROC) value in the Medcalc software (MedCalc - version 23.1.1). We used the AUROC of AGG for respiratory failure among ICU patients with DM in the work of Donagaon and Dharmalingam, 2018. Sample size calculation considered acceptable error as 5% and 80% strength. Our calculated minimum sample size was 54. We included a summary of the calculation in the design, place, population section of the revised manuscript.
Ref: Donagaon, S. & Dharmalingam, M., 2018. Association between Glycemic Gap and Adverse Outcomes in Critically Ill Patients with Diabetes. Indian journal of endocrinology and metabolism, 22(2), 208–211.
Fig: the screenshot of the software and sample size calculation.
All the variables were selected for this study as our literature review before and during the study showed these as potential factors that affect the need of MV or RRT among ICU patients. We revised and added this in the manuscript.
The four variables selected for logistic regression according to the general objective of the study, how AGG and other glycemic parameters (admission blood glucose, HbA1C, and ADAG) at ICU admission affect the need for MV and RRT in neurocritical patients with DM. Here, only simple logistic regression analyses were performed, and only single variables were selected for regression at a time, either with RRT or with mechanical ventilation. No multiple logistic regression models were performed. Since glycemic parameters, especially AGG, were the main predictor variables, we wanted to show any relation of each glycemic parameter with RRT and MV. Four simple logistic regressions were performed here. Did not build any model.
- 5 **Comment** Is the study design robust and appropriate to the stated objective(s)? No
Both the parametric and non-parametric testing approaches were applied without any justification. The results of the appropriate bivariate analysis are missing though the methodology mentioned about the bivariate analysis. Which bivariate analysis was performed here? (Table 2)--very ambiguous
"and 95% confidence interval (CI) was calculated simultaneously to identify the relationship of admission glycemic gap (AGG) with invasive mechanical ventilation and renal replacement therapy" (line 206-208)--is CI enough to speak about the association? Alpha (the pre-defined error) = 0.05, a popular value, not suitable for the sensitive analysis like this. Is this "alpha" same as for the sample size calculation and for the CI estimation? As the conclusions claiming about the prediction, it should be based on a suitable model.
What type of diagnostic check of multicollinearity was performed before going for the logistic regression? The results should be provided.

Response For normally distributed data, parametric tests were chosen, and tests were further selected based on the number of classes present to compare the mean, while for non-normally distributed data, non-parametric tests were chosen. We used skewness and kurtosis tests to identify the normality of the data. All the tests for bivariate analysis are listed below the table as separate notes including signs indicating the test's name for each variable.

We have corrected the relevant lines (line 206-208) in the corrected manuscript.

Alpha was the same for sample size calculation. Regression modeling was unsuitable for this study's prediction due to the lack of statistically significant associations between predictors and the outcome, indicating poor model fit.

The regression performed was just simple logistic regression addressing a single independent variable at a time. No modeling was done, that's why a multicollinearity check was not required for this simple logistic regression.

6 **Comment** Are statistics used appropriately and described fully? No

- no clear explanation about the sampling as well as the sample size calculation.
- the variable selection process for the overall study and for the consequent specific analysis are also missing
- lots of testing approaches without any justification
- association tests lack the specification of the null and the alternative hypotheses.
- the main drawback of this study is: the two-sided tests were carried out for all the specific tests. But, testing significance for a value from the pathological test must be set for one-sided tests. Testing with two-sided alternatives must mislead the results.

Response

- We detailed the sample size calculation in a previous query here, and also in the revised manuscript
- All the variables were selected for this study as our literature review before and during the study showed these as potential factors that affect the need of MV or RRT among ICU patients. We revised and added this in the manuscript
- Only relevant demographic, clinical and laboratory variables were included for analysis to see the potential association with the studied outcome.
- Since no predefined normal value was set for each category of dependent variable for the pathological test, a two-sided test was chosen. Similar studies conducted in different settings used two-sided tests for their study. I have attached the link to this. We have followed the method of these studies:

<https://journals.sagepub.com/doi/full/10.1177/08850666221101856>

<https://onlinelibrary.wiley.com/doi/full/10.1111/jdi.13606>

Thank you very much for your suggestions.

7 **Comment** Are the table(s) and figure(s) clear and appropriate to address the objective(s)? No
Do not provide the supportive results with the support of the study.

Response We revised and corrected/elaborated/ specified the objectives. We also made some changes in the tables to provide the supportive results.

8 **Comment** Is the Discussion section critical and comprehensive about the main message of the manuscript? No
Too large discussion is not supported by this very basic analysis.

Response We revised and edited and shortened the discussion section and removed parts that do not relate to the analysis in the result section.

9 **Comment** Are the conclusions drawn supported by the results/ data? No
Should be in detail. Very short and irrelevant with the too large description.

Response Thank you for the suggestions. We revised the conclusions according to the comment.

10 **Comment** Is the storytelling straightforward, clear (i.e., does not impede scientific meaning or cause confusion), and logical? No
Please have a look in the previous comments.

Response We revised the manuscript and made necessary changes according to all the previous comments.

Reviewer: M Mostafa Zaman, ORCID: 0000-0002-1736-1342

The authors have reported the predictive value of the admission glycemic gap and other indicators of the need for mechanical ventilation and renal replacement therapy in 60 ICU-based patients. Unfortunately, I do not see any predictive value in the study's findings. Therefore, I have major concerns about the manuscript.

11 **Comment** Is the work based on an author's thesis? This declaration is necessary for BSMMUJ.

Response This work is partially based on the data of the thesis work of Dr. Kazi Tuba-E Mozazfia, Exam Session: January 2024, Roll Number: 0103-001, BSMMU e-Registration: 19102010030102, Titled, "Effect of admission glycemic gap on short-term outcome in diabetic neurocritical patients". However, objective, further analyses, outcome measure, and results differ in the presented manuscript.

12 **Comment** The Methods section should have a subheading of "Ethical concerns" that the authors have addressed. The ethical approval has to be at the end of the manuscript, which the authors have provided.

Response Thank you for your observations and suggestions throughout the submission procedure.

- 13 **Comment** The most confusing area is the number of subjects. The authors recruited 60 patients, but the total number of those who required MV and RRT is 60 for each group! This has been presented persistently in Tables 1-3. The total is also 60. The analysis is for two parallel groups of MV and RRT. What do the authors want to prove here? Some variables are significantly associated with MV, but some are not. So what?
- Response** We are very sorry for any confusion. The authors recruited 60 patients, but the total number of those who required MV was n= 39 and RRT was n=13 in each group.
In all of Table 1-3, in columns 2 and 3, the groups are made to show the need for MV or RRT. Each of these two columns was subdivided into two more columns in row 2: No (those who didn't need MV/RRT) and Yes (those who needed MV/RRT). Therefore, in the 'need for MV' column, it shows that among the total 60 patients, n=21 patients didn't need MV and n=39 needed MV. And in 'need for RRT' shows n=47 patients didn't need RRT, and n=13 needed RRT. The subsequent rows present the data accordingly.
The authors used these tables to understand and show how and whether the variables affect the need for MV or RRT. The findings/ prove that patients with ischemic stroke, h/o insulin use, presenting with raised MAP, or higher ABGL, HbA1c (%), ADAG, AGG, are statistically more prone to require MV, can be helpful considering that the presence of any of this demographic/clinical/laboratory risk in patients should help the clinician in understanding the gravity of the patient condition.
- 14 **Comment** The text description of subjects differs in two places: 39 and 13 add to 52; elsewhere, it is 11 plus 39 plus 13, which sums up to 63.
- Response** Thank you for pointing out the possible pace of confusion. In the '39 and 13, which add to 52', the remaining 8 didn't need any of the MV and/or RRT. In the '11 plus 39 plus 13': among the 39 needing MV and 13 needing RRT, 11 are common who needed both the MV and RRT. These 11 patients are within the 52 (39+13) patients who needed MV or/and RRT. However, we made adjustments in the text to mitigate the possible confusion.
- 15 **Comment** The results in Table 4 are ORs (95% CIs). The title of the table indicates "regression," which is misleading. Do the authors mean linear regression (which does not provide ORs) or logistic regression? What were the dependent variables? How
- Response** Sorry for the ambiguous title. This should be a simple logistic regression analysis. Here, Mechanical ventilation (MV) and RRT were the dependent variables in each case. Mechanical ventilation and RRT were coded as 0 for a 'No' response (didn't need MV/RRT) and 1 for a 'Yes' response (needed MV/RRT). No multivariate modeling was done here; only simple logistic regression analysis was performed. We corrected the title of the table. Thank you again for your precious guidance throughout the submission.
- Responsible editor: Tahniyah Haq, ORCID: 0000-0002-0863-0619**
- 16 **Comment** Please omit the abbreviation "AGG" from the title. Title should not have any abbreviations.
- Response** Thank you for the suggestion. We also agree with your observation and edited the title accordingly.
- 17 **Comment** You do not need to write an overview. Please omit that. An overview of the study is given by the reviewers, as part of their comments
- Response** Thank you for the observation. We omitted the overview part.
- 18 **Comment** Instead of point by point highlights, please write the key message of your study in descriptive form in no more than 60 words. Our journal has changed this format.
- Response** Thank you for the correction. A key message part instead of highlights has been added in descriptive form (60 words) (Page 4, Lines 73-78).
- 19 **Comment** In the description of sample size calculation, you have provided us with a breakdown. Please mention the AUC values used in the text, so all the information needed to calculate sample size is in the text. Replace the word "strength" with
- Response** Thank you for your suggestion. We have revised and provided the AUC values used in the text (Page 7, Line 134), We also replaced the word "strength" with "power" in the mentioned line.
- 20 **Comment** In the description of participants in the results section (line 215-220), do not mention the frequency and percentages. Just describe in words?
- Response** Thank you for your suggestion. We have revised and in the mentioned section the frequency and percentages were removed and only described in words.
- 21 **Comment** Sample number should always be mentioned in all tables. It reflects the importance/meaning of the results.
- Response** Thank you for your valuable suggestion. We have added sample numbers in all tables.
- 22 **Comment** The superscripts (m,f etc) used are not the standard symbols used in tables. Please revise.
- Response** Thank you for your guidance here. We revised, and superscripts (m,f etc) were replaced with *, †, ‡, §.
- 23 **Comment** There is some overlap with the previous publication in Table 2 (investigation section of last column). Are these values
- Response** Thank you. We revised and the last column was removed as these values are not very necessary for overall result and