

The language quality of the article has been improved where necessary. All the additions and modifications have been highlighted by green highlight.

Reviewer 1:

Thank you for your comments. The response to each comment has been given below:

Comments: The following points about this systematic review on case report conducted for investigating SGLT2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis in COVID-19-Infected Patients are suggested 1. Objectives in abstract should be presented more clearly and completely.

Response: The objective in the introduction part of abstract has been improved.

2. How did you include unpublished studies in your review? which key terms you focused on?

Response: The unpublished studies were meant to be pre-prints or ahead-of-print articles. This word 'unpublished' has been changed in the abstract. The key terms have been mentioned in the methods part of abstract.

3. You wrote in results of abstract "...eight studies, encompassing a cohort of twelve patients..." how about other seven studies? Please revise and rewrite results; the results are not based on all studies.

Response: Our sample size comprised of 12 patients. There was one case series which had 5 patients and the other seven case reports had one patient each. All the studies were considered while writing the results. The has been clarified in the revised manuscript's abstract and main text.

4. It is expected to review with details the content of case report studies you included in your review in introduction section.

Response: Additions have been made to the last paragraph of the introduction.

5. How about the inclusion and exclusion criteria? 6. Please declare the PICO of your systematic review

Response: Inclusion, exclusion criteria, and PICO have been added to the methods.

7. Please refer to your search strategy in your methods section for those you appended at the end of manuscript.

Response: The search strategies given in supplement have been referred in the methods section..

8. How about the quality assessment, it is advisable to do it based on CARE checklist. You did it based on JBI , however where its results.

Response: The quality assessment has been redone using CARE checklist. Its results have been added in the results section. A table has been added as Supplementary Table 1.

9. Please present the key elements of each of the terms you mentioned them in the following sentence “. Information extracted from the articles included demographic background, comorbidities, disease onset, initial symptoms, laboratory tests, diabetes mellitus type, SGLT2 inhibitor type, study date, study design, treatment intervention, and case outcomes.”

Response: Details of all these parameters have been mentioned in Table 1.

10. What do you mean from study design , all included studies in your sys review are case report ?!!

Response: We only found relevant case studies which fit our PICO and they were qualitatively analyzed and discussed in our systematic review.

11. Diabetes mellitus type?!

Response: Both T2DM and T1DM were part of our inclusion.

12. Results: I see the sentence “We identified a total of eight studies, encompassing a cohort of twelve patients...” in abstract however I see other completely different sentence in main results section as “...including the United States (n=3), the United Kingdom (n=5), Brazil (n=1), Malaysia (n=1), and Belgium (n=2). “what do you mean from a cohort of patients consists of 12 ???

Response: This sentence in the results talks about the geographic location of patients included across our case reports. The cohort of 12 patients means our sample size consisted of 12 patients. Five patients from case series and seven patients from each case report.

13. The studies in this sentence “...including the United States (n=3), the United Kingdom (n=5), Brazil (n=1), Malaysia (n=1), and Belgium (n=2).” Should be referenced with their own reference number.

Response: The references have been cited in this sentence.

14. I see the following sentence “Out of the 12 patients, 11 had a favorable outcome and recovered” I results section; first :what is your sys review ‘s outcome? Second : what is the meaning of favorable? It should be declared in PICO ; Third: when I see the table 1 content , some (more than 1) did not report outcome?

Response: The outcomes have been defined in the PICO part of methods. The definition of favorable outcome has been added to the PICO part. The table 1 reported the outcome as whether the patients survived and discharged from the hospital or they died.

15. Generally your manuscript structure and content have not been organized in a way to infer clear conclusion with some big ambiguities as stated particularly in points no:12-14.

Response: The ambiguities have been cleared as mentioned above.

Reviewer # 2:

Comments: This review has an interesting topic. Authors elaborated the association between SGLT2 inhibitors and eu-DKA in diabetic patients with COVID-19. The results of this review can cause us to concern that SGLT2is might be used with great caution in COVID-19-infected diabetic patients. The article has delivered an important clinical message and should be of great interest to the readers. The submission is worthy of publication.

Response: Thank you for your rigorous review and comments on our article.

Reviewer # 3:

Comments: The paper from Khedar A. et al describes cases and a meta-analysis of euglycemic ketoacidosis (eu-DKA) in diabetes mellitus patients treated with SGLT2inhibitors and infected by SARS-COV-2. The paper is well written, the methodology used is adequate and the results, discussion and conclusions are well conducted. MAJOR CONCERN: The authors describe eu-DKA (pg. 11), as "severe metabolic acidosis despite normal glucose level", but in pg 9 they affirm that the glucose level of the patients was situated between 113 and 286 mg/dL. Therefore, you can talk about DKA and not about eu-DKA. Can you clarify this apparent controversy? As the authors recognized as a limitation in the discussion, the number of patients is very low in the current literature. I do not have MINOR concerns.

Response: We describe eu-DKA as “severe metabolic acidosis despite normal glucose level”, but also report that the glucose level of the patients was situated between 113 and 286 mg/dL. This may seem contradictory, but it is important to note that the definition of eu-DKA is not based on a specific glucose threshold, but rather on the absence of significant hyperglycemia. The normal range of blood glucose for non-diabetic individuals is between 70 and 140 mg/dL, but for diabetic patients, it may vary depending on their treatment goals and individual factors. Therefore, a blood glucose level of 113 to 286 mg/dL may not be considered high enough to cause DKA, but it may still be associated with eu-DKA in patients taking SGLT2 inhibitors. In fact, some studies have suggested that eu-DKA can occur even with blood glucose levels below 200 mg/dL. These articles are a source of evidence for the abovementioned statements:

1. <https://www.ncbi.nlm.nih.gov/books/NBK554570/>
2. <https://www.thediabetescouncil.com/euglycemic-diabetic-ketoacidosis/>
3. <https://link.springer.com/article/10.1007/s13340-020-00473-3>
4. <https://www.frontiersin.org/articles/10.3389/fsurg.2022.769041/full>

Reviewer # 4:

Comments: This manuscript submitted by Khedr A and co-workers investigated the outcomes and treatment of euglycemic diabetic ketoacidosis in COVID-19-infected diabetic patients taking SGLT2 inhibitors. Despite of some clinical interests, there was no in-depth analysis of the clinical features of the study population. Furthermore, the number of literatures and cases included in this systematic review was too few to conduct a sufficient meta-analysis and draw any definitive conclusions.

Response: Up to this point, the available literature primarily consists of case reports that discuss the pathophysiology of this intricate metabolic syndrome. As such, this systematic review represents a significant step forward in consolidating and analyzing the studies related to this topic. It is important to acknowledge that the nature of the evidence reviewed in this study limits our ability to draw definitive conclusions. Instead, this systematic review serves as a foundation for generating hypotheses and further exploration of the topic. By systematically evaluating the existing evidence, we aim to shed light on the potential associations and implications, paving the way for future research and more conclusive findings in this field.