Point-to-point response to reviewers' comments

We highly appreciate the comments raised by the editors and reviewers that help in improving our work and hope our replies and edits are sufficient. We really appreciate your time and effort.

Reviewer #1:

Dear authors, This is an important study and it has revealed significant results. However, there are still some comments:

1. Similarity Index: The similarity index is reported at 30%, which is considered high. The authors should review the manuscript for potential plagiarism and ensure that all sources are properly cited and paraphrased where necessary.

Many thanks for your comments. The manuscript was checked for potential plagiarism and it was reviewed again in our university system and now it is 18%. The report is attached.

2. IRB Approval: While the authors have attached the IRB approval, they did not state its number in the methodology. Including the IRB approval number is crucial for transparency and ethical compliance. This should be added to the methodology section.

Many thanks for your valuable comment. The IRB approval number is 00248/2021. and it was added in the manuscript.

3. Safety Reporting: The authors claim that dapagliflozin is safe but did not provide any literature on its safety concerning liver and heart functions. Additionally, they did not estimate liver enzymes, which is a significant omission given the patient population with cirrhosis. This weakens the claim of safety. Although: 3.1. Urinary infection was mentioned in the results of this work, it was not included in the final conclusion. and 3.2. It is common adverse reactions by "dapagliflozin " of include female genital mycotic infections, nasopharyngitis, and urinary tract infections. This omission could be perceived as biased and should be addressed for a balanced conclusion.

Many thanks for your valuable comment A - Dapagliflozin did not disrupt liver function tests. The apparent reduction in AST and neutral effect on other liver function parameters suggests dapagliflozin use as an add-on therapy to metformin in diabetic liver diseases. (Reference:- Hadid KA, Alassaf FA, Abed MN, Alsaaty MH. Assessment of Insulin Resistance, Oxidative Stress, and Liver Function in Type 2 Diabetic Patients on Dapagliflozin. Research Square; 2024. DOI: 10.21203/rs.3.rs-4456834/v1.)

B- Early dapagliflozin initiation did not increase diabetic, renal, or cardiovascular safety events, Early dapagliflozin during AHF hospitalization is safe and fulfills a component of Guideline- Directed Medical Therapy optimization.(Reference:- Zachary L., Sean P., Gabriel A., etal, Efficacy and Safety of Dapagliflozin in Patients With Acute Heart Failure, Journal of the American College of Cardiology Volume 83, Issue 14, 9 April 2024, Pages 1295-1306)

In our study, the incidence of urinary tract infection was lower in dapagliflozin treated group while the incidence of genital infection was higher among patients who received dapagliflozin treatment. No one of our studied patients complained of nasopharyngitis. (was addressed for balanced conclusion).

4. Sample Size: The study included 300 patients (100 on insulin and 200 on dapagliflozin), which seems reasonable. However, the justification for this sample

size should be provided to ensure it is statistically adequate for the outcomes measured.

Many thanks for this valuable comment. The sample size estimation is as the following

Epidemiology and preventive medicine department

Sample size estimation

Name: Zeinab Mohamed Seif el Din

Title of the study: Dapagliflozin as an oral Antihyperglycemic Agent in the Management of Diabetes Mellitus in patients with liver cirrhosis

Degree: MD's degree

Study design: COHORT study

Sample size estimation:

PS logging enabled 7/23/2024 2:12:21 PM
Version 3.1.2
Type of study: Dichotomous
Requested output: Sample size
How is the alternative hypothesis expressed? Two proportions
Matched or Independent? Independent
Case control? Prospective
Uncorrected chi-square or Fisher's exact test? Uncorrected chi-square test
alpha=0.05 power=0.8 P0=0.163 P1=0.041 M=1
Case sample size for uncorrected chi-squared test=95

We are planning a study of independent cases (exposed) and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.163. If the true failure rate for experimental subjects is 0.041, we will need to study 95

experimental subjects and 95 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared

Sample Sample size size: 100 per group

Ref

Dupont WD, Plummer WD: 'Power and Sample Size Calculations: A Review and Computer Program', Controlled Clinical Trials 1990; 11:116-28.

Sanden AK, Johansen MB, Pedersen L, Lervang HH, Schønheyder HC, Thomsen RW. Change from oral antidiabetic therapy to insulin and risk of urinary tract infections in Type 2 diabetic patients: a population-based prescription study. J Diabetes Complications. 2010 Nov-Dec;24(6):375-81. doi: 10.1016/j.jdiacomp.2010.01.002. Epub 2010 Mar 1. PMID: 20189833.

Shrikrishna A, Archana B. Prevalence of genitourinary infection in diabetic patients treated with SGLT 2 inhibitors. Afr Health Sci. 2023 Mar;23(1):270-275. doi: 10.4314/ahs.v23i1.29. PMID: 37545909; PMCID: PMC10398486.

Signature:

Sally Waheed Elkadry

Lecturer of Epidemiology &Biostatistics

5. Delay in Publication: The study was conducted in 2022, yet it has not been published. The reasons for this delay should be addressed. It might raise concerns about the study's validity or findings.

Death of one of supervisors and there was lag 9 months to change the supervisors.

6. Comparative Safety: The actions stated in the abstract are not sufficient to judge that dapagliflozin and its doses are safer than insulin treatment for these

patients. More comprehensive data on safety, including liver enzyme levels and heart function, are needed.

We appreciate this valued comment. Liver enzymes: AST was 49 before dapagliflozin then 44 after dapagliflozin while ALT was 30 before and after treatment with dapagliflozin so no substantial difference was observed in liver enzymes.

Heart function: Farxiga FDA Approval History

Last updated by Judith Stewart, BPharm on June 17, 2024.

FDA Approved: Yes (First approved January 8, 2014)

dapagliflozin) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor for use in the treatment of type 2 diabetes mellitus, heart failure, and chronic kidney disease.so in our study we did not approve its safety on heart functions.

7. Lack of Limitations: No limitations were stated in the study. Every study has limitations, and acknowledging them is important for understanding the context and generalizability of the findings. The authors should include a section on limitations.

Many thanks for your excellent supervision and valuable comment.

-Larger sample size is warranted.

-Short period of follow up.

-Lack of financial support.

-It was during the era of endemic Covid- 19which affect the enrollment of more patients.

8. Authors have to state the novelty of their work despite that this medicine"dapagliflozin" has been approved by FDA since 2014.

Many thanks for this valuable comment. The novelty is that we included cirrhotic patients even child C after their consent.

9. No references were cited in 2024. It is important to cite recent references to ensure the study is up-to-date with the latest research and developments in the field.

We really appreciate your meticulous observations. We changed the reference and did as you suggested.

6- Zachary L., Sean P., Gabriel A., etal, Efficacy and Safety of Dapagliflozin in Patients With Acute Heart Failure, Journal of the American College of Cardiology 2024 ; 83 (14): 1295-1306.

7- Hadid KA, Alassaf FA, Abed MN, Alsaaty MH. Assessment of Insulin Resistance, Oxidative Stress, and Liver Function in Type 2 Diabetic Patients on Dapagliflozin. Research Square; 2024. DOI: 10.21203/rs.3.rs-4456834/v1.