Peer Review Comments and Author Responses

Reviewer 1:

1. *This is an interesting systematic review concerning the efficacy and safety of gilteritinib in patients with Acute Myeloid Leukemia(AML) compared to salvage chemotherapy. The main findings are: (1)gilteritinib improves overall survival and remission rate; (2) combination therapy with Azacitidine is likely to be more effective than monotherapy;(3) gilteritinib shows some concerning adverse effects compared to the control group; and (4) this finding shows generality across multiple countries.*

Dear Reviewer 1,

Thank you for providing the feedback and suggestions. The addressed changes are explained below and made in the manuscript with track changes enabled.

My comments

Abstract:

2. *The background and aim of the study were explained very well. A suggestion is to be more concise in this part.*

We have concised the background and aim of the abstract in page 1.

3. *The methodological or aim section does not mention which will be their primary efficacy and safety outcome for this systematic review.*

Our systematic review focusses on the survival outcome and overall response from the treatment of gilteritinib as specified in the PICO (see page 3 and 4). We will not be addressing the safety outcome in this paper.

4. *Also, in the methods section, the author must address some of your study's most important eligibility criteria.*

We have corrected the important eligibility criteria as studies primarily on clinical trials and retrospective studies.

5. *The Results sections only focus on the efficacy outcomes. However, it is important to mention the safety findings of this study. Furthermore, some other major findings as the higher efficacy in combination therapy with Azacitidine should be mentioned.*

We have added in the results section of abstract.

6. *The conclusion also only gives an insight into the efficacy endpoint and not the safety. Our review focusses on the survival outcome and overall response from the treatment of gilteritinib.*

We will not be addressing the safety outcome in this paper

Introduction

7. *The author did a great job providing background on this systematic review. The only comment in this section would also mention the safety endpoints.*

We will not be addressing the safety, our focus is on survival outcome and response from gilteritinib in refractory/relapsed AML patients

Methods

8. *Very well explanation of the research question and also the gap in the literature.*

Thank you very much.

9. *The databases used, and a summary of the search strategy must be here.*

We have added the correction, see page 4 methods search strategy section

10. *Screening Process: How was the screening process done? The screening was done in one author, and in two authors, how was conflict resolved? Did the authors use any screening software, such as Zotero or Rayyan?*

The screening process was done by one author using endnote. Duplicates records were removed using endnote. See the Results study selection section for detailed screening process.

11. *Data Extraction: How was data extraction performed? Which variables did you plan to collect in your study? What outcomes did you collect for this systematic review?*

We have added Data Extraction in the Methods below search strategy section see page 5.

12. *How was the quality assessment performed? Did you use any quality assessment tools from Cochrane or did you New Castle Ottawa scale?*

We used Cochrane ROB2 tool for Randomized Clinical Trials and ROBINS-I for retrospective or observational studies for quality assessment. Please see the risk of bias explanation section and tool used in the risk of bias table (page 14).

13. *Did register the protocol for this systematic review in platforms like PROSPERO, as you mentioned you followed PRISMA guidelines one important step is to register the protocol from this study.*

The study was not registered in any platforms.

14. *The eligibility criteria were well described. However, there is no need to repeat the item that you used in the inclusion criteria in the exclusion criteria(e.g.: Studies published in English and Studies published in non-English languages.).*

Thank you. We have added the Correction.

Results

15. *Search strategy: This part here would be better placed in the methods section and them you present the results in of each search in the results section following the PRISMA Guidelines.*

Thank you for the reminder. We have added the Correction, see page 4.

16. *The authors should be congratulated for creating a well organized table 1. However, I recommend also to include some important baseline characteristics for the condition being studied. Also, please include a Legend section with the abbreviations at the bottom of the table.*

We have added a list of abbreviations below the table 1, page 8.

17. *In the Study Outcome Section, please also report the effect size and numerical values of each study's findings to help the reader to understand the magnitude of the efficacy and how reliable and robust those findings.*

We cannot assume the effect size in each selected article as it is not clearly stated. We cannot add that information to our paper.

18. *Great job creating the supplementary table and describing the safety outcomes. However, please state (if available) the effect size.*

We will not be focusing on the safety outcomes and its effect sizes..

19. *Risk of Bias: Please state in the text and in Table 5 the Overall Risk of Bias of the study.*

Please see page 14 risk of bias section.

Discussion

20. *The discussion focuses on the study's efficacy and generability. However, the major problem is the need for more explanation of the adverse effects and some opinions regarding the overall benefits for the patient when balancing efficacy and safety. The limitation of this systematic*

review based on the included articles exhibits a high level of listing of the adverse effects noticed. A proper reporting of the adverse effects were not detailed.

We cannot comment on the overall benefits for the patients based on the selected papers.

21. Also, in the observational studies, explain which confounders or other biases might influence the final results in these studies and how they can addressed in future research.

We have added in the discussion section see page 15

22. Try to explain the heterogeneity present in the study, giving a solid argument to sustain your opinion.

We have added in the discussion section see page 15

23. The limitation section presents only some of the possible problems in the evidence that you included. Please address this section adequately.

We have added in the conclusion section see page 15.

Conclusion

24. Please also include your safety major findings. Safety is not the aim of our research.

We would not be addressing it.

Thanks for the effort in writing this interesting paper.

Reviewer 2:
Recommendation: Revisions Required

This Systematic review provides a clear and comprehensive evaluation of the efficacy of gilteritinib in AML patients, FLT3 positive, highlighting the potential benefits of the therapy compare to traditional salvage chemotherapy, the introduction might benefit from a more detailed explanation of the key concepts and theories around the research question; equally important elaborating on gilteritinib's mechanism of action as a potent FLT3 inhibitor, is relevant in understanding its efficacy. Your discussion is thorough, however it would be beneficial to include more on the implications of these findings for clinical practice and future research directions.

Dear Reviewer 2,

Thank you providing the feedback. We have added more in the discussion and conclusion section regarding the future research directions (see page 15).

Reviewer 3:
Recommendation: Revisions Required

The authors successfully reviewed Gilteritinib clinical effectiveness in improving the overall survival outcome and its safety in the currently published literature. The RCTs included had low risk of bias and a considerable number of subjects, providing robustness to the report. After reading the review, it is clear that patients might benefit from this targeted therapy, potentially reducing adverse effects form alternative treatments. Regarding the observational studies, it was not entirely clear whether they were retrospective cohort studies. In addition, confounders and the methods used to control them (adjustments) were not mentioned.

The authors stated that "The Study outcome table covers only 3 of the 8 studies because of the incomplete data provided by the remaining studies 5.", but it is reasonable to argue that this incomplete data is relevant to readers and their conclusions. Perhaps included as a supplement to the main article. In addition, some results were reported in the discussion section.

Minor adjustments:

1. *References missing to support background literature in the introduction section.*
2. *References missing in the discussion section.*
3. *Line 179 – " The 5 retrospective (…) this patient with AML". patient referred in the text is not clear to the reader.*
4. *Line 184 – targeting instead of "targeted".*
5. *Line 323 –" In the 2 retrospective " – In 2 retrospective.*

Thank you providing the feedback. We have made all the above-mentioned corrections including addition of more studies in the study outcome table 3 (see page 11). References in the introductions are in superscript square brackets. We have explained about confounders and other factors in the Discussion and Conclusion section.

Reviewer 4:
Recommendation: Resubmit for Review

Hello Respected Authors

As per the review carried out the concerns from the review are the following:

Methods

1. *The sample size of the subjects seen in the retrospective & RCT studies were by far lesser in number & the concern was also regarding the study Hosono Et al- which had subjects in the comparison group- to various different combinations of treatment in small numbers where the outcomes cannot be consistently compared to one particular treatment & established better than it*

Results

2. *The outcomes of only 3 studies were reported clearly & the rest of the 5 studies were not reported to have a complete judgement of the outcomes added more in study outcome explanation and table 3.*

3. *The adverse effects of the studies- notably the RCT- ADMIRAL TRIAL- had discontinuation of gilteritinib - due to elevation of liver enzymes , similarly there was discontinuation of the study drug due to myelosuppression in Wang 2020 . Coming to the retrospective studies- there was 66.9% discontinuation of the study drug though promising initially - this poses significant safety concerns of the study drug to be able to implement safely especially in an elderly population.*

We are not focusing on the safety profile of the patients. Our aim is to assess the survival and response outcome from gilteritinib as specified in the methods PICO selection. (see page 3)

4. *The risk of bias assessment was not upto the mark for the retrospective studies - most of them having a high risk of bias in many domains - which would have questionable external & internal validity issues.*

We have explained in the risk of bias section see page number 15.

5. *Overall of the retrospective studies- have high risk of bias in most domains , missing outcomes data reported & high rate of adverse events , which leave with 3 RCT which were analyzed - of which 2 studies had severe adverse effects which led to discontinuation of the study drug, even though promising results, the questionable safety profile in these 2-3 valid studies with complete data , makes the review have significant concerns to summarize the study treatment of Gilterinitib being superior and a clear recommendation for future use.*

6. *More studies which includes larger population , having a good safety profile until the end , low risk of bias & conducted across various sociodemographic areas should be considered for a better systematic review*

   We have discussed this in the conclusion section. Thank you for your feedback. This review doesn't provide any treatment recommendation. This paper aims to focus on the survival and response outcome of gilteritinib from the published literature as described in the methods section. We would not be focusing on safety profile in our study. Furthermore, these papers do not provide detailed sociodemographic information. Due to the limitation

Discussion

The discussion predominantly accepts two of the major setbacks

1. *The preponderance of male population*
2. *Retrospective study biases with unmeasured confounders*

However, the review also has concerns regarding:

1. *The missing outcomes variables in retrospective studies (available only in 3 studies)*

   Thank you for the reminder. We have added 6 studies on the survival and response outcome, other 2 outcomes are discussed in the explanation of study outcome section.

2. *Safety profile of the study drug in RCT as well as retrospective studies – most of them have the drug discontinuation.*

   We will not be covering on safety profile from these studies, our focus is on the survival outcome and response outcome as described in the PICO question in the methods section.

3. *Concerns with confidently implementing the study drug completely.*

   We would not be able to provide any information on this. This is outside the scope of our research study.

4. *Small sample sizes – In a oncology study it is not possible to have large number but few studies have barely 20 participants & Comparison to different treatments (in very small cohorts of 1-2)- which makes it difficult to summarize that it is more effective than a particular SOC.*

   We agree with your statement. There is a challenge for small cohorts comparison. Results from small studies may not be generalizable to the broader population due to heterogeneity of the patient population. There is a clear need for larger studies that can address this challenge. Furthermore, patient profiling on how patients would respond to it as a first-line, or second-line treatment needs to be explored in future RCTs. These RCT reporting could focus on robust descriptions of the adverse events.