Answer letter

BPG Editorial Office

We were pleased to hear the reviewer's comments on our manuscript submission entitled “The prognosis value of Heat-Shock Proteins in esophageal cancer. A systematic review and meta-analysis”.

We are grateful to the Editor and reviewer since modifications introduced in response to their suggestions greatly improved the enclosed manuscript. Please find the changes highlighted in red within the manuscript and in the text below, where all issues raised by the reviewers were dealt with point-by-point.

We hope that, after evaluating our revision, you will find that we have dealt successfully with all issues raised and that the manuscript is now acceptable for publication.

Best regards,
The Authors
Reviewer 1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision

1. The aim of this article seems reasonable. But the title, abstract and main body of the article are not coincident as to what kind of disease been studied. Esophagogastric cancer or just esophageal cancer?
Authors' answer: We recognize the need for clarity and alignment of the title, abstract, and main body of the article. The focus has been revised to specifically address esophageal cancer throughout the manuscript.

2. Based on meta-analysis, the author goes to the conclusion that the overexpression of HSP40 and 60, and low HSF1 expression, are associated with long-term survival and lymph nodal dissemination in patients with esophageal cancer.
Authors' answer: The language in the conclusion has been adjusted to accurately reflect that the overexpression of HSP40 and HSP60, and low HSF1 expression, are associated with long-term survival and lymph nodal dissemination in patients with esophageal cancer.

3. As to the discussion part, there are some small mistakes such as “survival in non–non-small-cell lung carcinoma patients [64]”. There is not so much length to discuss the HSP and esophagogastric cancer. I hope the author to increase the space to discuss the HSP and esophagogastric cancer, maily.
Authors' answer: I have carefully reviewed your comments regarding the small mistakes, particularly the reference to "survival in non–non-small-cell lung carcinoma patients [64]." and we made the necessary corrections to ensure accuracy in the final version. Regarding the length of the discussion on HSP and esophageal cancer, I understand your suggestion to increase its depth. The
discussion section has been thoroughly revised, addressing minor mistakes and providing a more in-depth exploration of the relationship between HSP and esophagogastric cancer.

Reviewer 2

**Specific Comments to Authors:** The authors conducted a meta-analysis investigating the relationship between heat shock protein (HSP) expression and prognosis in esophageal cancer. They concluded that HSP40, HSP60, and HSF1 expression are associated with long-term survival and lymph node dissemination in patients with esophageal cancer.

1) I would like to thank the authors for sharing their excellent work and valuable experience. Meanwhile, there are still some remaining doubts in this manuscript. 1. Regarding the relationship between HSP and the prognosis of esophageal cancer, it seems that many studies have clarified the influence of the HSP family, including HSP40, HSP60, and HSF1, on the prognosis of esophageal cancer (include but not be limited to PMID: 15571964, PMID: 28454329), so what is the significance of conducting meta-analysis again for a question with a basically known answer?

**Authors’ answer:** Concerning the question about the significance of conducting a meta-analysis on the relationship between HSP and the prognosis of esophageal cancer, we acknowledge the existence of prior studies, including those cited (e.g., PMID: 15571964, PMID: 28454329), which have delved into this crucial area of research. Our meta-analysis aims to contribute to the existing body of knowledge by bringing several distinct elements to the forefront:

- **Extended Timeframe and Diverse Databases:** Unlike previous studies with more restricted search periods and databases, our meta-analysis
spans from the inception of databases to March 2023. This prolonged timeframe allows us to capture a more comprehensive range of evidence.

- **Inclusive Inclusion and Exclusion Criteria:** While the initial study focused on specific criteria, our meta-analysis adopts a broader approach, encompassing various study designs and extending inclusion criteria to ensure a diverse representation. This approach allows us to consider a wider spectrum of evidence and potentially identify nuances not evident in individual studies.

- **Patient outcomes:** In addition to these elements, we have considered patient outcomes, such as the grade of cellular differentiation, lymph node dissemination, tumor depth, and overall survival. By incorporating these parameters, our meta-analysis aims to provide a more comprehensive and prognostic understanding of the impact of HSP on esophageal cancer.

- **Methodological rigor:** The detailed information provided on our search strategy, inclusion and exclusion criteria, data extraction, statistical analysis, and bias assessment demonstrates the rigor employed in our meta-analysis. We believe that these methodological nuances, combined with the novel elements introduced, enhance the robustness and relevance of our findings.

2. Given that this is not the first meta-analysis to investigate the relationship between HSP and esophageal cancer prognosis, how does the current meta-analysis differ from its predecessors? How does the author view the differences and even contradictions between the conclusions of this manuscript and those of its predecessor (PMID: 26446629)?

**Authors' answer:** The current meta-analysis differs from its predecessors in terms of scope, inclusion criteria, and statistical analyses. We have considered additional parameters, e.g., grade of cellular differentiation, lymph node dissemination, tumor depth, and overall survival. Our inclusion criteria are more diverse, encompassing various study designs, diversified eligibility
criteria, with a more versatile framework, enhancing the precision and flexibility of the analysis, exploring relationships, and patterns more effectively.

3. The authors included different numbers of studies of esophageal squamous cell carcinoma (ESCC), esophagogastric adenocarcinoma, and one mixed type of neoplasm in this study. However, the potential differential expression of HSP family in ESCC and esophageal adenocarcinomas (EADC) may adversely affect the conclusions of the relationship between HSP and esophageal cancer prognosis in this study. Therefore, is the author willing to adjust this manuscript to a systematic review and meta-analysis of the prognosis value of HSP in ESCC?

**Authors’ answer:** Thank you for your insightful comments on our manuscript. We appreciate your attention to detail and would like to address the concern you raised regarding the limited representation of adenocarcinoma in our study. We performed a subgroup analysis according to the histological cancer type. The appropriate changes were made in the Methodology. Although we performed subgroup analysis for ESCC, the same subgroup analysis was not possible for adenocarcinoma due to the small number of articles. We acknowledge this limitation in the Discussion section.

**Revision reviewer:**

Thanks for the author's revision and reply. The authors have revised esophagogastric cancer to esophageal cancer in the title of the revised manuscript and labeled it in yellow. However, modifications that should have been observed in the method or results due to a change in the study topic were not present and not marked in yellow either. What confused me was that after the main topic of the meta-analysis was revised from esophagogastric cancer to esophageal cancer, the included studies (Tables 1 and 3) in this revised manuscript did not reveal any change compared with the original manuscript.
Authors’ answer: Thank you for your comments. We included both esophageal squamous cell carcinoma and esophagogastric adenocarcinoma. We made the appropriated changes to clarify. In addition, we increased the space to discuss the HSP and esophagogastric adenocarcinoma prognosis and carcinogenesis.