**Response to Editor and Reviewers**

**World Journal of Clinical Cases**

**RESPONSE TO COMMENTS**

**Manuscript No.: 85258, Systematic Reviews**

**Title: Primary Adrenal Ewing Sarcoma: A Systematic Review of the Literature**

Dear Editor,

We would like to thank you for extending our deadline and we would like to thank the reviewers for their thoughtful comments. We consider these comments really meaningful towards improving our manuscript.

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**Reviewers' Comments to Author:**

**Reviewer #1:**

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors: The authors reviewed the literature on primary adrenal ES/PNET over the past 30 years. And they further updated the diagnosis, treatment, and oncological outcomes of primary adrenal ES/PNET. While the clinical topic in the focus of this manuscript is certainly interesting, there are some issues to complete. And major revisions are needed.**

We appreciate the time and effort the reviewer has dedicated to our manuscript. We reviewed the text and proceeded with appropriate corrections.

**1. It should be clearly identified in the title and manuscript that it is a systematic review of case reports and case series.**

We would like to thank the reviewer for this comment. According to the PRISMA 2020 statement, title should identify the report as a systematic review. It is not reported in the PRISMA statement, that the title should clarify the type of articles that were included in the final study. Manuscript was changed to include this kind of information both in the abstract and the main text.

"Results:

Fifty-two studies (47 case reports and 5 case series) were included in the final analysis, describing 66 patients (Online resource)."

**2. The detailed search strategy for each database should be listed in the supplementary table.**

We would like to thank the reviewer for this valuable input. Figure 1 was updated to include the details of the search strategy for each database.

**3. The PRISMA guidelines for reporting in systematic reviews are suggested to be used during the selection and data analysis phases. The format of the flow chart (Figure 1) should comply with the PRISMA flow chart.**

We are thankful for this helpful comment. The PRISMA guidelines were used for the selection and data analysis phases, while the format of the flow chart was adjusted to comply with the PRISMA instructions.

"A systematic review of the English literature was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [7]."

7. Page MJ, McKenzie JE, Bossuyt PM, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:. https://doi.org/10.1136/BMJ.N71

**4. The authors should cite the included references in the results.**

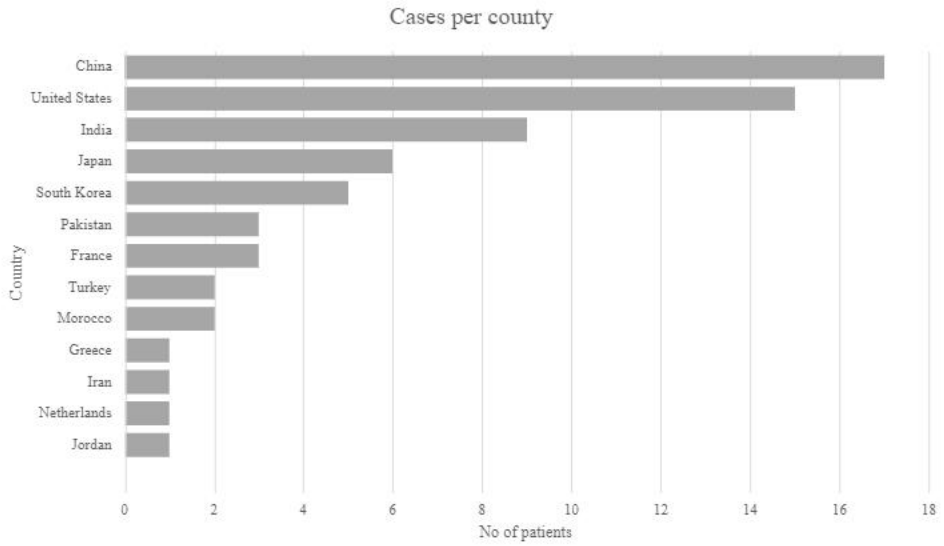
We value the reviewer's comment. All included studies were cited in the results.

"Fifty-two studies (47 case reports and 5 case series) were included in the final analysis, describing 66 patients (Online resource) [8-59]."

**5. The regional distribution of reported cases could be shown in a graph to be more intuitive.**

We appreciate the comment by the reviewer. A new graph demonstrating the regional distribution of reported cases was added to the article.

**"**As shown in figure 2, majority of the reported cases arise from China, United States and India.**"**




"Figure 2. Regional distribution of reported cases"

**6. The authors should record the overall number of patients in Table 1 and Table 2. The percentage of patients partly seems to be incorrect. And the style of Table 1 and Table 2 should also be adjusted.**

We would like to thank the reviewer for this valuable comment. All tables were changed to demonstrate the percentages and the overall number of patients. Due to the fact that one article was removed from our study; the numbers were adjusted accordingly, both in the tables and the manuscript.

**7. The introduction mentioned the recent advances in molecular biology. However, the discussion did not mention how molecular biology can guide novel therapeutic protocols. And also, how conventional therapeutic protocols, including radiotherapy, can be improved by novel techniques. Authors can refer to the articles below:**

**Artificial intelligence in radiotherapy. Seminars in cancer biology, 86(Pt 2), 160–171. https://doi.org/10.1016/j.semcancer.2022.08.005**

**SPOP and OTUD7A Control EWS-FLI1 Protein Stability to Govern Ewing Sarcoma Growth. Advanced science (Weinheim, Baden-Wurttemberg, Germany), 8(14), e2004846. https://doi.org/10.1002/advs.202004846**

**Multimodal analysis of cell-free DNA whole-genome sequencing for pediatric cancers with low mutational burden. Nature communications, 12(1), 3230. https://doi.org/10.1038/s41467-021-23445-w 8.**

**We would like**

We are thankful for this thoughtful comment. A paragraph was added at the end of the Discussion section, focusing on the advances and the future prospects of molecular biology and artificial technology.

"Research in Ewing sarcoma during the last years has focused on the identification of DNA fragments, which could potentially detect and distinguish between different cancer types and subcategories, monitor disease progression over time, as well as estimate survival and relapse probabilities at the time of diagnosis[67]. In addition, artificial intelligence has led to the development of large databases, biobanks and radiomics. In the future, both biomarkers and artificial intelligence science are anticipated to assist with stratifying patients into specific groups by creating patient profiles who share common features. These tools will lead into the development of individualized treatments and prognostic treatment-response scores in chemotherapy and/or radiotherapy [68,69]."

**8.There are some English mistakes. The English should be polished by native speakers or language experts.**

We would like to thank the reviewer for this comment. The English was polished by native speaker.

**Reviewer #2:**

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors: This systematic review reads well and summarizes information on clinicopathological data of a very rare disease Ewing**

**sarcoma localized to the adrenal gland. The study emphasizes how little we know of these rare tumors and which severely hampers effective treatment. Comments:**

**1. Page 2, introduction, line 10 – Please mention some EWSR1-FLI1 target genes by name especially the ones involved in tumorigenesis.**

We appreciate the reviewer's comment. A sentence was added to add this information.

"NR0B1 (DAX1), GLI1 and FOXO1 have been shown in literature to be the genes involved in the tumorigenesis of Ewing sarcoma [4]."

**2. Figure 1 – Clearly list eligibility criteria in the materials and methods section for the assessment of full text articles.**

We would like to thank the reviewer for this valuable input. The eligibility criteria were included.

"Both adult and paediatric cases were included in the review. Non-English articles were excluded… Articles, including case reports, case series, observational and clinical tries studies, were considered eligible for full text review, as long as they reported on cases of primary ES/PNET."

**3. Page 5, results, line 2 – Here it says fifty-six studies were included whereas Figure 1 indicates n=55. Please check and correct.**

We would like to thank the reviewer pointing this out. After double checking our data, we were able to correct our manuscript and figures. In addition, we rejected one study, which is available online, but is not approved yet for publication. Therefore, a total number of 52 articles were included in our study. The abstract, manuscript, tables and figures were adjusted accordingly.

**4. Are primary adrenal Ewing sarcoma molecularly distinct from bone localized Ewing sarcomas?**

We appreciate the reviewer's input. The text was adjusted to include this important information.

"The morphology between ESFT may vary; however skeletal and extra-skeletal ESFT are molecularly indistinguishable [6]."

**5. Please briefly give some future prospects. What burning questions should be answered regarding this particular tumor? How should the field progress to improve management and treatment of these rare tumors?**

We are thankful for this thoughtful comment. A paragraph was added at the end of the Discussion section, focusing on the advances and the future prospects of molecular biology and artificial technology.

"Research in Ewing sarcoma during the last years has focused on the identification of DNA fragments, which could potentially detect and distinguish between different cancer types and subcategories, monitor disease progression over time, as well as estimate survival and relapse probabilities at the time of diagnosis[67]. In addition, artificial intelligence has led to the development of large databases, biobanks and radiomics. In the future, both biomarkers and artificial intelligence science are anticipated to assist with stratifying patients into specific groups by creating patient profiles who share common features. These tools will lead into the development of individualized treatments and prognostic treatment-response scores in chemotherapy and/or radiotherapy [68,69]."