

To World Journal of Methodology

Dear Editor,

With reference to the review article titled 'Microvessel Density (MVD) in patients with Gastrointestinal Stromal Tumors: a systematic review and meta-analysis' (Manuscript NO.: 83248), we would like to submit the replies to the comments of the reviewers. All manuscript changes were highlighted.

Reviewer 1

Dear Reviewer 1

Thank you for your valuable comments

1. This manuscript, which systematically explored the impact of microvessel density on the DFS of patients with GIST, is well written with fluent language. The topic per se is of great clinical meaning, but is discounted by the limited and low-level clinical evidence. Especially the cutoff value to differentiate low MVD from high MVD was not consistent in researches included. If authors could give a uniform and clear cutoff value based on current data, the conclusion of the systematic review will be easier to extrapolate

As mentioned in the manuscript, the discrepancy in MVD assessment methods and cut-off points combined with the small number of included studies are among the most significant limitations of our study. The eligible trials implemented different methods (Chalkley, Horak, Weidner technique), thus increasing the overall heterogeneity, and limiting the significance of our findings. Subsequently, the calculation of a pooled and strict cut-off point was not achievable. This would prerequisite multiple clinical trials with a homogeneous MVD assessment technique.

The following was introduced in the Discussion section:

“Our study highlighted this heterogeneity; the use of different assessment methods and definitions of high and low MVD tumours prohibited the calculation of a pooled cut-off point.”

“More specifically, the implementation of different assessment methods and different cut-off points prohibited the strict definition of high and low MVD GISTs.”

2. Meanwhile, the title is too general, could be revised to better reflect the aims of the study

Based on your comment the manuscript title was revised:

“The impact of Microvessel Density in survival outcomes of patients with Gastrointestinal Stromal Tumors: a systematic review and meta-analysis”

3. Besides, key words were not appropriate, authors could use short phrases instead of the meaningless single word

Based on your comment the following keywords were introduced:

“vascularity, microvessel density, gastrointestinal stromal, survival, meta-analysis”

4. and a small mistake in sentence "If the discrepancies were not encountered, the opinion of a third investigator (K.D) was considered", "not encounter" should be "encountered"

Based on your comment the following was introduced:

"If the discrepancies were not resolved, the opinion of a third investigator (K.D) was considered"

Reviewer 2

Dear Reviewer 2

Thank you for your valuable comments

1. This is an interesting manuscript reviewing microvessel density (MVD) in patients with gastrointestinal stromal Tumors (GIST). A detail analysis as well as tables and figures has been given in the manuscript. Subgroup analysis according to tumor location, tumor size, or mitotic count is suggested if possible

Based on your comment a subgroup and meta-regression analysis was performed and added as supplementary material. The following was introduced in the manuscript:

"Subgroup analysis regarding the number of study centres and the antibody used were identical to the above-mentioned sensitivity analysis. Analysis of the studies that implemented the Weidner MVD assessment method, showed a statistically significant hazard ratio. Similarly, exclusion of the two studies that did not report blinded MVD evaluation, did not influence the heterogeneity. Further explanatory analyses (Supplementary Material Tables) included the meta-regression of the primary outcome with the number of spots examined, the percentage of high-risk tumours, gastric and small intestine tumours, large size tumours (≥ 5 cm) and spindle cell malignancies. A significant correlation was not confirmed with any of the previously mentioned variables."

Thank you for your valuable comments again. All manuscript changes were highlighted.

Should you need any further information, please do not hesitate to contact me.

Yours sincerely,

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