Peer Review File

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Reviewer A:

Comment 1, I suggest the authors indicate the median duration of the follow up of this study.

Reply 1: Revised (Abstract Line 37-38).

Comment 2, The abstract needs some revisions. The background did not indicate the clinical significance of this research focus and the objectives of this study. The methods did not describe the inclusion of subjects, the assessment of baseline factors including GI bleeding, and follow up procedures. Please also briefly describe the literature search, risk of bias assessment, and data extraction for the meta-analysis part. The results need to briefly summarize the clinical characteristics of the study sample. The conclusion needs comments for the reasons for the non-significant association and clinical implications of the findings.

Reply 2:

2.1 The background was revised (Line 81-89).

2.2 The "inclusion of subjects, assessment of baseline factors, and follow-up procedures" were revised in the *Materials and Methods* section (Line101-104, Line 127-128).

2.3 The "Literature search and selection" was added as following (Line 132-149):

"A comprehensive and systematic search of the PubMed, Embase, Cochrane Collaboration, and Medline databases was undertaken to identify relevant studies published between 2000 and 2022. The terms relating to "gastrointestinal stromal tumor", "gastrointestinal stromal tumour", and "GIST" were combined with terms relating to "bleeding" and "gastrointestinal bleeding". The following Medical Subject Headings (MeSH) were used: "Gastrointestinal stromal tumors", "Gastrointestinal Hemorrhage", "Hematemesis", and "Melena", combined with "Disease-Free Survival", "Recurrence", "Neoplasm Recurrence, Local", and "Survival Analysis". The references of the studies that met the inclusion criteria were searched for additional trials or reports relevant to this meta-analysis."

"The inclusion criteria were as follows: (1) The participants of included studies were diagnosed with primary GIST based on histology and immunohistochemistry; (2) the exposure of interest was GI bleeding; (3) the outcome of interest was RFS; (4) odds ratio (OR), relative risk (RR), or hazard ratio (HR) with a corresponding 95% confidence interval (CI) are provided; (5) Retrospective or prospective cohort study. No publication language restriction was applied in the present meta-analysis (Supplementary Fig. 1)."

2.4 The "Data extraction and quality assessment" was added as follows (Line 151-162):

"Data extraction was carried out by 2 authors independently. From each publication, the information extracted was as follows: author, publication year, country, study design, age of participants, date of diagnosis and treatment, follow-up period, GI-bleeding/non-GI-bleeding, and OR/RR/HR for RFS. The most adequately adjusted model to evaluate the risk value for the final analysis was selected. Differences in data extraction between investigators were resolved by consensus. "

"The Newcastle–Ottawa scale (NOS) was used to assess the quality of the included studies, which addressed 3 main quality parameters: 4 items for selection, 2 items for comparability, and 3 items for outcome assessment (19). The score of each study ranged from 0 to 9 stars, a score of ≥7 was considered to indicate a high quality study (Supplementary Table 1)."

"Comment 3, the introduction should review related studies around GI bleeding including its incidence rate and clinical significance. The authors need to present detailed examples to show the controversy, analyze the potential reasons, and explain why the current data can overcome the limitations of prior studies to address this controversy and why a meta-analysis of published studies can answer this research question. "

Reply 3: The Introduction was revised as advised (Line 81-90).

Comment 4, the methodology of the main text should be divided into two parts, because the methodology of meta-analysis was not detailed and not standardized. In part I, please accurately describe the clinical research design, sample size estimation, assessment of baseline factors, and follow up procedures. In statistics, please ensure $P<0.05$ is two-sided. In part II, the literature search in PubMed and limited the studies to be included to be English-language are problematic, which result in selection bias. The authors need to define the inclusion criteria according to the PICOS principles. The HR values extracted from included studies should be adjusted HR values, the authors should make this clear. Please describe the risk of bias assessment because level of risk of bias would also influence the bleeding-prognosis associations.

Reply:

4.1 **The methodology of the main text was revised as advised except for the sample size estimation (Line 100-101).**

"Due to the retrospective nature of present study, we reviewed the primary GIST patients who underwent complete resection and without adjuvant imatinib therapy from January 2003 to December 2008 in our hospital. For retrospective study, sample size calculation maybe not necessary (PMID: 22416102)."

4.2 Corrections have been made in revised version. "A two-sided P-value < 0.05 was considered significant." (Line 178)

4.3 Corrections have been made in revised version (Line 148).

The related statements are as follows: “No publication language restriction was applied in the present meta-analysis.”

4.4 Corrections have been made in revised version as follows (Line 143-147):
“The inclusion criteria were as follows: (1) The study subjects of included stidues were diagnosed with primary GIST based on histology and immunohistochemistry; (2) the exposure of interest was GI bleeding; (3) the outcome of interest was recurrence-free survival (RFS); (4) odds ratio (OR), relative risk (RR) or hazard ratio (HR) with corresponding 95% confident interval (CI) are provided; (5) Retrospective or prospective cohort study.”

4.5 Corrections have been made in revised version as follows (Line 155-156).
“The most adequately adjusted model to evaluate the risk value for the final analysis was selected”.

4.6 We have added the quality assessment of included studies as follows (Line 158-162):
“The Newcastle–Ottawa scale (NOS) was used to assess the quality of the included studies, which addressed 3 main quality parameters: 4 items for selection, 2 items for comparability, and 3 items for outcome assessment (19). The score of each study ranged from 0 to 9 stars, a score of ≥7 was considered to indicate a high quality study (Supplementary Table 1).”

Reviewer B:
Comment 1. The authors specified to investigate the association with GI bleeding and RFS. I believe it is clear endpoint. If you have information about perforation case, could you analyze an association of perforation of GIST and clinical outcome such as RFS?
Reply 1: Thanks for your suggestions. The perforation was considered as one of the worse prognostic factors for GIST patients in clinical guidelines. And the association of perforation of GIST and clinical outcome such as RFS was published in recently of our department (PMID: 35912441). In present study, we intended to investigate the associations with GI bleeding and RFS.

Comment 2. You mentioned defect of genetic study as a study limitation. Could you include other risk status of patients’ GIST, for instances, pathological index such as proliferation rate, aberrant markers, and so on?
Reply 2: Thanks for your suggestions. Recently, some studies reported the other prognostic factors such as proliferation rate, aberrant markers, and so on (PMID: 36691015, PMID: 36961557). However, the pathological reports of our study were collected retrospectively. The pathological indexes you mentioned were not commonly detected in our hospital. Therefore, the prognostic effect of proliferation rate and aberrant markers could not be evaluated in present study. Thanks for your suggestions, and we will investigate the prognostic factors as you mentioned in the future studies.