Does Gastrointestinal Bleeding Affect the Prognosis of Patients With Gastrointestinal Stromal Tumor: A Meta-analysis.

Yue Zhang
China Medical University
Qi Liu
China Medical University
Hao Xu (hxu@cmu.edu.cn)
China Medical University https://orcid.org/0000-0002-8001-8926

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Abstract

Background: The effect of gastrointestinal bleeding on the prognosis of gastrointestinal stromal tumors has been widely studied in recent years, but it is still controversial. Therefore, we performed the first comprehensive meta-analysis to evaluate the effect of gastrointestinal bleeding on the prognosis of gastrointestinal stromal tumors.

Methods: We searched PubMed, MEDLINE, Web of Science, EMBASE, and Cochrane Library databases to recruit studies on the effect of gastrointestinal bleeding on the prognosis of patients with gastrointestinal stromal tumor. Eight studies containing 2915 patients were involved in this meta-analysis until May 31, 2021. Pooled hazard ratios (HRs) with 95% confidence interval (95% CI) were calculated to estimate the effect using random-effects model.

Results: The pooled results revealed that gastrointestinal bleeding was not associated with relapse-free survival (HR = 1.33, 95% CI 0.66-2.68, P < 0.001; random-effects model I2=87.7, P < 0.001) and overall survival (HR = 1.29, 95% CI 0.43-3.87, P < 0.001; random-effects model I2=88.9, P < 0.001) in patients with gastrointestinal stromal tumors.

Conclusions: Our present a meta-analysis indicates that gastrointestinal bleeding has no effect on relapse-free survival and overall survival of patients with gastrointestinal stromal tumors, although gastrointestinal bleeding is one of the major clinical symptoms of gastrointestinal stromal tumors.

Background

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors, which can occur anywhere in the digestive tract(1). About 70% of GISTs are symptomatic, and GISTs have different clinical manifestations in different locations, such as abdominal pain, abdominal distension, gastrointestinal bleeding, intestinal obstruction(2, 3),and many patients often undergo emergency operations because of uncontrollable gastrointestinal bleeding. The main determinants of prognostic risk stratification recommended in the current versions of NCCN guidelines(4) and ESMO guidelines(5) are tumor size, tumor site, mitotic index and tumor rupture. At present, in the modified-NIH classification, tumor rupture is considered to be a high risk factor for recurrence(6). Patients with tumor rupture should be included in the high-risk group and need to be treated with Tyrosine Kinase Inhibitors (TKIs) represented by imatinib for at least 3 years.

The study of Nishida T et al defined six forms of rupture of gastrointestinal stromal tumors(7), but gastrointestinal bleeding was not included. Whether gastrointestinal bleeding is one of the forms of tumor rupture is still controversial. In recent retrospective studies, it is considered that gastrointestinal stromal tumors with gastrointestinal bleeding may be accompanied by excessive growth, high mitotic index, incomplete local tumor capsule and other factors leading to poor prognosis. it can be used as an index to predict the risk of postoperative recurrence of GISTs(8, 9), but some studies have shown that gastrointestinal bleeding can detect tumors as soon as possible and carry out medical intervention in time, which may be a protective factor and will lead to a better clinical outcome(10).

Nowadays, the research on the relationship between gastrointestinal bleeding and the prognosis of GISTs is increasing, which has attracted the attention of clinical treatment and postoperative management, but due to the

limitations of sample size and single-center study, the evidence is insufficient. Therefore, we conducted a systematic review and meta-analysis of GISTs with gastrointestinal bleeding in order to evaluate whether gastrointestinal bleeding has an impact on the prognosis of patients with GISTs.

Methods

This study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(11).

Search strategy

Two authors (Yue Zhang. and Qi Liu) searched PubMed, MEDLINE, Web of Science, EMBASE, and Cochrane Library databases for relevant studies published up until May 31, 2021. The following search terms were used: (Gastrointestinal Stromal Tumors) OR (Stromal Tumor, Gastrointestinal)) OR (Stromal Tumors, Gastrointestinal)) OR (Tumor, Gastrointestinal Stromal)) OR (Tumors, Gastrointestinal Stromal)) OR (Gastrointestinal Stromal Neoplasms)) OR (Neoplasm, Gastrointestinal Stromal)) OR (Neoplasms, Gastrointestinal Stromal)) OR (Stromal Neoplasm, Gastrointestinal)) OR (Stromal Neoplasms, Gastrointestinal)) OR (Gastrointestinal Stromal Tumor)) OR (Gastrointestinal Stromal Neoplasm)) OR (Gastrointestinal Stromal Sarcoma)) AND ((Hemorrhage) OR (Bleeding). The language of publication was restricted to English. The meta-analysis collected data from previously published studies; therefore, approval was not required from the ethical committee or medical institutional board.

Criteria for inclusion and exclusion

The inclusion criteria for eligible studies were as follows: (1) all patients were pathologically diagnosed as gastrointestinal stromal tumor; (2) the relationship between gastrointestinal bleeding and prognosis was reported; (3) the hazard ratios (HRs) with 95% confidence intervals (CIs) for survival outcomes were reported or sufficient data were given for calculating the HRs with 95% CIs. The following studies were excluded: (1) letters, reviews, and case reports; (2) duplicate studies; (3) studies with insufficient data; (4) a study of less than 10 patients.

Data extraction and quality assessment

Two independent investigators (Yue Zhang. and Qi Liu) extracted the data from eligible studies by using a standardized form. Any disagreements were resolved via discussion with a third investigator (Hao Xu). The extracted information included the name of the author, year of publication, country of study origin, sample size, tumor site, follow up, outcomes and HR with 95% CIs. The clinical outcomes included the recurrence-free survival (RFS) and overall survival (OS). The methodological quality of all the included studies was evaluated by using the Newcastle–Ottawa quality assessment scale (NOS)(12). The NOS assesses the quality of the included studies by using a score of 0 to 9 points. Studies with a NOS score of $\geq$ 6 points were regarded as high-quality studies.

Statistical analysis

The pooled HR with corresponding 95% CI was utilized to estimate the relationship between gastrointestinal bleeding and patients' prognosis. While the effect of gastrointestinal bleeding was described as the combined. Higgins I-squared tests were applied for checking the heterogeneity of the results. whereas I2 values > 50% and/or

P value < 0.1 indicated the existence of significant heterogeneity. When there was no homogeneous data, the fixed-effect framework was adopted, otherwise, the random-effect model was employed. Besides, probable publication bias was quantified with conducting Begg's funnel plot, respectively. Sensitivity analysis was also done by omission of each single study to investigate the stability of the accumulated results. All analyses were carried out using STATA software version 12.0 (Stata Corporation, College Station, TX, USA) P value < 0.05 was regarded as being statistically significant.

Results

Data selection and characteristics

The study selection process flow chart is shown in Fig. 1 and the initial search yielded 3508 studies from the four databases. After reviewing the titles and abstracts, 2608 studies were excluded because they were not relevant to what we were studying. After deleting some duplicates and incomplete records, night records were eventually included in our study. A total of 2915 patients were enrolled in the study, and they were all single-center studies. Of the eight studies, two were from South Korea and the remaining seven were from China. RFS and OS was selected as the major survival outcome for all the available studies in our meta-analysis. The Characteristics of the included studies are shown in Table 1.

Table 1
Characteristics of included 9 studies.

Author	Year	Country	Case number	Tumor site	Follow-up	Outcome	HR and 95% CI	NOS score
Gyu Young Pih (25)	2020	Korea	170	Duodenal	19 years	OS	HR = 0.719 (95% CI 0.277–1.864), p = 0.497	7
Gyu Young Pih (24)	2019	Korea	697	Gastric	17 years	OS	HR = 2.996 (95% CI 1.738–5.163), p < 0.001	7
Wenze Wan (10)	2019	China	800	Gastrointestinal tract	15 years and 11 months	RFS, OS	HR = 0.472 (95% CI 0.299–0.745), p < 0.001 HR = 0.441 (95% CI 0.250–0.776), p = 0.004	8
Yuqian Huang (22)	2018	China	333	Gastrointestinal tract	7 years and 11 months	RFS	HR = 0.573 (95% CI 0.372–0.885), P = 0.010	7
Zhijie Yin (23)	2017	China	526	Gastrointestinal tract	10 years and 8 months	RFS	HR = 0.474 (95% CI 0.254–0.823), P = 0.009	8

Author	Year	Country	Case number	Tumor site	Follow-up	Outcome	HR and 95% CI	NOS score
Qi Liu (8)	2017	China	170	Gastrointestinal tract	8 years and 6 months	RFS, OS	HR = 2.332 (95% CI 1.105–4.919), P = 0.026 HR = 3.116 (95% CI 1.057–9.181), P = 0.039	7
Hao Wang (20)	2014	China	84	Gastrointestinal tract	6 years	RFS	HR = 3.850 (95% CI 1.630–9.100), P = 0.002	6
Ang Lv (21)	2013	China	114	Gastrointestinal tract	9 years and 5 months	RFS	HR = 2.290 (95% CI 1.180–4.470), P = 0.059	8
C. C. Xiao (9)	2012	China	21	Rectum	23 years and 6 months	DFS	HR = 7.378 (95% CI 1.508–36.084), P = 0.014	6

Quality assessment

The quality of eligible publications was calculated based on the Newcastle–Ottawa Scale (NOS) that evaluated the selection of cohorts, comparability as well as exposure or outcome and had a score ranging from 0 to 9. Studies with higher or equal to 6 points could be considered as high quality

Meta-analysis results

Figure 2 shows the main results of this meta-analysis. Due to the significant statistical heterogeneity of the studies evaluating RFS (I2=87.7, P < 0.001) and OS (I2=88.9, P < 0.001), a random-effect model was used to incorporate HR. Gastrointestinal bleeding had no effect on the prognosis of patients with GISTs, either in RFS (HR = 1.33, 95% CI 0.66-2.68, P < 0.001; random-effects model I2=87.7, P < 0.001) or OS (HR = 1.29, 95% CI 0.43-3.87, P < 0.001; random-effects model I2=88.9, P < 0.001). Interestingly, notable heterogeneity (>50%) was found for

migration proportion outcomes among studies. Due to the small number of records included, only 9 records, further subgroup analysis could not be performed.

Sensitivity analysis

Sensitivity analysis was done through the sequential omission of single studies using a model with random-effects, and the result pattern was not obviously impacted by any single study (Figure 3).

Publication bias

The assessment of the publication bias for RFS and OS was done through the shape of the funnel plot revealed no evidence of asymmetry (Figure 4). The RFS (P=0.176) and OS (P= 1.00) of Begg's Funnel Plot test were performed respectively. Thus, the results of this meta-analysis are reliable.

Discussion

The clinical manifestations of patients with GISTs are non-specific and are related to factors such as tumor size and site. The most common clinical manifestations are abdominal pain (20%-50%), gastrointestinal bleeding (30%) and gastrointestinal obstruction (10%-30%)(2, 13, 14). GISTs with gastrointestinal bleeding as the main symptom often require emergency surgery due to uncontrolled bleeding and hypotension. Despite revolutionary changes in the prognosis of GISTs and the promotion of individualized management in treatment over the past decade (15), the prognosis and postoperative management of patients with GIST remains controversial. Although the current version of the guidelines recommends the four most important factors that currently influence prognosis: tumour size, tumour site, mitotic rate and tumor rupture, but there are still many valuable predictors being studied, including gastrointestinal bleeding, Ki67 index and the type of tumour gene mutation (16–18). Gastrointestinal bleeding has been shown to be an independent risk factor for poor prognosis in other digestive malignancies, such as colon or gastric cancer, because gastrointestinal bleeding can lead to the dissemination of tumor cells or disruption of the mucosal barrier, which ultimately leads to poor prognosis(14, 19). However, it remains controversial in the study of gastrointestinal stromal tumors. In 2013, Xiao et al. conducted a retrospective study on a small sample and revealed that rectal bleeding is an independent risk factor for prognosis of rectal stromal tumor(9). Over the next few years, several studies have also demonstrated that gastrointestinal bleeding causes poor DFS or OS in patients with GIST(20–22). Interestingly, two studies have shown that the prognosis in the group with gastrointestinal bleeding is better than that in the group without bleeding. Bleeding may be a protective factor for recurrence of GISTs(10, 23). However, Gyu Young Pih et al. from South Korea concluded in a large retrospective study that gastric bleeding leads to a poor prognosis for GISTs, while duodenal bleeding has no effect on GISTs(24, 25).

Although the risk classification criteria for gastrointestinal stromal tumors have been preliminarily established, some influencing factors, including gastrointestinal bleeding, are still controversial. Previous studies have shown that gastrointestinal bleeding caused by gastrointestinal stromal tumors can cause tumor dissemination, suggesting that this bleeding is another form of rupture and should be considered as tumor rupture(6, 8). The final conclusion of our study is that gastrointestinal bleeding had no effect on prognosis, possibly because gastrointestinal bleeding would indicate the occurrence of tumors, and medical intervention would be carried out earlier, thus changing the prognosis of patients.

In summary, we used this meta-analysis to demonstrate that there is no significant difference in prognosis between patients with gastrointestinal bleeding and patients with gastrointestinal stromal tumors without gastrointestinal bleeding, either in RFS (HR = 1.33, 95% CI 0.66–2.68, P < 0.001) or OS (HR = 1.29, 95% CI 0.43–3.87, P < 0.001). However, there was significant heterogeneity in the results (I2 = 87.7, P < 0.001; I2 = 88.9, P < 0.001), and we believed that the important reasons for such heterogeneity were the different tumor sites, genotypes, tumor stages and some pathological parameters. More importantly, due to the different years of the studies, the different perioperative treatment of these patients with stromal tumors, and the failure to classify patients for postoperative management according to the standard risk of recurrence, are important factors contributing to the higher heterogeneity. However, due to the small number of included studies or the small sample size of some articles, it is difficult to conduct further subgroup analysis, which are also the limitations of this study. But due to the current treatment guidelines about GISTs widely used, and the effectiveness of TKIs treatment, the treatment of GISTs strategy compared with before the revolutionary change, so it's hard to get a large sample of retrospective or prospective studies to confirm whether the gastrointestinal bleeding is an independent risk factors of poor prognosis for GISTs. Consequently, high-quality studies that are at large-scale are necessary for the verification of our conclusion.

Conclusions

This meta-analysis combined with all previous studies sought to elucidate the relationship between gastrointestinal bleeding and prognosis in patients with GISTs. The results of the analysis showed that gastrointestinal bleeding had no effect on the prognosis of patients with GISTs either RFS or OS. However, due to the insufficient included samples and other limitations, it is necessary to conduct more studies on the relationship between gastrointestinal bleeding and the prognosis of GISTs

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent for publication was obtained from the participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

WR collected and analyzed the data, wrote the paper; Yue zhang and Qi liu analyzed the data; Hao xu conceived and designed this study, analyzed the data; and all authors reviewed the paper. All authors read and approved the final manuscript.

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Figures

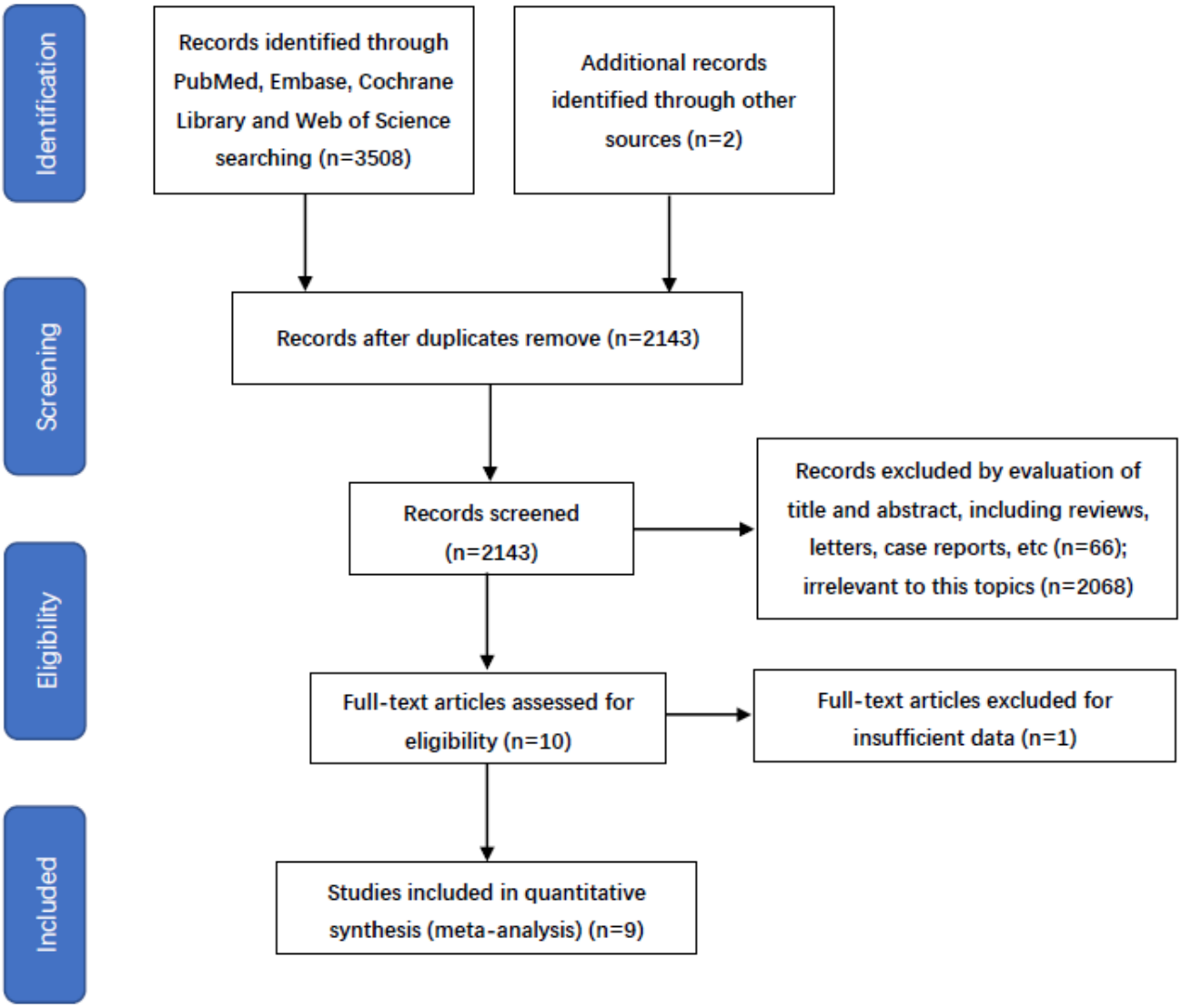

Figure 1

Flow diagram of the study selection process.

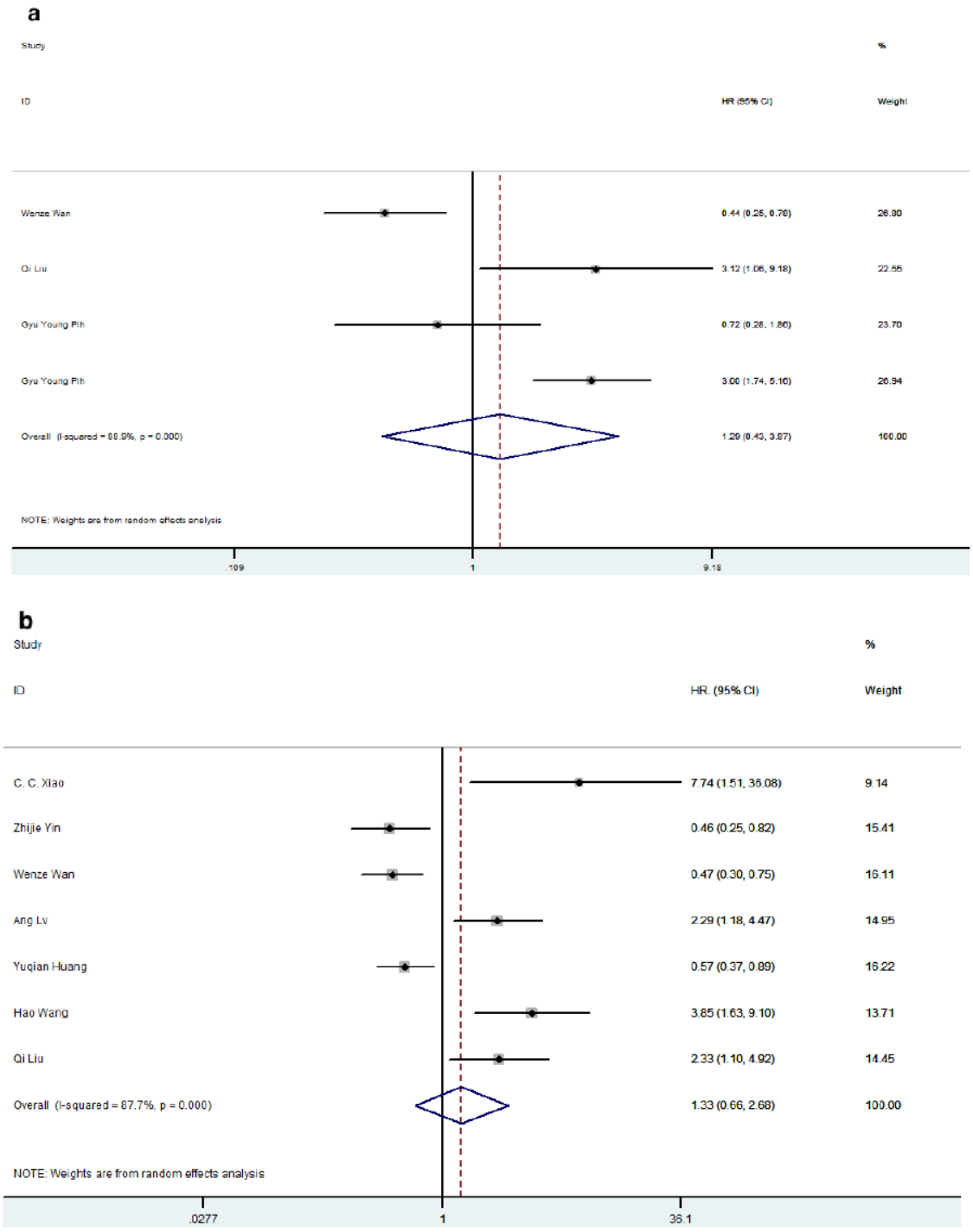

Figure 2

Forest plots of studies assessing HR of gastrointestinal bleeding in OS (a) and RFS (b).

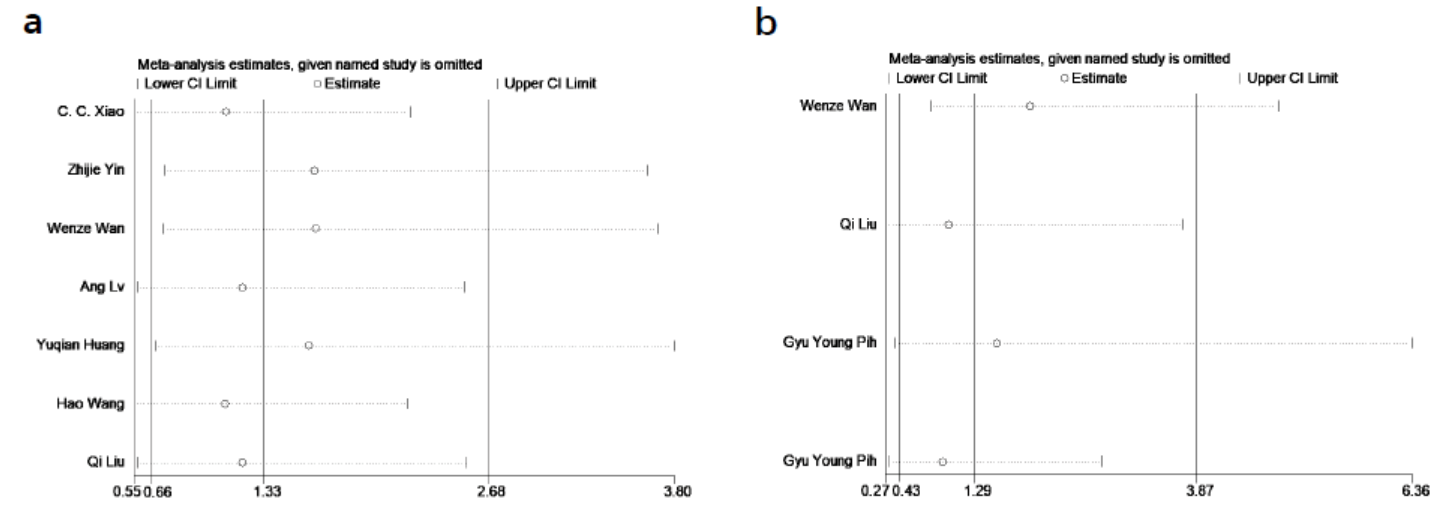

Figure 3

Sensitivity analysis for the correlation between gastrointestinal bleeding with RFS (a) and OS (b).

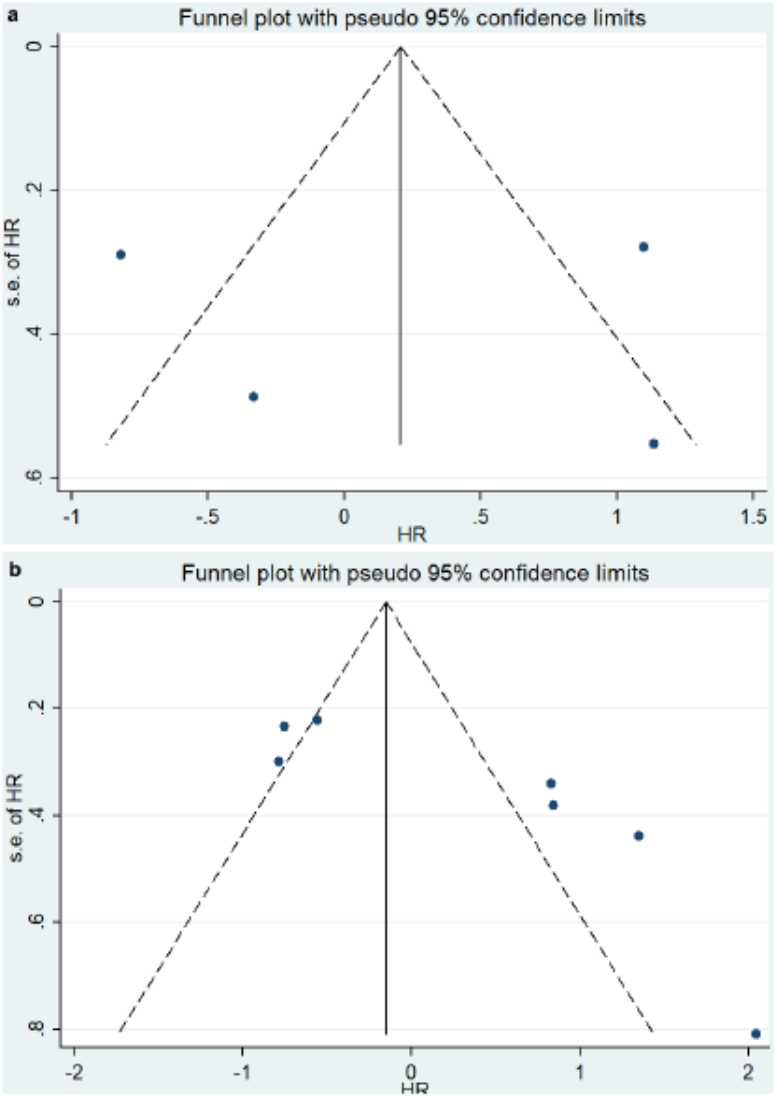

Figure 4

Begg’s funnel plot of publication bias for OS (a) and RFS (b).