INTRODUCTION

Review question / Objective: Gastrointestinal bleeding is the most common clinical manifestation of gastrointestinal stromal tumor. It is of great significance to the prognosis of patients. But the results are controversial. The purpose of this study was to evaluate the relationship between gastrointestinal bleeding and clinical prognosis in patients with GIST.

Condition being studied: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors in the...
digestive tract, accounting for about 1%-2% of gastrointestinal tumors, the most common of which are in the stomach, small intestine and colorectum respectively. About 69% of the patients with gastrointestinal stromal tumors may have clinical symptoms in the early stage. Gastrointestinal bleeding, as the most common clinical symptom, is of great significance to the prognosis of GIST. Gastrointestinal stromal tumor has the possibility of malignancy, and the prognosis is affected by many factors. The modified National Institutes of Health risk classification scheme (NIH) included tumor location, tumor size, mitotic count, and tumor rupture in the high risk classification of recurrence. However, the effect of gastrointestinal bleeding on the prognosis of GIST is not clear. Currently, it has been found that the recurrence free survival of GIST patients with gastrointestinal bleeding is significantly shorter than that of non-gastrointestinal bleeding patients, which is contrary to the conclusion of wan et al. Therefore, the effect of gastrointestinal bleeding on the prognosis of GIST remains to be explored. The purpose of this study was to evaluate the relationship between gastrointestinal bleeding and clinical prognosis in patients with GIST.

METHODS

Participant or population: Patients with gastrointestinal stromal Tumors.

Intervention: Inclusion criteria: (1) literature published in China and abroad; (2) the object of study is gastrointestinal stromal tumors; (3) bleeding on the prognosis of patients; (4) the statistics record of at least one of the following indicators: prognostic indicators of OS, DFS or RFS; (5) the risk ratio HR and 95% confidence interval or survival curve were reported to extract data. (6) If the articles of the same author were selected, Selection of highly rated literature according to the Newcastle-Ottawa scale. Exclusion criteria: (1) if the objective of the study was non-gastrointestinal stromal tumor; (2) Non-comparative study; (3) no observation index was reported; (4) complete clinical data was not provided, contact first author and no response was received; (5) repeated literature.

Comparator: The OS/RFS/the ageing factor/the location of GIST in the small intestine/tumor diameter ≥ 5cm/Mitotic index ≥ 5 / 50HPF and tumor rupture of GIST patients with GI non-GI bleeding.

Study designs to be included: A systematic literature search was performed in Pumbed, Cochrane Library, EMBASE, ClinicalTrials.gov, CNKI, VIP and wanfang databases with the pattern of unlimited languages. 12 studies with 2781 individuals were included in the final analysis. The overall survival (OS, recurrence-free survival/disease-free survival (RFS/DFS) and related factors affecting bleeding in patients with gastrointestinal stromal tumor (GIST) were extracted. Hazard ratio (HR) and 95% confidence interval (CI) were used for in the meta-analysis.

Eligibility criteria: Inclusion criteria: (1) literature published in China and abroad; (2) the object of study is gastrointestinal stromal tumors; (3) bleeding on the prognosis of patients; (4) the statistics record of at least one of the following indicators: prognostic indicators of OS, DFS or RFS; (5) the risk ratio HR and 95% confidence interval or survival curve were reported to extract data. (6) If the articles of the same author were selected, Selection of highly rated literature according to the Newcastle-Ottawa scale. Exclusion criteria: (1) if the objective of the study was non-gastrointestinal stromal tumor; (2) Non-comparative study; (3) no observation index was reported; (4) complete clinical data was not provided, contact first author and no response was received; (5) repeated literature.

Information sources: According to the inclusion criteria and exclusion criteria, the retrieved literature is read independently by two authors, when there are different views, the third author participated in the discussion and finally determines the inclusion of the literature. The two authors
extracted the data separately and checked the consistency of extracted data.

**Main outcome(s):** A total of 12 articles were included in the study, including 2781 patients with GIST, including 845 patients with gastrointestinal bleeding. The OS of GIST patients with gastrointestinal bleeding was significantly worse (HR=2.54, 95% CI=1.13-5.73, P=0.025). But there was no significant difference in RFS between gastrointestinal bleeding patients and non-bleeding patients (HR=1.35, 95% CI=0.70-2.61, P=0.371). Further analysis of the related factors of GI bleeding in GIST patients was observed, besides the ageing factor (HR=1.02, 95% CI=0.69-1.50, P=0.929), Small intestinal stromal tumor (HR=0.56-95, 95% CI=0.41-0.76, P<0.001), tumor diameter ≥ 5cm (HR=2.09, 95% CI=1.20-3.63, P=0.009), Mitotic index ≥ 5 / 50HPF (HR=1.66, 95% CI=1.11-2.49, P=0.014) and tumor rupture (HR=2.04, 95% CI=1.0-3.82, P=0.026) all increased the risk of GI bleeding in patients with GIST.

**Quality assessment / Risk of bias analysis:** The quality of the included literature was evaluated according to the Newcastle-Ottawa Scale (NOS) Literature quality Assessment scale. The evaluation items included selection, exposure and comparability, with a full score of 9 * and ≥ 6 * as high-quality literature.

**Strategy of data synthesis:** The authors extracted HR and 95% CI from each study to evaluate the prognostic role of gastrointestinal bleeding in patients with GIST. Q test was used to analyze the heterogeneity in the study. When I2 ≥ 50% and P ≤ 0.05, the random effect model was used to analyze the heterogeneity, and the fixed effect model was used to analyze the heterogeneity when I2 < 50%. All statistical analysis was carried out with STATA 15.0 (StataCorp, College Station, TX, USA), When the P ≤ 0.05 the results were deemed statistically significant.

**Subgroup analysis:** A total of 7 studies were conducted to analyze the difference between gastrointestinal bleeding in 1820 patients in gastric stromal tumor and intestinal stromal tumor. The random effect model was used to analyze and Meta-analysis showed that the difference between gastric stromal tumor and intestinal stromal tumor. The risk of gastrointestinal bleeding in small intestinal stromal tumors was significantly higher than that in gastric stromal tumors (HR=0.56, 95% CI=0.41-0.76, P<0.001). A total of 4 studies were conducted to analyze the ageing difference between gastrointestinal bleeding in 1756 patients. 60 years old was taken as the interception value. The random effect model was used to analyze and Meta-analysis showed that the risk of gastrointestinal bleeding in patients with GIST was not affected by ageing ≥ 60 years old (HR=1.02, 95% CI=0.69-1.50, P=0.929). A total of 6 studies were conducted to analyze the tumor size difference between gastrointestinal bleeding in 1681 patients, using 5cm as the interception value. The random effect model was used to analyze and Meta-analysis showed that the tumor size ≥ 5cm increased the risk of gastrointestinal bleeding in patients with GIST (HR=2.09, 95% CI=1.20-3.63, P=0.009). A total of 7 studies were conducted to analyze the mitotic index difference between gastrointestinal bleeding in 2377 patients. The mitotic index ≥ 5 / 50HPF was taken as the interception value. The random effect model was used to analyze and Meta-analysis showed that the mitotic index ≥ 5 HPF increased the risk of gastrointestinal bleeding in patients with GIST (HR=1.66, 95% CI=1.11-2.49, P=0.014). A total of 3 studies were conducted to analyze tumor rupture difference between gastrointestinal bleeding in 651 patients. The random effect model was used to analyze and Meta-analysis showed that tumor rupture increased the risk of gastrointestinal bleeding in patients with GIST (HR=2.04, 95% CI=1.0-3.82, P=0.026).

**Sensitivity analysis:** OS: Sensitivity analysis was performed to see whether some studies affected the final results, and the results showed that the deletion of any
literature did not significantly affect the final results, indicating that our conclusions were reliable. RFS/DFS:Sensitivity analysis was performed to see whether some studies affected the final results, and the results showed that the deletion of any literature did not significantly affect the final results, indicating that our conclusions were reliable.

Language: No language limits.

Country(ies) involved: China.

Keywords: gastrointestinal stromal tumors, gastrointestinal bleeding, prognosis, meta-analysis, value.

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