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SYSTEMATIC REVIEWS

Effect and safety of ripretinib in the treatment of advanced gastrointestinal stromal tumor: A systematic review and meta-analysis

Ji Li, Hao Zhang, Xiao-Dong Chen

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Abstract

BACKGROUND

Imatinib (IMA) has received approval as the primary treatment for gastrointestinal stromal tumors (GIST). Nonetheless, approximately half of the patients with advanced GIST show disease advancement following IMA treatment. Presently, the efficacy of secondary and tertiary medications in addressing various GIST secondary mutations is somewhat restricted. Consequently, there is a significant medical demand for the creation of kinase inhibitors that extensively block secondary drug-resistant mutations in advanced GIST. Ripretinib (RPT) is a new, switch-control tyrosine kinase inhibitors that can suppress different mutations of KIT and PDGFRA *via* a dual mechanism of action.

AIM

To investigate the literature on RPT to assess an effective, safe, and successful treatment strategy against advanced GIST.

METHODS

The present systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Embase, Cochrane, Web of Science and ClinicalTrials.gov databases were screened from January 1, 2003 to May 1, 2024.

RESULTS

A total of 4 studies were included, with a total of 507 patients enrolled. The objective response rate (ORR) of the RPT-treated advanced GIST was 17% (95%CI: 0.11-0.27), while the disease control rate (DCR) was 66% (95%CI: 0.59-0.73). The overall occurrence of adverse events with varying degrees was 97% (95%CI: 0.93-1), whereas that of grade ≥ 3 adverse reactions was 42% (95%CI: 0.28-0.63). The

sensitivity analysis revealed that omitting some studies did not yield statistically notable variances in the aggregate data regarding the ORR, DCR, and the occurrence of adverse events of grade 3 or higher. The publication bias was absent because no significant asymmetry was observed in Begg's funnel plot in all studies.

CONCLUSION
RPT has favorable efficacy profiles in GIST patients, but the adverse reactions are obvious, and patient management needs to be strengthened to achieve better safety and tolerability.

Key Words: Gastrointestinal stromal tumor; Ripretinib; PDGFRA; KIT; Meta-analysis

Core Tip: The current therapeutic drugs have limited effectiveness in treating secondary mutations in different gastrointestinal stromal tumor (GIST), and new treatment strategies need to be developed. Ripretinib (RPT) is a new, switch-control tyrosine kinase inhibitors that can suppress different mutations of KIT and PDGFRA *via* a dual mechanism of action. This study aims to investigate the literature on RPT to assess an effective, safe, and successful treatment strategy against advanced GIST.

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INTRODUCTION

The most prevalent gastrointestinal tract soft tissue sarcoma is gastrointestinal stromal tumor (GIST). Furthermore, 1%-3% of all malignant gastrointestinal tumors associated with the digestive tract[1] are predominantly originating because of gain-of-function mutations in receptor tyrosine kinases (RTKs), including PDGFRA or KIT[2,3]. Currently, the standard therapy for individuals with locally advanced metastatic GIST includes PDGFRA and KIT-based tyrosine kinase inhibitors (TKIs)[4-6], where Imatinib (IMA), a TKI, is approved as the first-line drug for GIST treatment[7]. The median progression-free survival (PFS) in IMA-treated GIST individuals was observed to be 1.7 to 2 years[8,9]. However, about 50% of advanced GIST patients indicate disease progression by 24 months, and the estimated 10-year PFS is approximately 9%[6,10,11]. GIST progresses to the advanced stage primarily because of the occurrence of secondary resistance mutations in the activation loop or ATP-binding domain of PDGFRA/KIT[12,13]. These secondary mutations can sterically disrupt the interaction of some TKIs or activate kinases[13]. A multi-targeted TKI, Sunitinib (STB), is a vascular endothelial growth factor receptor (VEGFR) antagonist[14], whereas Regorafenib (REG) predominantly acts against fibroblast growth factor RTK, VEGFR2, and platelet-derived growth factor receptor[15]. Both REG and STB are approved as the 3rd and 2nd line treatment drugs for advanced GISTs, respectively, and inhibit some resistance-associated mutations [3,16]. However, STB and REG both do not cover all the possible mutations, indicating a median PFS of 5.6 and 4.8 months, respectively[17,18]. The literature has indicated that STB acts against secondary mutations in KIT exons 13/14 (ATP-binding pocket); however, it has less efficiency against GIST individuals suffering from the mutations of secondary KIT exon 17/18 and primary KIT exon 11[19-21]. Another TKI, Avapritinib, has recently been authorized by the Food and Drug Administration for treating unresectable or metastatic GISTs with PDGFRA exon 18 mutations, accounting for 6% of the overall cases[22,23]. However, TKIs do not act against PDGFRA or KIT mutations in individuals with GIST after IMA failure.

Ripretinib (DCC-2618; RPT) is a new, switch-control TKI that can suppress different mutations of KIT and PDGFRA *via* a dual mechanism of action[24,25]. Furthermore, based on the phase III INVICTUS study, RPT has been approved for treating advanced GIST patients who have already undergone three or more TKI therapies, including IMA[26]. Moreover, phase I data indicated that RPT had increased efficacy as a second-line treatment for advanced GIST patients (median PFS = 10.7 months)[27]. In addition, RPT has also indicated higher *in vitro* anti-IMA-resistant secondary KIT mutations than other TKIs, indicating that RPT might be a superior second-line anti-GIST drug[25]. However, the current guidelines do not provide the most effective treatment strategy against advanced GIST individuals due to the lack of sufficient data. In addition, the consensus on the safety and efficacy of RPT in advanced GIST patients is still lacking. Consequently, the purpose of this comprehensive review and meta-analysis was to scrutinize RPT literature to evaluate a reliable, secure, and efficacious approach to treating advanced GISTs, and to provide management guidelines for GIST.

MATERIALS AND METHODS

Search strategy

This research adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This systematic review's protocol has been submitted to the International Platform of Registered Systematic Review and Meta-Analysis Protocols (registration no. INPLASY202460030; doi.org/10.37766/inplasy2024.6.0030).

For comprehensive analysis, different databases, including Web of Science (https://webofscience.clarivate.cn/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), ClinicalTrials.gov (https://clinicaltrials.gov/), EMBASE (https://www.embase.com/), and Cochrane (https://www.cochranelibrary.com/) were extensively searched. This investigation included articles published between January 1, 2003, and May 1, 2024. The publications were screened in all the languages, and pertinent articles were selected irrespective of the primary outcomes or language. The search terms employed included [Stromal Tumor, Gastrointestinal (Title/Abstract)] OR [Tumor, Gastrointestinal Stromal (Title/Abstract)] OR [Gastrointestinal stromal tumors (Title/Abstract)] OR [Neoplasm, Gastrointestinal Stromal (Title/Abstract)] OR [Tumors, Gastrointestinal Stromal (Title/Abstract)] OR [Neoplasms, Gastrointestinal Stromal (Title/Abstract)] OR [Gastrointestinal stromal tumors (Title/Abstract)] [Stromal Neoplasm, Gastrointestinal (Title/Abstract)] OR [Stromal Tumors, Gastrointestinal l (Title/Abstract)] OR [Stromal Neoplasms, Gastrointestinal (Title/Abstract)] OR [Gastrointestinal Stromal Neoplasms (Title/Abstract)] OR OR [Gastrointestinal Stromal Neoplasm (Title/Abstract)] OR [Gastrointestinal Stromal Sarcoma (Title/Abstract)] AND (Ripretinib).

Inclusion criteria

To assess the reliability and qualification of selected articles, the intervention (I), population (P), outcome (O), comparator (C), and study design (S) framework were employed. The inclusion parameters based on the described framework included, (P): Advanced GIST patients, (I): Studies on RPT, (C): GIST patients before the study was initiated, (O): Studies with data of disease control rate (DCR), the adverse reactions rate (ARR), and objective response rate (ORR), and (S): Cohort studies, randomized controlled trials (RCT), and case reports.

Exclusion criteria

(1) Articles on treatment with RPT in primary tumors other than GIST or those lacking survival data; (2) Articles on patients diagnosed with GIST or other malignancies that lacked separate results; As well as (3) reviews, conference abstracts, case reports, letters to the editor, and animal research were all excluded from this review.

Data extraction and quality assessment

The literature screening was carried out by 2 researchers, JL and HZ, who carefully reviewed the topic, picked articles that met the above criteria, and elucidated the selected article's full text and abstract. For RCT, two researchers cross-estimated the literature's quality based on the RCT Jadad method, double-blind method setting, from random allocation, randomized hiding, as well as exit and loss to follow-up (based on 7 point scores, 1–3 = inferior quality, 4–7 = high-quality literature)[28]. Moreover, they also elucidated the methodological quality of selected articles based on the guidelines of the Cochrane Review handbook. The Newcastle-Ottawa scale (NOS) was employed to elucidate cohort study quality[29]. The NOS is an extensive framework comprising 8 items grouped into 3 domains: Exposure or outcome evaluation, population selection, and comparability. A numerical score was assigned to each item between 0–9 scale, where > 5 scores represent a high-quality level[29]. Furthermore, 2 researchers (HZ and JL) independently recorded the following data: First author details, male patients %, publication date, type of research, number of participants in the article, the country where the research was conducted, and the median follow-up period. In case of any disagreement, a third researcher (XDC) was approached.

Statistical analysis

This research comprehensively carried out the meta-analysis of pertinent literature *via* the STATA 16.1 (StataCorp LLC, College Station, TX, United States) statistical software to elucidate various clinical outcomes. Furthermore, ORR, ARR, DCR, and grade ≥ 3 adverse reactions, as well as the outcomes and corresponding 95% confidence intervals (CIs), were also evaluated. The I^2 statistic and Cochran's Q test were carried out to assess the inter-study heterogeneity, where < 25% values = low, 25%-50% = moderate, and > 50% and < 75% = high levels of heterogeneity[30]. At > 75% values, a sensitivity test was carried out to assess the impact size and research heterogeneity. To ensure the result's stability, studies that significantly influenced heterogeneity were excluded. For combined analysis, a random effect model was employed, while funnel plots were drawn to elucidate publication bias. The potential bias and plot asymmetry were evaluated simultaneously using Begg's and Egger's tests. P value of < 0.05 was the threshold for the significant difference.

RESULTS

Study characteristics

After full-text assessment and the extraction of relevant data, 4 studies with 507 patients sample size were selected. The selection protocol followed the recommendations described in the PRISMA flowchart (Figure 1). This research also included RCT[26,31,32] and cohort studies[27]. Table 1 outlines the pertinent information on the selected articles.

Table 1 Characteristics of all studies included in the meta-analysis

Ref.	Country	Type	Patients(n)	Male (%)	Median follow-up time (months)
Blay *et al*[26], 2021	France	RCT	85	55	6.3
Janku *et al*[27], 2020	American	Cohort	142	58.5	10.6
Bauer *et al*[31], 2022	Germany	RCT	226	61.5	7.9
Li *et al*[32], 2023	China	RCT	54	36	13.8

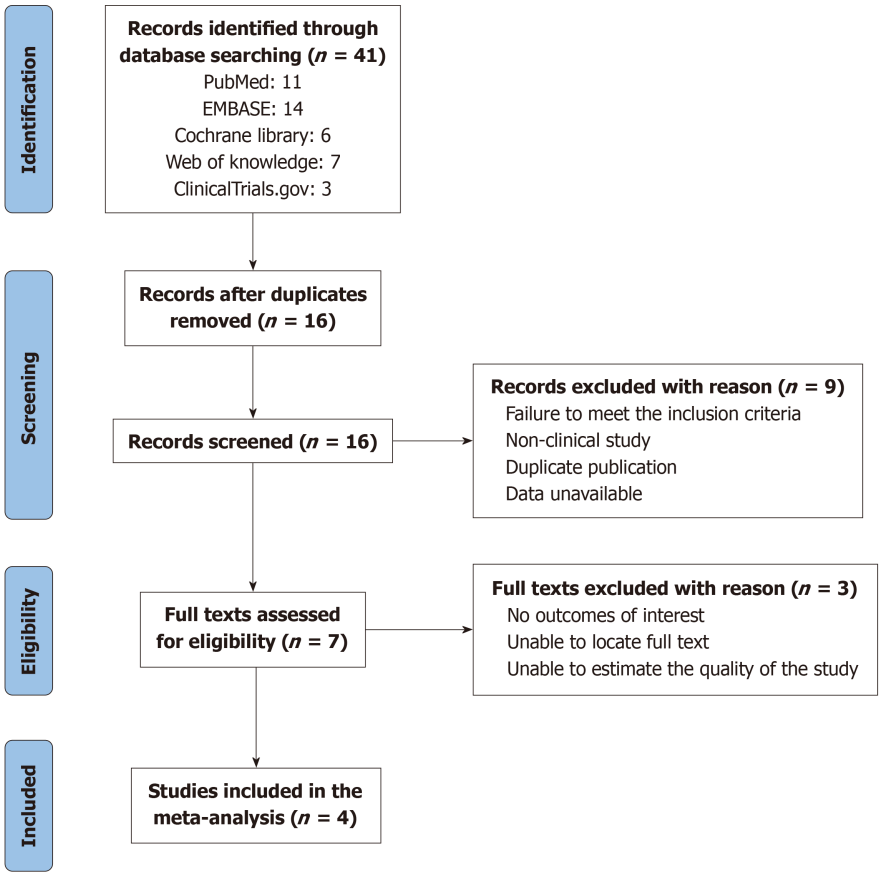

Figure 1 Screening strategy for the included studies.

Quality evaluation of the included studies

The RCT's quality was assessed using the Jadad method, where a 1-3 score indicated inferior quality, while a 4-7 score presented a high-quality study. The results indicated that 3 RCTs had high quality (Table 2). To assess the quality of the cohort studies, NOS was employed, where a score of 5-9 indicated good quality. The data revealed that the included cohort study had a score of 6, indicating a high quality (Table 3).

Meta-analysis

The ORR of the RPT-treated advanced GIST patients was 17% (95%CI: 0.11-0.27; Figure 2A), while the DCR was 66% (95%CI: 0.59-0.73; Figure 2B). Furthermore, the overall occurrence of adverse events with varying degrees was 97% (95%CI: 0.93-1; Figure 2C), whereas that of grade ≥ 3 adverse reactions was 42% (95%CI: 0.28-0.63; Figure 2D).

Publication bias assessment

Analysis of sensitivity showed that omitting certain studies did not significantly alter the aggregate data of ORR (Figure 3A), DCR (Figure 3B), yet the overall ARR's sensitivity test showed statistical significance (Figure 3C). Additionally, the statistical analysis of sensitivity for grade 3 or higher adverse events was not statistically (Figure 3D). Moreover, Begg's and Egger's analyses for ORR and DCR indicated *P* value of 0.431 and 0.105, respectively, while for ARR and grade ≥ 3, adverse reactions were 0.065 and 0.2, respectively. In addition, the publication bias was absent because no significant asymmetry was observed in Begg's funnel plot in all studies (Figure 4).

Table 2 Quality assessment using the Jadad Scale for randomized controlled trial

Ref.	Type	Random allocation	Randomized hiding	Double-blind method setting	Exit and loss to follow-up	Score
Blay *et al*[26], 2021	RCT	2	2	2	2	8
Bauer *et al*[31], 2022	RCT	1	2	2	2	7
Li *et al*[32], 2023	RCT	2	2	1	2	7

RCT: Randomized controlled trial.

Table 3 Quality assessment using the Newcastle-Ottawa Scale for cohort studies

Ref.	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Janku *et al*[27], 2020	1	0	1	1	1	1	0	1	6

DISCUSSION

The GIST is the highly prevalent sarcoma subtype that originates in the digestive tract, primarily because of the gain-of-function mutations in PDGFRA or KIT RTK[1-3]. For localized GIST, the current standard treatment includes complete surgical resection. The aim is an R0 surgery with complete tumor removal, including an intact pseudocapsule[33]. It has been indicated that first-line IMA treatment for advanced GIST initially inhibits tumor response and controls the disease; however, nearly all patients have revealed disease progression because of secondary mutations[10,11]. Currently, STB is the only authorized second-line therapy; however, it has relatively limited benefits and a high incidence rate of toxicity [12]. Furthermore, IMA re-challenge is an option for advanced-stage patients who do not receive benefits after their TKI therapy[34]. Kang *et al*[35] studied 81 patients with disease progression after two or more lines of TKI therapy and revealed that about 40% of the patients underwent at least 3 prior TKI treatments, including STB, IMA, and REG. Moreover, the median PFS of the IMA re-challenge cohort was only 1.8 months (95%CI: 1.7-3.6), and no patients achieved objective remission. Therefore, there is an increased medical for novel TKIs with broad activity and ability to inhibit secondary drug-resistant mutations in advanced GIST.

The RPT is a switch-control TKI that widely suppresses the signaling of the PDGFRA and KIT kinases *via* a dual mechanism of action[25]. It specifically and reliably interacts with both PDGFRA and KIT to activate the loop, thereby locking the kinase in the inactive state, thus inhibiting the downstream signaling and cell growth. This dual pathway promotes wide suppression of PDGFRA and KIT kinases, including their wild-type, as well as different primary and secondary mutations associated with GIST's drug resistance[36,37]. Smith *et al*[25] indicated that RPT had an increased efficacy than type I and II inhibitors for resistance and primary mutations in KIT exons 11, 9, 14, 17, 13, and 18, as well as for REG-resistant D816V mutation. The *in vitro* and other cell-based research have indicated substantial inhibitory activity against the proto-oncogenic kinase receptors VEGFR2, TIE2, PDGFRB, and BRAF[25]. A first human trial in GIST or other advanced solid tumor patients has recommended a phase 2 RPT dose of 150 mg/day, which was linked with tolerable profile. Furthermore, RPT was active in advanced GIST patients that were refractory to other TKIs used. Moreover, RPT doses of 150 mg twice a day were also well tolerated and indicated no clinically meaningful dose-limiting side effects[38], thereby providing evidence for RPT's clinical application. INVICTUS (NCT0335373) was the first phase III trial of RPT in the advanced GIST patients[26], which indicated a markedly improved primary endpoint of median PFS relative to placebo (6.3 *vs*. 1.0 months). Furthermore, the median overall survival was 18.2, 6.3, and 10.0 months in the RPT, placebo, and placebo transition to the RPT cohort, respectively. Moreover, the ORR in the RPT cohort was 11.8% compared to 0% in the placebo patients[26]. In addition, a global INTRIGUE study compared RPT with STB in the largest (n = 453) randomized, active-controlled phase 3 trial in second-line GIST[31]. Although the primary endpoint of PFS superiority over STB was not met, compared to STB, RPT indicated clinically essential benefit with a similar overall and a numerically longer median PFS in KIT exon 11-mutated patients (7.0 *vs*. 8.3 months; HR = 0.88, $P = 0.36$). These data indicated that in advanced GIST, RPT may inhibit secondary drug-resistant mutations more efficiently. However, further studies are needed to establish RPT's effectiveness and safety in GIST patients.

This investigation aimed to comprehensively review and meta-analyze the safety and efficacy of RPT against advanced GISTs. Furthermore, this research evaluated ORR, DCR, ARR, and incidence of grade ≥ 3 adverse reactions. The ORR of the RPT in advanced GIST patients was 17% (95%CI: 0.11-0.27; Figure 2A), while the DCR was 66% (95%CI: 0.59-0.73; Figure 2B). Moreover, the incidence of grade ≥ 3 adverse reactions was 42% (95%CI: 0.28-0.63; Figure 2D). These data suggested that RPT might have a favorable therapeutic outcome, but the incidence of grade 3 ARR is relatively high. The

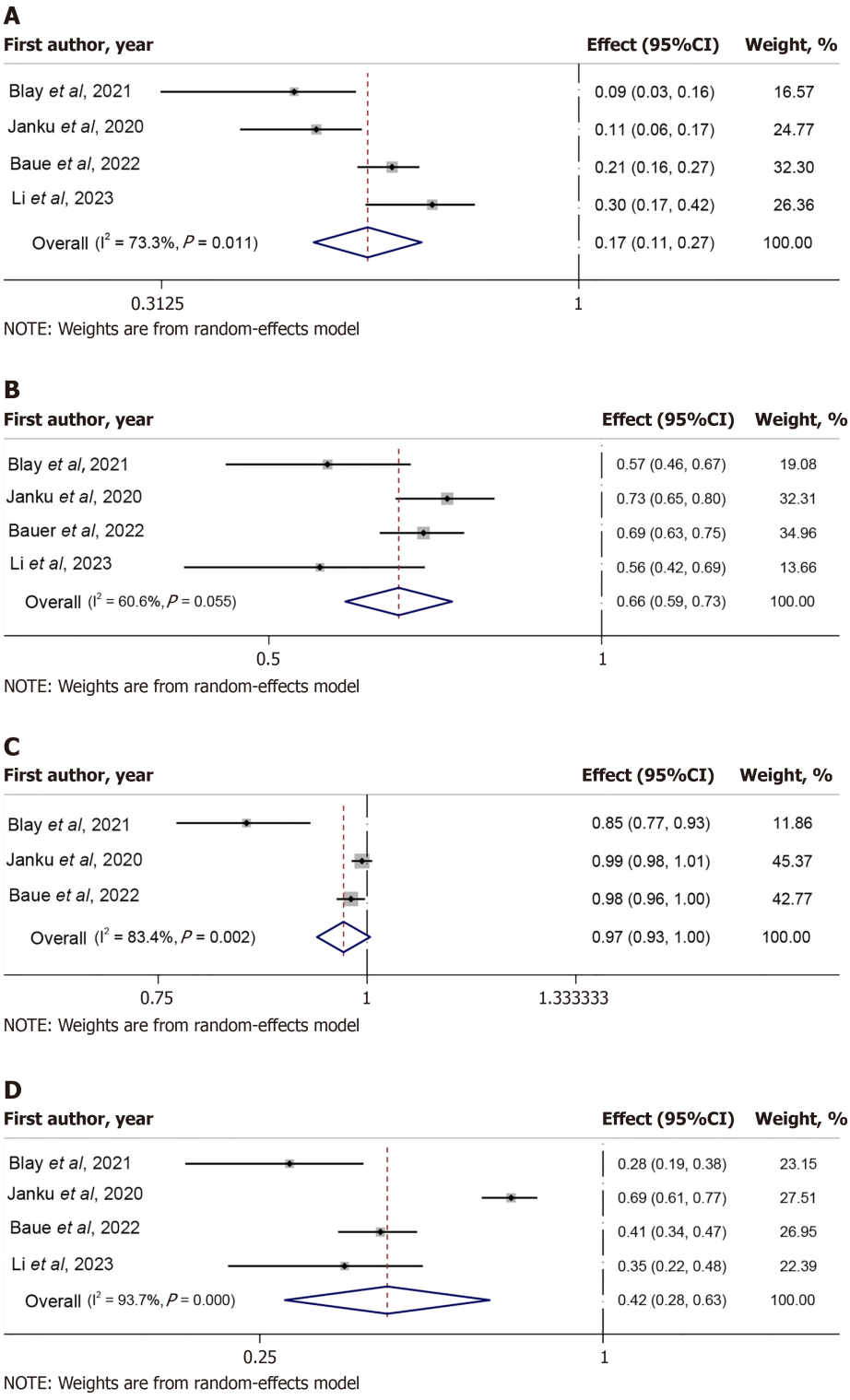

Figure 2 Meta-analyses. A: Meta-analysis of objective response; B: Disease control; C: Adverse reaction rate; D: Incidence of grade ≥ 3 adverse reactions of ripretinib in patients with gastrointestinal stromal tumor.

ARR in RPT-treated GIST patients was 97% (95%CI: 0.93-1), and the most common TEAEs included fatigue, alopecia, and myalgia, but most adverse reactions were grade 1 or 2[26,27,31,32]. The pathogenesis of the observed adverse effects remains undetermined; however, it can be secondary to the inhibition of related kinases (*e.g.*, VEGFR2, PDGRA, KIT, BRAF)[39]. Bauer *et al*[31] compared the safety profiles of RPT, STB, and RCT. The results indicated that RPT had fewer patients (26.5%) with grade 3/4 drug-related TEAEs compared with STB (55.2%). Moreover, grade 3/4 TEAEs were mostly reduced after RPT treatment compared to STB and included hypertension (8.5% *vs* 26.7%), PPES (1.3% *vs* 10%), diarrhea (0.9% *vs* 2.7%), hypertriglyceridemia (0.4% *vs* 3.2%), reduced lymphocyte count (0.4% *vs* 2.3%), reduced neutropenia or neutrophil count (0% *vs* 13.1%), and stomatitis (0% *vs* 2.7%). The most frequent grade 3/4 TEAE was hypertension in both the drugs; however, patients undergoing STB treatment were four times more prone to drug-related grade 3/4 hypertension (22.6%) than RPT patients (5.8%). Li *et al*[32] assessed the safety of RPT in Chinese GIST patients

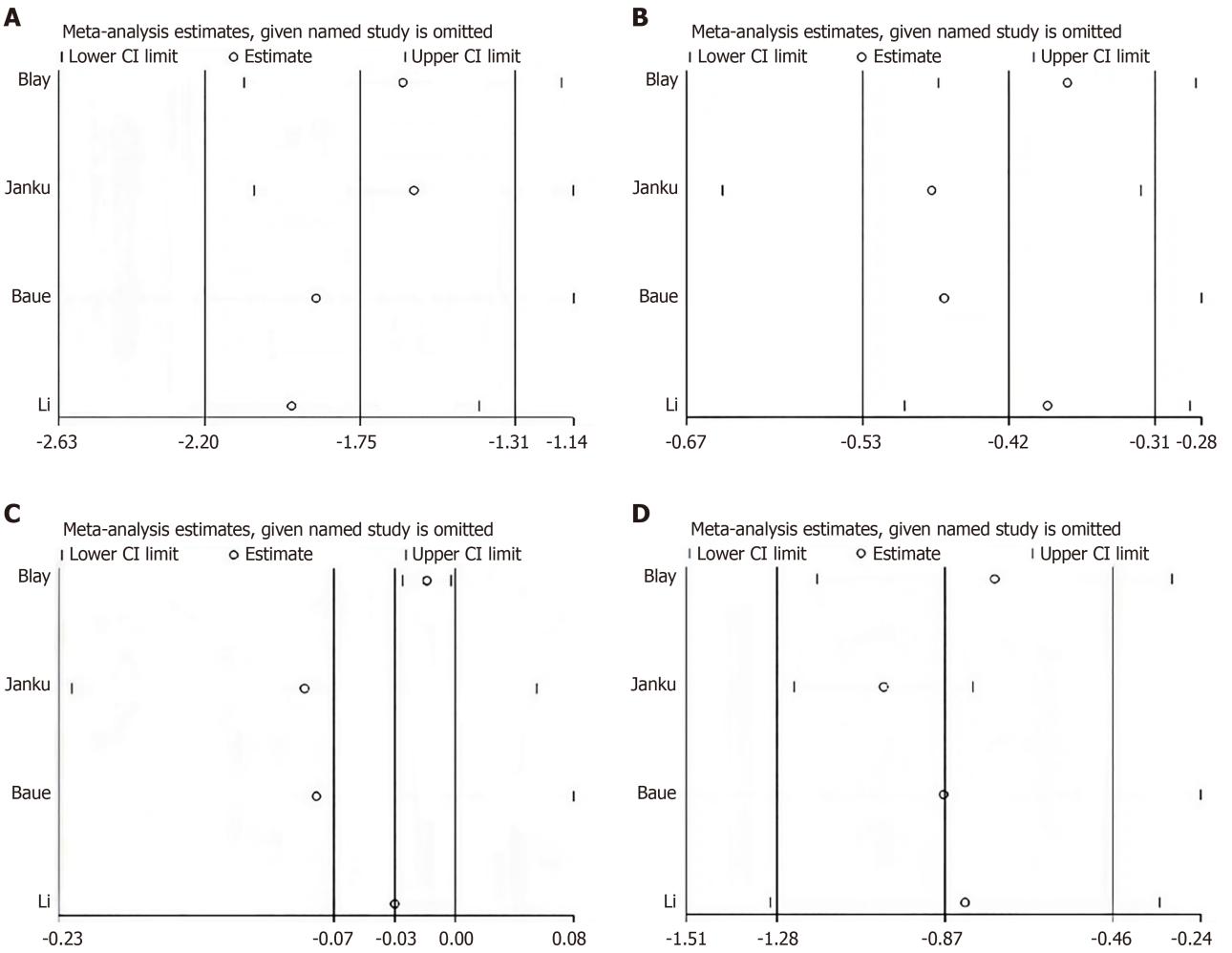

Figure 3 Sensitivity analysis. A: Sensitivity analysis of objective response; B: Disease control; C: Adverse reaction rate; D: Incidence of grade ≥ 3 adverse reactions of ripretinib in patients with gastrointestinal stromal tumor.

and showed that compared to RPT, the STB cohort had a higher incidence of palmar and plantar red syndrome, hematological toxicity, and hypertension. Compared with other TKI drugs, the incidence of grade 3 ARR of ripretinib is not significantly higher, and for advanced GIST that is resistant to first-line therapy, patients need to tolerate the side effects of the drug to a certain extent in order to achieve longer survival. Therefore, when RPT is used for advanced GIST patients, it is necessary to strengthen patient management, promptly respond to the occurrence of adverse reactions, alleviate the troubles caused by adverse reactions to patients, and ensure higher tolerance and safety.

There are certain limitations in this study: (1) The analysis included only 4 articles, excluding ongoing studies and individual case reports, therefore, the sample size was small. The choice of subjects may impact how patients respond to the selected drugs, thus, more RCTs are required to mitigate the influence of potential confounders; and (2) The sensitivity analysis on the total ARR indicated statistical significance, suggesting that the combined results of the total ARR might not be reliable. This might be because, in the study of Li *et al*[32], all patients indicated adverse reactions of various degrees, significantly impacting the combined results, which might be associated with the overall characteristics of the population included in the study. However, sensitivity assessment revealed reliable results for the incidence of grade > 3 adverse reactions and RPT, still suggesting good tolerability and safety.

CONCLUSION

In summary, this systematic review and meta-analysis revealed that RPT has favorable efficacy and safety profiles in GIST patients. Further rigorous prospective research and RCT are required to validate these findings. Future studies should elucidate the optimal RPT dose, potential biomarkers for patient selection, predictive biomarkers, and individualized treatment strategies for different mutations in advanced GIST.

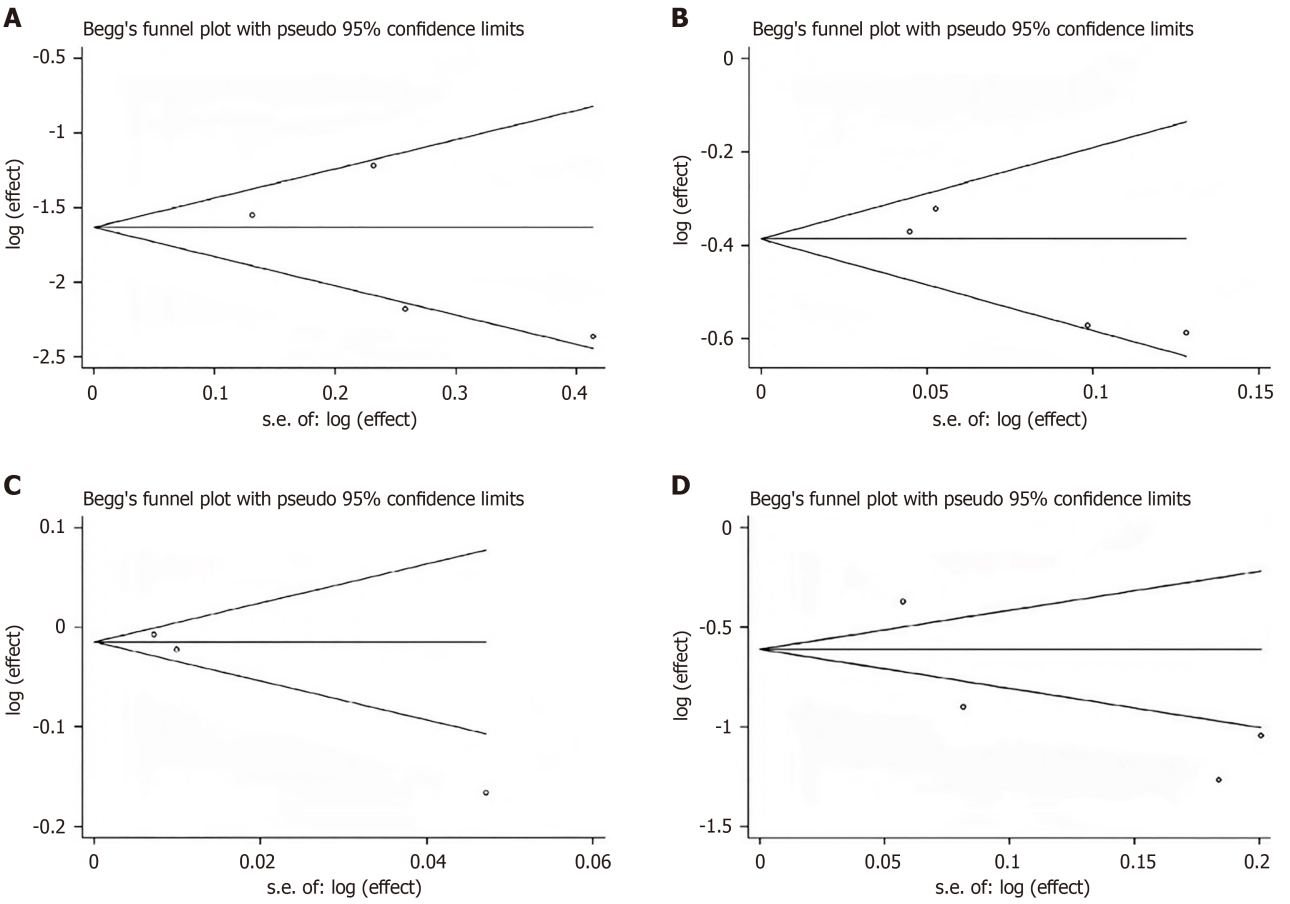

Figure 4 Begg's funnel plots for publication bias test with pseudo 95% confidence limits. A: Objective response; B: Disease control; C: Adverse reaction rate; D: Incidence of grade ≥ 3 adverse reactions of ripretinib in patients with gastrointestinal stromal tumor.

FOOTNOTES

Author contributions: Li J and Zhang H conceived and designed the study; Chen XD and Zhang H collected data and performed the database search; Li J and Zhang H performed statistical analysis; Li J, Zhang H, Chen XD drafted the manuscript; Li J and Chen XD confirm the authenticity of all the raw data; All authors revised the manuscript; All authors have read and approved the final manuscript.

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