Meta-Analysis

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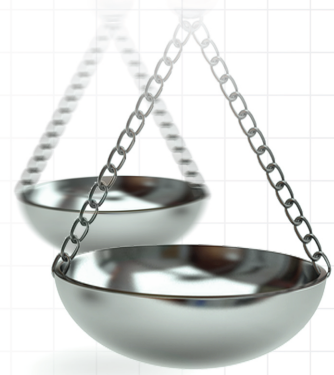

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Network meta-analysis of multiple doses of vonoprazan for the treatment of erosive esophagitis

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Aim: 20 mg of vonoprazan (VPZ20) is recommended in most countries to treat erosive esophagitis (EE). Whether other doses of vonoprazan, such as 5 mg (VPZ5), 10 mg (VPZ10), 20 mg (VPZ20), and 40 mg (VPZ40) are more effective is unknown. **Materials & methods:** Three databases were electronically searched to identify studies published before November 2021. Network meta-analysis was performed using STATA 14.0. **Results:** VPZ20 and VPZ40 were comparable to PPI, VPZ5 and VPZ10 in 4- and 8-week healing rates, and this was also detected in patients with refractory EE. All regimens resulted in similar treatment-emergent adverse events (TEAEs). However, VPZ40 ranked first for healing rate and TEAEs; however, VPZ20 ranked worst for TEAEs. **Conclusion:** Different doses of VPZ are comparable in efficacy and safety, but VPZ40 may be best in both effectiveness and safety.

Plain language summary

What is this article about? Erosive esophagitis refers to esophageal mucosal erosions on endoscopy and heartburn symptoms, accounting for 10% of gastroesophageal reflux disease (GERD). A recent meta-analysis has evaluated the efficacy and safety of 20 mg of vonoprazan as a novel potassium-competitive acid blocker. However, other doses, including 5 mg, 10 mg and 40 mg, are also used in practice. Therefore, this study aimed to determine the optimal dosing strategy of vonoprazan in treating erosive esophagitis.

What were the results? Different doses of vonoprazan had comparable efficacy and safety; however, 40 mg of vonoprazan may be the best option for treating erosive esophagitis from the perspective of both efficacy and safety.

What do the results of the study mean? In order to achieve a satisfactory healing rate and lower treatment-emergent adverse events for the treatment of erosive esophagitis in practice, priority should be given to choosing 40 mg of vonoprazan.

Tweetable abstract: A new network meta-analysis reveals that 40 mg of #vonoprazan may be the best dosing strategy for treating #erosive esophagitis from the perspective of both effectiveness and safety.

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Keywords: erosive esophagitis • gastroesophageal reflux disease • network meta-analysis • proton-pump inhibitors • vonoprazan

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder that results from the retrograde flow of stomach contents into the esophagus and is characterized by troublesome complications such as heartburn and acid regurgitation [1]. The prevalence of GERD has been increasing, and a recent meta-analysis of approximately 100 studies reported a global prevalence of 13.3%, 17.1% in Europe, 15.4% in North America and 10.0% in Asia [2]. GERD could be mainly classified into two subtypes based on endoscopic findings, including non-erosive

reflux disease and erosive esophagitis [3]. Erosive esophagitis, defined as esophageal mucosal erosions on endoscopy and heartburn symptoms [4], accounts for 10% of GERD [5].

The effective treatment of erosive esophagitis mainly starts from: relieving symptoms, accelerating esophageal mucosal healing, and preventing complications [6]. Although several strategies have been proposed and tested in practice [7], drugs are currently the mainstay of GERD treatment [8]. Among the available therapeutic agents, proton pump inhibitors (PPIs) have been demonstrated to have excellent mucosal healing and symptom relief because it strongly inhibits gastric acid secretion. Currently, PPIs are considered the most common first-line treatment for erosive esophagitis [9,10]. Unfortunately, approximately 20–40% of patients with mucosal erosions do not achieve mucosal healing or satisfactory symptom relief [11,12].

Some new acid inhibitors have been proposed and tested after PPIs. As a novel potassium-competitive acid blocker, vonoprazan (VPZ) can strongly inhibit H+, and K+ ATPase competitively and reversibly [13,14]. Compared with earlier PPIs, VPZ may have stronger and more sustained acid suppression but less variation in time to onset of action [15]. Several studies [14,16] have investigated the efficacy and safety of VPZ 20 mg (VPZ20) in treating GERD. Meanwhile, a recent meta-analysis concluded that VPZ20 is non-inferior to PPIs, or even more effective than PPIs, in patients with severe erosive esophagitis, with a similar safety profile [17].

In addition to the standard dose of 20 mg, multiple doses of VPZ are used in clinical practice, including 5 mg, 10 mg and 40 mg [18,19]. To date, only one study has directly compared all doses of VPZ in an individual study [18]. Therefore, it does not provide clinicians with conclusive information on the optimal dose for patients with erosive esophagitis. Fortunately, network meta-analysis enhances the strength of evidence by combining all available evidence [20]. Therefore, we performed this network meta-analysis, which combined direct and indirect evidence from all eligible studies, to compare the efficacy and safety of multiple doses of VPZ.

Methods

The present network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting network meta-analysis [21]. Ethics approval and informed consent did not apply, as the statistical analysis was performed based on the published data.

Literature retrieval

A comprehensive literature retrieval was performed by two independent reviewers (Jie He and Yuanyuan Gao) in PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant randomized controlled trials (RCTs) from their inception until December 2021. The following terms and analogs were used to construct a basic search query following the PICOS principle: "erosive esophagitis" and "vonoprazan". The detailed search strategies of three target English databases are shown in Supplementary Table 1. In addition, the reference lists of eligible studies and previous meta-analyses were screened as well. Disagreements were resolved by discussions between two reviewers (Jie He and Yuanyuan Gao) until a consensus was reached.

Selection criteria

Inclusion criteria for the present network meta-analysis included: (a) prospective RCTs; (b) patients with confirmed erosive esophagitis and aged ≥16 years; (c) PPIs administered at conventional doses as the control strategy; (d) VPZ was administered as the study strategy; and (e) 4- and 8-week endoscopic healing rates and treatment-emergent adverse events (TEAEs) were reported and data were applicable for statistical analysis. In addition, conference abstracts with sufficient data were also eligible for inclusion. Ineligible studies were excluded based on the following criteria: (a) duplicate reports that had insufficient data and relatively poor quality; (b) lack of data to conduct a network meta-analysis; (c) studies that did not report data for 4 or 8 weeks; and (d) animal studies, review papers, and observational studies.

Study selection

Two independent reviewers (Jie He and Yuanyuan Gao) selected eligible studies based on the following three-step selection criteria. First, duplicate studies were removed using the literature management software, namely EndNote (version X9, Clarivate Analytics). Second, irrelevant studies were excluded after screening the study title and abstract. Third, ineligible studies were further excluded by screening the full texts of the remaining studies. Disagreements were resolved by discussions between two reviewers (Jie He and Yuanyuan Gao) until a consensus was reached.

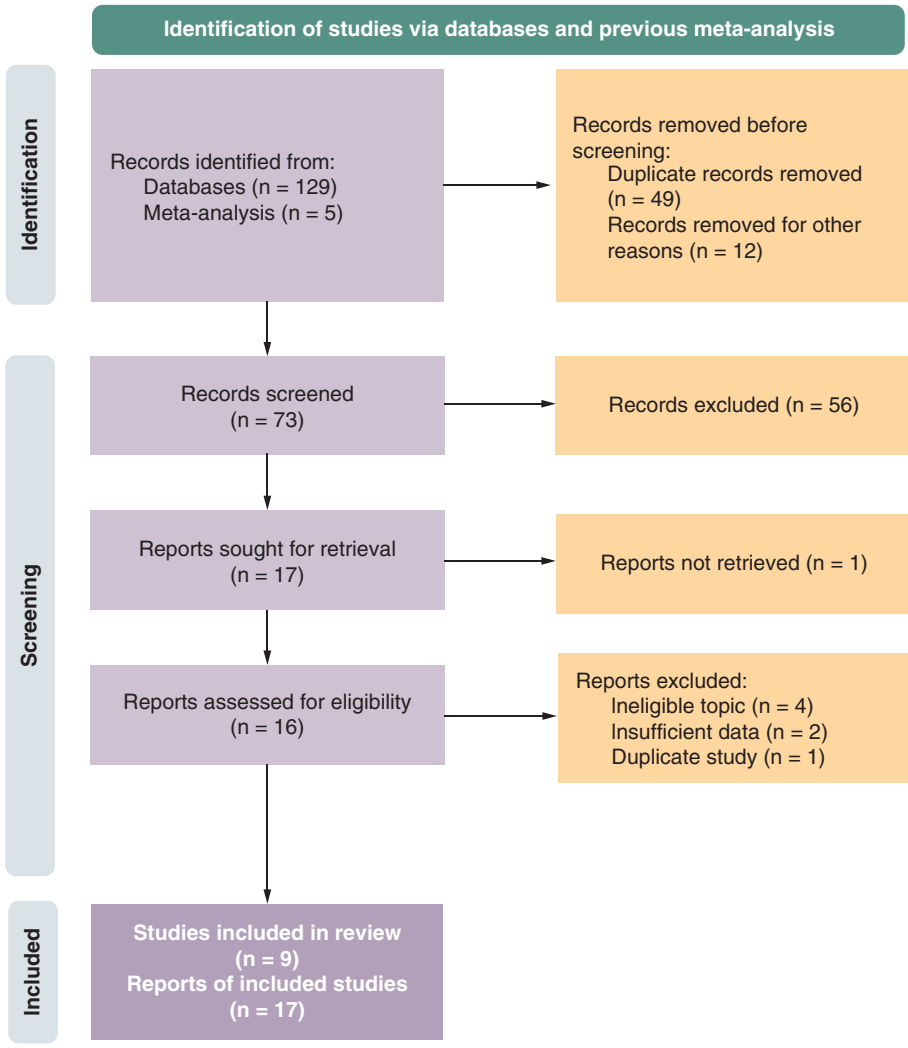

Figure 1. Study retrieval and selection.

Data extraction

Two independent reviewers (Jie He and Yuanyuan Gao) extracted the following data from included studies: the name of the first author, country of study, year of publication, study design, condition of disease, comparison details, sample size (including the percentage of male patients), the number of patients with different severity grades which were defined according to Los Angeles (LA) classification system, age distribution, duration of treatment, and outcome details. If needed, missing data were added by emailing the corresponding author.

Outcome measures

We defined the 4-week endoscopic healing rate as a primary outcome, and 8-week endoscopic healing rate, the 4- and 8-week healing rate in patients with LA grades of C and D, and the incidence of TEAEs as secondary outcomes. Mucosal healing of erosive esophagitis was assessed endoscopically as "no mucosal breaks", and endoscopic healing rate was defined as the percentage of patients with endoscopically confirmed mucosal healing. TEAEs were defined as undesirable medical symptoms or conditions that occurred throughout treatment.

Geometry of the evidence network

Network graphs were generated to show the evidence of the 4- and 8-week endoscopic healing rates and the TEAEs rate. Each node represented a treatment strategy in a single graph, and a solid line between two nodes indicated that two treatment strategies were directly compared in original studies. In general, the size of the nodes represented the

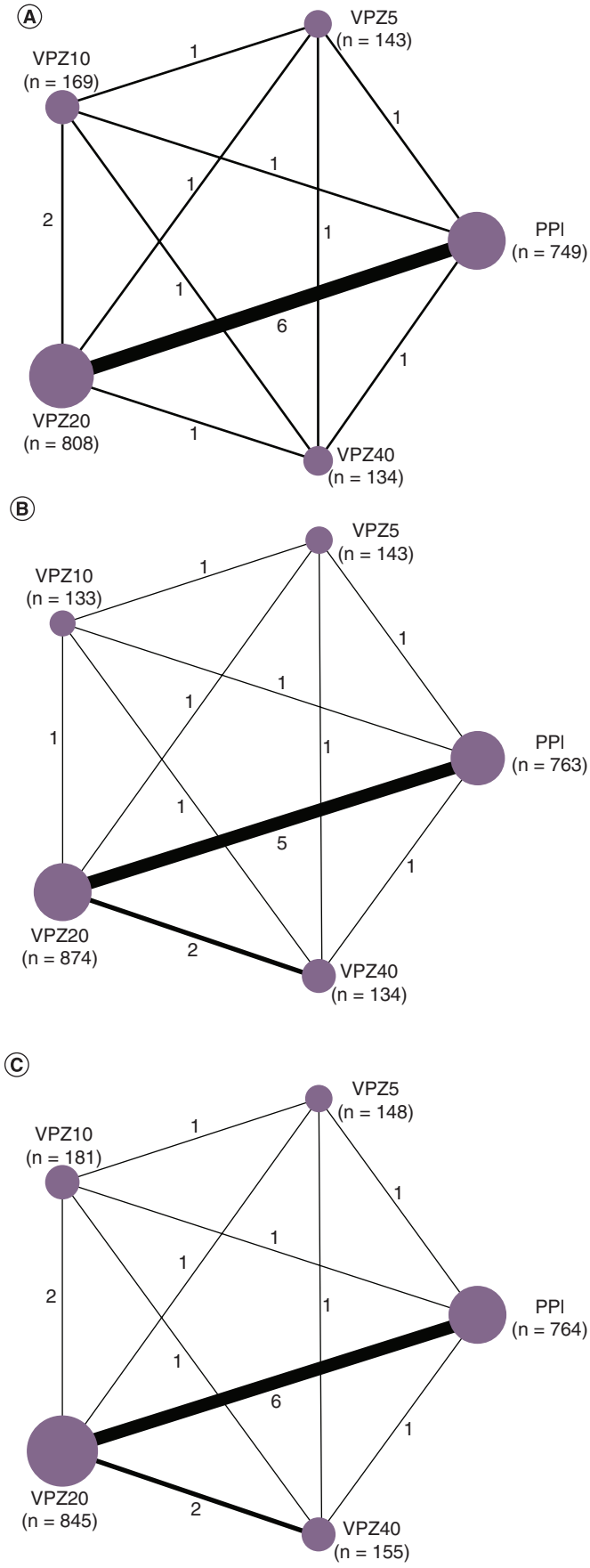

Figure 2. Network plots of the endoscopic healing rates at (A & B) 4 and 8 weeks and (C) treatment-emergent adverse events. The size of each node is corresponding to the number of patients, and the thickness of each solid line between two nodes is corresponding to the number of direct comparisons.
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events.

Table 1. Basic characteristics of eligible studies (n = 9).

Study, year	Origin	Design	Condition	Comparison	Sample size	Male patients	Age, years	Patients with grade A/B (n)	Patients with grade C/D (n)	Treatment period
Ashida, *et al.*, 2015	Japan	Multi-center	EE	VPZ5	148	110	57.9 ± 12.9	88	55	8 weeks
				VPZ10	145	113	57.3 ± 13.0	89	44	
				VPZ20	154	115	58.3 ± 13.8	94	50	
				VPZ40	146	114	57.6 ± 12.8	84	51	
				LPZ30	140	99	55.8 ± 13.9	86	47	
Ashida, *et al.*, 2016	Japan	Multi-center	EE	VPZ20	207	137	58.3 ± 13.8	132	75	8 weeks
				LPZ30	202	154	57.4 ± 13.2	129	73	
Chen, *et al.*, 2018	China	Multi-center	EE	VPZ20	142	105	51.8 ± 13.7	89	54	8 weeks
				LPZ30	133	110	51.5 ± 12.5	85	46	
Xiao, *et al.*, 2020	China	Multi-center	EE	VPZ20	244	176	54.1 ± 13.2	168	76	8 weeks
				LPZ30	237	179	53.8 ± 12.5	167	68	
Okanobu, *et al.*, 2021	Japan	Single-center	EE	VPZ10	36	24	62 (38–83)	29	7	4 weeks
				VPZ20	37	26	69 (35–85)	28	9	
Iwakiri, *et al.*, 2017	Japan	Multi-center	Refractory EE	VPZ20	9	5	73.8 ± 7.5	2	3	8 weeks
				VPZ40	10	3	71.2 ± 10.5	6	2	
Huang, *et al.*, 2021	China	Single-center	Refractory EE	VPZ20	30	14	44.3 ± 16.4	10	20	4 weeks
				EPZ20	30	17	45.5 ± 17.3	12	18	
Uemura, *et al.*, 2019	Japan	Multi-center	EE	VPZ20	139	n.a.	n.a.	n.a.	n.a.	8 weeks
				LPZ30	69	n.a.	n.a.	n.a.	n.a.	
Sakurai, *et al.*, 2019	Japan	Multi-center	EE	VPZ20	22	6	58.0 ± 13.8	10	3	4 weeks
				EPZ20	25	10	54.7 ± 13.2	9	3	

EE: Erosive esophagitis; EPZ: Esomeprazole; LPZ: Lansoprazole; n.a.: Not applicable; VPZ: Vonoprazan.

cumulative sample size, and the thickness of the solid line represented the number of reports that directly compared one strategy to another [22].

Risk of bias assessment

Two independent reviewers (Jie He and Yuanyuan Gao) assessed the methodological quality of the included studies using the Cochrane risk of bias assessment tool (RoB) [23]. Seven items were involved, each item rated as "low", "high", or "unclear" risk of bias. The overall level of methodological quality was rated as "high" if seven items were judged to be at "low" risk of bias, as "low" if at least one of seven items was judged to be at "high" risk of bias, or as "moderate" if at least one judged to be at "unclear" risk of bias but none was judged to be at "high" risk of bias. Disagreements were resolved by discussions between two reviewers (Jie He and Yuanyuan Gao) until a consensus was reached.

Statistical analysis

In this network meta-analysis, all outcomes were dichotomous variables, so an odds ratio (OR) with a 95% credible interval (CrI) was used to express the magnitude of the pooled results. We assessed the transitivity across studies by reviewing the most clinical and methodological characteristics [24,25]. Second, global and local consistency tests were performed using the design-by-treatment interaction method (Wald test) [26] and the node-splitting method [27], respectively. Third, we evaluated the loop inconsistency by calculating the value of the $\tau 2$ statistic, which was also estimated using the node-splitting method [28,29]. However, we performed a random-effects network meta-analysis to determine the relative efficacy of different treatment strategies regardless of the level of statistical heterogeneity [30]. In addition, subgroup analysis was performed to investigate the role of various doses in patients diagnosed with severe erosive esophagitis (defined as C and D based on the LA classification system). Sensitivity analysis was also performed to examine the robustness of the primary outcome by excluding studies that included patients with refractory erosive esophagitis. Fourth, ranking probabilities were estimated to determine the relative ranking of targeted treatment strategies. The surface under the cumulative ranking (SUCRA) was also calculated for each strategy [31]. Finally, adjusted funnel plots were made to examine the risk of publication bias by visually inspecting the symmetry criterion. We generated comparison-adjusted funnel plots for the individual outcome

for publication bias, with a symmetric plot indicating no publication bias [32]. Statistical analysis was performed using STATA 14.0 (StataCorp LP, College Station, Texas, USA) with the "network" command [33]. Furthermore, all results were presented graphically using the graphical tools developed by Chaimani *et al.* [34].

Results

Literature selection

A total of 134 studies were identified from the literature retrieval, including 129 studies from electronic databases and five studies from previous meta-analyses. First, 49 duplicate studies and 12 registered study protocols were removed. Then, based on the title and abstract, 56 irrelevant studies were excluded from the initial eligibility assessment. Finally, nine studies [6,18,19,35–40] were included in this network meta-analysis after excluding seven ineligible studies due to ineligible topics (n = 4), insufficient data (n = 2), and duplicate study (n = 1). The PRISMA flow diagram of study retrieval and selection is shown in Figure 1. Six treatment strategies, including VPZ 5 mg (VPZ5), VPZ 10 mg (VPZ10), VPZ 20 mg (VPZ20), VPZ 40 mg (VPZ40), LPZ 30 mg (LPZ30), and EPZ 20 mg (EPZ20) were identified. According to a previous network meta-analysis [41], LPZ30 was comparable to EPZ20 in 4- and 8-week endoscopic healing rates, so the combination of the two strategies was considered as a standard control group, named the PPI group. Network plots of 4- and 8-week endoscopic healing rates and the incidence of TEAEs are shown in Figure 2.

Study characteristics

All eligible studies were conducted in China (n = 3) [35,36,40] and Japan (n = 6) [6,18,19,37–39]. Most studies [6,18,19,35,38–40] recruited patients from multiple centers and two studies [36,37] recruited patients from a single center. Two

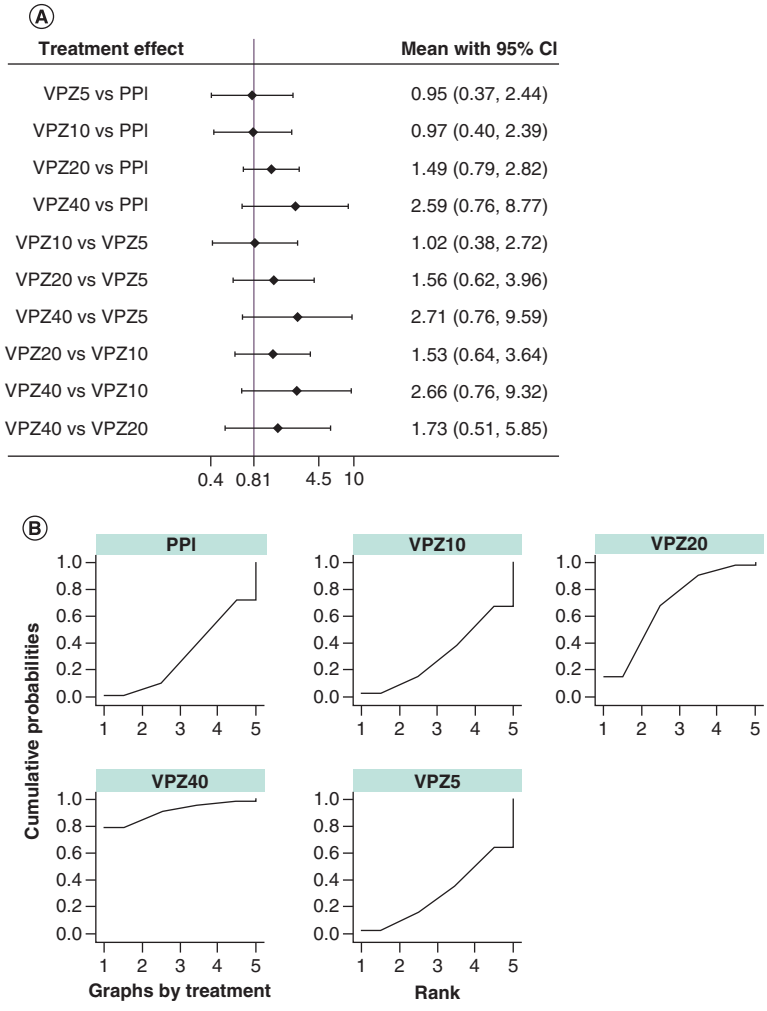

Figure 3. Relative efficacy and SUCRA of the endoscopic healing rates at (A & B) 4 and (C & D) 8 weeks.
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events; SUCRA: Surface under the cumulative ranking.

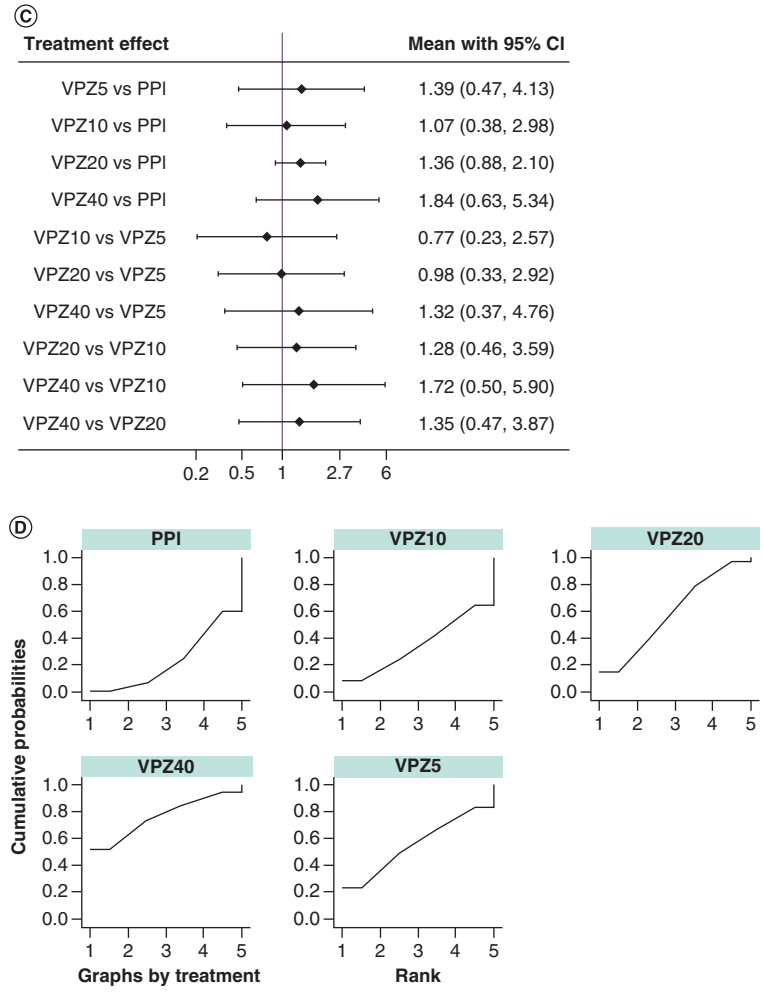

Figure 3. Relative efficacy and SUCRA of the endoscopic healing rates at (A & B) 4 and (C & D) 8 weeks (cont.).
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events; SUCRA: Surface under the cumulative ranking.

studies [19,36] explicitly reported recruiting patients with refractory erosive esophagitis. Eight studies [6,19,35–40] were designed with two arms, but one was designed with multiple arms [18]. The mean age of the 2305 patients included in our network meta-analysis was 57.49 years, and the percentage of male patients was 63.98%. Additional baseline characteristics of the included studies are shown in Table 1.

Risk of bias of eligible studies

Details of the risk of bias assessment are shown in Supplementary Figure 1. All studies [6,18,19,35–40] reported methods to generate random sequences, but only four studies [6,18,35,40] used appropriate methods to perform allocation concealment. Two studies [38,39] were judged to be high risk in allocation concealment, and blinding of participants, personnel, and outcome assessors due to the open-label study design. All studies were judged to be low risk for the remaining three items. Overall, in terms of the overall methodological quality, two studies were rated as "low" level, three studies as "moderate" level, and four studies as "high" level.

Meta-analysis of the endoscopic healing rate

A total of seven [6,18,35–38,40] and six [6,18,19,35,39,40] studies reported endoscopic healing rates at 4 and 8 weeks, respectively. As shown in Supplementary Figure 2, no significant inconsistency was identified for outcomes at 4 and 8 weeks by the global inconsistency test (A and B) and the node-split test (C and D). Meanwhile, as shown in Supplementary Figure 3, the loop-specific inconsistency test did not detect inconsistency for all closed loops of the endoscopic healing rates at 4 (A) and 8 (B) weeks. Therefore, the consistency model was used to estimate the relative efficacy of different treatment strategies. As shown in Figure 3, the pooled results show that patients receiving VPZ20 or VPZ40 had comparable healing rates at 4 (A) and 8 (C) weeks to those receiving PPI, VPZ5, or VPZ10. However, SUCRA suggested that VPZ40 had the highest probability of being best in mucosal healing

rate at 4 weeks (B) (93.0%), followed by VPZ20 (67.8%), PPI (33.5%), VPZ10 (28.5%), and VPZ5 (27.3%), and VPZ40 had the largest probability of being best in healing rate at 8 weeks (D) (75.9%), followed by VPZ20 (59.1%), VPZ5 (55.9%), VPZ10 (35.0%), and PPI (24.1%).

Subgroup analysis of the endoscopic healing rate

A total of five [6,18,35,37,40] and five [6,18,19,35,40] studies reported the endoscopic healing rate at 4 and 8 weeks in patients with severe erosive esophagitis, respectively. As shown in Supplementary Figure 4, no significant inconsistency was identified for outcomes at 4 and 8 weeks by the global inconsistency test (A and B) and the node-split test (C and D). Meanwhile, as shown in Supplementary Figure 3, the loop-specific inconsistency test did not detect inconsistency for all closed loops of the endoscopic healing rate at 4 (C) and 8 (D) weeks. We selected a consistency model to estimate the relative efficacy of different treatment strategies. As shown in Figure 4, the pooled results suggested comparable mucosal healing rates between different treatment strategies at both 4 (A) and 8 (C) weeks. However, SUCRA results told that VPZ20 had the largest probability of being the best healing rate at 4 weeks (B) (80.7%), followed by VPZ40 (74.6%), PPI (43.5%), VPZ5(30.7%), and VPZ10 (20.6%), and VPZ20 had the largest probability of being the best in healing rate at 8 weeks (D) (76.8%), followed by VPZ40 (56.9%), VPZ5(43.9%), PPI (41.9%), and VPZ10 (30.5%).

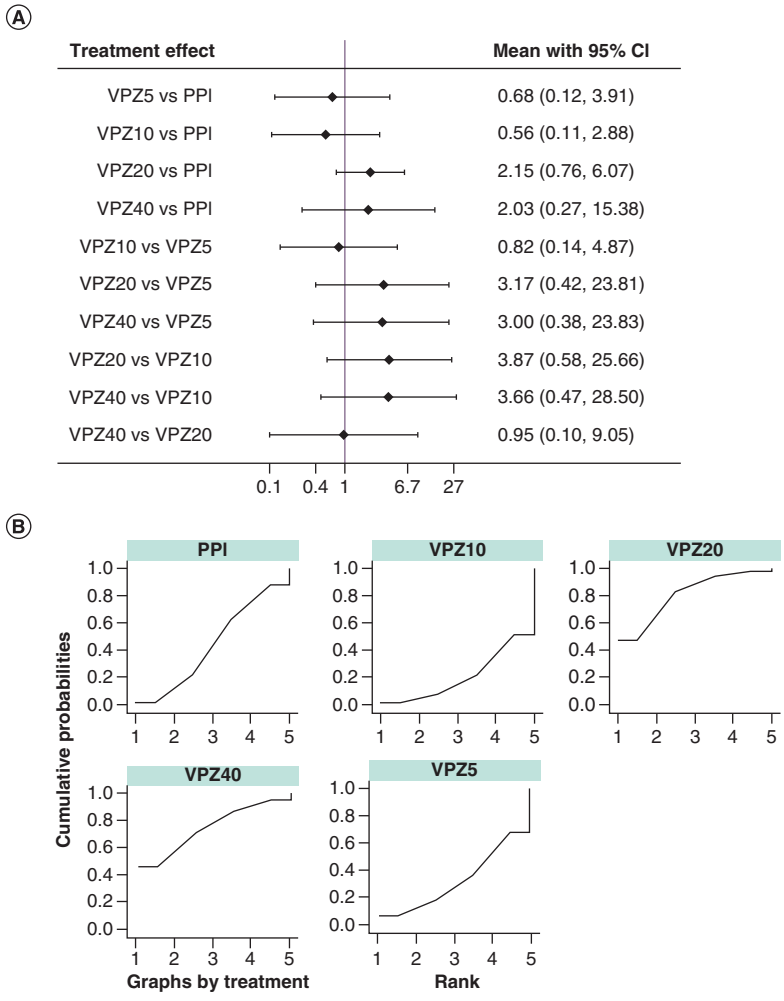

Figure 4. Relative efficacy and SUCRA of the endoscopic healing rates among patients with grade C/D at (A & B) 4 and (C & D) 8 weeks.
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events; SUCRA: The surface under the cumulative ranking.

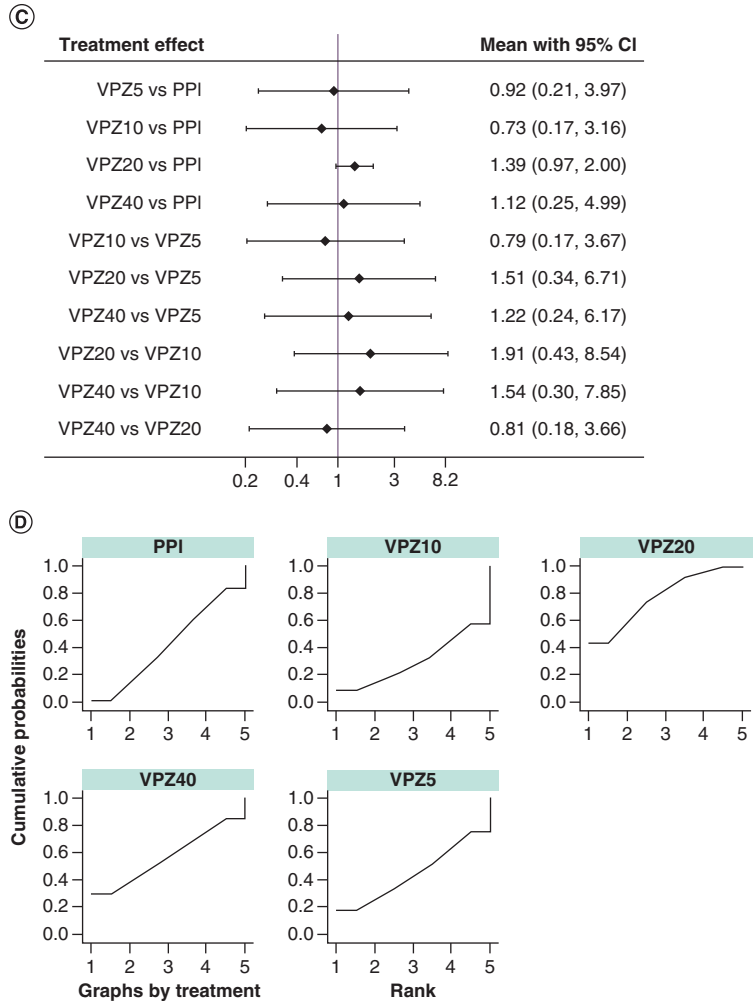

Figure 4. Relative efficacy and SUCRA of the endoscopic healing rates among patients with grade C/D at (A & B) 4 and (C & D) 8 weeks (cont.).
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events; SUCRA: The surface under the cumulative ranking.

Meta-analysis of the incidence of TEAEs

A total of eight studies [6,18,19,35–38,40] were analyzed in this network. As shown in Supplementary Figure 5, no significant inconsistency was identified by the global inconsistency test (A) and the node-split test (B). Meanwhile, as presented in Supplementary Figure 3, the loop-specific inconsistency test did not detect inconsistency for all closed loops (E). Therefore, the consistency model was used to estimate the comparative safety of different treatment strategies. As shown in Figure 5, the pooled results suggested no statistical difference in TEAEs rate between different treatment strategies, although the results of SUCRA suggested that n VPZ40 ranked best (49.1%), followed by VPZ5 (33.7%), VPZ10 (29.8%), PPI (39.4%), and VPZ20 (50.3%).

Sensitivity analysis & publication bias

For the primary outcome, as shown in Supplementary Figure 6, sensitivity analysis confirmed the robustness of the pooled results after excluding two studies that included only patients with refractory erosive esophagitis. Small study effects for individual outcomes were examined using adjusted funnel plots. As shown in Supplementary Figure 7, assumptions of small study effects were established for the endoscopic healing rate at 4 and 8 weeks and the incidence of TEAEs throughout treatment because all funnel plots were visually inspected to be asymmetric.

Discussion

GERD has become a prevalent gastrointestinal disorder worldwide, often leading to the development of erosive esophagitis [5]. Currently, PPIs remain the most common first-line therapeutic agents for esophageal mucosal healing and symptom control in patients with erosive esophagitis [7,42,43]. However, multiple doses may be needed to achieve maximal acid suppression and symptom improvement because many PPIs have a slow and cumulative

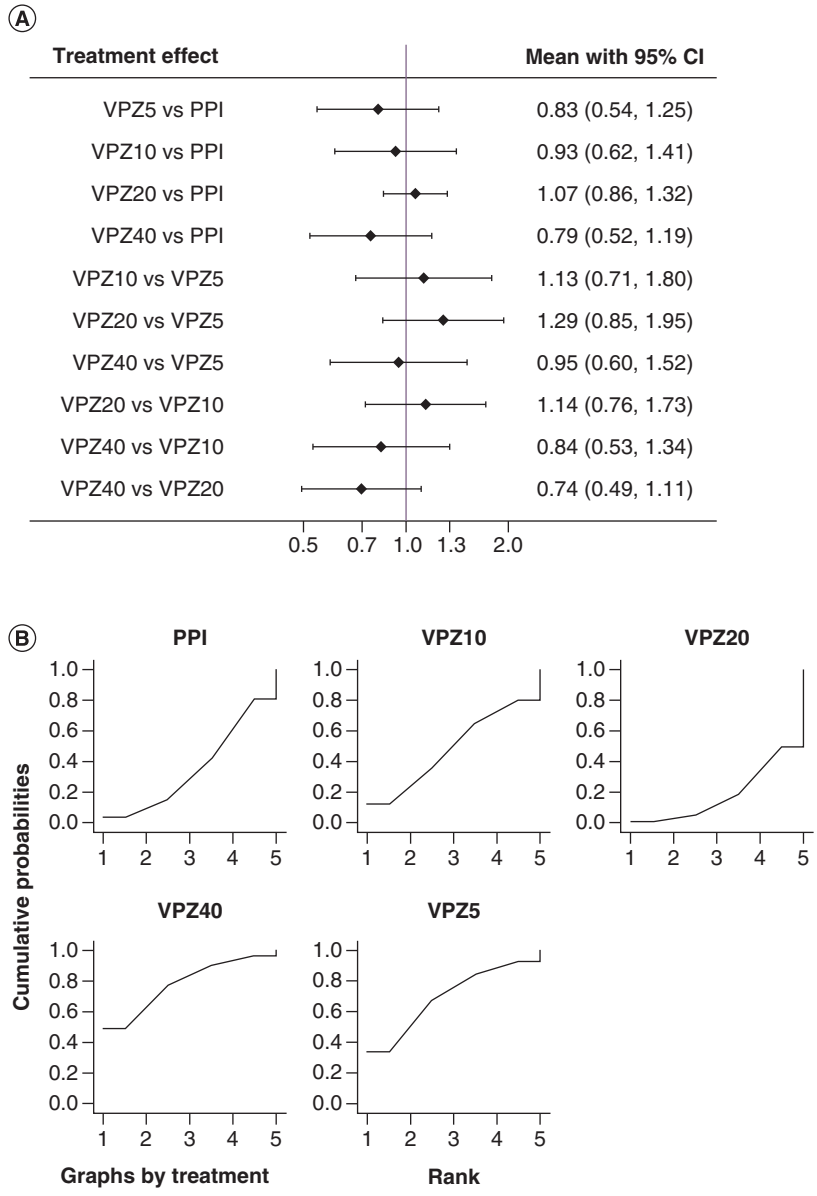

Figure 5. (A) Relative efficacy and (B) SUCRA of treatment-emergent adverse events during treatment.
PPI: Proton pump inhibitors; VPZ5: Vonoprazan 5 mg; VPZ10: Vonoprazan 10 mg; VPZ20: Vonoprazan 20 mg; VPZ40: Vonoprazan 40 mg; TEAEs: Treatment-emergent adverse events; SUCRA: Surface under the cumulative ranking.

onset of action [44]. Fortunately, as a new potassium-competitive acid blocker, VPZ has more rapid, potent, and sustained acid inhibition than conventional PPIs [13,15]. The non-inferiority of VPZ to PPIs in mucosal healing rate in erosive esophagitis has been demonstrated in a previous meta-analysis [17]. However, it's difficult to determine the optimal dose because the relative efficacy of multiple doses of VPZ has only been investigated in a single study [18]. In the current network meta-analysis, nine eligible studies, including 2305 patients, were included, and the pooled results showed no statistical differences for all comparisons in terms of all outcomes. However, based on SUCRA results, VPZ40 ranked first for the endoscopic healing rate and TEAEs in patients with erosive esophagitis, and VPZ20 ranked worst for the incidence of TEAEs.

To date, only one pair-wise meta-analysis [17] has been performed to investigate the efficacy and safety of a standard dose of VPZ compared with PPIs in the treatment of GERD. In this meta-analysis of six eligible studies, the non-inferiority of the standard VPZ dose (VPZ20) was demonstrated compared with PPIs. In addition, patients with severe erosive esophagitis obtained more benefits from VPZ20, reporting a safety profile comparable to PPIs.

Compared with this meta-analysis, the present study consistently confirmed the non-inferiority of VPZ20 in treating erosive esophagitis with similar safety compared with PPIs. However, our network meta-analysis could not confirm the inferiority of VPZ20 in patients with severe erosive esophagitis. It should be noted that previous meta-analysis has simultaneously included data from different time points into a separate quantitative synthesis, significantly increasing the bias caused by the analysis unit error. In contrast, our network meta-analysis investigated the efficacy of all strategies separately according to different time points, which significantly increased the reliability of the pooled results. In addition, our network meta-analysis also ranked different doses of VPZ after determining their relative efficacy, providing clinicians with more practical recommendations for decision-making.

The current network meta-analysis has several strengths: (a) the main methodological advantage is the use of a comprehensive literature retrieval strategy that allows us to identify more eligible studies, (b) the network meta-analysis allows us to estimate the relative efficacy of different doses of VPZ by combining direct and indirect evidence, (c) the SUCRA method was used to rank all treatment strategies, which benefits to select the optimal strategy in clinical practice, and (d) the overall methodological quality of each study was quantified using the Cochrane risk of bias assessment method, which incorporated the level of evidence into pooled results for decision-making.

We must acknowledge that our pooled results should also be interpreted with caution due to several limitations as follows: (a) a small study effect was detected for all outcomes based on asymmetric funnel plots, which may introduce some bias for our pooled results; (b) the limited number of eligible studies with limited sample size was included in this network meta-analysis, which may have a significantly negative influence on the robustness of the pooled results; (c) All studies were conducted in Asian countries, including Japan and China, and therefore our findings should be generalized with caution before further validation in other ethnic groups. More specifically, as differences in drug metabolism between ethnic groups have been demonstrated in many studies, additional studies should be conducted to assess the role of Vonoprazan in Caucasian patients. (d) two studies enrolled patients who were confirmed refractory erosive esophagitis, but sensitivity analysis was performed to confirm the robustness of the pooled results.

Conclusion

In conclusion, multiple doses of VPZ are comparable in efficacy and safety, but VPZ40 may come out on top in effectiveness and safety. More studies are also required to validate our findings further because this network meta-analysis has several limitations. In addition, more studies should be conducted to evaluate the role of Vonoprazan in Caucasian patients because there are differences in metabolic speed between Asians and Caucasians.

Expert opinion

With the great advancement of diagnostic techniques, gastroesophageal reflux disease (GERD) has become one of the most common gastrointestinal diseases that could be easily and effectively diagnosed. By its definition, GERD is thought to be the result of the retrograde flow of gastric contents into the esophagus. More specifically, GERD is characterized by troublesome symptoms and complications such as heartburn and acid regurgitation.

From the perspective of endoscopic results, GERD can be divided into two subtypes: non-erosive reflux disease and erosive esophagitis. In both subtypes, erosive esophagitis is defined as endoscopy-proven erosion of the esophageal mucosa, and patients reported distressing symptoms such as heartburn. Compared with non-erosive esophagitis, treating erosive esophagitis caused by mucosal injury requires more effective therapeutic strategies.

Traditionally, three essential aspects are especially emphasized in treating erosive esophagitis under the consideration of the pathology of this condition, including relieving symptoms, accelerating esophageal mucosal healing, and preventing complications. Based on these three aspects, a series of therapeutic strategies have been developed and then used in route practice. However, medication is still the mainstay of GERD treatment.

Among the current therapeutic agents, proton pump inhibitors (PPIs) have been extensively used for the treatment of GERD. The effectiveness and safety of PPIs have also been clearly demonstrated in accelerating esophageal mucosal healing and relieving symptoms because PPIs can strongly inhibit the secretion of gastric acid. As a result, PPIs have also been considered the most common first-line therapeutic agent for treating erosive esophagitis in clinical practice. It's regrettable that, approximately 20–40% of patients do not achieve satisfactory therapeutic effects because mucosal erosions do not reach mucosal healing or satisfactory symptom relief.

Because some patients could not benefit from PPIs, many novel acid-inhibitory agents have been developed and routinely used in practice. Among the available new potassium-competitive acid blockers, vonoprazan (VPZ) has been found to strongly inhibit H+, and K+ ATPase in a competitive and reversible manner. Compared with

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early-generation PPIs, VPZ may have stronger and more sustained acid suppression but less variation in time to onset of action. It's exciting that the efficacy and safety of VPZ 20 mg (VPZ20) in the treatment of GERD have been clearly demonstrated in several clinical studies. More importantly, a recent meta-analysis also suggested that VPZ20 is non-inferior to PPIs and even more effective than PPIs for patients with severe erosive esophagitis, with a similar safety profile. VPZ20 may become a preferred therapeutic agent in the treatment of erosive esophagitis.

It must be noted that, except for the standard dose of 20 mg, VPZ has also been prescribed for the treatment of erosive esophagitis in different doses in clinical practice, including 5 mg, 10 mg and 40 mg, which greatly confound practitioners to make a clinical decision in route practice effectively. More importantly, despite this confusion, only one study directly compared all dosages of VPZ in an individual study. Considering these facts, the present study comprehensively investigated the comparative efficacy and safety of available doses of VPZ with network meta-analysis technology on the basis of available evidence.

Based on these findings from this network meta-analysis, different doses of VPZ are comparable in efficacy and safety, but VPZ40 may come out on top in both efficacy and safety. Nevertheless, we suggest more studies to further directly compare various doses of VPZ due to only limited evidence in this network meta-analysis. In addition, more studies should be conducted to evaluate the role of Vonoprazan in Caucasian patients because there are differences in metabolic speed between Asians and Caucasians.

Summary points

- Vonoprazan is effective for treating erosive esophagitis.
- Multiple doses of vonoprazan are available in routine practice.
- It is unclear which doses of vonoprazan may be best for erosive esophagitis.
- Nine studies involving 2305 patients were included in this network meta-analysis.
- Different doses of vonoprazan were comparable in efficacy and safety.
- Vonoprazan 20 mg and 40 mg were comparable to PPI in healing rate.
- Vonoprazan 40 mg ranked best for healing rate and treatment-emergent adverse events.
- Vonoprazan 20 mg ranked worst for treatment-emergent adverse events.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0165

Author contributions

Substantially contributed to conception or design: Y Sun, J He. Contributed to acquisition, analysis, or interpretation of data: J He. Drafted the manuscript for important content: J He, Y Gao. Critically revised the manuscript for important intellectual content: G Bai, J Wang. Gave final approval: all authors.

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Data availability statement

All data generated or analyzed during this study are included in this published article/as supplementary information files.

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