Comparison of Potassium-Competitive Acid Blockers and Proton Pump Inhibitors in Preventing Delayed Bleeding after Endoscopic Submucosal Dissection of Early Gastric Cancer: An Update Systematic Review and Meta-Analysis

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Research Article

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Abstract

Background: Proton pump inhibitors (PPIs) and potassium-competitive acid blocker (PCAB) are two different drugs that may be used after upper gastrointestinal endoscopic submucosal dissection (ESD). However, whether PCAB can reduce postoperative complications more than PPIs is a matter of controversy.

Methods: We searched studies that reported the effectiveness of PCAB and PPIs in preventing delayed bleeding after gastric ESD by using PubMed, EMBASE, the Cochrane Library, Web of Science, etc. The Cochrane Risk of Bias Tool and Newcastle Ottawa Quality Assessment Scale were applied to evaluate the quality of the researches. All statistical analyses were carried out using Stata 15.1,including drawing the forest map, subgroup analysis, sensitivity analysis and detection of publication bias.

Results: Seventeen studies with 51294 patients were included. There was a statistically difference in the overall delayed bleeding rate between the Vonoprazan group and the PPIs group. The overall mean relative risk (RR) for delayed bleeding following the administration of Vonoprazan was 0.72 (P<0.05) with a 95% confidence interval (CI) (0.67-0.77). However, there was no statistically difference in the incidence of blood transfusion events between the two groups[RR=0.76,95% CI (0.41-1.40)]. There was a statistical difference in the shrinkage ratio between the Vonoprazan group and the PPIs group. The weighted mean difference was 2.68(*P*<0.05) with a 95% CI (0.44-4.91). The sensitivity analysis showed all results were robust.

Conclusions: Compared with PPIs, Vonoprazan showed a better efficacy in reducing the incidence of delayed bleeding and promoting the contraction of artificial ulcers. It might be an appropriate choice that postoperative management of gastric ESD in patients with stomach neoplasms.

Background

Gastric cancer (GC) is the fifth most common cancer and the third-leading cause of cancer deaths worldwide (1). There are appropriate treatments at different stages of the disease. Early gastric cancer (EGC) is defined as cancer limited to the mucosa or submucosa, regardless of nodal status (2), patients with which have a good long-term survival due to the improvement of the current diagnosis and treatment level. Endoscopic submucosal dissection (ESD) is a minimally invasive treatment method for EGC with almost no risk of lymph node etastasis (3). Unfortunately, it tends to create larger iatrogenic ulcers and is associated with a higher risk of delayed bleeding (4), which is extremely etrimental to the recovery of patients. And the incidence of this terrible complication is 4.7–15.6% (5, 6).

Proton pump inhibitors (PPIs), which are used to increase gastric pH by suppressing acid production, are recommended by the clinical guidelines as the first choice drugs after upper gastrointestinal ESD (7). Recently, a novel potassium-competitive acid blocker, Vonoprazan approved and marketed in Japan for the treatment of acid-related gastrointestinal disorders, including gastric ulcer, duodenal ulcer, peptic ulcer, reflux oesophagitis and Helicobacter pylori eradication (8). Vonoprazan inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway in a K+-competitive and reversible manner (9), showing a strong and long-lasting effect on gastric acid suppression.

Some studies have compared the effects of Vornoprazole and PPIs, but the results of the studies are different. In order to provide evidence for the clinical application of VPZ, we included more comprehensive literature and performed a meta-analysis of these two drugs in preventing delayed bleeding after gastric ESD and promoting ulcer healing.

Methods

Data sources and search strategies

We conducted a literature search on all English and Chinese articles published as of October 2021. The English databases retrieved are PubMed, EMBASE, The Cochrane Library and Web of Science. The Chinese databases include China National Knowledge Infrastructure, China Biology Medicine disc, China Science and Technology Journal Database and Wanfang Database. The search terms mainly were:"Stomach Neoplasms","Gastric Neoplasms","Stomach Cancer","Gastric Cancer","Endoscopic Submucosal Dissection","ESD","Vonoprazan","TAK 438","Proton Pump Inhibitors","Hemorrhage","Bleeding".Search terms with the same meaning were connected by "OR", and then each search result with a different meaning was connected by "AND".The references of published meta-analysis articles with similar content were also checked to avoid missing any articles that might potentially be included during the initial search.

Inclusion and exclusion criteria

Inclusion criteria of the articles were: (a) patients who had been diagnosed with or were highly suspected of gastric cancer received ESD treatment; (b) after ESD, patients were treated with either Vonoprazan or PPIs; (c)randomized controlled trials (RCTs) and observational studies, such as cohort and case control studies. Exclusion criteria of the articles were:(a) duplicate documents;(b)studies with none of the required outcome indicators;(c)abstract articles, case reports, review articles, meta-analysis, comments and letters.

Outcome indicators

Postoperative delayed bleeding between patients treated with Vonoprazan or PPIs was set as the primary outcome indicator of this meta-analysis. Delayed bleeding is defined as clear hemostasis during gastric ESD, but the postoperative hemoglobin concentration drops greater than or equal to 20g/L, or the clinical manifestations of postoperative ulcer bleeding such as severe hematemesis or melena (10). Secondary outcomes were blood transfusion events and changes in ulcer shrinkage ratio in the two groups. The shrinkage ratio was calculated using the following formula: ([ESD specimen area] − [ulcer area at 1, 2, 4 or 8 weeks post ESD])/(ESD specimen area) × 100 (%).

Study selection and data extraction

Two researchers conducted literature screening and data extraction independently, and the differences were resolved through discussion or intervention by a third party. Data were extracted directly from the selected

studies. In addition to the outcomes, the relevant information collected included the first author's last name, publication year, study design, interventions, number of patients and follow-up period duration.

Risk of bias within studies

Two authors, each used the Cochrane risk of bias tool (11) to assess the quality of randomized controlled trial articles independently, and used the Newcastle-Ottawa Scale (NOS) (12) to assess the quality of observational studies independently. A third author was referred when discrepancy occurred. The evidence quality of randomized controlled trials was evaluated from random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The NOS total score of cohort studies was considered from selection, comparability and outcome. Studies with NOS ≥6 were considered to be of high quality.

Statistical analysis

Statistical analyses were performed by using Stata 15.1. Dichotomous outcomes were expressed as RR with 95% CI (13). The heterogeneity test was performed using the I-squared (I^2) statistic. When I^2 <50%(P>0.05), it indicated that there was no statistical heterogeneity among the studies, and the fixed effects model was adopted; on the contrary, the random effects model was adopted. Subgroup analysis and sensitivity analysis were performed to find the source of the heterogeneity when it was significant. It needs to be emphasized that regardless of the heterogeneity, we had conducted the sensitivity analysis to examine the robustness of the results. We inspected the visual symmetry of the funnel plots to assess potential publication bias preliminarily. Egger's test was followed performed, and P<0.05 demonstrated that the difference was statistically significant, indicating that publication bias was significant.

Results

Selection and summary of studies

We first searched in various databases and obtained 95 articles. Specifically, there were 15 articles in PubMed, 26 articles in Embase, 15 trials in Cochrane Library, 23 articles in Web of Science, 13 articles in China National Knowledge Infrastructure, 1 article in China Science and Technology Journal Database, and 2 articles in Wanfang Database. Simultaneously, we added 21 additional documents by using methods such as document tracing. Then we removed 78 duplicate documents, 18 documents whose content or document type did not meet the requirements, and 3 abstract articles without full-text details. Finally,17 studies (10, 14-29) were included in our meta analysis,including 8 RCTs and 9 cohort studies. The flow diagram is shown in Figure 1. A total of 51294 patients were enrolled in all studies, of which 25747 patients were enrolled in the experimental (Vonoprazan) group, and 25547 patients were enrolled in the control (PPIs) group. The literature and baseline information of the included patients are shown in Table 1.

Table 1

Characteristics of each included studies.

Author	Year	Country	Study design	Intervention	N(I)	Control	N(C)	follow up (W)
Hirai(14)	2018	Japan	RCT	VPZ 20mg	61	LPZ 30mg	66	4,8
Abe(15)	2021	Japan	Cohort Study	VPZ, standard dose and low dose	23989	PPIs,standard dose and low dose	24040	NA
Ban(16)	2020	Japan	RCT	VPZ 20mg	101	LPZ 30mg	95	1,2,4,8
Hamada(17)	2019	Japan	RCT	VPZ 20mg	69	LPZ 30mg	70	8
Horikawa(18)	2018	Japan	Cohort Study	VPZ 20mg	62	LPZ 30mg	53	2
Ichida(19)	2019	Japan	RCT	VPZ 20mg, RBP 300mg	43	EPZ 20mg, RBP 300mg	39	4,8
Ishida(20)	2021	Japan	Cohort Study	VPZ 20mg	205	PPIs,standard dose	205	6
Ishii(21)	2018	Japan	RCT	VPZ 20mg, RBP 300mg	27	EPZ 20mg, RBP 300mg	26	4,8
Kagawa(22)	2016	Japan	Cohort Study	VPZ 20mg	75	RPZ 20mg	150	5,8
Kakushima(23)	2019	Japan	Cohort Study	VPZ 20mg	59	EPZ 20mg	71	NA
Komori(24)	2019	Japan	RCT	VPZ 20mg	18	RPZ 10mg	15	4
Marouka(25)	2017	Japan	Cohort Study	VPZ 20mg, RBP 300mg	31	EPZ 20mg, RBP 300mg	31	4
Shiratori(26)	2021	Japan	Cohort Study	VPZ	627	PPIs	627	8
Takahashi(27)	2016	Japan	RCT	VPZ 20mg	14	LPZ 30mg	12	4
Tsuchiya(10)	2017	Japan	RCT	VPZ 20mg	39	EPZ 20mg	41	8
Yamamoto(28)	2020	Japan	Cohort Study	VPZ 20mg	50	EPZ 20mg	116	NA
Yamasaki(29)	2018	Japan	Cohort Study	VPZ 20mg	77	LPZ 30mg	90	4

RCT: randomized controlled experiment; N:number of patients; NA:unknown; VPZ:Vonoprazan; PPIs:proton pump inhibitors; LPZ:lansoprazole; RPZ:rabeprazole; EPZ:esomeprazole; RBP:rebamipide; the standard dose in

Japan is 30, 10, 20 and 20 mg in lansoprazole, rabeprazole, esomeprazole,and omeprazole.

Study quality

The assessment of risk of quality showed that among the RCTs, one article reached level A in evidence quality (17), and the remaining 7 articles reached level B in evidence quality (10, 14, 16, 19, 21, 24, 27). The detailed description of the risk of bias in the studies was shown in Figure 2. Meanwhile, according to the NOS score, all 9 cohort studies were rated as high-quality (15, 18, 20, 22, 23, 25, 26, 28, 29), as shown in Figure 3.

Outcomes measurements

delayed bleeding

There are 14 literatures that reported delayed bleeding after gastric ESD (10, 14-17, 19, 20, 22-24, 26-29), while the other 3 literatures had a weight of 0 in this aspect (18, 21, 25). The heterogeneity of the various studies was relatively low (I^2=21.1%, *P*=0.224), so the fixed effects model was used for analysis. As shown in the forest diagram in Figure 4A, there was a statistical difference in the overall delayed bleeding rate between the test group and the control group. The overall mean RR for delayed bleeding following the administration of Vonoprazan was 0.72 (P<0.05) with a 95% CI (0.67-0.77).

A subgroup analysis was carried out according to the type of study, as shown in Figure 4B. There was a certain degree of heterogeneity (I2=52.5%, *P*=0.049) among cohort studies. The delayed bleeding rate between the two groups was statistically different. The RR was 0.72(*P*<0.05) with a 95% CI (0.67-0.77), and the weight reached 99.17%. In contrast, there was basically no heterogeneity (I^2=0.0%,*P*=0.76) in RCT articles. There was no statistically significant difference in the delayed bleeding rate between the Vonoprazan group and PPIs group [RR = 0.56, 95%CI (0.27, 1.15), *P*>0.05].

The sensitivity analysis was done by merging all the remaining articles every time an article was deleted, as shown in Figure 5A. Abe et al. was a source of heterogeneity (15), but the overall results were still robust.

A funnel plot analysis showed no publication bias (Figure 6A) and Egger's regression test was non-significant indicating symmetry in the funnel plot (*P*=0.725).

blood transfusion

There are 3 literatures that reported blood transfusion (20, 23, 26). Basically there was no heterogeneity between the three articles (I^2=0.0%, *P*=0.566), so the fixed effects model was used for analysis. There was no statistically difference in the incidence of blood transfusion events between these two groups (Figure 7). The overall mean RR for blood transfusion following the administration of Vonoprazan was 0.76 (*P*>0.05) with a 95% CI (0.41-1.40). The sensitivity analysis showed the overall results were robust (Figure 5B). The funnel plot

analysis showed no publication bias (Figure 6B). Egger's regression test was not significant (P=0.749), also suggesting no publication bias.

shrinkage ratio

There were 7 articles (16, 18, 19, 21, 22, 25, 27) reporting the shrinkage ratio of artificial ulcers whose data can be extracted for analysis. Because of the high heterogeneity (I^2=78.5%, P<0.05), the random effects model was used. There was a statistical difference in the shrinkage ratio between the Vonoprazan group and the PPIs group. The weighted mean difference was 2.68(P<0.05) with a 95% CI (0.44-4.91). Certainly, the subgroup analysis was carried out according to the postoperative recovery time. The subgroups at 1, 4, and 8 weeks after ESD had lower heterogeneity. However, the heterogeneity within the subgroup at 2 weeks after the operation was still high (I^2=92.1%, P<0.05). The detailed subgroup and total forest maps were shown in Figure 8. Therefore, we further conducted sensitivity analysis, finding the research of Horikawa et al. was the source of heterogeneity (18), but the overall results were still robust (Figure 5C). The funnel plot analysis showed no publication bias (Figure 6C) and Egger's regression test was non-significant indicating symmetry in the funnel plot (P=0.0725).

Discussion

This meta-analysis proves for the first time that vonoprazan is superior to PPIs for preventing delayed bleeding after gastric ESD, which already reaches statistical significance with low heterogeneity. This may be related to the suppress gastric acid mechanism of Vonoprazan competing with potassium to inhibit H+, K+-ATPase. Most of the delayed bleeding occurs within 48 hours after ESD and can last up to 2 weeks after operation (7). The key factor to prevent delayed bleeding is the rapid rise of pH in the stomach. While PPIs typically require approximately 3–5 days to exert a maximal effect on gastric acid secretion, Vonoprazan does not require acid-induced activation, producing strong and long-lasting inhibitory activity from the first dose (30). Another important reason for this statistically significant difference may be that the specific metabolic mechanisms of the two are not the same. Vonoprazan is metabolized mainly by CYP3A4/5 and to some extent by CYP2B6, CYP2C19,CYP2D6, and SULT2A1 (31), whereas PPIs are primarily inactivated in the liver by microsomal enzyme CYP2C19 (32), which is the most polymorphic in terms of genetics and phenotypes among the CYP2C subfamily, causing a large variation in efficacy among patients.

Previously, several meta-analysis articles (33–37) believed that observed differences between the two classes of drugs were non-significant in the prevention of delayed bleeding after ESD. The reason for the conflicting conclusions is that their study included a small sample size. As an adverse event, the incidence of delayed bleeding is extremely low, especially under the background of mature gastric ESD technology, standardized and skilled operators, and general intraoperative preventive hemostasis. On the basis of previous studies, we updated to add several documents to expand sample size, including a nationwide population-based high-quality cohort study which was also the reason for heterogeneity of the population. But this had also caused a limitation of this study: the experiment object is mainly from Japanese, lacking other countries or ethnic groups. This limitation may further cause an undeniable drawback: the nationwide retrospective cohort study may double-count some previous RCT cases. However, it is gratifying that the number of patients in our newly

included retrospective cohort study is far more than the number of patients in the previous RCT, or even not in the same order of magnitude. Therefore, the systematic error is very small and can be ignored.

Postoperative blood transfusion occurs in people who have severely delayed bleeding after the operation. In a sense, it is more serious adverse events with a lower incidence rate. Another new finding is that although the number of patients in the Vonoprazan group was less than the PPIs group after surgery, the difference between the two groups was not statistically significant. This also shows that many clinical trials comparing the efficacy of the two types of acid inhibitors are still needed in the future.

Our study also found that the contraction rate of iatrogenic ulcers in patients who used Vonoprazan after ESD was higher than that of patients who used proton pump inhibitors after operation at the same time, and it was statistically significant. This proves that Vonoprazan is better than PPI in promoting ulcer healing. This was similar to the results of Martin et al.'s research (33). We noticed that the study of Horikawa was heterogeneous with other studies at 2 weeks after ESD ,which considered the rate of ulcer reduction was significantly higher in the P-CAB group compared with the PPI group (18). Martin et al. proved that one important reason is the presence of Helicobacter pylori.(33) After careful reading and comparison, we believed that another reason might be related to the size of the patient's initial ulcer area. In the study of Horikawa, the median initial ulcer area was 1703mm^2 in the P-CAB group and 1400mm^2 in the PPI group (18). In contrast, the area of resected specimen was 762.7mm^2 in the Vonoprazan group and 817.6mm^2 in the PPI group in the study of Ban (16). As we all known, the initial area of the ulcer is an important factor affecting the healing of the ulcer. Therefore, we inferred that the larger the ulcer area, the better the effect of Vonoprazan in promoting ulcer healing.In short, the extensive clinical application of Vonoprazan needs more experiments to provide evidence, especially high-quality, large-sample randomized controlled trials in other races and countries.

Conclusions

As a new type of acid inhibitor, Vonoprazan can reduce the incidence of delayed bleeding and promote the contraction of artificial ulcers more effectively than PPIs after gastric ESD, guaranteeing the treatment effect of patients with gastric neoplasms.

Abbreviations

GC: gastric cancer; ESD: endoscopic submucosal dissection; EGC: early gastric cancer; PCAB: potassium-competitive acid blocker; Vpz: Vonoprazan; PPIs: proton pump inhibitors; RR: relative risk; CI: confidence interval; RCTs: randomized controlled trials; NOS: Newcastle-Ottawa Scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MZH and PL designed the research; MZH, HYS, RC and SML performed the research and analyzed the data; MZH wrote the manuscript; SYZ and PL reviewed the manuscript. All authors read and approved the final manuscript

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Figures

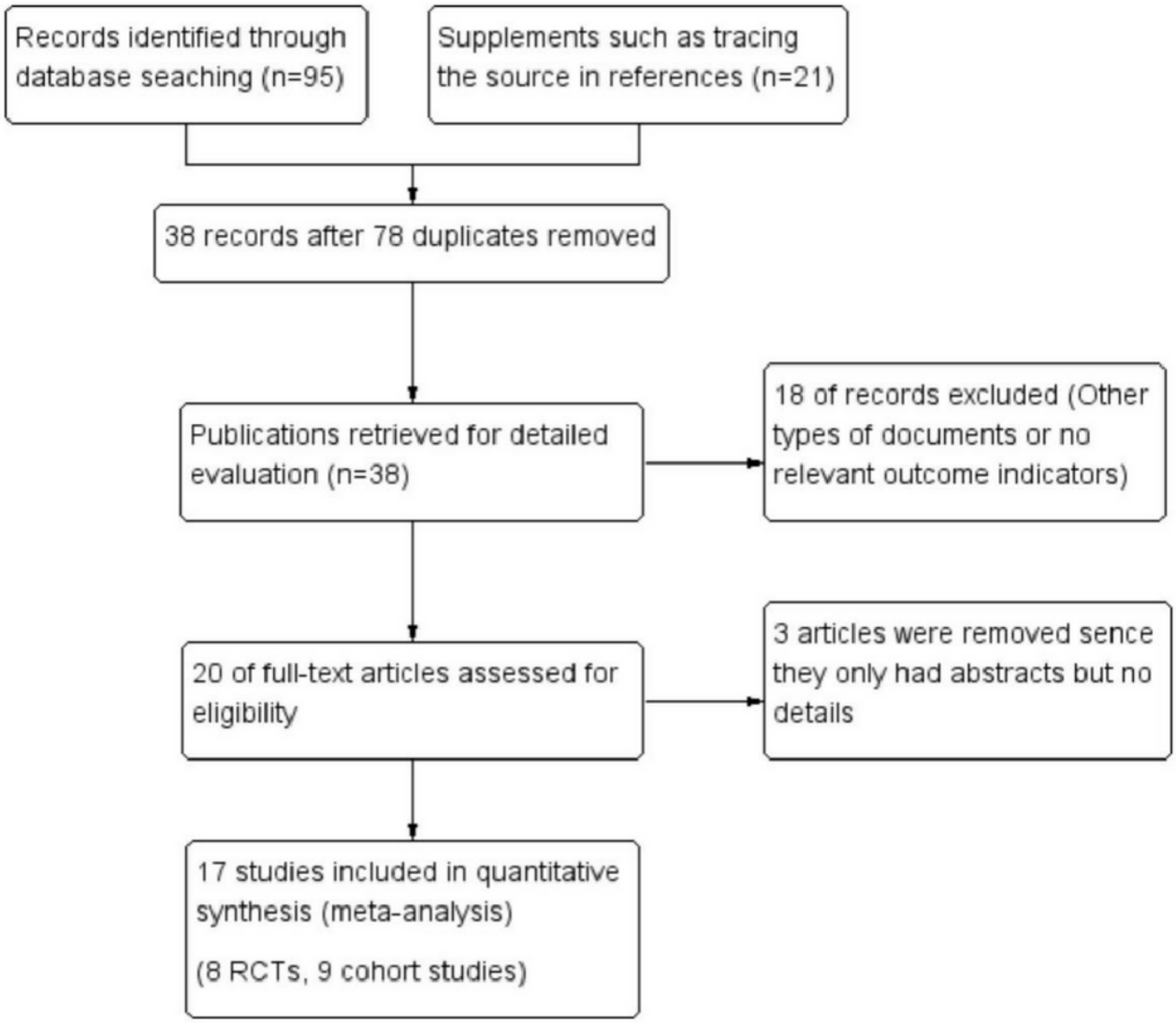

Figure 1

Flow diagram of study selection.

Figure 2

Quality evaluation results of randomized controlled experiment articles. A: Detail; B: Summary

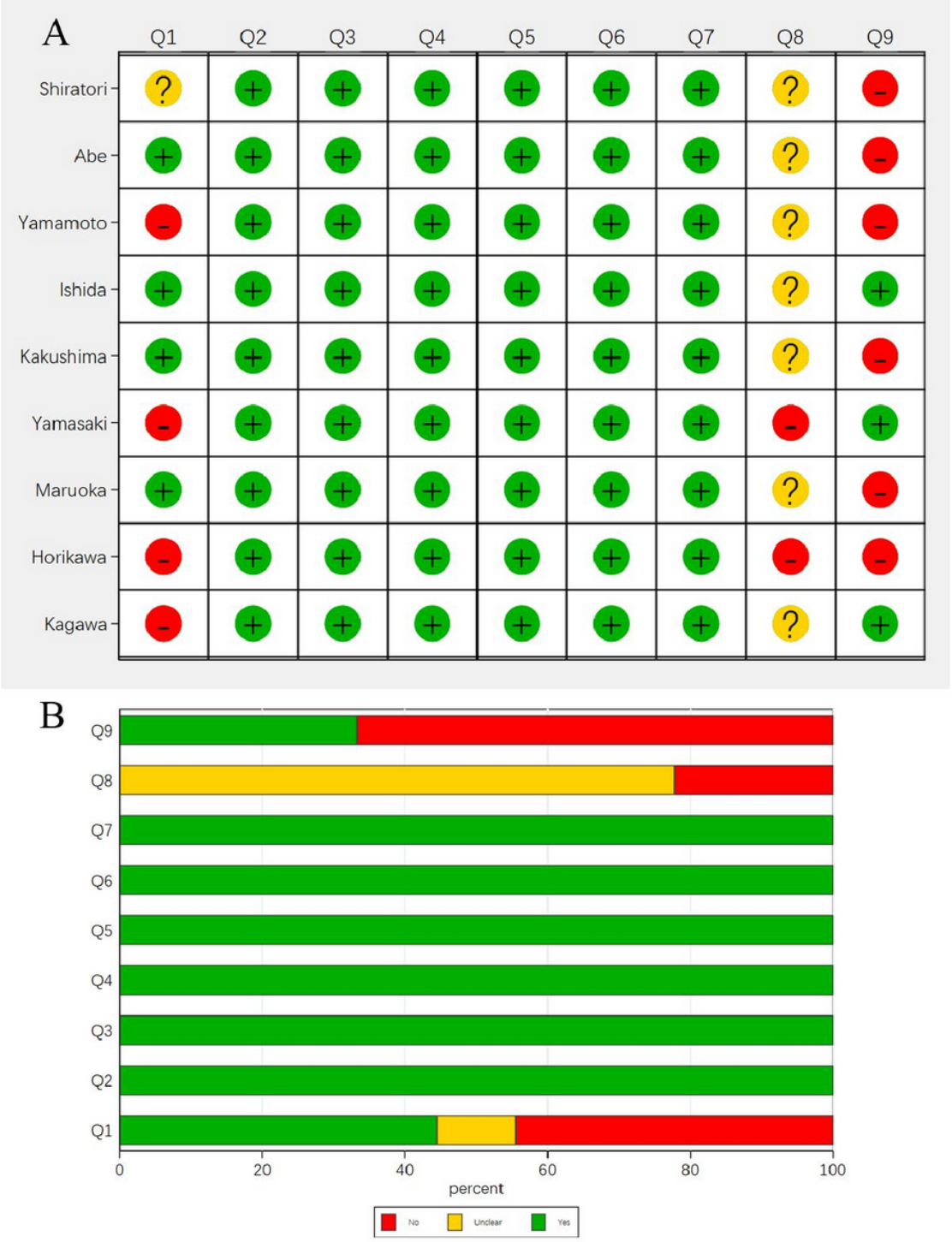

Figure 3

Quality evaluation results of cohort research articles. Q1: representativeness of the exposed cohort; Q2: selection of the unexposed cohort; Q3: ascertainment of exposure; Q4: outcome of interest not present at start of study; Q5-6: control for important factor or additional factor; Q7: assessment of outcome; Q8: follow-up long enough for outcomes to occur; Q9: adequacy of follow-up of cohorts. A: Detail; B: Summary

Figure 4

Forest plot showing the differences in delayed bleeding between vonoprazan group and PPIs group. A:Overall map; B:Subgroups according to the type of study. RR: relative risk.

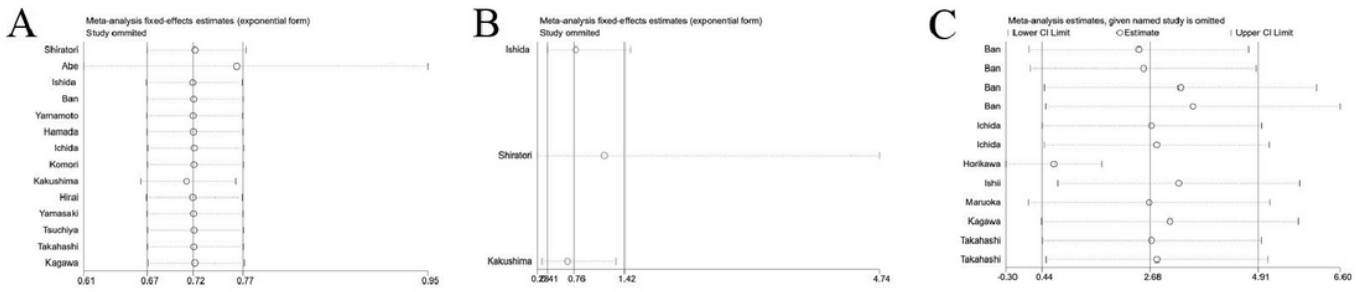

Figure 5

Sensitivity analysis. A: The effect of preventing delayed bleeding; B: Blood transfusion; C: Shrinkage ratio.

Figure 6

Funnel plots. A: The effect of preventing delayed bleeding; B: Blood transfusion; C: Shrinkage ratio. WMD: weighted mean difference.

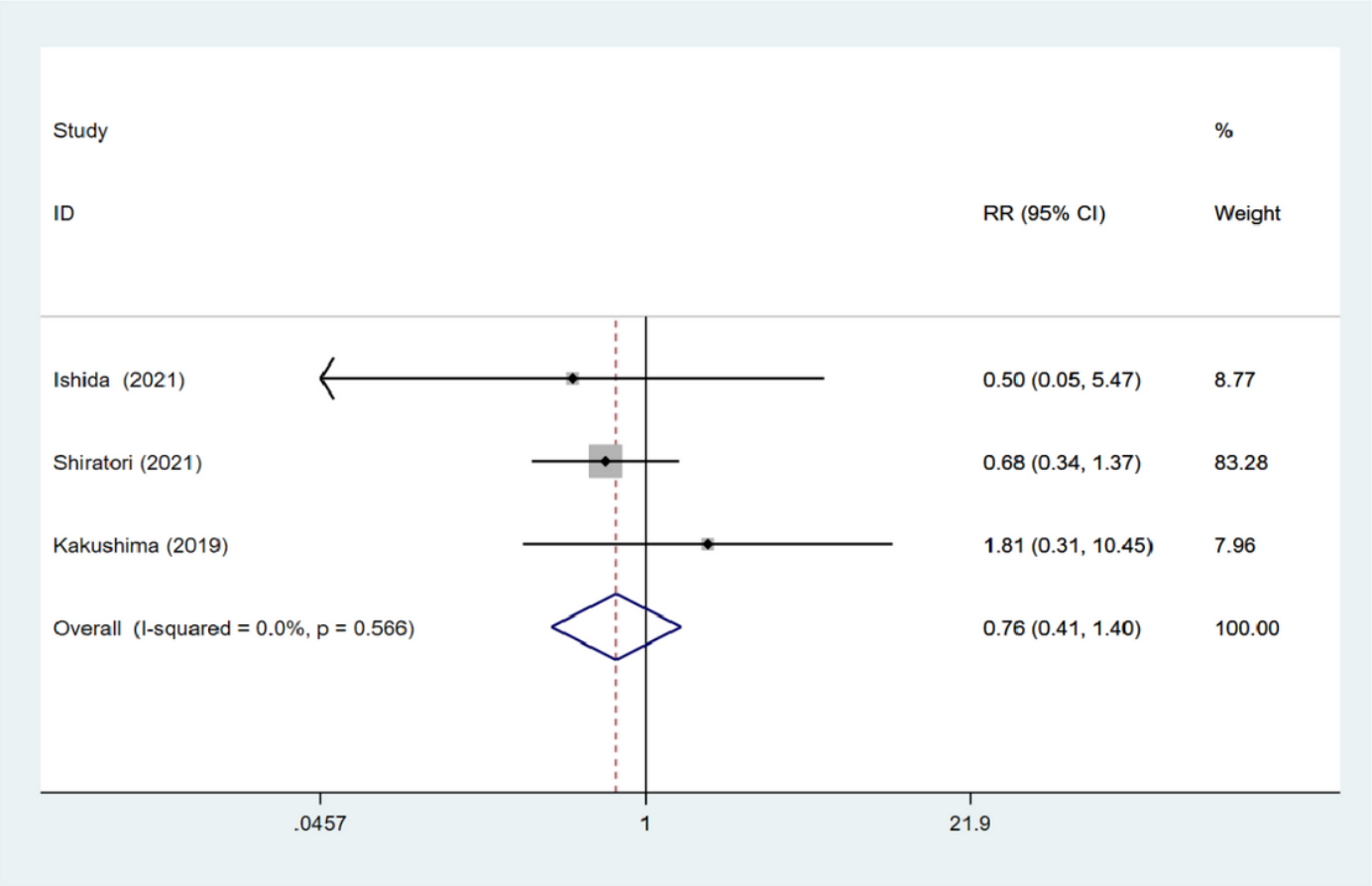

Figure 7

Forest plot showing the differences in blood transfusion. RR:relative risk.

Figure 8

Forest plot of the shrinkage ratio of artificial ulcers. A:The subgroups according to the postoperative observation time; B: Total forest plot. WMD: weighted mean difference.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Searchstrategies.pdf
- Shrinkageratio.pdf
- Studyquality.pdf
- bloodtransfusion.pdf
- delayedbleeding.pdf