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Review Article

ABO blood groups and prognosis of gastric cancer: a meta-analysis

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Abstract: Objective: The aim of the current study was to systematically investigate the relationship between ABO blood groups and prognosis of gastric cancer. Methods: The literature search was accomplished on December 1, 2018, including conference abstracts and articles, with no language restrictions. The following databases were searched: PubMed, EMBASE (Excerpta Medica database), and Web of Science (including Science Citation Index and Social Sciences Citation Index). Data were then extracted from eligible studies. Pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) for overall survival were calculated between blood type O and other blood types or between blood type AB and the others via a random-effects model (STATA/SE software). Results: Five studies, including a total of 8,024 gastric cancer patients, were involved in the current analysis. Taking blood type O as a reference, the pooled HR of blood type A was 1.10 (95% CI, 0.87 - 1.39), with high heterogeneity (I^2 = 84.7%; P < 0.001). The pooled HR of blood type B was 1.08 (95% CI, 0.96 - 1.21), with moderate heterogeneity (I^2 = 34.5%; P = 0.192). The pooled HR of blood type AB was 0.79 (95% CI, 0.55 - 1.15), with high heterogeneity (I^2 = 90.0%; P < 0.001). No statistically significant pooled risks were observed taking other blood types as references. Conclusion: Results suggest that ABO blood groups may not be prognostic for patients with gastric cancer.

Keywords: Gastric cancer, ABO blood groups, prognosis

Introduction

Gastric cancer accounts for the fifth most cancer cases and third most cancer-related deaths, worldwide [1]. In 2015, incidental cases of gastric cancer were over a half million in China, with a comparable number of patient deaths [2]. Due to difficulties in early detection and the absence of effective therapy, poor 5-year survival rates of gastric cancer continue to be a huge hurdle [3]. To improve prognosis and prolong survival times, substantial factors need to be identified, matching proper treatment with individualized management for patients with gastric cancer.

Since being discovered in the early twentieth century, ABO blood groups have been widely applied in transfusions and transplantation therapy methods [4]. The blood groups are determined by carbohydrate moieties located on the surface of red blood cells [4]. Their antigens are glycosyltransferases encoded by "A", "B", and "O" alleles. Recently, the blood groups were related to higher risks and different prognoses of various cancers, including gastric cancer [5-10]. The association between blood group A and gastric cancer has been confirmed in several large population-based cohort studies [9, 11]. However, results are still debatable regarding prognosis. For example, a study by Fan et al. [12] indicated that postsurgical gastric cancer patients with or without O blood type did not differ in prognosis. Another study showed that gastric cancer patients with blood type A may have worse prognosis than those with other blood types [13]. Inconsistencies across these existing studies may be due to the limited number of gastric cancer cases in each blood type group or the single-center study itself.

Currently there are no meta-analyses relating ABO blood groups to prognosis of gastric cancer patients. Thus, an evidence-based and

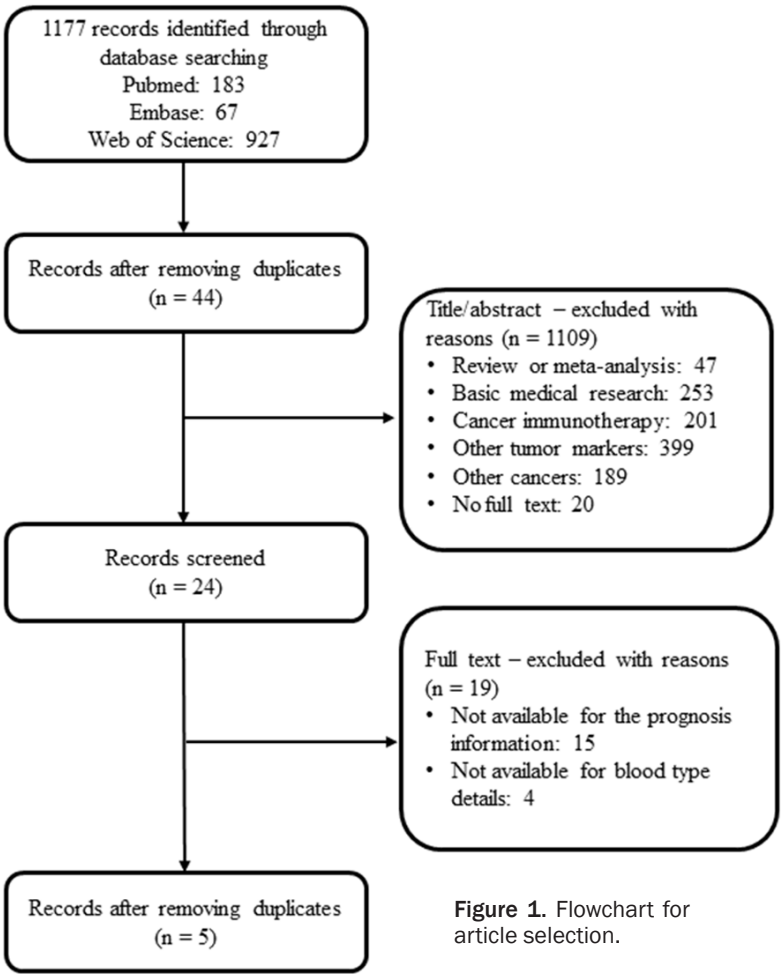

Figure 1. Flowchart for article selection.

comprehensive analysis is necessary to help reach an unbiased conclusion. Therefore, synthesizing all published studies on the subject, the current meta-analysis aimed to systematically investigate the relationship between ABO blood groups and prognosis of gastric cancer patients.

Methods

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Quality evaluation of articles involved was assessed by the NOS scale. Results are shown in Table S1 and Figure S1. All involved articles were high quality (≥ 6 stars).

Search strategy

A systematic literature search was conducted using the following electronic bibliographic databases: PubMed, EMBASE (Excerpta Medica database), and Web of Science (including Science Citation Index and Social Sciences Citation Index). The search strategy was expressed in the Boolean style. Subject terms were: ("Stomach Neoplasms" or "Stomach Neoplasm" or "Gastric Neoplasms" or "Gastric Neoplasm" or "Cancer of Stomach" or "Stomach Cancers" or "Gastric Cancer" or "Gastric Cancers" or "Stomach Cancer" or "Cancer of the Stomach") and ("Blood Group Antigens" or "Blood Groups" or "Blood Group" or "Blood Type" or "Blood Types") and ("Survival" or "Prognosis" or "Prognoses" or "Prognostic Factors" or "Prognostic Factor"). The literature search was completed on December 1, 2018, including conference abstracts and articles of any language. Finally, a total of 1,177 records were identified. A flowchart of the literature selection process is portrayed in **Figure 1**.

Selection criteria

Retained articles met inclusion criteria, as follows: (I) Gastric cancer must be proven by pathology; (II) Aimed to assess whether blood type system was the prognostic factor for patients with gastric cancer; (III) Information was sufficient on blood types for gastric cancer patients, as well as necessary statistical measures, including hazard ratios (HRs) and 95% confident intervals (95% CIs) or corresponding survival curves was available for extraction or inference; and (IV) Reviews, meta-analyses, case series, and basic medical studies were excluded.

Eligible articles were accessed, independently, by two members of the present study, according to the criteria above. A third party was consulted if there were any disagreements.

Exclusion criteria

Exclusion criteria: (I) Article type was review or meta-analysis; (II) Basic medical research, cancer immunotherapy, tumor markers, or other cancers; (III) Full-text was unavailable; and (IV) Not available for prognosis information or blood type details.

Data extraction

Various information was extracted, including the surname of the first author, published year, country, study design, case number of each ABO blood type, gastric cancer stage and location, demographics like age, ethnicity and gender, overall survival, hazard ratios (HR), and 95% confidence intervals (95% CI). For articles without available hazard ratios, overall survival was estimated via Kaplan-Meier curves by means of Engauge Digitizer software Release 4.0. Data extraction was independently conducted by two researchers. Discrepancies were resolved by discussion.

Statistical analysis

Pooled HRs and 95% CIs for overall survival were calculated between blood type O and other blood types or between blood type AB and the others via a random-effects model using the DerSimonian and Laird method [14, 15]. Heterogeneity between studies was evaluated with I^2, an index ranging from 0%-100% based on the Cochrane *Q* test. Heterogeneity was considered to be low between studies if I^2 ranged from 0% to 25%. Heterogeneity was moderate from 25% to 75% and high from 75% to 100% [16].

A filled funnel plot was used to visually present the presence of publication bias. Publication bias was inevitable due to unpublished studies with negative results or extreme deviations from previous results. Additionally, Egger's test, a weighted regression test helping to justify the asymmetry of funnel plots, was performed to assess the statistical evidence of publication bias. Significance is defined as P < 0.1. Considering potentially missing studies, an unbiased estimate was acquired using the trim and fill method. All statistical analyses were accomplished utilizing STATA/SE 14.0 software (StataCorp).

Results

Qualified studies

According to the search strategy, a total of 1,177 articles were obtained. After screening, five articles were identified [12, 13, 17-19]. The selection process is visually shown in detail in a flow diagram (**Figure 1**).

Baseline characteristics

Table 1 shows characteristics of the 5 involved studies, including a total of 8,024 gastric cancer patients. The publication year ranged from 2011 to 2018. All qualified publications were conducted in China [12, 13, 17, 18], except for one in USA [19]. All patients in these studies were diagnosed by pathology. The shortest follow-up time was 5 years, while the longest was up to 15 years. The proportion of male patients of these studies ranged from 62% to 78%.

Overall analysis

A series of paired-comparisons were conducted between different blood types, including blood type A versus O, blood type B versus O, blood type AB versus O, blood type A versus B, blood type A versus AB, and blood type B versus AB. Results are shown in **Figures 2**, **3**. Taking blood type O as a reference, the pooled HR of blood type A was 1.10 (95% CI, 0.87 - 1.39), with high heterogeneity (I^2 = 84.7%; P < 0.001). The pooled HR of blood type B was 1.08 (95% CI, 0.96 - 1.21), with moderate heterogeneity (I^2 = 34.5%; P = 0.192). The pooled HR of blood type AB was 0.79 (95% CI, 0.55 - 1.15), with high heterogeneity (I^2 = 90.0%; P < 0.001) (**Figure 2A-C**). Taking blood type B as a reference, the pooled HR of blood type A was 1.06 (95% CI, 0.89 - 1.26). Heterogeneity between studies was moderate (I^2 = 63.9%; P = 0.026) (**Figure 3A**). No statistically significant pooled risks were observed for blood type A (HR, 1.25; 95% CI, 0.82 - 1.89) or blood type B (HR, 1.31; 95% CI, 0.88 - 1.95), compared with blood type AB. Levels of heterogeneity were high (both I^2 > 75.0% and P < 0.001) (**Figure 3B** and **3C**).

Cumulative and sensitivity analyses

Performing cumulative meta-analysis and sensitivity analysis, it was found that neither the

Table 1. Characteristics of the 5 included studies in this meta-analysis

Author (year)	Country	Follow-up (years)	Diagnose Criteria	Patients source	Gender (M/F), %	No. of Patients					HRs					
						Total	O	A	B	AB	O/A†	O/B†	O/AB†	B/A‡	AB/A§	AB/A§
Qiu (2011)	China	5	Pathology-proven	Hospital based	0.65/0.35	474	196	124	114	40	1.19	0.85	1.16	1.40	1.00	0.70
Xu (2016)	China	5	Pathology-proven	Hospital based	0.69/0.31	1412	407	516	346	143	1.66	1.35	0.53	1.25	2.50	2.34
Xiao (2017)	China	7	Pathology-proven	Hospital based	0.78/0.22	3234	988	980	935	331	1.09	1.06	1.08	1.03	1.01	0.98
Fan (2018)	China	5-15	Pathology-proven	Hospital based	0.75/0.26	2781	1116	824	638	203	0.98	1.09	1.00	0.90	0.99	1.10
Martinson (2018)	USA	8	Pathology-proven	Hospital based	0.62/0.38	123	30	55	8	30	0.56	0.97	0.49	0.58	1.14	1.95

†, HRs were evaluated taking blood type O as reference. ‡, HRs were evaluated taking blood type B as reference. §, HRs were evaluated taking blood type AB as reference. Abbreviations: HRs, hazard ratios.

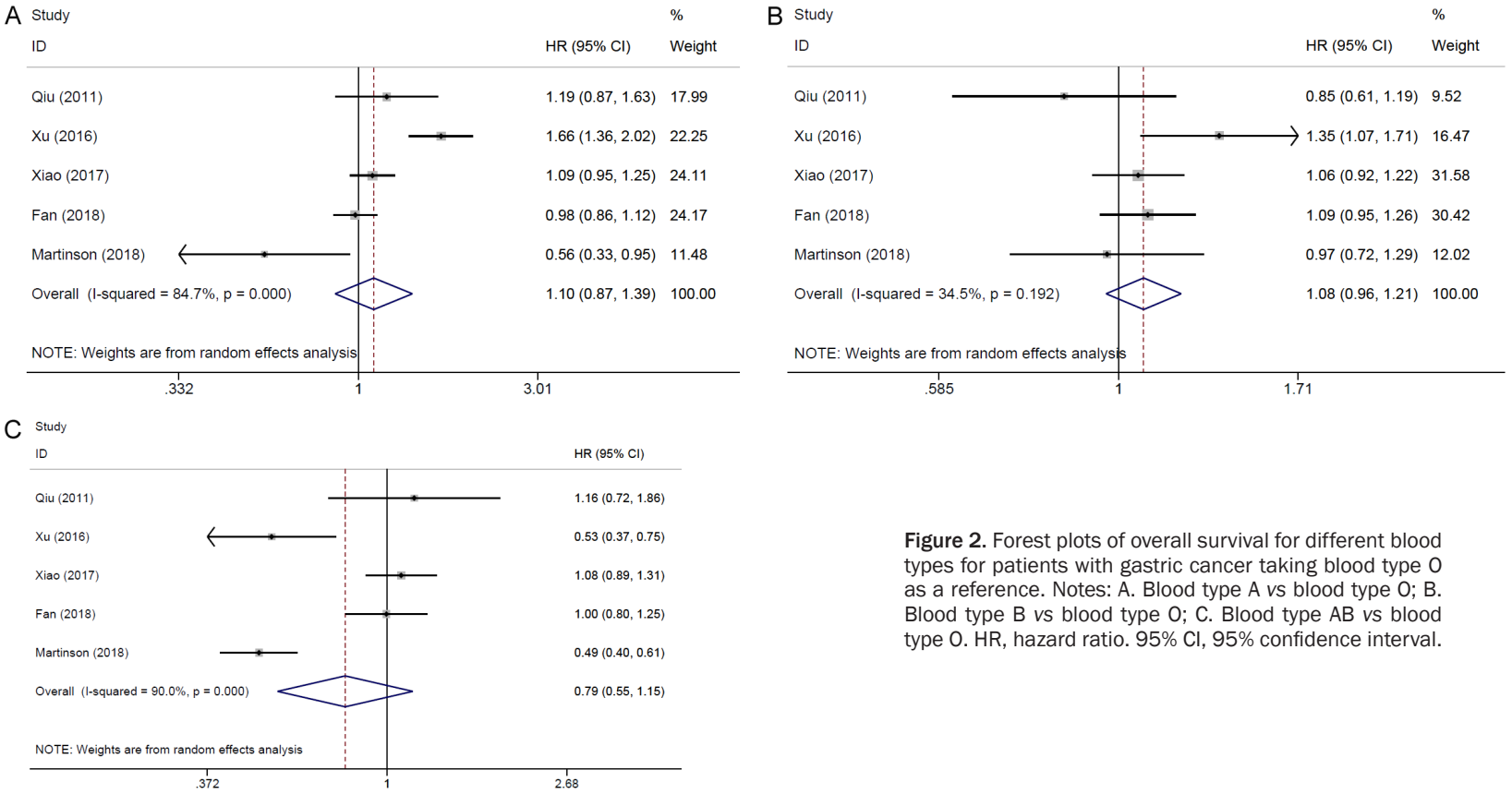

Figure 2. Forest plots of overall survival for different blood types for patients with gastric cancer taking blood type O as a reference. Notes: A. Blood type A *vs* blood type O; B. Blood type B *vs* blood type O; C. Blood type AB *vs* blood type O. HR, hazard ratio. 95% CI, 95% confidence interval.

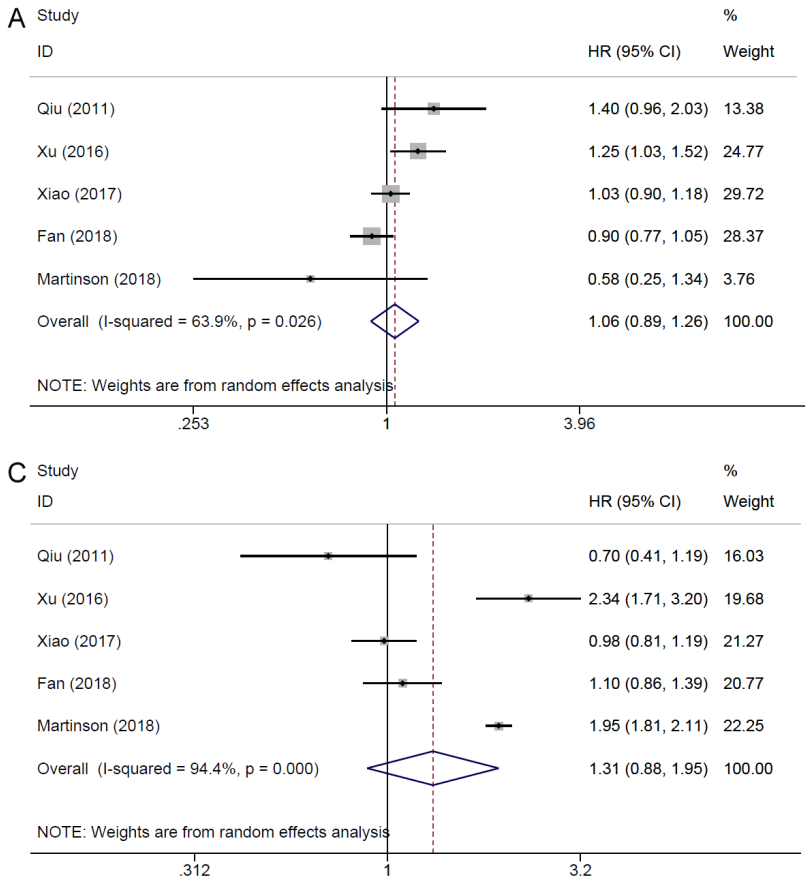

Figure 3. Forest plots of overall survival for different blood types for patients with gastric cancer taking blood type B or AB as a reference. Notes: A. Blood type A *vs* blood type B; B. Blood type A *vs* blood type AB; C. Blood type B *vs* blood type AB. HR, hazard ratio. 95% CI, 95% confidence interval.

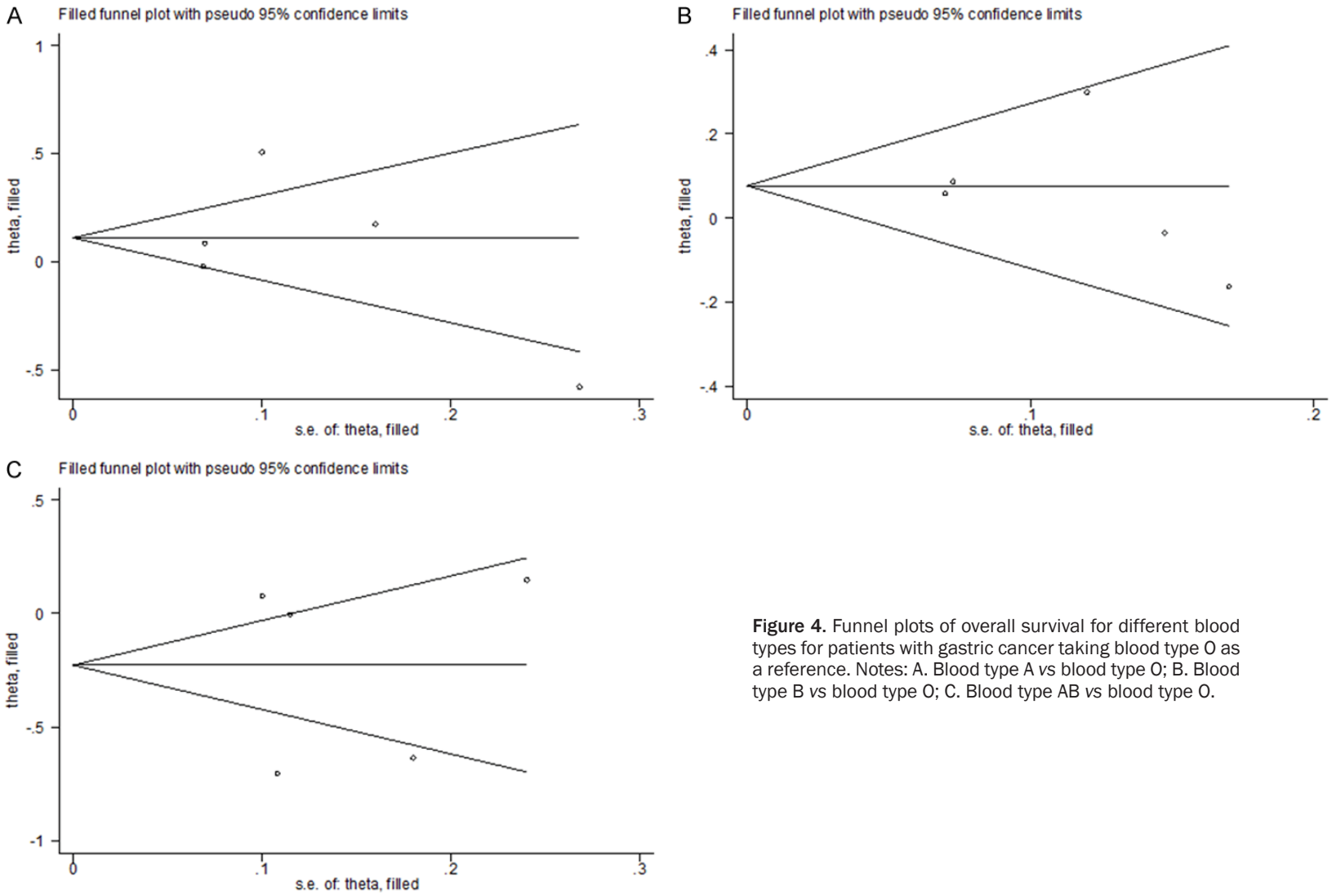

Figure 4. Funnel plots of overall survival for different blood types for patients with gastric cancer taking blood type O as a reference. Notes: A. Blood type A *vs* blood type O; B. Blood type B *vs* blood type O; C. Blood type AB *vs* blood type O.

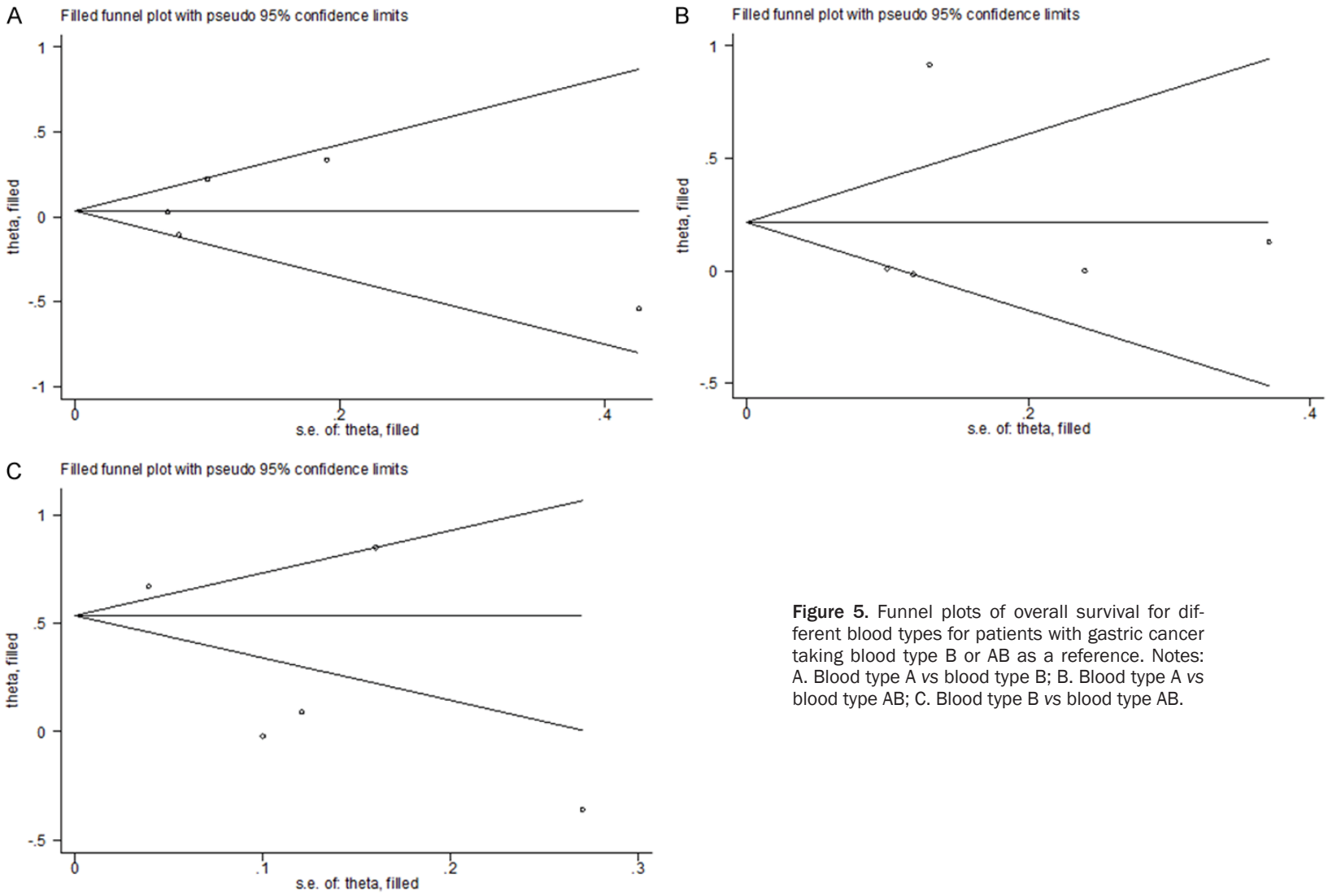

Figure 5. Funnel plots of overall survival for different blood types for patients with gastric cancer taking blood type B or AB as a reference. Notes: A. Blood type A *vs* blood type B; B. Blood type A *vs* blood type AB; C. Blood type B *vs* blood type AB.

first published study nor any single study influenced the others (Figures S2 and S3).

Publication bias

According to the funnel plot (**Figures 4** and **5**) and asymmetry statistics of Egger's regression, no significant publication bias was detected for the paired-comparison groups: Blood type A versus O (P = 0. 873), blood type B versus O (P = 0. 698), blood type AB versus O (P = 0.944), blood type A versus B (P = 0.907), blood type A versus AB (P = 0.941), and blood type B versus AB (P = 0.225). Further evidence of a filled funnel plot indicated that no additional articles were necessary to make the funnel more meristic, indicating that results of the present study are trustworthy.

Discussion

To the best of our knowledge, the current study is the first attempt to systematically investigate the prognostic effects of ABO blood groups on gastric cancer via meta-analysis. Incorporating the five latest articles, results suggest that the ABO blood groups may not be prognostic for patients with gastric cancer.

The relationship between gastric cancer and ABO blood groups was first reported by Aird et al. [20]. Afterward, blood types were reported as risk factors for gastric cancer [8-11]. Based on previous studies, ABO antigens or glycosyltransferases may influence tumorigenesis and the process of cancer by participating in intercellular adhesion, immune response to the host, and modulation of circulating von Willebrand factor levels in plasma [21-23]. In addition, ABO blood groups may also be linked to cancer initiation and spread by association with some inflammatory cytokines, including soluble intercellular adhesion molecule-1, P-selectin, and tumor necrosis factor-alpha [24-26]. These cytokines are expressed distinctly in different blood types. For example, circulating soluble intercellular adhesion molecule-1 level is significantly lower in populations with the non-O blood type. This may result in the promotion of metastatic spread if they develop any endothelial cell carcinoma [27-29]. Moreover, antigens of "ABO" blood groups tend to be overexpressed in gastrointestinal cells [30] and specific blood type antigens may mediate the attachment to human gastric mucosa of Helicobacter pylori (*H. pylori*), which is the main cause of gastric cancer [31]. Under these circumstances, it would be reasonable to deduce that ABO blood groups may influence the prognosis of individuals with gastric cancer, as well as survival status.

To date, several studies have explored the relationship between ABO blood groups and prognosis of gastric cancer, presenting inconsistent conclusions [12, 13, 17-19]. Although the patients were all proven pathologically, sample sizes ranged from 123 to 3,234. The studies were conducted in China and USA. This may be a potential source of heterogeneity. After systematical and comprehensive analysis, the current meta-analysis found that, regardless of the blood type taken as reference, ABO blood groups were not prognostic for patients with gastric cancer. However, present results should be confirmed by future studies.

There were some limitations to the present study, possibly affecting results. First, information concerning *H. pylori* infections was not obtained from involved studies. Second, the limited number of included studies made it difficult to explore heterogeneity between studies. Third, included studies were carried out in two countries. Thus, study quality, patient selection, and follow-up processes might have contributed to heterogeneity. Fourth, publication bias is possible even though results of the funnel plot and Egger's tests showed a low probability of publication bias. Fifth, only five articles were selected after an extensive literature search. This may have reduced the power of analysis.

Disclosure of conflict of interest

None.

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Table S1. Quality evaluation of involved articles

Study	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the de-sign or analysis	Assess-ment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Qiu (2011)	1	1	1	1	1	1	1	0
Xu (2016)	1	1	1	1	1	1	1	1
Xiao (2017)	1	1	1	1	1	1	1	1
Fan (2018)	1	1	1	1	1	2	1	0
Martinson (2018)	1	1	1	1	0	1	1	1

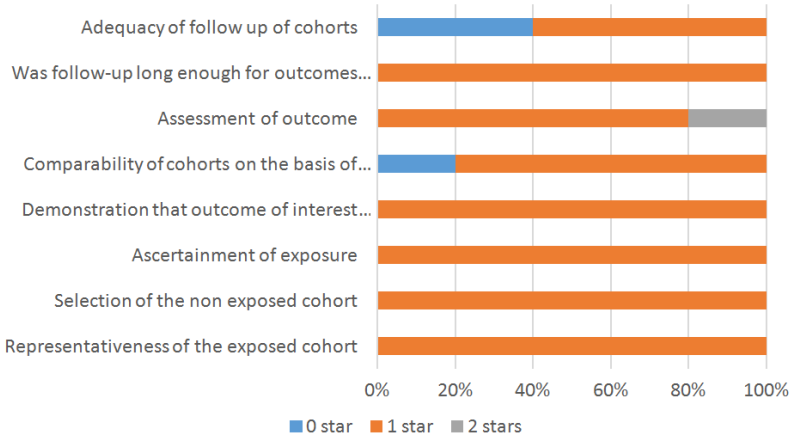

Figure S1. Quality stars of involved articles.

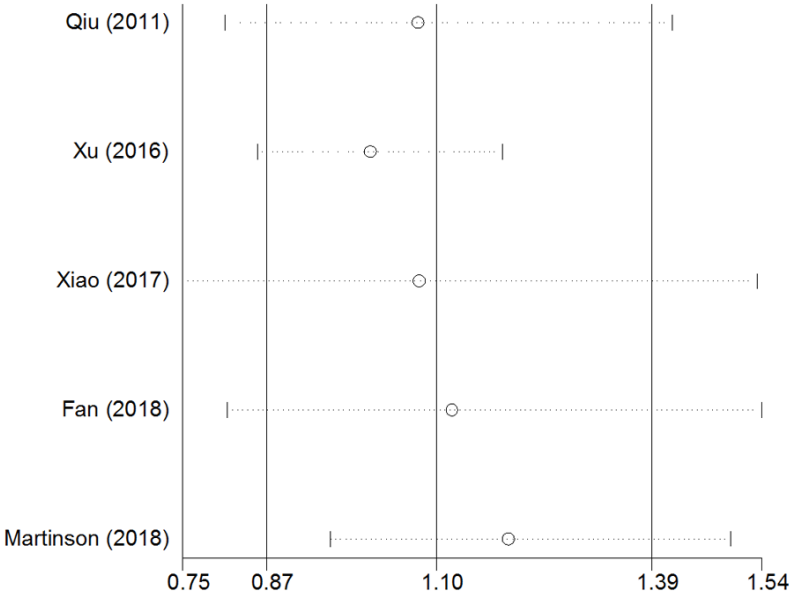

Figure S2. Sensitivity analyses.

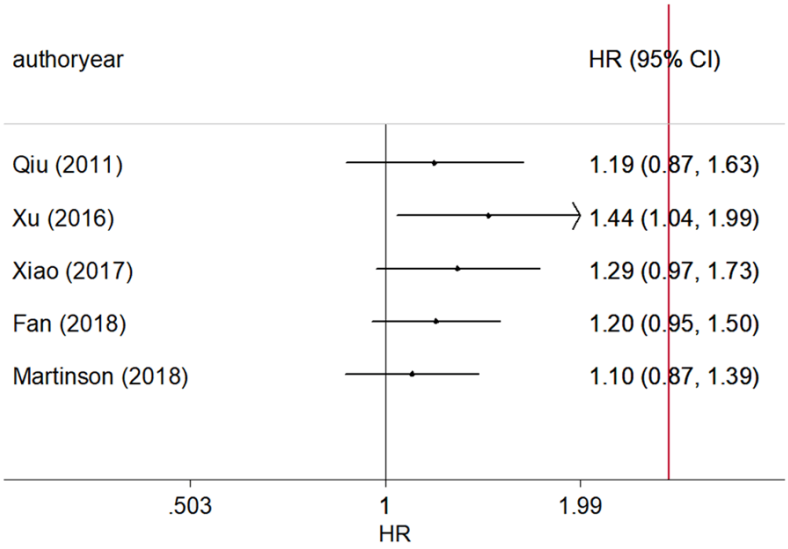

Figure S3. Cumulative analyses.