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# Relationship Between Coagulation and Prognosis of Gastric Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

*Background:* The hypercoagulable state of cancer patients is associated with their high mortality rate. Coagulation indicators may have an important role in the prognosis of gastric cancer patients and deserve to be explored in various aspects.
*Objective:* We conducted a meta-analysis to explore the correlation between coagulation and prognosis of gastric cancer.
*Methods:* A comprehensive systematic search was conducted in PubMed, Embase, Web of Science databases, and the Cochrane Library up to February 16, 2024. Literature screening and data extraction were performed by two independent reviewers. The processed data we pooled using either a random-effects model or a fixed-effects model and finally described overall survival with a risk ratio (hazard ratio [HR]) and predicted the likelihood of different clinicopathological events with a dominance ratio (OR).
*Results:* A total of 64 studies were screened for inclusion in the data analysis. Performing a meta-analysis of three indicators we derived that the risk of D-dimer (D-D), fibrinogen (FIB), and platelets (PLTs) were: HR = 1.85 (95% confidence interval [CI]: 1.59–2.15, $N = 15$), HR = 1.77 (95% CI: 1.57–1.99, $N = 28$), HR = 1.16 (95% CI: 1.12–1.21, $N = 29$). In addition to this, all three were associated with advanced clinicopathological stage (D-D: OR = 2.25, FIB: OR = 2.07, PLT: OR = 1.84), T stage (D-D: OR = 2.30, FIB: OR = 2.38, PLT: OR = 2.22) and lymph node metastasis (D-D: OR = 1.79, FIB: OR = 1.70, PLT: OR = 1.51).
*Conclusion:* Overall, the findings suggest that the three indicators, D-D, FIB, and PLT count, have significant predictive value for the prognosis of gastric cancer. They were associated with an advanced clinicopathological stage and a high risk of lymph node metastasis.



## Introduction

Stomach cancer is one of the major culprits that threaten the health and safety of human life. It is estimated that more than 700,000 people die from stomach cancer each year, making it the fifth most diagnosed and third most deadly malignancy worldwide.[1] In addition, gastric cancer is a multifactorial disease. On the one hand, it is influenced by the environment, such as age, gender, smoking, alcohol consumption, race, *Helicobacter pylori* infection, and dietary factors.[2–4] On the other hand, it is controlled by genes, such as CEA and CA 19-9.[5] Despite the great progress in treatment with the continuous development of medicine, the survival rate is still unsatisfactory.[6] And in the foreseeable future, as aging increases, more cases of stomach cancer will arise.[7] One of the reasons is because that the development and progression of gastric cancer is a multiannual and multistage process.[8] On the other hand, early diagnosis of gastric cancer is currently performed using endoscopy, a method that permits early detection and removal of the cancer. However, endoscopes are only used when symptoms appear, when it is already too late.[8] In the area of treatment, traditional biomarkers such as CEA and CA19-9 lack sufficient specificity and sensitivity in current clinical applications. Drugs targeting HER-2 significantly prolonged the survival of pa-

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tients with HER-2-positive GC, but their prognostic and predictive value performance remains unclear. Therefore, the development of novel and effective GC biomarkers is necessary.[9,10]

The coagulation process is a highly conserved biological behavior that involves direct activation, adhesion, and aggregation of platelets (PLTs) (primary hemostasis), together with deposition and maturation of a fibrin network (secondary hemostasis).[11] There is growing evidence of a significant correlation between cancer and activation of coagulation. They usually present with low-grade diffuse intravascular coagulation or venous thromboembolism (VTE), such as gastrointestinal tumors, lung cancer, and pancreatic cancer.[12,13] At the same time, there is evidence that the incidence of thrombosis is highest in metastatic, fast-growing, biologically aggressive cancers and is associated with a poor prognosis.[14]

Ample of evidence has reported that gastric cancer is associated with hypercoagulability by involving activation of coagulation and the fibrinolytic system at clinical or subclinical levels. According to recent evidence, VTE has been implicated in GC progression and metastasis, so much so that a coagulation score based on levels of preoperative PLTs, fibrinogen (FIB), and D-dimer (D-D, a product of fibrin degradation) was recently proposed as a promising predictor for postoperative complications and recurrence after gastrectomy in stage II/III GC patients.[15,16] And most of the studies on the relationship between coagulation and the prognosis of gastric cancer are related to these three indicators.[17–19] Therefore, this study conducted a meta-analysis on the above three indicators.

As a degradation product of fibrin, D-D was produced when cross-linked fibrin was degraded by plasmin-induced fibrinolytic activity. Researchers recently reported that D-D can not only affect cellular signaling systems, promote cell proliferation, and induce angiogenesis, but also stimulate the cellular adhesion of gastric cancer cells to endothelial cells, affect PLTs and extra-cellular matrix, and ultimately, induce the growth and spread of gastric cancer.[20] D-D has been proposed as a valid prognostic factor and indicator for thrombosis in many cancers including GC.[11] Liu et al.[20] found that the average plasma D-D level in GC patients was significantly higher than in healthy individuals, with a correlation with the depth of invasion, lymph node metastasis, peritoneal dissemination, tumor size, and TNM stage, with plasma D-D level resulting as a valuable biomarker for peritoneal dissemination. FIB is a plasma coagulation factor synthesized primarily in hepatocytes.[21] In malignancies, it has been suggested that the presence of fibrin(ogen) affects the progression of tumor cell growth and metastasis by acting as a scaffold to support the binding of tumor growth factors and to sustain and promote angiogenesis and the cellular responses of adhesion, proliferation, and migration of tumor cells. Indeed, fibrin was found to enhance PLT adhesion to circulating tumor cells and thereby facilitate metastatic spread. In the particular case of GC, the clinical relevance of FIB has been analyzed in preoperative plasma as a predictor of lymphatic and hematogenous metastasis, tumor progression, and tumor stage and survival.[22,23] PLTs contribute to metastasis by forming a physical shield around tumor cells which protects them from host natural killer cells. PLTs have also been shown to promote an epithelial-to-mesenchymal transition in tumor cells, which is associated with an invasive phenotype.[24,25] Hu et al.[26] 136 found that the frequency of abnormal PLT counts correlated with D-Ds, together with FBG concentrations, tumor size, and TNM stage classification, and that PLT count returned to a normal level following gastric resection and increased again at tumor recurrence.

Although emerging data suggest that serum D-D and FIB levels and PLT counts correlate with tumor stage and prognosis in gastric cancer. However, their value as prognostic markers remains elusive. Therefore, we performed this meta-analysis to explore their prognostic role in gastric cancer.

## Methods

This study was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol for reporting systematic reviews and meta-analyses.[27]

### *Search strategy*

As of February 16, 2024, a preliminary search was conducted by two independent researchers in the Cochrane Library, PubMed, Web of Science, and Embase databases to explore the association between three indicators (D-D, FIB, and PLT count) and the prognosis of gastric cancer. The search was limited to English-language manuscripts. The search terms used were “fibrin fragment D” OR “D-dimer” OR “D-dimer fibrin” OR “Fibrinogen” OR “Coagulation Factor I” OR “Platelet Count” OR “Platelet Number”) AND (“Stomach Neoplasms” OR “Gastric Cancer” OR “Stomach Cancer” OR “Gastric Neoplasm”).

### *Inclusion and exclusion criteria*

Inclusion criteria were as follows: (1) patients with a pathological diagnosis of gastric cancer; (2) patients were provided with D-D or FIB or PLT count data; (3) patients were evaluated for hazard ratio (HR) and its 95% confidence interval (CI) or extractable survival curve; (4) if overlapping data were found in multiple studies by the same investigator, only the most complete data were included. Exclusion criteria were as follows: (1) duplicate published studies; (2) published in languages other than English; (3) full text unavailable; (4) no relevant data provided; (5) patients with other serious comorbidities.

### *Data extraction*

Two trained researchers independently selected papers and rigorously extracted data based on inclusion/exclusion criteria, and the selections were cross-checked. Disagreements are resolved by consensus through negotiation. The following information was organized according to a preestablished data extraction table, which included authors, year of publication, country, and study type; age, sex (male predominance), cutoff value, number of included study cases (high/low), and follow-up time; and HR with 95% CI. When HR was not directly available, survival data from Kaplan–Meier curves were calculated using Engauge Digitizer version 10.8 (software downloaded from the website: http://digitizer.sourceforge.net/).

### *Quality assessment and statistical analysis*

For quality assessment, we chose the Newcastle–Ottawa scale (NOS), and all included studies were assessed according to each item in the scale, and the process was conducted independently by two reviewers. The scale assesses three aspects of choice, comparability, and outcome. And contains four, one, and three questions, respectively. Therefore, the interval for mass fraction is 0 (lowest) to 9 (highest) and studies greater than or equal to 7 are considered to be of high quality.[28]

The meta-analysis was performed using STATA (version 12.0) software. Pooled HR with its corresponding 95% CI was calculated to evaluate the impact of the association between coagulation and prognosis of gastric cancer. Heterogeneity between studies was estimated using the $I^2$ statistic. Statistical heterogeneity was considered to exist among the studies if $I^2 > 50.0\%$ or $P < 0.05$ and analyzed using a random-effects model. Otherwise, a fixed-effects model was used. A sensitivity analysis was then performed to verify the stability of the combined results by omitting the studies

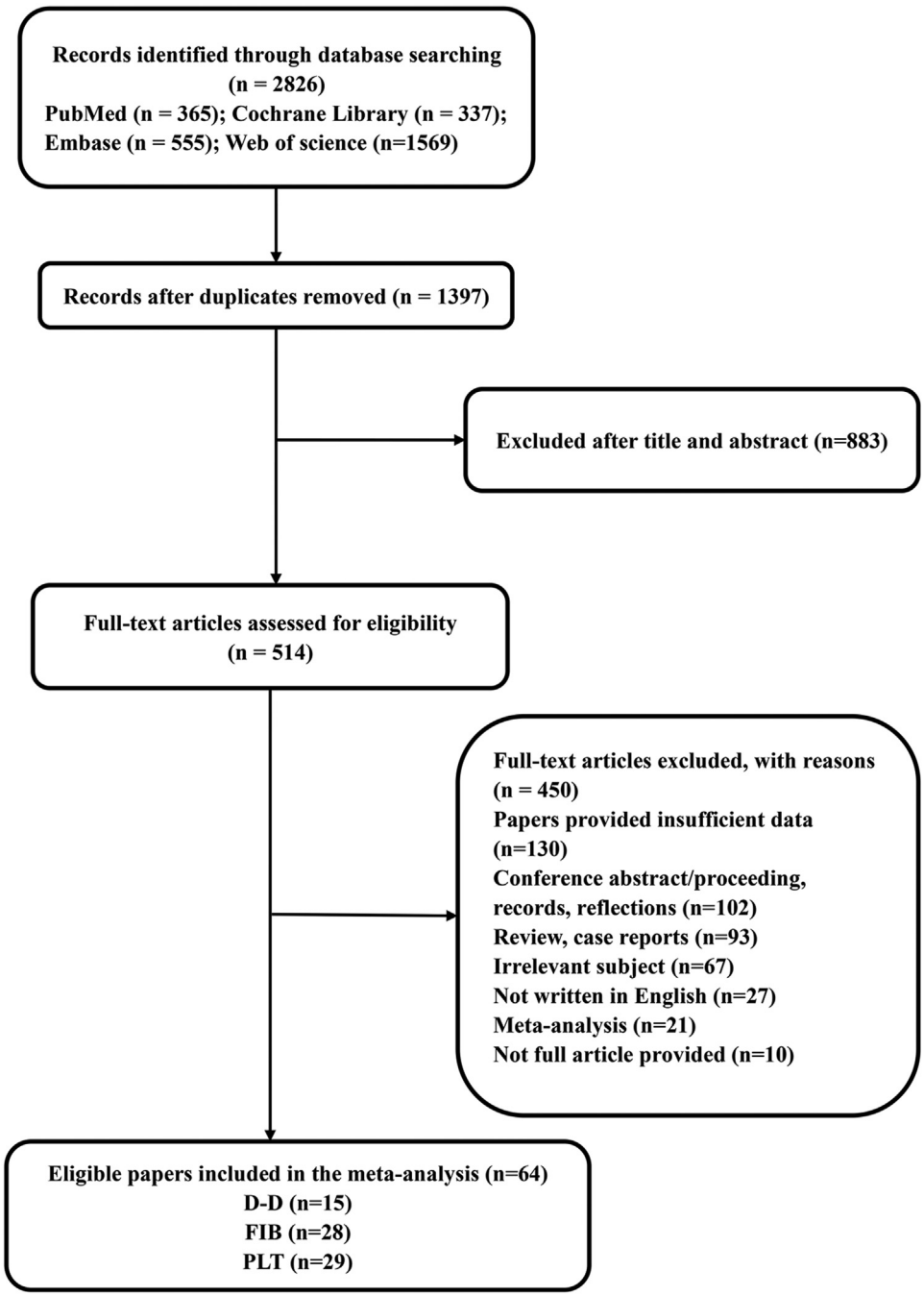


**Figure 1.** Flow diagram for study inclusion.

one by one. In addition to this, to explore the sources of heterogeneity, subgroup analyses, and meta-regression analyses were performed by country, sample size, follow-up time, cut-off values, and quality scores. And then, we investigated the effects of plasma D-D, FIB, and PLT count on the clinicopathological characteristics of patients with gastric cancer. Finally, publication bias was assessed by Begg's funnel plot and Egger's test.[29,30]

## Results

### *Literature search*

An initial search yielded a total of 2826 potentially relevant studies. After removing duplicate papers, there were 1397 research articles available for analysis. Based on the initial screening of titles and abstracts, 833 studies were eliminated, resulting in 514 papers for the subsequent round of screening. Full-text reading eliminated a total of 405 studies, including 130 with no available data, 102 nonstudy papers (conference abstracts, proceedings, etc.), 93 reviews and case reports, 67 that did not match the study topic, 27 that were not published in English, 21 meta-analyses, and 10 for which the full text was not retrieved. Finally, 64 studies were included (15 for D-D, 28 for FIB, and 29 for PLT). Among these 64 articles, 1 article contains both D-D, FIB, and PLT,[31] and 1 article with both D-D and FIB,[16] and 3 articles with both FIB and PLT.[32–34] The literature screening process is shown in Figure 1.

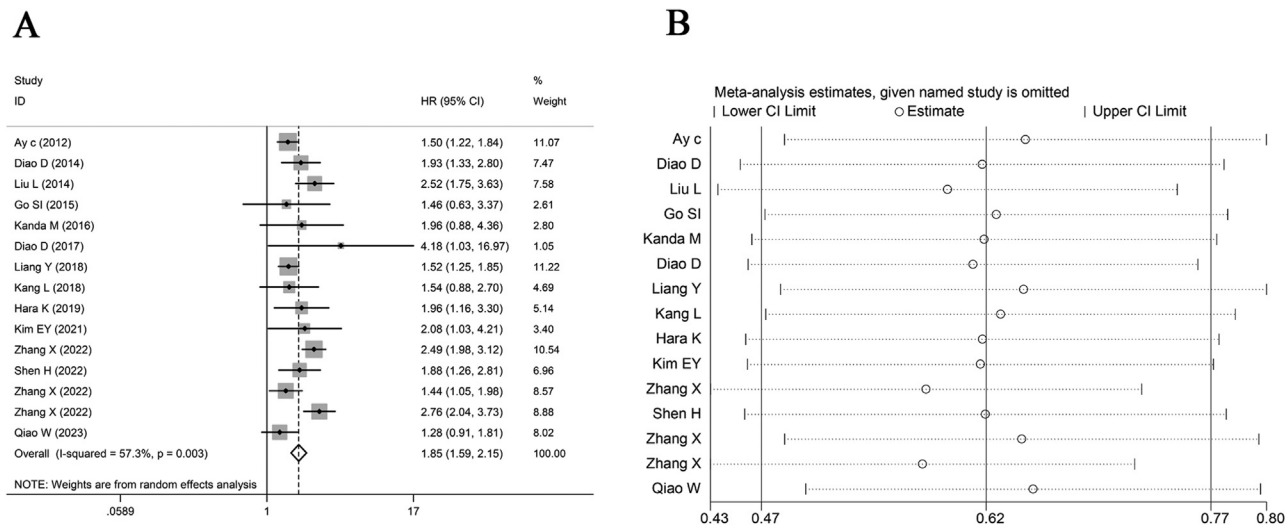


**Figure 2.** (A) Association between D-dimer and the risk of gastric cancer; (B) sensitivity analysis of D-dimer.

*Study characteristics*

A total of 15 studies examining the relationship between D-Ds and the prognosis of gastric cancer were included in this analysis. Of these studies, 10 were conducted in China, 3 in Japan, and 1 each in Korea and Austria. A total of 8249 participants from 2012 to 2024 were included to evaluate the relationship between D-D and the prognosis of gastric cancer. All studies ranged from 0.35 to 1.5 mg/L except for one study with a cut-off value of 4.9 mg/L.[35] The quality of the included studies was relatively high, with four studies scoring 8, eight scoring 7, and only three scoring 6.

A total of 28 studies containing FIB data were included, 21 from China, 6 from Japan, and 1 from Korea, containing a total of 15,945 participants from 2006 to 2024, involved in assessing the association between FIB and GC risk. With the exception of one study with a cut-off value of 0.03 g/L, all other studies ranged from 2.6 to 4.07 g/L.[36] There were 7 articles with NOS scores of 8, 16 articles with scores of 7, and 5 articles with scores of 6. The quality of the articles is moderate to high.

A comprehensive analysis was conducted on a total of 29 studies that provided PLT data. Out of these studies, 19 were conducted in China, 6 in Japan, 5 in Korea, and 1 each in the United Kingdom (UK), Turkey (Türkiye), and Poland. The collective sample size consisted of 24,710 participants, spanning from 2002 to 2024, who were included, participating in the assessment of the association between PLT and GC risk. The cut-off values ranged from $205.5 \times 109$/L to $400 \times 109$/L in all studies except 3 studies whose cut-off values were not stated in the text.[37,38] The quality of all studies was moderate to high. There were 5 studies with NOS scores of 9, 10 studies with scores of 8, 11 studies with scores of 7, and 7 articles with scores of 6. Detailed information is shown in Table 1.

*D-D and prognosis of gastric cancer*

The combined HR between elevated D-D and GC prognosis was 1.85 (95% CI 1.59–2.15), and there was slight heterogeneity between studies ($I^2 = 57.3\%$, $P = 0.003$), Figure 2A. Subgroup analyses were performed according to country, sample size, follow-up time, cut-off value, quality scores, and status of the patient (Table 2). The results of the study did not change relative to the whole. Country (based on China: pooled HR 1.91, 95% CI 1.57–2.31; based on Japan: pooled 1.99, 95% CI 1.37–2.89), sample size (for sample size ≤350: pooled HR 1.72, 95% CI 1.44–2.04; for sample size >350: pooled HR 1.94, 95% CI 1.32–2.79), and follow-up time (follow-up time ≤32 months: pooled HR 1.53, 95% CI 1.32–1.79; follow-up time >32 months: pooled HR 1.78, 95% CI 1.40–2.26). In addition, higher cut-off values were associated with worse GC prognosis (cut-off <1.0 mg/L: HR 1.52; cut-off ≥1.0 mg/L: HR 2.15). In addition to this, depending on the timing of the blood collection and the treatment status, we found that neither preoperative blood collection, prechemotherapy blood collection, nor postoperative blood collection affected the overall results (preoperative: pooled HR 1.86, 95% CI 1.53–2.25; prechemotherapy: pooled HR 1.79, 95% CI 1.25–2.57; postoperation: pooled HR 1.94, 95% CI 1.43–2.63). Subsequently, our findings were confirmed to be stable and reliable by sensitivity analysis (Figure 2B).

As a biomarker, our further studies determined the relationship between elevated D-D and a variety of clinicopathologic features (gender, differentiation, T stage, TNM stage, and lymph node metastasis). Pooled estimates showed that elevated D-D was associated with advanced T stage (OR = 2.30, 95% CI: 1.52–3.47), TNM stage (OR = 2.25, 95% CI: 1.78–2.84), and lymph node metastasis (OR = 1.79, 95% CI: 1.44–2.23) without significant heterogeneity. However, no correlation was observed between D-D and sex (OR = 0.85, 95% CI: 0.71–1.03) and degree of differentiation (OR = 1.04, 95% CI: 0.85–1.28) (Table 3).

*FIB and prognosis of gastric cancer*

As shown in Figure 3A, there was a significant positive correlation between elevated FIB and overall GC survival, with a combined HR for GC risk of 1.77 (95% CI: 1.57–1.99), with heterogeneity between studies ($I^2 = 83.0\%$, $P < 0.05$).

In subgroup analyses, the prognostic value of elevated FIB for GC differed between countries. In China (HR = 1.70, 95% CI 1.49–1.95) the prognosis was better than in Japan (HR = 2.28, 95% CI 1.76–2.94). Shorter follow-up periods (follow-up time ≤32 months: combined HR 1.50, 95% CI 0.90–2.48), in contrast to longer follow-up periods (follow-up time >32 months: combined HR 1.83, 95% CI 1.63–2.05), were not statistically significant. In addition, higher cut-off values did not increase the correlation between FIB and GC prognosis (cut-off <3.5 g/L: HR 1.84; cut-off ≥3.5 g/L: HR 1.76) (Table 2). Subsequent sensitivity analyses showed that the results were stable (Figure 3B). However, our analysis by subgroup analysis as well as meta-regression showed that geographic region ($P = 0.996$), sample size ($P = 0.640$), duration of follow-up ($P = 0.149$), cut-off value ($P = 0.201$), and quality of the literature ($P = 0.393$) were not statistically significantly associated with heterogeneity. Because blood was collected preoperatively in all of the

**Table 1**
Summary of included eligible studies for meta-analysis in the present study.

| Study | Country | Study design | Age | Gender (male ratio) | D-D/Fib/PLT cut-off | Cases (high/low) | Follow-up time (mo) | Risk estimates and 95% CIs | NOS |
|---|---|---|---|---|---|---|---|---|---|
| D-D | | | | | | | | | |
| Ay (2012) | Austria | Study P | NA | NA | 0.71 μg/mL | 50 | 24.4 (median) | D-D (high vs low): 1.5 (1.2–1.8) | 8 |
| Diao[17] | China | Study R | NA | NA | 1.5 mg/L | 391 (108/283) | 36 | D-D (high vs low): 1.93 (1.33–2.80) | 7 |
| Liu[20] | China | Study R | 58.47 (mean) | 66.8% | 1.465 μg/mL | 247 | 37 (median) | D-D (high vs low): 2.52 (1.87–3.89) | 7 |
| Go (2015) | Korea | Study R | High/low cases (median): 58/64 | High/low cases: 75%/85.7% | 1.5 μg/mL | 46 (32/14) | 10.5 (median) | D-D (high vs low): 1.46 (0.63–3.35) | 8 |
| Kanda (2016) | Japan | Study R | NA | NA | 1.00 μg/mL | 126 (39/87) | 60 | D-D (high vs low): 1.96 (0.88–4.36) | 6 |
| Diao[17] | China | Study R | NA | NA | 1.5 mg/L | 29 (13/16) | 42 (median) | D-D (high vs low): 4.18 (1.03–16.98) | 6 |
| Liang (2018) | China | Study P | 62 (median) | 72.7% | 500 μg/L | 1025 (163/862) | 36 (median) | D-D (high vs low): 1.52 (1.25−1.85) | 8 |
| Kang (2018) | China | Study R | NA | 54.2% | 0.5 μg/mL | 96 (42/52) | NA | D-D (high vs low): 1.54 (0.88–2.71) | 6 |
| Hara[35] | Japan | Study R | 67 (median) | 65.4% | 4.9 μg/mL | 448 (230/218) | NA | D-D (high vs low): 1.96 (1.16–3.30) | 7 |
| Kim (2021) | Japan | Study P | 57.6 (mean) | 65.3% | 0.35 μg/mL | 666 (159/505) | NA | D-D (high vs low): 2.08 (1.03–4.22) | 7 |
| Zhang[31] | China | Study R | Age ≥65 y: 32.1% | 76.1% | 1.00 mg/L | 903 (161/742) | NA | D-D (high vs low): 2.49 (1.98–3.12) | 7 |
| Shen (2022) | China | Study R | 61 (median) | 71.9% | 0.58 ug/mL | 153 (122/31) | 6 (median) | D-D (high vs low): 1.88 (1.26–2.81) | 7 |
| Zhang[31] | China | Study R | NA | 81.7% | 1.00 mg/L | 120 (81/39) | 12 | D-D (high vs low): 1.44 (1.02–1.92) | 8 |
| Zhang[31] | China | Study R | 61 (median) | 72.6% | 1.00 mg/L | 3447 (1449/1998) | NA | D-D (high vs low): 2.76 (2.04–3.73) | 7 |
| Qiao (2023) | China | Study R | 62 (median) | 72.1% | 0.75 mg/L | 502 | 60 | D-D (high vs low): 1.28 (0.91–1.81) | 7 |
| FIB | | | | | | | | | |
| Yamashita (2006) | Japan | Study R | NA | NA | 310 mg/dL | 240 | 60 | FIB (high vs low): 2.01 (0.73–5.49) | 6 |
| Lee[18] | Korea | Study R | 60 (mean) | 67.6% | 407 mg/mL | 923 (228/695) | 40 (median) | FIB (high vs low): 1.83 (1.44–2.34) | 7 |
| Arigami (2016) | Japan | Study R | 66 (mean) | 65.1% | 305 mg/dL | 275 (163/112) | 40 (median) | FIB (high vs low): 1.91 (0.86–4.26) | 7 |
| Suzuki (2016) | Japan | Study R | 69 (mean) | 67.3% | 350 mg/dL | 315 (122/193) | 28 (median) | FIB (high vs low): 2.61 (1.18–5.76) | 8 |
| Yamamoto (2016) | Japan | Study R | High/low cases (median: 68/66 | High/low cases: 73.2%/71% | 350 mg/dL | 609 (164/445) | 55 (median) | FIB (high vs low): 2.25 (1.55–3.28) | 7 |
| Yu (2016) | China | Study R | 57 (median) | 73.4% | 3.9 g/L | 1090 (250/840) | 44 (median) | FIB (high vs low): 1.78 (1.49–2.13) | 8 |
| Yu (2016) | China | Study R | Age ≥40 y: 94% | 74% | 4.0 g/L | 1196 (246/887) | 60 | FIB (high vs low): 1.97 (1.65–2.35) | 7 |
| Kanda (2016) | Japan | Study R | NA | NA | 400 mg/dL | 126 (37/89) | 60 | FIB (high vs low): 4.35 (1.56–12.51) | 7 |
| Zhang[36] | China | Study R | 58 (median) | 72.5% | 3.0 mg/dL | 360 (164/196) | 36 | FIB (high vs low): 2.14 (1.48–3.09) | 8 |
| Liu (2018) | China | Study R | 59 (median) | 68.2% | 400 mg/dL | 1293 (263/1030) | 35 (median) | FIB (high vs low): 1.62 (1.33–1.97) | 7 |
| Song[34] | China | Study R | 62 (mean) | 73.6% | 3.75 g/L | 1946 (597/1349) | 37 (mean) | FIB (high vs low): 1.57 (1.38–1.79) | 7 |
| Wakatsuki (2018) | Japan | Study R | Age ≥65 y: 47.3% | 75.3% | 260 mg/dL | 182 | >12 | FIB (high vs low): 2.04 (1.16–3.68) | 7 |
| Cong (2019) | China | Study R | Age range for cases: 32–76 | 78.7% | 3.09 g/L | 356 (186/170) | 54.2 (mean) | FIB (high vs low): 2.60 (1.85–3.65) | 7 |
| Wu (2019) | China | Study R | 60.5 (mean) | 74.7% | 3.39 g/L | 842 (321/521) | 83.9 (median) | FIB (high vs low): 1.41 (1.15–1.73) | 8 |
| Wu (2019) | China | Study R | 60 (median) | 69.3% | 4.0 g/L | 396 | NA | FIB (high vs low): 1.67 (1.21–2.32) | 7 |
| Feng (2020) | China | Study R | 60 (median) | 68.1% | 400 mg/dL | 401 (29/372) | 40 (median) | FIB (high vs low): 1.681 (1.032–2.739) | 8 |
| Gao (2020) | China | Study R | 60.5 (median) | 67.9% | 4.0 g/L | 240 | NA | FIB (high vs low): 1.68 (1.17–2.42) | 6 |
| Zhang (2020) | China | Study R | Age ≥60 y: 53% | 73% | 4.0 g/L | 341 (72/269) | 60 | FIB (high vs low): 2.61 (1.63–4.18) | 6 |
| Zhao (2020) | China | Study R | Age>=65 y: 30.64% | 70.31% | 3.20 g/L | 842 (421/421) | 120 | FIB (high vs low): 1.11 (1.03–1.46) | 8 |
| Wang (2021) | China | Study R | 61 (median) | 75.6% | 3.30 g/L | 689 | 56 (median) | FIB (high vs low): 2.12 (1.72–2.62) | 7 |
| Wang (2021) | China | Study R | 61 (median) | 75.8% | 3.37 g/L | 608 (258/350) | 56 (median) | FIB (high vs low): 2.1 (1.7–2.6) | 7 |
| Zhou (2021) | China | Study R | 26 (median) | 47.5% | 4.0 g/L | 99 (32/67) | 26 (median) | FIB (high vs low): 0.94 (0.57–1.53) | 7 |
| Dinc (2021) | China | Study R | 63.99 (mean) | 70% | 350 mg/dL | 130 (102/28) | 60 | FIB (high vs low): 1.84 (0.99–3.41) | 6 |
| Li[32] | China | Study R | 65.6 (mean) | 66.2% | 3.5 g/L | 281 (71/210) | NA | FIB (high vs low): 2.27 (1.27–4.07) | 7 |
| Zhang[31] | China | Study R | Age ≥65 y: 32.1% | 76.1% | 3.8 g/L | 903 | NA | FIB (high vs low): 1.73 (1.39–2.15) | 7 |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Country | Study design | Age | Gender (male ratio) | D-D/Fib/PLT cut-off | Cases (high/low) | Follow-up time (mo) | Risk estimates and 95% CIs | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Wei (2022) | China | Study R | 59 (median) | 67.4% | 4 g/L | 218 (59/159) | 15.5 (median) | FIB (high vs low): 1.64 (1.14–2.35) | 8 |
| Qiao (2023) | China | Study R | 62 (median) | 72.1% | 3.25 g/L | 502 | 60 | D-D (high vs low): 1.87 (1.26–2.79) | 7 |
| Wang (2023) | China | Study R | 58 (median) | 75.3% | NA | 542 | NA | D-D (high vs low): 1.15 (1.09–1.23) | 6 |
| PLT | | | | | | | | | |
| Ikeda (2002) | Japan | Study R | 63.5 (mean) | 69.91% | $400 \times 10^9$/L | 369 | 60 | PLT (high vs low): 2.48 (1.13–5.22) | 6 |
| Crumley (2006) | UK | Study R | 65 (median) | 66.67% | $400 \times 10^9$/L | 120 | 55 (median) | PLT (high vs low): 0.69 (0.22–2.23) | 7 |
| Shimada (2010) | Japan | Study R | 65 (median) | 69% | $350 \times 10^9$/L | 1028 (876/152) | 60 | PLT (high vs low): 1.54 (1.7–2.0) | 7 |
| Lv (2010) | China | Study R | 57.75 (mean) | 70.94% | $300 \times 10^9$/L | 203 (21/182) | 38 (mean) | PLT (high vs low): 4.39 (2.34–8.21) | 6 |
| Aliustaoglu[19] | Turkey | Study R | 60.1 (mean) | 67.80% | $300 \times 10^9$/L | 168 (100/68) | 48 | PLT (high vs low): 1.33 (0.78–2.26) | 7 |
| Wang (2012) | China | Study R | Age>=65 y: 29% | 69.44% | $400 \times 10^9$/L | 324 (27/297) | 39.9 (median) | PLT (high vs low): 1.21 (0.71–2.06) | 7 |
| Hwang (2012) | Korea | Study R | 56 (mean) | 69.55% | $400 \times 10^9$/L | 1593 (102/1491) | 200 | PLT (high vs low): 1.59 (1.20–2.11) | 9 |
| Wang (2012) | China | Study R | Age>50 y: 53.1% | 72.45% | 400 | 98 (21/77) | 70 | 3.47 (1.67–7.23) | 6 |
| Li (2014) | China | Study R | 60 (mean) | 70.60% | $400 \times 10^9$/L | 1596 (120/1476) | 100 | PLT (low vs high): 0.81 (0.71–0.93) | 8 |
| Ishizuka (2014) | Japan | Study R | Age>70 y: 41% | 70.80% | $350 \times 10^9$/L | 425 | 147 | PLT (high vs low): 2.51 (1.54–4.08) | 7 |
| Ishizuka (2014) | Japan | Study R | Age>75 y: 25.1% | 73.00% | $300 \times 10^9$/L | 544 | 148 | PLT (high vs low): 1.94 (1.38–2.74) | 8 |
| Hu[26] | China | Study R | 63 (mean) | NA | $300 \times 10^9$/L | 313 (213/100) | 60 | PLT (high vs low): 1.04 (0.77–1.41) | 8 |
| Zhou (2016) | China | Study R | Age>=60 y: 55.2% | 71.80% | $205.5 \times 10^9$/L | 431 | 37.7 (median) | PLT (high vs low): 1.25 (0.98–1.6) | 6 |
| Chen (2017) | China | Study R | 57 (median) | 71% | $262 \times 10^9$/L | 292 (146/146) | NA | PLT (high vs low): 1.04 (0.64–1.69) | 7 |
| Pan (2018) | China | Study R | 60 (median) | 74.5% | $252 \times 10^9$/L | 870 (361/509) | 59.9 (median) | PLT (high vs low): 0.99 (0.81–1.24) | 7 |
| Feng (2018) | China | Study R | 58 (median) | 78.3% | $260 \times 10^9$/L | 3423 (768/2475) | 24.9 (median) | PLT (high vs low): 1.34 (1.18–1.53) | 6 |
| Wakatsuki (2018) | Japan | Study R | Age ≥65 y: 47.3% | 75.3% | $23 \times 10^4$ μL | 182 | >12 | PLT (high vs low): 1.13 (0.66–1.96) | 8 |
| Song[34] | China | Study R | 62 (mean) | 73.7% | $290.5 \times 10^9$/L | 1946 (633/1313) | 37 (mean) | PLT (high vs low): 1.23 (1.10–1.36) | 9 |
| Oh (2019) | Korea | Study R | 56.4 (mean) | 65.5% | $25.5 \times 10^4$ μL | 4643 (1583/3060) | 59.5 (mean) | PLT (high vs low): 1.19 (1.03–1.37) | 8 |
| Wang (2020) | China | Study R | 61 (median) | 82.5% | $300 \times 10^9$/L | 114 (35/79) | 41.8 (mean) | PLT (high vs low): 3.26 (1.96–5.39) | 9 |
| Lnoue (2021) | Japan | Study R | 67 (median) | 64.70% | $272 \times 10^9$/L | 447 (109/338) | 60 | PLT (high vs low): 2.80 (1.42–5.53) | 8 |
| Chen (2022) | China | Study R | Age ≥59 y: 53.4% | 70% | $232 \times 10^9$/L | 146 (74/72) | NA | PLT (high vs low): 0.58 (0.35–0.97) | 8 |
| Konopka (2022) | Poland | Study R | NA | 67.6% | $400 \times 10^3$/μL | 105 (28/77) | 60 | PLT (high vs low): 1.81 (1.12–2.93) | 8 |
| Park (2022) | Korea | Study R | 55 (mean) | 60.30% | $240.5 \times 10^9$/L | 692 (346/346) | 79 (median) | PLT (high vs low): 1.24 (0.88–1.74) | 8 |
| Li[32] | China | Study R | 65.6 (mean) | 66.2% | $222.5 \times 10^9$/L | 281 | NA | PLT (high vs low): 2.80 (1.55–5.04) | 8 |
| Zhang[31] | China | Study R | Age ≥65 y: 32.1% | 76.1% | $300 \times 10^9$/L | 903 | NA | PLT (high vs low): 1.02 (0.74–1.41) | 9 |
| Qiao (2023) | China | Study R | 62 (median) | 72.1% | $260 \times 10^9$/L | 511 | 60 | PLT (high vs low): 1.01 (1.00–1.01) | 7 |
| Zhang (2023) | China | Study R | NA | NA | $246 \times 10^9$/L | 402 (54/348) | 48 | PLT (high vs low): 1.89 (1.39–2.59) | 7 |
| Zhu (2023) | China | Study R | NA | 56% | NA | 600 | NA | PLT (high vs low): 1.00 (0.99–1.00) | 6 |

D-D = D-dimer; FIB = fibrinogen; NA = not available; NOS = Newcastle–Ottawa scale; PLT = platelet; Study P = prospective cohort study; Study R = retrospective.

**Table 2**
Subgroup meta-analysis of pooled HRs for OS.

| | D-D | | | FIB | | | PLT | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | Summary HR (95% CI) | $I^2$ | *N* | Summary HR (95% CI) | $I^2$ | *N* | Summary HR (95% CI) | $I^2$ |
| Overall | 15 | 1.85 (1.59–2.15) | 57.3% | 28 | 1.77 (1.57–1.99) | 83% | 29 | 1.16 (1.12–1.21) | 90.8% |
| Subgroup | | | | | | | | | |
| Country | | | | | | | | | |
| China | 10 | 1.91 (1.57–2.31) | 68.2% | 20 | 1.70 (1.49–1.94) | 86.4% | 17 | 1.05 (1.02–1.09) | 88.5% |
| Japan | 3 | 1.99 (1.37–2.89) | 0.0% | 6 | 2.28 (1.76–2.94) | 0.0% | 6 | 1.83 (1.44–2.32) | 53.8% |
| Korea | | | | 1 | 1.83 (1.44–2.34) | - | 3 | 1.30 (1.09–1.54) | 38.2% |
| Other | 2 | 1.50 (1.23–1.82) | 0.0% | 1 | 1.84 (0.99–3.41) | - | 3 | 1.43 (0.96–2.13) | 19.8% |
| Sample size | | | | | | | | | |
| <=350 | 8 | 1.72 (1.44–2.04) | 22.9% | 11 | 1.87 (1.52–2.29) | 28.7% | 12 | 1.56 (1.11–2.20) | 79.9% |
| >350 | 7 | 1.94 (1.53–2.45) | 72% | 17 | 1.73 (1.51–1.99) | 88.3% | 17 | 1.13 (1.09–1.17) | 93.0% |
| Follow-up time (mo) | | | | | | | | | |
| <=32/32/50 | 4 | 1.53 (1.32–1.79) | 0.0% | 3 | 1.50 (0.90–2.48) | 64.2% | 8 | 1.59 (1.30–1.96) | 78.9% |
| >32/32/50 | 6 | 1.78 (1.40–2.26) | 52% | 19 | 1.83 (1.63–2.05) | 67.6% | 14 | 1.40 (1.18–1.65) | 92.9% |
| NA | 5 | 2.38 (2.03–2.80) | 1.2% | 6 | 1.63 (1.26–2.11) | 86.7% | 7 | 1.09 (0.88–1.36) | 66.5% |
| Cut-off value (mg/L, g/L, $10^9$/L) | | | | | | | | | |
| <1.0/3.5/300 | 6 | 1.52 (1.35–1.72) | 0.0% | 10 | 1.84 (1.48–2.28) | 78.7% | 13 | 1.23 (1.08–140) | 64.1% |
| >=1.0/3.5/300 | 9 | 2.15 (1.79–2.57) | 39.4% | 17 | 1.76 (1.62–1.91) | 23.2% | 15 | 1.64 (1.30–2.07) | 88.3% |
| NA | | | | 1 | 1.15 (1.08–1.22) | - | 1 | 1.00 (0.99–1.00) | - |
| Article quality (NOS) | | | | | | | | | |
| <=7 | 11 | 2.07 (1.75–2.45) | 40.5% | 21 | 1.84 (1.58–2.13) | 85.4% | 15 | 1.13 (1.08–1.17) | 93% |
| >7 | 4 | 1.50 (1.32–1.70) | 0.0% | 7 | 1.60 (1.30–1.96) | 72.1% | 14 | 1.35 (1.12–1.63) | 84.7% |
| Status of the patient | | | | | | | | | |
| Preoperative | 11 | 1.86 (1.53–2.25) | 69.0% | 27 | 1.79 (1.63–1.96) | 59.2% | 24 | 1.14 (1.10–1.18) | 91.1% |
| Prechemotherapy | 2 | 1.79 (1.25–2.57) | 0.0% | 0 | - | | 4 | 1.30 (0.77–2.08) | 81.3% |
| Postoperation | 2 | 1.94 (1.43–2.63) | 0.0% | 1 | 1.15 (1.06–1.22) | - | 1 | 3.26 (1.97–5.41) | - |

D-D = D-dimer; FIB = fibrinogen; HRs = hazard ratios; $I^2$ = I-squared; *N* = no. of studies; NA = Not available; NOS = Newcastle–Ottawa scale; OS = overall survival; PLT = platelet.

**Table 3**
Association of D-D/FIB/PLT expression with clinicopathological features.

| Clinicopathological parameters | D-D | | | FIB | | | PLT | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | OR (95% CI) | $I^2$ | *N* | OR (95% CI) | $I^2$ | *N* | OR (95% CI) | $I^2$ |
| Sex (men vs women) | 6 | 0.85 (0.71–1.03) | 42.2% | 10 | 1.12 (1.00–1.26) | 0.0% | 5 | 0.65 (0.59–0.72) | 0.0% |
| Age (older vs younger) | - | - | - | 8 | 1.72 (1.40–2.11) | 61.2% | 4 | 0.96 (0.70–1.32) | 58.8% |
| Histology (undifferentiated vs differentiated) | 5 | 1.04 (0.85–1.28) | 38.7% | 9 | 1.07 (0.95–1.21) | 0.0% | 6 | 0.96 (0.74–1.26) | 71.5% |
| T stage (T3/T4 vs T1/T2) | 5 | 2.30 (1.52–3.47) | 59.2% | 7 | 2.38 (1.76–3.16) | 72.8% | 5 | 2.22 (1.98–2.49) | 32.4% |
| N stage (N1/N2/N3 vs N0) | 3 | 1.79 (1.44–2.23) | 0.0% | 8 | 1.70 (1.33–2.18) | 65.7% | 4 | 1.51 (1.36–1.68) | 1.9% |
| TNM stage (III/IV vs I/II) | 3 | 2.25 (1.78–2.84) | 0.0% | 6 | 2.07 (1.75–2.44) | 0.0% | 5 | 1.84 (1.60–2.11) | 19.8% |
| Tumor size (big vs small) | - | - | - | 7 | 2.37 (1.58–3.57) | 89.5% | 3 | 2.16 (1.83–2.56) | 45.2% |
| Tumor location (lower vs upper/middle) | - | - | - | - | - | - | 4 | 1.23 (0.90–1.68) | 64.6% |

D-D = D-dimer; FIB = fibrinogen; $I^2$ = I-squared; *N* = no. of studies; OR = odds ratio; PLT = platelet.

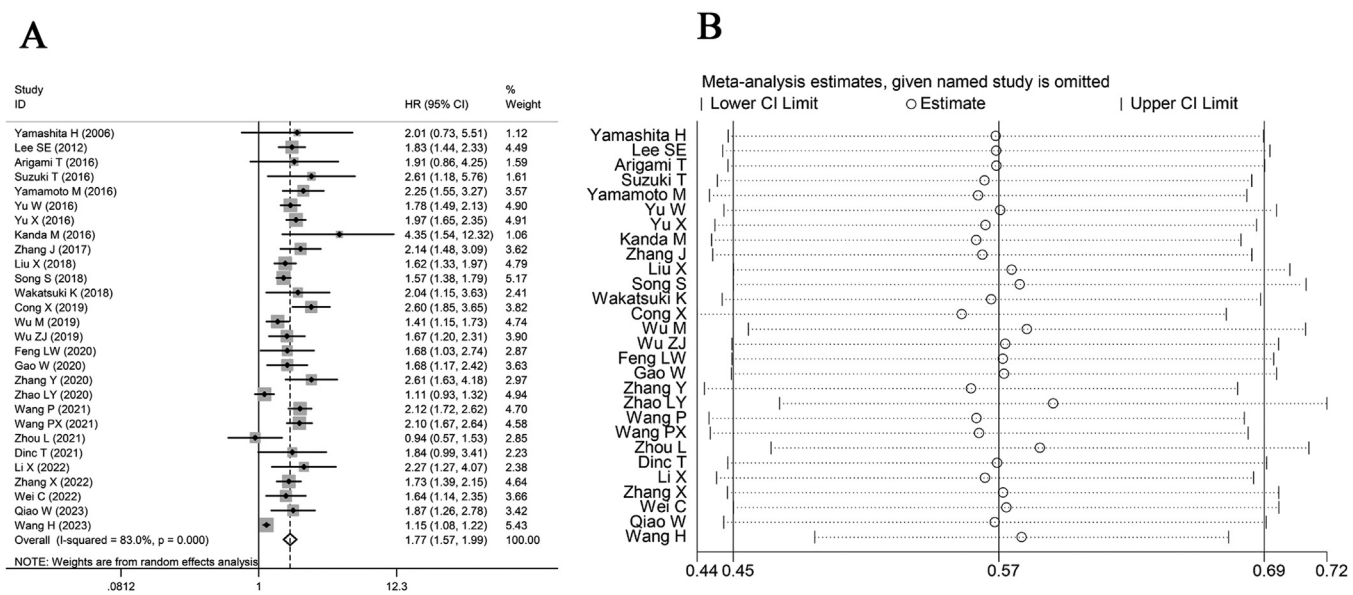


**Figure 3.** (A) Association between fibrinogen and the risk of gastric cancer; (B) sensitivity analysis of fibrinogen; (C) association between fibrinogen and risk of gastric cancer after deletion of two studies; (D) sensitivity analysis of fibrinogen after deletion of two studies.

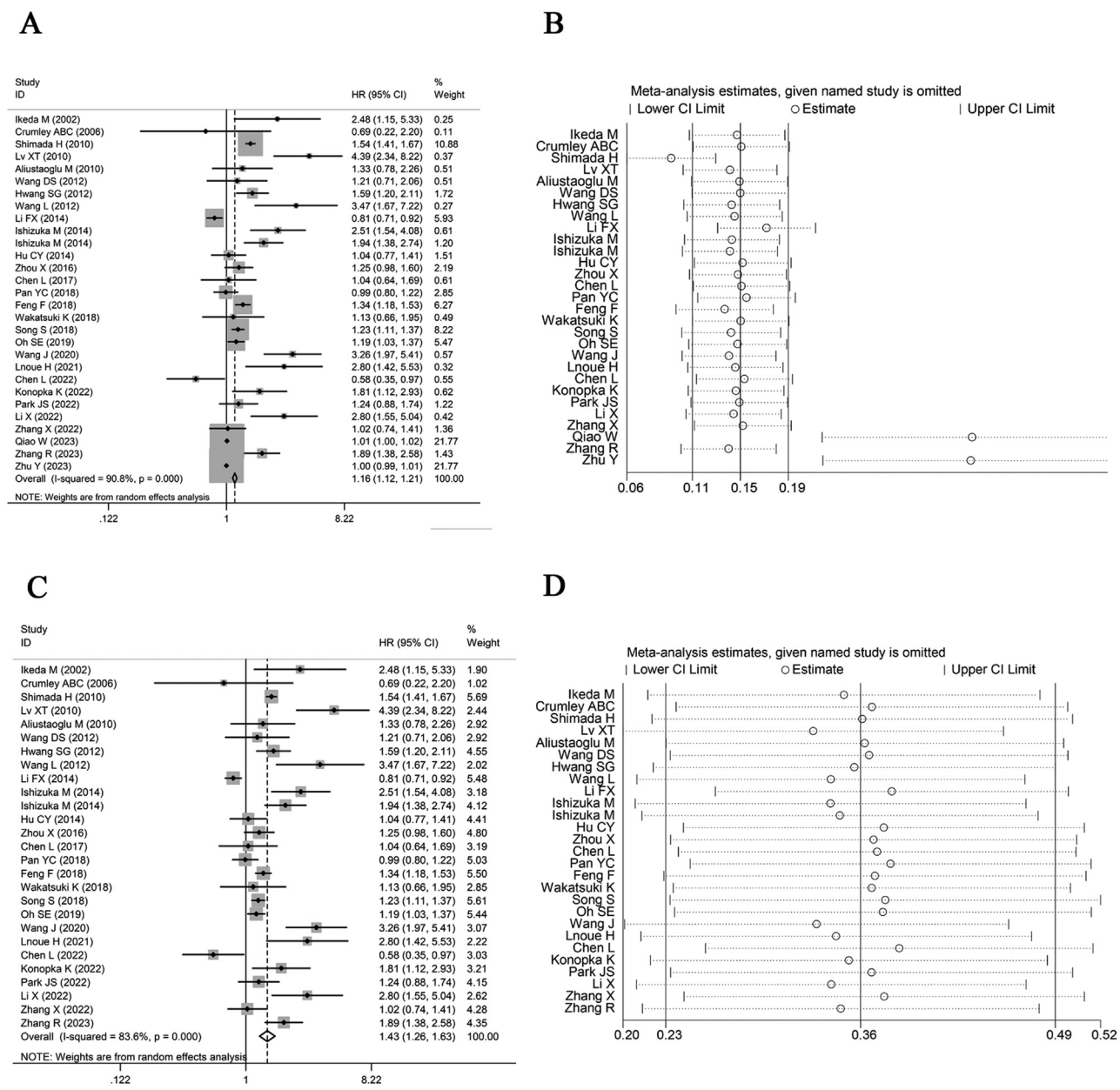


**Figure 4.** (A) Association between platelet count and the risk of gastric cancer; (B) sensitivity analysis of platelet count.

studies included for FIB, it is not possible to prove whether these associations are correct in primary patients or whether they are influenced by first- or second-line GC therapies, and a large number of basic studies will be needed to clarify this in the future. The analysis of the risk level between FIB and clinicopathologic characteristics of GC patients showed that elevated FIB was associated with sex (OR = 1.12, 95% CI: 1.00–1.26), age (OR = 1.72, 95% CI: 1.40–2.11), depth of infiltration (OR = 2.38, 95% CI: 1.76–3.16), lymph node metastasis (OR = 1.70, 95% CI: 1.33–2.18), significant correlation between TNM stage (OR = 2.07, 95% CI: 1.75–2.44) and tumor size (OR = 2.37, 95% CI: 1.58–3.57), whereas no correlation existed with the degree of differentiation (OR = 1.07, 95% CI: 0.95–1.21) (Table 3).

*PLT count and prognosis of gastric cancer*

There was a significant positive correlation between PLT and prognosis of gastric cancer patients with a combined HR of 1.16 (1.12–1.21) (Figure 4A) with significant heterogeneity between studies ($I^2 = 90.8\%$, $P < 0.05$). The subsequent findings from subgroup analyses incorporating various sample characteristics, such as country, sample size, follow-up time, and cut-off value, indicated that the subgroup results remained consistent in comparison to the overall results. Unexpectedly, depending on the timing of blood collection and treatment status, we found that preoperative blood collection was consistent with the overall results (preoperative: pooled HR 1.14, 95% CI 1.10–1.18; postoperation: pooled HR 3.26, 95% CI 1.97–5.41), but the results of preoperative chemotherapy patients were opposite to the overall results (prechemotherapy: pooled HR 1.30, 95% CI 0.77–2.08). This may be due to the limited subgroup inclusion of data, with only 3 articles, so more studies are needed in the future to further demonstrate this (Table 2). Subsequently, we used meta-regression analysis but did not find a source of heterogeneity, geographic region ($P = 0.789$), sample size ($P = 0.453$), duration of follow-up ($P = 0.09$, cut-off value ($P = 0.451$), quality of the literature ($P = 0.711$) and

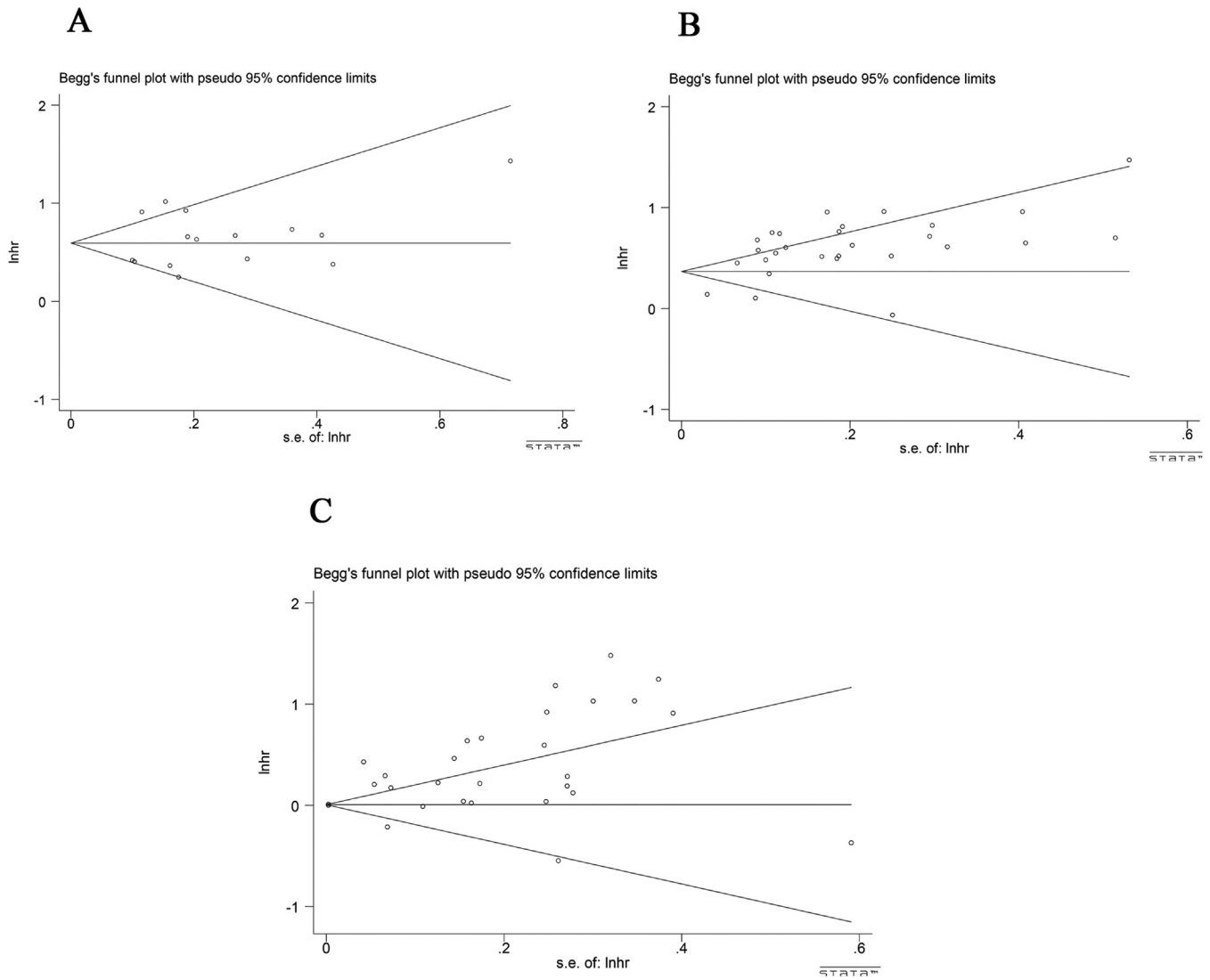


**Figure 5.** Begg's funnel plots for detecting publication bias. (A) D-dimer; (B) fibrinogen; (C) platelet count.

status of the patient. Sensitivity analyses indicated significant heterogeneity in Qiao et al and Zhu et al. However, we found no change in the overall results by removing these two studies, indicating that the results were stable (Figure 4B–D).

Analysis of the risk between PLT and clinicopathologic characteristics of GC patients showed that elevated PLT was associated with female (OR = 1.54, 95% CI: 1.39–1.70), gastric cancer infiltration depth (OR = 2.22, 95% CI: 1.98–2.49), lymph node metastasis (OR = 1.51, 95% CI: 1.36–1.68), TNM stage (OR = 1.84, 95% CI: 1.60–2.11) and tumor size (OR = 2.16, 95% CI: 1.83–2.56) showed a significant positive correlation, while no correlation existed with age, degree of differentiation, and tumor location.

### *Publication bias*

In response to publication bias, we find that the funnel plot is largely symmetric and there is no publication bias. We examined Begg's funnel plot and Egger's linear regression test and found no significant publication bias for D-D ($P = 0.692$, Figure 5A), FIB ($P = 0.540$, Figure 5B), and PLTs ($P = 0.896$, Figure 5C).

## Discussion

A large number of studies have explored the prognostic value of D-D, FIB, and PLT levels in patients with GC, but their reported results are inconsistent. Therefore, we wanted to use this study to estimate the prognostic value of these 3 coagulation indices for GC more comprehensively and precisely. In this meta-analysis, we systematically summarized the results of 57 studies. The results showed that elevated D-D and FIB levels as well as increased PLT counts predicted a poorer prognosis for patients with gastric cancer, and also implied poorer TNM staging and higher odds of lymph node metastasis.

Compared to previous studies, the present meta-analysis had several strengths. Regarding PLT counts, our findings were similar to those of a previous meta-analysis. Both demonstrated a significant correlation between PLT count and prognosis of gastric cancer and correlated with lymph node metastasis and clinical stage. However, we added 19 new papers to the previous study. And we also found that PLT counts correlated with TNM stage and tumor size, greatly complementing previous findings.[39] For FIB, we included 14 new studies. Based on their findings, we also found that

FIB was associated with gender, age, and tumor size in gastric cancer.[40] In addition to this, this meta-analysis is the first to examine the correlation between D-D and the prognosis of gastric cancer. There has only been one prior study on the connection between D-D and the prognosis of digestive system tumors.[41] Consequently, our meta-analysis had a larger sample size, effectively increasing the statistical power of the meta-analysis and further strengthening the results.

The coagulation system is often over-activated in cancer patients, with severe complications of deep vein thrombosis leading to death, which is associated with reduced survival rates.[42] The mechanism of this process is that cancer cells secrete a variety of cytokines, such as tissue factor, thrombin, FIB, and heparinase, to activate the coagulation cascade in vivo, which involves the participation of a variety of coagulation factors and signaling pathways.[11]

Although the definitive pathophysiological mechanisms underlying the prognostic significance of elevated plasma FIB levels in patients with gastric cancer are unknown, studies suggest that FIB may play a key role in tumor progression.[43] Cancer cells can produce endogenous FIB. On the one hand, they can promote tumor proliferation and angiogenesis by binding to other growth factors (e.g., vascular endothelial growth factor) and assisting in the binding of these factors to receptors on the cell surface.[44,45] On the other hand, together with other adhesion glycoproteins, they are deposited outside the cell as scaffolds to provide traction during motility, which in turn promotes the processes of adhesion, proliferation and migration during tumor growth.[46] In addition, FIB is able to interact with PLTs to form a plug around the tumor cells, protecting them from the immune system's cleanup.[47] All of these findings demonstrate the ability of FIB to promote the malignant biological behavior of tumor cells, making it an important marker for prognostic factors in gastric cancer. Elevated D-D, a degradation product of fibronectin, has been observed in the plasma of patients with gastrointestinal tumors in a meta-analysis conducted by Lin et al.[48] In addition to this, existing studies have confirmed that PLTs can promote tumor progression in a number of ways.[49] PLT activation leads to the secretion of alpha granule-releasing activators, MP formation and angiogenic phospholipids, molecules that promote endothelial migration, survival and vascular stabilization; and its derived angiogenic factors, which promote the formation of capillary-like structures by mediating cell-to-cell adhesion and interacting with the vascular endothelium, all of which provide a great boost to tumor angiogenesis, which then enhances the invasive and metastatic ability of tumor cells.[50,51]

Our study involved several limitations. First, there was significant heterogeneity in the HR of FIB ($I^2 = 83\%$, $P < 0.05$) and PLT ($I^2 = 90.8\%$, $P < 0.05$). Despite the use of sensitivity analyses and meta-regression, the origin of heterogeneity could not be fully traced. Second, most of the included studies were retrospective in design, of low quality, and subject to recall bias. Third, since the included articles were largely from Asia, and race may be an intrinsic factor influencing the association between coagulation and disease prognosis. Therefore, more basic studies from European countries are needed in the future to better illustrate the correlation between coagulation and the prognosis of gastric cancer. Fourth, for other coagulation factors, their effects on gastric cancer prognosis could not be investigated due to the limited number of eligible ones at the time of the initial literature search for meta-analysis, and a large amount of basic literature is needed to provide support in the future. Finally, since none of the included studies depicted which of the four subtypes the gastric cancer belonged to, it was not possible to demonstrate whether coagulation was affected by the different subtypes. In addition, the detailed mechanisms causing hypercoagulability in gastric cancer patients need to be further investigated, with a view to accurately predicting the prognosis and enhancing the therapeutic effects of gastric cancer patients.

## Conclusion

The meta-analysis observed that increased levels of plasma D-D, FIB, and PLT counts in individuals with gastric cancer serve as risk factors for prognosis, as well as predictors of more advanced TNM stage and increased likelihood of lymph node metastasis. Consequently, future medical practitioners should prioritize early screening of coagulation indices in gastric cancer patients to minimize further complications.

## Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

## Author Contributions

The corresponding author (Prof. Hui Cai) has the right to grant on behalf of all authors. Lihui Zhu contributed to the conception and design of the study; Lihui Zhu and Shuo Liu contributed to the statistical analysis and editing of the manuscript; Shuo Liu and Da Wang contributed to data acquisition; Miao Yu contributed to the interpretation of the data. Hui Cai provided financial support and supervision. All co-authors have seen and agreed with the contents of this research.

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