Systematic Review and Meta-Analysis

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High pretreatment plasma D-dimer levels predict poor prognosis in gastrointestinal cancers

A meta-analysis

Guoyi Rong, MD[a], Wenxin Fan, BD[b], Jian Shen, BD[a,*]

Abstract

Background: High pretreatment plasma D-dimer levels can predict poor prognosis in various types of gastrointestinal carcinomas. Our meta-analysis explored the correlation between plasma D-dimer levels and prognosis in gastrointestinal malignancies.

Methods: Two independent reviewers conducted a comprehensive search from PubMed, ScienceDirect, Embase, Web of Science and the Cochrane Library. All articles evaluating the correlation between pretreatment plasma D-dimer levels and prognosis in gastrointestinal malignancies were searched. We chose overall survival (OS) as the primary survival outcome measure and progression-free survival (PFS), disease-free survival (DFS) and cancer-specific survival (CSS) as the secondary survival outcome measures. We extracted hazard ratios (HRs) and 95% confidence intervals (CIs) from the eligible publications.

Results: We included 30 studies involving 5928 gastrointestinal cancer patients. There was an obvious correlation between high D-dimer levels and poor OS (HR = 2.01, 95% CI = 1.72–2.36, $P < .01$). High plasma D-dimer levels were correlated with shorter PFS (HR = 1.34, 95% CI = 1.05–1.70, $P = .32$), DFS (HR = 1.67, 95% CI = 1.12–2.50, $P < .01$) and CSS rates (HR = 1.93, 95% CI = 1.49–2.49, $P = .66$).

Conclusions: Elevated pretreatment plasma D-dimer levels might help predict poor prognosis in patients with gastrointestinal malignancies.

Abbreviations: CI = confidence interval, OS = overall survival, PFS = progression-free survival, DFS = disease-free survival, CSS = cancer-specific survival, DIC = disseminated intravascular coagulation, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, NOS = Newcastle-Ottawa Scale.

Keywords: clinical value, D-dimer, gastrointestinal carcinoma, meta-analysis, prognosis

1. Introduction

Gastrointestinal cancer, including esophageal cancer, gastric cancer, pancreatic cancer, hepatoma, cholangiocarcinoma and colorectal cancer, is the main type of digestive system neoplasm worldwide.[1] Nearly 30% of carcinoma morbidity and 32% of carcinoma mortality worldwide are attributed to gastrointestinal carcinoma.[2] Gastrointestinal carcinomas pose a dramatic clinical challenge because of their high morbidity and mortality. Patients with gastrointestinal cancers are often already in advanced or terminal stages and show resistance to chemotherapy at the time of diagnosis. In fact, gastrointestinal malignancies can be treated at an early stage.[3] For example, gastroscopy has been indicated to effectively decrease the incidence rate of gastric cancer by approximately 30%.[4] Similarly, colorectal cancer could be prevented by performing regular colonoscopies to find precancerous lesions across the large intestine.[5] The early diagnosis of cancer is crucial because colorectal cancer could be treated if diagnosed early; the American Cancer Society reported dramatic differences in 5-year survival rates between non-metastatic and metastatic colorectal cancer of 90% and 11%, respectively.[6] However, endoscopic techniques are expensive and invasive, thus further limiting the practicality of detecting gastrointestinal cancer by these techniques. Thus, effective, inexpensive and non-invasive biomarkers for patient diagnosis and prognosis need to be discovered.

The inappropriate activation of both coagulation and fibrinolysis is usually discovered in carcinoma patients, especially in patients with metastatic carcinoma.[7–11] Coagulation is the process by which blood changes from liquid to gel and then forms clots. Cancer cells can have significant procoagulant activities, activating the coagulation system and depositing fibrin, therefore causing the phenomenon of coagulation.[12] The formation of a platelet-fibrin-carcinoma cell offers an extracellular microenvironment to promote carcinoma cell proliferation and survival.

D-dimer is the product of fibrin degradation and is composed of 2 cross-linked D fibrin fragments.[13] Some studies have reported that pretreatment plasma D-dimer levels are obviously

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increased in patients with various carcinomas, including nasopharyngeal carcinoma, lung cancer, breast cancer and cervical cancer.[14–17] The association between elevated plasma D-dimer levels and poor survival outcomes is also observed in gastrointestinal carcinomas, such as esophageal carcinoma, gastric cancer, pancreatic carcinoma, hepatoma, cholangiocarcinoma and colorectal cancer.[18–47] However, no systematic studies have identified the prognostic significance of D-dimer in gastrointestinal carcinomas. Thus, the aim of our systematic review and meta-analysis was to assess the prognostic significance of D-dimer levels in gastrointestinal carcinomas.

2. Materials and methods

2.1. Search strategy

This meta-analysis was strictly conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[48] Two independent reviewers conducted a comprehensive electronic search to find eligible studies in ScienceDirect, PubMed, Embase, Web of Science and the Cochrane Library dating up to July 5, 2018. The key terms of this analysis included "D-dimer" or "D-dimer" and "tumor" or "cancer" or "carcinoma" or "neoplasm" and "prognosis" or "survival" from 2001 to 2018. The search outcomes were restricted to human research published in English.

2.2. Inclusion and exclusion criteria

The inclusion criteria of our analysis were as follows:

1. clinical studies about the association between D-dimer levels and prognosis in gastrointestinal tumors;
2. outcome indicators including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) or cancer-specific survival (CSS); and
3. data on hazard ratios (HRs) and 95% confidence intervals (CIs) or survival curves.

The exclusion criteria of this analysis were as follows:

1. the same studies published more than once;
2. animal studies;
3. non-English articles;
4. reviews, case reports, conference abstracts, letters and meta-analyses; and
5. unavailable HR and 95% CI or survival curve data.

There independent researchers (Guoyi Rong, Wenxin Fan, and Jian Shen) evaluated all titles and abstracts of the eligible studies to identify duplicated data and irrelevant records. If the included study was not identified by the abstract, the full publication was read. Any disagreements were settled by discussion to reach a consensus.

2.3. Data extraction

All information was extracted from the included studies by 2 independent investigators (Guoyi Rong and Jian Shen). The survival outcomes were extracted, including OS, PFS, DFS, CSS, and HRs with 95% CIs or survival curves with *P* values. Other data from these studies were also collected: first author, research institute, publication year, country, research design, patient number, patient age, follow-up period, survival analysis models, cancer stage, cancer site, cut-off value, detection method, and therapy.

2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the eligible studies by 2 independent investigators (Guoyi Rong and Jian Shen).[49] An assessment of every study was performed in 3 parts, including the selection, comparability and outcomes of the study.

2.5. Statistical analysis

We carried out this meta-analysis by employing R software (version 3.50) (https://www.r-project.org/). We regarded OS as the primary outcome in our research, while PFS, DFS and CSS were regarded as the secondary outcomes. HRs with 95% CIs were directly extracted from every study. If a study provided only survival curves, data would be assessed by employing the Engauge Digitizer software (version 4.1).[50,51] The prognostic significance of plasma D-dimer levels in patients with gastrointestinal tumors was assessed by HRs and 95% CIs. HRs > 1 predicted poor prognosis in patients with high serum D-dimer levels. HRs < 1 frequently implied a favorable prognosis in patients with increased serum D-dimer levels. The statistical heterogeneity of the eligible studies was calculated by Q-test and the I^2 statistic. When heterogeneity was nonsignificant ($P \geq .10$, I^2 value $<50\%$), a fixed effect model was employed; however, if there was significant heterogeneity, a random effects model was employed and a subgroup analysis was conducted to find the sources of heterogeneity. Subgroup analyses were stratified by

1. tumor site;
2. country (Asian, non-Asian);
3. therapy;
4. detection method;
5. D-dimer cut-off value;
6. HR estimation; and
7. the HRs provided from the study.

In addition, we employed sensitivity analyses to identify each study's influence on the pooled effect by sequentially eliminating one study at a time. Simultaneously, a meta-regression was carried out to evaluate whether any relevant variables impacted the pooled effect size for OS, PFS, DFS, and CSS. Publication bias was assessed by Begg funnel plots.

3. Results

3.1. Literature search

The flowchart for the selection of literature is shown in Figure 1. A total of 1152 publications were first confirmed following our search scheme. After excluding duplicate studies, a total of 901 studies were included. Animal research, reviews, case reports, conference abstracts, letters and meta-analyses were removed after screening the titles and abstracts of each article. Then, 43 included studies were evaluated in full text. After further inspection, 13 studies were removed, of which HRs could not be extracted from 3 studies, and 10 were missing relevant outcome indicators. Finally, 30 studies involving 5928 patients were included in our research.

3.2. Study characteristics

The main features of the eligible studies are listed in Table 1. All eligible articles were published between 2001 and 2018. Fourteen

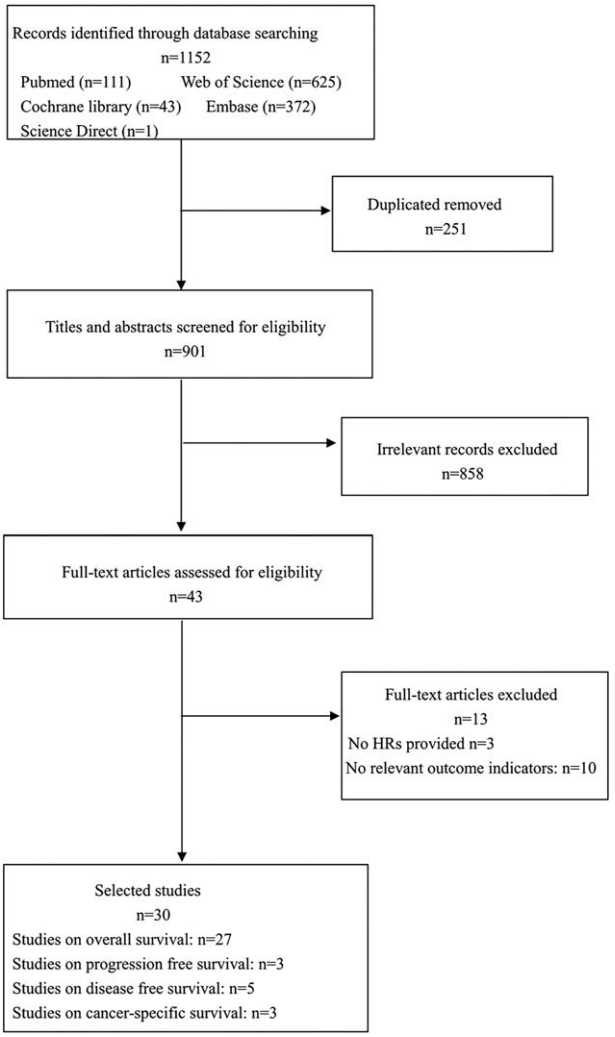

Figure 1. Flowchart of search strategy in the meta-analysis.

studies acquired data retrospectively, while the remaining studies applied a prospective research design. The D-dimer levels were tested by immunoturbidimetry, enzyme-linked immunosorbent assay (ELISA), latex agglutination test or enzyme-linked immunofiltration assay (ELIFA). Of all the eligible studies, 5 publications reported on esophageal tumors (n = 5),[21,27,39,41,45] 4 on gastric cancer (n = 4),[22,32,46,47] 4 on pancreatic cancer (n = 4),[18,23,34,35] 1 on hepatoma (n = 1),[36] 1 on cholangiocarcinoma (n = 1),[29] and 15 on colorectal cancer (n = 15).[19,20,24–26,28,30,31,33,37,38,40,42–44] Twenty-seven studies used OS, 3 studies employed PFS, 5 studies employed DFS and 3 studies employed CSS as the survival outcomes. The quality assessment of each included article measured by NOS is shown in Table 2.

3.3. Primary outcome: overall survival

Twenty-seven studies involving 5446 patients provided appropriate information about OS analysis. The results indicated that elevated pretreatment D-dimer levels were predictive of shorter OS in a random effects model (HR = 2.01, 95% CI = 1.72–2.36) with significant heterogeneity among the studies ($I^2 = 67\%$, $P < .01$) (Fig. 2A).

The stability of our result was verified through a sensitivity analysis that employed a model in which 1 study was removed at a time. The observed effect size (multivariable adjusted HR) of OS was not dramatically influenced when a certain study was removed in every round (Fig. 2B).

3.4. Subgroup analysis

3.4.1. Tumor site. We performed subgroup analyses on the basis of the cancer site. As shown in Figure 3A, we found that the highest prognostic significance of high D-dimer levels on OS was in hepatoma (HR = 3.13, 95% = 1.41–6.94), followed by colorectal cancer (HR = 2.24, 95% CI = 1.73–2.88), gastric cancer (HR = 2.02, 95% CI = 1.51–2.71), pancreatic cancer (HR = 1.69, 95% CI = 1.35–2.10) and esophageal cancer (HR = 1.69, 95% CI = 1.01–2.82). High heterogeneity was discovered among the studies on colorectal tumors ($I^2 = 78\%$, $P < .01$) and esophageal cancer ($I^2 = 74\%$, $P < .01$).

3.4.2. Asian and non-Asian countries. Ten publications originated from Europe and America (Denmark, Turkey, Italy, and America), and seventeen originated from Asia (China, Japan, South Korea, and North Korea). When we conducted a subgroup analysis of patients' countries, we found a dramatic correlation between high D-dimer values and poor OS in patients from Asian (HR = 2.01, 95% CI = 1.64–2.46) and non-Asian countries (HR = 2.02, 95% CI = 1.55–2.63) (Fig. 3B).

3.4.3. Therapies. The main therapies in the included studies were surgery, non-surgery, and mixed therapy (chemotherapy and surgery). Since therapies might affect prognosis, we employed subgroup analysis to further study the prognostic significance of D-dimer levels. The HR and 95% CI for OS were 2.07 [1.71, 2.50] in the surgery group, 1.92 [1.31, 2.82] in the non-surgery group, and 1.95 [1.35, 2.80] in the mixed therapy group (Fig. 3C).

3.4.4. Detection methods. The detection methods used in the eligible studies were immunoturbidimetry assay, ELISA, latex agglutination assay, ELIFA and unknown. Because detection methods might affect prognosis, we conducted subgroup analysis to further identify the prognostic significance of D-dimer levels. The HR and 95% CI for OS were 2.10 [1.59, 2.79] for the immunoturbidimetry assay, 1.99 [1.70, 2.34] for ELISA, 2.83 [1.11, 7.24] for the latex agglutination assay, 2.28 [1.36, 3.82] for ELIFA, and 1.78 [1.24, 2.54] for unknown method used (Fig. 3D).

3.4.5. Other groups. We also divided the studies according to a cut-off value (cut-off $\geq$ 600 ng/ml or $<$ 600 ng/ml), the HR estimation (HR and 95% CI or survival curves) and the HRs provided from multivariate analysis or univariate analysis groups. We discovered that the HR and 95% CI for OS in the cut-off $\geq$600 group was 1.76 [1.42, 2.19] and in the cut-off $<$600 group was 2.17 [1.89, 2.50]. In the HR and 95% CI and survival curve groups, the HRs and 95% CI for OS were 1.98 [1.66, 2.36] and 2.30 [1.46, 3.64], respectively. We also discovered that the HR and 95% CI for OS in the multivariate analysis was 1.97 [1.62, 2.39] and for the univariate analysis was 2.12 [1.62, 2.78] (Fig. 4).

The results of the subgroup analysis for OS are shown in Table 3.

3.4.6. Publication bias. We employed Begg funnel plot to inspect publication bias. The result indicated no publication bias and was statistically significant (Fig. 2C).

Table 1

Main characteristic of the included studies in the meta-analysis.

Author	Country	Research Design	Stage	Disease Site	Case No.	Age (yr) Median/ mean(range)	Follow-up Median months (range)	Cut-off	Detection Method	Outcome	HRs provided from	HR estimation
Sun[22]	China	Retrospective	I–IV	Pancreatic cancer	139	58.9 (3–80)	12	598.57 ng/ml	ITM	OS	MV	HR and 95% CI
Lee[23]	South Korea	Prospective	I–IV	CRC	170	63 (28–84)	72	1400 ng/ml	ITM	OS	UV	Survival curves
Stender[24]	Denmark	Prospective	I–IV	CRC	157	68 (33–94)	12	300 ng/ml	ITM	OS	MV	HR and 95% CI
Zhang[25]	China	Retrospective	I–III	Esophageal cancer	468	60 (36 - 81)	49.1(3.2–114.5)	207 ng/ml	NA	OS, DFS	MV	HR and 95% CI
Liu[26]	China	Prospective	I–IV	Gastric cancer	247	58.47(NA)	37.0 (1–84)	1465 ng/ml	ELIFA	OS	MV	HR and 95% CI
Liu[27]	China	Retrospective	I–IV	Pancreatic cancer	168	61(34–83)	14 (3–48)	500 ng/ml	ITM	OS	MV	HR and 95% CI
Pedrazzani[28]	Italy	Prospective	NA	CRC	199	67.6(26–94)	48	250 ng/ml	ITM	OS	UV	Survival curves
Sunesen[29]	Denmark	Prospective	NA	CRC	166	NA	60	NA	NA	OS	MV	HR and 95% CI
Hong[30]	China	Prospective	NA	CRC	505	63 (27–93)	43(4–62)	216 ng/ml	ITM	OS	MV	HR and 95% CI
Diao[31]	China	Prospective	I–IV	Esophageal cancer	66	NA(38–78)	36	1100 ng/ml	ITM	OS	MV	HR and 95% CI
Tellioglu[32]	USA	Prospective	IV	CRC	242	63(NA)	22 (NA)	1000 ng/ml	NA	OS, DFS	MV	HR and 95% CI
Watanabe[33]	Japan	Retrospective	I–IV	Cholangiocarcinoma	55	NA(36–84)	50	1300 ng/mL	NA	CSS	UV	Survival curves
Blackwell[34]	USA	Prospective	IV	CRC	104	61 (23–85)	30	133.2 ng/ml	ITM	OS, PFS	MV	HR and 95% CI
Tekesin[35]	Turkey	Prospective	I–IV	CRC	134	62.5(31–84)	18(4–31)	960 ng/ml	ELISA	OS	UV	HR and 95% CI
Diao[36]	China	Prospective	IIIB–IV	Gastric cancer	41	NA(40–83)	25	1500 ng/ml	ELISA	OS	UV	Survival curves
Watanabe[37]	Japan	Retrospective	I–IV	CRC	90	NA(38–83)	50	600 ng/ml	NA	CSS	MV	HR and 95% CI
Stender[38]	Denmark	Prospective	I–IV	Pancreatic cancer	95	68 (53–85)	36	1000 ng/ml	ITM	OS	MV	HR and 95% CI
Cao[39]	China	Retrospective	I–II	Pancreatic cancer	119	NA	60(3–60)	500 ng/ml	ELISA	OS, PFS	UV	Survival curves
Liu[40]	China	Retrospective	I–IV	Hepatoma	192	59 (39–83)	46(NA)	700 ng/ml	ELISA	OS	MV	HR and 95% CI
Zhu[41]	China	Retrospective	IV	CRC	74	55.5(31–74)	18.4 (6.3–30.4)	1900 ng/ml	ITM	OS, PFS	MV	HR and 95% CI
Oya[42]	Japan	Retrospective	I–IV	CRC	93	61.8(38–85)	54.7(NA)	850 ng/ml	LatexAssay	OS	UV	Survival curves
Li[43]	China	Retrospective	I–IV	Esophageal cancer	294	58(38–70)	120	500 ng/ml	LEIA	OS,DFS	MV	HR and 95% CI
Yamamoto[44]	Japan	Retrospective	IV	CRC	42	NA	14.1(NA)	5000 ng/ml	ELISA	OS	MV	HR and 95% CI
Feng[45]	China	Retrospective	I–IV	Esophageal cancer	337	59.0(36–80)	60	500 ng/ml	ITM	CSS	MV	HR and 95% CI
Kilic[46]	Turkey	Prospective	I–IV	CRC	51	60.9(29–80)	20(NA)	375 ng/ml	ELISA	OS	UV	Survival curves
Motavaf[47]	Denmark	Prospective	NA	CRC	166	69 (38–94)	60(NA)	300 ng/ml	ITM	OS	UV	HR and 95% CI
Sunesen[48]	Denmark	Prospective	I–III	CRC	166	NA	NA	300 ng/ml	ITM	OS	MV	HR and 95% CI
Liu[49]	China	Retrospective	I–IV	Esophageal cancer	260	59(39–83)	35 (1–91)	500 ng/ml	ITM	OS, DFS	MV	HR and 95% CI
Go[50]	Korea	Retrospective	IV	Gastric cancer	46	64(50–78)	16.2 (2.2–25.8)	1500 ng/ml	ITM	OS	MV	HR and 95% CI
Diao[51]	China	Retrospective	I–IV	Gastric cancer	1042	NA(22–88)	25	1500 ng/ml	ITM	OS, DFS	MV	HR and 95% CI

CRC =i colorectal cancer, ITM =i immunoturbidimetry, NA =i not available, MV=i multivariate analysis, UV=i univariate anlysis.

Table 2

Quality assessment of included articles.

Author	Source	Selection				Comparability	Outcome			Score
		1	2	3	4	1	1	2	3	
Sun, 2015	Cochrane Library	1	1	1	1	1	1	0	1	7
Lee, 2017	Cochrane Library	1	0	1	1	0	1	0	0	4
Stender, 2012	Cochrane Library	0	0	1	1	0	1	1	1	5
Zhang, 2016	Embase	1	0	1	1	0	1	1	1	6
Liu, 2014	Embase	1	0	1	1	0	1	1	0	5
Liu, 2015	Embase	1	0	1	1	0	1	1	0	5
Pedrazzani, 2010	Embase	1	0	1	1	0	1	1	0	5
Sunesen, 2011	Embase	1	0	1	1	0	1	1	0	5
Hong, 2017	Embase	1	0	1	1	0	1	1	1	6
Diao, 2013	Embase	1	0	1	1	0	1	1	1	6
Tellioglu, 2012	Embase	0	0	1	1	0	1	1	0	4
Watanabe, 2016	PubMed	1	0	1	1	0	1	1	0	5
Blackwell, 2004	PubMed	0	0	1	1	0	1	1	0	4
TekeGin, 2016	PubMed	1	0	1	1	0	1	1	1	6
Diao, 2017	PubMed	1	0	1	1	0	1	1	1	6
Watanabe, 2018	PubMed	1	0	1	1	0	1	1	0	5
Stender, 2016	PubMed	1	0	1	1	0	1	1	1	6
Cao, 2017	PubMed	1	1	1	1	1	1	1	0	7
Liu, 2017	PubMed	1	1	1	1	1	1	1	0	7
Zhu, 2014	PubMed	1	0	1	1	0	1	1	1	6
Oya, 2001	PubMed	1	1	1	1	1	1	1	1	8
Li, 2017	PubMed	1	0	1	1	0	1	1	0	5
Yamamoto, 2012	PubMed	1	0	1	1	0	1	1	1	6
Feng, 2016	PubMed	1	0	1	1	0	1	1	0	5
Kilic, 2007	PubMed	1	0	1	1	0	1	1	0	5
Motavaf, 2014	PubMed	1	0	1	1	0	1	1	0	5
Sunesen, 2012	SicenceDirect	1	0	1	1	0	1	1	0	5
Liu, 2016	Web of Science	1	0	1	1	0	1	1	0	5
Go, 2015	Web of Science	1	0	1	1	0	1	1	0	5
Diao, 2014	Web of Science	1	0	1	1	0	1	1	0	5

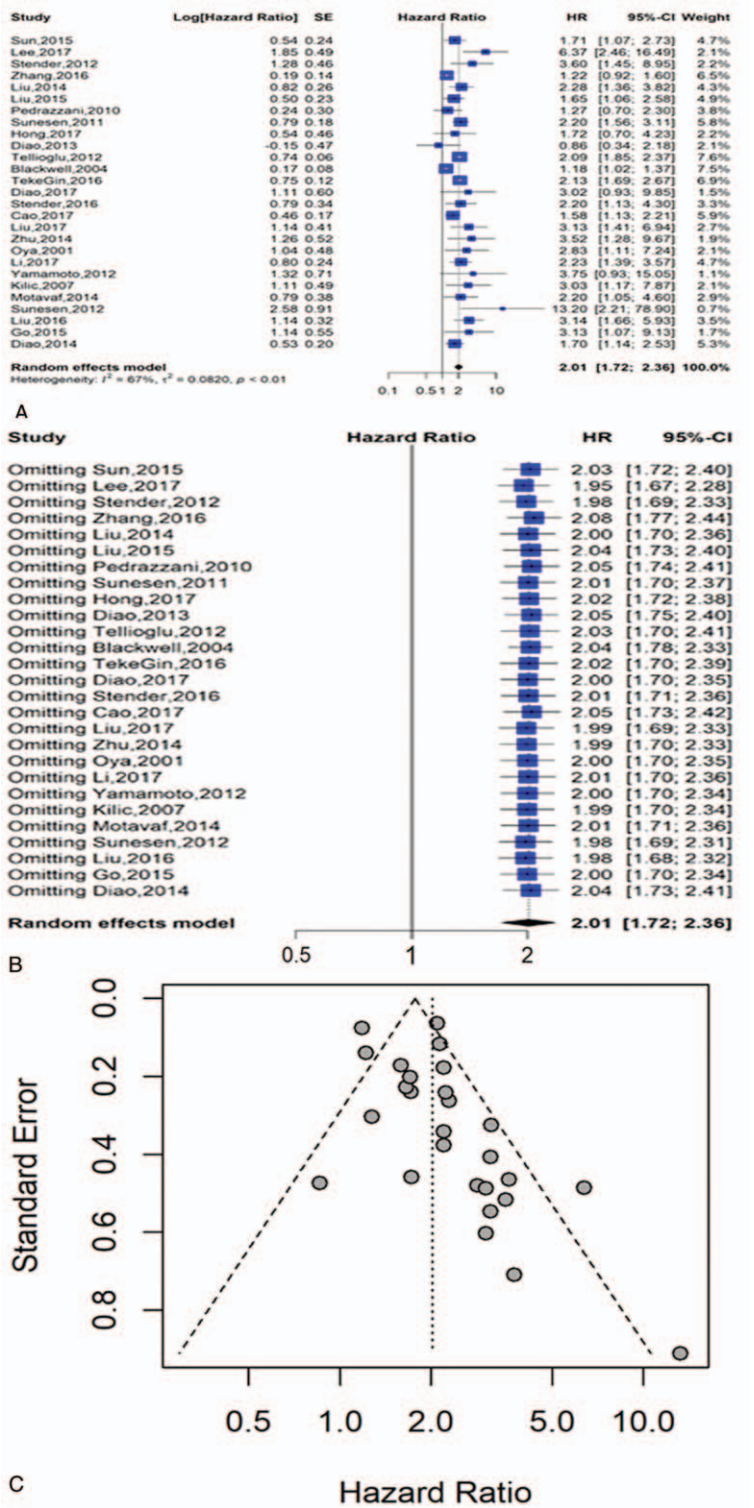

Figure 2. Analysis for overall survival; (A) forest plots of hazard ratios for overall survival; (B) sensitivity analysis of all eligible publications for overall survival; (C) funnel plot of publication bias in the meta-analysis.

3.4.7. Secondary outcome: progression-free survival, disease-free survival and cancer-specific survival. Three studies involving 294 patients provided appropriate data for PFS analysis. The results indicated that elevated pretreatment D-dimer levels predicted shorter PFS in a fixed effects model (HR = 1.34, 95% CI = 1.05–70) with significant heterogeneity among the studies (I^2 = 12%, P = .32) (Fig. 5A).

Five studies involving 2306 patients provided appropriate information for DFS analysis. The results indicated that a high D-dimer level predicted poor DFS in a random effects model

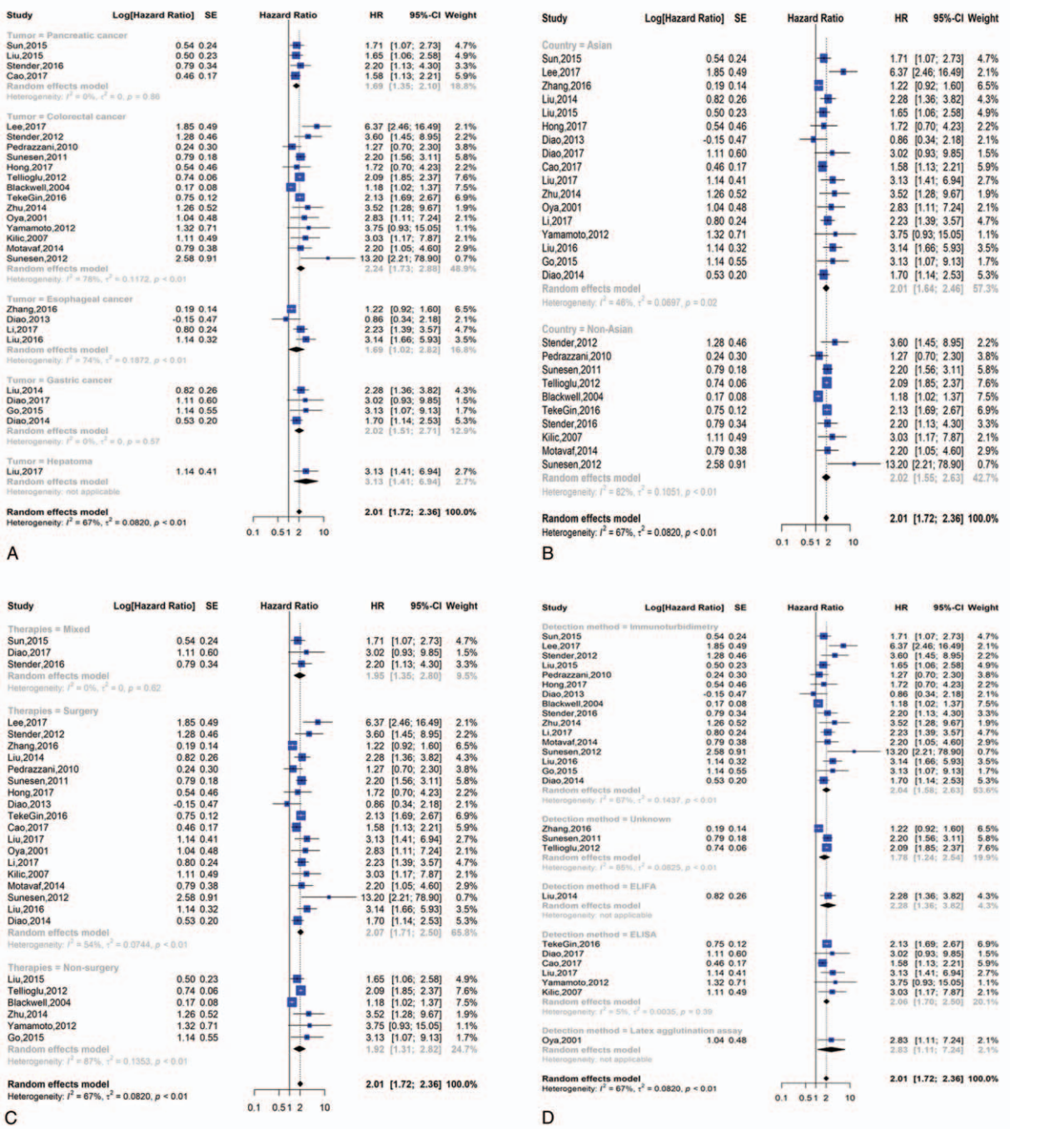

Figure 3. Subgroup analysis of overall survival; (A) forest plot of tumor site; (B) forest plot of countries; (C) forest plot of therapies; (D) forest plot of detection methords.

(HR = 1.67, 95% CI = 1.12–2.50) with nonsignificant heterogeneity among the studies (I^2 = 84%, P < .01) (Fig. 5B).

Five studies involving 482 patients provided appropriate information for CSS analysis. As Figure 5C shows, the HR and 95% CI for CSS was 1.93 [1.49–2.49].

The stability of our result was verified through a sensitivity analysis that employed a model in which 1 study was removed at a time. The observed effect sizes (multivariable adjusted HR) of PFS, DFS, and CSS were not dramatically impacted when 1 study was removed in every round (Fig. 6). PFS and CSS did not require subgroup analysis because there were 3 eligible articles about PFS and CSS.

3.5. Subgroup analysis

3.5.1. Tumor site. We performed subgroup analyses on the basis of the cancer site. As Figure 7A shows, we found that the highest prognostic significance of high D-dimer levels on DFS was in gastric carcinoma (HR = 2.44, 95% CI = 1.63–3.65), followed by esophageal cancer (HR = 1.81, 95% CI = 1.10–2.98) and colorectal carcinoma (HR = 0.95, 95% CI = 0.71–1.26). High

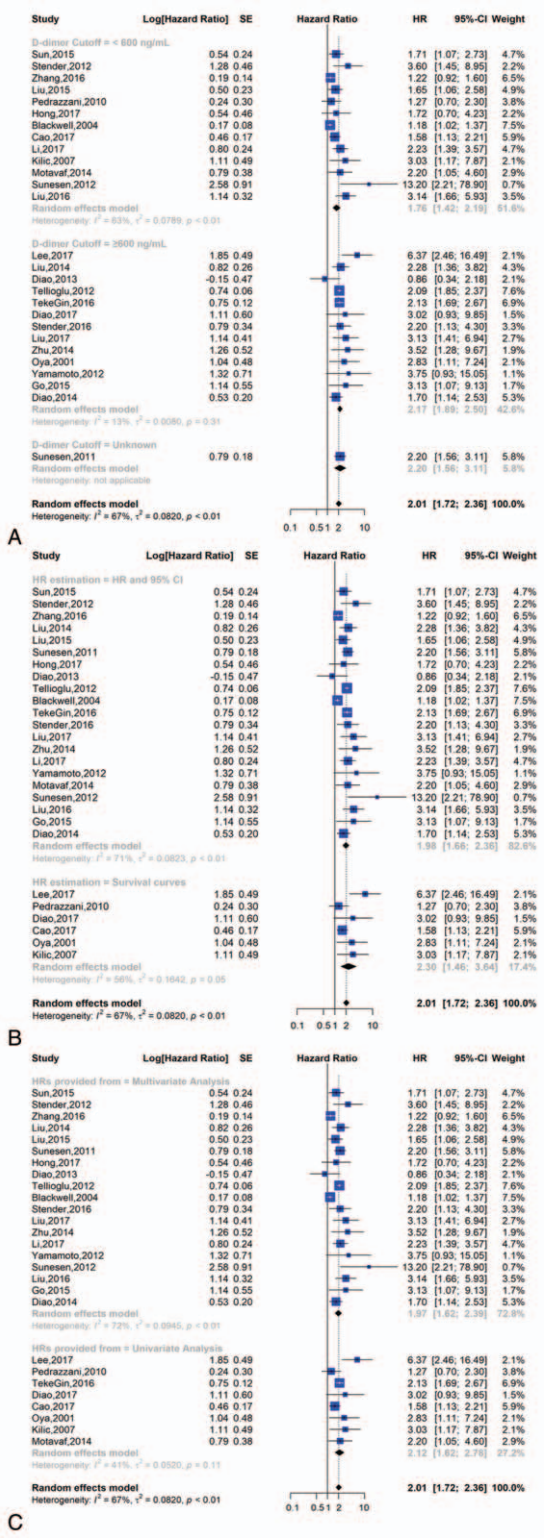

Figure 4. Subgroup analysis of overall survival; (A) forest plot of D-dimer cut-off value; (B) forest plot of HR estimation; (C) forest plot of HRs provided from.

heterogeneity was discovered among the studies on esophageal tumors ($I^2 = 84\%$, $P < .01$).

3.5.2. Asian and non-Asian countries. One report originated from America, and 4 originated from Asia. When we conducted a subgroup analysis of patients' countries, we found a dramatic correlation between high D-dimer values and poor DFS in both Asian (HR = 1.94; 95% CI = 1.29–2.93) and non-Asian countries (HR = 0.95; 95% CI = 0.71–1.26) (Fig. 7B).

3.5.3. Therapies. The main therapies in the included studies were surgery and non-surgery. Since therapies might affect prognosis, we employed subgroup analysis to further identify the prognostic significance of D-dimer levels. The HR and 95% CI for DFS were 1.94 [1.29, 2.93] in the surgery group and 0.95 [0.71, 1.26] in the non-surgery group (Fig. 7C).

3.5.4. Detection method. The main detection methods in the eligible studies were immunoturbidimetry assays and unknown. Because detection methods might affect prognosis, we performed subgroup analysis to further identify the prognostic significance of D-dimer levels. The HR and 95% CI for DFS were 2.33 [1.82, 2.98] for the immunoturbidimetry assay and 1.06 [0.86, 1.32] for the unknown methods used (Fig. 7D).

3.5.5. Other groups. We also divided the studies according to a cut-off value (cut-off ≥600 ng/ml or <600 ng/ml), the HR estimation (HR and 95% CI or survival curves) and the HRs provided by multivariate analysis or univariate analysis. We discovered that the HR and 95% CI for DFS in the cut-off ≥600 group was 1.50 [0.60, 3.80] and in the cut-off <600 group was 1.81 [1.10, 2.98]. In the HR and 95% CI and survival curve groups, the HRs and 95% CIs for DFS were 1.58 [0.99, 2.54] and 2.09 [1.43, 3.05], respectively. We also discovered that the HR and 95% CI for DFS in the multivariate analysis was 1.58 [0.99, 2.54] and in the univariate analysis was 2.09 [1.43, 3.05] (Fig. 8).

The results of the subgroup analysis for DFS are shown in Table 4.

3.6. Publication bias

We employed Begg funnel plot to inspect publication bias. The result indicated no publication bias and was statistically significant (Fig. 9).

4. Discussion

In this study, we assessed the correlation between poor survival outcomes and pretreatment plasma D-dimer levels in gastrointestinal cancers. The HR and 95% CI for OS were 2.01 [1.72–2.36]. The correlation between shorter secondary outcomes (PFS, DFS, and CSS) and elevated pretreatment plasma D-dimer levels was in accordance with that of OS with all HRs >1. This finding demonstrates that the D-dimer level is an adverse factor of prognosis for gastrointestinal carcinoma patients. The outcomes regarding the prognostic significance of D-dimer levels (OS, PFS, DFS, and CSS) were robust after sensitivity analysis, indicating that the HRs were not dramatically influenced by any individual study. In the subgroup analysis of OS, the adverse prognostic effects of elevated D-dimer levels were still significant with different tumor sites, different countries, different therapies, various detection methods, different cut-off values, different HR estimations and different HRs provided from the studies. We believe that our research is beneficial in determining the significance of the prognostic value of plasma D-dimer levels in gastrointestinal cancers.

To the best of our knowledge, our research was the first study that employed prognostic publications on all gastrointestinal

Table 3

Pooled multivariable-adjusted HRs for OS according to subgroup analyses.

Subgroup	Studies	Cases	Heterogeneity (I^2)	Pool HR	95%CI	*P*	*P* for subgroup differences
HRs provided from							.6641
Multivariate Analysis	19	4473	72.3%	1.97	1.62–2.39	<.0001	
Univariate Analysis	8	973	40.9%	2.12	1.62–2.78	<.0001	
HR estimation							.5396
HR and 95% CI	21	4892	70.7%	1.98	1.66–2.36	<.0001	
Survival curves	6	554	55.8%	2.30	1.46–3.64	.0003	
Country							.9901
Asian	17	3966	46.3%	2.01	1.64–2.46	<.0001	
Non-Asian	10	1480	82.0%	2.01	1.55–2.63	<.0001	
Detection methord							.8606
ELIFA	1	247	NA	2.28	1.36–3.82	.0017	
ELISA	7	579	0.0%	1.99	1.70–2.34	<.0001	
ITM	15	3651	69.0%	2.10	1.59–2.79	<.0001	
Latex text	1	93	NA	2.83	1.11–7.24	.0299	
NA	3	876	84.7%	1.78	1.24–2.54	.0016	
D-dimer Cut-off (600 = median)							.2619
<600 ng/mL	13	2796	62.8%	1.76	1.42–2.19	<.0001	
≥600 ng/mL	13	2484	13.3%	2.17	1.89–2.50	<.0001	
NA	1	166	NA	2.20	1.56–3.11	<.0001	
Therapies							.9239
Mixed	3	275	0.0%	1.95	1.35–2.80	.0004	
Surgery	18	4495	54.2%	2.07	1.71–2.50	<.0001	
Non-surgery	6	676	87.0%	1.92	1.31–2.82	.0009	

CI = confidence interval, HR = hazard ratio, ITM = immunoturbidimetry.

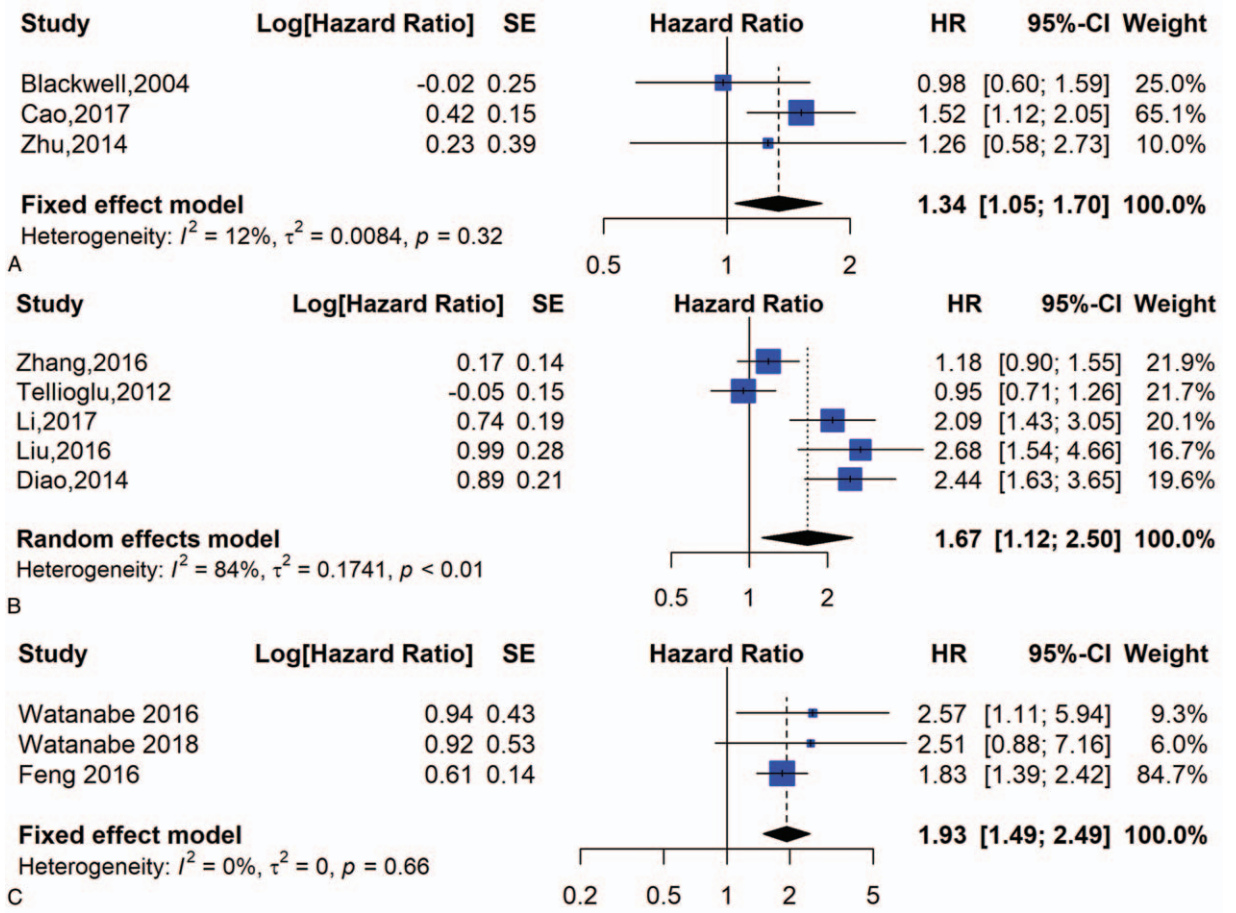

Figure 5. Forest plot of PFS, DFS and CSS; (A) forest plots of hazard ratios for PFS; (B) forest plots of hazard ratios for DFS; (C) forest plots of hazard ratios for CSS.

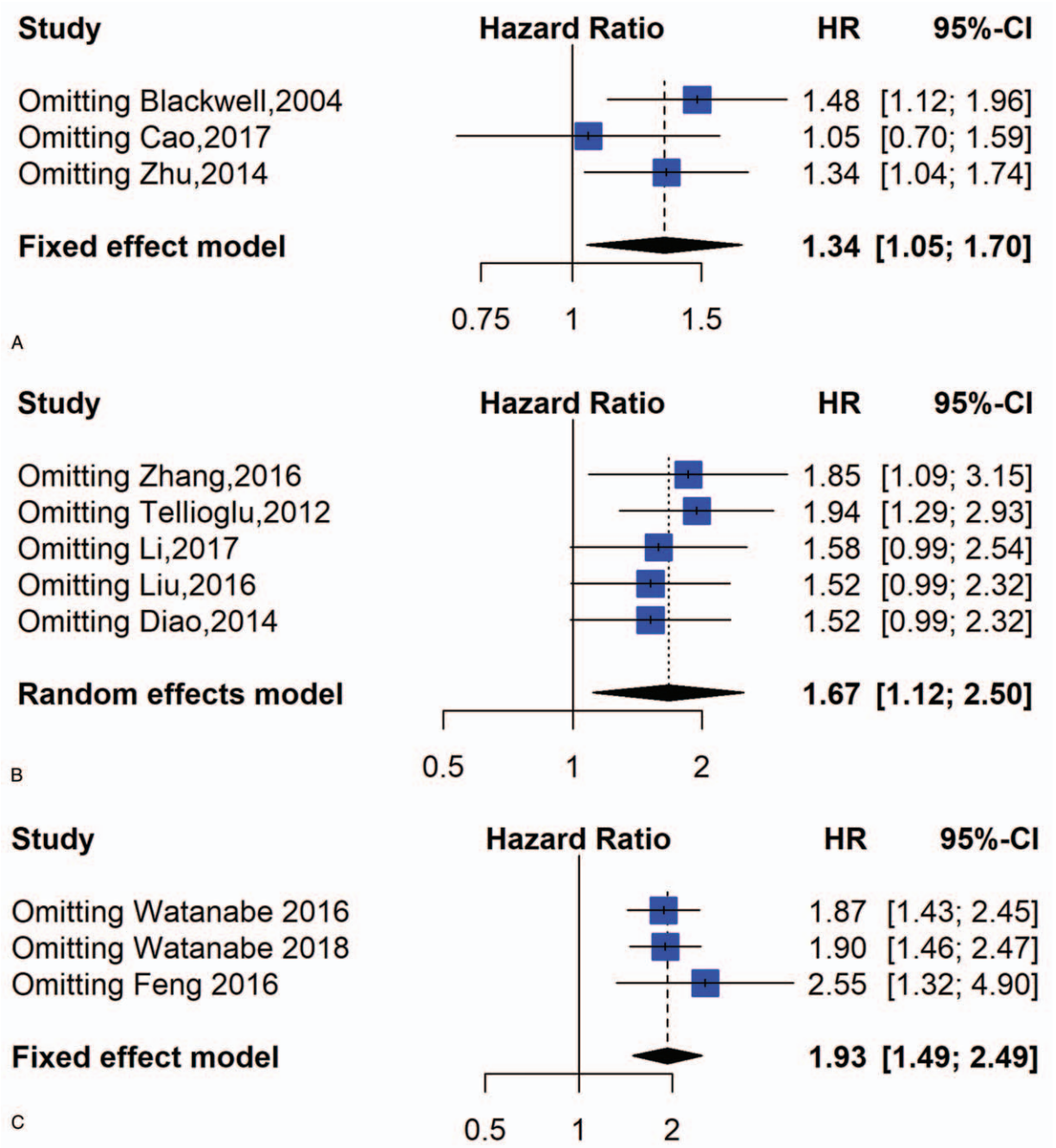

Figure 6. Sensitivity analysis of PFS, DFS and CSS; (A) Sensitivity analysis for PFS; (B) Sensitivity analysis for DFS; (C) Sensitivity analysis for CSS.

carcinomas to identify the prognostic significance of pretreatment plasma D-dimer levels. We employed only HR rather than OR or relative risks (RRs) to evaluate the significance of prognosis because the latter 2 parameters are not credible or are difficult to interpret. Moreover, we included only studies that had data on pretreatment D-dimer levels and HRs. For these reasons, our study may be unique from others, and the quality and credibility of our research are guaranteed.

There are some defects in the carcinoma prognostic evaluation system, such that patients with the same TNM stage frequently have disparate prognoses. D-dimer is a kind of easily available, routinely measured molecular biomarker. In addition, some studies have reported that pretreatment plasma D-dimer levels are dramatically increased in patients with various carcinomas.[14–17] Thus, D-dimer levels could be used as a complementary biomarker to increase the accuracy of prognosis estimations.

Although the exact mechanism by which D-dimer influences survival outcomes is still unclear, some publications postulated that D-dimer affects carcinoma patients' survival outcome by means of the formation of venous thromboembolisms (VTEs). VTEs are a common complication in malignancies.[52] Nevertheless, Ay et al[53] reported that D-dimers and VTEs are independent of each other regarding the poor survival outcomes of carcinoma patients.

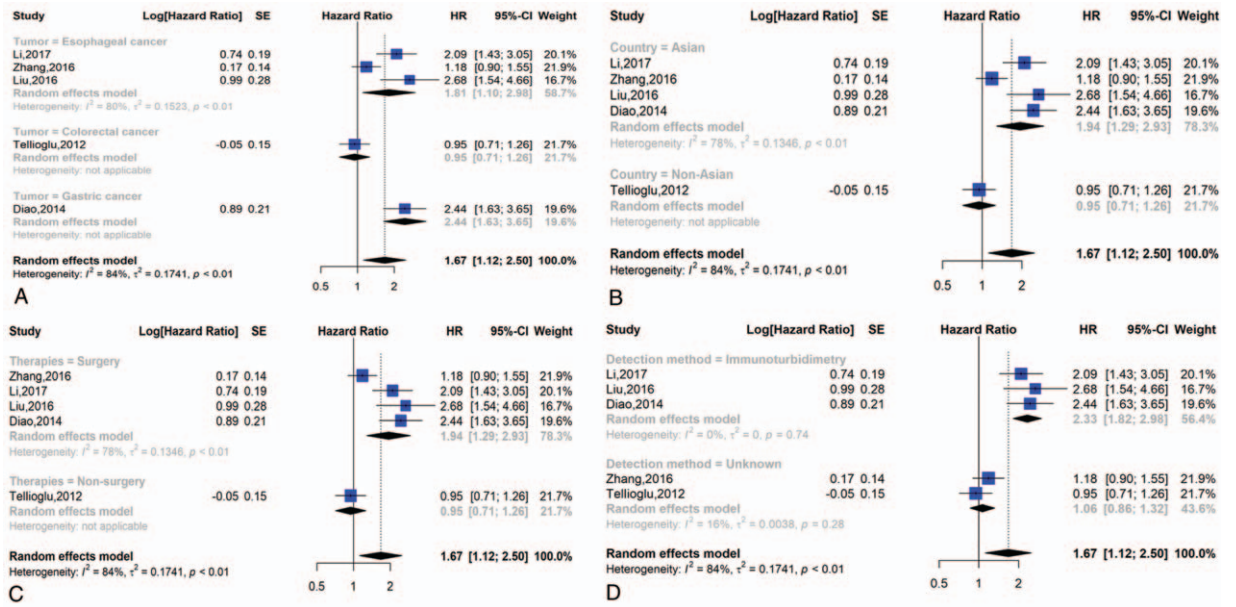

Figure 7. Subgroup analysis of DFS; (A) forest plot of tumor site; (B) forest plot of countries; (C) forest plot of therapies; (D) forest plot of detection methords.

The unfavorable survival outcome of carcinoma patients is consistent with metastasis and angiogenesis. Fibrin remodeling is involved in multiple processes of metastasis and has been proven to play a significant role in angiogenesis.[54] D-dimer is a sensitive biomarker of the fibrinolytic process. Some clinical trials involving carcinomas that could activate the coagulation system indicate that high D-dimer levels could be related to advanced tumor stage and unfavorable survival outcomes.[55–57] The effect of the mechanism by which D-dimer affects the progression of malignant tumors needs to be determined in further studies.

Although our research provides a more persuasive conclusion that D-dimer levels can be used as a method for predicting the survival outcome of gastrointestinal cancer patients, certain inevitable limitations should be taken into consideration:

1. some HR estimations could be extracted directly, while other HR estimations were extracted from the survival curve, and these were jointly incorporated to guarantee data integrity. We intensively deliberated the calculations of each publication 3 times through the above methods to avoid using unreasonable outcomes.
2. Some studies provided low-quality data with a short follow-up period.
3. The cut-off value that determined high and low D-dimer levels varied among the eligible studies, which enhanced the difficulty of performing a pooled study.

Table 4

Pooled multivariable-adjusted HRs for DFS according to subgroup analyses.

subgroup	Studies	Cases	Heterogeneity (I^2)	Pool HR	95%CI	*P*	*P* for subgroup differences
HRs provided from							.3681
Multivariate Analysis	4	2012	85.6%	1.58	0.99–2.54	.0559	
Univariate Analysis	1	294	NA	2.09	1.43–3.05	.0001	
HR estimation							.3681
HR and 95% CI	4	2012	85.6%	1.58	0.99–2.54	.0559	
Survival curves	1	294	NA	2.09	1.43–3.05	.0001	
Country							.0052
Asian	4	2064	77.9%	1.94	1.29–2.93	.0016	
Non-Asian	1	242	NA	0.95	0.71–1.26	.7155	
Disease							<.0001
Immunoturbidimetry	3	1596	0.0%	2.33	1.82–2.98	<.0001	
NA	2	710	15.70%	1.06	0.86–1.32	.5765	
D-dimer Cut-off (600 = median)							.7332
<600 ng/mL	13	2921	62.8%	1.76	1.42–2.19	<.0001	
≥600 ng/mL	13	2484	13.3%	2.17	1.89–2.50	<.0001	
Therapies							.0052
Surgery	4	2064	77.9%	1.94	1.29–2.93	.0016	
Non-surgery	1	242	NA	0.95	0.71–1.26	.7155	

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, ITM = immunoturbidimetry.

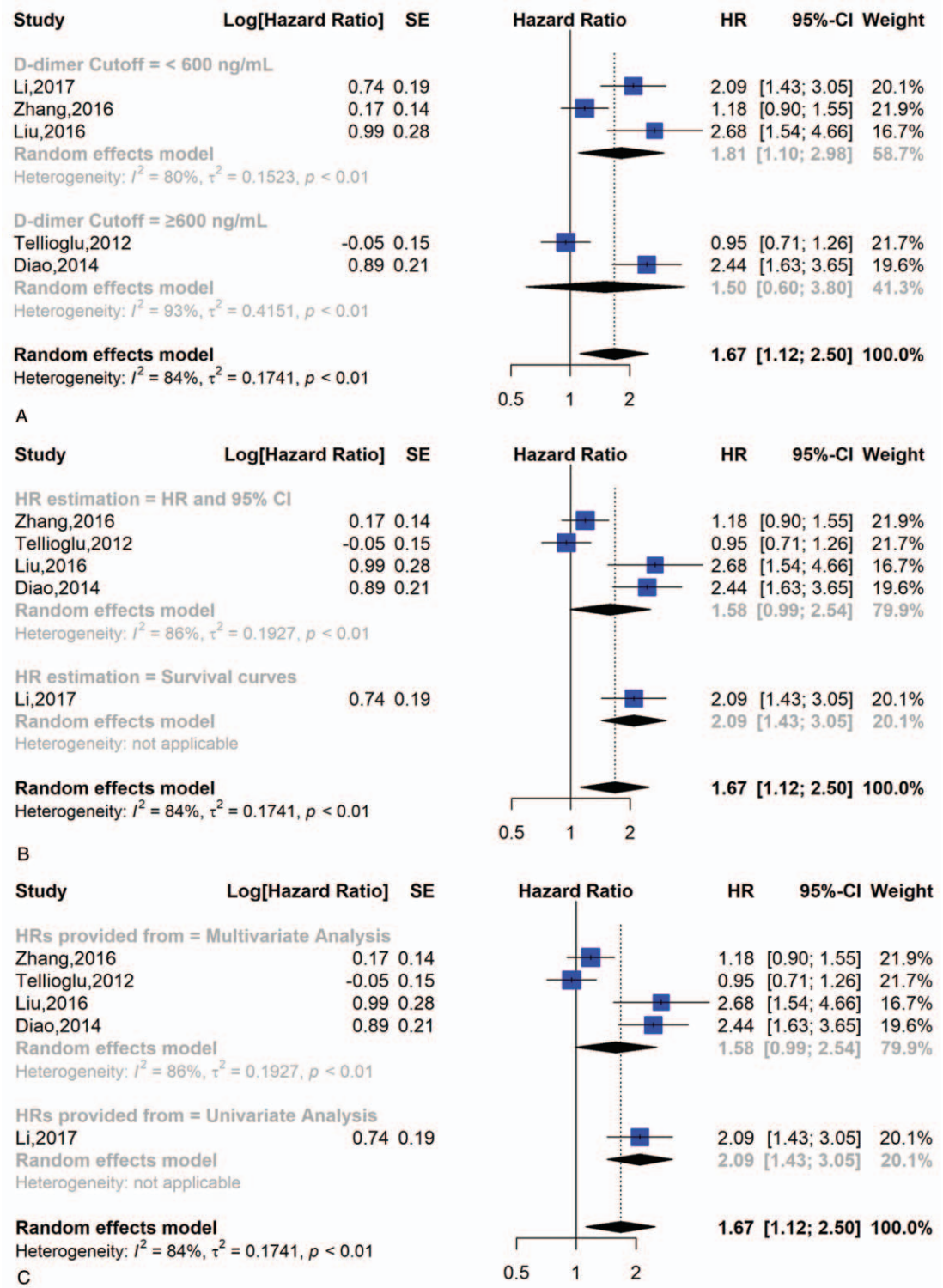

Figure 8. Subgroup analysis of DFS; (A) forest plot of D-dimer cut-off value; (B) forest plot of HR estimation; (C) forest plot of HRs provided from.

4. Some studies that reported on the prognostic significance of D-dimer levels were eliminated if they did not report HRs or allow HRs to be calculated.
5. Although no apparent publication bias was discovered in our research, there might have been some potential biases that were not published.

5. Conclusions

In summary, this research suggests that higher pretreatment plasma D-dimer levels could predict adverse survival outcomes among patients with different types of gastrointestinal carcinomas. Additionally, we should conduct further observation and research to determine whether plasma D-dimer levels could be introduced into the carcinoma staging

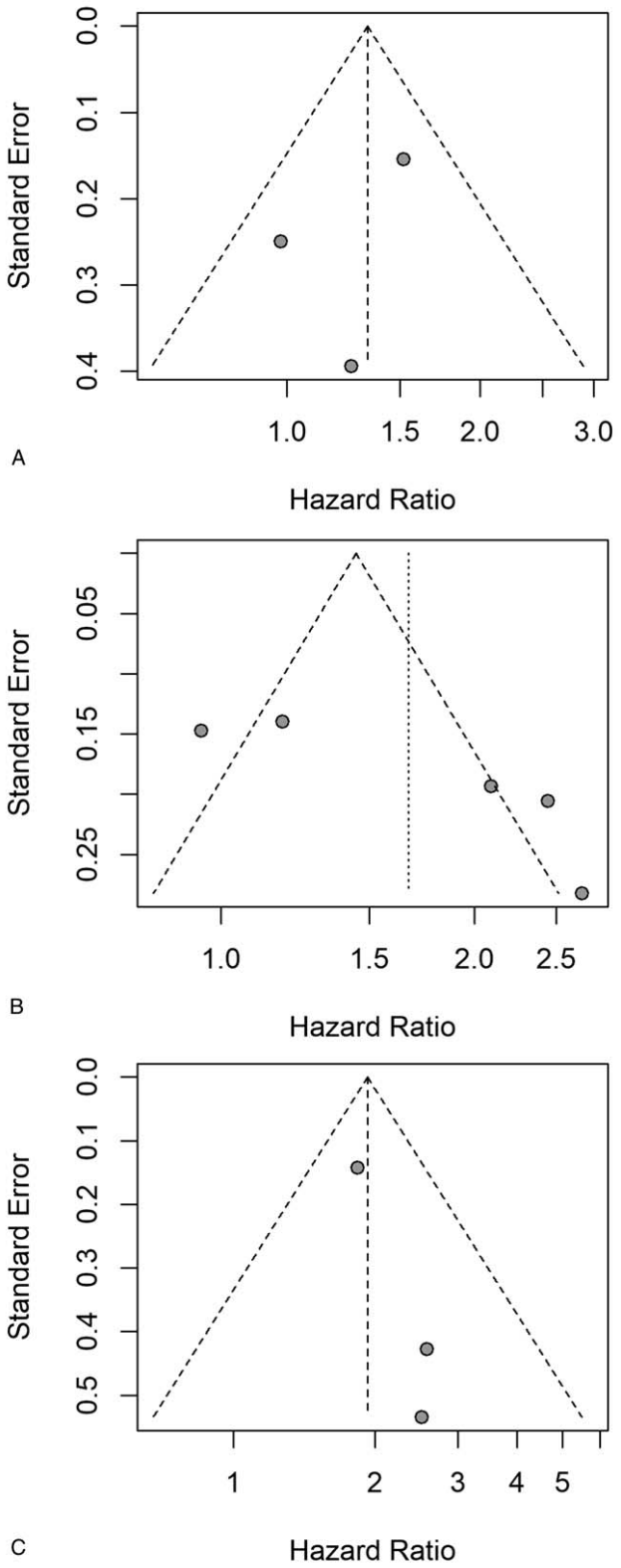

Figure 9. Funnel plots of PFS, DFS and CSS; (A) funnel plots of PFS; (B) funnel plots of DFS; (C) forest plot of CSS.

system. Moreover, additional studies need to be conducted to demonstrate the correlation and mechanism between elevated plasma D-dimer levels and gastrointestinal carcinoma progression.

Author contributions

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Investigation: Guoyi Rong, Wenxin Fan, Jian Shen.
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Resources: Guoyi Rong, Wenxin Fan, Jian Shen.
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Writing – review & editing: Guoyi Rong, Wenxin Fan, Jian Shen.

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