Original Article

Prognostic value of combined pretreatment fibrinogen and neutrophil-lymphocyte ratio in digestive system cancers: a meta-analysis of 17 retrospective studies

Rongqiang Liu[1,2#], Tianxing Dai[1#], Shiyang Zheng[3#], Mingbin Deng[1], Guozhen Lin[1], Yuanda Bao[2], Zhihua Guo[4], Guoying Wang[1]

[1]Department of Hepatic Surgery and Liver Transplantation Center, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]Department of Hepatobiliary Surgery, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [3]Department of Breast Surgery, the Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [4]Department of Thoracic Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Contributions: (I) Conception and design: Z Guo, G Wang; (II) Administrative support: G Wang; (III) Provision of study materials or patients: R Liu, T Dai, S Zheng, M Deng, G Lin, Y Bao; (IV) Collection and assembly of data: R Liu, T Dai, S Zheng; (V) Data analysis and interpretation: R Liu, T Dai, S Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Guoying Wang. Department of Hepatic Surgery and Liver transplantation Center, The Third Affiliated Hospital of Sun Yat-sen University, No. 600, Tianhe Street, Tianhe District, Guangzhou 510220, China. Email: wanggy3@126.com; Zhihua Guo. Department of Thoracic Oncology, the First Affiliated Hospital of Guangzhou Medical University, No. 151, Yanjiang West Road, Yuexiu District, Guangzhou, China. Email: guozhihua84@126.com.

Background: Several epidemiological studies have reported the relationship between the combined pretreatment fibrinogen and neutrophil-lymphocyte ratio (F-NLR) and prognosis of digestive system cancers (DSCs). However, the results are controversial. We aimed to assess the prognostic value of F-NLR in patients with DSCs.

Methods: A comprehensive search for relevant studies was conducted until June, 2020. Studies that evaluated the association of the F-NLR score with survival outcome in patients with any DSCs were included. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using a fixed-effects model. All data analyses were performed using the STATA 12.0 software.

Results: A total of 17 studies involving 5,767 participants were included in the meta-analysis. We found that high F-NLR score was significantly associated with poor overall survival (OS) in patients with DSCs (HR =2.0; 95% CI, 1.78–2.24). In addition, patients with high F-NLR score had poor disease-free survival/progression-free survival/recurrence-free survival (DFS/PFS/RFS) (HR =2.01; 95% CI, 1.47–2.74) and DFS (HR =1.97; 95% CI, 1.35–2.87). Sensitivity analyses for OS confirmed that the results were stable.

Conclusions: High F-NLR score is significantly associated with poor prognostic outcomes in patients with DSCs and can serve as an effective prognostic indicator for the Asian population.

Keywords: Fibrinogen; neutrophil-lymphocyte ratio; prognosis; digestive system cancers (DSCs); meta-analysis

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Introduction

Digestive system cancers (DSCs) are the most common malignancies, composing approximately 30% of all cancers. In the United States, nearly 350,000 new diagnosed DSC cases occur annually and approximately half die (1). Over 3.4 million new cases of DSCs and 1.5 million

deaths are estimated to happen each year worldwide (2). The occurrence and development of DSCs are closely related to heredity, chronic disease history, lifestyle, and environmental factors. In recent years, the incidence of DSCs in developing countries has significantly increased. In China, stomach, esophageal, and liver cancers were also commonly diagnosed and were identified as leading causes of cancer death (3). Despite recent improvements in various detection and therapy methods, the prognosis of patients with DSCs remains unsatisfactory. Many different prognostic markers have been used for digestive system tumors, but the clinical application effect is not obvious. Therefore, it is essential to identify new more effective prognostic biomarkers for DSCs.

Recently, a new scoring system, termed fibrinogen and neutrophil-lymphocyte ratio (F-NLR), that combines pretreatment fibrinogen levels with neutrophil-lymphocyte ratio (NLR) has gradually attracted considerable research attention. The F-NLR score has been reported as a promising prognostic marker in patients with DSCs (4-20). However, the results remain controversial. Therefore, this study aimed to comprehensively determine the prognostic value of F-NLR score in patients with DSCs by integrating data in a meta-analysis. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2482).

Methods

Search strategy

Three independent investigators (RL, TD and SZ) conducted a literature search. Relevant studies were systematically searched in PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure, and Wanfang Data until June, 2020. The following key words were used: "fibrinogen" AND "neutrophil lymphocyte ratio" OR "neutrophil-lymphocyte ratio" OR "neutrophil to lymphocyte ratio" OR "neutrophil-lymphocyte-ratio" OR "neutrophil-lymphocyte "OR "NLR" AND "cancer" OR "carcinoma" OR "neoplasm" OR "tumour" OR "tumor" AND "prognosis" OR "prognostic" OR "survival" OR "outcome". Titles, abstracts, full texts, and reference lists were carefully screened to identify objective studies. There were no language restrictions and a manual search was conducted for references in the included studies.

Study selection

All articles were independently assessed by the three investigators (RL, TD and SZ). Discrepancies were resolved by consensus. The inclusion criteria for studies were: (I) evaluated the association of the F-NLR score with survival outcome in patients with any DSCs; and (II) provided sufficient data to allow calculation of the hazard ratio (HR) with 95% confidence interval (CI). The exclusion criteria were: studies with insufficient data; animal experiments; letters; case reports; and abstracts.

Data extraction and quality assessment

Data were independently extracted by two researchers (RL and SZ). A standardized data collection form was used to extract the following information: first author name, publication year, country, study design, tumor type, sample size, overall survival (OS), disease-free survival/progression-free survival/recurrence-free survival (DFS/PFS/RFS), as well as the HR and the corresponding 95% CI. For studies reporting the results of both univariate and multivariate analyses, those obtained from the latter were selected, as this approach considers confounding factors and is more accurate. The quality of each study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) (21).

Statistical analysis

The HR and corresponding 95% CI were used to analyze pooled data. Statistical variables described in the studies were directly used in the present analysis. Otherwise, the data were extracted from graphical survival plots according to the methods described by Tierney (22). Data from the Kaplan-Meier survival curves were analyzed using the Engauge Digitizer version 4.1 software. Heterogeneity was assessed based on I^2. For I^2 <50% and ≥50%, fixed-effects and random-effects models were used, respectively. Sensitivity analysis was conducted to test the stability of the results. Begg's and Egger's tests were used to evaluate publication bias. All data analyses were performed using the STATA 12.0 software (Stata Corp., College Station, TX, USA). P values <0.05 denoted statistically significant differences.

Results

Search results

Through a systematic literature search of the designated databases, a total of 353 articles were initially collected. After removing 171 duplicates, 182 articles remained. After

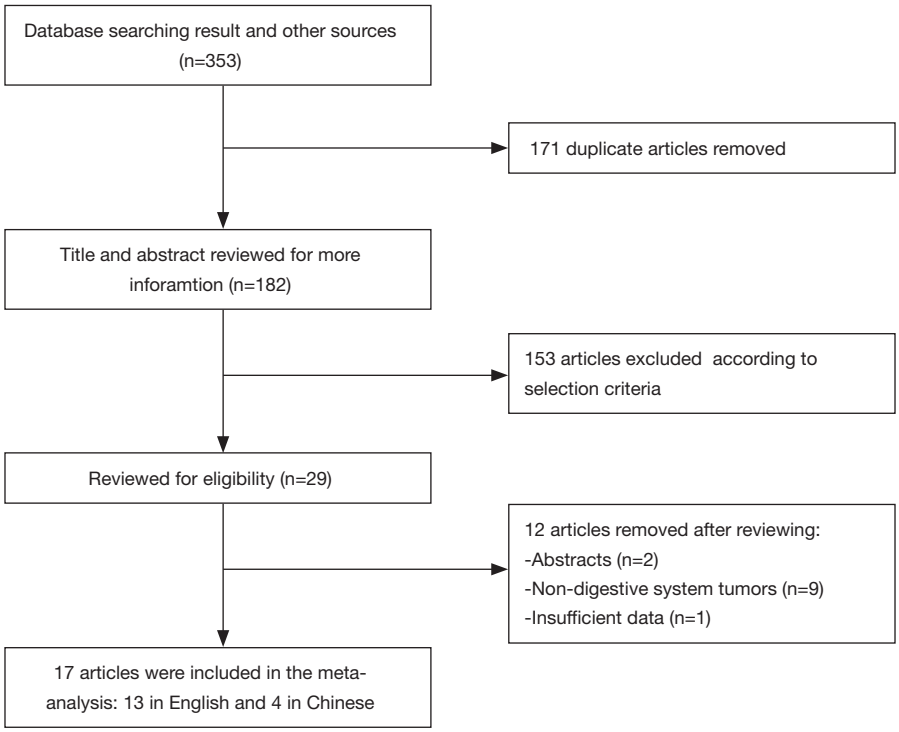

Figure 1 Flow diagram of the literature search.

screening the titles and abstracts, 153 articles which did not meet the inclusion criteria were removed. After full-text review, 12 articles were further excluded. Eventually, 17 retrospective articles that investigated the association of the F-NLR score with the prognostic outcome in patients with DSCs were included in the final analysis. The flow chart for study identification is presented in *Figure 1*.

Study characteristics

The total number of patients in the included articles was 5,767, ranging from 68 to 1,293 per study. Sixteen studies presented OS data, four reported DFS data, two covered PFS, and one reported RFS. Eleven studies were conducted in China, and six in Japan. Five different types of DSCs were assessed in this study, including esophageal carcinoma (EC) (4,8,13,17,18), gastric cancer (GC) (5,6,11,14,16,20), colorectal cancer (CRC) (10,12,19), hypopharyngeal carcinoma (HPC) (9), hepatocellular carcinoma (HCC) (7,15). The characteristics of the included studies are summarized in *Table 1*.

F-NLR score on OS

Sixteen studies, including 5,688 participants, focused on OS analysis. The fixed effects model was adopted since there was no heterogeneity (I^2=0%). The results of meta-analysis revealed that a high F-NLR score was significantly associated with poor OS in DSCs (HR: 2.0; 95% CI: 1.78–2.24) (*Figure 2*).

We performed subgroup analyses according to tumor type, country, analysis type and treatments (*Table 2*). The findings revealed that the high F-NLR score was an effective prognostic indicator for OS in GC (HR: 2.35; 95% CI: 1.89–2.91), EC (HR: 1.82; 95% CI: 1.50–2.22), HCC (HR: 2.12; 95% CI: 1.52–2.94), and CRC (HR: 2.29; 95% CI: 1.27–4.15). Regardless of gastrointestinal or non-gastrointestinal tract cancers, the high F-NLR score indicated poor OS (HR: 2.09; 95% CI: 1.78–2.45 and HR: 1.90; 95% CI: 1.61–2.25, respectively). We also found that the high F-NLR score was obviously associated with unfavorable OS for the surgery group (HR: 1.90; 95% CI: 1.67–2.17), no-surgery group (HR: 2.13; 95% CI: 1.47–3.09), and mixed group (HR: 2.92; 95% CI: 1.61–5.29). In

Table 1 The basic information of included studies

Study	Year	Country	Study type	Tumor type	Sample	Treatment methods	Analysis type	Survival analysis	NOS score
Arigami	2015	Japan	Retrospective	ESCC	238	With-surgery	Multivariate-	OS	7
Arigami	2016A	Japan	Retrospective	GC	275	No-surgery	Univariate	OS	7
Arigami	2016B	Japan	Retrospective	GC	68	With-surgery	Multivariate	OS	7
Fu	2017	China	Retrospective	HCC	130	With-surgery	Univariate	OS, DFS	8
Kijima	2017	Japan	Retrospective	ESCC	98	No-surgery	Multivariate	OS	7
Kuwahara	2018	Japan	Retrospective	HPC	111	No-surgery	Univariate	OS, PFS	8
Li	2018	China	Retrospective	CRC	693	With-surgery	Univariate	OS, DFS	8
Liu	2018	China	Retrospective	GC	1,293	With-surgery	Multivariate	OS	7
Sun	2020	China	Retrospective	LARC	317	Mixed	Univariate	OS, DFS	8
Guo	2018	China	Retrospective	ESCC and AEG	356	With-surgery	Multivariate	OS	7
Cong	2019	China	Retrospective	AEG and UGC	356	With-surgery	Univariate	OS	7
Kong	2020	China	Retrospective	HCC	292	With-surgery	Multivariate	OS, DFS	8
Yamamoto	2020	Japan	Retrospective	GC	666	Mixed	Univariate	OS, RFS	8
Lin	2019	China	Retrospective	ESCC	327	With-surgery	Multivariate	OS	6
Feng	2019	China	Retrospective	ESCC	218	Mixed	Multivariate	OS	6
Qin	2017	China	Retrospective	CRC	250	With-surgery	Univariate	OS	6

ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HPC, hypopharyngeal carcinoma; CRC, colorectal cancer; LARC, locally advanced rectal cancer; AEG, adenocarcinoma of the esophagogastric junction; UGC, upper gastric cancer; OS, overall survival; DFS, disease-free survival.

addition, in the subgroup based on country, the merged HRs were 2.22 (95% CI: 1.71–2.88) and 1.95 (95% CI: 1.71–2.21) for Japan and China, respectively.

F-NLR score on DFS/PFS/RFS

Seven studies involving 2,288 participants that reported DFS/PFS/RFS showed obvious heterogeneity (I^2=71.7%) (*Figure 3*). For these studies, we calculated the pooled HR using a random effects model. Comprehensive analysis indicated that the high F-NLR score was significantly associated with poor DFS/PFS/RFS (HR: 2.01; 95% CI: 1.47–2.74). Furthermore, data were analyzed based on DFS and RFS (*Table 3*). We found that the high F-NLR score might be a significant biomarker for DFS (HR =1.97; 95% CI: 1.35–2.87), but was not associated with RFS (HR =2.12; 95% CI: 0.65–6.88).

Sensitivity analysis

Sensitivity analysis was conducted by excluding each study in turn for OS and DFS/PFS/RFS. As shown in *Figure 4*, the results did not differ significantly from those of the overall analysis, revealing that the outcomes were stable.

Publication bias

The funnel plot was used to qualitatively determine the publication bias, and Egger's was employed to quantify the publication bias. As shown in *Figures 5* and *6* P values of Egger's for OS and DFS/PFS/RFS was 0.017 and 0.20, respectively, indicating there was publication bias for OS. Through the trim-and-fill method, we found that the pooled HR for OS was 1.776 (95% CI: 1.609–1.961), further confirming that the result was unaffected.

Discussion

To the best of our knowledge, this is the first meta-analysis to comprehensively assess the prognostic value of the F-NLR score in DSCs. A total of 17 studies involving 5,767

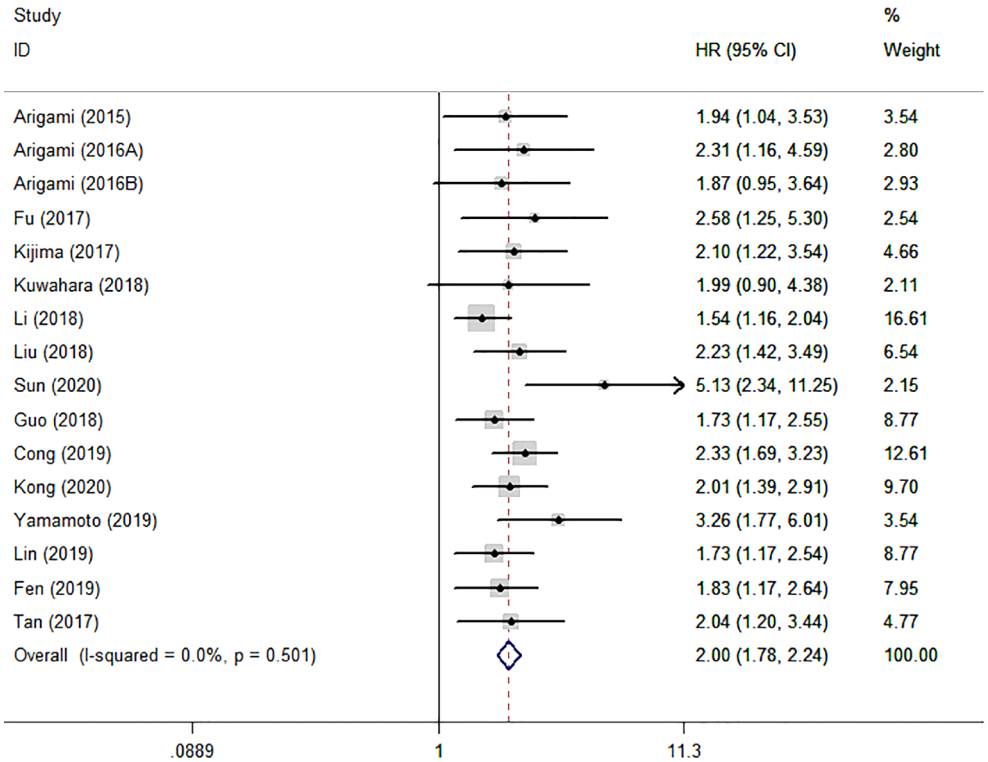

Figure 2 Forest plot of the relationship between pretreatment fibrinogen and neutrophil-lymphocyte ratio and overall survival.

patients were included. Of those, sixteen studies assessed the prognostic role of F-NLR score in OS and seven studies evaluated the prognostic role of the F-NLR score in DFS/PFS/RFS. Our results demonstrated that the high F-NLR score was significantly associated with poor OS (HR: 2.0; 95% CI: 1.78–2.24). Subgroup analysis for OS showed that the high F-NLR score mainly displayed the adverse prognosis in GC (HR: 2.35; 95% CI: 1.89–2.91), ESCC (HR: 1.82; 95% CI: 1.50–2.22), HCC (HR: 2.12; 95% CI: 1.52–2.94), and CRC (HR: 2.29; 95% CI: 1.27–4.15). In addition, the meta-analysis revealed that there was obvious association between the high F-NLR score and poor DFS/PFS/RFS (HR: 2.01; 95% CI: 1.47–2.74). Sensitivity analysis indicated that the results of the meta-analysis were stable. Based on the above results, we have sufficient reasons to believe that F-NLR score may be a suitable and effective prognostic indicator for DSCs in clinical practice.

F-NLR score, based on fibrinogen levels and neutrophil and lymphocyte counts, was first identified as an effective prognostic indicator in ESCC (4). Subsequently, its prognostic value was also confirmed in numerous other tumors, such as glioblastoma multiforme, ovarian cancer, and non-small cell lung cancer (23-25). Similarly, increasing evidence suggests that the F-NLR score could be a good predictive marker in DSCs. Fibrinogen, as an acute-phase response protein, has been associated with poor prognosis in patients with various tumors (26-28). NLR, as a useful marker for the assessment of inflammatory response, is calculated by dividing the neutrophil count by the lymphocyte count. A number of studies have reported that elevated NLR is associated with poor prognosis in patients with various malignancies, including DSCs (29-31). F-NLR score combined pretreatment fibrinogen level with neutrophil-lymphocyte ratio better reflects inflammatory responses and the cancer microenvironment. Fibrinogen or NLR alone may exert a limited effect on tumor progression. The F-NLR score overcomes the unfavorable effect of fibrinogen and NLR, and effectively improves the predicted value for patients with DSCs.

Several mechanisms may explain that F-NLR score can be used as an effective predictor in DSC. Fibrinogen is a key factor in hemostasis, which induces cell growth and migration, and is often abnormally activated in patients with cancer (32). When stimulated with inflammatory

Table 2 Subgroup analysis of the studies reporting the effect of high F-NLR score in OS

Stratified study	No. of studies	No. of patients	Pool HR (95% CI)	P value	Heterogeneity I^2 (%)	PQ
Cancer type						
GC	5	2,658	2.35 (1.89–2.91)	0	0	0.808
EC	5	1,237	1.82 (1.50–2.22)	0	0	0.978
HCC	2	422	2.12 (1.52–2.94)	0	0	0.547
CRC	3	1,260	2.29 (1.27–4.15)	0.006	75.70	0.016
HPC	1	111	1.99 (0.90–4.38)	–	–	–
GI-tract cancers	8	3,918	2.09 (1.78–2.45)	0	42.90	0.092
Non-GI-tract cancers	8	1,770	1.90 (1.61–2.25)	0	0	0.985
Analysis type						
Univariate analysis	8	2,591	2.11 (1.78–2.49)	0	43.60	0.088
Multivariate analysis	8	3,097	1.91 (1.63–2.23)	0	0	0.991
Treatments						
With-surgery	10	4,210	1.90 (1.67–2.17)	0	0	0.795
No-surgery	3	277	2.13 (1.47–3.09)	0	0	0.959
Mixed	3	1,201	2.92 (1.61–5.29)	0	67.5	0.046
Country						
Japan	6	1,456	2.22 (1.71–2.88)	0	0	0.837
China	10	4,232	1.95 (1.71–2.21)	0	21.50	0.245

GC, gastric cancer; EC, esophageal carcinoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; HPC, hypopharyngeal carcinoma; GI, gastrointestinal; OS, overall survival; F-NLR, fibrinogen and neutrophil-lymphocyte ratio.

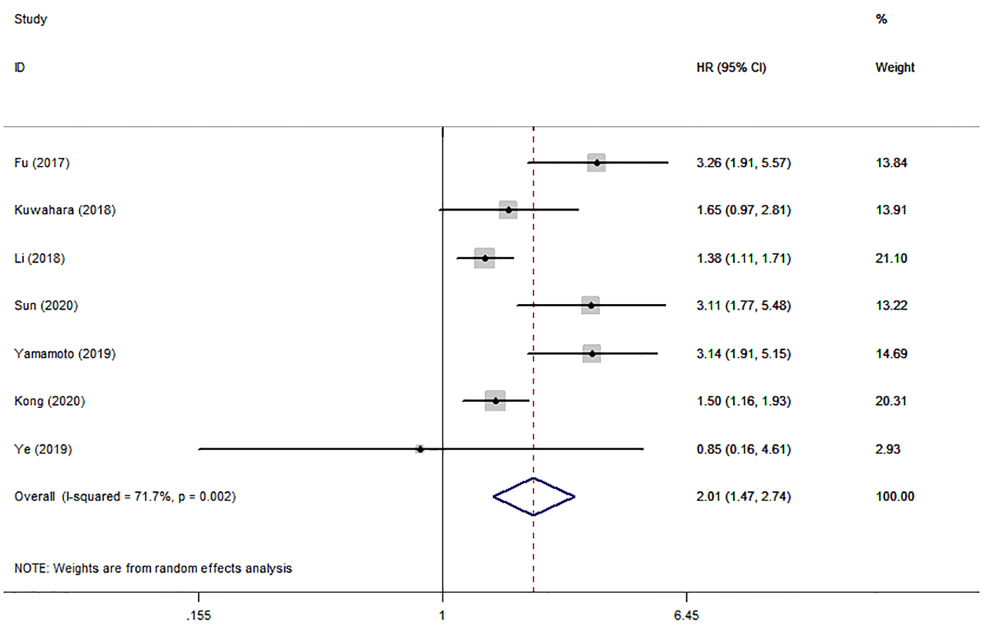

Figure 3 Forest plot of the relationship between pretreatment fibrinogen and neutrophil-lymphocyte ratio and disease-free survival/progression-free survival/recurrence-free survival.

Table 3 Analysis results based on DFS/PFS/RFS

Stratified study	No. of studies	No. of patients	Pool HR (95% CI)	P value	Heterogeneity I^2 (%)	PQ
DFS	4	1,432	1.97 (1.35–2.87)	0	78.80	0.003
RFS	2	745	2.12 (0.65–6.88)	0.213	52.70	0.146
PFS	1	111	1.65 (0.97–2.81)	–	–	–

DFS/PFS/RFS, disease-free survival/progression-free survival/recurrence-free survival.

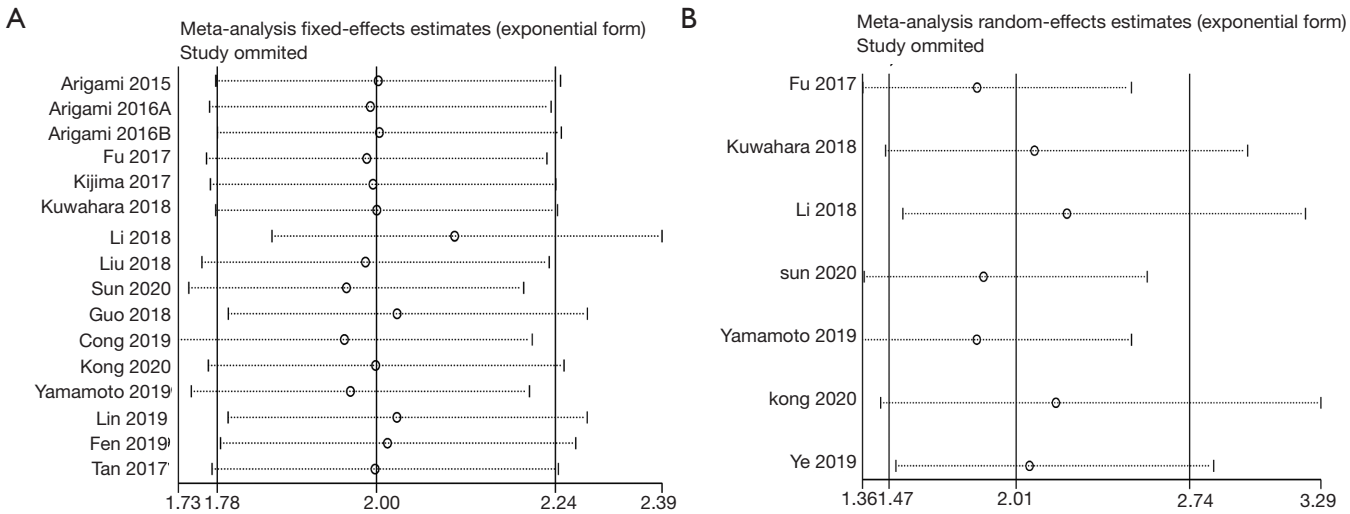

Figure 4 Funnel plot of sensitivity analysis. (A) Sensitivity analysis for overall survival. (B) Sensitivity analysis for disease-free survival/progression-free survival/recurrence-free survival.

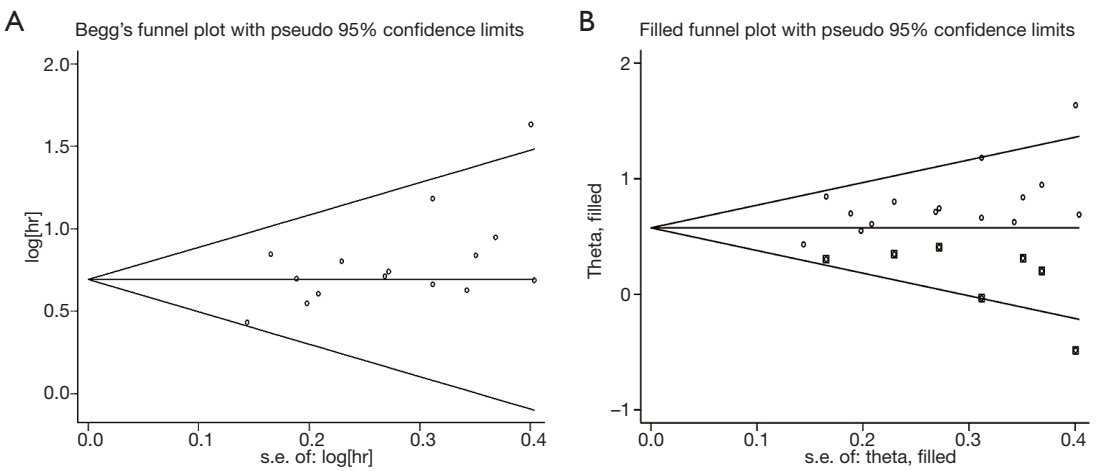

Figure 5 Funnel plots for publication bias for overall survival. (A) Begg's test to evaluate overall survival data. (B) Trim and fill to evaluate overall survival data.

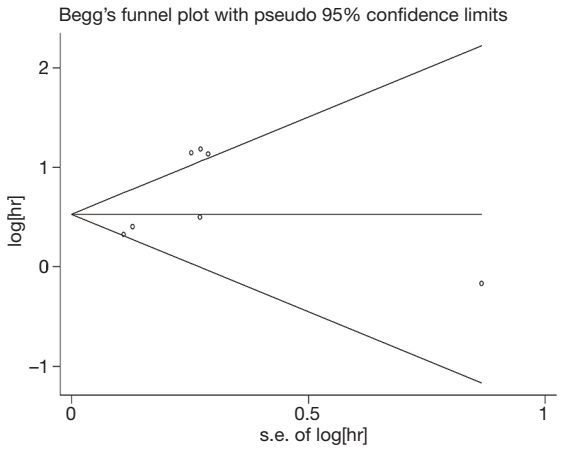

Figure 6 Funnel plots for publication bias for disease-free survival/progression-free survival/recurrence-free survival.

factors or by tumors, activated thrombin can transform fibrinogen into fibrin, which can form a stable framework and extracellular matrix around tumor cells, preventing tumor cell killing by immune cells (33). It is established that tumor progression and prognosis is closely associated with inflammation (34,35). Neutrophils, as a marker of inflammation, can promote tumor invasion, metastasis, and angiogenesis by producing various cytokines (36,37). In addition, lymphocytes play important roles in anti-tumor immune defense, and their reduction may be considered an immune deficiency. Studies have reported that lymphopenia is associated with poor prognosis in GC (38). Therefore, high F-NLR, elevated fibrinogen, increased neutrophils, and decreased lymphocytes, represent intense inflammatory reactions and fragile immune response, which may contribute to the occurrence and development of tumors.

There were certain limitations in the present meta-analysis. Firstly, all included studies had small sample sizes, and their results may not be reliable. Secondly, some of the HR and CI values extracted from the survival curve may not be equal to the true value. Thirdly, all included studies were retrospective studies. Fourthly, most studies included in the meta-analysis were conducted in Asia. Future studies involving patients of different races and from various regions are warranted. Finally, publication bias existed in our analysis. This may be related to the different research methods and quality of included literature

Although there are some defects, this meta-analysis also has some strengths. Firstly, this was the first meta-analysis to investigate the relationship between the F-NLR score and prognostic outcomes in DSCs. Secondly, sensitivity analysis displayed that the results were stable. Thirdly, there was no heterogeneity for OS in the meta-analysis. Furthermore, the trim-and-fill method confirmed that the results of the meta-analysis were unaffected by the possible publication bias. More importantly, F-NLR score as the serum biomarker, is more convenient and rapid. This can be an efficacious method for dynamically monitoring the prognosis and therapeutic effects.

In summary, we demonstrated that the high F-NLR score is associated with poor prognostic outcomes in DSCs and may serve as an effective prognostic indicator in DSCs for the Asian population. Undoubtedly, further large-sample, prospective, multicentric, and well-designed studies are warranted to validate the present results and explore the prognostic role of the F-NLR score in various types of cancer.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2482

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2482). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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