AHEAD OF PRINT

Meta-analysis

Gastroenterology; oncology; surgery

Clinicopathological and prognostic value of DLL4 expression in gastric cancer: A systematic review and meta-analysis

*Qingyu Du[1,2,B–D,F], *Chenglin Zhao[1,2,B–D,F], *Chunling Sun[3,B–D,F], Guo Zu[1,4,A,B,E,F], Shaohua Du[1,2,B,C,F]

[1] Department of Gastrointestinal Surgery, Central Hospital of Dalian University of Technology (Dalian Municipal Central Hospital), China
[2] Graduate School, Dalian Medical University, China
[3] Surgery Room, Central Hospital of Dalian University of Technology (Dalian Municipal Central Hospital), China
[4] Department of General Surgery, Central Hospital of Dalian University of Technology (Dalian Municipal Central Hospital), China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Address for correspondence
Guo Zu
E-mail: zushanghai@163.com

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*Qingyu Du, Chenglin Zhao, and Chunling Sun contributed equally to this work.

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Abstract

Background. The clinicopathological significance and prognostic value of *Delta-like ligand 4 (DLL4)* expression in gastric cancer (GC) remain controversial. Therefore, we conducted a meta-analysis to ascertain the correlation between *DLL4* expression and the clinicopathological features and prognosis of GC patients.

Objectives. To clarify the association between *DLL4* expression, clinicopathological parameters, and the prognosis of GC patients, as well as to resolve the existing controversies.

Materials and methods. A systematic retrieval was performed according to the selection criteria. The hazard ratio (HR) or odds ratio (OR) and 95% confidence interval (95% CI) were applied to assess the clinicopathological and prognostic value of *DLL4* expression in patients with GC.

Results. A total of 1,535 patients with GC were included across 7 articles. *DLL4* expression was correlated with lymph node metastasis (OR = 5.612, 95% CI: 1.332–23.644; p = 0.019), venous invasion (OR = 3.807, 95% CI: 1.557–9.310, p = 0.003), and TNM stage (OR = 4.183, 95% CI: 1.270–13.775, p = 0.003). However, *DLL4* expression was not related to sex (OR = 0.976, 95% CI: 0.767–1.242, p = 0.845), age (OR = 0.765, 95% CI: 0.389–1.506, p = 0.438), T stage (OR = 1.306, 95% CI: 0.717–2.380, p = 0.384), tumor differentiation (OR = 0.952, 95% CI: 0.687–1.318, p = 0.072), or Lauren classification (OR = 1.224, 95% CI: 0.620–2.417, p = 0.560). Furthermore, high *DLL4* expression was associated with poorer overall survival (OS) (HR = 1.530, 95% CI: 1.272–1.841, p = 0.000) in patients with GC. The Kaplan–Meier Plotter database confirmed that patients with high *DLL4* expression in GC had a poorer prognosis (HR = 1.35, 95% CI: 1.08–1.68, p = 0.009).

Conclusions. *DLL4* expression was associated with venous invasion, lymph node metastasis, TNM stage, and poor OS in GC patients, but was not associated with age, sex, T stage, Lauren classification, or tumor differentiation.

Key words: prognosis, meta-analysis, *DLL4*, gastric cancer, clinicopathological parameters

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Highlights

- High *DLL4* expression is associated with aggressive clinicopathological features in gastric cancer.
- *DLL4* overexpression predicts poor overall survival in gastric cancer patients.
- *DLL4* correlates with lymph node metastasis, venous invasion, and advanced TNM stage.
- *DLL4* may serve as a prognostic biomarker and therapeutic target in gastric cancer.

Introduction

Gastric cancer (GC) was the 5th most commonly diagnosed malignancy worldwide in 2020, with 1,089,103 new cases accounting for 5.6% of all newly diagnosed cancers.[1] Gastric cancer also ranked as the 4th leading cause of cancer-related mortality worldwide. Despite substantial advances in modern diagnostic and therapeutic strategies, GC morbidity and mortality remain high, largely because many patients are diagnosed at an advanced stage. Early detection of solid tumors primarily relies on imaging techniques and the identification of serum or tissue biomarkers. Compared with imaging methods, biomarker detection is faster and more convenient and cost-effective.[2] Therefore, the identification of reliable biomarkers for early diagnosis and prognostic assessment remains crucial in GC management.

Delta-like ligand 4 (DLL4) is one of the ligands involved in the regulation of the Notch signaling pathway.[3] *DLL4* plays a critical role in essential biological processes, including angiogenesis and cell proliferation.[4] Angiogenesis, a key mechanism underlying tumor growth and progression, contributes to tumor invasion, gastric vascular dysplasia, and the development of metastatic lesions.[5,6] Previous studies have demonstrated that *DLL4* expression is associated with prognosis in breast, colon, and nasopharyngeal cancers.[7–9] More recently, increasing evidence has shown that *DLL4* is also overexpressed in GC.[10–16] However, the clinicopathological and prognostic significance of *DLL4* expression in GC remains controversial. Kim et al. reported no association between high *DLL4* expression and lymph node metastasis or vascular invasion in GC.[10] In contrast, Ishigami et al. demonstrated significant associations between high *DLL4* expression and tumor invasion depth, venous invasion, and lymph node metastasis.[11]

Objectives

The aim of this meta-analysis was to evaluate the association between *DLL4* expression, clinicopathological characteristics, and prognosis in patients with GC, and to clarify the existing controversies regarding its clinical significance.

Materials and methods

Search studies

First, a comprehensive search was conducted in the Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), Cochrane Library, and WanFang databases from inception to September 30, 2024. The following keywords were used: ("gastric carcinoma" OR "gastric cancer" OR "stomach cancer" OR "GC") AND ("Delta-like 4" OR "DLL4"). In addition, the reference lists of the identified studies were screened to ensure comprehensive inclusion of eligible articles. This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Selection criteria

The following inclusion criteria were applied to identify eligible studies: 1) patients diagnosed with GC based on pathological examination; 2) studies evaluating the association between *DLL4* expression and clinicopathological parameters (e.g., sex, age, TNM stage, and lymph node metastasis) and/or prognosis in patients with GC; and 3) studies providing sufficient data to calculate 95% confidence intervals (95% CIs).

The exclusion criteria were as follows: 1) studies involving other cancer types; 2) patients who received radiotherapy or chemotherapy before surgery; 3) review articles, conference abstracts, systematic reviews, case reports, letters, and meta-analyses; 4) unavailable full text; and 5) duplicate publications or overlapping patient cohorts. These criteria were applied to minimize potential bias and improve the reliability of the meta-analysis.

Data extraction

Two researchers (Q.D. and C.Z.) independently screened the titles and abstracts of the studies identified through the database search and excluded irrelevant or low-quality articles. The extracted data included the authors, study period, country, publication year, study design, age, sex, tumor differentiation, T stage, lymph node metastasis, venous invasion, Lauren classification, TNM stage, and overall survival (OS). Any discrepancies between the 2 researchers

were resolved through discussion. Effect estimates were reported as hazard ratios (HRs) with 95% CIs. Study quality was independently assessed by 2 researchers (Q.D. and C.Z.) using the Newcastle–Ottawa Scale (NOS), which ranges from 0 to 9 points. Studies with NOS scores of 6–9 were considered high-quality.

Statistical analyses

Stata v. 15.0 (StataCorp, College Station, USA) was used for statistical analyses. Review Manager (RevMan) v. 5.4 (The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) was used to assess the quality of the included studies. The Kaplan–Meier Plotter database (http://www.kmplot.com) was used to evaluate the association between *DLL4* expression and OS in patients with GC. Odds ratios (ORs), HRs and 95% CIs were extracted or calculated to assess the association between *DLL4* expression and clinicopathological characteristics and prognosis in GC patients. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic. I^2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively. Heterogeneity was prioritized as the primary criterion for model selection, and a half-normal prior distribution was applied for the heterogeneity parameter τ. Specifically, the positive expression rate of *DLL4* in GC patients was calculated separately for each of the 7 included studies, and the median value (0.48) was used as the prior estimate. Accordingly, τ was assigned a half-normal (0, 0.48) prior distribution. A random-effects model was applied when the posterior mean of τ was >0, whereas a fixed-effects model was used when τ was approx. 0. Clinical considerations took precedence over statistical heterogeneity when selecting the meta-analytic model. If clinically relevant differences existed among the included studies, a random-effects model was applied regardless of the statistical heterogeneity results. A leave-one-out approach was used for sensitivity analysis.[17] Each study was sequentially excluded, and the pooled OR/HR and 95% CI were recalculated after each exclusion. If the pooled effect estimates showed no substantial fluctuation and statistical significance remained consistent following removal of any single study, the meta-analysis results were considered stable and unlikely to be substantially influenced by an individual study. Conversely, marked changes in the pooled estimates suggested potential instability, and the heterogeneity and quality of the included studies required further evaluation.

Results

Literature search and study characteristics and risk of bias assessment

Initially, 110 articles were identified through the database search. After screening the titles and abstracts, 103 articles were excluded, including duplicate studies (n = 36), studies involving other cancer types (n = 20), review articles (n = 16), unavailable full texts (n = 17), studies including patients who had received radiotherapy or chemotherapy before surgery (n = 12), and studies with overlapping populations (n = 2). Ultimately, 7 studies were included in the meta-analysis. The study selection process is presented in Fig. 1, and the risk-of-bias assessment generated using RevMan is shown in Fig. 2. In total, the meta-analysis included 1,535 patients with GC. The main characteristics and quality assessments of the included studies are summarized in Table 1.[10–16]

DLL4 expression and clinicopathological factors

The associations between *DLL4* expression and the clinicopathological characteristics of GC are presented in Table 2[10–16] and Fig. 3. The pooled analysis showed that *DLL4* expression was not significantly associated with sex (OR = 0.976, 95% CI: 0.767–1.242, p = 0.845) (Fig. 3A), age (OR = 0.765, 95% CI: 0.389–1.506, p = 0.438) (Fig. 3B), T stage (OR = 1.306, 95% CI: 0.717–2.380, p = 0.384) (Fig. 3C), tumor differentiation (OR = 0.952, 95% CI: 0.687–1.318, p = 0.772) (Fig. 3D), or Lauren classification (OR = 1.224, 95% CI: 0.620–2.417,

Table 1. Main characteristics and results of each study

Study	Year	Journal	Country	Study period	Sample size	M/F	Method	NOS
Kim et al.[10]	2019	*J Cancer*	South Korea	2004–2008	336	217/119	IHC	7
Ishigami et al.[11]	2013	*J Exp Clin Cancer Res*	Japan	2001–2004	180	128/52	IHC	7
Segami et al.[12]	2021	*In Vivo*	Japan	2002–2012	413	120/293	IHC	6
Miao et al.[13]	2016	*Cancer Med*	China	2006–2009	383	276/107	IHC	6
Reza et al.[14]	2024	*J Gastrointest Cancer*	Iran	2010–2015	135	96/39	IHC	7
Zhang et al.[15]	2010	*J Clin Surg*	China	2006–2008	45	31/14	SP	6
Wei et al.[16]	2018	master's thesis	China	2015–2016	43	28/15	IHC	5

M – male; F – female; NOS – Newcastle–Ottawa Scale; IHC – immunohistochemistry; SP – streptavidin-peroxidase.

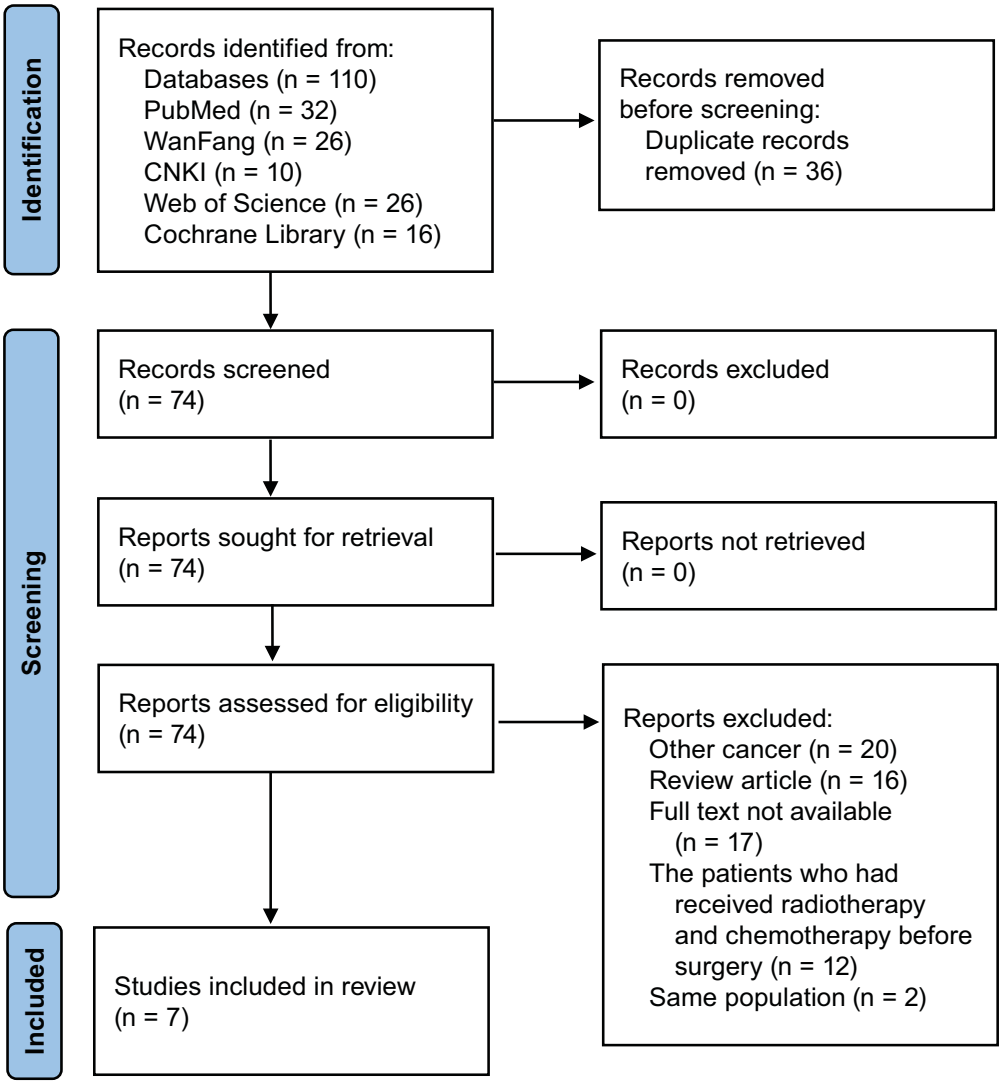

Fig. 1. Flowchart of the study selection process

CNKI – China National Knowledge Infrastructure.

Table 2. The relationship between *DLL4* expression and clinicopathological factors of gastric cancer (GC) patients

Factor	References	Number of patients	Pooled OR (95% CI)	p-value	Heterogeneity		
					I^2	p-value	model
Sex (male vs female)	10,11,12,13,14,15,16	1535	0.976	0.845	0.00%	0.938	fixed
Age (>60 vs ≤60 years)	10,13,15,16	807	0.765	0.438	62.90%	0.044	random
T stage (T3–4 vs T1–2)	10,11,12,13,14,15,16	1535	1.306	0.384	79.10%	0.000	random
Venous invasion (yes vs no)	11,12,14	728	3.807	0.003	83.20%	0.003	random
Tumor differentiation (PD vs WD MD)	10,11,14,15,16	739	0.952	0.766	46.60%	0.112	fixed
Lymph node metastasis (yes vs no)	11,12,14,15,16	816	5.612	0.019	90.50%	0.000	random
Lauren classification (intestinal vs diffuse)	10,12,13	1132	1.224	0.560	83.80%	0.002	random
TNM stage (III–IV vs I–II)	10,15,16	424	4.183	0.019	59.10%	0.087	random

PD – poorly differentiated; MD – moderately differentiated; WD – well differentiated; 95% CI – 95% confidence interval; OR – odds ratio.

p = 0.560) (Fig. 3E). In contrast, high *DLL4* expression was significantly associated with lymph node metastasis (OR = 5.612, 95% CI: 1.332–23.644, p = 0.019) (Fig. 3F), venous invasion (OR = 3.807, 95% CI: 1.557–9.310, p = 0.003) (Supplementary Fig. 1A), and advanced TNM stage (OR = 4.183, 95% CI: 1.270–13.775, p = 0.003) (Supplementary Fig. 1B).

Publication bias

Publication bias was assessed visually using funnel plots. The funnel plots illustrate the distribution of standard error (SE) against the OR for the analyzed clinicopathological parameters. In Fig. 4A, B, C, and E, the data points were distributed relatively symmetrically around

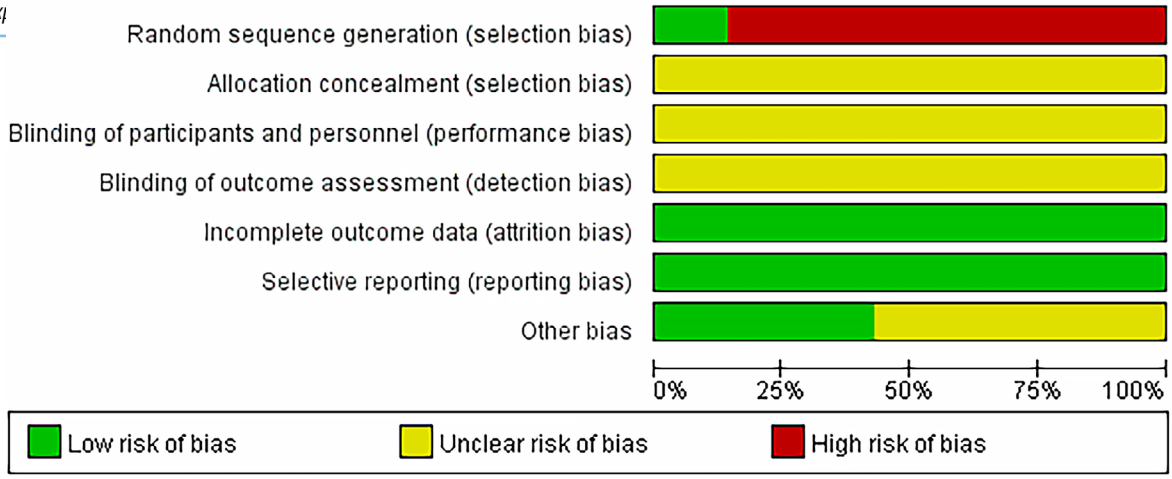

Fig. 2. Risk-of-bias assessment of the included studies

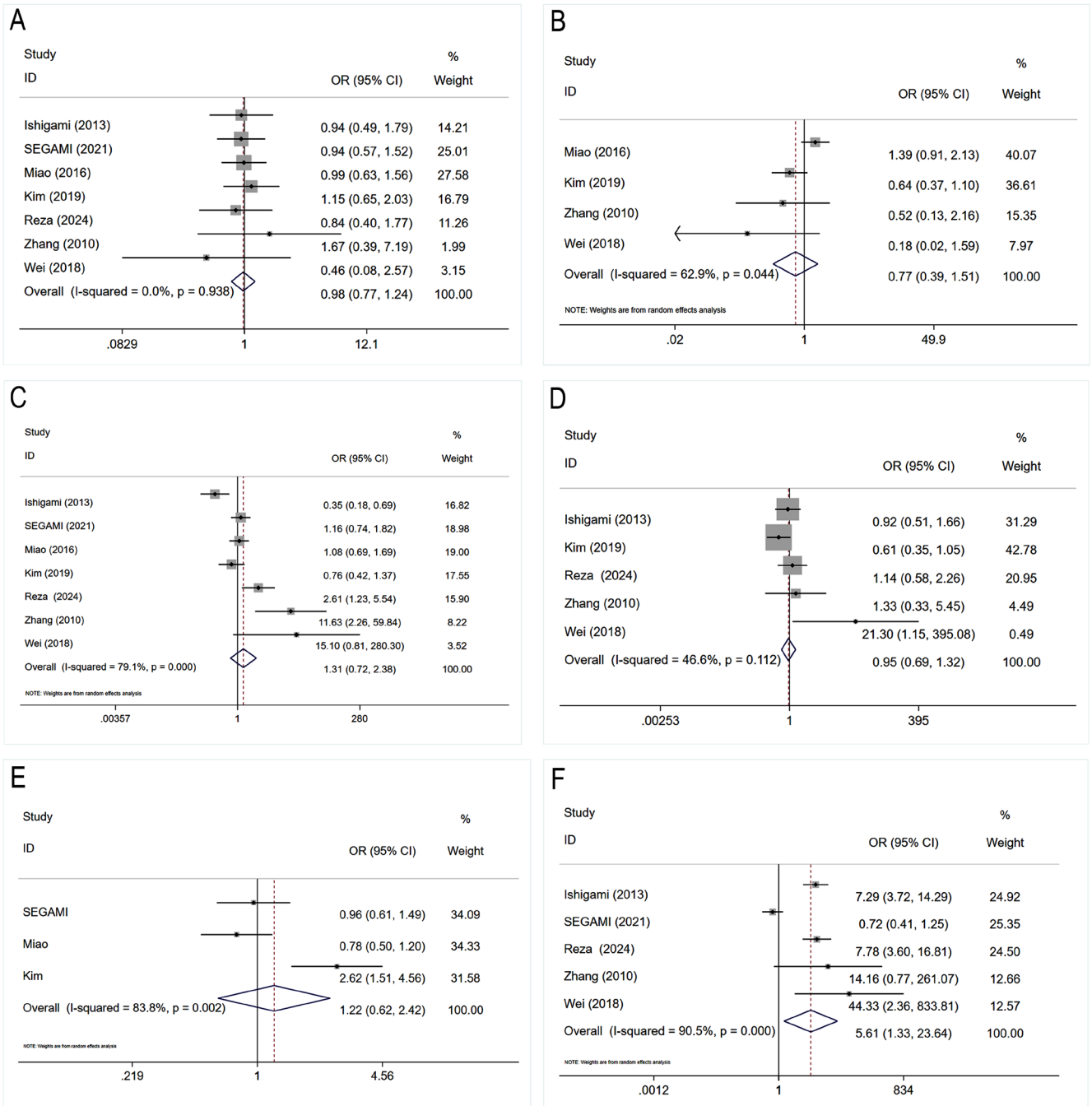

Fig. 3. Forest plots showing the association between *DLL4* expression and clinicopathological parameters: (A) sex, (B) age, (C) T stage, (D) tumor differentiation, (E) Lauren classification, and (F) lymph node metastasis

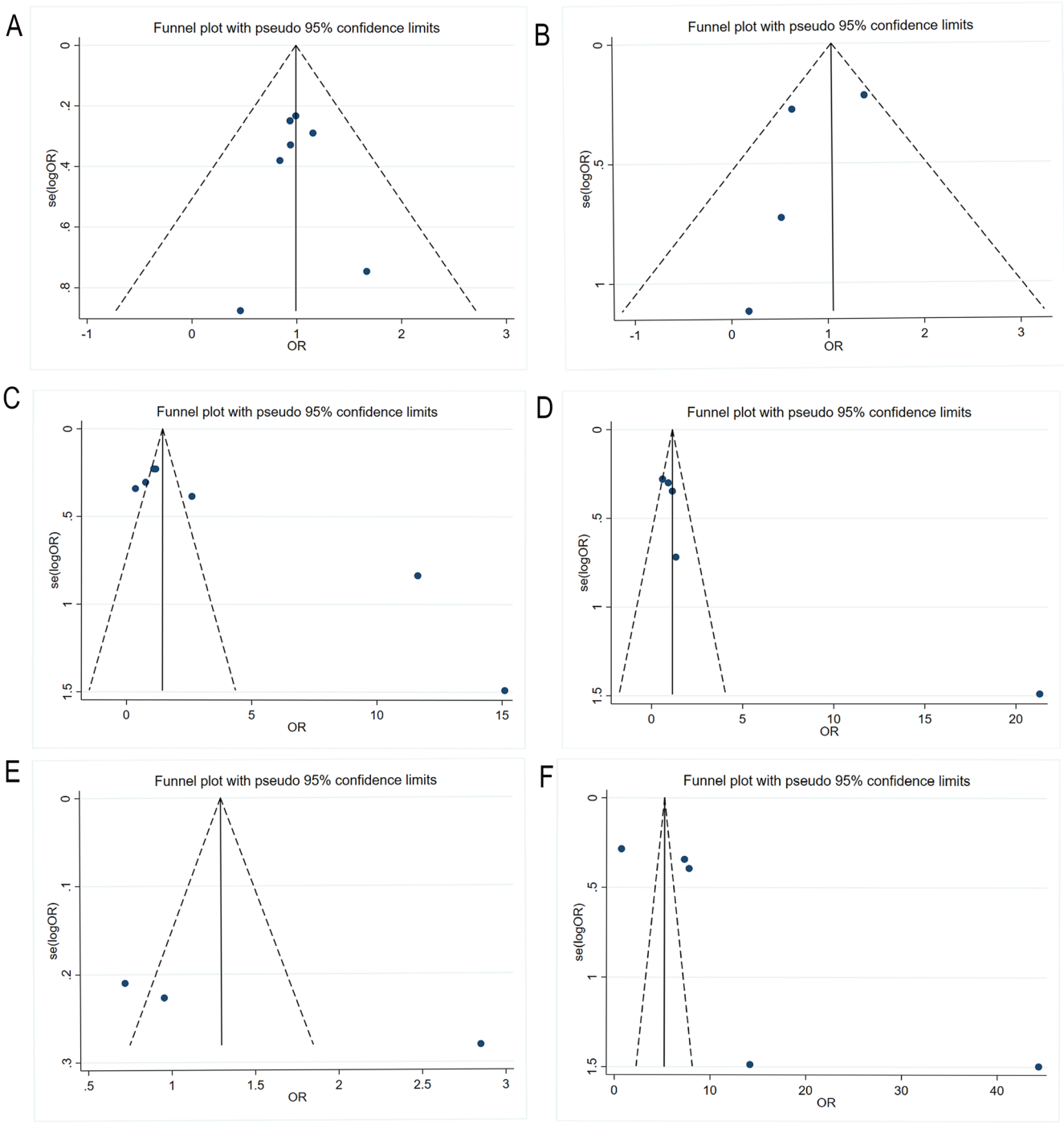

Fig. 4. Funnel plots showing the association between *DLL4* expression and clinicopathological parameters: (A) sex, (B) age, (C) T stage, (D) tumor differentiation, (E) Lauren classification, and (F) lymph node metastasis

the central vertical line, suggesting no major asymmetry in the effect estimates. In contrast, Fig. 4D and F and Supplementary Fig. 1C and D showed a sparser distribution of data points, with several studies located near the outer boundaries of the pseudo 95% confidence limits, indicating variability in estimate precision. Nevertheless, the overall funnel plot patterns remained approximately symmetrical. No evident publication bias was observed for the associations between *DLL4* expression and sex (Fig. 4A), age (Fig. 4B), T stage (Fig. 4C), tumor differentiation (Fig. 4D), Lauren classification (Fig. 4E), lymph node metastasis (Fig. 4F), venous invasion (Supplementary Fig. 1C), or TNM stage (Supplementary Fig. 1D).

Sensitivity analysis

Sensitivity analysis was performed to evaluate the stability and reliability of the associations between *DLL4* expression and clinicopathological characteristics in patients with GC. The results demonstrated that the pooled estimates for

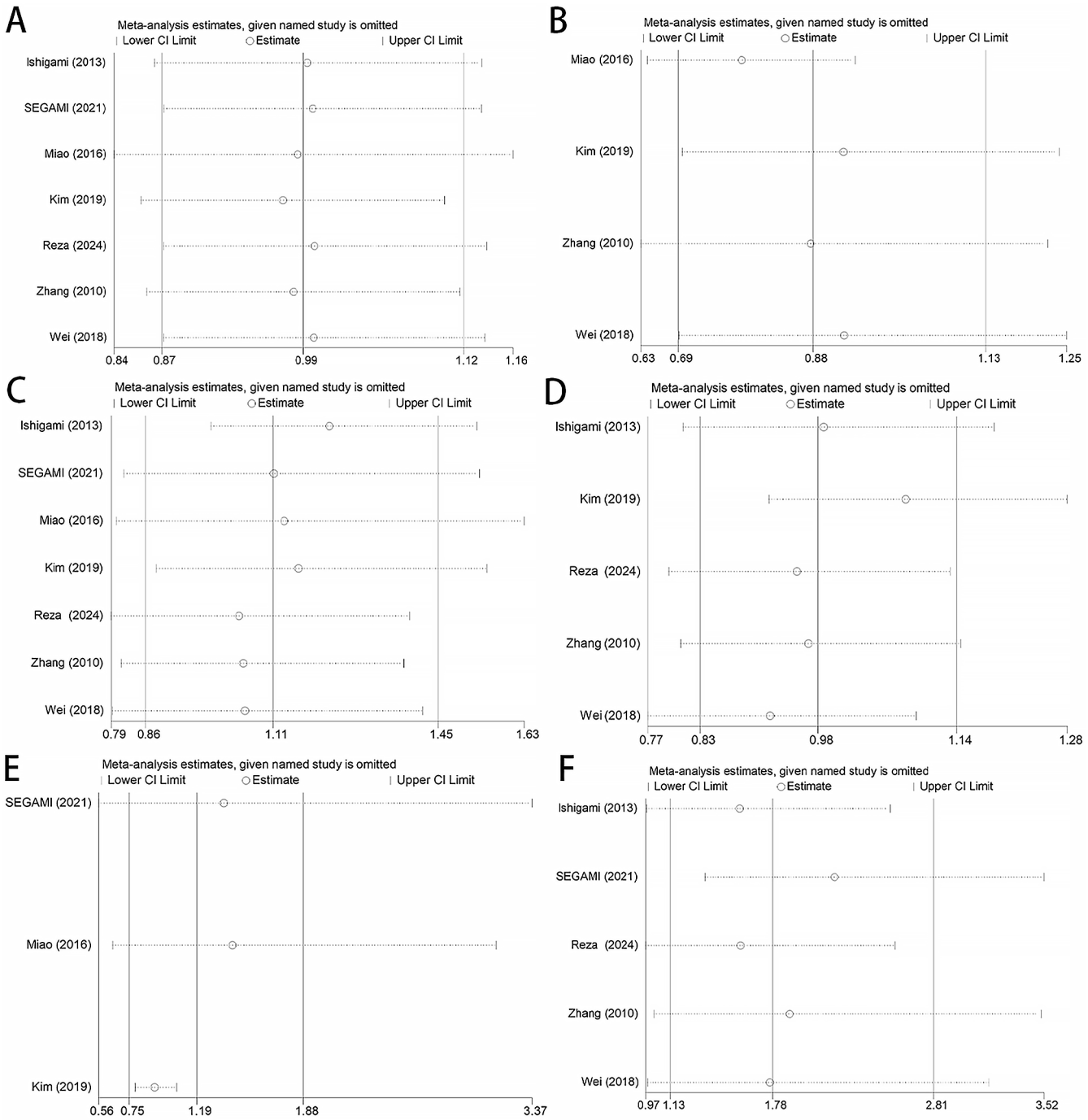

Fig. 5. Sensitivity analyses for the association between *DLL4* expression and clinicopathological parameters: (A) sex, (B) age, (C) T stage, (D) tumor differentiation, (E) Lauren classification, and (F) lymph node metastasis

sex (Fig. 5A), age (Fig. 5B), T stage (Fig. 5C), tumor differentiation (Fig. 5D), Lauren classification (Fig. 5E), lymph node metastasis (Fig. 5F), venous invasion (Supplementary Fig. 1E), and TNM stage (Supplementary Fig. 1F) remained stable after sequential exclusion of individual studies, indicating good robustness of the meta-analysis results.

Descriptive statistical analysis

Descriptive statistical analyses were performed for 3 clinicopathological parameters (venous invasion, Lauren classification, and TNM stage), as these analyses were based on only 3 included studies and the corresponding results from the forest plots, funnel plots, and sensitivity analyses may therefore be unreliable. The findings of the descriptive analyses for these 3 clinicopathological parameters are summarized in Table 3.

DLL4 expression and OS of GC patients

A total of 1,267 patients with GC from 4 studies were included in the analysis evaluating the association between

Table 3. Descriptive statistics of partial variables

VarName	Mean	SD	Min	Median	Max
DLL4 + venous invasion YES	61.33	20.841	43	57	84
DLL4 – venous invasion YES	82.67	109.418	18	21	209
DLL4 + venous invasion NO	25.33	4.933	22	23	31
DLL4 – venous invasion NO	73.33	22.591	52	71	97
DLL4 + Lauren type intestinal	77.67	58.347	42	46	145
DLL4 – Lauren type intestinal	114.33	17.926	103	105	135
DLL4 + Lauren type diffuse	57.67	31.134	25	61	87
DLL4 – Lauren type diffuse	127.67	69.082	48	164	171
DLL4+ TNM stage III+IV	22.33	3.512	19	22	26
DLL4 – TNM stage III+IV	16.67	25.403	2	2	46
DLL4 + TNM stage I+II	23.00	21.794	8	13	48
DLL4 – TNM stage I+II	79.33	124.420	7	8	223

SD – standard deviation.

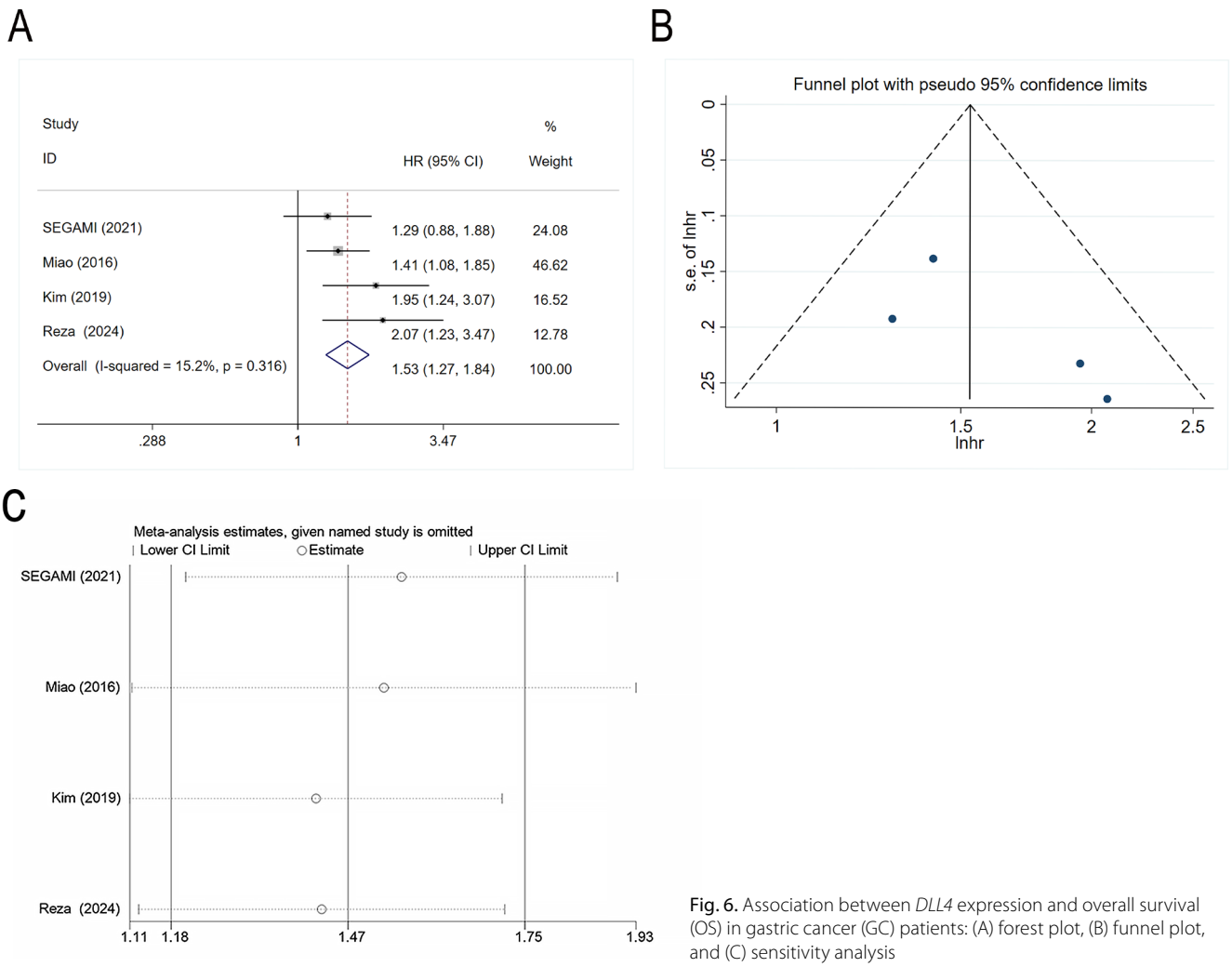

Fig. 6. Association between *DLL4* expression and overall survival (OS) in gastric cancer (GC) patients: (A) forest plot, (B) funnel plot, and (C) sensitivity analysis

DLL4 expression and OS. The pooled analysis demonstrated that high *DLL4* expression was significantly associated with poor prognosis in GC patients (HR = 1.530, 95% CI: 1.272–1.841, p < 0.001) (Fig. 6A). The funnel plot shown in Fig. 6B demonstrated a relatively symmetrical distribution of data points around the central vertical line, suggesting no major asymmetry in the effect estimates. No evident publication bias was observed for the association between *DLL4* expression and OS. Sensitivity analysis showed that sequential exclusion of individual studies did

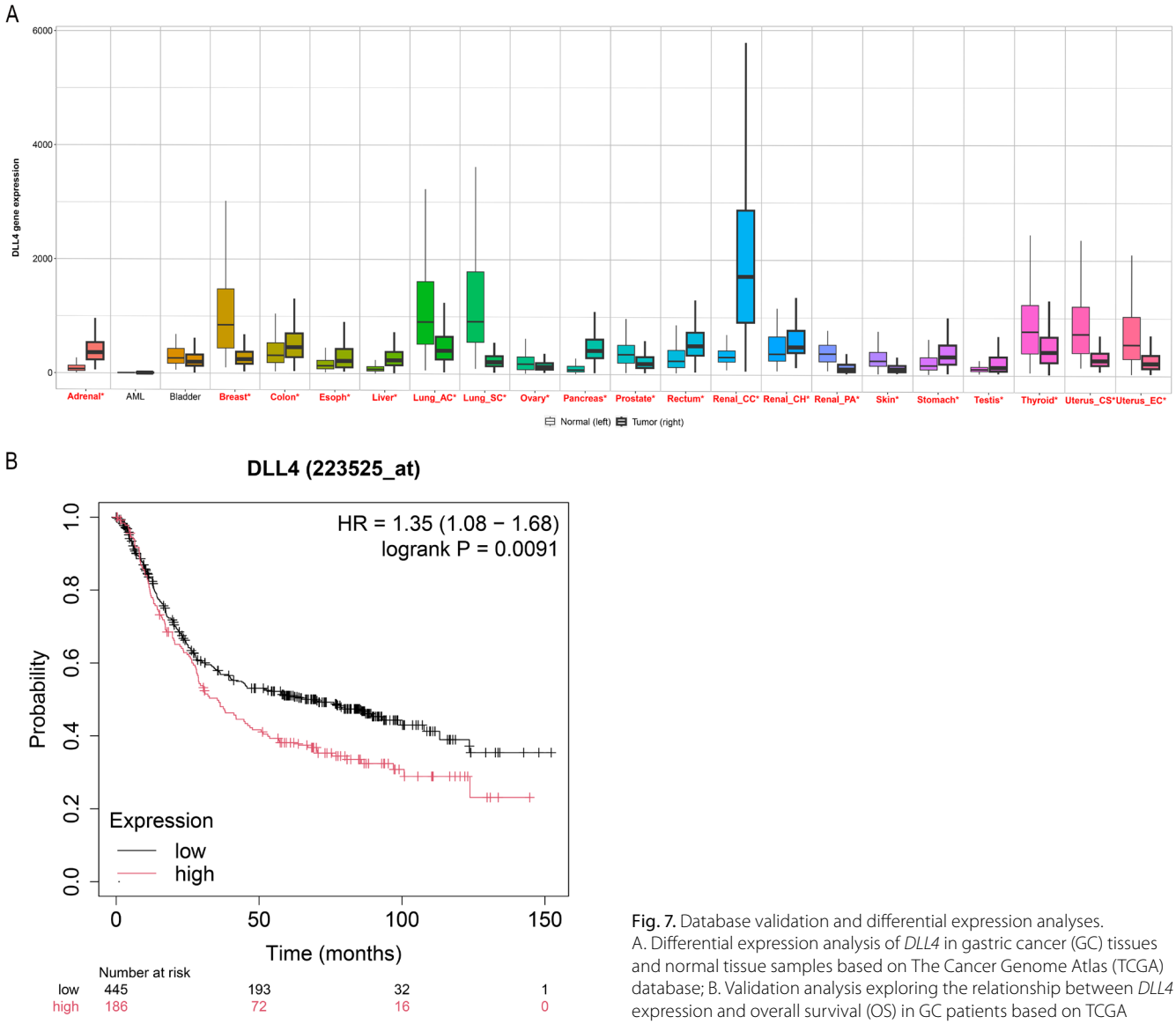

Fig. 7. Database validation and differential expression analyses. A. Differential expression analysis of *DLL4* in gastric cancer (GC) tissues and normal tissue samples based on The Cancer Genome Atlas (TCGA) database; B. Validation analysis exploring the relationship between *DLL4* expression and overall survival (OS) in GC patients based on TCGA

not substantially alter the pooled results, indicating good robustness of the findings (Fig. 6C).

Database validation and differential expression analysis

Analysis using the Kaplan–Meier Plotter database (https://www.kmplot.com/analysis/) demonstrated that *DLL4* expression was significantly higher in GC tissue than in normal gastric tissue (Fig. 7A). Survival curve analysis further showed that high *DLL4* expression was significantly associated with poorer OS in patients with GC (HR = 1.35, 95% CI: 1.08–1.68, p = 0.009) (Fig. 7B).

Discussion

Cancer is a major cause of mortality in both developed and developing countries. Gastric cancer is one of the most common malignancies of the digestive tract and a leading cause of cancer-related death worldwide. It ranks as the 5th most frequently diagnosed cancer globally in terms of newly diagnosed cases.[17] Several studies have demonstrated that early diagnosis and treatment can significantly improve the prognosis of GC patients.[18,19] Therefore, the identification of effective biomarkers for early diagnosis and prognostic assessment remains essential in GC. Our previous research demonstrated that *UCP2* is associated with the clinicopathological characteristics and prognosis of GC patients and may serve as a useful prognostic biomarker.[20] Recent studies have also suggested that *DLL4* is associated with the clinicopathological features and prognosis of GC; however, the reported findings remain controversial. In the present meta-analysis, high *DLL4* expression was significantly associated with advanced TNM stage, lymph node metastasis, venous invasion, and poor OS, but not with sex, age, T stage, tumor differentiation, or Lauren classification in GC patients.

These findings suggest that high *DLL4* expression may serve as a prognostic biomarker in GC.

Angiogenesis is a fundamental process in tumor growth and progression that contributes to aggressive and metastatic tumor behavior.[17] Accumulating evidence indicates that the Notch signaling pathway plays a critical role in cell proliferation, differentiation, vascular development, and angiogenesis.[21] Notably, *DLL4* is a key regulator of tumor angiogenesis and neovascularization.[22–24] Overexpression of *DLL4* has been associated with clinicopathological characteristics and prognosis in multiple cancer types. Wang et al. reported that increased *DLL4* protein expression in breast cancer was associated with shorter OS.[25] Kim et al. demonstrated that patients with positive *DLL4* expression had significantly poorer OS than those with negative *DLL4* expression in colorectal cancer.[26] Kuramoto et al. confirmed that *DLL4* plays a crucial role in liver metastasis of small cell lung cancer.[27] Drouillard et al. reported that high *DLL4* expression predicted poorer OS and shorter disease-free survival (DFS) following resection of pancreatic adenocarcinoma.[28] Furthermore, several studies have investigated the role of *DLL4* expression in GC tissues.[10,12–14] Previous studies demonstrated that *DLL4* expression is significantly elevated in GC cells and tissues.[29] In addition, associations between *DLL4* expression and clinicopathological characteristics of GC patients have been reported. Several studies showed that high *DLL4* expression was associated with venous invasion in GC. However, the relationship between *DLL4* expression and clinicopathological characteristics in GC remains controversial. Kim et al. found no significant association between *DLL4* expression and venous invasion in 336 GC patients.[10] Moreover, some studies suggested that *DLL4* expression is associated with TNM stage in GC.[10,15,16] In contrast, Ishigami et al. reported no significant association between *DLL4* expression and TNM stage in GC tissues.[11] According to our meta-analysis, high *DLL4* expression was significantly associated with advanced TNM stage, lymph node metastasis, and venous invasion.

Several studies have assessed the effect of anti-*DLL4* therapy on the frequency of cancer stem cells. These findings showed that anti-*DLL4* treatment led to a twofold reduction in cancer stem cell frequency.[30] Additionally, some authors reported a significant correlation between T stage and high *DLL4* expression in patients,[14–16] whereas others found no such association in patients with GC.[10–13] Similarly, several studies reported no correlation between *DLL4* expression and Lauren classification,[10,11,13] and others found no association between *DLL4* expression and tumor differentiation.[10,11,14–16]

In our study, *DLL4* expression was not associated with tumor differentiation, T stage, or Lauren classification. However, the clinical significance of *DLL4* expression and its relationship with T stage, tumor differentiation, and Lauren classification in GC patients should be further investigated in randomized controlled trials (RCTs) with larger sample sizes. Further studies are also needed to elucidate the key regulatory mechanisms of the *DLL4* signaling pathway in GC cells.

DLL4 plays a significant role in several cancer types and acts as an oncogene-like factor.[25–28] Numerous studies have demonstrated that *DLL4* expression is associated with poor survival across a variety of tumor types.[25,26,28,31] Furthermore, several authors have evaluated the potential prognostic significance of *DLL4* expression in patients with GC. However, the relationship between *DLL4* expression and OS in GC patients remains controversial. According to Segami et al., there was no significant difference in the 5-year survival rate between GC patients with *DLL4*-positive and *DLL4*-negative expression.[12] In contrast, other studies reported lower survival rates in GC patients with high *DLL4* expression compared with those with low *DLL4* expression.[10,11,13,14]

Our meta-analysis demonstrated that GC patients with high *DLL4* expression had poorer OS. The Cancer Genome Atlas (TCGA) database and a comprehensive survival analysis using the Kaplan–Meier Plotter were further used to validate these findings.

Limitations of the study

Several limitations of this meta-analysis should be acknowledged. First, although extensive searches were conducted across multiple databases, the relatively small number of included studies may have introduced bias into the findings. Second, the included studies applied different criteria for certain clinicopathological parameters, including patient selection and research methodologies, and the heterogeneity resulting from these differences could not be ignored. Finally, the relatively limited sample size prevented detailed analyses of individual cases.

Conclusions

This meta-analysis revealed that *DLL4* expression was associated with venous invasion, lymph node metastasis, TNM stage, and poor OS, but was not associated with age, T stage, sex, tumor differentiation, or Lauren classification. These findings suggest that *DLL4* may serve as a predictor of poor prognosis in GC patients. Further large-scale studies with more homogeneous patient populations are needed to better clarify the relationship between *DLL4* expression and the clinicopathological characteristics and prognosis of GC patients.

Supplementary data

The supplementary materials are available at https://doi.org/10.5281/zenodo.19742186. The package contains the following files:

Supplementary Fig. 1. Forest plots for the relationship of *DLL4* expression with venous invasion (A) and TNM stage (B). Funnel plots for the relationship between *DLL4* expression with venous invasion (C) and TNM stage (D). Sensitivity analysis for the relationship between *DLL4* expression with venous invasion (E) and TNM stage (F).

Use of AI and AI-assisted technologies

Not applicable.

ORCID iDs

Qingyu Du https://orcid.org/0009-0000-5799-8754
Chenglin Zhao https://orcid.org/0009-0007-3899-1144
Chunling Sun https://orcid.org/0009-0003-6576-6365
Guo Zu https://orcid.org/0000-0002-6333-8573
Shaohua Du https://orcid.org/0009-0001-2734-4175

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