Systematic Review and Meta-Analysis

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The relationship between hepatoma-derived growth factor and prognosis in non-small cell lung cancer

A systematic review and meta-analysis

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Abstract

Background: Hepatoma-derived growth factor (HDGF) promotes cancer progression and metastasis by interacting with vascular endothelial growth factor, thereby inducing epithelial-to-mesenchymal transition and angiogenesis. Recent studies have correlated increased HDGF levels with poor prognosis in various malignancies, including lung cancer. This meta-analysis systematically assessed the prognostic significance of HDGF expression in patients with non-small cell lung cancer (NSCLC).

Methods: Eligible studies were identified by searching literature in PubMed, Embase, Scopus, and the Cochrane library until June 2020. The pooled hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) was determined to assess the relationship between HDGF expression and clinical outcome in patients with NSCLC.

Results: The pooled HRs between high HDGF expression and clinical outcome were 2.20 (95% CI 1.75–2.76, $P < .001$) and 2.77 (95% CI 1.79–4.29, $P < .001$) for overall survival and disease-free survival, respectively. High HDGF expression was significantly correlated with a larger tumor size (OR 1.59, 95% CI 1.02–2.46, $P = .040$).

Conclusion: HDGF expression is related to clinical outcome and may be a prognostic marker in patients with NSCLC.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HDGF = hepatoma-derived growth factor, HR = Hazard ratio, NSCLC = non-small cell lung cancer, OR = odds ratio, OS = overall survival, VEGF = vascular endothelial growth factor.

Keywords: hepatoma-derived growth factor, meta-analysis, non-small cell lung cancer, prognosis

1. Introduction

Lung cancer is the leading cause of cancer-related mortality, and non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancers.[1] Despite recent developments in its treatment, the prognosis of lung cancer remains poor. Thus, investigating the molecular mechanism for cancer progression and identifying prognostic biomarkers is essential for choosing better treatment options for patients with NSCLC.[2]

Hepatoma-derived growth factor (HDGF) was originally identified as a heparin-binding growth factor in hepatoma-derived cells.[3] Studies have cited its key role in various biological processes, including early tissue development, wound repair, and angiogenesis.[2,3] Additionally, HDGF is involved in the development and progression of cancer, and many studies have reported that increased HDGF level is correlated with poor prognosis in breast, gastric, pancreatic, esophageal, liver, and lung cancer.[2,4–12]

However, the integrated clinical impact of HDGF expression in patients with NSCLC has not been explored. Thus, the present study aimed to elucidate the prognostic and clinicopathological significance of HDGF expression in patients with NSCLC.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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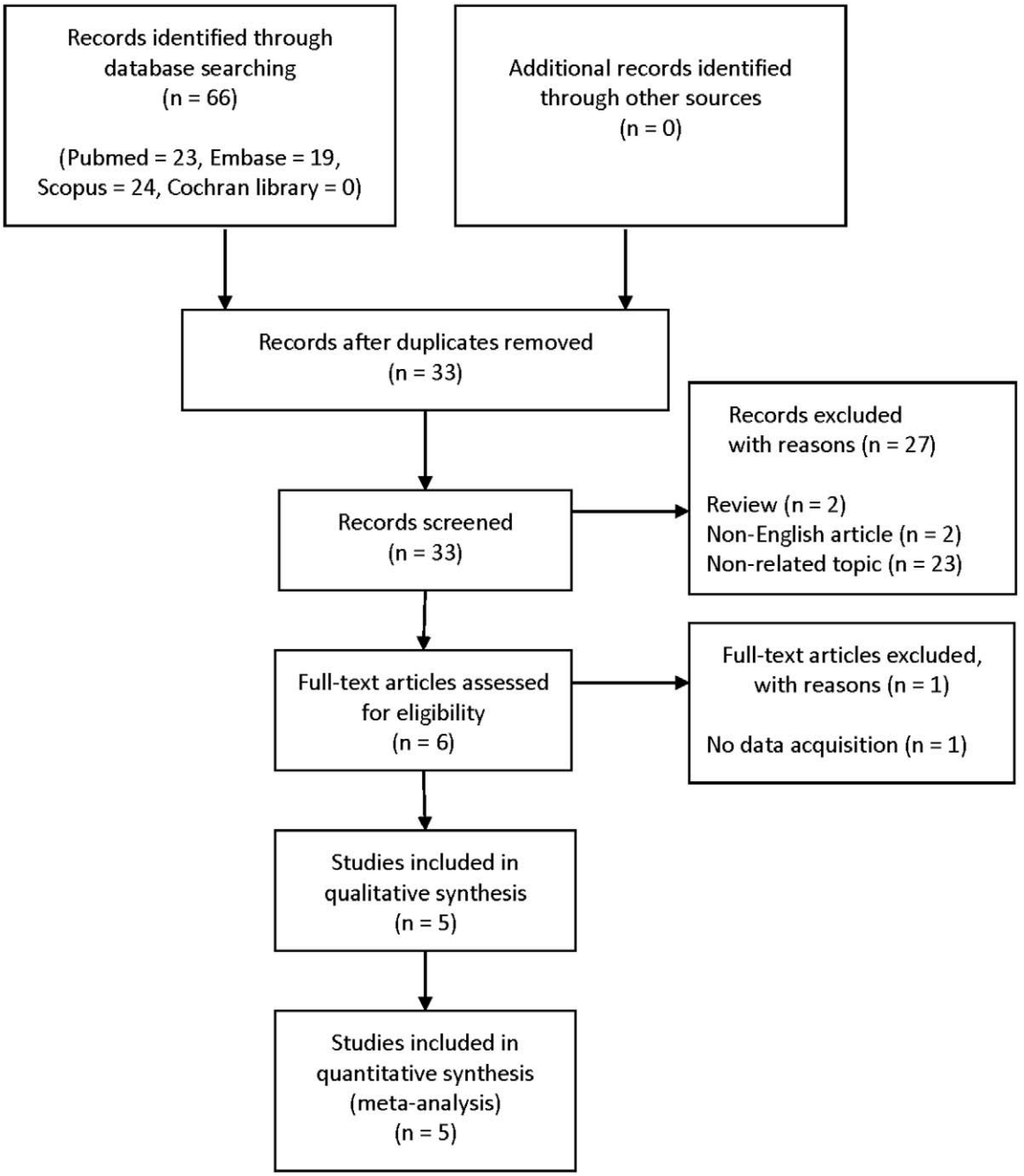


Figure 1. Flow diagram of study selection.

2. Materials and methods

2.1. Literature search

The literature searches are HDGF or hepatoma-derived growth factor; and lung cancer or lung carcinoma; and prognostic, predict, prognosis, survival, or outcome. A manual search was also conducted. This study was based on previously published reports; therefore, ethical approval and informed consent were not required.

2.2. Inclusion and exclusion criteria

The eligibility criteria for studies included the following:

1. HDGF expression was identified in patients with lung cancer and
2. the hazard ratio (HR) with 95% confidence interval (CI) for the relationship between HDGF expression and clinical outcome was provided.

Studies were excluded if they met any of the following criteria:

1. duplicate publications and
2. conference abstracts, reviews, and non-English articles.

2.3. Data extraction and quality assessment

Two authors independently extracted the basic information of the included studies. The extracted data included the first author, publication year, country, histologic type, clinicopathological factors, study period, follow-up duration, detection method, and cutoff value of HDGF expression. The quality of included studies was also assessed by the two authors independently using the Newcastle-Ottawa Scale. If there were different opinions, an agreement was reached through discussion.

2.4. Statistical analyses

The pooled HR or odds ratio (OR) with 95% CI was calculated to investigate the prognostic and clinicopathological significance of HDGF expression. The heterogeneity between the included studies was assessed using the I^2 value. Funnel plots and Egger's tests were used to show publication bias. Sensitivity analysis was conducted to reveal the effects of individual studies. All statistical analyses were performed using StataSE 12 (Stata, College Station, TX). *P*-Values less than .05 were considered statistically significant.

3. Results

3.1. Search results and study information

Five eligible studies were adopted through the process of study selection (Fig. 1). The basic characteristics of the studies are listed in Table 1. The studies included 426 cases of adenocarcinoma, 180 cases of squamous cell carcinoma, and 15 cases of other histologic types. A total of 374 male patients and 247 female patients were included. As for the stage, the analysis included 298 stage I and II patients and 323 stage III and IV patients. Most patients underwent surgery while some had chemotherapy or centesis. Four studies evaluated HDGF expression via immunohistochemistry. The remaining studies used an enzyme-linked immunosorbent assay. All studies, except one, reported survival analysis using a multivariate method. The included studies were given a good quality rating, with seven or more points.

3.2. Relationship between HDGF expression and overall survival (OS)

Five studies evaluated the relationship between HDGF expression and OS in 621 patients with NSCLC. According to the fixed-effect model analysis (I^2 = 37.0%, P = .175), the pooled HR for OS in patients with high HDGF expression was 2.20 (95% CI 1.75–2.76, P < .001). This indicated that high HDGF expression was related to decrease OS in patients with NSCLC (Fig. 2). The results of the subgroup analysis via HDGF detection method revealed that HDGF expression could act as a prognostic factor in the group with immunohistochemistry (HR 2.55, 95% CI 1.82–3.58, P < .001) (Table 2) (Fig. 3A). On multivariate analysis, HDGF expression was a potential independent prognostic factor for OS (HR 2.18, 95% CI 1.70–2.78, P < .001) (Table 2) (Fig. 3B).

Table 1

The basic characteristics of included studies.

Study	Country	Histologic type (case number)	Sex (male/female)	Mean or median age (years)	Overall stage (case number)	Treatment	Study period	Follow-up (months)	Clinical outcome	HDGF detection method	Cut-off value of HDGF expression	Survival analysis	NOS
Jiang et al (2019)	China	ADC (123)	67/56	NA	I–II (76) III–IV (47)	Surgery or centesis	2007–2009	Until August 2014	OS	IHC	≥3 (the sum of staining intensity and extent)	MVA	8
Zhang et al (2017)	China	ADC (141) SCC (94)	129/106	NA	III (127) IV (108)	Chemotherapy	2006–2016	NA	OS	ELISA	>385 pg/mL (by ROC curve)	MVA	7
Zhang et al (2014)	China	ADC (48) SCC (15)	35/28	60	I (63)	Surgery	2000–2006	NA	OS	IHC	>Average staining index (the multiplication of staining intensity and percentage)	MVA	7
Iwasaki et al (2005)	Japan	ADC (70) SCC (32)	69/33	64	I–II (61) III–IV (41)	Surgery	1994–1997	Median 61.3	OS, DFS	IHC	≥65%	MVA	8
Ren et al (2004)	USA	ADC (44) SCC (39) Other* (15)	74/24	62.8	I (98)	Surgery	1975–1990	Median 120	OS, DFS	IHC	>Mean labeling index (185) (the multiplication of staining intensity and number of positive cells)	UVA	8

ADC = adenocarcinoma, DFS = disease-free survival, ELISA = enzyme linked immunosorbent assay, HDGF = hepatoma-derived growth factor, IHC = immunohistochemistry, MVA = multivariate analysis, NA = not available, NOS = Newcastle-Ottawa Scale, OS = overall survival, ROC = receiver operating characteristic, SCC = squamous cell carcinoma, UVA = univariate analysis.

* Other: bronchioalveoli (7), large cell (3) and mixed (5).

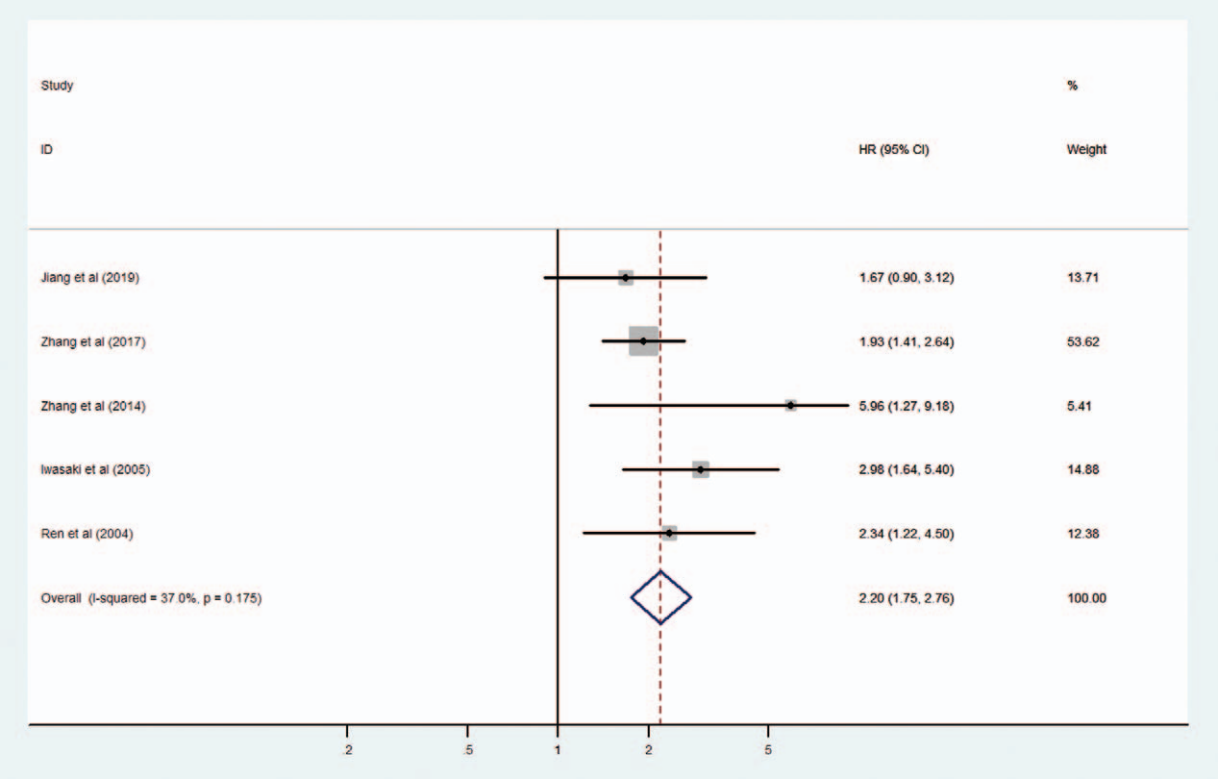


Figure 2. Forest plot for the relationship between HDGF expression and overall survival.

3.3. Relationship between HDGF expression and DFS

Two studies assessed the relationship between HDGF expression and disease-free survival (DFS) among 200 patients with NSCLC. According to the fixed-effect model analysis ($I^2 = 0.0\%$, $P = .733$), the pooled HR for DFS in patients with high HDGF expression was 2.77 (95% CI 1.79–4.29, $P < .001$). This suggested that high HDGF expression was related to reduce DFS in patients with NSCLC (Fig. 4).

3.4. Relationship between HDGF expression and clinicopathological factors

High HDGF expression was significantly correlated with a larger tumor size (OR 1.59, 95% CI 1.02–2.46, $P = .040$) (Table 3) (Fig. 5A). Higher tumor grade and stage (OR 1.25, 95% CI 0.75–2.08, $P = .399$; OR 1.71, 95% CI 0.81–3.61, $P = .162$), lymph node metastasis (OR 2.18, 95% CI 0.40–11.86, $P = .367$), and higher overall stage (OR 3.41, 95% CI 0.35–33.07, $P = .290$) were also related to high HDGF expression, although these were not statistically significant (Table 3) (Fig. 5B–H).

3.5. Publication bias and sensitivity analysis

The funnel plot was slightly asymmetrical, although the Egger's test did not confirm publication bias ($P = .181$) (Fig. 6A). The filled funnel plot showed that two studies were added, and the results (HR 1.94, 95% CI 1.57–2.39, $P < .001$) were still significant (Fig. 6B).

Because the results of the sensitivity analysis were similar to the initial pooled results (HR 2.20, 95% CI 1.75–2.76), the influence of individual studies was insignificant (Fig. 6C).

Table 2

Subgroup analysis of the relationship between HDGF expression and overall survival in non-small cell lung cancer.

Group	Number of studies	Number of patients	Pooled HR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	*P*
HDGF detection method						
IHC	4	386	2.55 (1.82–3.58)	<.001	39.1	.177
ELISA	1	235	1.93 (1.41–2.64)	<.001	–	–
Survival analysis						
Multivariate	4	523	2.18 (1.70–2.78)	<.001	52.4	.098
Univariate	1	98	2.34 (1.22–4.49)	.011	–	–

CI = confidence interval, ELISA = enzyme linked immunosorbent assay, HDGF = hepatoma-derived growth factor, HR = hazard ratio, IHC = immunohistochemistry.

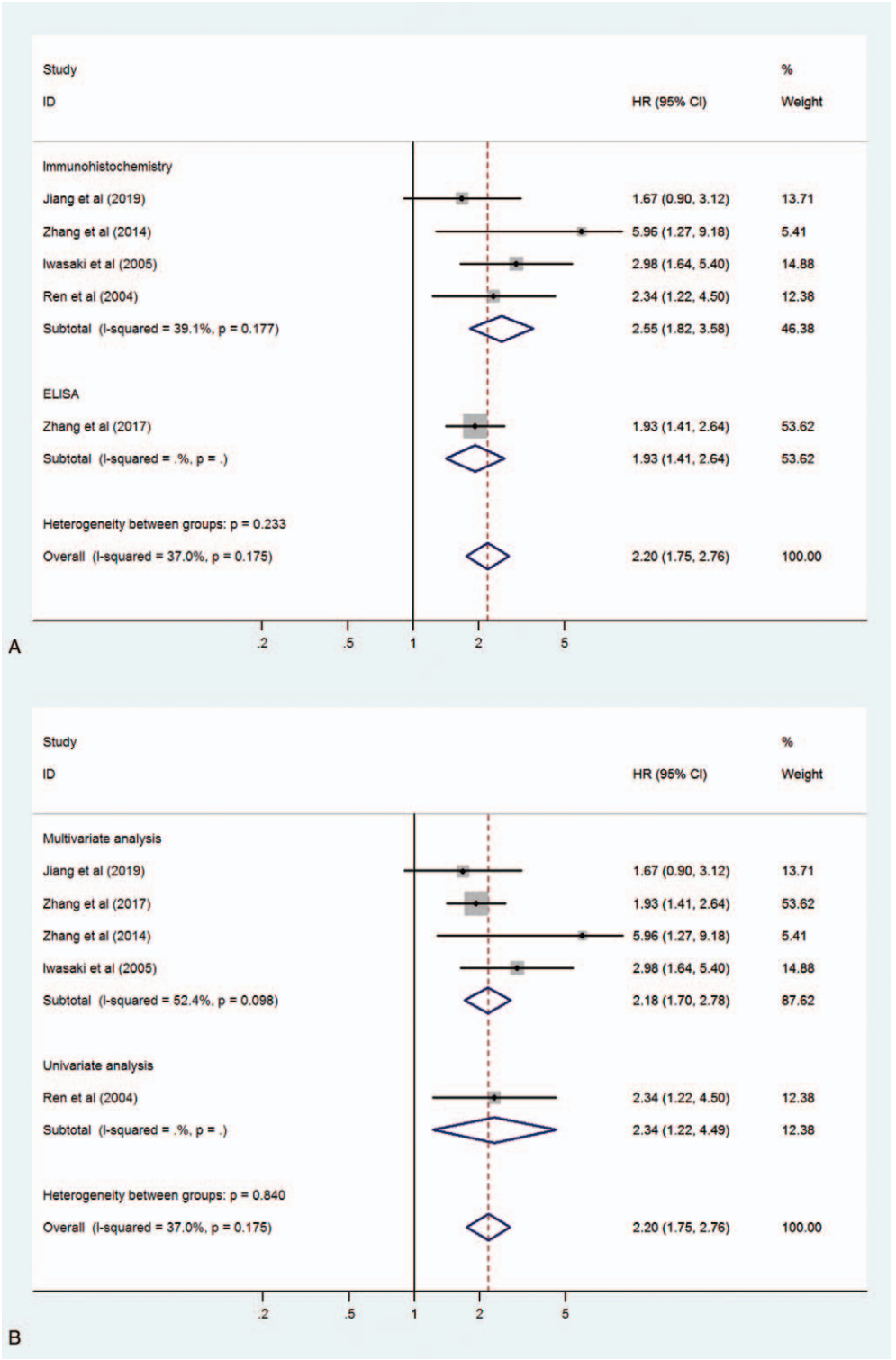


Figure 3. Subgroup analysis stratified by HDGF detection method (A) and by survival analysis (B).

4. Discussion

HDGF is an important molecule in cancer development, progression, and metastasis.[3] It induces epithelial-to-mesenchymal transition and angiogenesis by interacting with vascular endothelial growth factor (VEGF).[3] Recent studies have shown that HDGF enhances VEGF-dependent angiogenesis in NSCLC cells, and HDGF downregulation is involved in the inhibition of NSCLC cell growth.[1,13] Moreover, high HDGF expression is related to poor prognosis in patients with NSCLC.[8–12]

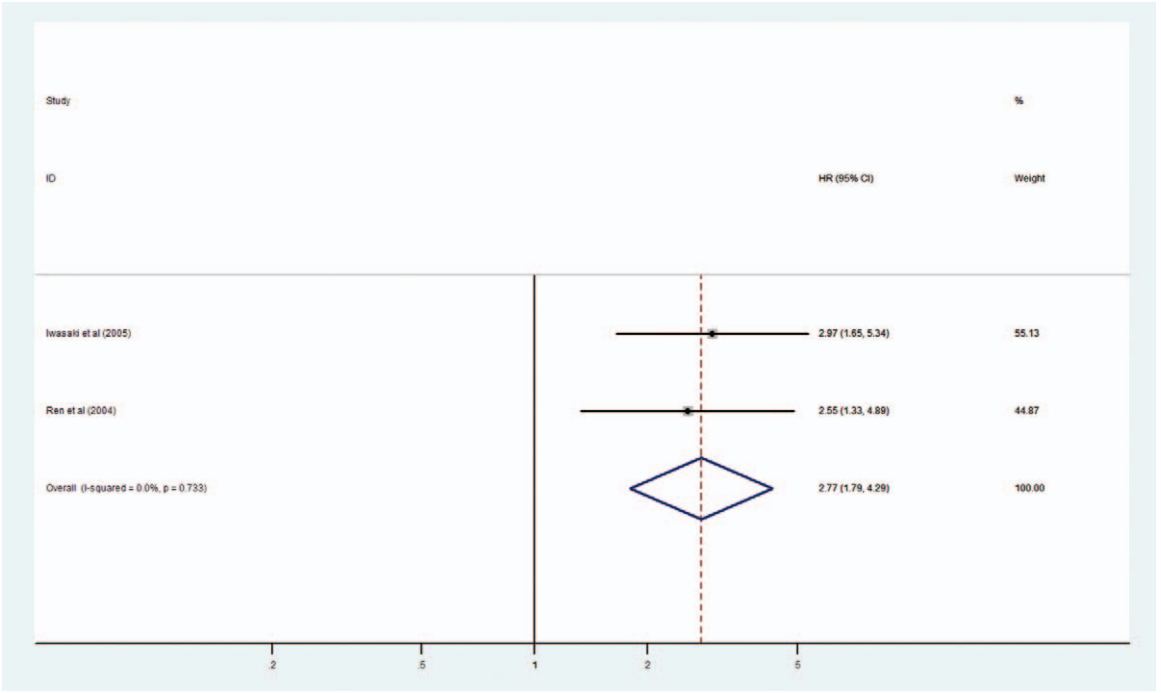


Figure 4. Forest plot for the relationship between HDGF expression and disease-free survival.

Jiang et al[8] related HDGF expression with clinical stage, tumor and node classification, and lymph node metastasis. Patients with lung adenocarcinoma with high HDGF expression exhibited poorer OS than those with low HDGF expression. Zhang et al[9] revealed that high serum HDGF levels were significantly correlated with bone metastasis and unfavorable prognosis in NSCLC. Zhang et al[10] demonstrated that high HDGF expression was an independent factor of shortened survival time in resected stage I NSCLC, and HDGF promoted the invasion and metastasis of NSCLC cells. Iwasaki et al[11] considered HDGF as a useful prognostic marker for patients with completely resected NSCLC. Ren et al[12] also suggested that HDGF expression is a strong prognosticator in patients with early stage NSCLC.

In the present study, we systematically explored the relationship between HDGF expression and prognosis among patients with NSCLC. High expression of HDGF was significantly related to unfavorable prognosis and correlated with a larger tumor size. Moreover, we demonstrated that our results were still significant, even when the influence of individual studies was excluded. Our findings indicated that HDGF expression may be a prognostic marker for patients with NSCLC. To the best of our knowledge, this report is the first to show the prognostic significance of HDGF expression in NSCLC.

Table 3

The relationship between HDGF expression and clinicopathological factors in patients with non-small cell lung cancer.

Factor	Number of studies	Number of patients	Pooled OR (95% CI)	*P*	Heterogeneity I^2 (%)	Heterogeneity *P*	Heterogeneity Model
Age (old vs young)	3	460	0.91 (0.62–1.35)	.644	0.0	.637	Fixed
Sex (male vs female)	4	558	1.34 (0.77–2.32)	.304	56.2	.077	Random
Histologic type (SCC vs ADC)	3	420	0.82 (0.55–1.21)	.318	11.4	.324	Fixed
Tumor size (large vs small)	2	337	1.59 (1.02–2.46)	.040	0.0	.576	Fixed
Tumor grade (MD,PD vs WD)	2	337	1.25 (0.75–2.08)	.399	0.0	.554	Fixed
Tumor stage (III,IV vs I,II)	2	225	1.71 (0.81–3.61)	.162	13.7	.282	Fixed
Lymph node metastasis(present vs absent)	2	225	2.18 (0.40–11.86)	.367	89.5	.002	Random
Overall stage (III,IV vs I,II)	2	225	3.41 (0.35–33.07)	.290	92.3	<.001	Random

ADC = adenocarcinoma, CI = confidence interval, HDGF = hepatoma-derived growth factor, MD = moderately differentiated, OR = odds ratio, PD = poorly differentiated, SCC = squamous cell carcinoma, WD = well differentiated.

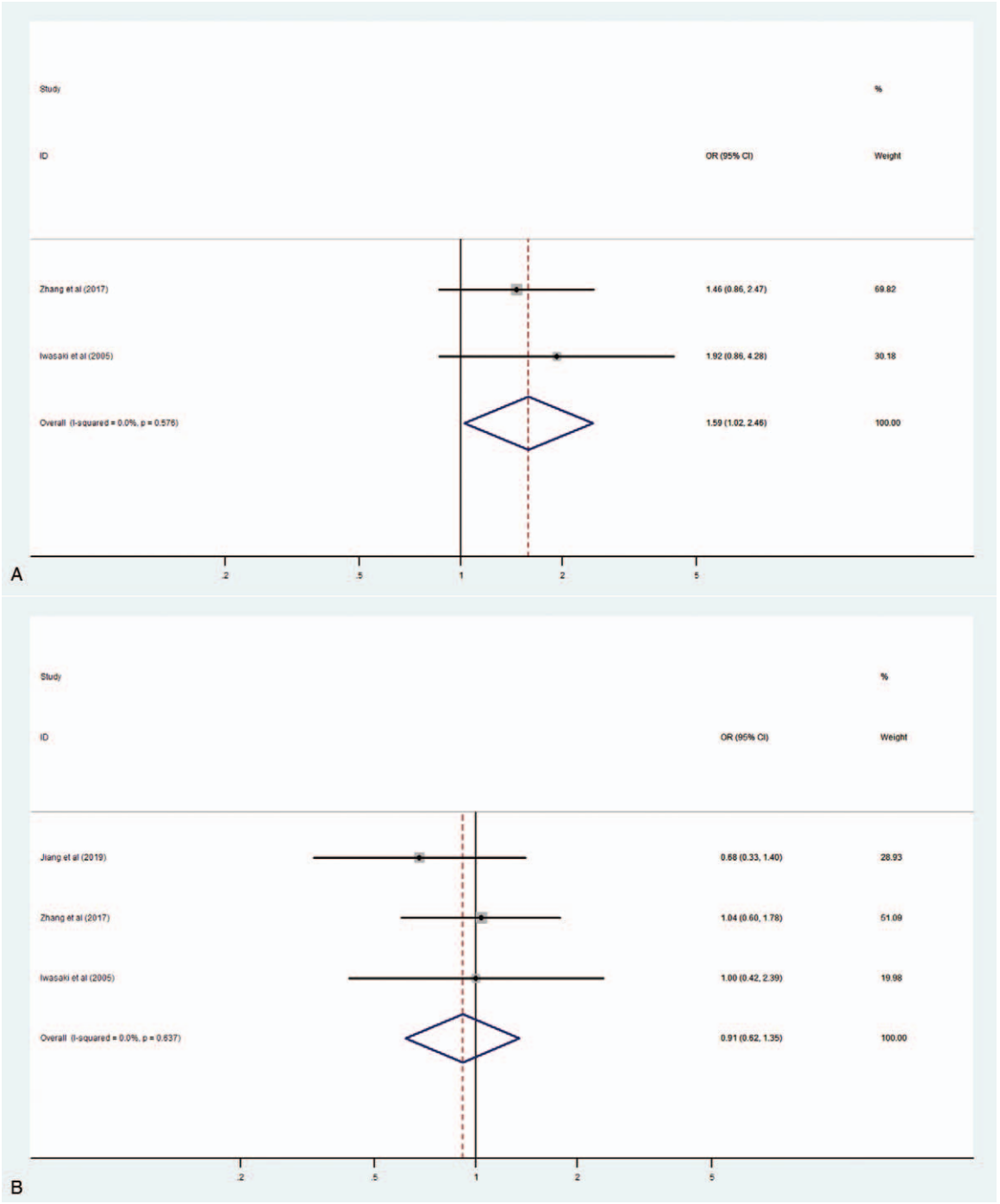
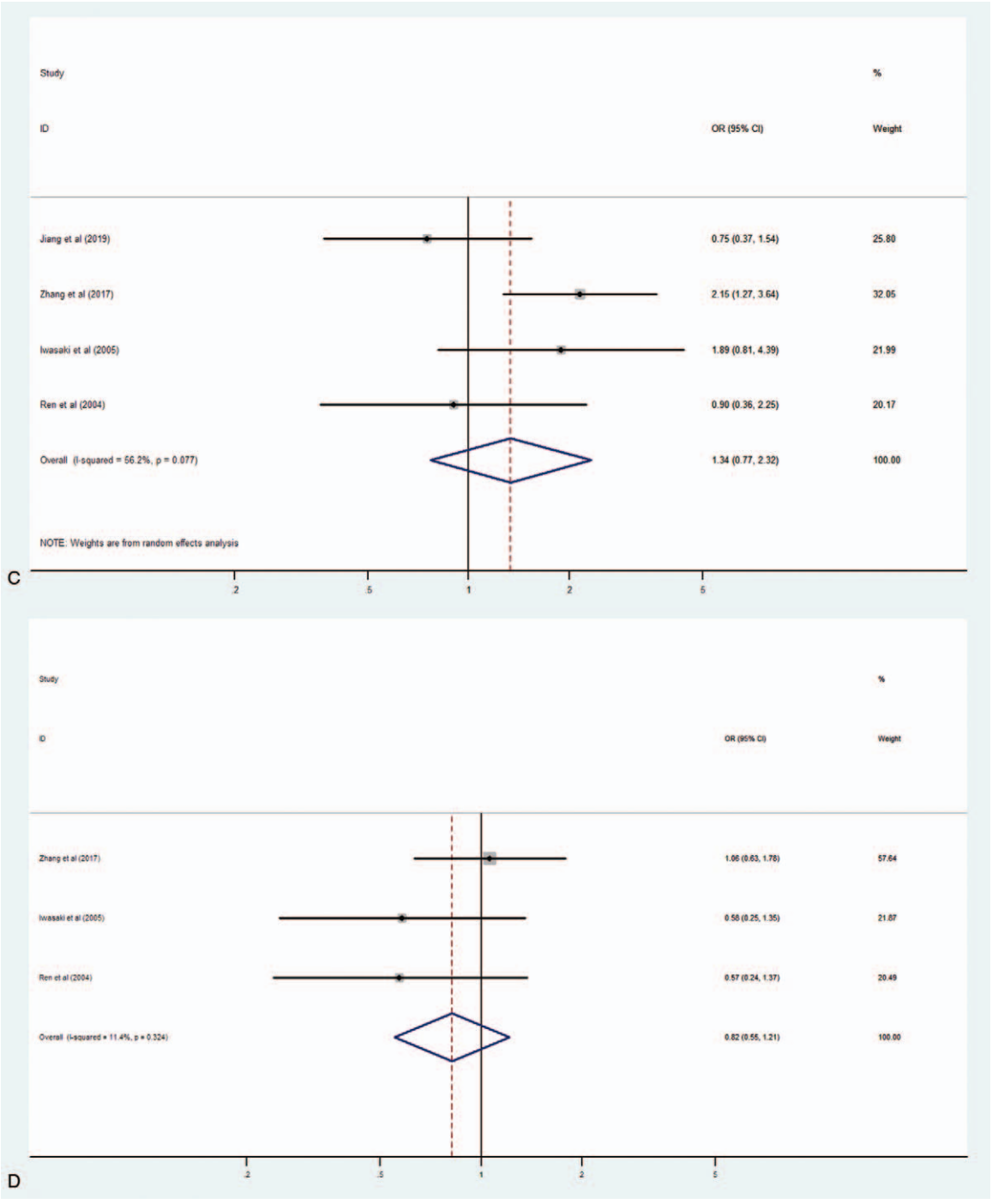


Figure 5. Forest plot for the relationship between HDGF expression and clinicopathological factors. Tumor size (A), age (B), sex (C), histologic type (D), tumor grade (E), tumor stage (F), lymph node metastasis (G), and overall stage (H).



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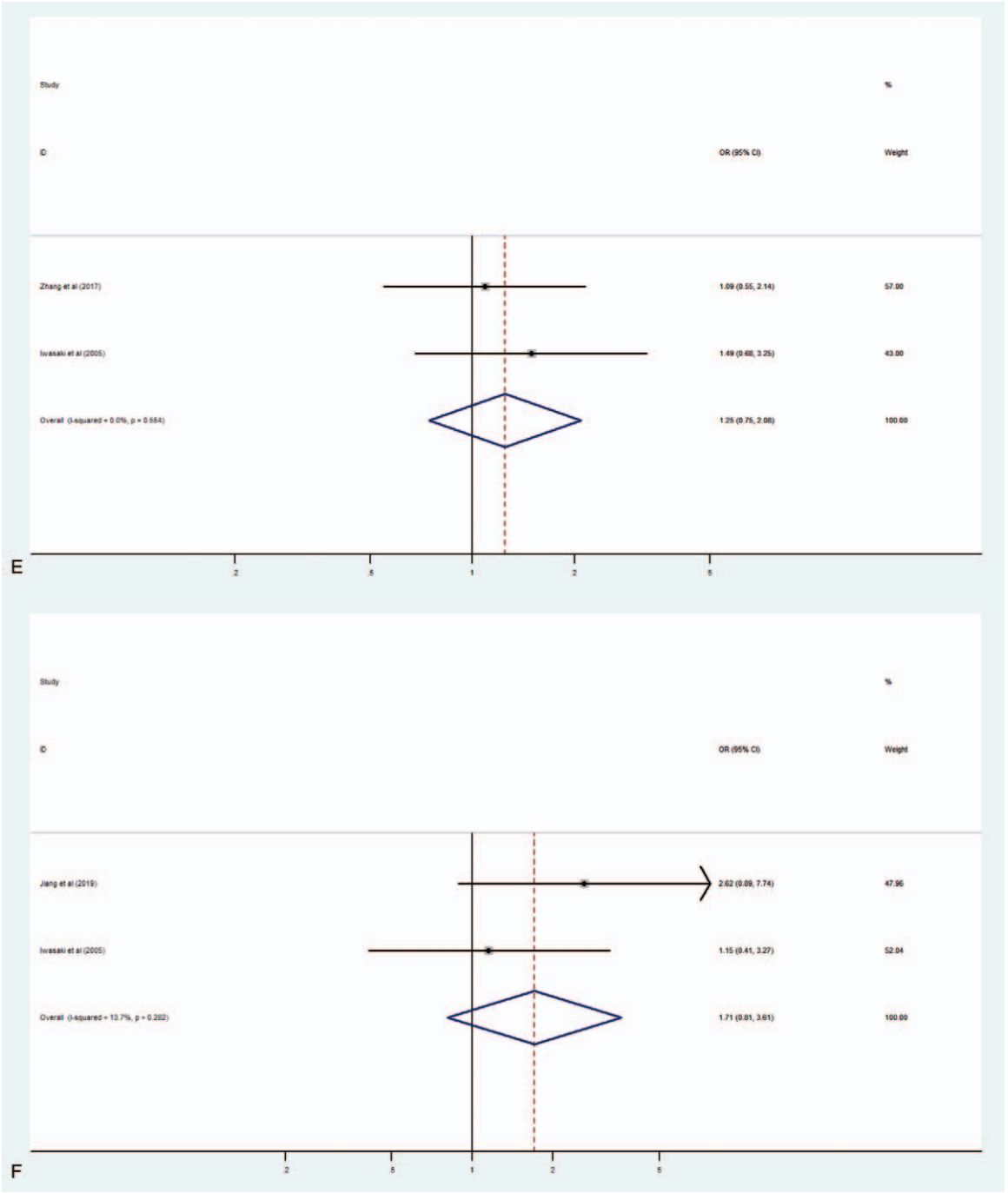

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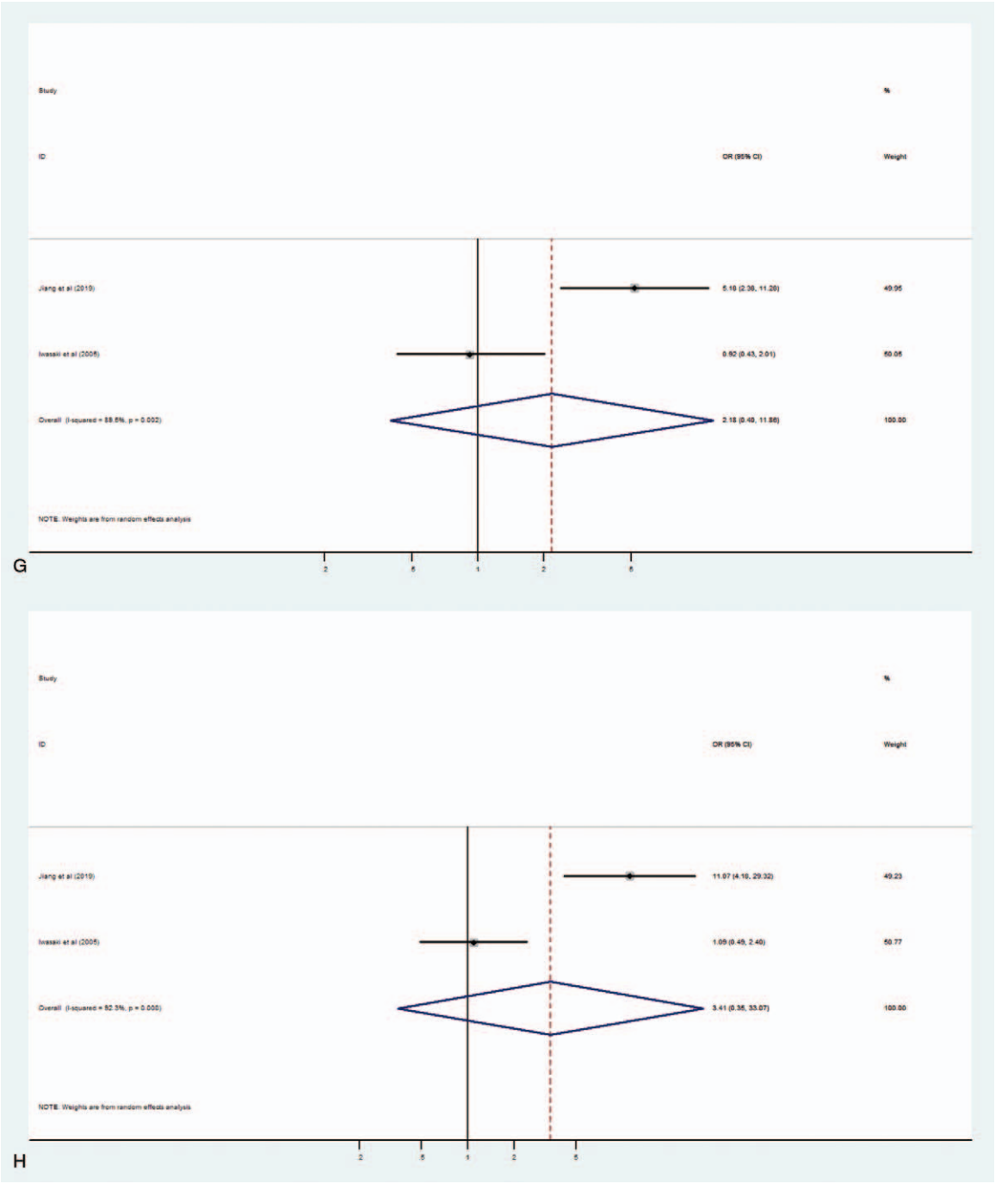

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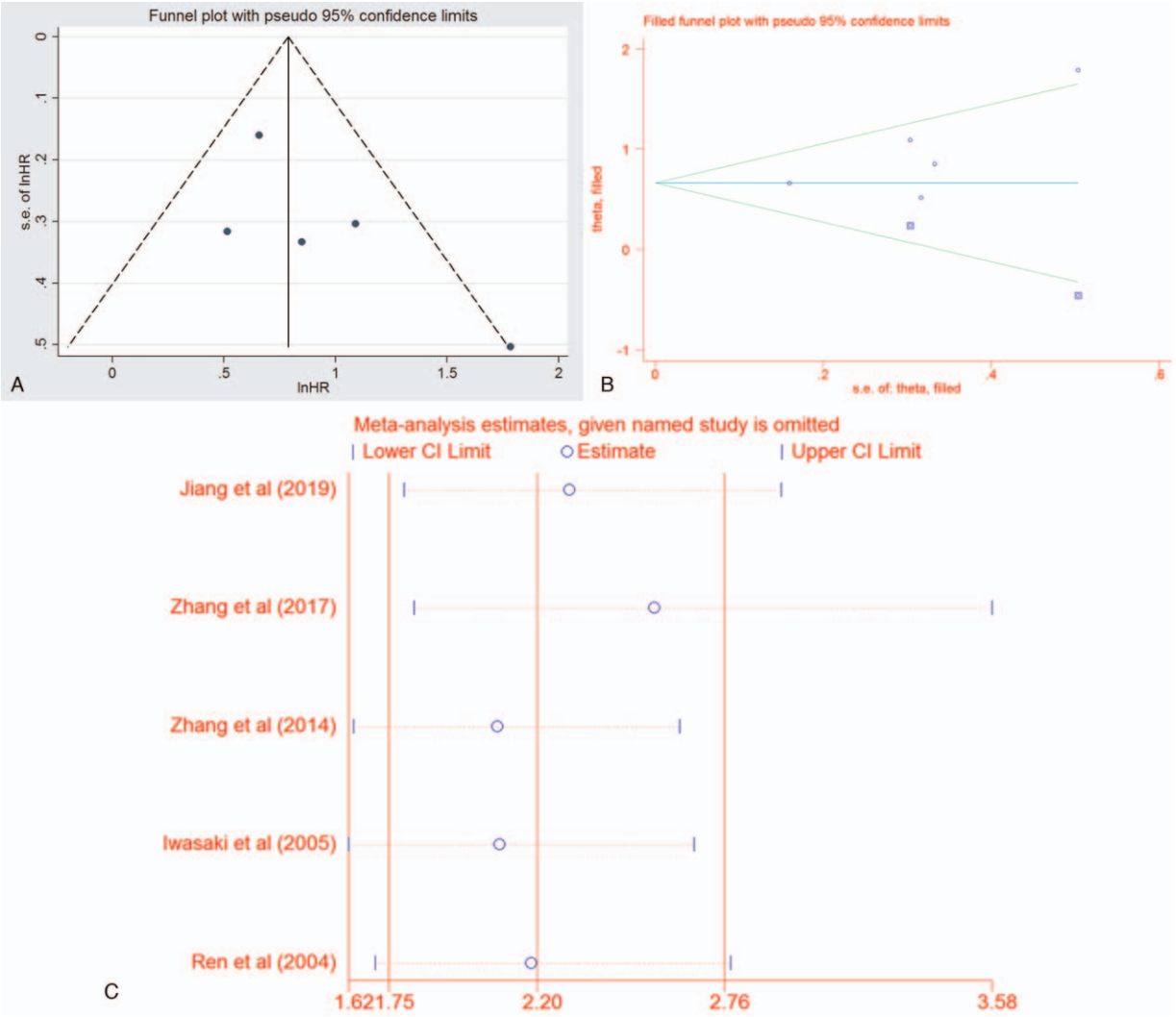

Figure 6. Funnel plot (A), filled funnel plot (B), and sensitivity analysis (C).

5. Limitations

Only five studies with a small number of cases were included in the analysis. Thus, it did not reveal the relationship between HDGF expression and the type of cancer, initial staging, type of treatment, and subsequent survival. In the future, we hope that more thoroughly designed research will be conducted to overcome these limitations.

6. Conclusion

We revealed that the expression of HDGF, which has recently been noted as an important target for anti-angiogenic treatment, is significantly related to the prognosis of patients with NSCLC.

Author contributions

Conceptualization: Hyun Min Koh, Chang Lim Hyun, Bo Gun Jang, Hyun Ju Lee.
Data curation: Hyun Min Koh, Chang Lim Hyun.
Formal analysis: Hyun Min Koh, Bo Gun Jang.
Investigation: Hyun Min Koh, Chang Lim Hyun, Bo Gun Jang, Hyun Ju Lee.
Resources: Hyun Min Koh, Chang Lim Hyun, Bo Gun Jang, Hyun Ju Lee.
Supervision: Hyun Ju Lee.
Validation: Hyun Min Koh, Hyun Ju Lee.
Writing – original draft: Hyun Min Koh.
Writing – review & editing: Hyun Min Koh.

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