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.\textsuperscript{[2]} 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.\textsuperscript{[2]}

Hepatoma-derived growth factor (HDGF) was originally identified as a heparin-binding growth factor in hepatoma-derived cells.\textsuperscript{[3]} Studies have cited its key role in various biological processes, including early tissue development, wound repair, and angiogenesis.\textsuperscript{[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 cancers.\textsuperscript{[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.
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 I² 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 in 621 patients with NSCLC. According to the subgroup 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 (I² = 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 a decrease in 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).
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 reduced 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**

| Group                  | Number of studies | Number of patients | Pooled HR (95% CI) | $P$  | $I^2$ (%) | $P$  |
|------------------------|------------------|-------------------|--------------------|------|---------|------|
| 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.
4. Discussion

HDGF is an important molecule in cancer development, progression, and metastasis.\(^1\) It induces epithelial-to-mesenchymal transition and angiogenesis by interacting with vascular endothelial growth factor (VEGF).\(^1\) 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.\(^8-12\)

![Subgroup analysis stratified by HDGF detection method (A) and by survival analysis (B).](image-url)
Jiang et al\textsuperscript{[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\textsuperscript{[9]} revealed that high serum HDGF levels were significantly correlated with bone metastasis and unfavorable prognosis in NSCLC. Zhang et al\textsuperscript{[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\textsuperscript{[11]} considered HDGF as a useful prognostic marker for patients with completely resected NSCLC. Ren et al\textsuperscript{[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

| Factor                                      | Number of studies | Number of patients | Pooled OR (95% CI) | P   | $I^2$ (%) | P   | Model |
|---------------------------------------------|-------------------|--------------------|--------------------|-----|-----------|-----|-------|
| Age (old vs young)                          | 3                 | 490                | 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 (II,IV vs I,II)                 | 2                 | 225                | 1.71 (1.01–3.06)   | .162| 13.7      | .282| Fixed |
| Lymph node metastasis(present vs absent)    | 2                 | 225                | 2.18 (1.40–3.36)   | .367| 89.5      | .002| Random|
| Overall stage (II,IV vs I,II)               | 2                 | 225                | 3.41 (2.35–5.07)   | .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).
Figure 5. (Continued).
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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.
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Supervision: Hyun Ju Lee.
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Writing – review & editing: Hyun Min Koh.

References

[1] Eguchi R, Wakabayashi I. HDGF enhances VEGF-dependent angiogenesis and FGF-2 is a VEGF-independent angiogenic factor in non-small cell lung cancer. Oncol Rep 2020;44:14-28.
[2] Chen X, Yun J, Fei F, et al. Prognostic value of nuclear hepatoma-derived growth factor (HDGF) localization in patients with breast cancer. Pathol Res Pract 2012;208:437-43.
[3] Bao C, Wang J, Ma W, et al. HDGF: A novel jack-of-all-trades in cancer. Future Oncol 2014;10:2675–85.
[4] Yamamoto S, Tomita Y, Hoshida Y, et al. Expression of hepatoma-derived growth factor is correlated with lymph node metastasis and prognosis of gastric carcinoma. Clin Cancer Res 2006;12:117-22.
[5] Uyama H, Tomita Y, Nakamura H, et al. Hepatoma-derived growth factor is a novel prognostic factor for patients with pancreatic cancer. Clin Cancer Res 2006;12(20 Pt 1):6043–8.
[6] Yamamoto S, Tomita Y, Hoshida Y, et al. Expression level of hepatoma-derived growth factor correlates with tumor recurrence of esophageal carcinoma. Ann Surg Oncol 2007;14:2141–9.
[7] Yoshida K, Tomita Y, Okuda Y, et al. Hepatoma-derived growth factor is a novel prognostic factor for hepatocellular carcinoma. Ann Surg Oncol 2006;13:159–67.
[8] Jiang H, Fu Q, Song X, et al. HDGF and PRKCA upregulation is associated with a poor prognosis in patients with lung adenocarcinoma. Oncol Lett 2019;18:4936–46.
[9] Zhang G, Liu Z, Chen Y, et al. High serum HDGF levels are predictive of bone metastasis and unfavorable prognosis in non-small cell lung cancer. Tohoku J Exp Med 2017;242:101–8.

[10] Zhang J, Chen N, Qi J, et al. HDGF and ADAM9 are novel molecular staging biomarkers, prognostic biomarkers and predictive biomarkers for adjuvant chemotherapy in surgically resected stage I non-small cell lung cancer. J Cancer Res Clin Oncol 2014;140:1441–9.
[11] Iwasaki T, Nakagawa K, Nakamura H, et al. Hepatoma-derived growth factor as a prognostic marker in completely resected non-small-cell lung cancer. Oncol Rep 2005;13:1075–80.
[12] Ren H, Tang X, Lee JJ, et al. Expression of hepatoma-derived growth factor is a strong prognostic predictor for patients with early-stage non-small-cell lung cancer. J Clin Oncol 2004;22:3230–7.
[13] Zhao W, Wang Y, An Z, et al. Downregulation of miR-497 promotes tumor growth and angiogenesis by targeting HDGF in non-small cell lung cancer. Biochem Biophys Res Commun 2013;435:466–71.