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Plasma hepatocyte growth factor as a noninvasive biomarker in small cell lung cancer

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Abstract

Background Hepatocyte growth factor (HGF) is a peptide-containing multifunctional cytokine, which is overexpressed and/or activated in multiple malignancies and is reported to be associated with tumor development and inferior survival. At present, the role of HGF in small cell lung cancer (SCLC) has not been fully explored yet.

Materials and methods The expression of HGF and its value in predicting survival in SCLC were explored from GEO database and in pan-cancer analysis. Furthermore, we detected the expression of HGF using tumor tissue and paired plasma samples from a validation cohort of 71 SCLC patients at our institute. Correlation between tumor and plasma HGF expression and the prognostic values were analyzed.

Results GEO database analysis revealed that tumor tissue had lower HGF expression than paired normal tissue in SCLC. At our institute, immunohistochemical staining showed negative expression of HGF in tumor tissue of SCLC at our institute (47/47, 100%). The average baseline plasma HGF was 1.28 (range,0.42–4.35) ng/ml. However, plasma HGF was higher in SCLC patients with patients with N_3, M_1, liver metastasis (LM) and bone metastasis (BM) disease compared with those N_{0-2} (1.25 vs. 1.75 ng/mL, $P=0.000$), M_0 (1.26 vs. 1.63 ng/mL, $P=0.003$), non-LM (1.32 vs. 2.06 ng/mL, $P=0.009$), and non-BM (1.35 vs. 1.77 ng/mL, $P=0.047$), respectively. Multivariate analysis revealed plasma HGF was an independent predictor for LM and prognostic factor of OS.

Conclusion Our results revealed that plasma HGF rather than tumor HGF exhibited a potential role in predicting metastasis and survival in SCLC. Plasma HGF might be used as a non-invasive detecting and monitoring tool for SCLC.

Keywords Hepatocyte growth factor, Plasma, Pan-cancer analysis, Small cell lung cancer, Metastases

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Introduction

SCLC is identified as one of the most deadly malignancies with limited therapeutic efficacy worldwide [1]. Patients especially those with extensive stage disease progress rapidly with a median OS of only 6–8 months [2–4]. For the last few decades, as drug after drug has failed and fallen due to little impact on progression-free survival (PFS) or OS, SCLC has been notorious for its lack of progress [5, 6]. Therefore, it is in urgent need to discover novel biomarkers with therapeutic potential for SCLC at present.

In several tumors, MET/HGF axis is aberrantly activated and represents one of the most important mechanisms of progression and invasiveness, which is proved to promote proliferation, migration, invasion, angiogenesis and tumorigenesis. It is also demonstrated to be associated with drug resistance and inferior survival for cancer patients [7–11].

HGF, secreted from stromal and mesenchymal cells, is a peptide-containing multifunctional cytokine that acts on various epithelial cells to regulate cell growth, morphogenesis, and organizing multistep of angiogenesis in many organs [12]. Apart from HGF detected in tumor tissue, elevated HGF in blood expression was associated with high risk for metastasis and inferior OS in breast, bladder, gastric, esophageal, colorectal cancers, ovarian cancer and myeloma [13–17].

Previous studies find that the MET/HGF axis appears to be a signaling pathway frequently altered in SCLC [18–20]. Rygaard et al. concluded that the MET/HGF axis was frequently active in SCLC, possibly by a paracrine regulatory pathway of HGF [21].

Paracrine of HGF maybe influence the level of plasma HGF, which maybe associated with prognosis of SCLC. The role of plasma HGF in SCLC, however, has not been systematically explored so far. Since few data on SCLC is avaliable from on-line database, we explore the expression of HGF in pan-cancer and analyzed its potential predictive value. Furthermore, using an independent cohort of 71 SCLC patients at our institute, we identified HGF expression in tumor tissue and paired plasma and also explored the potential use of plasma HGF in predicting metastasis and prognosis. We found that plasma HGF might be used as a high sensitivity and specificity monitoring tool for metastasis and survival in SCLC, establishing theoretical basis for clinical decision-making.

Materials and methods

Pan-cancer analysis of HGF expression and its prognostic value

The gene expression of HGF were downloaded and recomputed via the Sangerbox 3.0 web (http://vip.sangerbox.com/home.html) from the cancer genome atlas (TCGA) and genotype-tissue expression (GTEx) [22]. All expression data were normalized via log2 conversion. R (version 4.2.0) was used to investigate the expression of HGF between different cancers and corresponding adjacent tissues or normal tissue. The genetic variations of HGF were analyzed using the cBioPortal tool (https://www.cbioportal.org/, accessed on 20 June 2021) [23]. We selected the "TCGA Pan Cancer Atlas Studies" module in cBioPortal, and then entered the HGF gene to query the cancer types summary, and obtained the alteration frequency. Survival analysis and K-M plotter were used to analyze the prognosis value of HGF, regarding to OS and progression-free interval (PFI).

Detection of DEGs in SCLC based on GEO database

The differentially expressed genes (DEGs) between SCLC and adjacent normal lung tissues were screened out using EdgeR. Samples were divided into HGF^{low} and HGF^{high} groups using a cutoff value of median expression level. DEGs between them were screened out using EdgeR of R. DEGs were defined with FDR < 0.05 and |logFC| > 1.

Validation of HGF expression and its potential role in SCLC at our institute

Study design and participants

This was an exploratory retrospective study of 71 consecutive patients who were diagnosed with SCLC between December 2017 and April 2020 at our institute. Inclusion criteria: pathologically diagnosed with SCLC; available plasma samples at diagnosis for enzyme linked ELISA detection. Patients with insufficient samples, incomplete record, or lost follow-up were excluded. Clinicopathological data including age, sex, smoking history, TNM stage, metastasis, serum carcinoembryonic, treatment and others were collected. This study was approved by the Ethics Committee of Beijing Chest Hospital.

Sample collection

A total of 71 frozen plasma samples and 47 tumor specimens were included and stored in the refrigerator at -80℃. Tumor specimens were collected using core needle biopsies, endobronchial biopsies, or tissue resection.

Detection of HGF in plasma and tumor tissue

71 samples were selected for HGF ELISA. 6ml peripheral venous blood was drawn into Ethylene Diamine Tetraacetie Acid (EDTA)anticoagulant tube. Samples were centrifuged for 2 h (3500 rpm/min, 5 min) to separate plasma, which were stored in the refrigerator at −80℃. Enzyme linked immunosorbest assay (ELISA) was used to measure plasma HGF (ELISA kits, USCN Life Sciences, Wuhan, China, Code: BAH-MET-HGF-1) and an ELISA reader (Immunoscan, BioTek Instruments, Ins, USA). The evaluation was performed according to the manufacturer's protocol and published studies [19, 20].
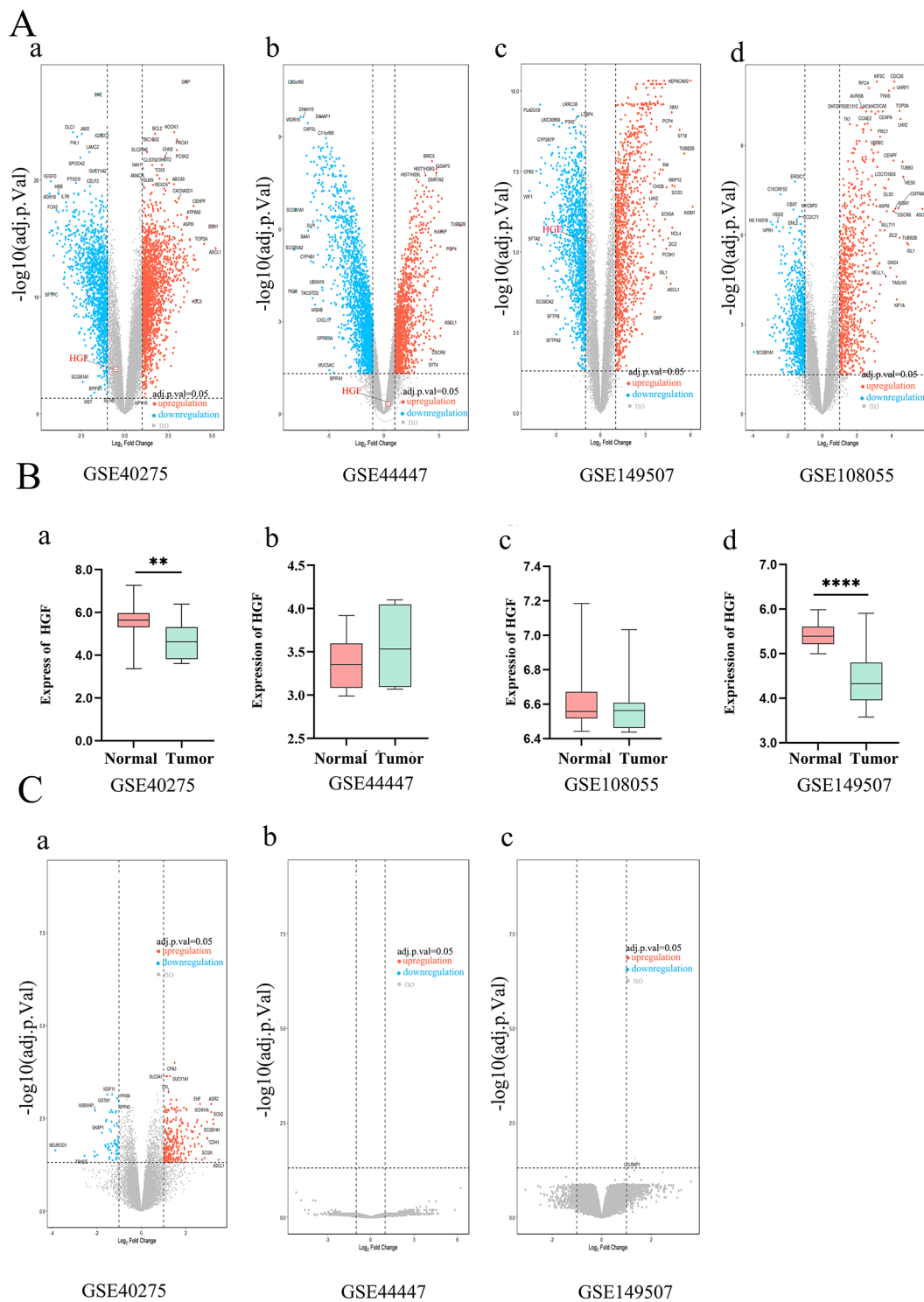
Fig. 1 A: The detection of DSE between SCLC and adjacent normal lung tissues in SCLC in GEO, Volcano plot of the expression level of differentially expressed genes in four datasets(a;GSE40275,b:GES4447,c:GSE108055,d:GSE149507). B: The expression level of HGF in SCLC between normal tissue and primary tissue of selected tumors(a;GSE40275,b:GES4447,c:GSE108055,d:GSE149507). C:Volcano plot of the expression level of differentially expressed genes in HGF^{low} and HGF^{high} groups from GSE40275, GSE44447, and GSE149507. Red dots represent a high expression of genes and blue dots represent a low expression of genes (Fig. 1C(a-c)). * $p<0.05$,** $p<0.01$, *** $p<0.001$,**** $p<0.0001$

IHC staining was carried out on formalin-fixed, paraffin-embedded (FFPE) tissue sections of tumor specimens.

The sections were then reacted with primary antibodies (HGFβ[D6S7D] XP® Rabbit, Cell Signaling, Code:
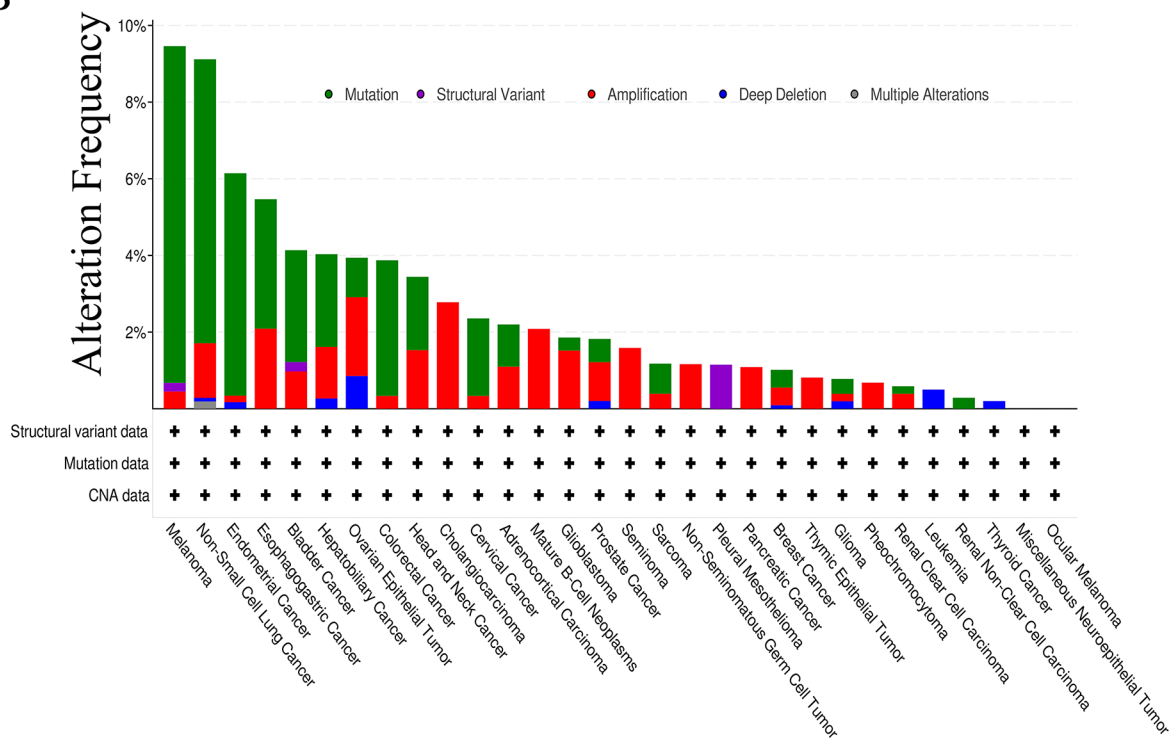
A
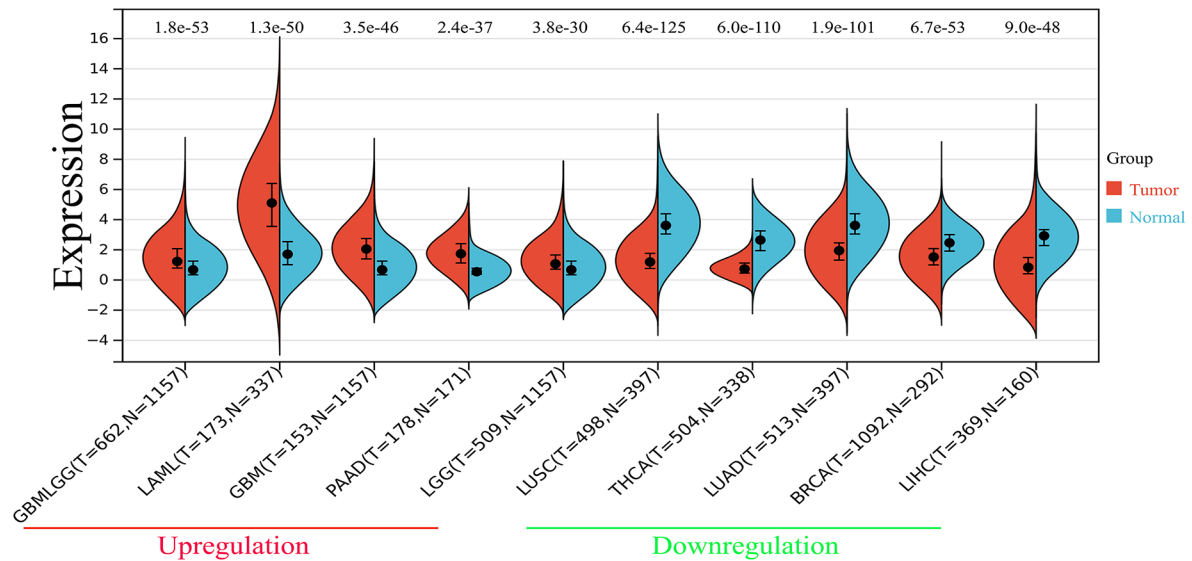
B

Fig. 2 A: Upregulated and downregulated mRNA expression of HGF in pan-cancer. HGF expression was remarkably increased in 5 cancer types above the red line. And the HGF expression was remarkably reduced in 5 cancer types above the green line. B: Genetic alternation of HGF in different tumors, the alteration frequency with mutation type was displayed

52,445). The protocol and evaluation were performed according to the manufacturer's protocol and published studies [24].

Statistical analysis
OS was calculated from the date of initial diagnosis to the date of death from any cause, or the last follow-up. PFS was defined as the interval from the date of diagnosis
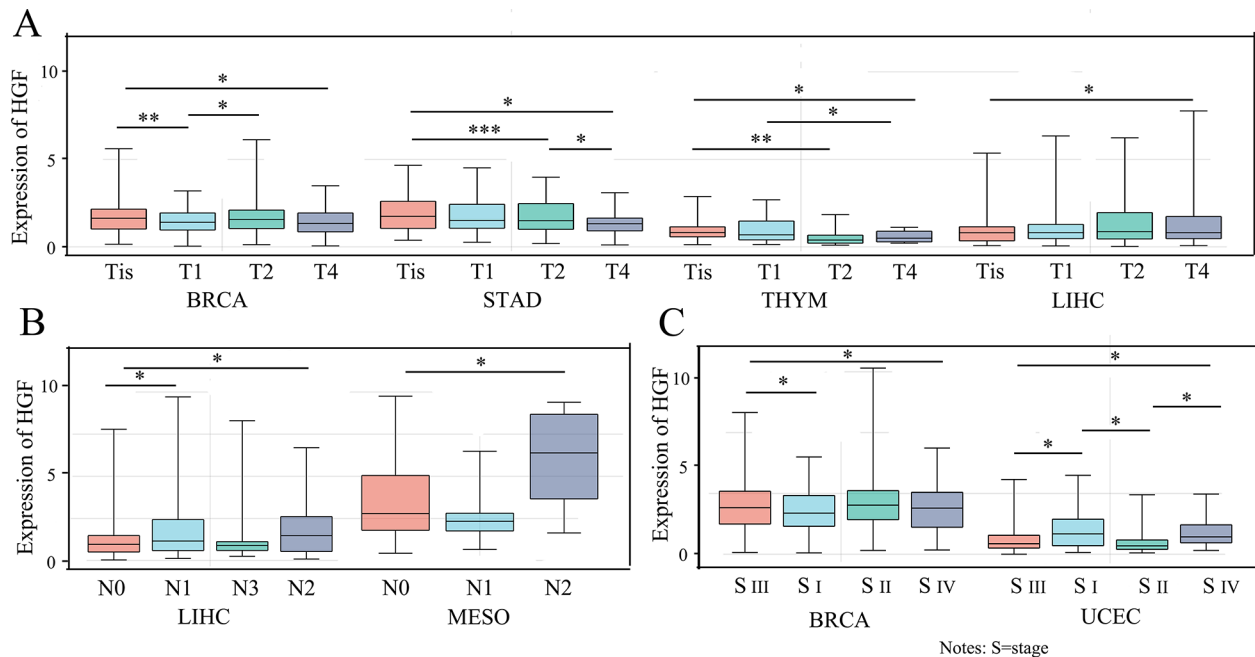
Fig. 3 Correlations between the HGF expression and Clinicopathology, were investigated based on the TCGA data. A: T stage of BRCA, STAD, THYM and LIHC, B: N stage of LIHC and MESO, C: the main pathological stages including stage I, stage II, stage III, and stage IV of BRCA and UCEC. Log2 (TPM + 1) was used for log scale. ∗$p < 0.05$, ∗∗$p < 0.01$, and ∗∗∗$p < 0.001$

to the date of first progression, death or last follow-up. Data were analyzed using the SPSS 22.0, GraphPad Prism (San Diego, CA, USA) and R software package (version 4.2.0: http://www.Rproject.org). The continuous variables and categorical variables were assessed by the Student's t test and the Pearson's chi-square respectively. Multivariate analysis was conducted by logistic regression model and Cox proportional hazards models. A Kaplan–Meier survival analysis in different subgroups was performed. If *P* value in the univariable analysis was less than 0.05, this variable should be adjusted in multivariate analysis. A two-tailed $P < 0.05$ was considered statistically significant in all analyses.

Results

HGF expression in SCLC in GEO database

HGF were significantly downregulated in SCLC specimens in comparison to adjacent normal tissues in GSE40275, GSE108055 and GSE149507 datasets. However, it was upregulated in SCLC in GSE44447, though the difference was not statistically significant ($P = 0.06$, Fig. 1A). DEGs between SCLC and adjacent normal lung tissues were screened out using EdgeR. But according to the threshold values for DEGs identification, HGF was not screened in neither upregulative and downregulative DSEs in GSE40275, GSE44447 and GSE149507 datasets. HGF was not detected in GSE149507 datasets (Fig. 1B). DEGs between HGF^low and HGF^high groups were shown in Fig. 1C and no significant genes with clinical meaning

were sorted out in SCLC. In summary, HGF expression of SCLC was not identical according to different database; besides, its clinical relevance and predictive value in SCLC remained undefined at present.

Pan-carcinogenic analysis of HGF

The regulation of the HGF expression between various types of cancer and normal tissues was investigated from the GTEx database and TCGA. As shown in Fig. 2A, upregulated HGF expression in tumor was observed in some solid tumors. Whereas, it was downregulated in lung squamous cell carcinoma (LUSC), lung adenocarcinoma (LUAD), thyroid carcinoma (THCA), breast invasive carcinoma (BRCA) and liver hepatocellular carcinoma (LIHC). Apart from expression, we observed various genetic alternations of HGF in tumors from TCGA cohort (Fig. 2B). Melanoma and non-small cell lung cancer (NSCLC) had the highest frequency of HGF genetic alteration (>8%) with mutation as the main variation. HGF expression was significantly associated with tumor burden reflected by stage especially T stage and N stage in some certain types of cancer as shown in Fig. 3A-C. Among BRCA and STAD, T1 disease had higher HGF expression than T4 lesion(Figure 3A). Besides, N1 had higher HGF expression compared to N0 disease in LIHC and MESO (Fig. 3B). HGF expression negatively correlated with stage in BRCA and UCEC (Fig. 3C).

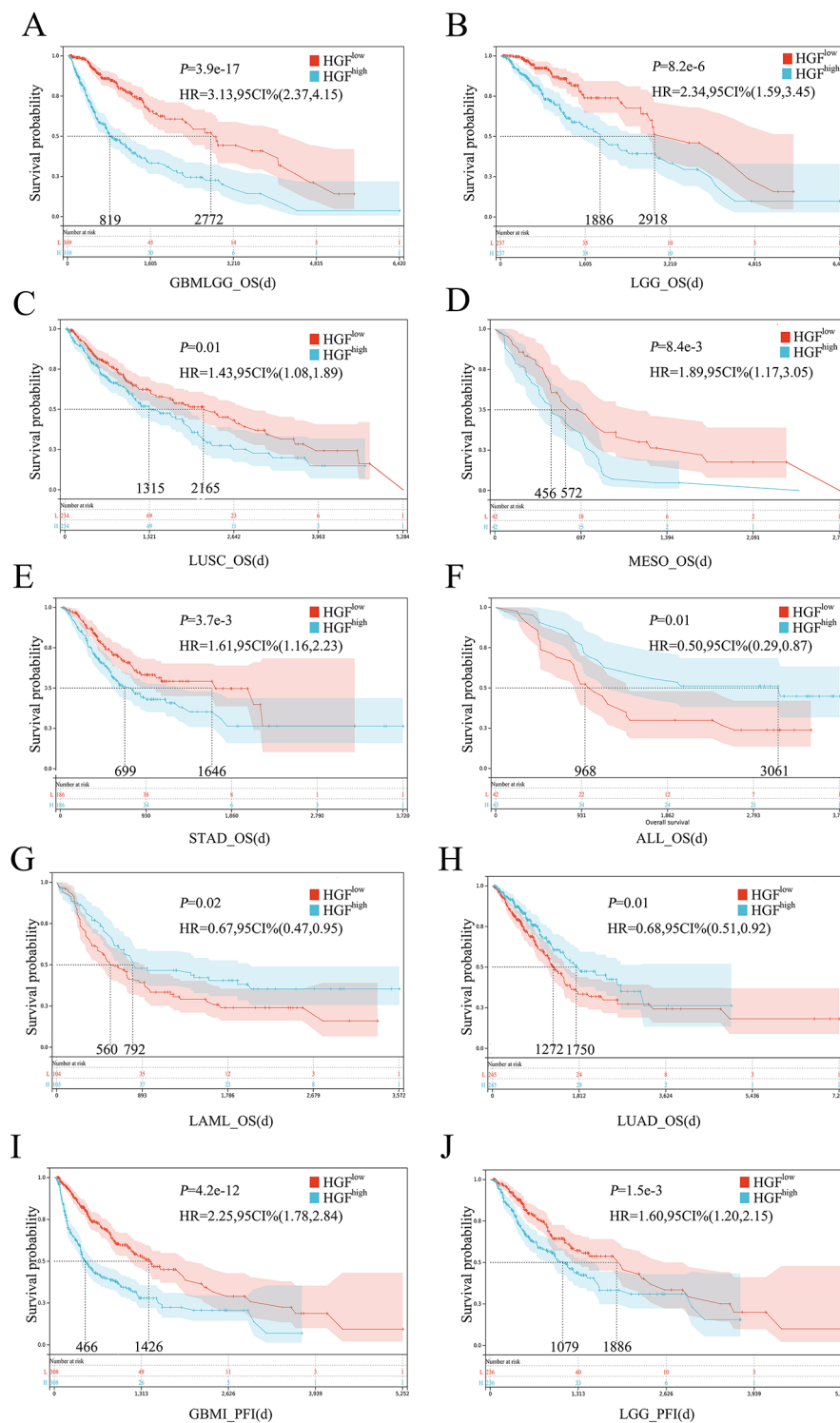Pan-cancer analysis revealed different prognostic value of HGF expression in various cancer types (Fig. 4A-J).

Fig. 4 Association between the HGF expression and the prognosis of cancer patients. Kaplan-Meier survival curves of OS for patients stratified by the different expressions of HGF in GBMLGG, LGG, LUSC, MESO, STAD ALL, LAML and LUAD(A-H). And Kaplan-Meier survival curves of PFI for patients stratified by the different expressions of HGF in GBMI and LGG(I-J).

Upregulation of HGF was significantly associated with inferior OS in GBMLGG, LGG, LUSC, MESO and STAD (Fig. 4A-E). In contrast, upregulation of HGF indicated

superior OS in ALL, LAML and LUAD (Fig. 4F-H). Likewise, a correlation was also observed that the
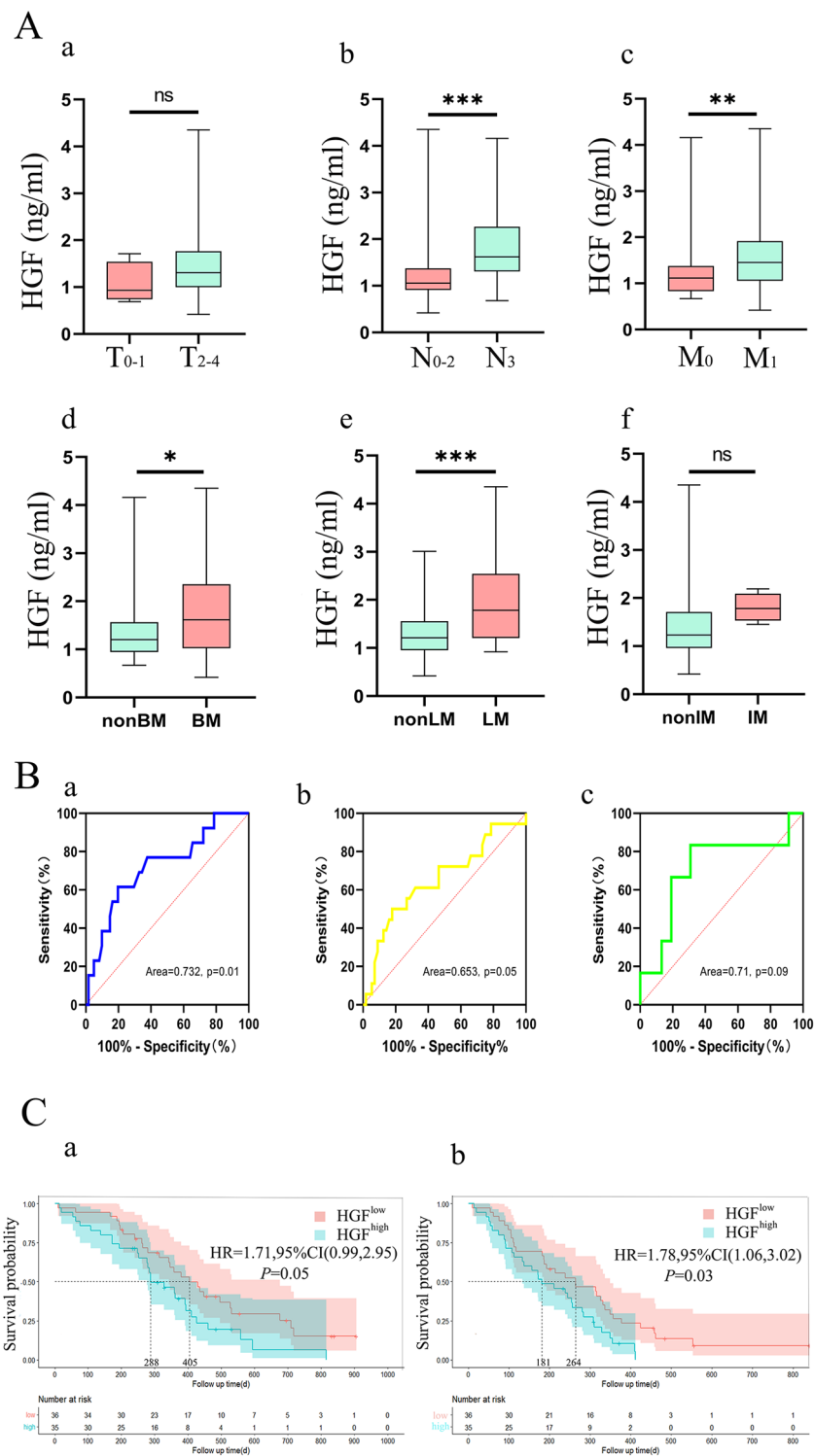
Fig. 5 A: Compared the level of plasma HGF in different group (a: T stage, b: N stage, c: M stage, d: LM, e: BM, f:IM). B: Receiver operating curve analysis of metastases (a: LM, b:BM; c:IM). C: Survival analysis of patients with SCLC in the HGF^{low} and HGF^{high} groups (a: PFS, b: OS) ,* $p<0.05$,** $p<0.01$, *** $p<0.001$

upregulation of HGF was significantly associated with inferior PFI in GBMI, LGG(Fig. 4I-J).

HGF expression in tumor and plasma in SCLC at our institute

A total of 71 patients were included in this analysis and the baseline characteristics were summarized in

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Table 1 Uni-and multivariate analysis for LM

Parametres	Univariate analysis		Multivariate analysis	
	OR(95% CI)	*p*	OR(95% CI)	*p*
HGF	3.374(1.414–8.054)	0.006	1.499(1.023–2.196)	0.038
Sex	1.589(0.312–8.094)	0.577		
Age	0.783(0.215–2.856)	0.711		
Smoking history	3.467(0.411–29.210)	0.253		
LDH	1.000(0.998–1.001)	0.694		
AST	0.993(0.965–1.022)	0.653		
ALT	0.978(0.940–1.018)	0.282		
ALB	0.902(0.808–1.006)	0.063		
CEA	1.015(0.997–1.034)	0.106		
NSE	1.008(0.998–1.018)	0.101		
SCC	0.594(0.054–6.548)	0.670		
CYFRA21-1	1.251(1.053–1.486)	0.011	1.081(1.016–1.151)	0.014
Pro-GRP	1.001(1.000-1.001)	0.003		

AST: aspartate transaminase; ALT: Alanine aminotransferase; LDH: lactate dehydrogenase; ALB:albumin; CEA: carcinoembryonic antigen ; NSE: neuron-specific enolase; SCC:Squamous cell carcinoma antigen;CYFRA21-1:Soluble fragment of cytokeratin 19;Pro-GRP: pro-gastrin-releasing peptide

Table 2 Uni-and multivariate analysis for OS

Parametres	Univariate analysis		Mutlivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*P*
HGF	1.721(1.213–2.442)	0.002	1.629(1.110–2.392)	0.013
Sex	0.588(0.276–1.253)	0.169		
Age	1.374(0.784–2.409)	0.267		
Smoking history	2.171(0.977–4.824)	0.057		
ECOG-PS	3.157(1.475–6.754)	0.003		
T stage	2.765(0.670-11.418)	0.160		
N stage	2.220(1.278–3.858)	0.005		
M stage	2.933(1.669–5.153)	0.000	2.287(1.261–4.150)	0.006
CEA	1.009(1.005–1.014)	0.000	1.008(1.003–1.013)	0.002
NSE	1.005(1.000-1.009)	0.034		
SCC	0.578(0.237–1.411)	0.229		
CYFRA21-1	1.084(1.022–1.150)	0.007		
Pro-GRP	1.000(1.000–1.000)	0.319		

ECOG-PS=Eastern Cooperative Oncology Group performance status; CEA=carcinoembryonic antigen ; NSE=neuron-specific enolase; SCC: Squamous cell carcinoma antigen;CYFRA21-1=Soluble fragment of cytokeratin 19;Pro-GRP: pro-gastrin-releasing peptide

Supplementary Table 1. The patients included 56 male and 15 female patients, Limitation stage 27, extension stage 44. At diagnosis, 13 cases had LM, 18 with BM and 4 with intracranial metastasis (IM). IHC staining on the paraffin-embedded tumor specimens from 47 SCLC patients showed negative expression of HGF in each sample (Supplementary Fig. 1). However, HGF was detected in plasma samples from 71 SCLC patients with a median concentration of 1.46ng/mL.

Plasma HGF as an indicator for LM in SCLC at our institute

Plasma HGF was higher in patients with N_3, M_1, LM and BM groups than that in patients with N_{0-2} (1.25 vs. 1.75 ng/mL, $P=0.000$), M_0 (1.26 vs. 1.63 ng/mL, $P=0.003$), non-LM (1.32 vs. 2.06 ng/mL, $P=0.009$), and non-BM (1.35 vs. 1.77 ng/mL, $P=0.047$), respectively (Fig. 5A b-e). Plasma HGF was higher in T_{2-4} and IM groups compared to T_{0-1} and non-IM groups, though the difference did not reach statistical significance (both $P>0.05$, Fig. 5A a,f). ROC curve analysis showed similar results for LM, BM and IM (AUC: 0.723, 0.653 and 0.71, respectively), LM had a largest AUC of 0.73. This suggests that HGF was a potential biomarker for LM (Fig. 5B a-c). Besides, mutivariavte analysis showed HGF as independent predictive factors of LM (OR=1.499, 95% CI, 1.023–2.196, $P=0.038$; Table 1).

Univariate and multivariate analysis of survival in SCLC

Patients were subdivided into HGF^high and HGF^low group based on a cutoff value of 1.72 ng/mL of plasma HGF, which was calculated via ROC using LM as the point. Till the last visit in April 2022, the median follow-up period

reached 10.5 months. A total of 63 patients had recurrence or metastases, 54 cases of which died of cancer-related causes. Patients in HGF^low group achieved much more favorable OS (13.5 vs. 9.6 months, $P=0.03$) and PFS (8.8 vs. 6.0 months, $P=0.05$) compared with those in HGF^high group (Fig. 5C). Univariate analysis showed that plasma HGF were negatively associated with OS (OR=1.721, 95% CI, 1.213–2.442, $P=0.002$) and PFS (OR=1.443, 95% CI, 1.052–1.98, $P=0.023$). Furthermore, plasma HGF was demonstrated as an independent prognostic factor for OS via multivariate Cox regression (OR=1.629, 95% CI, 1.110–2.392, $P=0.013$, Table 2).

Discussion

In this study, we analyzed the expression and its association with clinical parameters and its influence on survival in pan-cancer based on public database; furthermore, we validated the conclusions using an independent cohort of 71 patients with SCLC at our institute. And to our knowledge, this is a comparably large sampled study which first focuses on HGF expression in both tumor and plasma in SCLC. Our results revealed that plasma HGF rather than tumor HGF might be a reliable biomarker for LM and inferior survival in SCLC, and its potential value for non-invasive disease monitoring needs to be further explored.

SCLC is typically diagnosed in small biopsies or cytology specimens, with routine immunostaining only [1]. Result from GEO database presented that the expression levels of HGF was downregulated in SCLC specimens in comparison to adjacent normal tissues (Fig. 1A). HGF wasn't DEGs between SCLC and normal tissues (Fig. 1B).

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What's more, IHC staining on the paraffin-embedded sections of 47 SCLC at our institute presented negative expression for each patient. Our result was contradictive with some published studies, in which expression of HGF and its receptor c-MET has been reported to be increased in lung, colon, breast, thyroid, renal carcinoma, melanoma and various sarcomas [25, 26]. The heterogeneity of cancers and unique tumor environment might be one reason for this controversy. Therefore, tumor HGF may not be a feasible biomarker for SCLC. Most cancer cells do not express HGF, and HGF is secreted mainly by cells of mesenchymal origin, acts in a paracrine manner on cells that express the c-MET receptor [27]. HGF/c-MET interactions are activated by stromal cell HGF, which produces a suitable microenvironment for cancer cell growth and invasion, and in an autocrine manner by c-MET produced by cancer cells [28, 29]. These studies suggest us that HGF in plasma may play an important biological role in SCLC. In advanced ovarian cancer, HGF in serum was demonstrated as an indicator of poor prognosis [16, 30]. Hitomi Umeguchi and his teamwork [31] showed that HGF in plasma was significantly higher in the advanced stage of cancer and predicted poor survival as determined using 315 plasma samples from 225 lung cancer patients. Consistently, our results showed plasma HGF was demonstrated as an independent predictive factor for LM (OR$=$1.499, 95% CI, 1.023–2.196, $P=$0.038; Table 1) with a ROC of 0.73 for LM diagnosis and an independent prognostic factor for OS (OR$=$1.629, 95% CI, 1.110–2.392, $P=$0.013).

In conclusion, plasma HGF might be of great value as a non-invasive biopsy tool for SCLC. It overcomes the difficulty of obtaining tumor tissue in some certain circumstances. Additionally, it can avoid the risk of bleeding and pain of patients and can be used for dynamic monitoring. As is known to all, little progression on treatment and prognosis is obtained in SCLC in the past three decades, and reliable prognostic predictor is also in lack for SCLC. Therefore, our result that plasma HGF might be a potential predictive factor for LM and OS did provide a promising perspective. However, the true value of plasma HGF in SCLC needs to be further validated in large-sample prospective studies.

Supplementary Information

The online version contains supplementary material is available at https://doi.org/10.1186/s12885-023-10995-z.

Supplementary Table 1

Supplementary Figure 1

Data Availability
The datasets generated and/or analysed during the current study are available in the GEO[https://www.ncbi.nlm.nih.gov/geo] and TCGA [https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga]. The clinical data used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Beijing Chest Hospital. All methods were performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients provided written informed consent.

Consent for publication
Not applicable.

Supervision,Software, Validation. All authors
Writing,Reviewing and Editing.

References
1. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. Cancers (Basel) 2021, 13(4).
2. Iams WT, Shiuan E, Meador CB, Roth M, Bordeaux J, Vaupel C, Boyd KL, Summitt IB, Wang LL, Schneider JT, et al. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes. J Thorac Oncol. 2019;14(11):1970–81.
3. Ding X, Zhang J, Liu D, Xu W, Lu DY, Zhang LP, Su B. Serum expression level of IL-6 at the diagnosis time contributes to the long-term prognosis of SCLC patients. J Cancer. 2018;9(5):792–6.
4. Remiszewski P, Roszkowski-Sliz K, Wiatr E, Roszkowska-Sliz B, Zych J, Kurzyna M, Jodkiewicz Z, Rowinska-Zakrzewska E. [Prognosis in limited disease (LD) small cell lung cancer (SCLC) patients according to status performance, local extension of lesions, type of treatment and the completeness of staging]. Pneumonol Alergol Pol. 2003;71(3–4):139–47.
5. Takuma S, Inoue Y, Karayama M, Tsuchiya K, Tsukui H, Hozumi H, Suzuki Y, Furuhashi K, Enomoto N, Fujisawa T, et al. EGFR-Mutated lung adenocarcinoma successfully treated with Osimertinib after spontaneous Transformation to SCLC and Adenocarcinoma with neuroendocrine differentiation: Case Report. JTO Clin Res Rep. 2022;3(1):100264.
6. Sutherland KD, Ireland AS, Oliver TG. Killing SCLC: insights into how to target a shapeshifting tumor. Genes Dev. 2022;36(5–6):241–58.
7. Sjostrom M, Veenstra C, Holmberg E, Karlsson P, Killander F, Malmstrom P, Nimeus E, Ferno M, Stal O. Expression of HGF, pMet, and pAkt is related to benefit of radiotherapy after breast-conserving surgery: a long-term follow-up of the SweBCG91-RT randomised trial. Mol Oncol. 2020;14(11):2713–26.
8. Liang QL, Mo ZY, Wang P, Li X, Liu ZX, Zhou ZM. The clinical value of serum hepatocyte growth factor levels in patients undergoing primary radiotherapy for glioma: effect on progression-free survival. Med Oncol. 2014;31(9):122.

9. Osada S, Matsui S, Komori S, Yamada J, Sanada Y, Ihawa A, Tanaka Y, Tokuyama Y, Okumura N, Nonaka K, et al. Effect of hepatocyte growth factor on progression of liver metastasis in colorectal cancer. Hepatogastroenterology. 2010;57(97):76–80.

10. Kwon Y, Godwin AK. Regulation of HGF and c-MET Interaction in Normal Ovary and Ovarian Cancer. Reprod Sci. 2017;24(4):494–501.

11. Zi X, Zhang G, Qiu S. Up-regulation of LINC00619 promotes apoptosis and inhibits proliferation, migration and invasion while promoting apoptosis of osteosarcoma cells through inactivation of the HGF-mediated PI3K-Akt signalling pathway. Epigenetics. 2022;17(2):147–60.

12. Zhao Y, Ye W, Wang YD, Chen WD. HGF/c-Met: a key promoter in liver regeneration. Front Pharmacol. 2022;13:808855.

13. Chau GY, Lui WY, Chi CW, Chau YP, Li AF, Kao HL, Wu CW. Significance of serum hepatocyte growth factor levels in patients with hepatocellular carcinoma undergoing hepatic resection. Eur J Surg Oncol. 2008;34(3):333–8.

14. Hezode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, De Ledinghen V, Poynard T, Samuel D, Bourliere M, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology. 2014;147(1):132–142e134.

15. Kim CH, Moon SK, Bae JH, Lee JH, Han JH, Kim K, Choi EC. Expression of hepatocyte growth factor and c-Met in hypopharyngeal squamous cell carcinoma. Acta Otolaryngol. 2006;126(1):88–94.

16. Klotz DM, Link T, Wimberger P, Kuhlmann JD. Prognostic relevance of longitudinal HGF levels in serum of patients with ovarian cancer. Mol Oncol. 2021;15(12):3626–38.

17. Kilic-Baygutalp N, Ozturk N, Orsal-Ibisoglu E, Gundogdu B, Ozgeris FB, Bakan N, Bakan E, Kilic AF. Evaluation of serum HGF and CK18 levels in patients with esophageal cancer. Genet Mol Res 2016, 15(3).

18. Miao L, Lu Y, Xu Y, Zhang G, Huang Z, Gong L, Fan Y. PD-L1 and c-MET expression and survival in patients with small cell lung cancer. Oncotarget. 2017;8(33):53978–88.

19. Jagadeeswaran R, Jagadeeswaran S, Bindokas VP, Salgia R. Activation of HGF/c-Met pathway contributes to the reactive oxygen species generation and motility of small cell lung cancer cells. Am J Physiol Lung Cell Mol Physiol. 2007;292(6):L1488–1494.

20. Maulik G, Kijima T, Ma PC, Ghosh SK, Lin J, Shapiro GI, Schaefer E, Tibaldi E, Johnson BE, Salgia R. Modulation of the c-Met/hepatocyte growth factor pathway in small cell lung cancer. Clin Cancer Res. 2002;8(2):620–7.

21. Rygaard K, Nakamura T, Spang-Thomsen M. Expression of the proto-oncogenes c-met and c-kit and their ligands, hepatocyte growth factor/scatter factor and stem cell factor, in SCLC cell lines and xenografts. Br J Cancer. 1993;67(1):37–46.

22. Liu J, Wang Y, Yin J, Yang Y, Geng R, Zhong Z, Ni S, Liu W, Du M, Yu H, et al. Pan-Cancer Analysis revealed SRSF9 as a New Biomarker for Prognosis and Immunotherapy. J Oncol. 2022;2022:3477148.

23. Wu C, Duan Y, Gong S, Kallendrusch S, Schopow N, Osterhoff G. Integrative and comprehensive Pancancer Analysis of Regulator of chromatin condensation 1 (RCC1). Int J Mol Sci 2021, 22(14).

24. Yano S, Wang W, Li Q, Matsumoto K, Sakurama H, Nakamura T, Ogino H, Kakiuchi S, Hanibuchi M, Nishioka Y, et al. Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. Cancer Res. 2008;68(22):9479–87.

25. Serilmez M, Ozgur E, Karaman S, Gezer U, Duranyildiz D. Detection of serum protein and circulating mRNA of cMET, HGF EGF and EGFR levels in lung cancer patients to guide individualized therapy. Cancer Biomark. 2019;25(2):177–84.

26. Lorenzato A, Olivero M, Patane S, Rosso E, Oliaro A, Comoglio PM, Di Renzo MF. Novel somatic mutations of the MET oncogene in human carcinoma metastases activating cell motility and invasion. Cancer Res. 2002;62(23):7025–30.

27. Czyz M. HGF/c-MET signaling in Melanocytes and Melanoma. Int J Mol Sci 2018, 19(12).

28. Saigusa S, Toiyama Y, Tanaka K, Yokoe T, Fujikawa H, Matsushita K, Okugawa Y, Inoue Y, Uchida K, Mohri Y, et al. Inhibition of HGF/cMET expression prevents distant recurrence of rectal cancer after preoperative chemoradiotherapy. Int J Oncol. 2012;40(2):583–91.

29. Hisadome M, Ohnishi T, Kakimoto K, Kusuyama J, Bandow K, Kanekura T, Matsuguchi T. Hepatocyte growth factor reduces CXCL10 expression in keratinocytes. FEBS Lett. 2016;590(20):3595–605.

30. Aune G, Lian AM, Tingulstad S, Torp SH, Forsmo S, Reseland JE, Stunes AK, Syversen U. Increased circulating hepatocyte growth factor (HGF): a marker of epithelial ovarian cancer and an indicator of poor prognosis. Gynecol Oncol. 2011;121(2):402–6.

31. Umeguchi H, Sueoka-Aragane N, Kobayashi N, Nakamura T, Sato A, Takeda Y, Hayashi S, Sueoka E, Kimura S. Usefulness of plasma HGF level for monitoring acquired resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer. Oncol Rep. 2015;33(1):391–6.

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