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ORIGINAL PAPER

High expression of HM13 correlates with poor prognosis in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) has a high mortality rate, and the identification of early prognostic markers is crucial for improving patient outcomes. This study aimed to investigate the correlation between the expression of Histocompatibility Minor 13 (HM13) and the prognosis of HCC patients. HM13 protein expression was assessed in HCC tissues and cells through immunohistochemistry (IHC), quantitative reverse transcription PCR (qRT-PCR), and western blot. The relationship between *HM13* expression and clinicopathological data of HCC was evaluated. Bioinformatics analyses, including Gene Expression Omnibus (GEO) database, Gene Expression Profiling Interactive Analysis (GEPIA), and Kaplan-Meier plotter (K-M plotter), were employed to analyze HM13 expression and its association with patient survival. *HM13* was significantly overexpressed in HCC tissues and cells compared to normal controls. IHC revealed that HM13 protein was primarily localized in the cytoplasm and highly expressed in HCC tissues. Interestingly, patients with high *HM13* expression had significantly poorer overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), and disease-specific survival (DSS) than those with low expression. *HM13* expression was associated with Edmondson grade, metastasis, microvascular invasion, and alpha-fetoprotein (AFP) levels. Multivariate analysis identified HM13 as an independent prognostic factor for poor OS in HCC. *HM13* was markedly overexpressed in HCC and correlated with poor prognosis, suggesting its potential as a promising biomarker for early prognostic detection in HCC patients.

Keywords HM13 · Hepatocellular carcinoma · Biomarker · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the predominant form of liver cancer, representing 75–85% of cases, and is the primary type of liver cancer worldwide with the second highest mortality rate (He et al. 2022; Li et al. 2021; Zhou et al. 2021). Symptoms of liver cancer can include right upper abdominal pain, loss of appetite, decreased quality of life, and obstructive jaundice. However, many patients are asymptomatic and clinical signs typically emerge late in the course of the illness (Hamdoun et al. 2021; Hu et al. 2021; Husa et al. 2021; Wang et al. 2021; Zhang et al. 2021). Therefore, a significant challenge in clinical practice is to investigate the prognostic mechanisms of liver cancer development and identify prognostic markers in early stage patients.

Histocompatibility Minor 13 (*HM13*) encodes an integral membrane protein with sequence motifs characteristic of the presenilin-type aspartic proteases, which is present on

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the cell surface and is recognized by alloreactive T lymphocytes (Casillo et al. 2019; Kamasaka et al. 2020; Yokoyama et al. 2021). Numerous studies indicated that HM13 protein is implicated in the regulation of malignant features of tumor cells, such as cell proliferation, migration, and invasion (Di Guida et al. 2020; Wei et al. 2017; Yang et al. 2022). Particularly, HM13 serves as an oncogenic factor in breast cancer by dampening autophagy and prompting the activity of PI3K-AKT-mTOR pathway (Yang et al. 2022). HM13 affected epidermal growth factor receptor variant III (EGFRvIII) secretion and thereby promoted glioblastoma progression (Wei et al. 2017). Recent studies have highlighted the potential role of HM13 in HCC. *HM13* as a prognostic factor and a predictive biomarker for immunotherapy in HCC, suggesting its potential as a responsiveness indicator in HCC immunotherapy (Zhang et al. 2022). *HM13* is an unfavorable prognostic biomarker in HCC, promoting cell proliferation, migration, and invasion (Liu et al. 2022). Furthermore, *HM13* is involved in the gene regulation network of eukaryotic translation initiation factor 2 subunit 2 (EIF2S2), which contributes to HCC progression (Ji et al. 2021). Despite these findings, the prognostic value of *HM13* in HCC development and progression have not been verified in large cohort of HCC subjects.

This study aimed to investigate the correlation between *HM13* expression and prognosis in HCC. We assessed *HM13* expression in HCC tissues and cells, and evaluated its relationship with clinicopathological data. Bioinformatics analyses using the Gene Expression Omnibus (GEO) database, the Gene Expression Profiling Interactive Analysis (GEPIA), and Kaplan-Meier plotter were employed to analyze *HM13* expression and patient survival. Our findings revealed significant *HM13* overexpression in HCC, correlating with poorer overall survival, progression-free survival, recurrence-free survival, and disease-specific survival. *HM13* expression associated with Edmondson grade, metastasis, microvascular invasion, and alpha-fetoprotein levels. Multivariate analysis identified *HM13* as an independent prognostic factor for poor overall survival in HCC. These results suggest *HM13* as a potential prognostic biomarker and therapeutic target in HCC.

Methods and materials

Tissue specimens

HCC tissues were acquired from 90 patients who underwent surgical resection at Yantai Yuhuangding Hospital between January 2018 and December 2021. Inclusion criteria: pathologically diagnosed as HCC, no prior chemotherapy or radiotherapy, and patients provided written informed consent. The study was approved by the Ethics Committee Board of Yantai Yuhuangding Hospital. Fresh tissue samples were immediately snap-frozen in liquid nitrogen and stored at −80 °C until further analysis.

Bioinformatics analysis

Gene expression data and clinical information were obtained from the Gene Expression Omnibus (GEO) databases GSE102079 and GSE76427. The GSE102079 dataset included 105 non-tumor liver tissues and 152 HCC tissues, while GSE76427 contained 52 non-tumor liver tissues, 115 HCC tissues, and 167 clinical data points. The GEO2R online tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/) was used to analyze the differentially expressed genes between HCC and normal liver tissues. The Kaplan-Meier Plotter (http://kmplot.com/analysis/), an online survival analysis tool, was employed to assess the prognostic value of HM13 in HCC patients. The Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) database was used to analyze *HM13* expression and its correlation with overall survival (OS) and disease-free survival (DFS) in HCC patients.

Immunohistochemical (IHC) analysis

Formalin-fixed, paraffin-embedded HCC tissue Sect. (4 μm thick) from all 90 patients were subjected to IHC analysis. After deparaffinization and rehydration, antigen retrieval was performed by heating the sections in 10 mM citrate buffer (pH 6.0) for 10 min. Endogenous peroxidase activity was quenched by incubating the sections with 3% hydrogen peroxide for 10 min. Sections were then blocked with 5% bovine serum albumin (BSA, Sigma-Aldrich, A9647) for 1 h at room temperature and incubated overnight at 4 °C with a rabbit polyclonal anti-HM13 antibody (1:200 dilution, Abcam, ab266584). The specificity of the anti-HM13 antibody was validated by the manufacturer using knockout cell lines. After washing with PBS, the sections were incubated with a horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG secondary antibody (1:500 dilution, Abcam, ab6721) for 1 h at room temperature. The chromogenic reaction was developed using the 3,3'-diaminobenzidine (DAB) substrate kit (Vector Laboratories, SK-4100) according to the manufacturer's instructions. The sections were counterstained with hematoxylin, dehydrated, and mounted with Permount (Fisher Scientific, SP15-100). Negative controls were prepared by omitting the primary antibody. The samples were visualized under EVOS 3000 imaging platform (Thermo Fisher Scientific).

The staining intensity was evaluated by two independent pathologists blinded to the clinical data using an

immunoreactive score (IRS) system. The IRS considered both the percentage of positive cells (0: 0%, 1: 1–25%, 2: 26–50%, 3: 51–75%, 4: 76–100%) and the staining intensity (0: negative, 1: weak, 2: moderate, 3: strong). The IRS was calculated by multiplying the scores for percentage and intensity, ranging from 0 to 12. An IRS ≥ 6 was considered high HM13 expression, while an IRS < 6 was regarded as low expression.

Cell culture

Human hepatocellular carcinoma cell lines (Huh7, HB-8064; HCCLM3, CBP60518; Hep3B, HB-8064) and the immortalized human normal hepatocyte cell line (L02, GNHu 39) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Huh7, HCCLM3, and Hep3B cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM, Gibco, 11965-092) supplemented with 10% fetal bovine serum (FBS, Gibco, 16000-044), 100 U/mL penicillin, and 100 µg/mL streptomycin (Gibco, 15140-122). L02 cells were maintained in Endothelial Cell Basal Medium (EBM, Lonza, CC-3156) with the following supplements: 10% FBS, 0.1% human epidermal growth factor (hEGF, Lonza, CC-4015), 0.1% hydrocortisone (Lonza, CC-4035), and 0.1% gentamicin/amphotericin (GA-1000, Lonza, CC-4083). All cell lines were cultured in a humidified incubator at 37 °C with 5% CO2. Cells were regularly passaged at 80–90% confluency using 0.25% Trypsin-EDTA (Gibco, 25200-056) to detach cells from the culture flasks.

RNA extraction and quantitative reverse transcription PCR (qRT-PCR)

Total RNA was extracted from HCC tissues (10 mg) and cell lines (5 × 10^5 cells) using the TRIzol reagent (Invitrogen, 15596026) according to the manufacturer's protocol. RNA concentration and purity were determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific). One microgram of total RNA was reverse-transcribed into cDNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, 4368814). The mRNA expression levels of HM13 and the internal control GAPDH were quantified by qRT-PCR using the PowerUp SYBR Green Master Mix (Applied Biosystems, A25742) on a QuantStudio 6 Flex Real-Time PCR System (Applied Biosystems). The following primer sequences were used: *HM13* forward, 5'-ACCAGCTTTGCAGCCTACAT-3' and reverse, 5'-GGATTTGACTCCTCATAACTGAACA-3'; *GAPDH* forward, 5'-AGAAGGCTGGGGCTCATTTG-3' and reverse, 5'-AGGGGCCATCCACAGTCTTC-3'. The qRT-PCR conditions were: 95 °C for 3 min, followed by 40 cycles of 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s. All reactions were performed in triplicate. The relative HM13 expression levels were calculated using the $2^{\wedge-\Delta\Delta Ct}$ method and normalized to GAPDH.

Western blot analysis

Total protein was extracted from HCC tissues (20 mg) and cell lines (1 × 10^6 cells) using RIPA lysis buffer (Thermo Scientific, 89900) supplemented with a protease and phosphatase inhibitor cocktail (Thermo Scientific, 78442). Protein concentrations were determined using the Pierce BCA Protein Assay Kit (Thermo Scientific, 23225). Equal amounts of protein (20 µg) were separated by 10% SDS-PAGE and transferred onto PVDF membranes (Millipore, IPVH00010). After blocking with 5% non-fat milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 1 h at room temperature, the membranes were incubated overnight at 4 °C with the following primary antibodies: anti-HM13 (1:1000, Abcam, ab266584) and anti-GAPDH (1:5000, Abcam, ab8245). After washing with TBST, the membranes were incubated with an HRP-conjugated goat anti-rabbit IgG secondary antibody (1:5000, Abcam, ab6721) for 1 h at room temperature. The immunoreactive bands were visualized using the SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Scientific, 34095) and imaged on the ChemiDoc MP Imaging System (Bio-Rad). The relative protein levels were quantified by densitometry using Image Lab software (Bio-Rad) and normalized to GAPDH.

Statistical analysis

Graphpad Prism 5 software (GraphPad Software, San Diego, CA, USA) was used for statistical drafting and analysis. The differences between the two groups were compared by Student's t-test. Kaplan-Meier curves and the Gene Expression Profiling Interactive Analysis (GEPIA) test were applied to analyze the relationship between HM13 expression and prognosis of hepatocellular carcinoma (HCC) patients. Cox proportional hazards regression analysis was used to evaluate HCC-related prognostic factors. A p-value < 0.05 was considered statistically significant.

Results

HM13 is highly expressed in HCC tissue

Analysis of the GEPIA database revealed that *HM13* mRNA levels are significantly higher in HCC tissues compared to normal tissues (Fig. 1a-b). Consistent with this, data from the GEO datasets GSE102079 and GSE76427 showed elevated *HM13* expression in HCC samples (Fig. 1c-d). qRT-PCR

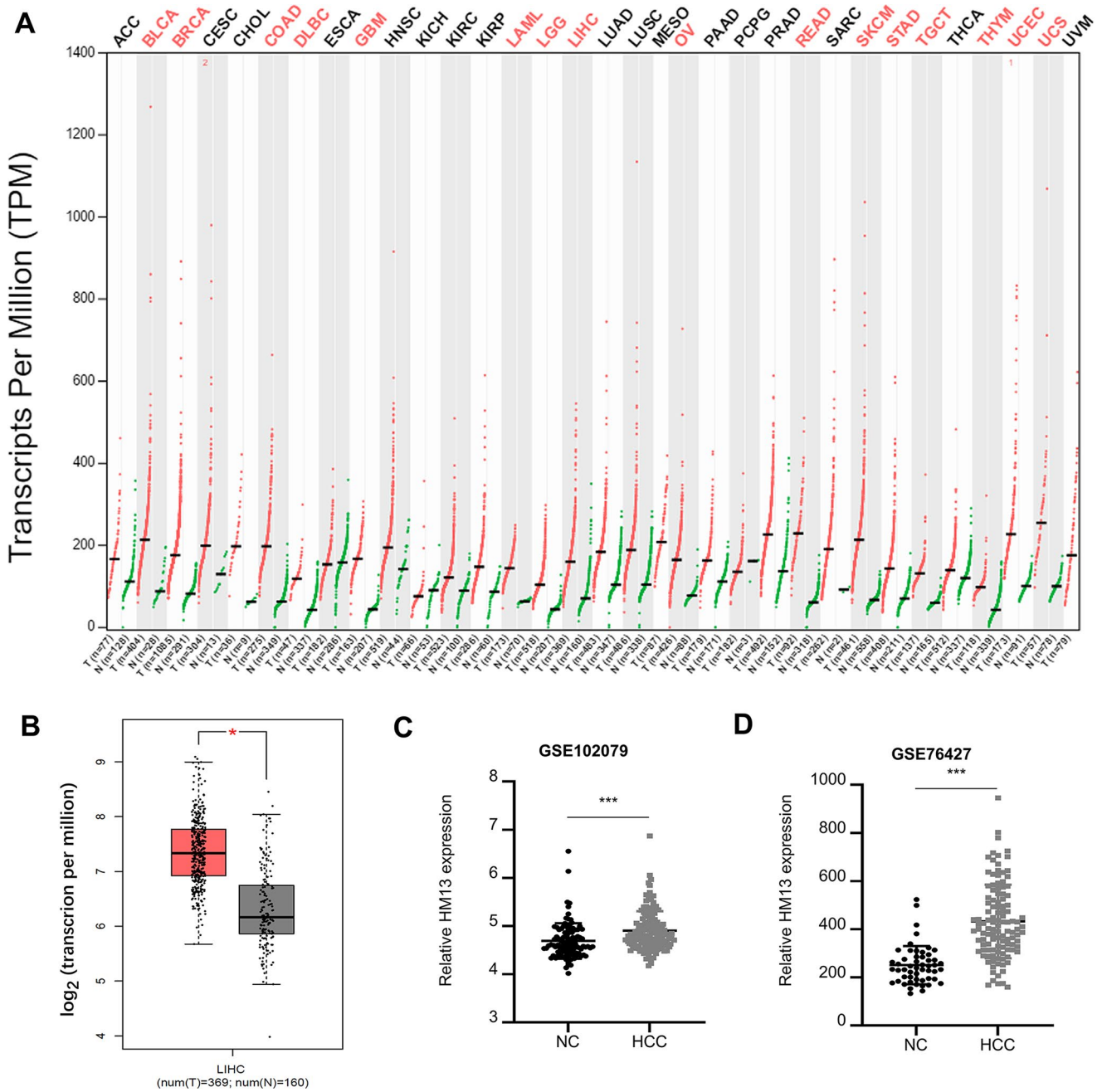

Fig. 1 *HM13* is Overexpressed in HCC (hepatocellular carcinoma) Tissues. **a** Relative *HM13* gene expression pattern analysis in different malignancies using Gene Expression Profiling Interactive Analysis (GEPIA) database; **b** GEPIA database revealed significantly higher *HM13* messenger RNA (mRNA) expression levels in hepatocellular carcinoma (HCC) tissues compared to normal tissues. **c-d** Data from the Gene Expression Omnibus (GEO) datasets GSE102079 and GSE76427 showed elevated HM13 protein expression in HCC samples

analysis of 90 HCC patient samples in our study cohort also demonstrated significantly upregulated *HM13* mRNA levels in tumor tissues relative to adjacent non-cancerous tissues (Fig. 2a). Western blot analysis of 5 randomly selected paired HCC and non-tumor tissues further confirmed higher HM13 protein expression in HCC (Fig. 2b). Immunohistochemical staining revealed that HM13 protein was primarily localized in the cytoplasm and membrane, and was highly expressed in HCC tissue sections compared to normal liver tissue (Fig. 2c).

High *HM13* expression correlates with poor survival in HCC patients

Analysis of 364 HCC patients from the GEPIA database showed that patients with high *HM13* expression had

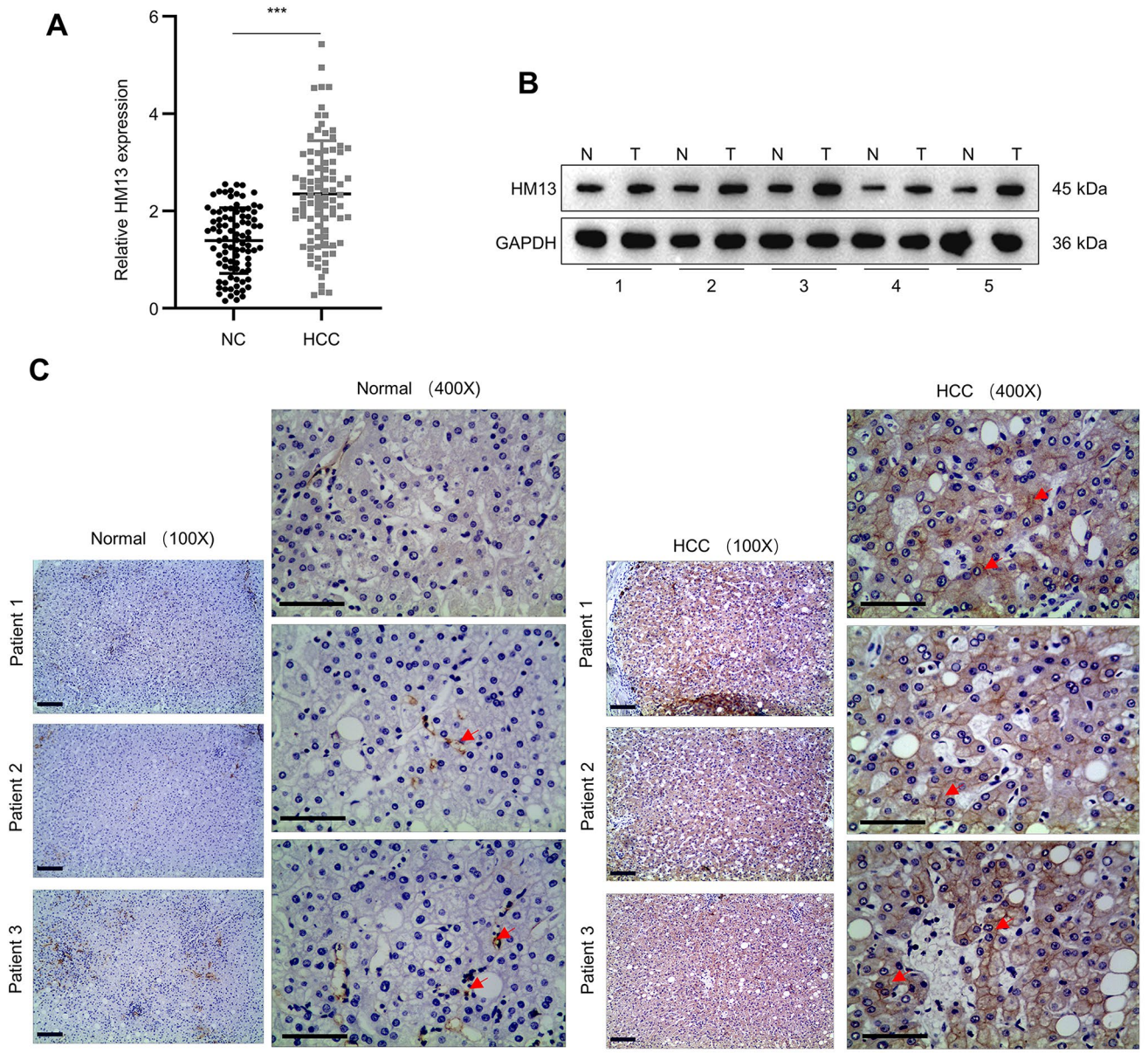

Fig. 2 Validation of *HM13* Overexpression in HCC Patient Samples. **a** Quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis of 90 HCC patient samples demonstrated significantly upregulated *HM13* mRNA levels in tumor tissues compared to adjacent non-cancerous tissues. $^{***}P < 0.001$. **b** Western blot analysis of 5 randomly selected paired HCC and non-tumor tissues confirmed higher HM13 protein expression in HCC. **c** Immunohistochemical (IHC) staining of HM13 protein in HCC tissue sections compared to normal liver tissue. Scale bar, 50 μm in

significantly worse overall survival (OS) and disease-free survival (DFS) compared to those with low expression (Fig. 3a-b). Kaplan-Meier plotter analysis further demonstrated that elevated *HM13* levels were associated with inferior OS, progression-free survival (PFS), recurrence-free survival (RFS), and disease-specific survival (DSS) in HCC patients (Fig. 3c-f). Consistent with these findings, estimation of patient survival time in our cohort revealed dramatically shorter OS in the *HM13* high-expression group versus the low-expression group (Fig. 3g).

HM13 expression correlates with clinicopathological characteristics

Chi-square analysis was performed to evaluate the relationship between *HM13* expression and clinicopathological parameters in HCC patients (Table 1). The results indicated that high *HM13* expression was significantly associated with higher Edmondson grade, presence of metastasis, microvascular invasion, and elevated alpha-fetoprotein (AFP) levels.

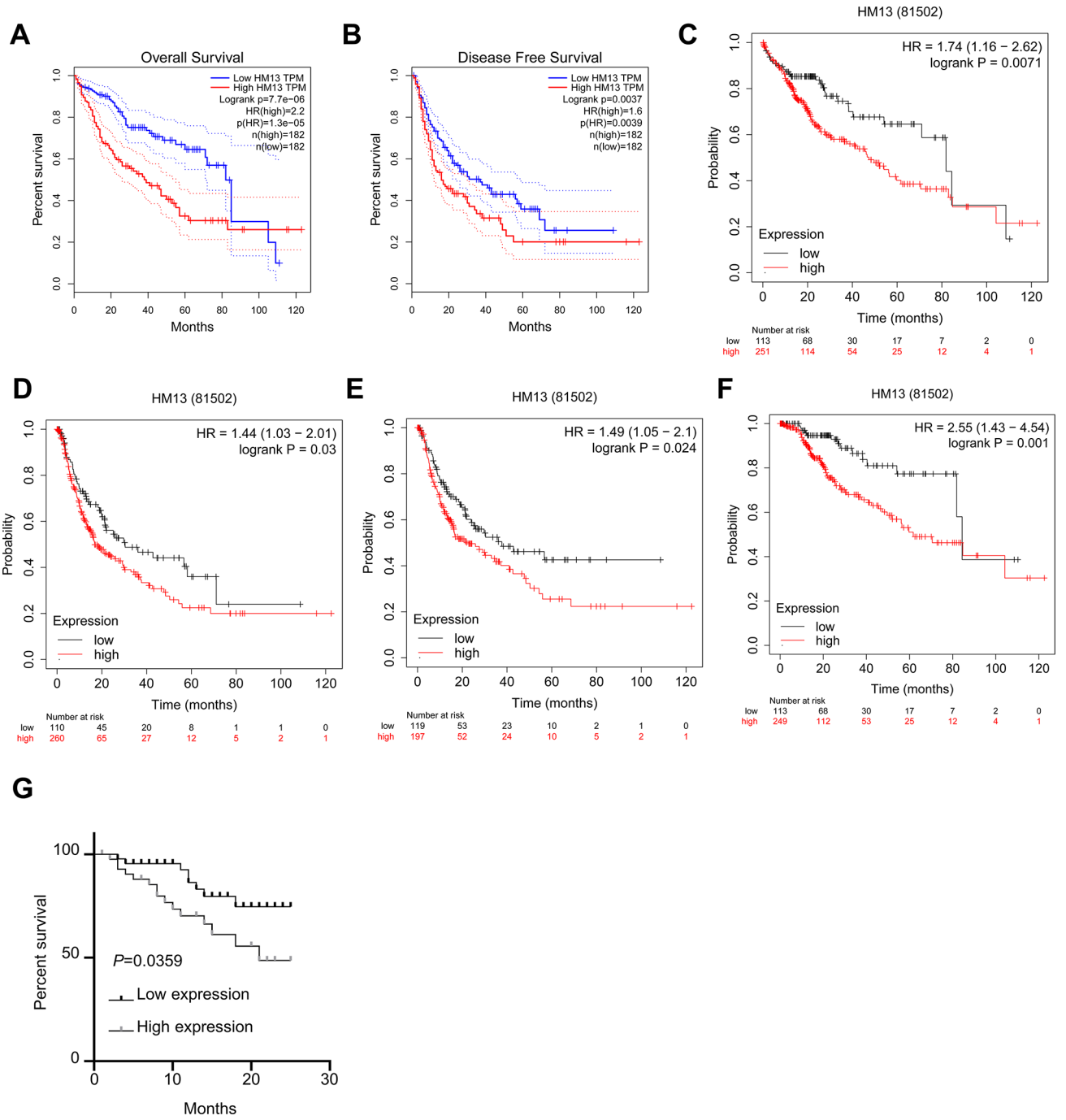

Fig. 3 High HM13 Expression Correlates with Poor Survival in HCC Patients. **a-b** Analysis of 364 HCC patients from the GEPIA database showed that patients with high *HM13* expression had significantly worse overall survival (OS) and disease-free survival (DFS) compared to those with low expression. **c-f** Kaplan-Meier plotter analysis demonstrated that elevated *HM13* levels were associated with inferior OS, progression-free survival (PFS), recurrence-free survival (RFS), and disease-specific survival (DSS) in HCC patients. **g** Estimation of patient survival time in the study cohort revealed dramatically shorter OS in the *HM13* high-expression group versus the low-expression group

Table 1 Relationship between HM13 expression and clinicopathological data of HCC

Clinical pathologic parameters	Group	Case	HM13 expresssion		*P*
			Low ($n=45$)	High ($n=45$)	
Age (years)	< 55	44	19	25	0.2058
	≥ 55	46	26	20	
Gender	Male	59	31	28	0.5057
	Female	31	14	17	
Tumor size (cm)	< 5	40	18	22	0.3961
	≥ 5	50	27	23	
Tumor number	Single	46	25	21	0.399
	Multiple	44	20	24	
Edmondson grade	I + II	39	26	13	0.0057
	III	51	19	32	
Metastasis	Negative	43	27	16	0.0203
	Positive	47	18	29	
Microvascular invasion	Absence	32	21	11	0.0277
	Presence	58	24	34	
AFP (μg/L)	< 50	48	30	18	0.0112
	≥ 50	42	15	27	
Cirihosis	Negative	40	18	22	0.3961
	Positive	50	27	23	

However, *HM13* expression did not correlate with patient age, gender, tumor size, tumor number, or cirrhosis status.

HM13 is an independent prognostic factor for poor OS in HCC

Univariate and multivariate Cox proportional hazards regression analyses were conducted to determine independent prognostic factors for overall survival in HCC patients (Table 2). Univariate analysis revealed that high Edmondson grade, presence of metastasis, microvascular invasion, elevated AFP levels, and high *HM13* expression were associated with poor OS. Importantly, multivariate analysis identified *HM13* overexpression as an independent predictor of shorter OS, along with high Edmondson grade, metastasis, and microvascular invasion.

HM13 is highly expressed in HCC cell lines

To further validate the expression pattern of *HM13* in HCC, we examined its expression in human hepatoma cell lines (Huh7, HCCLM3, and Hep3B) and the immortalized normal hepatocyte cell line L02. qRT-PCR and western blot analyses showed significantly higher *HM13* mRNA and protein levels in the HCC cell lines compared to L02 cells (Fig. 4a-b).

Discussion

Our demonstrated that *HM13* is markedly upregulated in HCC tissues and cell lines. High *HM13* expression correlates with aggressive clinicopathological features and serves as an independent predictor of poor prognosis in HCC patients, highlighting its potential as a prognostic biomarker. Currently, the primary focus of liver cancer research lies in the later stages, with limited knowledge of the disease in its early stages (Akbulut et al. 2020; Choudhuri et al. 2019; Gasser et al. 2022; Guo et al. 2018). Therefore, identifying early markers for liver cancer is crucial for improving the prognosis of HCC. Pervious investigation showed that by suppressing vascular endothelial growth factor (VEGF), a marker for HCC, the activity of macrophages can be reduced (Okikawa et al. 2022). A strong correlation was found between high expression of thyroid hormone responsive gene (THRSP) and a poor prognosis for HCC patients (Ding et al. 2022). Additionally, heighten expression of alpha-fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA)-II were found to be correlated with post-transplant recurrence of HCC (Lee et al. 2022). These tumor markers are currently used in the clinical screening and monitoring of HCC. However, these markers are limited to

Table 2 Univariate and multivariate Cox regression curves were used to analyze the overall survival and prognosis of HCC patients

Clinical pathologic parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.25	0.43–3.26	0.62			
Gender	2.58	1.11–4.85	0.54			
Tumor size (cm)	1.86	0.34–2.59	0.01	1.14	0.59–2.24	0.57
Tumor number	1.77	0.54–5.16	0.32			
Edmondson grade	2.76	1.04–4.15	< 0.01	2.27	1.26–3.18	0.01
Metastasis	4.41	2.12–6.71	< 0.01	3.07	1.17–5.22	0.03
Microvascular invasion	2.52	1.37–3.84	< 0.01	1.84	0.85–4.32	0.36
AFP (μg/L)	2.13	1.25–3.18	< 0.01	1.64	0.97–3.01	0.18
Cirihosis	1.86	0.62–5.15	0.25			
HBs antigen	2.21	0.81–6.13	0.12			
HM13 expresssion	3.11	1.11–5.25	< 0.01	2.64	0.88–3.75	0.02

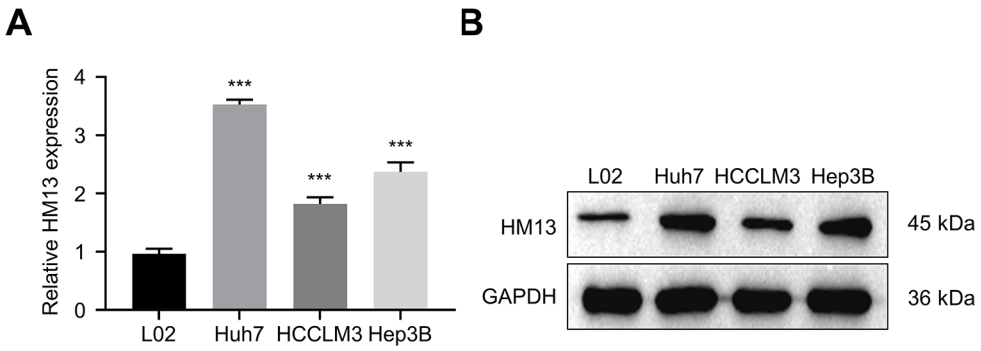

Fig. 4 HM13 Expression in HCC Cell Lines. **a** Quantitative reverse transcription polymerase chain reaction (qRT-PCR) and **b** western blot analyses showed significantly higher *HM13* mRNA and protein levels in human hepatoma cell lines (Huh7, HCCLM3, and Hep3B) compared to the immortalized normal hepatocyte cell line L02. $^{***}P < 0.001$

specific conditions, making them insufficient for screening the early stage HCC cases.

HM13, also known as non-metastatic cells protein 7 (NME7), is an integral membrane protein that exhibits sequence motifs characteristic of presenilin-type aspartic proteases (Yao et al. 2022). Accumulating evidence suggests that HM13 plays a crucial role in promoting cancer progression and malignancy across multiple tumor types. In breast cancer, HM13 has been shown to dampen autophagy and activate the PI3K-AKT-mTOR pathway, thereby functioning as an oncogenic factor (Yang et al. 2022). Furthermore, *HM13* overexpression in breast cancer cells enhanced their proliferative, migratory, and invasive capabilities, while its knockdown elicited the opposite effects.

Of note, the upregulation of *HM13* in breast cancer is featured by loss of DNA demethylation at the gene loci (Goovaerts et al. 2018). In glioblastoma, HM13 affects the secretion of epidermal growth factor receptor variant III (EGFRvIII), contributing to tumor progression (Wei et al. 2017). Notably, high *HM13* expression correlated with poor prognosis in glioblastoma patients, suggesting its potential as a prognostic marker (Zong et al. 2022). Our findings of significantly elevated *HM13* expression in HCC tissues and cell lines, along with its correlation with aggressive clinicopathological features and poor survival outcomes, further corroborate the oncogenic role of HM13 in facilitating HCC development and progression.

Previous studies have highlighted the potential involvement of *HM13* in HCC pathogenesis. *HM13* is identified as a prognostic factor and a predictive biomarker for immunotherapy responsiveness in HCC (Zhang et al. 2022), while *HM13* is reported to promotes HCC cell proliferation, migration, and invasion (Liu et al. 2022). Moreover, *HM13* participates in the gene regulation network of EIF2S2, thereby contributing to HCC progression (Ji et al. 2021). Consistent with these reports, our comprehensive analysis using multiple publicly available databases, along with our patient cohort data, firmly establishes *HM13* as a potent prognostic biomarker in HCC. Importantly, we identified *HM13* overexpression as an independent predictor of poor overall survival, underscoring its potential clinical utility as a prognostic indicator for HCC patients.

While our study provides compelling evidence for the prognostic value of *HM13* in HCC, there are certain limitations that warrant further investigation. Firstly, the underlying molecular mechanisms by which *HM13* promotes HCC progression remain elusive and warrant in-depth mechanistic studies. Secondly, the potential of *HM13* as a therapeutic target in HCC needs to be explored through functional experiments, such as gene knockdown and animal study. Additionally, larger multi-center cohort studies are required to validate the prognostic significance of *HM13* in different stages of HCC cases. Future research should also focus on the potential role of *HM13* in predicting and monitoring therapeutic response, particularly in the context of emerging immunotherapies for HCC.

Conclusion

To conclude, our study establishes *HM13* as a novel prognostic biomarker in HCC, with its overexpression correlating with aggressive clinicopathological features and poor survival outcomes. *HM13* was identified as an independent predictor of worse overall survival, underscoring its potential clinical utility. However, further research is needed to elucidate the underlying mechanisms, explore *HM13* as a therapeutic target through functional studies, and validate its prognostic value in larger multi-center cohorts. Additionally, investigating the role of *HM13* in predicting and monitoring treatment responses, particularly for immunotherapies, could facilitate its application in personalized HCC management strategies.

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Author contributions Meimei Xu, Lili Yan, Zhihui Tan, Ji lv and Hongyu Jiamainly participated in literature search, study design, writing and critical revision. Lili Yan, Shanshan Li, Tao Wang, Yanan Du, Haiyang Song, Jiewei Sun, Wenjin Jiang and Zhiying Xu mainly participated in data collection, data analysis and data interpretation. All authors read and approved the final manuscript.

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Data availability The datasets during and/or analyzed during the current study are available from the corresponding authors.

Declarations

Ethics approval and consent to participate The study was approved by the Ethics Committee Board of Yantai Yuhuangding Hospital and written informed consent was obtained from each patient in accordance with institutional guidelines.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

Akbulut S, Yagmur Y, Sakarya H et al (2020) Relationship between clinical and histopathological features of patients undergoing cholecystectomy. Prz Gastroenterol 15:131–137. https://doi.org/10.5114/pg.2019.86772

Casillo A, Di Guida R, Carillo S et al (2019) Structural elucidation of a Novel Lipooligosaccharide from the Antarctic bacterium OMVs producer Shewanella sp. HM13. Mar Drugs 17. https://doi.org/10.3390/md17010034

Choudhuri G, Gupta V, Negi TS, Ojha R (2019) Potential implications of detecting HBsAg in Asymptomatic people in an Endemic Community through Medical Camps. J Clin Exp Hepatol 9:43–49. https://doi.org/10.1016/j.jceh.2018.02.005

Di Guida R, Casillo A, Yokoyama F et al (2020) Detailed Structural Characterization of the Lipooligosaccharide from the Extracellular Membrane Vesicles of Shewanella vesiculosa HM13. Mar Drugs 18. https://doi.org/10.3390/md18050231

Ding Y, Liu X, Yuan Y et al (2022) THRSP identified as a potential hepatocellular carcinoma marker by integrated bioinformatics analysis and experimental validation. Aging 14:1743–1766. https://doi.org/10.18632/aging.203900

Gasser E, Sancar G, Downes M, Evans RM (2022) Metabolic messengers: fibroblast growth factor 1. Nat Metab 4:663–671. https://doi.org/10.1038/s42255-022-00580-2

Goovaerts T, Steyaert S, Vandenbussche CA et al (2018) A comprehensive overview of genomic imprinting in breast and its deregulation in cancer. Nat Commun 9:4120. https://doi.org/10.1038/s41467-018-06566-7

Guo D, Song X, Guo T et al (2018) Vimentin acetylation is involved in SIRT5-mediated hepatocellular carcinoma migration. Am J Cancer Res 8:2453–2466

Hamdoun FZ, Hassani Y, Abid H et al (2021) The Prognostic Value of the ART score before the second Transarterial Chemoembolization. Gulf J Oncolog 1:32–35

He J, Meng M, Wang H (2022) A Novel Prognostic Biomarker LPAR6 in Hepatocellular Carcinoma via associating with Immune infiltrates. J Clin Transl Hepatol 10:90–103. https://doi.org/10.14218/JCTH.2021.00047

Hu X, Hu X, Wang Q (2021) Propofol induces apoptosis of hepatocellular carcinoma cells by upregulating miR-134 expression. Transl Cancer Res 10:3004–3012. https://doi.org/10.21037/tcr-21-830

Husa P, Snopkova S, Husa P Jr. (2021) [Hepatitis D screening is important in the Czech Republic as well]. Klin Mikrobiol Infekc Lek 27, 98–103. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/35170745

Ji P, Wang H, Cheng Y, Liang S (2021) Prognostic prediction and gene regulation network of EIF2S2 in hepatocellular carcinoma based on data mining. J Gastrointest Oncol 12:3061–3078. https://doi.org/10.21037/jgo-21-748

Kamasaka K, Kawamoto J, Chen C et al (2020) Genetic characterization and functional implications of the gene cluster for selective protein transport to extracellular membrane vesicles of Shewanella vesiculosa HM13. Biochem Biophys Res Commun 526:525–531. https://doi.org/10.1016/j.bbrc.2020.03.125

Lee TY, Choi HJ, Ahn J, Hong T, H,You YK (2022) Efficacy of tumor markers after liver transplantation in patients with Hepatocellular Carcinoma. Transpl Proc 54:461–467. https://doi.org/10.1016/j.transproceed.2022.01.007

Li J, Cheng L, Jia H et al (2021) IFN-gamma facilitates liver fibrogenesis by CD161(+)CD4(+) T cells through a regenerative IL-23/IL-17 axis in chronic hepatitis B virus infection. Clin Transl Immunol 10:e1353. https://doi.org/10.1002/cti2.1353

Liu J, Li W, Wu L (2022) Pan-cancer analysis suggests histocompatibility minor 13 is an unfavorable prognostic biomarker promoting cell proliferation, migration, and invasion in hepatocellular carcinoma. Front Pharmacol 13:950156. https://doi.org/10.3389/fphar.2022.950156

Okikawa S, Morine Y, Saito Y et al (2022) Inhibition of the VEGF signaling pathway attenuates tumor–associated macrophage activity in liver cancer. Oncol Rep 47. https://doi.org/10.3892/or.2022.8282

Wang J, Li Y, Zhang C et al (2021) A hypoxia-linked gene signature for prognosis prediction and evaluating the immune microenvironment in patients with hepatocellular carcinoma. Transl Cancer Res 10:3979–3992. https://doi.org/10.21037/tcr-21-741

Wei JW, Cai JQ, Fang C et al (2017) Signal peptide peptidase, encoded by HM13, contributes to Tumor Progression by affecting EGFRvIII secretion profiles in Glioblastoma. CNS Neurosci Ther 23:257–265. https://doi.org/10.1111/cns.12672

Yang H, Li Z, Wang Z et al (2022) Histocompatibility minor 13 (HM13), targeted by miR-760, exerts oncogenic role in breast cancer by suppressing autophagy and activating PI3K-AKT-mTOR pathway. Cell Death Dis 13:728. https://doi.org/10.1038/s41419-022-05154-4

Yao T, Xiao H, Wang H, Xu X (2022) Recent advances in PROTACs for drug targeted protein research. Int J Mol Sci 23. https://doi.org/10.3390/ijms231810328

Yokoyama F, Imai T, Aoki W et al (2021) Identification of a putative sensor protein involved in regulation of vesicle production by a Hypervesiculating Bacterium, Shewanella vesiculosa HM13. Front Microbiol 12:629023. https://doi.org/10.3389/fmicb.2021.629023

Zhang L, Hu S, Chen J et al (2021) Comprehensive analysis of the MIR4435-2HG/miR-1-3p/MMP9/miR-29-3p/DUXAP8 ceRNA network axis in hepatocellular carcinoma. Discov Oncol 12:38. https://doi.org/10.1007/s12672-021-00436-3

Zhang G, Lv X, Yang Q, Liu H (2022) Identification of HM13 as a prognostic indicator and a predictive biomarker for immunotherapy in hepatocellular carcinoma. BMC Cancer 22:888. https://doi.org/10.1186/s12885-022-09987-2

Zhou X, Li TM, Luo JZ et al (2021) CYP2C8 suppress Proliferation, Migration, Invasion and Sorafenib Resistance of Hepatocellular Carcinoma via PI3K/Akt/p27(kip1) Axis. J Hepatocell Carcinoma 8:1323–1338. https://doi.org/10.2147/JHC.S335425

Zong RQ, Zhang HY, Li XY, Li YR, Chen Y (2022) Overexpressed Histocompatibility Minor 13 was Associated with Liver Hepatocellular Carcinoma Progression and Prognosis. Genet Res (Camb) 2022, 7067743. https://doi.org/10.1155/2022/7067743

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