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ORIGINAL ARTICLE

Basic Study

Downregulation of huntingtin-associated protein 1 predicts poor prognosis in gastric cancer

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Abstract

BACKGROUND

Highly expressed in the gastrointestinal mucosa, huntingtin-associated protein 1 (HAP1) is closely associated with tumor development and prognosis.

AIM

To investigate the clinical utility of HAP1 expression in gastric cancer (GC).

METHODS

We randomly selected 124 GC patients had not undergone preoperative radiotherapy or chemotherapy, they were diagnosed at the Central Hospital of Wuhan between May 2013 and October 2018. Immunohistochemistry was used to detect HAP1 expression in paraffin-embedded GC tissues, as well as metastatic lymph nodes. Their clinical data were collected and all participants were follow up for 5 years. Western blotting and quantitative polymerase chain reaction were used to detect HAP1 levels in 20 matched pairs of fresh GC tissues.

RESULTS

HAP1 protein and mRNA levels were lower in fresh GC tissues than in normal

mucosal tissues ($P < 0.001$, respectively). Immunohistochemistry also revealed lower HAP1 expression in GC tissues and metastatic lymph nodes than in normal mucosal tissues ($P < 0.05$). HAP1 expression in GC was closely associated with differentiation, lymph node metastasis, lymph node ratio, remote metastasis, clinical stage, tumor location, and survival time ($P < 0.05$). Furthermore, HAP1 expression independently predicted GC ($P < 0.05$) and was more accurate in advanced GC than in early GC ($P < 0.05$).

CONCLUSION
HAP1 is an important prognostic biomarker for GC, with low HAP1 expression positively correlating with poor overall survival, especially in advanced clinical stages.

Key Words: Huntingtin-associated protein 1; Gastric cancer; Prognostic utility; Biomarker; Clinical stage

Core Tip: The clinical utility of huntingtin-associated protein 1 (HAP1) expression in gastric cancer (GC) was assessed. HAP1 expression was significantly lower in GC tissues than in normal gastric mucosa, and was strongly associated with GC progression and metastasis. Downregulation of HAP1 correlates with poor overall survival in patients with GC, especially in advanced clinical stages. Thus, HAP1 is a promising prognostic marker for GC, with important implications for advancing treatment.

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INTRODUCTION

Gastric cancer (GC) is a malignant tumor with a high incidence in the digestive system and the third most common cancer worldwide[1]. Its occurrence, development, and metastasis involves multiple genetic pathways[2]. Generally, symptoms appear during the middle and late stages, with surgical resection rates decreasing significantly in the late stage. Major treatment methods (*i.e.*, radiotherapy, chemotherapy, targeted therapy, and immunotherapy) yield unsatisfactory outcomes on advanced GC. Therefore, early detection is important for effective therapy. Serum tumor markers are relatively noninvasive and simple to use. Thus, identifying novel biomarkers will improve screening, disease monitoring, and prognosis, while also providing new therapeutic targets.

Huntingtin-associated protein 1 (HAP1) interacts with huntingtin, a protein associated with Huntington's disease (HD)[3]. While primarily found in the central nervous system, HAP1 is also present in the digestive system, expressed at varying levels throughout the gastrointestinal mucosa. In particular, gastric mucosa highly expresses HAP1[4-6]. HAP1 is crucial to gene transcriptional regulation, membrane endocytosis, inclusion body formation, vesicle transport, and signal transduction[7]. These functions explain why HAP1 is associated with the biological characteristics, radiosensitivity, and drug resistance of malignancies such as pancreatic and breast cancers[4,8]. Its expression is closely related to tumor development and prognosis, suggesting potential as a cancer biomarker.

Cell proliferation, migration and invasion were inhibited in GC cells overexpressing HAP1. HAP1 also triggered apoptosis during glucose deprivation, further reduced adenosine triphosphate production and elevates reactive oxygen species levels, which disrupting cellular redox and increasing the likelihood of tumor cell death[9]. Furthermore, the application of HAP1 as a therapeutic target has already been empirically demonstrated in several diseases[10-14]. For example, HAP1 expression negatively correlated with the sensitivity of acute lymphoblastic leukemia cells to L-asparaginase[15].

However, no empirical data are available regarding whether HAP1 expression is indeed correlated with GC clinical features and prognosis. Therefore, this study investigated HAP1 expression in patients with GC to understand the relationship between HAP1 levels and clinicopathological characteristics. Our findings should clarify the clinical utility of HAP1 expression in GC progression and prognosis.

MATERIALS AND METHODS

Patients and specimens

Between May 2013 and October 2018, 124 paraffin-embedded GC samples were obtained. All individuals with GC [56 male and 68 female patients; age, 28-88 years (mean = 61 years)] were diagnosed at the Central Hospital of Wuhan and had not undergone preoperative radiotherapy or chemotherapy. Clinical data were collected from all participants. Follow

up was 5 years; during this period, 104 patients died and 30 patients presented with distant metastases. Informed consent was waived for by the Institutional Review Board (No. WHZXKYL2024-207) of the Central Hospital of Wuhan.

During August to October 2023, 20 matched pairs of fresh GC specimens were collected. Fresh clinical specimens comprised tumor tissues and normal adjacent mucosa. Specimens were stored in liquid nitrogen immediately after surgery. This study was approved by the Ethics Committee of Central Hospital of Wuhan (No. WHZXKYL2024-207). Written informed consent was obtained from all 20 patients.

Real-time polymerase chain reaction

Total RNA was extracted from 20 matched pairs of frozen GC tissues using TRIzol reagent (Invitrogen), following manufacturer protocol. Reverse transcription (RT) was performed using a high-capacity cDNA RT kit (Applied Biosystems, Foster City, CA, United States) on an access RT system (Promega, Madison, WI, United States), followed by quantitative polymerase chain reaction (qPCR) using a SYBR Green master mix kit (Applied Biosystems). Each specimen was tested in triplicate. The internal control was glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Relative mRNA content was calculated as: Flod change = $2^{-\Delta\Delta Ct}$. Primer sequences were as follows: HAP1, 5′-ATGCGCCCGAA-GAGGTTGG-3′ and 5′-CTGCAGATCGTCGTGCCGATGA-3□; GAPDH, 5′-CCATGTTCGTCATGGGTGTGAACCA-3′ and 5′-GCCAGTAGAGGCAGGGATGATGTT C-3′.

Western blot analysis

Frozen GC and normal mucosal tissues were crushed into powder, placed on ice, and lysed in radioimmunoprecipitation assay buffer (Pierce, IL, United States) containing protease inhibitors (Pierce, IL, United States). Proteins were quantified using a bicinchoninic acid assay. Proteins were loaded into their respective lanes, electrophoresed, and transferred onto polyvinylidene difluoride membranes (Millipore, Burlington, MA, United States). Membranes were blocked in 5% non-fat dry milk, followed by overnight incubation at 4 °C with anti-HAP1 polyclonal antibodies (1:1000 dilution; Santa Cruz Biotechnology, CA, United States), anti-β-actin antibody (1:10000 dilution; Santa Cruz Biotechnology, CA, United States), and their corresponding horseradish peroxidase-conjugated secondary antibodies (1:5000 dilution; Invitrogen, CA, United States). Signals were detected using enhanced chemiluminescence (Pierce, IL, United States).

Immunohistochemical analysis

Tissue sections of patients with GC were oven-dried at 68 °C for 30 minutes. Samples were deparaffinized and hydrated in graded xylene and ethanol. Subsequently, they were incubated in 0.3% hydrogen peroxide for 15 minutes, placed into boiling sodium citrate buffer (potential of hydrogen = 6.0) for 15 minutes, and blocked for 30 minutes using anti-HAP1 polyclonal antibodies at room temperature. Tissue sections were incubated with horseradish peroxidase-conjugated secondary antibodies (1:1000 dilution; Invitrogen, CA, United States) at 4 °C for 30 minutes. Sections were then placed sequentially in diaminobenzidine solution, hematoxylin, 1% ethyl alcohol, 1% ammonium hydroxide, graded xylene, and ethanol. Finally, slides were sealed with neutral gum.

Two pathologists scored the slides on staining range and intensity; their scores were averaged for the final result. Staining range scores were assigned as follows: 1 point (1%-25%), 2 points (26%-50%), 3 points (51%-75%), and 4 points (76%-100%). Staining intensity scores were assigned as follows: 0 (negative), 1 (weakly positive), 2 (moderately positive), and 3 (strongly positive). Final staining scores were classified into four levels: (-), < 3; (+), 3; (++), 4; and (+++), ≥ 5. Scores of 0-3 and 4-7 were considered low and high HAP1 expression, respectively.

Statistical analysis

Paired-sample or two-sample *t*-tests were used to analyze HAP1 expression in GC, normal adjacent mucosa, and metastatic lymphatic tissues. HAP1 mRNA and protein levels in GC and normal adjacent mucosa were compared with a paired-sample *t*-test. The correlation between HAP1 and GC clinicopathological features was analyzed by Pearson's χ^2 test. Uni- and multivariate Cox proportional hazards model was applied to determine the relationships between HAP1, clinical characteristics, and survival. Overall survival was calculated as duration from operation day to death or last follow-up. Kaplan-Meier plots and log-rank tests were used for survival analyses. All statistics were performed in statistical product and service solutions 19.0. Significance was set at $P < 0.05$.

RESULTS

HAP1 levels in GC tissues and normal adjacent mucosa

Western blotting on 20 matched pairs of frozen GC specimens and adjacent normal mucosa revealed HAP1 protein downregulation in 15 GC samples, while the remaining five had concentrations nearly equal to or higher than concentrations in mucosa (Figure 1A and B). Results from qPCR demonstrated that HAP1 mRNA was downregulated from mucosa levels in 16 GC tissues, whereas four had nearly equal or higher expression (Figure 1C and D). Overall, mucosa HAP1 protein and mRNA levels were nearly two and three times higher, respectively, than levels in matched GC tissues ($P < 0.001$).

Immunohistochemical analysis of HAP1 in GC specimens

HAP1 expression in GC tissues were lower than those in normal mucosa (Figure 2A-C). Weak or negative signals were detected in metastatic lymph nodes (Figure 2D). Among the 124 GC samples, 85 (68.5%) lowly expressed (0 to 1 +) and 39

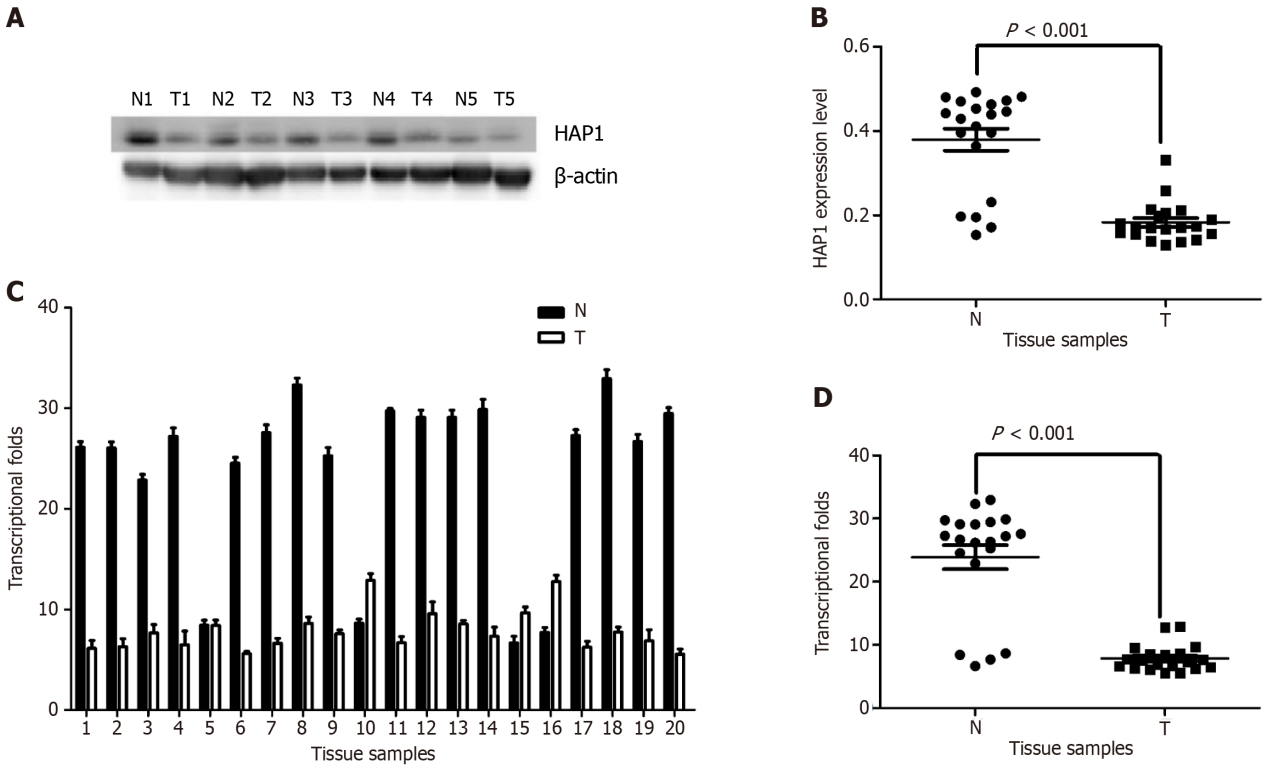

Figure 1 Huntingtin-associated protein 1 expression in gastric cancer tissues. A: Western blot analysis of huntingtin-associated protein 1 (HAP1) expression in tumor tissues and normal adjacent mucosa; B: Relative HAP1 protein level in 20 matched pairs of gastric cancer tissues and adjacent mucosa. β-actin was the control. HAP1 expression was obviously lower in tumor tissues than in normal mucosa ($P < 0.001$); C: Quantitative polymerase chain reaction measurement of HAP1 mRNA in tumor tissues and normal adjacent mucosa; D: Relative HAP1 mRNA expression in 20 matched pairs of gastric cancer tissues and adjacent mucosa; mucosa from sample 1 was the reference. HAP1 was lower in tumor tissues than in normal mucosa ($P < 0.001$). Glyceraldehyde 3-phosphate dehydrogenase was used as a control. means ± SD are shown. HAP1: Huntingtin-associated protein 1; N: Normal adjacent mucosa; T: Tumor tissues.

(31.5%) highly expressed (2 + to 3 +) HAP1 (Table 1). Both GC ($\chi^2 = 35.631$, $P < 0.001$) and lymphatic metastatic ($\chi^2 = 39.376$, $P < 0.001$) tissues had significantly lower HAP1 expression than adjacent normal mucosa (Table 1). Additionally, HAP1 expression was lower in GC tissues with lymphatic metastasis than in those without lymphatic metastasis ($\chi^2 = 5.494$, $P = 0.019$; Table 1). HAP1 expression did not differ between GC tissues with lymphatic metastasis and lymphatic metastasis tissues ($\chi^2 = 0.036$, $P = 0.85$; Table 1).

In GC tissues, HAP1 expression was clearly correlated with clinicopathological features. Specifically, HAP1 expression was related to lymphatic metastasis ($P = 0.019$), tumor differentiation ($P = 0.014$), remote metastasis ($P = 0.035$), lymph node ratio ($P = 0.009$), tumor location ($P = 0.038$), and clinical stage ($P = 0.021$) (Table 2). In contrast, HAP1 expression was not associated with sex ($P = 0.354$), age ($P = 0.733$), tumor size ($P = 0.599$), or serosal invasion ($P = 0.117$) (Table 2).

Relationship between HAP1 and overall survival

Independent prognostic factors in patients with GC was evaluated by the Cox proportional hazards model. In the single-variable analysis, HAP1 levels ($P = 0.011$), clinical stage ($P = 0.012$), lymph node metastasis ($P = 0.031$), remote metastasis ($P = 0.009$), and tumor location ($P = 0.034$) were significant predictors (Table 3). Multivariate analysis suggested that the independent prognostic factors for overall survival were HAP1 expression ($P = 0.029$), clinical stage ($P = 0.014$), and remote metastasis ($P = 0.012$) (Table 3).

Next, results from Kaplan-Meier curve analysis indicated that in patients with early-stage GC ($n = 34$), overall survival was not related to HAP1 levels in GC tissues ($P = 0.669$; Figure 3A). However, overall survival was related to HAP1 levels in patients at advanced-stage ($n = 90$, $P = 0.006$; Figure 3B) and all-stage ($n = 124$, $P = 0.004$; Figure 3C) GC. Patients with low HAP1 levels had significantly lower 5-year survival rates than those with high HAP1 expression. Hence, HAP1 downregulation may be related to worse prognosis in patients with advanced GC.

DISCUSSION

Our findings indicate that HAP1 is an independent prognostic factor for overall survival in patients with GC. Patients with advanced-stage GC had lower 5-year survival rates if HAP1 was lowly expressed than if HAP1 was highly expressed. Survival analysis indicated that HAP1 played a significant role in the prognosis of advanced-stage GC, implying that HAP1 may be an important biomarker for such patients.

Table 1 Expression of huntingtin-associated protein 1 in patients with gastric cancer

Groups	HAP1 expression				Total
	-	+	++	+++	
Adjacent normal mucosas	11	27	33	53	124
GC tissues	48	37	28	11	124[1]
GC tissues with lymphatic metastasis	30	28	10	8	76[2]
GC tissues without lymphatic metastasis	17	10	11	10	48
Lymphatic metastasis tissues	45	12	13	6	76[3]

[1]Adjacent normal mucosas *vs* gastric cancer tissues; $\chi^2 = 35.631$, $P < 0.001$.
[2]Gastric cancer tissues with lymphatic metastasis *vs* gastric cancer tissues without lymphatic metastasis; $\chi^2 = 5.494$, $P = 0.019$.
[3]Adjacent normal mucosas *vs* lymphatic metastasis tissues; $\chi^2 = 39.376$, $P < 0.001$.
HAP1: Huntingtin-associated protein 1; GC: Gastric cancer.

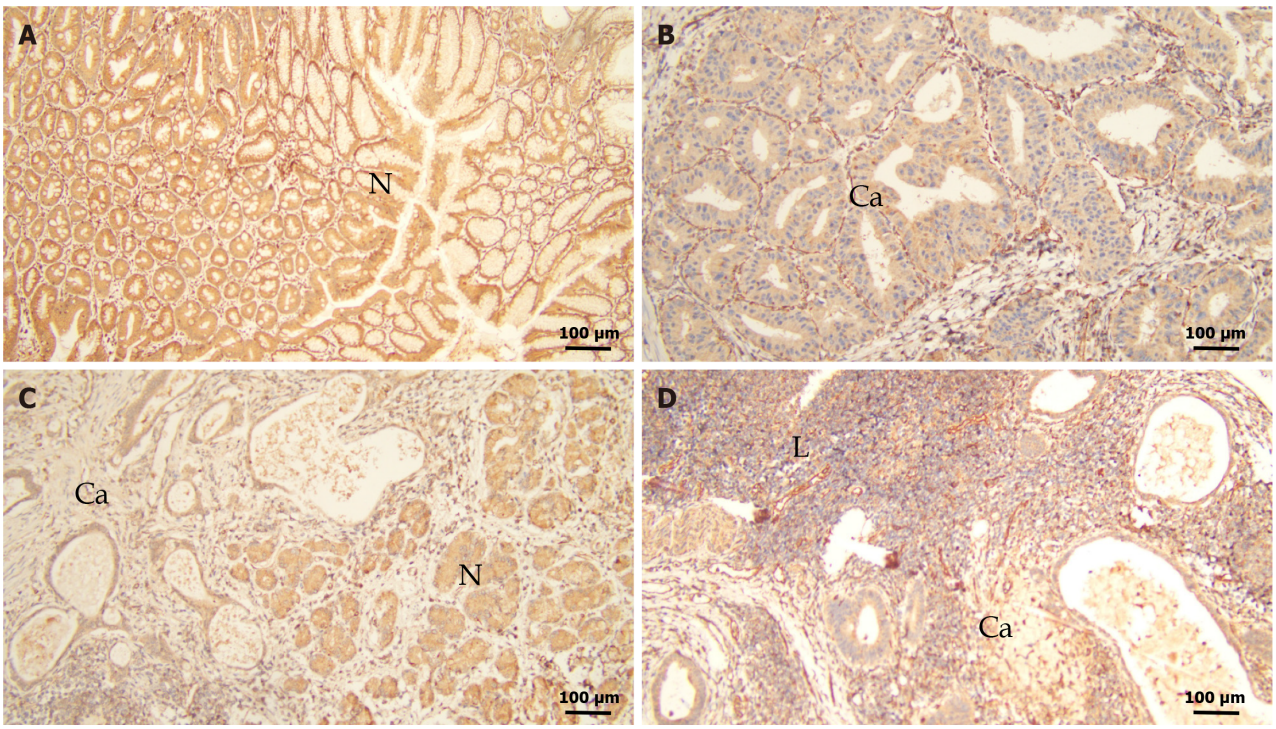

Figure 2 Immunohistochemistry of huntingtin-associated protein 1 expression in gastric cancer tissues. A: Immunohistochemical staining of huntingtin-associated protein 1 (HAP1) expression in normal gastric mucosa (200 ×); B: HAP1 expression in gastric cancer tissue (200 ×); C: HAP1 expression is elevated in the normal gastric mucosa and downregulated in gastric cancer tissue (200 ×); D: HAP1 expression in metastatic lymph nodes (200 ×). Scale bars represent 100 μm. N: Normal gastric mucosa; L: Lymph nodes; Ca: Gastric cancer tissue.

Despite widespread scientific investigation and massive efforts to develop effective targeted therapies, GC has a poor prognosis and is incurable. Therefore, new treatments and biomarkers are urgently needed to improve therapeutic efficacy for GC. Molecular-targeted therapies exploited to suppress malignant proliferation has potent antitumor activity and remarkably reduces the risk of mortality and recurrence of patients.

Several studies have shown that patients with HD have a relatively low incidence of cancer[16,17]. The nosogenesis of HD involves abnormal repeat amplification of polyglutamine in huntingtin[18]. HAP1 is linked to HD through its interaction with huntingtin[3,19,20]. HAP1 is a multifunctional protein participated in many biological pathways. Current research suggests that HAP1 is associated with the biological characteristics and drug resistance of certain cancers. HAP1 stimulates apoptosis of breast cancer cells, indicating its potential use as a cancer biomarker[8]. However, the potential molecular mechanism of HAP1 affecting cancer remains unclear. HAP1 is also implicated in various cancer types; its downregulation promotes tumor occurrence and development[3]. These studies suggest that HAP1 is a tumor suppressor gene. Our findings support it and demonstrate that HAP1 protein and mRNA are lower in GC tissues than in normal adjacent mucosae. Low HAP1 expression was also related to poor prognosis, consistent with previous results in breast cancer[8].

Table 2 Relationship between huntingtin-associated protein 1 expressions and clinicopathologic features in patients with gastric cancer

Features	Low	High	*P* value	χ^2
Cases	85	39		
Age				
< 55 years	30	15	0.733	0.116
≥ 55 years	55	24		
Sex				
Male	36	20	0.354	0.861
Female	49	19		
Tumor size				
< 3 cm	37	16	0.599	0.276
≥ 3 cm	48	23		
Differentiation				
Low	40	10	0.014	8.506
Moderate	28	12		
High	17	17		
Serosal invasion				
No	33	21	0.117	2.454
Yes	52	18		
Lymphatic metastasis				
No	27	21	0.019	5.494
Yes	58	18		
LNR				
< 27	33	25	0.009	6.862
≥ 27	52	14		
Remote metastasis				
No	60	35	0.035	4.458
Yes	25	4		
Clinical stage				
Early	18	16	0.021	5.293
Advanced	67	23		
Tumor location				
Proximal	58	19	0.038	4.327
Distal	27	20		

LNR: Lymph node ratio. Positive lymph node/total examined lymph nodes × 100%. Tumor size was measured based on the length of the largest tumor nodule.

Results from immunohistochemical confirmed that GC and metastatic lymphatic tissues had lower HAP1 expression than normal mucosa. Additionally, HAP1 expression was lower in GC tissues with lymphatic metastasis than in those without lymphatic metastasis. Furthermore, HAP1 expression was associated with major clinicopathological features, including tumor differentiation, lymphatic metastasis, lymph node ratio, remote metastasis, clinical stage, and tumor location. Overall, our data indicated that HAP1 inhibited GC progression and metastasis, consistent with previous reports indicating that HAP1 upregulation limited breast cancer cell growth *in vitro*, suppressing cell migration and invasion[8]. Notably, we observed that HAP1 expression was lower in proximal tumors than in distal tumors. Therefore, proximal GC may be more likely to metastasize and has a lower survival rate than distal GC[21].

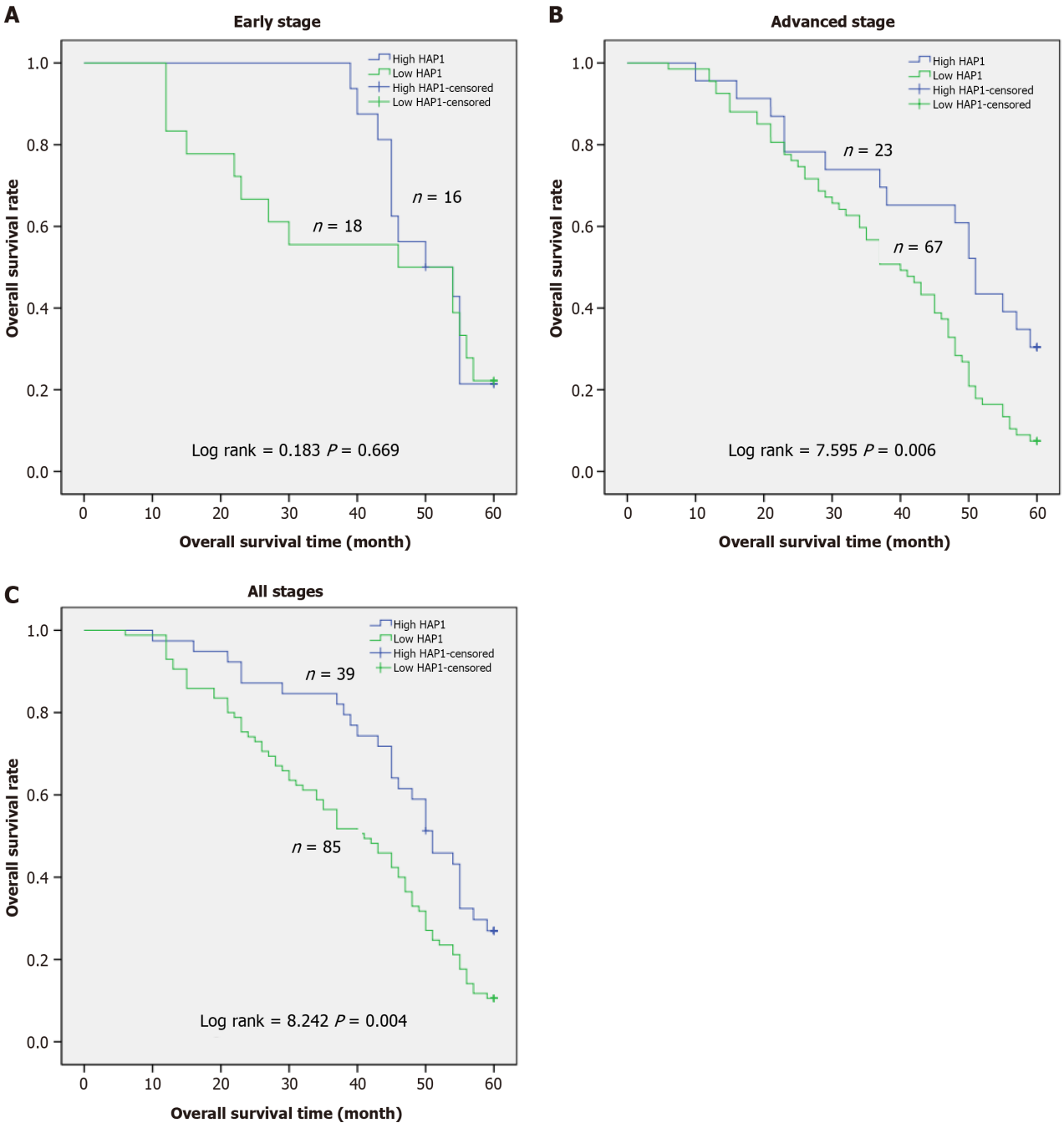

Figure 3 Relationship between huntingtin-associated protein 1 level and overall survival of patients with gastric cancer. A: At the early stage (n = 34), huntingtin-associated protein 1 (HAP1) protein levels in cancer tissues were not correlated with overall survival (P = 0.669); B: At the advanced stage (n = 90), low HAP1 level in cancer tissues was correlated with poor overall survival (P = 0.006); C: At all stages (n = 124), low HAP1 level in cancer tissues was related to poor overall survival (P = 0.004). HAP1: Huntingtin-associated protein 1.

This study had certain limitations. First, patients came from a single center, meaning our data were inherently biased and may not be applicable to a larger population. Prospective multicenter studies are required to validate our findings. In addition, the lack of a standardized HAP1 expression assessment may introduce bias in clinical practice. Finally, validation using animal models is necessary to better assess the potential for clinical use.

CONCLUSION

HAP1 is strongly associated with GC progression and metastasis. Moreover, HAP1 downregulation correlates with poor overall survival in patients with GC, especially at advanced clinical stages. HAP1 is thus a promising candidate for a diagnostic and prognostic marker of GC. Importantly, it may also serve as a novel therapeutic target for GC. Further studies are required to elucidate the molecular mechanisms underlying the role of HAP1 in GC.

Table 3 Cox proportional hazards model of the relationship between individual parameters and overall survival

Variables[1]	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
HAP1 (low)	2.367 (1.876-4.012)	0.011	1.932 (1.142-2.867)	0.029
Age (≥ 55 years)	1.358 (0.768-1.152)	0.934		
Sex (female)	0.736 (0.864-1.784)	0.869		
Tumor size (≥ 3 cm)	0.805 (0.653-1.251)	0.211		
Differentiation (low)	0.854 (0.671-1.126)	0.217		
Clinical stage (advanced)	2.675 (1.765-3.467)	0.012	1.878 (1.342-3.247)	0.014
Lymph metastases (yes)	2.348 (1.854-2.637)	0.031	1.641 (0.856-2.536)	0.091
LNR (≥ 27)	0.843 (0.743-1.987)	0.451		
Remote metastasis (yes)	2.986 (1.897-4.567)	0.009	2.657 (1.564-3.782)	0.012
Tumor location (distal)	2.283 (1.891-3.147)	0.034	2.154 (1.965-3.012)	0.061
Serosal invasion (yes)	1.786 (1.056-2.435)	0.091		

[1]Variables in parentheses are the reference.
HR: Hazard ratio; CI: Confidence interval; LNR: Lymph node ratio.

FOOTNOTES

Author contributions: Wang XY, Yang FH, and Yuan ZY conducted the experiments; Zhang HF and Xu ZH designed experiments; Wang XY, Zhang HF, and Xu ZH analyzed the data; Wang XY, Yang FH, Yuan ZY, Wang ZJ, Zhang HF, Xu ZH drafted and approved the manuscript; Zhang HF and Xu ZH are co-corresponding authors of this manuscript, contributing equally to manuscript revision.

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Institutional review board statement: All procedures involving human participants in this study were in accordance with the ethical standards of the institutional and national research committee. The Ethics Committee of Central Hospital of Wuhan approved this study (No. WHZXKYL2024-207).

Institutional animal care and use committee statement: This study is not involving animal subjects.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: All the data are available without resection. Researchers can obtain data by contacting the corresponding author.

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