High expression of fibronectin 1 indicates poor prognosis in gastric cancer

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Abstract. Fibronectin 1 (FN1) is involved in the occurrence and development of various tumors and is upregulated in multiple cancer types. FN1 has been demonstrated to promote cell proliferation and migration in gastric cancer cell lines. However, the relationship between the expression of FN1 and clinicopathological factors and prognosis is not clear in gastric cancer (GC). The aim of the present study was to investigate the association between FN1 expression and clinicopathology and prognosis of gastric cancer. In this study, 17 publicly available GC cohorts (n=2,376) with gene expression data from the Gene Expression Omnibus (GEO), The Cancer Genome Atlas (TCGA) and Oncomine databases were tested. In addition, FN1 protein expression was validated by immunohistochemistry in a separate cohort. The results demonstrated that FN1 may serve as a new prognostic marker for GC.

Introduction

Gastric cancer is also the third leading cause of cancer-related mortality in China (2). Although surgery combined with radiotherapy, chemotherapy and targeted therapy prolongs survival, the 5-year overall survival rate of patients with advanced gastric cancer remains poor. The 5-year overall survival rates of patients with pathological T stage 2, 3 and 4 disease were 68.3, 33.0 and 24.0% respectively (3,4). Therefore, new biomarkers of gastric cancer to determine prognosis are necessary.

Fibronectin 1 (FN1) mediates the interaction between cells and the extracellular matrix and serves an important role in cell adhesion, migration, growth and differentiation (5). FN1 is a ligand for numerous members of the integrin receptor family (6). FN1 is involved in the occurrence and development of various tumors. FN1 activates the PI3K/Akt pathway by binding to its integrin receptor α5β1 in breast cancer (7). In addition, FN1 has been demonstrated to promote cell proliferation and migration in esophageal squamous cell carcinoma, oral squamous cell carcinoma (OSCC), nasopharyngeal carcinoma, colorectal, ovarian, renal and thyroid cancer (8-14). However, little is known about the expression of FN1 in gastric cancer. FN1 is upregulated in GC tissues compared with normal gastric tissues (15). FN1 knockdown inhibits cell migration and invasion in vitro, and FOXF1 adjacent non-coding developmental regulatory RNA and microRNA-200c promote the proliferation, migration and invasion of GC cells by negatively targeting FN1 (15-17). Overall, FN1 is a potential biomarker candidate for GC prognosis, but the relationship between FN1 expression and clinical factors and prognosis has not been reported, and thus it is necessary to verify and clarify the role of FN1 in GC.

The aim of the present study was to investigate FN1 gene expression in GC and its association with clinicopathological factors and prognosis by examining 17 publicly available GC cohorts. Furthermore, FN1 protein expression was validated by immunohistochemistry in a separate cohort. The results demonstrated that FN1 may serve as a new prognostic marker for GC.

Materials and methods

Data collection. Microarray data were downloaded from the following datasets in the Gene Expression Omnibus (GEO;
Independent sample t-tests were used in SPSS for continuous data analysis and Pearson's $\chi^2$ tests were used for categorical data analysis. The gene expression value was equal to three, $\geq 3/3$ were defined as high expression and the $<1/3$ as low expression. Overall survival (OS) rate was analyzed using Kaplan-Meier plots and the log-rank test or Gehan-Breslow-Wilcoxon test. When the two survival functions were parallel, the log-rank test was used, whereas the Gehan-Breslow-Wilcoxon test was used if the data crossed over. A Cox regression model was used to assess the hazard ratio (HR) and perform multivariate analysis. All tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference.

Meta-analyses were performed using RevMan 5.3. First, the heterogeneity between the results of each study was analyzed by the $\chi^2$ test. The threshold was set to $\alpha=0.100$, and the extent of heterogeneity was assessed by combining $I^2$. If $P>0.10$ and $I^2\leq50\%$, the homogeneity between the results was considered high, and the fixed effect model was used; if $P\leq0.10$ or $I^2>50\%$, the random effects model was used.

**Results**

**Patient cohorts.** Data from 17 independent GC cohorts were downloaded from the Gene Expression Omnibus (GEO), The Cancer Genome Atlas (TCGA) and Oncomine, including 2,670 samples, which comprised 2,376 cancer tissues and 294 adjacent normal tissues. Eight of the 17 cohorts included tumor and normal samples. The IHC cohort comprised 190 GC samples and 20 adjacent tissue samples. The clinicopathological characteristics of the patients are presented in Table I.

**FN1 expression in gastric cancer.** A total of eight independent cohorts that included expression data from cancer and normal samples were analyzed; the results revealed upregulated $FN1$ mRNA levels in tumor tissues compared with normal tissues (Fig. 1A). Meta-analysis of all the cohorts revealed a significant combined mean difference of 1.99 ($P<0.001$; Fig. 2A). These results indicated that $FN1$ expression was significantly higher in GC tissues compared with that in adjacent normal tissues.

**Association between $FN1$ expression and clinicopathological factors.** Compared with that in the early T stage (T1) group, the expression of $FN1$ was significantly increased in the advanced T stage (T2+T3+T4) group ($P=0.002$; Fig. 1B) in one cohort, which was further confirmed by meta-analysis in all examined cohorts ($P<0.001$; Fig. 2B). The expression of $FN1$ was not associated with differentiation in any cohort (Figs. IC and 2C). Only two cohorts exhibited increased $FN1$ expression in patients with high clinical Tumor-Node-Metastasis (TNM) stage (36) (II + IV) compared with that in patients with low clinical TNM stage (I + II) (Fig. 1D). No significant differences between patients with high and low TNM stage were observed in the meta-analysis of all cohorts (Fig. 2D).

**High $FN1$ expression level indicates poor clinical outcomes.** Kaplan-Meier survival analysis was performed using clinical data. OS analysis demonstrated that high $FN1$ expression was associated with unfavorable prognosis compared with low $FN1$ expression.
Table I. Clinicopathological characteristics of patients in different datasets.

| Characteristic                      | IHC cohort | GSE13861 | GSE15456 | GSE15459 | GSE26253 | GSE26899 | GSE26901 | GSE29272 | GSE34942 | GSE35809 | GSE66229 | TCGA, n (%) |
|-------------------------------------|------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|-------------|
| **Sex**                             |            |          |          |          |          |          |          |          |          |          |          |              |
| Total                               | 190 (100)  | 65 (100) | 30 (100) | 192 (100)| 432 (100)| 92 (100) | 109 (100)| 134 (100)| 56 (100) | 70 (100) | 300 (100) | 415 (100)   |
| Male                                | 144 (75.8) | 46 (70.8)| 17 (56.7)| 125 (65.1)| 280 (64.8)| 73 (79.3)| 69 (63.3)| 103 (76.9)| 36 (64.3)| 48 (68.6)| 199 (66.3)| 268 (64.6)  |
| Female                              | 46 (24.2)  | 19 (29.2)| 13 (43.3)| 67 (34.9)| 152 (35.2)| 19 (20.7)| 40 (36.7)| 31 (23.1)| 20 (35.7)| 22 (31.4)| 101 (33.7)| 147 (35.4)  |
| Median age, years (min, max)        | 59 (25, 85)| 63 (32, 83)| 73 (53, 83)| 66 (23, 92)| 53 (23, 74)| 59 (36, 83)| 58 (28, 74)| 59 (23, 73)| 69 (43, 84)| 67 (32, 85)| 64 (24, 86)| 67 (30, 90)  |
| **T stage**                          |            |          |          |          |          |          |          |          |          |          |          |              |
| 1                                   | 15 (7.9)   | 2 (3.1)  | -        | 8 (4.2)  | -        | -        | -        | -        | -        | -        | 2 (0.7)   | 22 (5.3)    |
| 2                                   | 32 (16.8)  | 23 (35.4)| -        | 45 (23.4)| -        | -        | -        | -        | -        | -        | 186 (62)  | 88 (21.2)   |
| 3                                   | 24 (12.6)  | 34 (52.3)| -        | 107 (55.7)| -        | -        | -        | -        | -        | -        | 91 (30.3) | 181 (43.6)  |
| 4                                   | 119 (62.6)| 1 (1.5)  | -        | 1 (0.5)  | -        | -        | -        | -        | -        | -        | 21 (7)    | 115 (27.7)  |
| Unknown                             | 0 (0)      | 5 (7.7)  | -        | 31 (16.1)| -        | -        | -        | -        | -        | -        | 0 (0)     | 9 (2.2)     |
| **TNM stage**                       |            |          |          |          |          |          |          |          |          |          |          |              |
| I                                   | 29 (15.3)  | 12 (18.5)| 6 (20)   | 31 (16.1)| 68 (15.7)| 11 (12.0)| 38 (29.5)| 5 (3.7)  | 11 (19.6)| 13 (18.6)| 31 (10.3)| 57 (13.7)  |
| II                                  | 60 (31.6)  | 2 (3.1)  | 4 (13.3) | 29 (15.1)| 167 (38.7)| 18 (19.6)| 40 (31)  | 5 (3.7)  | 11 (19.6)| 16 (22.9)| 97 (32.3)| 123 (29.6) |
| III                                 | 91 (47.9)  | 35 (53.8)| 15 (50)  | 72 (37.5)| 130 (30.1)| 27 (29.3)| 36 (27.9)| 115 (85.8)| 19 (33.9)| 33 (47.1)| 95 (31.7)| 169 (40.7) |
| IV                                  | 10 (5.3)   | 16 (24.6)| 5 (16.7) | 60 (31.3)| 67 (15.5)| 36 (39.1)| 15 (11.6)| 9 (6.7)  | 13 (23.2)| 7 (10)   | 77 (25.7)| 41 (9.9)   |
| Unknown                             | 0 (0)      | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 0 (0)    | 2 (3.6)  | 1 (1.4)  | 0 (0)     | 25 (6.0)   |
| **Tumor grade**                     |            |          |          |          |          |          |          |          |          |          |          |              |
| Low                                 | 48 (24)    | 20 (30.8)| 2 (6.7)  | 6 (3.1)  | -        | -        | -        | 1 (0.7)  | -        | 2 (2.9)  | -         | 12 (2.9)   |
| Intermediate                        | 66 (33)    | 15 (23.1)| 13 (43.3)| 53 (27.6)| -        | -        | -        | 48 (35.8)| -        | 22 (31.4)| -         | 148 (35.7) |
| High                                | 76 (38)    | 6 (9.2)  | 15 (50)  | 86 (44.8)| -        | -        | 85 (63.4)| -        | 26 (37.1)| -        | 246 (59.3) |
| Undifferentiated                    | 10 (5)     | 24 (36.9)| 0 (0)    | 47 (24.5)| -        | -        | -        | 0 (0)    | 20 (28.6)| -        | 9 (2.2)    |
| Follow-up endpoint (death)          |            |          |          |          |          |          |          |          |          |          |          |              |
| Occurred                            | 101 (50.5) | -        | -        | 95 (49.5) | -        | -        | -        | 31 (23.1)| 27 (48.2)| -        | 159 (53)  | 144 (34.7) |
| Not occurred                        | 99 (49.5)  | -        | -        | 97 (50.5) | -        | -        | -        | 95 (70.9)| 29 (51.8)| -        | 141 (47)  | 214 (51.6) |
| No data                             | 0 (0)      | -        | -        | 0 (0)    | -        | -        | 8 (6)    | 0 (0)    | -        | 0 (0)    | 57 (13.7)  |

-, data not available; TNM, Tumor-Node-Metastasis.
expression in four of the six cohorts containing prognostic information (Fig. 3). A meta-analysis of all cohorts validated this result, as it exhibited a significant combined FN1 hazard ratio (HR) of 1.67 (P<0.001; Fig. 2E). This indicated that the expression of FN1 is a potential indicator of clinical outcome in patients with GC.

**FN1 immunohistochemistry.** FN1 is expressed in cancer cells and the intratumoral matrix in GC (Fig. 4). In the IHC cohort, normal epithelial cells exhibited no FN1 expression. E-FN1 expression was positive in 85 of the 190 cases (44.7%). S-FN1 expression was graded as no/weak in 11 (5.8%), moderate in 71 (37.4%) and strong in 108 (56.8%) cases (Table II). No association was identified between E-FN1 and S-FN1 expression (P=0.112; Table III). E-FN1 expression in GC exhibited a significant association with tumor size (P=0.037), whereas S-FN1 expression was associated with sex (P=0.027) (Table II).

E-FN1-positive patients with GC in the IHC cohort exhibited worse OS compared with E-FN1-negative patients (P=0.009; Fig. 5A). S-FN1 expression exhibited no significant effect on OS (P=0.075, Fig. 5B). In addition, in patients with high clinical TNM stage (III + IV), E-FN1 positivity was strongly associated with OS; however, in patients with low clinical TNM stage (I + II), no difference was observed in overall survival between patients with low and high E-FN1 expression (Fig. 5C and D). E-FN1 was also confirmed as an independent predictor of overall survival in GC by multivariate analysis (HR, 2.115; 95% CI, 1.343-3.333; P=0.001; Table IV).

**Discussion**

In this study, FN1 gene expression was analyzed in 17 independent GC cohorts. The results demonstrated an increase in FN1 expression in GC compared with normal tissues and a possible increase in the advanced T stage (T2+T3+T4) group compared with that in the early T stage (T1) group; however, no association between FN1 expression levels and differentiation or clinical TNM stage was identified. In addition, upregulation of the FN1 gene may be a predictor of poor prognosis following radical gastrectomy for GC. In summary, the results of the present study support FN1 as a biomarker of poor prognosis in GC.
Figure 2. Forest plot and meta-analysis of FN1 expression in gastric cancer. (A) Forest plot of the log₂ fold change in FN1 expression in tumor tissues compared with that in normal tissues. (B) Forest plot of the log₂ fold change in FN1 expression in the advanced T stage group (T2 + T3 + T4) compared with that in the early T stage group (T1). (C) Forest plot of the log₂ fold change in FN1 expression in the low differentiation group (high tumor grade) compared with that in the high differentiation group (intermediate and low tumor grade). (D) Forest plot of the log₂ fold change in FN1 expression in the high clinical TNM stage (III+IV) group compared with that in the low clinical TNM stage (I+II) group. (E) Forest plot of the comparison of overall survival in patients with gastric cancer with high and low FN1 expression (The gene expression value was equal to three, the first two-thirds were defined as high expression and the last one-third as low expression). FN1, fibronectin 1; TNM, Tumor-Node-Metastasis; CI, confidence interval.
FN1, which is an extracellular matrix glycoprotein, is involved in cell proliferation, embryogenesis, wound healing, host defense, epithelial-mesenchymal transition (EMT) and metastasis, as well as oncogenic transformation (5). FN1 is involved in the occurrence and development of various tumors and is upregulated in multiple cancer types, such as esophageal squamous cell carcinoma, colorectal cancer, OSCC, and thyroid cancer (8-10,14). For instance, FN1 is upregulated in OSCC with lymph node metastasis (LNM); FN1 increases the expression of vascular endothelial growth factor C, lymphangiogenesis and LNM through FAK activation and promotes EMT in SAS human OSCC cells (37). FN1 is a key mediator of glioma progression, as its inhibition delays tumor progression and immunosuppression through a mechanism that involves the maintenance of integrin β1 FN receptors (38). In GC, FN1 is highly expressed in tumor tissues compared with that in non-tumor tissues, and knockdown of FN1 represses GC cell proliferation, adhesion and metastasis in vitro (15). The present study aimed to analyze the relationship between FN1 expression in GC and clinicopathological factors and prognoses.

The results of the present study demonstrated that the FN1 gene was upregulated in gastric cancer tissues compared with that in normal tissues in eight cohorts, and these data were confirmed by meta-analysis of combinations of all datasets. This result was consistent with the results of Xu et al (15) and Zhang et al (16), who used immunohistochemical methods to analyze tumor and normal tissue specimens from 40 and 52 patients with gastric cancer, respectively. In summary, previous studies have reported that the expression of the FN1 gene was increased in GC tissues compared with that in normal gastric tissues, but the studies were all small-scale. The present
study used multiple cohorts to provide substantial validation of increased FN1 expression in GC.

To the best of our knowledge, the association between FN1 expression and clinicopathological features or patient prognosis, have not been reported previously. In the present study, compared with that in the early T stage group, the expression of FN1 was significantly increased in the advanced T stage group, which was further confirmed by meta-analysis in all the examined groups. OS analysis revealed that high FN1 expression was associated with unfavorable prognosis in four of the six cohorts containing prognostic information. A meta-analysis of all cohorts further validated this finding. These results indicated that the expression of FN1 may be a potential indicator of clinical outcomes in patients with GC. FN1 is expressed in cancer cells and the intratumoral matrix in GC. Hanamura et al (39) reported that the expression of S-FN1 mRNA was positively correlated with deep invasion and LNM of colon cancer. Bae et al (34) reported that E-FN1-positive patients exhibited lower OS and disease-free survival compared with FN1-negative breast cancer patients. E-FN1 was an independent predictor for survival in breast cancer in multivariate analysis, but the expression of S-FN1 had no significant effect on patient survival (34). In the present study, E-FN1-positive patients with GC exhibited worse OS compared with E-FN1-negative patients, whereas S-FN1

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Table II. Patient characteristics based on the immunohistochemistry results of FN1 expression in gastric cancer.

| Characteristic       | No. of patients (n=190) | Expression of E-FN1 (%) | Expression of S-FN1 (%) | P-value |
|----------------------|-------------------------|--------------------------|-------------------------|---------|
|                      | No/weak (n=11) | Moderate (n=71) | Strong (n=108) | No/weak (n=11) | Moderate (n=71) | Strong (n=108) |         |
| Sex                  |                          |                          |                         | 0.380   | 0.027*      |                   |         |
| Female               | 18 (39.14) | 28 (60.9)     | 13 (28.3) | 33 (71.7) | 0.508       | 0.361         |         |
| Male                 | 67 (46.5)  | 77 (53.5)     | 58 (40.3) | 75 (52.1) | 11 (7.6)   | 58 (40.3)     | 75 (52.1) |
| Age (years)          |                          |                          |                         | 0.037*  | 0.639       |                   |         |
| <60                  | 47 (47.0)  | 53 (53.0)     | 41 (41.0) | 55 (55.0) | 4 (4.0)    | 30 (33.3)     | 53 (58.9) |
| ≥60                  | 38 (42.2)  | 52 (57.8)     | 7 (7.8)   | 53 (58.9) | 11 (7.6)   | 58 (40.3)     | 75 (52.1) |
| Tumor diameter (cm)  |                          |                          |                         | 0.080   | 0.616       |                   |         |
| <5                   | 58 (50.9)  | 56 (49.1)     | 41 (41.0) | 65 (57.0) | 3 (3.9)    | 30 (33.3)     | 43 (56.6) |
| ≥5                   | 27 (35.5)  | 49 (64.5)     | 7 (7.8)   | 53 (58.9) | 11 (7.6)   | 58 (40.3)     | 75 (52.1) |
| T stage              |                          |                          |                         | 0.037*  | 0.510       |                   |         |
| T1 + T2              | 22 (46.8)  | 25 (53.2)     | 18 (38.3) | 26 (55.3) | 3 (3.9)    | 30 (33.3)     | 43 (56.6) |
| T3 + T4              | 63 (44.1)  | 80 (55.9)     | 53 (37.1) | 82 (57.3) | 8 (7.1)    | 42 (37.5)     | 62 (55.4) |
| N stage              |                          |                          |                         | 0.080   | 0.616       |                   |         |
| N0 + N1              | 56 (50.0)  | 56 (50.0)     | 42 (37.5) | 62 (55.4) | 8 (7.1)    | 42 (37.5)     | 62 (55.4) |
| N2 + N3              | 29 (37.2)  | 49 (62.8)     | 29 (37.2) | 46 (59.0) | 3 (3.8)    | 30 (33.3)     | 46 (59.0) |
| TNM stage            |                          |                          |                         | 0.352   | 0.510       |                   |         |
| I + II               | 43 (48.3)  | 46 (51.7)     | 32 (36.0) | 50 (56.2) | 7 (7.9)    | 32 (36.0)     | 50 (56.2) |
| III + IV             | 42 (41.6)  | 59 (58.4)     | 49 (53.6) | 58 (57.4) | 4 (4.0)    | 39 (38.6)     | 58 (57.4) |

*P<0.05, FN1, fibronectin 1; S-FN1, stromal FN1; E-FN1, epithelial FN1; TNM, Tumor-Node-Metastasis.

Table III. Association between epithelial and stromal expression of FN1 in gastric cancer.

| Expression of S-FN1 | Expression of E-FN1 (%) |
|---------------------|--------------------------|
| No/Weak             | Negative (%) | Positive (%) | Total (%) | P-value |
| FN1, fibronectin 1; S-FN1, stromal FN1; E-FN1, epithelial FN1. | 7 (63.6) | 4 (36.4) | 11 (5.8) | 0.112 |

| Moderate            | 34 (47.9) | 37 (52.1) | 71 (37.4) |         |
| Strong              | 44 (40.7) | 64 (59.3) | 108 (56.8) |         |
| Total (%)           | 85 (100.0) | 105 (100.0) | 190 (100.0) | 0.112 |
expression had no significant effect on OS. In addition, in patients with high clinical TNM stage (III + IV), E-FN1 positivity was strongly associated with OS. FN1 was also confirmed as an independent predictor of overall survival in patients with GC by multivariate analysis.

Xu et al (15) and Zhang et al (16) demonstrated no FN1 expression in the stroma of gastric cancer. In the IHC cohort of the present study, FN1 was expressed in tumor cells and stromal cells, but not in normal epithelial cells. No association was observed between E-FN1 and S-FN1. E-FN1 expression in GC was significantly associated with tumor size. Soikkeli et al (40) reported that FN1 is required for tumor and stromal cell growth. It may be speculated in large tumors, the central region is likely to be necrotic, and the expression of FN1 may promote the migration of tumor cells and reduce necrosis.

In the present study, increased expression of the FN1 gene at the protein and mRNA level in GC tissues was observed; FN1 was highly expressed at the mRNA level in the advanced T stage group compared with that in the early T stage group, and the expression of FN1 at the protein level was positively associated with tumor size. In addition, FN1 expression at the protein and mRNA level was a predictor of poor prognosis following radical resection of GC. In conclusion, the expression of FN1 in GC tissues may be upregulated, and FN1 may be a biomarker of poor prognosis in patients with GC.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions
YS wrote the manuscript and performed the majority of the experiments. CZ and YS participated in the study design, data acquisition and revision of the manuscript. YL and YH performed immunohistochemistry scoring, followed up the patients and collected clinical information. YY, HM and ZW analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Written informed consent was obtained from all patients, and the study was approved by the Biomedical Ethics Committee of The First Affiliated Hospital of Zhengzhou University.

Patient consent for publication
Patients provided their consent for publication.

Competing interests
The authors declare that they have no competing interests.

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