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# High Expression of Angiogenic Factor with G-Patch and FHA Domain1 (AGGF1) Predicts Poor Prognosis in Gastric Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** Angiogenic factor with G-patch and FHA domain1 (AGGF1 or VG5Q) is a newly identified human angiogenic factor. The aim of this study was to explore AGGF1 expression level in gastric cancer and detect its correlation with the prognosis.

**Material/Methods:** Immunohistochemistry was performed to detect AGGF1 level in gastric cancer and its adjacent noncancerous samples of 198 cases, and the relationships among the expression levels of AGGF1, vascular endothelial growth factor (VEGF), and prognosis were analyzed.

**Results:** Expression of AGGF1 in gastric cancer samples was significantly higher than that in adjacent noncancerous samples ($P<0.001$). The overall survival rate (OS) of patients with high AGGF1 expression was significantly lower than that of patients with low AGGF1 expression ($P=0.000$). The Cox model analysis demonstrated that expression of AGGF1 was an independent biomarker for prediction of patients' survival in gastric cancer.

**Conclusions:** High expression of AGGF1 predicts poor prognosis in gastric cancer patients. AGGF1 can be used as an independent factor to predict postoperative survival of patients with gastric cancer.

**MeSH Keywords:** Angiogenesis Inducing Agents • Stomach Neoplasms • Vascular Endothelial Growth Factor A

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## Background

Gastric cancer (GC) is one of the most aggressively malignant tumors of the digestive tract. Most patients have been in advanced stage at diagnosis and the effectiveness of surgery is limited. Invasion and metastasis is the main cause of death in patients with gastric cancer. Among the potential promoting factors, tumor angiogenesis plays an important role [1,2]. Tumor angiogenesis is the basis of tumor growth and metastasis. Therefore, it an important focus in the study of angiogenesis in gastric cancer and the search for new potential therapeutic targets.

Angiogenic factor with G-patch and FHA domain1 (AGGF1 or VG5Q), as a newly identified human angiogenic factor, was first reported by Tian et al. [3] in 2004. The gene is highly expressed in vascular endothelial cells and the encoded protein has a strong angiogenesis ability *in vitro*. Recent studies have found that AGGF1 is expressed in some types of malignant tumors and is closely related to tumor angiogenesis [4–7]. Obviously, persistent angiogenesis, as one of the main signs of tumor, is closely related to the growth, invasion, metastasis, and recurrence of gastric cancer [1,2], but the expression level of AGGF1 and its prognostic value in patients with gastric cancer have not been reported.

Therefore, in the present study, the protein expression levels of AGGF1 and vascular endothelial growth factor (VEGF) were examined by immunohistochemistry in GC and corresponding noncancerous samples. Next, Kaplan-Meier curves and log rank test were applied to analyze the survival rate. Lastly, Cox regression method was used to explore the prognostic value of AGGF1 in gastric cancer.

## Material and Methods

### Patient and clinicopathologic data

We selected specimens from 198 cases of gastric cancer (GC), along with the corresponding noncancerous tissues, from patients diagnosed at the Anhui Provincial Hospital of Anhui Medical University (Hefei, China) between 2007 and 2011. Detailed pathological and clinical data (including age, sex, tumor size, Borrmann type, degree of differentiation, histological type, metastasis of lymph node, invasion depth, and TNM staging) were obtained from each patient's medical records. The samples were obtained from 58 female and 140 male patients with an average age of 56±13 years old (range, 26–82 years). None of the patients had received radiotherapy or chemotherapy before surgery. The specimens were fixed in formalin and embedded in paraffin for pathological analysis and confirmation of the diagnosis. Complete clinical follow-up data was obtained from the gastric cancer database of our hospital. The study was approved by the Anhui Medical University Human Research Ethics Committee. Written informed consent was obtained from each patient.

### Immunohistochemical study

Immunohistochemistry for AGGF1 and VEGF (both antibody concentrations were 1: 500) was performed on each cancerous and corresponding noncancerous tissue. The samples (4-μm thick) were cut onto salinized glass slides consecutively. Two-step immunohistochemistry was used to detect these proteins expression according to the manufacturer's instructions.

Every section was scored on the basis of the stained tumor cells fraction and staining intensity. The proportion was classified as 0 (≤1%), 1 (2% to 25%), 2 (26% to 50%), 2 (51% to 75%), and 4 (≥76%). The staining intensity was scored as 0 (no staining), 1 (weak), 2 (moderate), and 3 (strong). The expression result was calculated according to the formula: percentage score multiplied by intensity score. Total scores (0–12) were categorized as low (score 0–3) or high (score 4–12).

### Statistical analysis

SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Chi-square test and Spearman correlation test were used to analyze the immunohistochemical results. Kaplan-Meier and log rank test were applied to analyze the survival rates of patients. Cox regression method was used to determine the prognostic value. A *P*-value less than 0.05 was considered to indicate statistical significance.

## Results

### AGGF1 expression in cancerous and noncancerous gastric tissues

In total, 198 paired cancerous and noncancerous tissue samples were analyzed by immunohistochemistry for AGGF1 expression. The AGGF1 immunoreactivity was mainly observed in the cytoplasm of neoplastic cells. High expression of AGGF1 was found in most cancer samples (132/198) and in fewer noncancerous samples (48/198). The expression level of AGGF1 in gastric cancer was dramatically higher than that in noncancerous samples ($P<0.001$). Representative GC samples with different AGGF1 expression patterns are shown in Figure 1.





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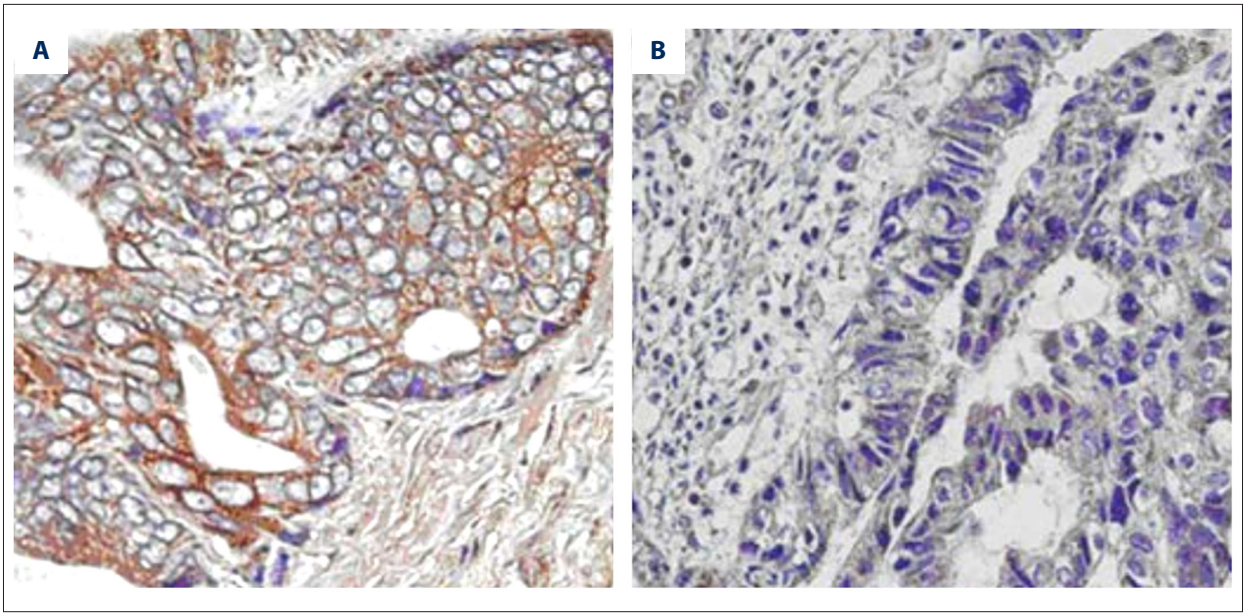


**Figure 1.** Positive (**A**) and negative (**B**) expression of AGGF1 in gastric cancer and corresponding noncancerous tissues by immunohistochemistry, respectively (200× magnification).

### Correlation of AGGF1 with clinicopathological factors and VEGF

As shown in Table 1, the expression of AGGF1 was remarkably associated with lymph node metastasis (P=0.022), invasion depth (P=0.006), and TNM stage (P<0.001). Additionally, we also found there was a significantly positive correlation between VEGF and AGGF1 expression in gastric cancer samples (P=0.017, Figure 2).

### Correlation of AGGF1 with patients' prognosis

Kaplan-Meier method was plotted to compare the OS and DFS according to AGGF1 expression patterns. Patients with high-expression tumors showed a more unfavorable prognosis than those with low-expression tumors (Figure 3). Univariate survival analysis (Tables 2, 3) revealed AGGF1 expression was remarkably associated with OS (P<0.001) and DFS (P<0.001), in addition to lymph node metastasis (P<0.001 for OS, P <0.001 for DFS), invasion depth (P=0.001 for OS, P<0.001 for DFS), and TNM stage (P<0.001 for OS, P<0.001 for DFS). In multivariate analysis, lymph node metastasis (P=0.001 for OS, P=0.002 for DFS), invasion depth (P=0.024 for OS, P =0.024 for DFS), TNM stage (P<0.001 for OS, P<0.001 for DFS), and AGGF1 expression (P<0.001 for OS, P<0.001 for DFS) remained as independent factors (Tables 4, 5).

## Discussion

Since the gene was first reported, AGGF1 and its physiological functions were further revealed, especially in the cardiovascular system. Chen et al. [8] explored the function of AGGF1 in the angiogenesis of zebrafish and found that AGGF1 regulated the formation of blood vessels and the differentiation of veins. Lu et al. [9] administered the angiogenic therapy in a mouse hindlimb ischemia model by using AGGF1 gene, which improved blood supply to the ischemic area. Another study found that AGGF1 inhibits vascular inflammatory response and improves endothelial function [10]. Based on these findings, we speculate that AGGF1 plays an important role in the growth, metastasis, and invasion of gastric cancer. We found the expression level of AGGF1 protein was significantly higher in gastric cancer tissue than that in the corresponding noncancerous tissue. Similar to our results, a recent study found that hepatocellular carcinoma also displays overexpression of AGGF1 [7]. Furthermore, patients with high AGGF1 expression had dramatically lower DFS and OS than those with low AGGF1 expression. Additionally, high AGGF1 expression in patients with gastric cancer was closely related to poor prognosis, as demonstrated by univariate and multivariate analyses.

Tumor angiogenesis plays a pivotal role in the progression and development of gastric cancer. Overexpression of VEGF is associated with unfavorable prognosis and aggressive behavior of tumors [11]. Moreover, several studies have demonstrated that increased VEGF expression and microvessel density (MVD) are strongly related to worse prognosis in gastric cancer patients [12–15]. Therefore, to explore the role of AGGF1 in angiogenesis of gastric cancer, we explored the relationships between VEGF and AGGF1 expression levels in GC tissues. We also found a significantly positive relationship between AGGF1 and VEGF expressions in gastric cancer tissues,





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**Table 1.** Correlations between AGGF1 protein expressions and clinicopathological factors in patients with gastric cancer.

| variables | Total | AGGF1 expression | | | |
|---|---|---|---|---|---|
| | | Low (n=66) | High (n=132) | $\chi^2$ | *P* value |
| Gender | | | | | |
| Male | 140 | 44 | 96 | 0.780 | 0.377 |
| Female | 58 | 22 | 36 | | |
| Age at surgery (yeas) | | | | | |
| ≤60 | 94 | 35 | 59 | 1.225 | 0.268 |
| >60 | 104 | 31 | 73 | | |
| Size of primary tumor (cm) | | | | | |
| ≤5 | 101 | 34 | 67 | 0.010 | 0.920 |
| >5 | 97 | 32 | 65 | | |
| Borrmann type | | | | | |
| I+ II type | 67 | 23 | 44 | 0.045 | 0.832 |
| III+IV type | 131 | 43 | 88 | | |
| Degree of differentiation | | | | | |
| Well/moderate | 85 | 30 | 55 | 0.258 | 0.612 |
| Poor and not | 113 | 36 | 77 | | |
| Histological type | | | | | |
| Adenocarcinoma | 167 | 57 | 110 | 0.306 | 0.580 |
| Others | 31 | 9 | 22 | | |
| Depth of invasion | | | | | |
| T1 | 8 | 5 | 3 | 12.388 | 0.006 |
| T2 | 24 | 14 | 10 | | |
| T3 | 62 | 20 | 42 | | |
| T4 | 94 | 27 | 77 | | |
| Lymph node metastasis | | | | | |
| N0 | 44 | 20 | 24 | 9.602 | 0.022 |
| N1 | 47 | 20 | 27 | | |
| N2 | 56 | 16 | 40 | | |
| N3 | 51 | 10 | 41 | | |
| TNM stage | | | | | |
| I | 13 | 9 | 4 | 18.044 | 0.000 |
| II | 57 | 29 | 34 | | |
| III | 119 | 25 | 83 | | |
| IV | 9 | 3 | 11 | | |
| VEGF expression | | | | | |
| Low | 76 | 33 | 43 | 5.648 | 0.017 |
| High | 122 | 33 | 89 | | |





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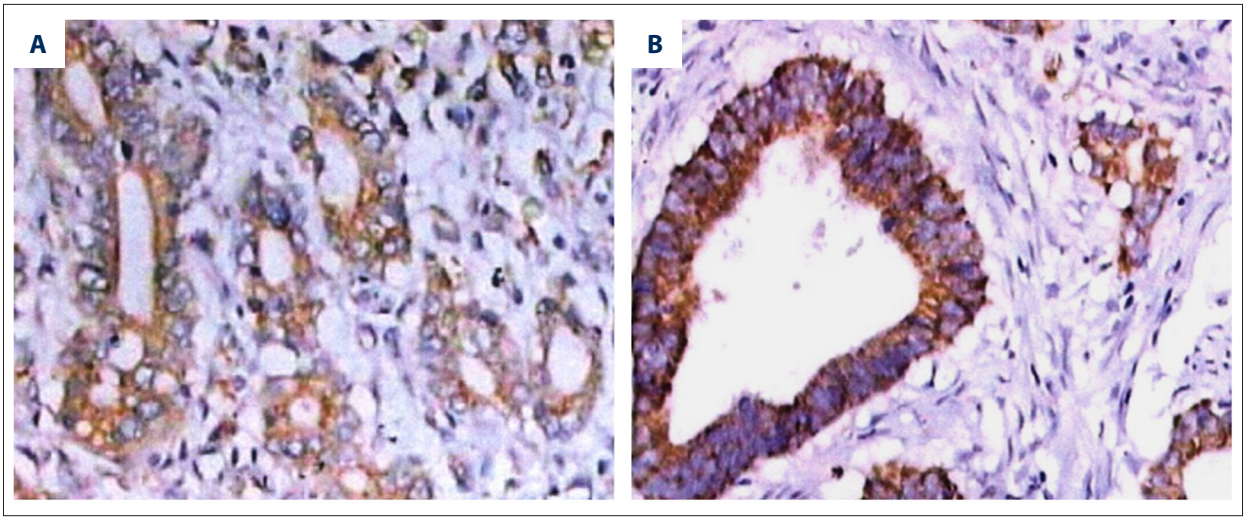


**Figure 2.** High expression levels of AGGF1 (**A**) and VEGF (**B**) in gastric cancer (200× magnification).

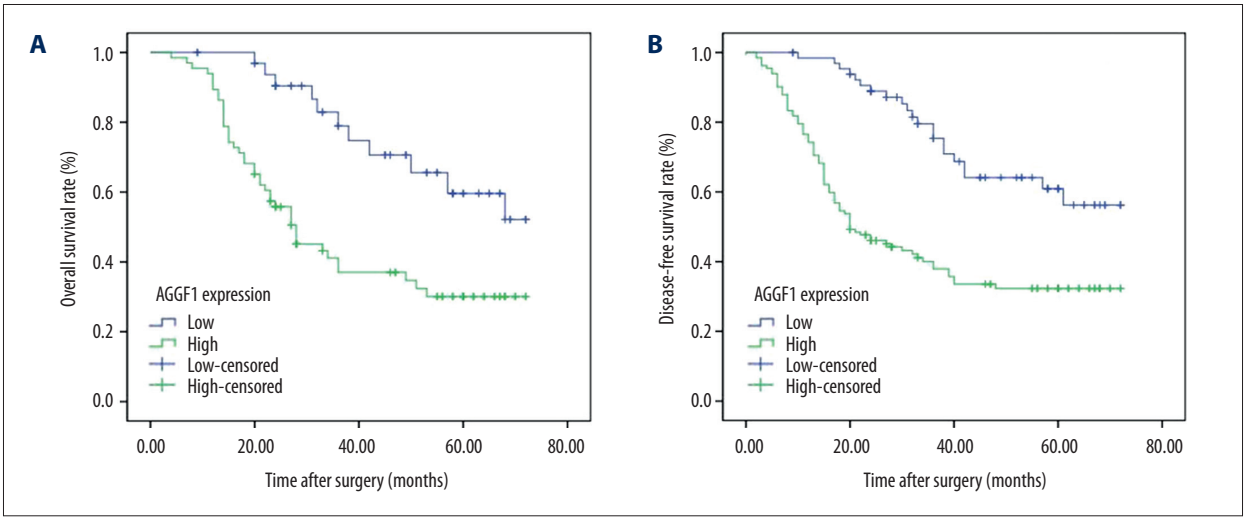


**Figure 3.** Kaplan-Meier analysis of overall survival (OS) and disease-free survival (DFS) curves of patients with gastric cancer based on AGGF1 expression as positive or negative. (**A**) OS curve of patients with gastric cancer based on AGGF1 expression; (**B**) DFS curve of patients with gastric cancer based on AGGF1 expression.

suggesting that AGGF1, probably cooperating with VEGF, is involved in tumor angiogenesis of gastric cancer. The potential underlying mechanisms may be that AGGF1 induces the expression of VEGF through β-catenin-dependent signaling [4].

However, some limitations should be acknowledged in this study. Firstly, it was a retrospective study with relatively small samples. Secondly, we only used immunohistochemical method to examine the protein expression levels of AGGF1 and VEGF in gastric cancer tissues, and the gene expression level was not assessed. Lastly, the exact underlying mechanisms in the participation of AGGF1 in angiogenesis of gastric cancer need to be further explored.

## Conclusions

In summary, our preliminary results show that AGGF1 protein is overexpressed in gastric cancer tissues and it can be used as an independent parameter to evaluate and predict the postoperative survival time of gastric cancer patients. The potential mechanism is probably related to the promotion of tumor angiogenesis. In future, targeting AGGF1 for the inhibition of angiogenesis may be a new therapeutic strategy for gastric cancer patients.

### Conflicts of interest

The authors declare that they have no conflicts of interest.





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**Table 2.** Univariate analysis of the correlation between clinicopathological parameters and overall survival time of patients with gastric cancer.

| Variables | Mean survival time (m) | 95% CI | Log-rank test | *P* value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 45.013 | 40.729–49.296 | 0.344 | 0.557 |
| Female | 42.637 | 35.896–49.379 | | |
| Age at surgery (yeas) | | | | |
| ≤60 | 45.585 | 40.366–50.803 | 0.377 | 0.539 |
| >60 | 43.358 | 38.348–48.367 | | |
| Size of primary tumor (cm) | | | | |
| ≤5 | 43.387 | 38.485–48.289 | 0.236 | 0.627 |
| >5 | 45.577 | 40.253–50.901 | | |
| Borrmann type | | | | |
| I+ II type | 46.035 | 39.715–52.354 | 0.396 | 0.529 |
| III+IV type | 43.472 | 39.063–47.881 | | |
| Degree of differentiation | | | | |
| Well/moderate | 48.339 | 42.980–53.697 | 3.494 | 0.062 |
| Poor and not | 41.237 | 36.406–46.067 | | |
| Histological type | | | | |
| Adenocarcinoma | 43.013 | 39.097–46.930 | 2.770 | 0.096 |
| Others | 50.453 | 41.753–59.153 | | |
| Depth of invasion | | | | |
| T1 | 71.000 | 69.303–72.697 | 16.372 | 0.001 |
| T2 | 60.055 | 51.567–68.544 | | |
| T3 | 42.322 | 35.986–48.657 | | |
| T4 | 39.659 | 34.737–44.580 | | |
| Lymph node metastasis | | | | |
| N0 | 52.465 | 45.378–59.551 | 21.639 | 0.000 |
| N1 | 53.543 | 46.738–60.348 | | |
| N2 | 40.204 | 33.820–46.588 | | |
| N3 | 33.154 | 26.253–40.056 | | |
| TNM stage | | | | |
| I | 71.200 | 69.798–72.602 | 50.264 | 0.000 |
| II | 49.310 | 43.488–55.132 | | |
| III | 41.309 | 36.395–46.223 | | |
| IV | 16.698 | 11.017–22.379 | | |
| AGGF1 expression | | | | |
| Low | 57.777 | 53.817–62.737 | 22.538 | 0.000 |
| High | 37.830 | 33.433–42.227 | | |





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**Table 3.** Univariate analysis of the correlation between clinicopathological parameters and disease free survival time of patients with gastric cancer.

| Variables | Mean survival time (m) | 95% CI | Log-rank test | *P* value |
|---|---|---|---|---|
| Gender | | | | |
| Male | 42.455 | 37.772–47.138 | 0.124 | 0.725 |
| Female | 40.506 | 33.253–47.758 | | |
| Age at surgery (yeas) | | | | |
| ≤60 | 43.372 | 37.678–49.067 | 0.328 | 0.567 |
| >60 | 40.841 | 35.408–46.274 | | |
| Size of primary tumor (cm) | | | | |
| ≤5 | 40.844 | 35.509–46.179 | .327 | .567 |
| >5 | 43.252 | 37.460–49.044 | | |
| Borrmann type | | | | |
| I+ II type | 43.836 | 37.014–50.657 | 0.458 | 0.499 |
| III+IV type | 41.056 | 36.244–45.869 | | |
| Degree of differentiation | | | | |
| Well/moderate | 45.897 | 40.024–51.769 | 2.837 | 0.092 |
| Poor and not | 41.237 | 33.779–44.274 | | |
| Histological type | | | | |
| Adenocarcinoma | 40.579 | 36.340–44.818 | 2.430 | 0.119 |
| Others | 48.141 | 38.375–57.907 | | |
| Depth of invasion | | | | |
| T1 | 69.250 | 64.582–73.918 | 16.505 | 0.001 |
| T2 | 59.471 | 50.651–68.290 | | |
| T3 | 40.118 | 33.162–47.074 | | |
| T4 | 36.727 | 31.346–42.108 | | |
| Lymph node metastasis | | | | |
| N0 | 50.134 | 42.355–57.914 | 19.960 | 0.000 |
| N1 | 51.141 | 43.721–58.561 | | |
| N2 | 37.224 | 30.221–44.228 | | |
| N3 | 30.373 | 22.813–37.934 | | |
| TNM stage | | | | |
| I | 70.429 | 67.577–73.280 | 44.100 | 0.000 |
| II | 47.130 | 40.785–53.474 | | |
| III | 38.787 | 33.389–44.186 | | |
| IV | 12.800 | 7.380–18.220 | | |
| AGGF1 expression | | | | |
| Low | 56.509 | 51.135–61.882 | 23.489 | 0.000 |
| High | 34.898 | 30.098–39.699 | | |





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**Table 4.** Multivariate analysis of the correlation between clinicopathological parameters and overall survival time of patients with gastric cancer.

| Covariates | HR | 95% CI for HR | *P* value |
|---|---|---|---|
| Gender (male *vs.* female) | 0.817 | 0.527–1.267 | 0.367 |
| Age (≥60 *vs.* <60 cm) | 1.052 | 0.704–1.573 | 0.803 |
| Tumor size (≥5 *vs.* <5 cm) | 1.031 | 0.679–1.566 | 0.886 |
| Borrmann type (type I, II *vs.* III, IV) | 1.131 | 0.734–1.743 | 0.578 |
| Degree of differentiation | 0.877 | 0.584–1.318 | 0.528 |
| Histological type | 1.539 | 0.822–2.882 | 0.178 |
| Depth of invasion (T3, T4 *vs.* T1, T2) | 0.341 | 0.135–0.865 | 0.024 |
| Lymph node metastasis | 0.311 | 0.157–0.615 | 0.001 |
| TNM stage (stage I *vs.* II *vs.* III *vs.* IV) | 0.161 | 0.079–0.331 | 0.000 |
| AGGF1 expression (low *vs.* high) | 0.354 | 0.213–0.586 | 0.000 |

**Table 5.** Multivariate analysis of the correlation between clinicopathological parameters and disease free survival time of patients with gastric cancer.

| Covariates | HR | 95% CI for HR | *P* value |
|---|---|---|---|
| Gender (male *vs.* female) | 0.895 | 0.579–1.382 | 0.616 |
| Age (≥60 *vs.* <60 cm) | 1.030 | 0.688–1.543 | 0.886 |
| Tumor size (≥5 *vs.* <5 cm) | 1.045 | 0.689–1.586 | 0.836 |
| Borrmann type (type I, II *vs.* III, IV) | 1.102 | 0.715–1.696 | 0.660 |
| Degree of differentiation | 0.909 | 0.605–1.364 | 0.644 |
| Histological type | 1.483 | 0.792–2.778 | 0.218 |
| Depth of invasion (T3, T4 *vs.* T1, T2) | 0.347 | 0.138–0.869 | 0.024 |
| Lymph node metastasis | 0.334 | 0.169–0.658 | 0.002 |
| TNM stage (stage I *vs.* II *vs.* III *vs.* IV) | 0.196 | 0.096–0.401 | 0.000 |
| AGGF1 expression (low *vs.* high) | 0.366 | 0.222–0.604 | 0.000 |

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