Role of FBXW7 expression in gastric cancer: Meta-analysis and bioinformatics analysis

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Abstract. F-box/WD repeat domain-containing 7 (FBXW7, also known as CDC4) is a member of the F-box protein family, which is a component of the E3 ubiquitin ligase complex. There is an association between expression of FBXW7 and the prognosis of gastric cancer. Therefore, the search for novel tumor biomarkers is key to predict the occurrence, recurrence and metastasis of gastric cancer. In the present study, systematic meta-analysis and bioinformatics analysis were performed to determine the expression levels of prognostic marker FBXW7 in gastric cancer. A literature search was conducted on August 10, 2022, using PubMed, SinoMed, Wanfang data and China National Knowledge Infrastructure databases. The meta-analysis included six studies and showed that the expression of FBXW7 was significantly downregulated in gastric cancer compared with normal mucosal tissues (P<0.05). FBXW7 expression was positively associated with lymph node metastasis, TNM stage and differentiation (P<0.05). According to the Oncomine database, FBXW7 mRNA expression was higher in gastric cancer than in normal tissue (P<0.05). Kaplan-Meier plots showed that FBXW7 mRNA expression was positively associated with the overall and progression-free survival of patients with gastric cancer. According to the UALCAN and Gene Expression Profiling Interactive Analysis databases, FBXW7 expression was downregulated in gastric cancer compared with normal tissue. FBXW7 may be involved in the entire process of gastric carcinogenesis and its low expression may make it a potential marker for the prognosis of patients with gastric cancer.

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Key words: F-box/WD repeat domain-containing 7, gastric cancer, meta-analysis, bioinformatics analysis, prognosis

Introduction

Gastric cancer is currently one of the most common types of malignancy and a primary cause of death worldwide (1). To the best of our knowledge, however, there are no particularly effective therapeutic approaches for progressive or metastatic gastric cancer. Therefore, it is essential to determine the molecular mechanisms of apoptosis and proliferation of gastric cancer cells, as well as to explore novel prognostic markers. F-box/WD repeat domain-containing 7 (FBXW7) is a component of the E3 ubiquitin ligase complex, which serves a role as a tumor suppressor by regulating the action of tumor proteins such as p53 and exerts key effects on tumor cell motility, invasion and metastasis (2). Li *et al* (3) found that expression of Fbxw7 in cancer tissue is decreased, and Fbxw7 inhibits the progression of cancer by inducing cell apoptosis and growth arrest. In addition, after the overexpression or knockout of Fbxw7, the migration and invasion of gastric cancer decreased or increased respectively, while after the inhibition or overexpression of Fbxw7, the expression of various kinds of epithelial-mesenchymal transition (EMT) markers, such as E-cadherin, N-cadherin and vimentin, changed. The study also found that Fbxw7 inhibits EMT by downregulating Snail 1 and ZEB 1, which is the upstream transcription factor promoting this process.

Ma *et al* (4) showed that FBXW7 expression is downregulated in esophageal cancer and may promote proliferation, cell cycle transition and inhibition of apoptosis in esophageal cancer cells by increasing expression of c-Myc and Cyclin D1. Lu *et al* (5) found that FBXW7 expression is elevated in normal endometrial. The tumor suppressor function of FBXW7 is regulated by multiple regulators, mutations, splicing and upstream cellular signaling pathways, such as cyclin E, c-myc and Notch signaling pathways (6,7).

Certain studies have found that FBXW7 expression is downregulated in various types of human cancer, such as breast, colorectal, prostate and pancreatic cancer (2,8). Therefore, a meta-analysis and bioinformatics analysis were performed to elucidate the association between FBXW7 expression and clinicopathological factors in gastric cancer.

Materials and methods

Study search and screening criteria. Literature search was performed on August 10, 2022 using PubMed (pubmed.

ncbi.nlm.nih.gov/), SinoMed (sinomed.ac.cn/), Wanfang (https://www.wanfangdata.com.cn/) and CNKI (https://kns.cnki.net/). Search terms were as follows: FBXW7 and (stomach or gastric) and (cancer or carcinoma or tumor or adenocarcinoma). Study inclusion criteria were as follows: i) Patients with gastric cancer; ii) immunohistochemical detection of FBXW7 expression and iii) patients did not receive radiotherapy or chemotherapy before surgery. Exclusion criteria were as follows: i) Abstracts, case reports, reviews and conference proceedings; ii) small sample size (n<50); iii) duplicate publications or data and iv) studies containing only western blot, reverse transcription-quantitative (RT-q)PCR, cDNA microarray or transcriptome sequencing for FBXW7 expression. Meta-analysis was performed following the PRISMA checklist (9).

Data extraction and quality assessment. Information from all eligible publications was extracted by two reviewers (JS and YB), including author, year of publication, country, antibody company, number of cases and controls, cancer risk. The quality of studies was determined according to the Newcastle-Ottawa Scale (10) based on methodology, including sample selection, comparability and determination of outcomes. No disagreement was found between the two reviewers. Publication bias was assessed using funnel plots. The funnel plot was assessed using Begg's and Egger's tests.

Bioinformatics analysis. FBXW7 gene expression levels were analyzed using Oncomine (oncomine.org), a cancer microarray database and web-based data mining platform for genome-wide expression analysis of novel findings. The prognostic significance of FBXW7 mRNA expression was analyzed using Kaplan-Meier plots (kmplot.com/). FBXW7 expression levels were divided into high and low expression groups according to the best cut-off values provided on Kaplan-Meier plotted line graphs. The expression of FBXW7 mRNA in gastric cancer and normal gastric mucosal tissue was analyzed using The Cancer Genome Atlas (TCGA) and Genotype Tissue Expression data from the Gene Expression Profiling Interactive Analysis (GEPIA) website (gepia.cancer-pku.cn/). The expression of FBXW7 mRNA was analyzed by performing TCGA numbering analysis on UALCAN (ualcan.path.uab.edu/). Based on the Human Protein Atlas (HPA) database (proteinatlas.org/), FBXW7 mRNA and protein levels in gastric cancer and normal gastric mucosal tissue were analyzed and compared. Cancer and the normal tissue samples were derived from the same individuals. Representative immunohistochemical images of gastric cancer tissue with different FBXW7 protein expression levels were downloaded from the HPA database). Using the Timer database (timer.cistrome.org/), the association between immune cells and survival prognosis in gastric cancer and the association between gastric cancer and immune cell infiltration and FBXW7 gene expression were analyzed.

Statistical analysis. Revman (version 5.3; cochrane.es/Download/Files/revman.htm) was used for data analysis. Odds ratio and 95% CI were used to estimate FBXW7 expression based on clinicopathological parameters of patients with gastric cancer. If heterogeneity was not significant, a fixed-effects model (Mantel-Haenszel method) was used. Otherwise, a random effects model (Der Simonian and Laird method) was used. The I^2 test was used to quantify the heterogeneity effect. Heterogeneity was classified as low, moderate, or high degree heterogeneity based on cut-off values of 25, 50 and 75%, respectively. Publication bias was assessed using funnel plots, and compliance with the funnel plots was assessed using Begg's and Egger's test. Meta-analysis was performed using Revman software 5.3. Two-sided P<0.05 was considered to indicate a statistically significant difference.

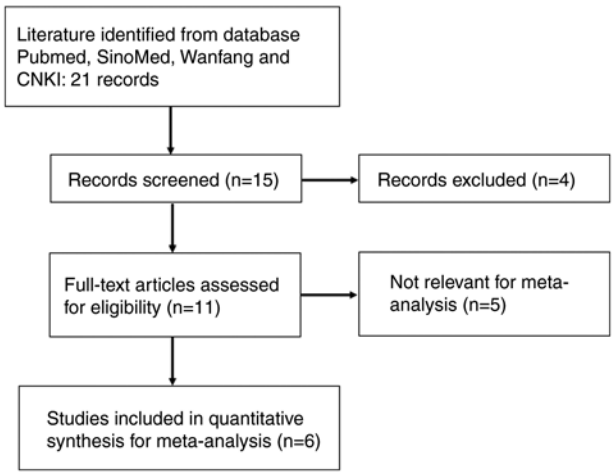

Figure 1. Flow diagram of article selection. CNKI (China National Knowledge Infrastructure).

Results

Literature search results. Duplicate studies, animal experiments and reviews were excluded based on the abstract. Initially, 45 articles were retrieved, but only six investigated the association between FBXW7 expression and clinicopathological or prognostic indicators of gastric cancer (Fig. 1). A total of six articles (11-16) that discussed the clinicopathological characteristics of FBXW7 expression and gastric cancer, including results of normal gastric tissue, were identified (Table I). The quality of studies was determined according to the Newcastle-Ottawa Scale based on methodology, including sample selection, comparability and determination of outcomes.

Association between FBXW7 expression and the clinicopathological characteristics of gastric cancer. Forest plots of the OR of the association between FBXW7 expression and clinicopathological parameters of gastric cancer were constructed. A total of six articles included data on 235 patients with gastric cancer and 145 healthy controls. FBXW7 expression was downregulated in gastric cancer compared with normal mucosal tissue (Fig. 2A). Meta-analysis showed that FBXW7 expression was associated with lymph node metastasis, differentiation, TNM stage, but not associated with age, sex and depth of invasion (Fig. 2B-G). Articles were excluded if specific clinicopathological features were missing.

Table I. Characteristics of eligible studies.

First author	Year	Country	Antibody supplier	Cases	Controls	Regulation in cancer	NOS score	(Refs.)
Huang *et al*	2015	China	Stanta	40	40	Down	8	(11)
Li *et al*	2017	China	Bioss	546	-	-	8	(16)
Zhang *et al*	2011	China	Stanta	60	20	Down	8	(12)
Huang *et al*	2011	China	Stanta	60	60	Down	8	(13)
Li *et al*	2012	China	Stanta	75	25	Down	8	(14)
Calcagno *et al*	2013	China	Abnova	33	-	-	7	(15)

NOS, Newcastle-Ottawa Scale.

Publication bias. As shown in Fig. 3, we use funnel graph to test the heterogeneity between studies. Sensitivity analysis is used to evaluate the impact of a single study on the summary results by deleting a single study from the summary analysis each time. The results showed that there was no obvious publication bias in this meta-analysis.

Bioinformatics analysis results. Oncomine dataset showed that FBXW7 mRNA expression was downregulated in gastric cancer compared with normal gastric tissue (Fig. 4A-C). Kaplan-Meier plots (Fig. 4D and E) showed that downregulated FBXW7 mRNA expression was negatively associated with the overall and progression-free survival of patients with gastric cancer. Prognosis of patients with gastric cancer was significantly associated with patient sex and slightly associated with TNM stage, treatment, degree of differentiation, Lauren's staging, and HER2 expression (Table II). The UALCAN database showed that the mRNA expression of FBXW7 was upregulated in gastric cancer compared with gastric mucosal tissue but the difference was not significant (Fig. 4F). The GEPIA database showed that mRNA expression of FBXW7 was upregulated in gastric mucosal tissue (Fig. 4G). A significant association between FBXW7 expression and stage was also found (Fig. 4H) but the effect of FBXW7 expression on survival time of patients with gastric cancer was not significant (Fig. 4I). Screening analysis of the HPA database revealed notable difference in hematoxylin and eosin staining between gastric cancer and normal gastric mucosal tissue (Fig. 5A and B) and the expression of FBXW7 in normal gastric tissue(Fig. 5C) is higher than that in gastric cancer tissue (Fig. 5D). Patients with higher FBXW7 expression had a longer survival time (Fig. 5E). Analysis of the Timer database showed that FBXW7 was associated with immune cells in gastric carcinogenesis and development and with the degree of infiltration of immune cells, including B, CD8+ and CD4+T cells, macrophages, neutrophils and dendritic cells (Fig. 6A). The survival time of patients with gastric cancer was prolonged when the degree of macrophage infiltration was downregulated. However, the survival prognosis of patients with gastric cancer was not significantly associated with the degree of infiltration of other immune cells (Fig. 6B). FBXW7 gene expression was also not significantly associated with prognosis of patients with gastric cancer (Fig. 6C). The DNA copy variation data showed that diploid/normal was more common than deep deletion in B and CD8+ and CD4+T cells, macrophages, neutrophils and dendritic cells, which were associated with gastric carcinogenesis and development, arm-level deletion and gain and high amplication (Fig. 6D).

Discussion

Gastric cancer is one of the most common types of human cancer. Despite improvements in the detection and treatment of gastric cancer, prognosis is poor (11). FBXW7, which is also known as FBW7, FBXW6, FBX30, CDC4, and SEL-10, is a member of the SCF protein family and serves a key role in the degradation of proteins that regulate the progression of the G1-S cell cycle (17). FBXW7 gene encodes three protein isoforms, FBXW7 a-, b- and c-types, which are translated from 50 transcribed mRNAs. The mRNAs are transcribed from 50 exons that have independent and unique promoters and are associated with 10 genes mapped to the 4q31 region. This region is deleted in certain types of cancer, including glioblastoma, nasopharyngeal carcinoma and small cell carcinoma of the breast (18). Thus, deletion of FBXW7 in cancer may affect pathways that govern cell division, differentiation and apoptosis (19). FBXW7 was mutated in 84 cell lines of 10 organs, and the mRNA expression of FBXW7 was found highly suppressed in human glioma cell lines, especially in type b (19). Bredel *et al* (20) showed that FBXW7 is downregulated in glioma. Gu *et al* (21) found that FBXW7 serves as a tumor suppressor by targeting cell cycle initiators in the colon cancer cell line SCC.

The tumor suppressive function of FBXW7 in gastric cancer is hypothesized to be achieved through substrates, such as c-myc, c-jun and Notch. FBXW7 deregulates cyclin E, cytokinesis, cell proliferation, apoptosis and cell differentiation (15). In addition, mutations of the FBXW7 gene have been shown to be associated with endometrial DNA aneuploidy variants. Abnormal FBXW7 regulation is a key factor in mutations of colon adenoma (22). The FBXW7 locus is a circulating chromosome that is mutated in ~5% of gastric tumors and FBXW7 is expressed at the mRNA level in gastric cancer, while abnormal FBXW7 mRNA expression is associated with lymph node metastasis and gastric cancer stages III-IV (23). In gastric cancer, the microRNA-223 is significantly upregulated. The downregulation of the miR-223 results in the downregulation of FBXW7 at mRNA and protein

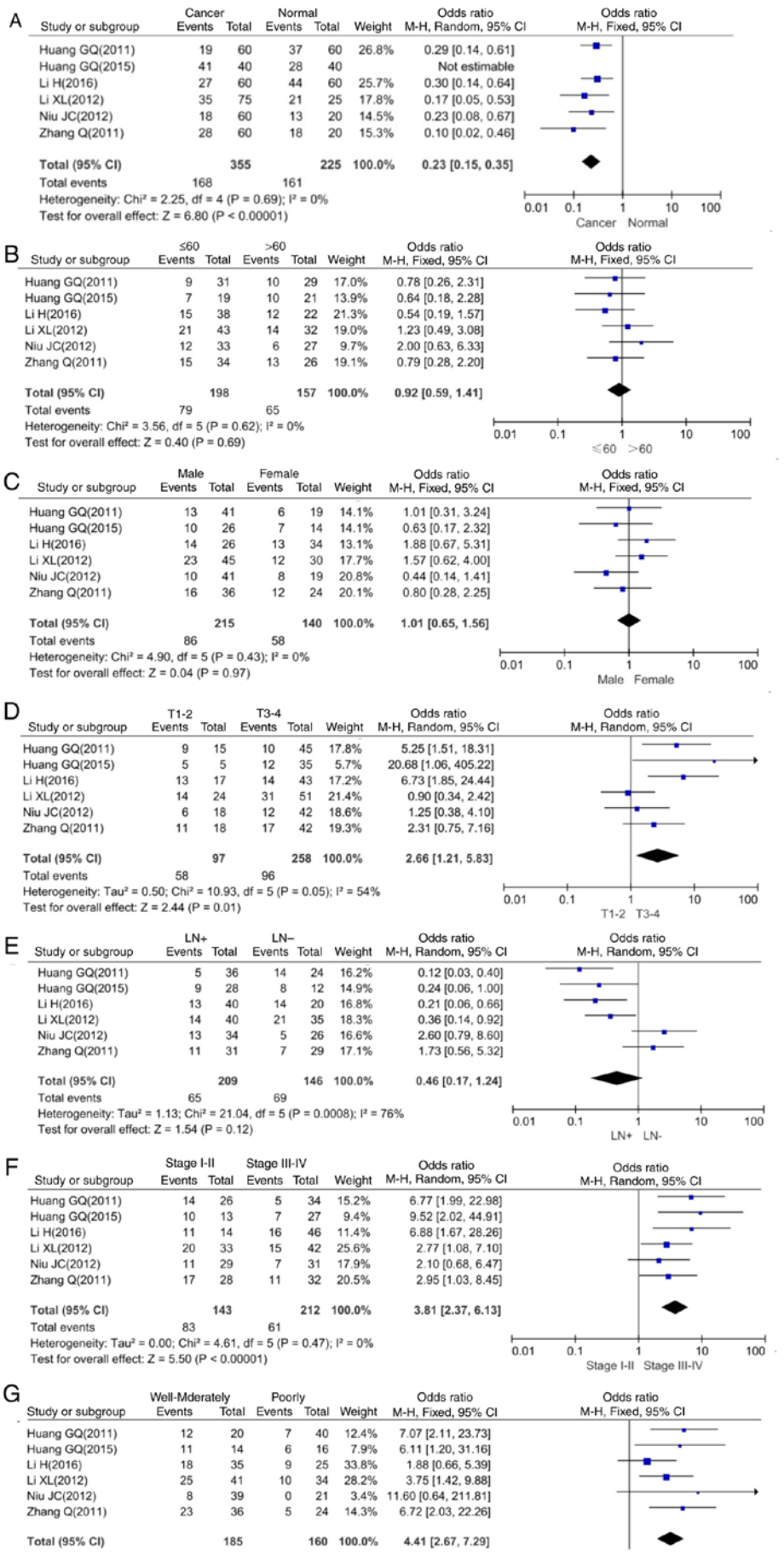

Figure 2. Association between FBXW7 expression and clinicopathological features of gastric cancer. (A) Cancer and normal tissue. Association between (B) age, (C) sex, (D) LN metastasis, (E) differentiation, (F) TNM stage and (G) depth of invasion and FBXW7 expression. LN, lymph node; FBXW7, F-box/WD repeat domain-containing 7.

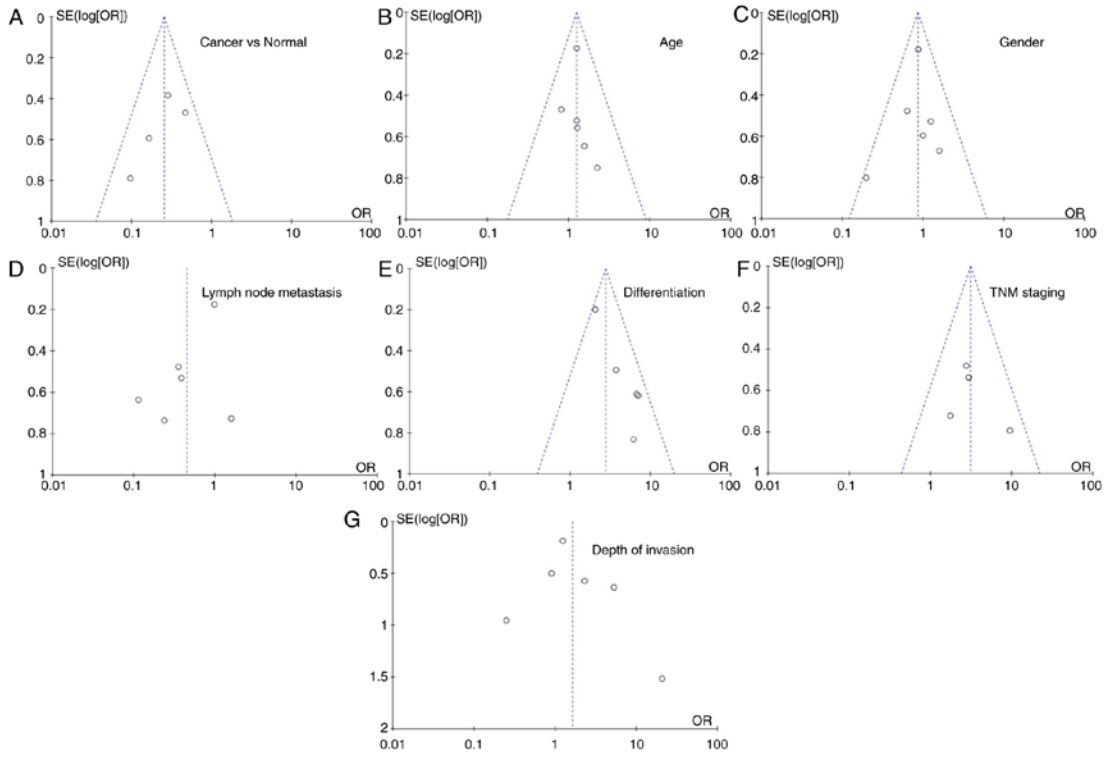

Figure 3. Publication bias between F-box/WD repeat domain-containing 7 expression and gastric cancer. G (A) Cancer and normal tissue. (B) Age. (C) Sex. (D) Lymph node metastasis (E) Differentiation. (F) TNM stage. (G) Depth of invasion.

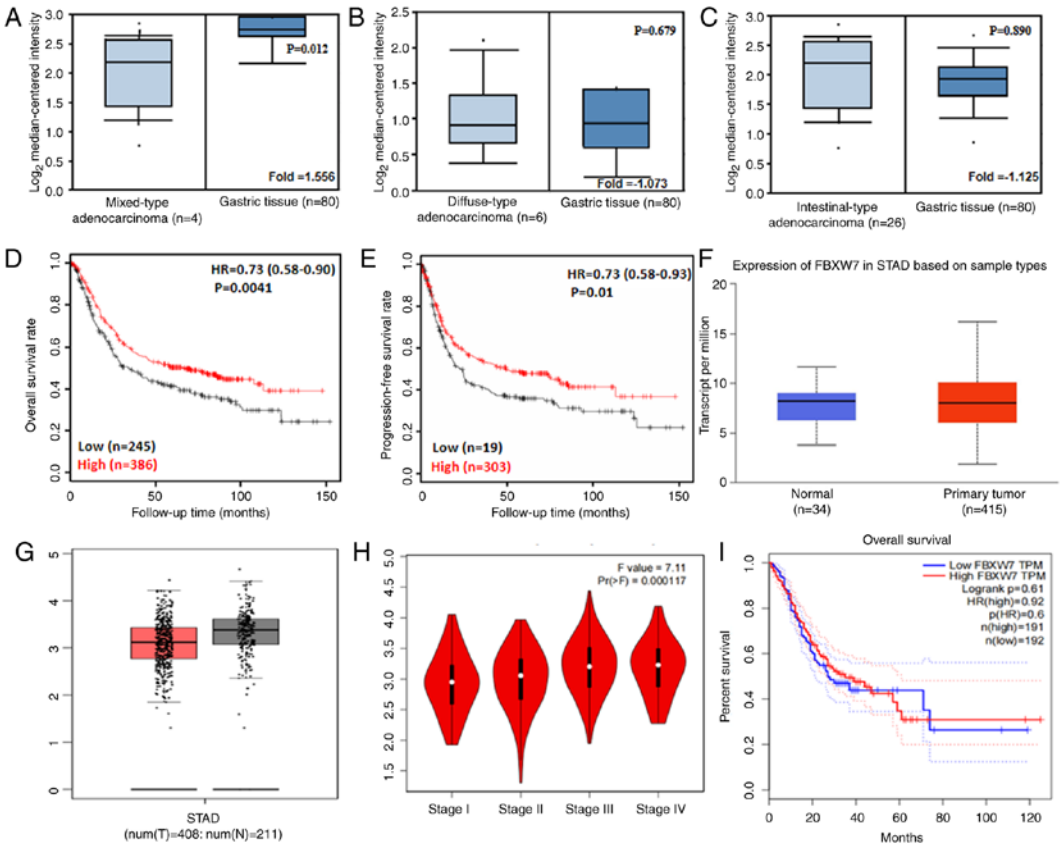

Figure 4. Oncomine bioinformatics analysis of FBXW7 mRNA expression in gastric cancer. FBXW7 expression in (A) gastric cancer was lower than in normal gastric mucosal tissues. There was no significant difference between the expression of FBXW7 in diffuse (B) and intestinal (C) gastric cancer tissues and normal gastric mucosa tissues. FBXW7 mRNA expression was positively correlated with (D) overall and (E) disease-free survival of patients with gastric cancer. (F) FBXW7 mRNA expression was not significantly different between gastric cancer and normal gastric tissue. (G) FBXW7 mRNA expression was higher in gastric cancer than in normal gastric tissue. (H) FBXW7 mRNA expression in gastric cancer association with TNM stage (H). (I) FBXW7 mRNA expression association with prognosis of patients with gastric cancer. FBXW7, F-box/WD repeat domain-containing 7; TPM, transcripts per million.

Table II. Prognostic significance of F-box/WD repeat domain-containing 7 mRNA in gastric cancer.

Clinicopathological feature	Overall survival		Progression-free survival	
	Hazard ratio	P-value	Hazard ratio	P-value
Sex				
Female	0.660 (0.430-1.020)	0.059	0.660 (0.440-1.010)	0.052
Male	0.640 (0.480-0.860)	0.003	0.710 (0.530-0.950)	0.020
TNM stage				
1	0.300 (0.090-0.960)	0.031	0.330(0.100-1.060)	0.049
2	0.840 (0.440-1.240)	0.590	0.550 (0.250-1.190)	0.120
3	0.550 (0.380-0.800)	0.001	0.620 (0.420-0.890)	0.010
4	0.630 (0.420-0.940)	0.022	0.750 (0.500-1.130)	0.170
T stage				
2	1.370 (0.870-2.160)	0.170	1.240 (0.790-1.940)	0.350
3	0.550 (0.390-0.780)	0.001	0.640 (0.460-0.900)	0.010
4	0.650 (0.280-1.480)	0.300	0.490 (0.220-1.080)	0.073
N stage				
0	0.490 (0.210-1.140)	0.092	0.490 (0.210-1.140)	0.091
1-3	0.620 (0.480-0.810)	<0.001	0.650 (0.500-0.830)	0.001
1	0.680 (0.440-1.040)	0.075	0.640 (0.430-0.940)	0.024
2	0.340 (0.220-0.540)	<0.001	0.430 (0.280-0.660)	<0.001
3	0.680 (0.400-1.150)	0.150	0.690 (0.380-1.250)	0.210
M stage				
0	0.720 (0.540-0.950)	0.021	0.750 (0.570-0.980)	0.033
1	0.410 (0.220-0.740)	0.003	0.550 (0.280-1.090)	0.082
No perforation	0.750 (0.470-1.200)	0.230	0.720 (0.450-1.130)	0.150
Treatment				
Surgery alone	1.26 (0.92-1.72)	0.150	1.180 (0.860-1.620)	0.290
5-FU-based adjuvant	0.350 (0.100-1.200)	0.081	0.470 (0.190-1.200)	0.110
Other adjuvant	3.230 (1.290-8.120)	0.008	3.560 (1.480-8.530)	0.002
Differentiation				
Well	-	-	-	-
Moderate	0.690 (0.350-1.330)	0.260	0.730 (0.380-1.380)	0.320
Poorly	0.730 (0.430-1.240)	0.250	0.720 (0.450-1.130)	0.150
Lauren's classification				
Intestinal	0.500 (0.350-0.720)	<0.001	0.610 (0.430-0.860)	0.005
Diffuse	0.780 (0.550-1.110)	0.170	0.780 (0.550-1.110)	0.170
Mixed	4.720 (0.630-38.090)	0.092	2.220 (0.630-7.890)	0.210
HER2 expression				
Negative	0.750 (0.560-0.970)	0.031	0.740 (0.540-1.010)	0.058
Positive	0.680 (0.460-1.000)	0.049	0.620 (0.400-0.960)	0.031

FU, fluorouracil; HER2 (Human epidermal growth factor receptor-2).

levels in 7901 cells (24). Luciferase activity assay has shown that miR-223 can bind to the 3'-untranslated region of the FBXW7 transcript (24). FBXW7 expression is downregulated in glioma and is associated with patient survival. A previous study found that FBXW7 mRNA expression is significantly downregulated in colorectal cancer compared with normal tissue (25). FBXW7 expression is also associated with tumor progression and lymph node metastasis; 32% of patients with early-onset gastric cancer lose FBXW7 expression, which is significantly associated with the absence of FBXW7 expression (25). FBXW7 induces apoptosis and cell cycle arrest of tumor cells partially by inhibiting EMT via downregulation of the RhoA signaling pathway in gastric cancer (26).

To determine FBXW7 expression and demonstrate its clinicopathological significance, the present study analyzed four studies using NOS scores to ensure high quality.

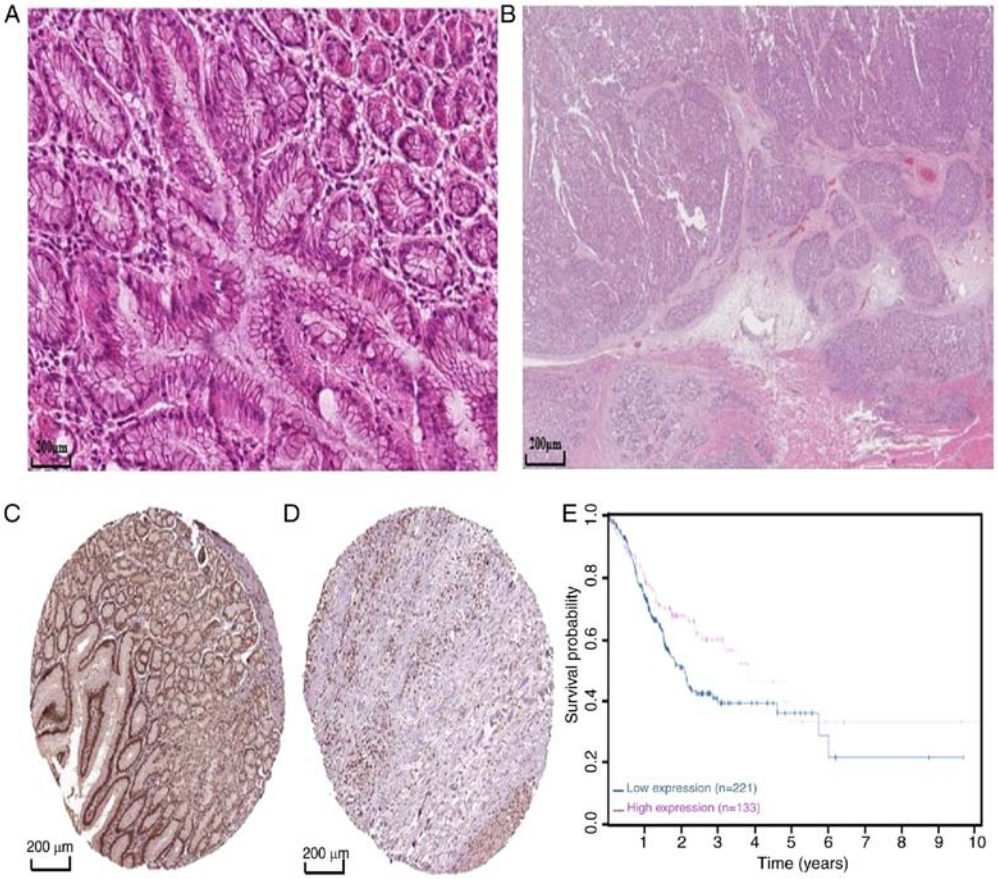

Figure 5. Prognostic value of FBXW7 expression in gastric cancer patients in HPA databases. Hematoxylin and eosin staining of (A) normal gastric mucosa and (B) gastric cancer tissue. Magnification, x200. Immunohistochemical staining of FBXW7 in (C) normal gastric tissue and (D) gastric cancer tissue. (E) Association between FBXW7 expression and prognosis of patients with gastric cancer. FBXW7, F-box/WD repeat domain-containing 7.

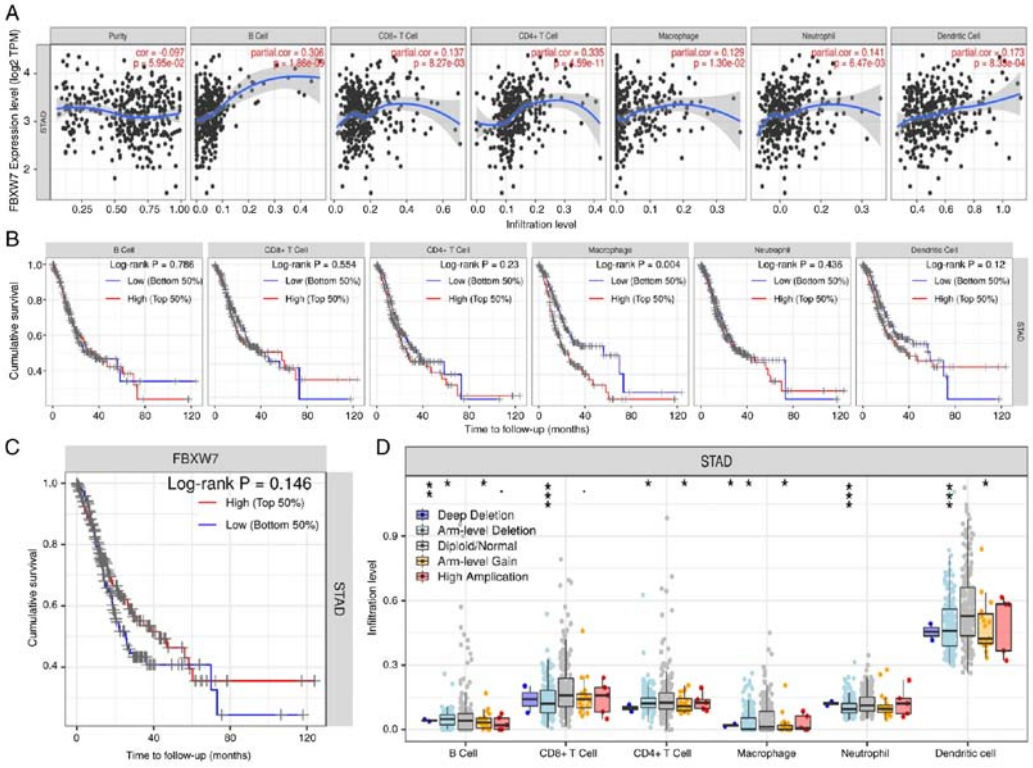

Figure 6. Immune cell infiltration of FBXW7 in gastric cancer tissue. (A) Association between FBXW7 expression and immune cells in gastric cancer tissue. Association between (B) degree of immune cell infiltration and prognosis and (C) FBXW7 expression and survival of patients with gastric cancer. (D) Gastric cancer copy variation mechanism in different immune cells. FBXW7, F-box/WD repeat domain-containing 7; TPM, transcripts per million.

Previous study have shown that aberrant activation of FBXW7 inhibits tumor growth, metastasis and dedifferentiated ovarian cancer (27). FBXW7 expression is reported to be negatively correlated with the poor prognosis of patients with rectal and pancreatic cancer (28,29). In the present study, the expression of FBXW7 was downregulated at both mRNA and protein levels in gastric cancer tissue compared with normal gastric mucosa, suggesting the involvement of FBXW7 expression in gastric carcinogenesis. FBXW7 expression was positively associated with differentiation, TNM stage and lymph node metastasis. This finding indicates that abnormal expression of FBXW7 at the mRNA level, which indicates its expression at the protein level, may be used to predict the pathological behavior of gastric cancer. Meta-analysis was performed following the PRISMA checklist (9). The present study integrated previous studies, observed the overall trend of FBXW7 gene expression, validated gene expression from other databases and finally analyzed the impact of FBXW7 on the prognosis of patients with gastric cancer.

There were some limitations in the meta-analysis. First, potential publication bias stems from the fact that published results were predominantly positive. Second, small sample sizes may affect the validity of reported results. The patients included in the study were only from Asia and the United States. Because different experimental methods may be used, the level of medical development in different regions may also affect the results to detect the expression of FBXW7.

FBXW7 serves a complex role in the development of tumor. Expression of FBXW7 was downregulated in patients with gastric cancer. FBXW7 expression was positively associated with differentiation, TNM stage and lymph node metastasis. FBXW7 expression may serve as a marker for prognosis of patients with cancer, providing novel methods for prevention and treatment.

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Availability data and materials

The datasets generated and/or analyzed during the current study are available in the Kaplan-Meier plotter (http://www.kmplot.com), Oncomine (http://www.oncomine.org), HPA(https://www.proteinatlas.org/), GEPIA(http://gepia.cancer-pku.cn/) and UALCAN(http://ualcan.path.uab.edu/) repository.

Authors' contributions

JS and ZF performed the meta-analysis and wrote the manuscript. JS and YB analyzed the data. JS and ZF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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