Original Article

Increased expression of FBW7 may improve the prognosis of lung adenocarcinoma after pemetrexed chemotherapy by transforming the epithelial-to-mesenchymal process

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Background: FBW7 is a tumor suppressor in cancer. However, few studies have examined the role of FBW7 in lung adenocarcinoma (LUAD), especially the relationship between FBW7 and chemotherapy drug resistance in LUAD. This study analyzed the relationship between FBW7 expression and the clinicopathological features of LUAD patients, and investigated the effect of FBW7 on the efficacy of pemetrexed chemotherapy and its relationship with epithelial-to-mesenchymal transformation (EMT).

Methods: A total of 101 patients admitted to Zhoushan Hospital from February 2014 to May 2018 who were pathologically diagnosed with LUAD and received pemetrexed chemotherapy were included in the study. Immunohistochemistry (IHC) was used to detect the expression of FBW7 and EMT-related target proteins in the cancer tissues of the patients, and the relationship between FBW7 and the clinicopathological features, prognosis, and EMT of the LUAD patients was analyzed.

Results: FBW7 expression was high in 70 LUAD patients and low in 31 LUAD patients. The patients were followed up for 8–112 months. The 5-year progression-free survival (PFS) and overall survival (OS) were significantly higher in the high FBW7 expression group than the low FBW7 expression group (P<0.001). The Cox regression analysis showed that the higher serum carcinoembryonic antigen (CEA) [hazard ratio (HR) =2.818, 95% confidence interval (CI): 1.100–7.223, P=0.03], higher cytokeratin 19 fragment (Cyfra21-1) (HR =3.587, 95% CI: 1.168–11.015, P=0.03), radical surgery (HR =0.044, 95% CI: 0.006–0.307, P=0.002), and FBW7 expression level (HR =6.270, 95% CI: 2.106–18.660, P=0.001) were independent predictors of OS in patients with LUAD receiving pemetrexed chemotherapy. The Spearman correlation analysis showed that the expression of FBW7 was positively correlated with the expression of E-cadherin (r_s=0.314, P=0.001), and negatively correlated with the expression of N-cadherin (r_s=–0.325, P=0.001).

Conclusions: In patients with LUAD receiving pemetrexed chemotherapy, the high FBW7 expression group had a better prognosis than the low FBW7 expression group. Thus, high expression of FBW7 may affect the efficacy of pemetrexed in patients with LUAD through EMT. Our findings may provide new treatment ideas for patients with LUAD who are resistant to pemetrexed.

Keywords: Lung adenocarcinoma (LUAD); FBW7; epithelial-to-mesenchymal transformation (EMT); prognosis; pemetrexed

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Introduction

Lung cancer is the leading cause of cancer morbidity and mortality, and accounts for about one-fifth of cancer-related deaths (1,2). Currently, lung adenocarcinoma (LUAD) is the most common histological type of lung cancer (1,2). Pemetrexed is widely used in the clinical treatment of non-squamous non-small cell lung cancer (NSCLC) (3), but it still produces chemical resistance and reduces the therapeutic effect after long-term use (4). Epithelial-to-mesenchymal transformation (EMT) refers to the biological process in which epithelial cells are transformed into cells with a stromal phenotype through a specific procedure. The occurrence of EMT in epithelial-derived malignant tumor cells can promote tumor progression, and eventually metastasis (5). A study has found that the activation of the EMT pathway in NSCLC cell lines is associated with pemetrexed resistance; however, pemetrexed efficacy returns after blocking the EMT pathway (6).

FBW7 is a tumor suppressor that regulates the cell cycle, metabolism, differentiation, apoptosis, EMT, and other biological processes by promoting the ubiquitination degradation of various oncoproteins. FBW7 plays a central role in maintaining cell cycle checkpoints, preventing genomic instability, and promoting apoptosis by targeting and degrading a variety of cell cycle progression and anti-apoptotic proteins (7). *FBW7* gene mutation or downregulation can induce EMT formation and tumor invasion and metastasis in acute lymphoid leukemia and bile duct cancer cells (8-10). In recent years, it has been proposed that FBW7 modifiers Snail protein by ubiquitination to promote its degradation, thereby inhibiting EMT process (5). Existing studies mostly focus on the role of EMT in the natural progression of tumors. At present, few studies have examined the relationship between FBW7 and pemetrexed resistance. In this study, the expression of FBW7 and EMT-related target proteins in the cancer tissues of LUAD patients receiving pemetrexed chemotherapy was detected by immunohistochemistry (IHC), and the correlation between FBW7 and EMT, as well as its relationship with clinicopathological features and prognosis, was analyzed to provide a reference for research on the mechanism of drug resistance to pemetrexed in LUAD. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-134/rc).

Highlight box

Key findings

- The results of this study suggest that patients with lung adenocarcinoma (LUAD) receiving pemetrexed chemotherapy with a high expression of FBW7 had a better prognosis than those with a low expression of FBW7.

What is known, and what is new?

- FBW7 is a tumor suppressor that regulates epithelial-to-mesenchymal transformation (EMT) biological processes by promoting ubiquitination degradation of various cancer proteins.
- FBW7 may influence the efficacy of pemetrexed in patients with LUAD by modulating the EMT process.

What is the implication, and what should change now?

- FBW7 can be used as a potential biomarker to evaluate tumor prognosis and treatment. Our findings provide a reference for the study of the mechanism of drug resistance to pemetrexed in LUAD.

Methods

Patients

A total of 101 patients with LUAD confirmed by pathology and receiving pemetrexed chemotherapy were selected from the Zhoushan Hospital from February 2014 to May 2018. The patients had an average age of 61.43±8.24 years, and 45 were male and 56 were female. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have a diagnosis of LUAD confirmed by surgery or puncture pathology, and have been treated with pemetrexed chemotherapy; (II) have primary LUAD and have not received any other anti-tumor therapy before chemotherapy; and (III) have complete clinicopathological information. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had severe heart, liver, kidney, brain, or other organ dysfunction; (II) had a previous history of other malignant tumors; (III) had received an interrupted pemetrexed chemotherapy course; and/or (IV) had been lost to follow up. This study

was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Zhoushan Hospital Ethics Committee (No. 2021-046). The requirement of informed consent was waived due to the retrospective design of the study.

The patients' clinicopathological data were collected

The clinicopathologic data, including age, sex, smoking history, tumor markers at diagnosis, tumor size, tumor-node-metastasis (TNM) stage, lymph node metastasis (LNM), pleural invasion, and Ki-67 expression, of all patients were collected.

IHC and evaluations

FBW7, E-cadherin, and N-cadherin were detected by IHC

The expression of FBW7, E-cadherin, and N-cadherin in the tissues was detected by IHC. Surgical excisions or biopsy specimens of all patients were collected, and paraffin embedding, sectionalization, dehydration and antigen repair were performed. The first antibody of FBW7, E-cadherin, and N-cadherin (rabbit anti-human polyclonal antibodies, all 1:200 diluted, purchased from Affinity, USA) were added, and then incubate at room temperature for 30 minutes. Diaminobenzidine (Beijing Solaibao Technology Co., Ltd., Beijing, China) was used for color development, the hematoxylin was re-dyed, and neutral gum was used for sealing after washing.

Interpretation of results

FBW7 expression was localized in the nucleus, and E-cadherin and N-cadherin expression was localized in the cell membrane. All the IHC sections were semi-quantitatively scored by two senior pathologists according to the staining intensity and staining ratio (11). Staining intensity was scored as follows—0 points: no coloring; 1 point: light yellow; 2 points: claybank; and 3 points: sepia. The proportion of positive cells in all cancer cells was scored as follows: 1 point for <25% positive cells; 2 points for 25–49% positive cells; 3 points for 50–74% positive cells; and 4 points for ≥75% positive cells. The product of the two scores was used as the final score, with a score of 0–3 classified as negative, 4–6 as weak positive, 7–8 as positive, and 9–12 as strong positive. FBW7 expression was measured according to the average score of the final score; a score of 1 to 6 indicated "low" expression, and a score of 7 to 12 indicated "high" expression.

Prognostic follow up

The prognostic information of all the included patients was collected by telephone return visit, and outpatient return visit, and the termination time of the follow up was the time of death or June 31, 2023. Overall survival (OS) and 5-year progression-free survival (PFS) at the end of the follow-up period were recorded.

Statistical analysis

SPSS 21.0 software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The measurement data are expressed as the mean ± standard deviation. The count data are presented as the example or rate. The Fisher exact test or Chi-squared test was used for comparisons between groups. The Kaplan-Meier survival curve was used to evaluate the survival of the patients. Univariate and multivariate Cox regression analyses were performed to determine the prognostic factors of patients with LUAD who received pemetrexed chemotherapy. A Spearman correlation analysis was performed to examine whether FBW7 was correlated with E-cadherin and N-cadherin expression. A P value <0.05 was considered statistically significant.

Results

Relationship between FBW7 expression and clinicopathological features in LUAD

Of the patients, 70 had high FBW7 expression and 31 had low FBW7 expression. There were statistically significant differences in tumor maximum diameter, TNM stage, serum carcinoembryonic antigen (CEA) elevation, LNM, and Ki-67 expression between the high and low FBW7 expression groups (P<0.05), but there were no statistically significant differences in age, sex, smoking history and pleural invasion (P>0.05) (*Table 1*). FBW7 expression was low in the tissue samples of four LUAD patients who did not receive surgical treatment and had a late clinical stage.

Relationship between FBW7 expression and prognosis in patients with LUAD

As at the end of follow up on June 31, 2023, the patients

Table 1 Relationship between FBW7 expression and the clinicopathological features of lung adenocarcinoma

Variables	FBW7 expression, n (%)		P value
	Low (n=31)	High (n=70)	
Age (years)			0.80
<60	12 (29.27)	29 (70.73)	
≥60	19 (31.67)	41 (68.33)	
Gender			0.61
Male	15 (33.33)	30 (66.67)	
Female	16 (28.57)	40 (71.43)	
Smoking			0.14
Smoker	12 (41.38)	17 (58.62)	
Non-smoker	19 (26.39)	53 (73.61)	
Tumor size			<0.001
<3 cm	14 (19.44)	58 (80.56)	
≥3 cm	17 (58.62)	12 (41.38)	
Stage			0.02
I–II	23 (26.44)	64 (73.56)	
III–IV	8 (57.14)	6 (42.86)	
CEA			<0.001
>5 ng/mL	18 (64.29)	10 (35.71)	
≤5 ng/mL	13 (17.81)	60 (82.19)	
CA199			0.55
≥34 U/mL	3 (50.00)	3 (50.00)	
<34 U/mL	28 (29.47)	67 (70.53)	
SCCA			0.84
>3 ng/mL	2 (22.22)	7 (77.78)	
≤3 ng/mL	29 (31.52)	63 (68.48)	
Cyfra21-1			0.14
>3.30 ng/mL	6 (54.55)	5 (45.45)	
≤3.30 ng/mL	25 (27.78)	65 (72.22)	
NSE			–
>10 ng/mL	0	0	
≤10 ng/mL	31 (30.69)	70 (69.31)	
LNM			0.01
Present	12 (52.17)	11 (47.83)	
Absent	19 (24.36)	59 (75.64)	
PI			0.25
Present	11 (39.29)	17 (60.71)	
Absent	20 (27.40)	53 (72.60)	
Ki-67 expression			0.04
<25%	15 (23.44)	49 (76.56)	
≥25%	16 (43.24)	21 (56.76)	
Operation			0.002
Yes	27 (27.84)	70 (72.16)	
No	4 (100.00)	0	

CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; SCCA, squamous cell carcinoma antigen; Cyfra21-1, cytokeratin 19 fragment; NSE, neuron-specific enolase; LNM, lymph node metastasis; PI, pleural invasion.

had been followed up for 8 to 112 months. Of the 101 patients with LUAD, 75 survived, with a survival rate of 74.30%, and a 5-year OS rate of 81.20%. The Kaplan-Meier survival analysis showed that the 5-year PFS of the high FBW7 expression group (97.29±1.65 months) was significantly higher than that of the low FBW7 expression group (60.94±8.14 months; P<0.001). The OS of the high FBW7 expression group (95.86±1.87 months) was significantly higher than that of the low FBW7 expression group (60.90±6.84 months; P<0.001) (*Figure 1*).

The univariate Cox regression analysis showed that the maximum tumor diameter (P<0.001), TNM stage (P=0.02), elevated serum CEA (P<0.001), cytokeratin 19 fragment (Cyfra21-1; P<0.001), LNM (P=0.001), radical surgery (P<0.001), Ki-67 expression level (P=0.003), and FBW7 expression level (P<0.001) were associated with OS in the patients with LUAD treated with pemetrexed chemotherapy. The multivariate Cox regression analysis showed that elevated serum CEA, Cyfra21-1, radical surgical treatment, and FBW7 expression level at diagnosis were independent predictors of prognosis in LUAD patients receiving pemetrexed chemotherapy (*Table 2*).

Correlation between FBW7 expression and EMT in LUAD

The expression of FBW7 is mainly located in the nucleus,

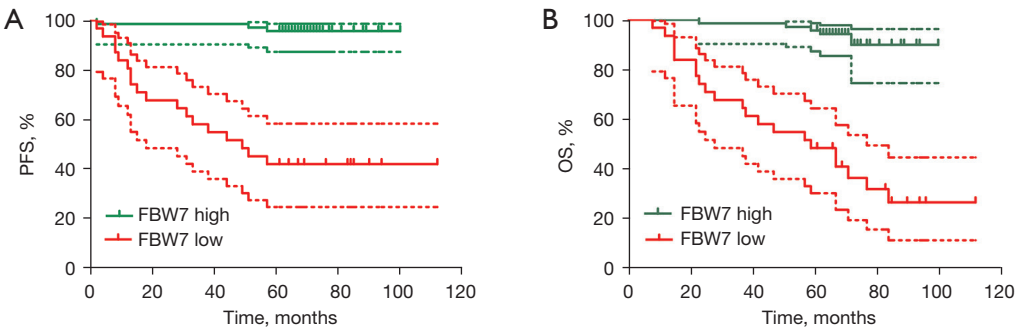

Figure 1 Relationship between FBW7 expression and prognosis in lung adenocarcinoma. (A) Comparison of 5-year PFS with a high and low expression of FBW7. (B) Comparison of OS with a high and low expression of FBW7. PFS, progression-free survival; OS, overall survival.

Table 2 Univariate and multivariate Cox regression analyses of prognosis in patients with lung adenocarcinoma

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (<60 *vs.* ≥60 years)	1.094	0.494–2.422	0.82	–	–	–
Gender (male *vs.* female)	1.050	0.482–2.290	0.90	–	–	–
Smoking (smoker *vs.* never-smoker)	0.815	0.354–1.879	0.82	–	–	–
Tumor size (>3 *vs.* ≤3 cm)	4.169	1.903–9.133	<0.001	1.507	0.627–3.626	0.36
Stage (I–II *vs.* III–IV)	2.949	1.237–7.032	0.02	1.109	0.317–3.875	0.87
CEA (>5 *vs.* ≤5 ng/mL)	4.402	2.013–9.624	<0.001	2.818	1.100–7.223	0.03
CA199 (≥34 *vs.* <34 U/mL)	0.541	0.073–4.011	0.55	–	–	–
SCCA (>3 *vs.* ≤3 ng/mL)	1.018	0.239–4.339	0.98	–	–	–
Cyfra21-1 (>3.3 *vs.* ≤3.3 ng/mL)	5.434	2.238–13.195	<0.001	3.587	1.168–11.015	0.03
NSE (>10 *vs.* ≤10 ng/mL)	–	–	–	–	–	–
LNM (present *vs.* absent)	3.935	1.808–8.566	0.001	1.310	0.393–4.363	0.66
PI (present *vs.* absent)	1.722	0.781–3.798	0.18	–	–	–
Ki-67 expression (<25% *vs.* ≥25%)	3.603	1.561–8.315	0.003	1.293	0.455–3.676	0.63
Operation (yes *vs.* no)	0.015	0.003–0.068	<0.001	0.044	0.006–0.307	0.002
FBW7 expression (high *vs.* low)	12.660	4.741–33.808	<0.001	6.270	2.106–18.660	0.001

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; SCCA, squamous cell carcinoma antigen; Cyfra21-1, cytokeratin 19 fragment; NSE, neuron-specific enolase; LNM, lymph node metastasis; PI, pleural invasion.

and the expression of E-cadherin and N-cadherin is located in the cell membrane (*Figure 2*). The Spearman correlation analysis showed that the expression of FBW7 was positively correlated with the expression level of E-cadherin [r_s=0.314, 95% confidence interval (CI): 0.121–0.485, P=0.001], and negatively correlated with the expression level of N-cadherin (r_s=–0.325, 95% CI: –0.494 to –0.133, P=0.001).

Discussion

FBW7, an evolutionarily conserved member of the F-box protein family, acts as a substrate recognition subunit in the SKP1-CUL1-F-box (SCF) ubiquitination ligase complex, and regulates cell division, proliferation, differentiation, and EMT development by promoting the ubiquitination

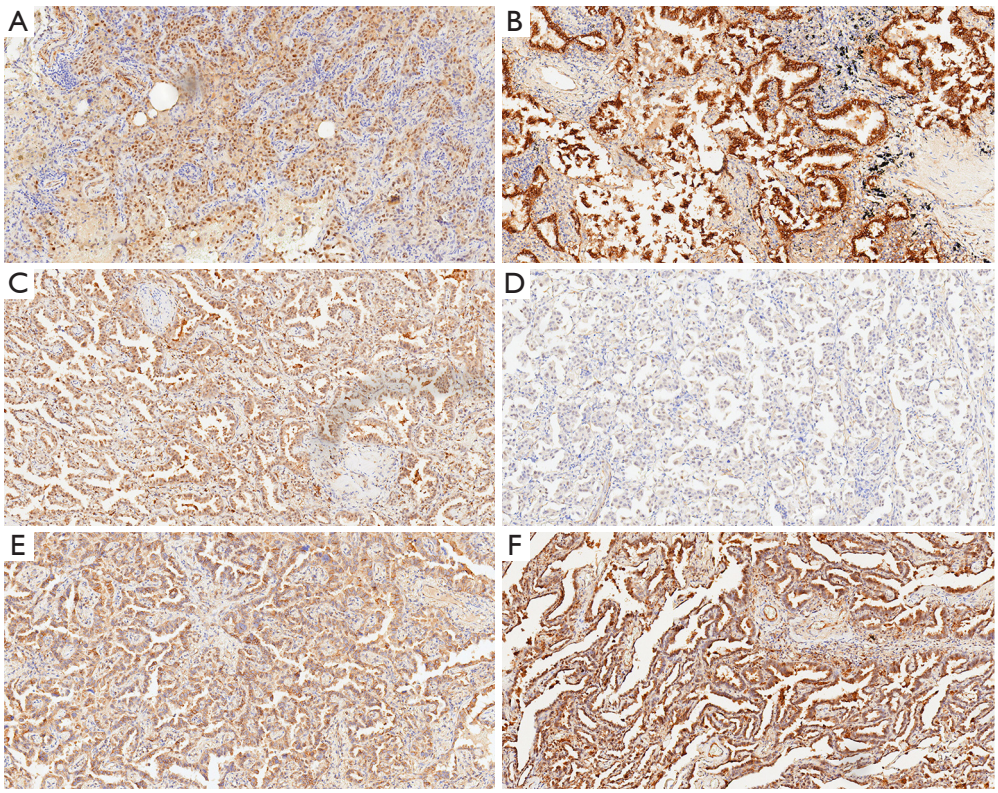

Figure 2 The expression of FBW7, E-cadherin and N-cadherin in tissues was detected by immunohistochemistry (original magnification ×400). (A) High expression of FBW7; (B) strongly positive for E-cadherin; (C) positive for N-cadherin; (D) low expression of FBW7; (E) positive for E-cadherin; (F) strongly positive for N-cadherin.

degradation of various oncoproteins (7). Studies have found that changes in FBW7 expression are significantly related to the prognosis of colorectal cancer, gastric cancer, liver cancer, and bile duct cancer (12-15). However, few studies have examined the role of FBW7 in LUAD, especially the relationship between FBW7 and chemotherapy drug resistance in LUAD. Therefore, this study detected the expression of FBW7 and EMT-related target proteins in the cancer tissues of LUAD patients receiving pemetrexed chemotherapy, and analyzed the correlation between FBW7 and EMT, as well as its relationship with clinicopathological features and prognosis.

It has been found that FBW7 exerts a tumor suppressive effect in cancer (7,16). Enkhbold *et al.* explored the correlation between FBW7 expression and the clinicopathological variables of intrahepatic cholangiocarcinoma, and found that FBW7 expression was significantly correlated with stage and tended to be related to LNM (15). The PFS rate of the low FBW7 expression group was significantly lower than that of the high FBW7 expression group. The multivariate analysis showed that the low expression of FBW7 was an independent prognostic factor affecting OS and PFS (13). It has also been reported that the mutation rate of FBW7 in cholangiocarcinoma is as high as 35% (17). Yokobori *et al.* found that the low level of FBW7 expression in primary gastric cancer was associated with LNM, larger tumors, and a poor prognosis (13). Tu *et al.* found that the low FBW7 expression in liver cancer was associated with adverse clinicopathological features, such as a large tumor size, venous infiltration, a high pathological grade, and a late TNM stage, and that patients with positive FBW7 expression had a higher 5-year survival rate than those with negative FBW7 expression (14). These studies suggest that FBW7 can be used as a potential biomarker to evaluate tumor prognosis and treatment.

In the present study, there were statistically significant differences in maximum tumor diameter, late TNM stage, elevated serum CEA, LNM and Ki-67 expression between the high and low expression groups of FBW7 in LUAD, which are clinical factors suggestive of poor prognosis

(P<0.05). The Kaplan-Meier survival analysis showed that the 5-year PFS and OS in patients with LUAD treated with pemetrexed chemotherapy were significantly higher in the high FBW7 expression group than the low FBW7 expression group. The Cox univariate and multivariate regression analyses indicated that the low expression of FBW7 was a risk factor for a poor prognosis in LUAD patients receiving pemetrexed chemotherapy.

To further explore the role of FBW7 in the mechanism of drug resistance to pemetrexed in LUAD, this study explored the relationship between FBW7 and EMT-related target proteins, and the results showed that the expression of FBW7 was positively correlated with the expression level of E-cadherin, and negatively correlated with the expression level of N-cadherin. Thus, the expression of FBW7 may be related to a reduction in the efficacy of pemetrexed chemotherapy by EMT in LUAD. In the human body, EMT is mainly involved in embryo formation, organ development and tissue damage repair. In the tumor formation environment, EMT can change the interaction between tumor cells, and tumor cells and stroma, and promote tumor cell invasion and metastasis (18). E-cadherin and N-cadherin are classical molecular markers involved in EMT, the mechanism of which is related to the downregulation of E-cadherin and the upregulation of N-cadherin (19). Therefore, detection of E-cadherin and N-cadherin expression levels in tumor tissues can be used to evaluate EMT.

A number of studies have shown that cells can be induced to develop chemotherapy resistance by increasing the expression of EMT markers (20-24). Yu *et al.* showed that the expression level of FBW7 affected the resistance of liver cancer cells to Adriamycin and the invasion ability of liver cancer cells, and found that the upregulation of the FBW7 expression level changed the direction of EMT (25). Liang *et al.* found that chemotherapy resistance of multi-target anti-folate chemotherapy drug pemetrexed required the activation of the EMT pathway, the induction of the EMT process promoted chemotherapy resistance of NSCLC, and the administration of kaempol at the same time eliminated pemetrexed resistance (6). Zhang *et al.* showed that FBW7 inhibited the expression of the E-cadherin cell compact linking protein by inducing ubiquitination and proteolysis of the transcription factor snail (26). In addition, Kim *et al.* had reported that FBW7 is also correlated with chemotherapy sensitivity of other tumors, which found that FBW7 gene enhances the chemotherapy sensitivity of decitabine to retinoblastoma through gasdermin E (GSDME)-mediated pyroptosis (27). The IHC results of this study showed that the expression of FBW7 in LUAD was positively correlated with the expression level of E-cadherin but was negatively correlated with the expression level of N-cadherin, suggesting that the expression of FBW7 may be related to the promotion of pemetrexed chemotherapy resistance by EMT in LUAD. However, the specific mechanism needs further study.

Conclusions

The results of this study showed that low expression of FBW7 in the cancer tissues of LUAD patients was closely related to larger tumors, a later clinical stage, and a poor prognosis, and also confirmed that LUAD patients receiving pemetrexed chemotherapy with a high expression of FBW7 in the cancer tissues had a better prognosis. FBW7 may affect the efficacy of pemetrexed in LUAD patients through EMT. Our findings can serve as a reference for the study of drug resistance mechanism of pemetrexed in LUAD.

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None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-134/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-134/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-134/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as amended in 2013) and approved by the Zhoushan Hospital Ethics Committee (No. 2021-046). The requirement of informed consent was waived due to the retrospective design of the study.

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