Long non-coding RNA FTX predicts a poor prognosis of human cancers: a meta-analysis

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Abstract

Background
Several studies assessed the relationship between FTX expression level and clinicopathological features and survival outcomes in patients with cancer, but these results were conflicting. This meta-analysis aimed to synthesize existing data to clarify the association of FTX with prognosis of cancers.

Methods
Electronic databases of PubMed, Embase, Cochrane library, Web of Science, Chinese CNKI, and the Chinese WanFang databases were used to search for relevant studies. Role of FTX in cancers was evaluated by pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs).

Results
In total, 11 studies compromising 1210 participants including colorectal cancer (CRC), hepatocellular carcinoma (HCC), gastric cancer (GC), renal cell carcinoma (RCC), osteosarcoma (OSC), and glioma, were enrolled in this analysis. The meta-analysis showed that high FTX expression was associated with lymph node metastasis, distant metastasis, tumor size and TNM/clinical stage. More importantly, the pooled results from survival analysis revealed that there was a significant correlation between high FTX expression and a shorter OS in patients with HCC, CRC, GC, OSC, and glioma, and that FTX overexpression could be an independent predictive marker for shorter OS in patients with CRC, HCC, OSC, and glioma.

Conclusions
FTX may be a potential oncogene, and high FTX expression be associated with a poor prognosis in patients with CRC, HCC, OSC, and glioma.

Background
The latest statistics of cancers show that cancer is the leading cause of human death both in the world and in China[1, 2], which produces serious economic burdens. Modern treatments for cancer including surgery, adjuvant therapy and supportive therapy have been a dramatic improvement in recent years. However, many patients are at an advanced stage of cancer at the time of diagnosis, which leads to a poor prognosis.

Long non-coding RNAs (lncRNAs) are RNA molecules comprising a transcription length of more than 200 nucleotides and lack of protein-coding capacity[3]. Recent studies have shown that lncRNAs are found to be crucial in regulating cellular processes such as cell cycle, growth, and apoptosis that ensure homeostasis[4]. A large number of lncRNAs are associated with various types of cancer, which may exhibit tumor-suppressive and -promoting (oncogenic) functions, and therefore they hold strong hope as a biomarker for the early diagnosis and prognostic prediction of cancers, thus also having the potential possibility to be a target of molecular targeted therapy[5].

LncRNA ve prime to Xist (FTX) is a kind of highly conserved transcript with 2300 nucleotides encoded by FTX gene, which is identified as an activator of Xist in mouse ES cells and a novel non-coding RNA involved in XCI[6]. Increasing studies have shown that FTX is related to the clinicopathological features and prognosis of patients with cancer, including colorectal cancer (CRC)[7], osteosarcoma (OSC)[8], gastric cancer (GC)[9], and renal cell carcinoma (RCC)[10]. However, these studies were limited by sample size and had opposite outcomes. For example, Liu et al.[11] indicated that FTX significantly downregulated in hepatocellular carcinoma (HCC) tissues compared with paired adjacent liver tissues, and the high FTX group had better tumor differentiation, intact tumor encapsulation, smaller tumors, and a better overall survival. On the contrary, Li et al.[12] revealed that compared with paired adjacent liver tissues, the HCC tissues had higher FTX expression that was significantly associated with tumor differentiation and metastasis, and predicted poor prognosis. Therefore, it is necessary to conduct a comprehensive meta-analysis of the existing data to assess the correlation between FTX and clinicopathological features and survival outcomes in patients with cancer.

Methods

Search strategy and study selection
A protocol was registered with PROSPERO (registration number: CRD42020199238) before the study begins. The systematic literature search was conducted in PubMed, Embase, Cochrane library, Web of Science, Chinese CNKI, and the Chinese WanFang databases from inception through August 01, 2020. The keywords for searches were "long non-coding RNA FTX" OR "LncRNA FTX" AND "cancers" or "neoplasm" or "tumors". The citation lists of relevant studies were also rigorously screened.

Studies that meet the following criteria were allowed to be included: (1) the expression of FTX in patients with cancers was examined in tumor tissues and assessed using qRT-PCR; (2) the results provided survival information including overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and recurrence-free survival (RFS); (3) hazard ratios (HRs) for survival outcomes were provided or could be calculated from survival curves; and (4) the most recent paper was selected in cases of a repeat study.

The exclusion criteria for this study were as follows: (1) laboratory articles, reviews, case reports, letters, editorials and conference reports; (2) non-human subject studies; and (3) inability to calculate HR based on the data provided.
Data extraction and quality assessment

The full texts of potentially eligible articles were scrutinized independently by 2 authors (WWC and YTL). Disagreements were resolved by consensus. The extracted data included the first author's name, the year of publication, country, number of cases, type of cancer, clinicopathological features, survival outcome. Newcastle-Ottawa-Scale (NOS) criteria[13] were used to assess the quality of the studies. When the NOS score was ≥ 6 the article was considered to be high-quality. An NOS score < 6 was indicative of a low-quality study.

Statistical analysis

All the statistical data were analyzed using STATA 14.2 software. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the relationship between high FTX expression and clinicopathological characteristics that included gender (male vs female), tumor size (the bigger group vs the small group), differentiation (low vs high and moderate), lymph node metastasis (yes vs no), distant metastasis (yes vs no), TNM/clinical stage (III + IV vs I + II). HRs with 95% CIs were calculated to assess the correlation between the overexpression of FTX and survival outcome. HRs and 95% CIs analyzed by Cox regression analysis were extracted directly from publications. If HRs and 95% CIs analyzed by Kaplan-Meier method could not be obtained, the software Engauge Digitizer and published method[14] were used to extract the survival data from a Kaplan–Meier curve in related articles. Heterogeneity was assessed by $I^2$ test and Q test, and the random effects model was used if the $I^2 > 50\%$, otherwise, a fixed effects model was used. The potential publication bias was assessed by Begg's funnel analysis. P < 0.05 was considered to be statistically significant. Sensitivity analysis was used to calculate the source of heterogeneity and stability of results.

Results

Study identification and characteristics

As shown by the search flow diagram (Fig 1), a total 11 studies[7-12, 15-19] with 1210 patients were enrolled in this meta-analysis according to the inclusion criteria, including 3 studies on CRC, 3 studies on HCC, 2 studies on GC, 1 study on RCC, 1 study on OSC, and 1 study on glioma. The included studies were published from 2015 to 2020, and sample sizes ranged from 30 to 187 patients. All of included studies were from China. Nine studies were published in English and two in Chinese. All of included studies received scores ≥ 6 in methodological assessments, which meant they had high quality. The clinicopathological characteristics and survival information obtained from these studies are summarized in Table 1 and Table 2.

FTX expression and clinicopathological characteristics

The pooled ORs with 95% CI are shown in Table 3. The results revealed that elevated FTX expression was significantly related to lymph node metastasis (yes vs no: OR = 2.47, 95% CI = [1.45, 4.22], p = 0.001, Fig. 2b) in 7 studies[7, 9, 10, 12, 16-18] (3 studies on CRC, 2 studies on GCI, 1 study on HCC, and 1 study on RCC), distant metastasis (yes vs no: OR = 3.87, 95% CI = [2.38, 6.30], p < 0.001, Fig. 2c) in 5 studies[7, 8, 12, 17, 18] (2 studies on CRC, 1 study on GCI, 1 study on HCC, and 1 study on OSC), bigger tumor size (the bigger group vs the small group: OR = 2.10, 95% CI = [1.15, 3.85], p = 0.016, Fig. 2d) in 9 studies[7-12, 17-19] (2 studies on CRC, 2 studies on GCI, 1 study on HCC, and 1 study on RCC, and 1 study on OSC), and later TNM/clinical stage (III + IV vs I + II: OR = 2.38, 95% CI = [1.85, 3.06], p < 0.001, Fig. 2f) in 10 studies[7-11, 15-19] (3 studies on CRC, 2 studies on GCI, 2 studies on HCC, 1 study on RCC, 1 study on OSC, and 1 study on glioma). The overexpression of FTX was not associated with gender (male vs female: OR = 0.87, 95% CI = [0.68, 1.22], p = 0.271, Fig. 2a) in all aforementioned 11 studies and differentiation (low vs high and moderate: OR = 1.33, 95% CI = [0.53, 3.33], p = 0.546, Fig. 2e) in 7 studies[9, 11, 12, 16-19] (2 studies on CRC) and clinicopathological features (including gender, tumor size, differentiation, lymph node metastasis, distant metastasis, TNM/clinical stage, and later TNM/clinical stage: OR ≥ 1.13, p < 0.007, Fig. 3a). In addition, the 2 heterogeneous studies[12, 19] (I² = 86.8%, P = 0.006) with 199 patients with HCC were included, and the pooled results indicated that high FTX expression was related to a shorter DFS (high vs low: HR = 3.78, 95% CI = [1.08, 13.22], p = 0.0037, Fig. 3b).

Another meta-analysis was conducted using the data from survival analysis by multivariate Cox regression model in four studies[8, 12, 15, 16] (1 study on CRC, 1 study on HCC, 1 study on OSC, and 1 study on glioma), which included 531 patients. The role of FTX as an independent prognostic factor for OS of patients with cancer was assessed. The pooled results showed that high FTX expression was an independent prognostic factor for a shorter OS of patients with the aforementioned 4 cancers (HR = 2.63, 95% CI = [2.01, 3.45], p < 0.001, Fig. 3c).

Sensitivity analysis

We performed sensitivity analyses to evaluate the robustness of the prognostic value. The results (Supplementary table 1 and Supplementary table 2) were not significantly impacted when any individual study was removed, demonstrating that the results were reliable.

Publication bias

Begg's funnel analysis was conducted to evaluate publication bias. As shown in Fig. 4, there was no publication bias for gender (p = 0.276), lymph node metastasis (p = 0.764), distant metastasis (p = 1.0), tumor size (p = 0.754), differentiation (p = 1.0), TNM/clinical stage (p = 0.858), OS (p = 0.174), DFS (p = 1.0).
Discussion

In the 1980s, the first regulatory non-coding RNA (ncRNA) was initially identified in bacteria, and from then on, a large number of ncRNAs have been found in most eukaryotic organisms[20]. LncRNAs belong to the typical class of non-coding RNAs (ncRNAs), which were initially dismissed as merely transcriptional “noise”[21]. However, emerging evidences have revealed that lncRNAs are associated with the development of cancer by regulating various cellular functions, including proliferation, migration, and DNA stability[22]. Because of the tissue-specific characteristics of IncRNAs, they would be the next generation of biomarkers or targets for human cancer[23].

LncRNA FTX is a member of the IncRNA family. In recent years, the change of FTX expression in different type of cancers and the influence of FTX expression on cancers have attracted much attention. However, the effect of FTX expression on the development and prognosis of cancer is still controversial. Therefore, we combined all published studies on this issue to conduct this meta-analysis. In the present study, a total of 11 eligible studies with 1210 cancer patients, reporting six common cancer types, finally were included. Our results showed that high FTX expression was significantly associated with several clinicopathological characteristics, including lymph node metastasis in patients with CRC, GC, HCC, and RCC, distant metastasis in patients with CRC, GC, HCC, and OSC, bigger tumor size in patients with CRC, GC, HCC, OSC, and OSC, and later TNM/clinical stage in patients with CRC, GC, HCC, OSC, and glioma. However, there were no significant differences between the high and low FTX expression groups with respect to gender and tumor differentiation. On the other hand, the significant association between high FTX expression and shorter OS in patients with CRC, GC, HCC, OSC, and glioma, or shorter DFS in patients with HCC was observed. Moreover, further meta-analysis showed that high FTX expression could be an independent predictive marker for shorter OS in patients with CRC, HCC, OSC, and glioma. Taken together, these results suggest that FTX may be a candidate oncogene, and the overexpression of FTX is associated with a poor prognosis in common solid malignant tumors, such as CRC, HCC, OSC, and glioma.

The mechanisms of promoting cancer by FTX may be involved in the following aspects. FTX significantly promoted proliferation and invasion of glioma cells by negatively regulating miR-342-3p[24]. FTX exerted its oncogenic role in OSC via up-regulating the expression of TXNRD1 through sponging miR-320a[25]. FTX promoted proliferation and invasion of gastric cancer via miR-144/ZFX Axis[26]. FTX functioned as an oncogene to contribute to CRC progression by regulating miR-192-5p/EIF5A2 Axis[7].

Our results were similar to previous reports. For example, in the meta-analysis about lncRNA GHET-1, the results revealed that GHET-1 expression was closely correlated with tumor size, lymph node metastasis, distant metastasis and TNM stage, and that increased GHET-1 expression may be a potential prognostic biomarker in human cancers including HCC, GC, OSC, breast cancer (BC), bladder cancer (BLC), cervical cancer, non-small lung cancer (NSCLC), and esophageal cancer (ESCC)[27]. Zhu et al[28] conducted a meta-analysis which demonstrated that elevated lncRNA XIST expression predicted poor OS, poor DFS, larger tumor size, increased distant metastasis and advanced tumor stage, suggesting that high lncRNA XIST expression may serve as a novel biomarker for poor prognosis and metastasis in cancers (CRC, GC, HCC, ESCC, pancreatic cancer (PC), nasopharyngeal carcinoma (NPC), and glioma).

Nevertheless, several limitations existed in this meta-analysis. The main limitation of this study was a small number of included studies and patients (11 studies and 1210 patients), so further subgroup analysis was not able to be performed according to type of cancer, age group, and tumor site. Secondly, all of the studies were from China, so the results may only be applicable to the Chinese populations. Large-scale and well-designed studies are still needed to verify the clinical value of FTX in different ethnicities. Thirdly, some studies did not give HRs directly, an available software was used to calculate the HRs, which may have introduced errors. Fourthly, the included studies had different criteria for the classification of FTX expression.

Conclusions

FTX may be a potential oncogene, and high expression be associated with a poor prognosis in patients with CRC, HCC, OSC, and glioma. Additional high-quality studies involving large numbers of patients are needed to confirm the findings.

Abbreviations

HR: Hazard ratio; OR:Odds ratio; 95% CI: 95% confidence interval; qRT-PCR:Quantitative reverse transcription PCR; NA:Not available; OS:Overall survival; DFS:disease-free survival; PFS:progression-free survival; RFS:recurrence-free survival; CRC:colorectal cancer; HCC:hepatocellular carcinoma; GC:gastric cancer; RCC:renal cell carcinoma; OSC:osteosarcoma; ESCC:esophageal cancer; PC:pancreatic cancer; NPC:nasopharyngeal carcinoma; BC:breast cancer; BLC:bladder cancer; NSCLC:non-small lung cancer.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials
All data are included in this article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Idea and design: TSH, CWW. Data collection: CWW, LYT. Data analysis: ZCX, GLLZ. Manuscript writing: CWW. Manuscript revision: TSH, CWW. All authors read and approved the version of the manuscript to be published. All authors take responsibility for appropriate content.

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Tables

Table 1 Characteristics of studies included in the meta-analysis

| Study       | Year | Country | Cancer type | Detection method | Sample size | LncRNA FTX expression | Total | LNM | DM | HS | LD | Bigger TS | M | Total | LNM | DM | HS | LD | Bigger TS |
|-------------|------|---------|-------------|------------------|-------------|-----------------------|-------|-----|----|----|----|-----------|--|-------|-----|----|----|----|-----------|
| Zhao et al  | 2020 | China   | CRC         | qRT-PCR          | 30          | high                  | 15    | 9   | 11 | 10 | NA | 10        | 9 | 15    | 6   | 7  | 7  | NA | 6         |
| He et al    | 2017 | China   | RCC         | qRT-PCR          | 150         | high                  | 82    | 63  | NA | 65 | NA | 76        | 42 | 68    | 30  | NA | NA | 76 | 34        |
| Liu et al   | 2016 | China   | HCC         | qRT-PCR          | 129         | high                  | 64    | NA  | NA | 16 | 43 | 45        | 51 | 65    | NA  | 16 | 56 | 57 | NA        |
| Li et al    | 2018 | China   | OSC         | qRT-PCR          | 84          | high                  | 39    | NA  | 17 | 23 | NA | 25        | 22 | 45    | NA  | 9  | 14 | NA | 22        |
| Zhang et al | 2020 | China   | GC          | qRT-PCR          | 71          | high                  | 32    | 25  | NA | 26 | 19 | 17        | 17 | 39    | 21  | NA | 18 | 11 | 18        |
| Liang et al | 2020 | China   | glioma      | qRT-PCR          | 187         | high                  | 95    | NA  | NA | 50 | NA | 40        | 92 | NA    | NA  | 26 | NA | NA | NA        |
| Guo et al   | 2015 | China   | CRC         | qRT-PCR          | 187         | high                  | 75    | 46  | NA | 44 | 38 | NA        | 14 | 112   | 71  | NA | 60 | 51 | NA        |
| Jiang et al | 2019 | China   | GC          | qRT-PCR          | 93          | high                  | 48    | 34  | 15 | 36 | 27 | 35        | 31 | 45    | 26  | 4  | 23 | 6  | 14        |
| Li et al    | 2019 | China   | HCC         | qRT-PCR          | 73          | high                  | 37    | 18  | 18 | NA | 2  | 23        | 27 | 36    | 6   | 6  | NA | 12 | 21        |
| Yang et al  | 2018 | China   | CRC         | qRT-PCR          | 80          | high                  | 40    | 27  | 25 | 26 | 12 | 26        | 27 | 40    | 15  | 12 | 17 | 14 | 17        |
| Liu et al   | 2016 | China   | HCC         | RT-qPCR           | 126         | high                  | 65    | NA  | NA | 32 | 28 | 50        | 61 | NA    | NA  | 8  | 12 | 10 | NA        |

LNM: lymph node metastasis, DM: distant metastasis, HS: high TNM/clinical stage (III/IV), LD: low differentiation, Bigger TS: the bigger tumor size group, M: recurrence-free survival, PFS: progression-free survival, DFS: disease-free survival

Table 2 Survival data of studies included in the meta-analysis
| Study       | Year | Cancer type | Detection method | Sample size | Survival Information | HR statistic |
|------------|------|-------------|------------------|-------------|-----------------------|--------------|
|            |      |             |                  |             | Overall survival (OS) |              |
|            |      |             |                  |             | Univariate analysis   | Multivariate |
|            |      |             |                  |             | Pooled OR (95% CI)    | PHet         |
|            |      |             |                  |             | p Value               | Model used   |
| Liu et al  | 2016 | HCC         | qRT-PCR          | 129         | 0.59(0.34-1.03)       | NA           |
| Li et al   | 2018 | OSC         | qRT-PCR          | 84          | 2.636 (1.458-4.767)   | NA           |
| Zhang et al| 2020 | GC          | qRT-PCR          | 71          | 2.07 (1.33-3.24) (E)  | NA           |
| Liang et al| 2020 | glioma      | qRT-PCR          | 187         | 1.36(0.90-2.07) (E)   | 1.69 (1.15-2.49) (E) |
| Guo et al  | 2015 | CRC         | qRT-PCR          | 187         | 1.51 (0.98-2.32) (E)  | 6.323 (2.213-9.934) |
| Li et al   | 2019 | HCC         | qRT-PCR          | 73          | 12.456 (1.607-96.543) | 7.484 (3.398-16.486) |
| Yang et al | 2018 | CRC         | qRT-PCR          | 80          | 1.32 (0.80-2.17) (E)  | 6.411 (2.859-14.375) |
| Liu et al  | 2016 | HCC         | qRT-PCR          | 126         | 1.92 (1.23-2.92) (E)  | 2.08 (1.32-3.27) (E) |

HR statistic:
- Survival curve
- Data in paper
- Both of two

*a: recurrence-free survival; b: progression-free survival; c: disease-free survival*

**Table 3 LncRNA FTX clinicopathological features for cancers**

| Clinicopathological features | No. of studies | No. of patients | Pooled OR (95% CI) | PHet | I² (%) | p Value | Model used |
|------------------------------|----------------|-----------------|-------------------|------|--------|---------|------------|
| Gender                       | 11             | 1210            | 0.87 (0.68-1.12) | 0.555| 0      | 0.271   | Fixed      |
| Lymph node metastasis       | 7              | 684             | 2.47 (1.45-4.22) | 0.002| 59.5   | 0.001   | Random     |
| Distant metastasis          | 5              | 360             | 3.87 (2.38-6.30) | 0.973| 0      | 0.001   | Fixed      |
| Tumor size                  | 9              | 836             | 2.10 (1.15-3.85) | 0    | 72.5   | 0.016   | Random     |
| Differentiation             | 7              | 759             | 1.33 (0.53-3.33) | 0    | 86.2   | 0.546   | Random     |
| TNM/clinical stage          | 10             | 1137            | 2.38 (1.85-3.06) | 0.248| 21.2   | 0.001   | Fixed      |

**Figures**
Figure 1
Flow diagram of study.
Figure 2

Forest plot of studies evaluating the relationship between FTX expression and clinicopathological features. a. gender, b. lymph node metastasis, c. distant metastasis, d. tumor size, e. differentiation, f. TNM/clinical stage
Figure 3

Forest plot of studies evaluating the relationship between FTX expression and the survival rate. a. overall survival (OS) rate b. disease-free survival (DFS) rate c. independent predictive factor for OS
Figure 4

Begg's publication bias plots for FTX related studies. a. gender, b. lymph node metastasis, c. distant metastasis, d. tumor size, e. differentiation, f. TNM/clinical stage, g. overall survival (OS) rate, h. disease-free survival (DFS) rate, i. independent predictive factor for OS

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.doc