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Review

LncRNA ZEB1-AS1 expression in cancer prognosis: Review and meta-analysis

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ABSTRACTS

Backgrounds: Several studies have explored the prognostic value of long non-coding RNA ZEB1 antisense RNA 1 (lncRNA ZEB1-AS1) in various types of cancer. However, the role of lncRNA ZEB1-AS1 in cancer prognosis remains unclear. This study aimed to summarize the prognostic value of lncRNA ZEB1-AS1 in cancer.

Methods: PubMed, Web of Science, Embase and Cochrane Library were thoroughly searched. All relevant studies satisfying the inclusion criteria were enrolled. The endpoints used in this study included overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) and various clinical parameters.

Results: 11 studies containing 891 cancer patients were finally included into this study. The results showed that, compared to the patients with low expression of lncRNA ZEB1-AS1, the patients with high ZEB1-AS1expression tended to have shorter OS (HR = 1.59, 95%CI = 1.41–1.80, P < 0.01), DFS (HR = 2.70, 95%CI = 1.38–5.27, P < 0.01) and RFS (HR = 1.82, 95%CI = 1.37–2.42, P < 0.01). In addition, compared to patients with low ZEB1-AS1 expression, the patients with high ZEB1-AS1 expression were obviously associated with worse differentiation (P < 0.01), deeper invasion (P < 0.01), a more advanced clinical stage (P < 0.01), earlier organ metastasis (P < 0.01) and earlier lymph node metastasis (P < 0.01).

Conclusions: High expression of lncRNA ZEB1-AS1 was an unfavorable predictor of cancer prognosis in terms of OS, DFS, RFS, tumor differentiation, depth of invasion, clinical stage, organ metastasis and lymph node metastasis. Therefore, the expression of lncRNA ZEB1-AS1 might be used as a promising prognostic biomarker for cancer.

1. Introduction

Cancer has become a major public problem and has significantly increased the financial burden of the society and the families of cancer patients [1]. In recent years, the incidence of cancer has risen sharply due to aging of the overall population. It was estimated that 14.1 million new cancer cases and 8.2 million cancer related deaths occurred in 2012 worldwide [2]. Despite of great advancement in cancer diagnosis and treatment, the prognosis of many cancer patients remains poor [3]. In view of this situation, the identification of appropriate biomarkers to predict cancer prognosis has become a critical issue for cancer research [4–6].

Long non-coding RNAs (lncRNAs), which are transcripts of longer than 200 nucleotides, are important gene regulators due to their capabilities and complex functions in cellular biology [7–9]. Increasing evidence has indicated that lncRNAs play key roles in tumorigenesis as well as the invasion and metastasis of cancer [10, 11]. Recently, several lncRNAs, such as PCAT-1 [12], AFAP1-AS1 [13], CRNDE [14] and TUG1 [15], have been implicated in cancer prognosis. In particular, lncRNA ZEB1 antisense RNA1 (lncRNA ZEB1-AS1), a non-coding antisense transcript derived from the promoter of ZEB1, is dysregulated in several types of cancer [16]. Plenty of publications have explored the prognostic value of lncRNA ZEB1-AS1 in human cancer. However, the results obtained from these studies remain controversial [17–25]. For example, *Zhang* et al. analyzed 76 gastric cancer patients, and they found no association between the expression of lncRNA ZEB1-AS1 and the level of tumor differentiation (P = 0.13) [26]. Similar results were observed by *Gong* et al. in a study of 63 colorectal cancer patients (P = 0.09) [18]. Nevertheless, an obvious relationship between lncRNA ZEB1-AS1 expression and tumor differentiation was found in gastric

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cancer (P = 0.03) [21] and bladder cancer (P < 0.01) [19]. Therefore, this review and meta-analysis were performed to explore the prognostic value of lncRNA ZEB1-AS1 in various types of cancer.

2. Materials and methods

This study was performed in strict compliance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [27].

2.1. Literature search

PubMed (National Library of Medicine, Bethesda, Maryland, USA), Web of Science (Clarivate Analytics, Philadelphia, Pennsylvania, USA), Embase (Elsevier, Amsterdam, The Netherlands) and Cochrane Library (Cochrane Collaboration, London, UK) were thoroughly searched up to March 2, 2018. The following combinations of keywords were used in the search: ("long noncoding RNA ZEB1-AS1" OR "lncRNA ZEB1-AS1" OR "ZEB1-AS1" OR "ZEB1 antisense RNA 1") AND ("cancer" OR "tumor" OR "neoplasm"). The references of retrieved articles were also carefully checked to look for other relevant publications.

2.2. Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) containing randomized controlled trials (RCTs) or observational studies; (2) focusing on the prognostic value of lncRNA ZEB1-AS1 in cancer; (3) reporting overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) or other clinical parameters; (4) with sufficient data. The following papers were excluded from this study: letters, reviews, duplicate publications, cell experiments, animal experiments or papers with insufficient data.

2.3. Data extraction and quality assessment

The data extraction and quality assessment were independently completed by two authors of this study. Any disagreement in the above process was solved by discussing with a third author. The following information was extracted from each article included in this study: the name of the first author, the year of publication, the number of patients, the gender of the patients, detection method of lncRNA ZEB1-AS1 expression, cut-off value, prognostic parameters (e.g., OS, RFS or DFS), clinical parameters (e.g., tumor size, clinical stage, and metastasis), cancer type and the model used for analysis. Particularly, in terms of prognostic parameters (e.g., OS, RFS or DFS), the hazard ratio (HR) and its corresponding 95% confidence interval (CI) were directly extracted from the articles. If an article failed to report HR or its 95% CI, such information would be indirectly obtained as described by *Tierney* et al. [28]. In addition, the quality of included studies was evaluated by the Newcastle-Ottawa Scale (NOS) [29].

2.4. Statistical analysis

All analyses were conducted by Review Manager 5.3 (Cochrane Collaboration, London, UK) and Stata 12.0 software (StataCorp LLC, College Station, Texas, USA). For prognostic variables (e.g., OS), HR and its corresponding 95% CI were utilized to detect the overall effects. In terms of clinical parameters, such as age, gender, tumor size and differentiation, the odds ratio (OR) and its corresponding 95% CI were used. I^2 statistic was used to assess the inter-study heterogeneity. An I^2 value of ≤50% indicated no obvious heterogeneity among the included studies, and a fixed-effect model should be utilized under these conditions. Otherwise, a random-effect model should be used. A funnel plot was generated to detect the bias among the included studies. In particular, the publication bias in the meta-analysis of OS was also assessed by Begg's test. A sensitivity analysis was applied to check the robustness of results. Moreover, subgroup analyses of OS were performed. All P values were two sided and P < 0.05 indicated significance.

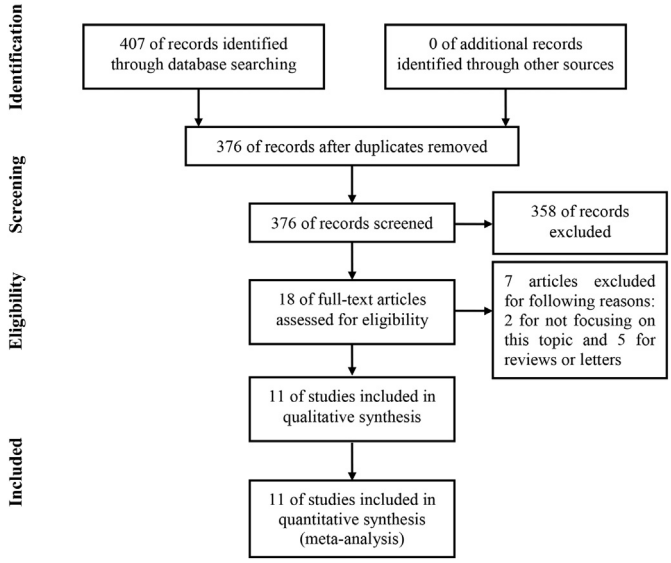

Fig. 1. Flowchart presenting the steps of literature search and selection.

3. Results

3.1. Literature search

As shown in Fig. 1, a total of 407 papers were initially retrieved. Among them, 376 papers were retained after excluding duplicate publications. Subsequently, 358 papers were directly excluded by reading the titles or abstracts. Therefore, the full-texts of 18 papers were reviewed, but 7 papers were excluded for the following reasons: 2 papers were excluded because their content was irrelevant, and 5 papers were excluded because they were review articles or letters. Ultimately, 11 studies were included in this review and meta-analysis [17–26, 30].

3.2. Demographics of included studies

As presented in Table 1, the 11 studies finally included into this study contained 891 cancer patients [17–26, 30]. The sample size in these articles ranged from 30 to 124. One study did not report the information of gender [20], whereas the percentage of males in other studies ranged from 50.00% to 72.73% [17–19, 21–26, 30]. The level of lncRNA ZEB1-AS1 expression in all studies was detected by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). With respect to cut-off values, 9 studies used the median level of ZEB1-AS1 expression as the cut-off value [17, 18, 20–23, 25, 26, 30], while the other 2 studies failed to report the details of cut-off values [19, 24]. In addition, there were 443 patients in the group of high ZEB1-AS1 expression and 448 patients in the group of low ZEB1-AS1 expression. In terms of disease outcomes, 9 studies reported OS [17, 18, 20–22, 24–26, 30], 1 study reported DFS [17], 3 studies reported RFS [18, 21, 22] and 10 studies reported clinical parameters [17–19, 21–26, 30]. In additions, 9 types of cancer were analyzed, including esophageal squamous cell carcinoma (ESCC) [17], hepatocellular carcinoma (HCC) [25], osteosarcoma [22], glioma [24], colorectal cancer [18, 30], bladder cancer [19], gastric cancer [21, 26], B-lymphoblastic leukemia (BLL) [20] and prostate cancer [23]. Regarding the analysis model of OS, multivariate analysis was used in 4 studies [17, 21, 24, 30], while univariate analysis was employed in 5 studies [18, 20, 22, 25, 26]. The adjusted variables in the multivariate analysis are listed in Supplementary Table 1. Moreover, the NOS score was > 6 in each of the included studies.