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Review

# The utility of long non-coding RNA ZEB1-AS1 as a prognostic biomarker in human solid tumors: A meta-analysis

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ABSTRACT

*Purpose:* This meta-analysis aims to assess the prognostic value of long non-coding RNA ZEB1-AS1 in human solid tumors.

*Methods:* We searched the available databases up to January 2018. Pooled hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were used to examine the prognostic impact of ZEB1-AS1 on patient survival.

*Results:* Eight eligible studies with a total of 586 patients were enrolled. A significant association was observed between ZEB1-AS1 overexpression and poor overall survival (OS; HR = 2.195, 95% CI: 1.749–2.755) as well as unfavorable recurrence-free survival (pooled HR = 2.205, 95% CI: 1.486–3.270), and no heterogeneity was found across these studies ($p = .962$, $I^2 = 0\%$). Subsequent subgroup analyses showed that cancer type, sample size, follow up months, and HR estimation method did not alter the significant prognostic value of ZEB1-AS1. ZEB1-AS1 expression was indicated to be an independent prognostic factor for tumor OS (pooled HR = 2.177, 95% CI:1.545–3.069). Furthermore, we found that increased ZEB1-AS1 expression was significantly associated with tumor stage [III-IV vs. I-II: odds ratio (OR) = 1.644, 95% CI: 1.201–2.249] and lymph node metastasis (Positive vs. Negative: OR = 2.413, 95% CI: 1.504–3.873).

*Conclusion:* High expression level of ZEB1-AS1 was associated with unfavorable survival outcome for cancer patients, and ZEB1-AS1 could be used as a prognostic predictor for cancers.

## 1. Introduction

Cancer is becoming a major public health problem worldwide and a leading cause of morbidity and mortality over past decades [1]. To date, the mechanisms of oncogenesis have not been completely elucidated, and the clinical outcome of cancer remains unsatisfactory [2]. However, widely used prognostic factors are still histological differentiation and tumor stage. Therefore, it is vital to identify novel potential biomarkers for predicting prognosis for cancer patients.

Long non-coding RNAs (lncRNAs), defined as transcripts > 200 nucleotides, evolve quite differently from protein-coding genes. Though initially claimed to be transcriptional "noise" or "dark matter" of the genome, lncRNAs have recently started to be considered important in gene regulatory network [3]. Emerging evidence implies that lncRNAs participate in gene expression regulation at different levels and play a crucial role in a wide range of biological pathways [4]. With the rapid development of effective high-throughput expression analysis technologies, an increasing number of lncRNAs have been proved cancer-related [5, 6]. Aberrant lncRNA expression is observed in tumorigenesis, and the expression patterns of some lncRNAs are highly correlated with tumor development, progression, invasion, and clinical outcomes, making lncRNAs potential biomarkers for cancer prognosis. Lu et al. found that the expression level of lncRNA NNT-AS1 is increased in HCC, and NNT-AS1 promotes HCC cells proliferation and invasion through sponging miR-363 [7]. Grelet et al. showed that lncRNA-PNUTS serves as a competitive sponge for miR-205, promoting epithelial–mesenchymal transition and tumor progression [8].

Zinc finger E-box-binding homeobox 1 antisense 1 (ZEB1-AS1) is an antisense lncRNA originated from the promoter region of ZEB1. In NCBI database, the full length of ZEB1-AS1 is 2568 nt, including two exons

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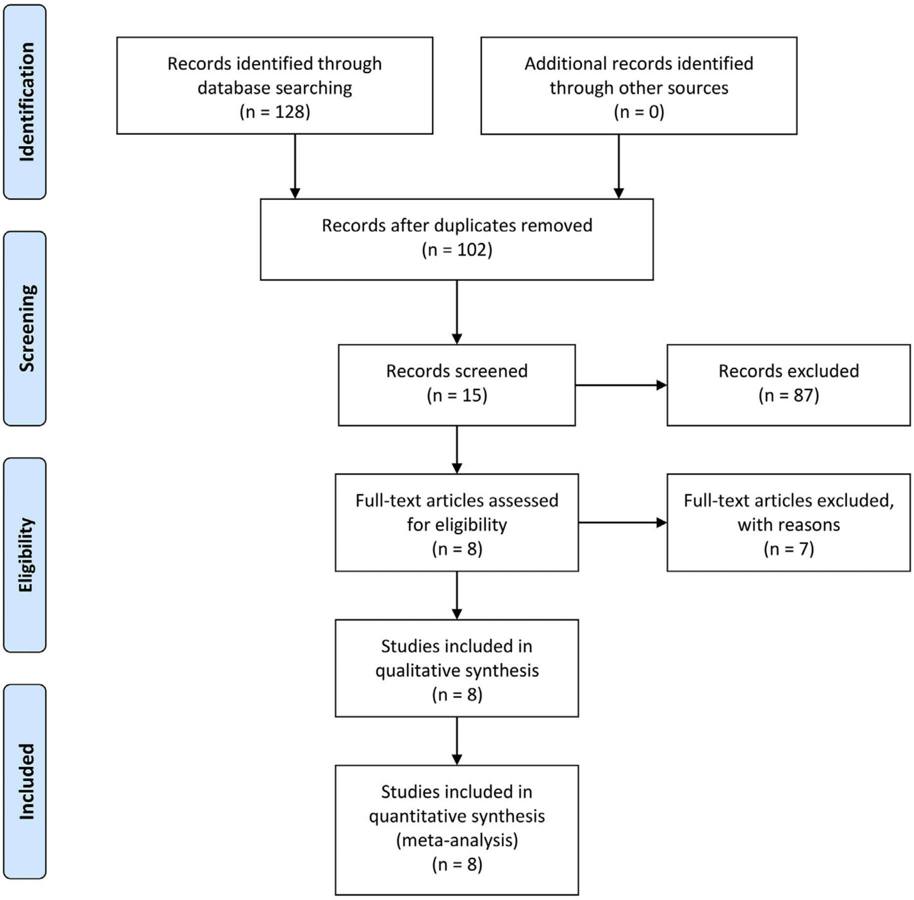

**Fig. 1.** Flow chart of the studies search and selection in this meta-analysis.

and one intron. It has been reported that ZEB1-AS1 is involved in gene expression modulation and contributes to the development of various human cancers, including gastric cancer [9], prostate cancer [10], non-small cell lung cancer [11], osteosarcoma [12], and hepatocellular carcinoma [13]. Several studies also demonstrated that ZEB1-AS1 promoted proliferation, migration, and epithelial to mesenchymal transition of cancer cells [10, 14, 15].

With an increasing number of studies casting light on the biological functions of ZEB1-AS1 in carcinogenesis, the clinical prognostic value of ZEB1-AS1 in human cancers has also been examined. However, previous studies on the relationship between ZEB1-AS1 and solid tumors are still inadequate due to insufficient sampling or methodological restrictions. To overcome these limitations, we comprehensively retrieved all pertinent literatures and performed the current study addressing the association of ZEB1-AS1 expression with solid tumor prognosis and clinicopathological characteristics. This current meta-analysis was aimed to further determine whether ZEB1-AS1 could serve as an effective prognostic biomarker in human solid tumors.

## 2. Materials and methods

### 2.1. Search strategy

In order to identify relevant published studies, electronic searches of PubMed, Web of Science, EMBASE, Cochrane Library, Google Scholar, Chinese Biological Medical Literature database (CBM), Chinese National Knowledge Infrastructure database (CNKI), and Wanfang database were done for the query “ZEB1-AS1” and “cancer or carcinoma or tumor or tumour or neoplasm or malignancy”. Additional studies were identified by a hand search of references of original or review articles on this topic. The literature search included all pertinent studies published until January 2018 for which an abstract or paper was available for review.

### 2.2. Inclusion criteria and exclusion criteria

Inclusion criteria for the meta-analysis were: (i) the study explored any type of solid tumors, (ii) the link between ZEB1-AS1 and clinical prognosis was assessed, (iii) the study provided available and usable data for estimating HRs and 95% CIs for survival outcomes. The exclusion criteria for articles included: (i) non-solid tumors, (ii) duplicate publications, (iii) animal studies, case reports, and review articles, (iv) studies without complete data.

### 2.3. Data extraction

Titles and abstracts of potentially relevant articles were screened by two independent investigators (Z.X.L. and C.Z.Q.) and full text manuscripts meeting initial screening criteria were obtained. The same investigators independently examined all full text articles for inclusion in the review; any discrepancies were discussed by the investigators. If they were unable to reach consensus, a third investigator (C.J.) was consulted. Standardized data extraction tables were created, and data extraction was completed by Z.X.L. and checked by M.J.D for accuracy. Information was extracted including the first author's name, year of publication, country, type of cancer, tumor stage, number of patients, cut-off value, ZEB1-AS1 detection method, preoperative treatment, follow up months, survival analysis and HRs with the corresponding 95% CIs. If HRs and their 95% CIs could not be acquired directly from publications, they were extracted from Kaplan-Meier survival curve using the Engauge Digitizer Version 4.1 [16]. The quality of literatures was evaluated according to the Newcastle-Ottawa Scale (NOS) [17],