Prognostic and clinicopathologic significance of long non-coding RNA opa-interacting protein 5-antisense RNA 1 in multiple human cancers

Xiaolei Ren*, Jiuyu He*, Lin Qi, Shuangqing Li, Chenghao Zhang, Zhixi Duan, Wanchun Wang, Chao Tu, and Zhihong Li*

*Department of Orthopedics, The Second Xiangya Hospital, Central South University, Changsha, People’s Republic of China; **Department of Geriatrics, The Second Xiangya Hospital, Central South University, Changsha, People’s Republic of China; *** Hunan Key Laboratory of Tumor Models and Individualized Medicine, The Second Xiangya Hospital, Central South University, Changsha, People’s Republic of China

ABSTRACT

Background: OIP5-AS1 has been reported to be aberrantly expressed in multiple cancers and associated with clinical outcomes. We conducted this study to assess the generalized prognostic value of OIP5-AS1 in cancers.

Methods: PubMed, Web of science, and Cochrane Library were searched for eligible studies. Hazards ratios (HRs) or odd ratios (ORs) with 95% confidence intervals (CIs) were pooled to estimate the prognostic value of OIP5-AS1 in cancers, including overall survival (OS), age, gender, tumor size, clinical stage, and lymph node metastasis (LNM). Publication bias was measured by Begg’s test and funnel plot. Sensitivity analysis were used to detect the stability of pooled results.

Results: Overall, eleven studies containing 713 patients were eventually enrolled. The pooled results showed that high OIP5-AS1 expression was correlated with shorter OS (HR = 0.48, 95%CI: 0.35–0.64), regardless of the sample size, tumor type and follow-up time. Furthermore, elevated expression of OIP5-AS1 indicated advanced clinical stage (OR = 2.12, 95% CI: 1.06–4.23), but not associated with age, gender, tumor size and LNM. No publication bias was detected.

Conclusion: High expression of lncRNA OIP5-AS1 may predict a poor OS and advanced clinical stage, implicating that OIP5-AS1 may be a possible prognostic factor in cancers.

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Introduction

Cancer has been posed a threat to human health with high morbidity and mortality, and the global social-economic burden attributed to cancer is still increasing. It was reported that the number of new cancer patients and cancer-related deaths worldwide were 14.1 million and 8.2 million, respectively in 2012, and rose to 18.1 million and 9.6 million in 2018 [1,2]. Moreover, it is projected that the new cancer cases per year will be 26 million by 2030 [3]. Over the past few decades, despite tremendous advancement been acquired in surgery, radiotherapy, chemotherapy, targeted therapy, and even immunotherapy, the five-year survival rate of cancer is still relatively low and the overall prognosis remains unsatisfactory [4]. One possible reason for this dilemma is the shortage of effective predictive factors to identify high-risky patients during early stage, and most cancer cases are diagnosed with locally advanced or metastatic stage, and consequently suffered from worse clinical outcomes [5].

Long noncoding RNAs (lncRNAs) are classified into a type of noncoding RNA transcripts with length of more than 200 nucleotides (nt) [6]. LncRNAs could regulate a variety of cellular processes including proliferation, apoptosis, invasion, and angiogenesis and therefore exert a pivotal effect in aging, degeneration and carcinogenesis [7,8]. Of late, emerging evidence showed that lncRNAs (such as CASC2, ZEB1-AS1, XIST, and HOXA11-AS) were involved in regulation of cancer related genes and signalling pathways [9–12]. Meanwhile, numerous lncRNAs have been proved to have potential application as diagnostic biomarkers and therapeutic targets in human cancers [13–16].

LncRNA opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) is a newly identified cytoplasmic lncRNA and was first known as cyrono in zebrafish, implicating a critical role in early development of central nervous system [17,18]. Kim et al. initially reported that OIP5-AS1 could act as a competing endogenous RNA (ceRNA) for RNA-binding protein (RBP) HuR and hampered HuR-induced proliferative phenotypes. Meanwhile, OIP5-AS1 could also impair GAK expression and thereby lead to suppression of cell division and proliferation by control mitosis [17,19]. Subsequently, lncRNA OIP5-AS1 has been demonstrated to be involved in regulation of apoptosis, metastasis, epithelial-mesenchymal transition (EMT) progress, cancer stemness, chem- and radio-resistance,
indicating an important application of OIP5-AS1 in cancers [20–26].

Recently, emerging evidences have shown that the OIP5-AS1 level was abnormally expressed among human cancers and may serve as possible prognostic marker for cancers. Specifically, most investigations demonstrated that OIP5-AS1 expression was dramatically elevated in tumor tissues or cell lines, such as osteosarcoma [25–27], lung adenocarcinoma [5,28], bladder cancer [29], hepatoblastoma [21], cervical cancer [30], breast cancer [31], glioma [32,33], malignant melanoma [34], and undifferentiated oral tumor [20]. While, other researchers found that OIP5-AS1 was downregulated and may serve as tumor suppressor in certain cancers, including non-small cell lung cancer (NSCLC), multiple myeloma, and colorectal cancer (CRC) [23,24,35,36]. Given the discrepancies existed among those aforementioned studies and relatively small number of cases in each study, the role of OIP5-AS1 in clinical practice is still unavailable. Accordingly, we performed this comprehensive study with all related eligible studies and calculated the pooled results to further address the feasibility of OIP5-AS1 as a noninvasive predictor in cancers.

Materials and methods

Publication search strategy

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement as described previously [37]. Potential eligible literature was thoroughly searched in related databases, including PubMed, Web of science, and Cochrane Library from inception to April 1, 2019. The following keywords were used as searched terms in variable combinations: ("long noncoding RNA" OR "lncRNA"), ("OIP5-AS1" OR "opa-interacting protein 5 antisense transcript 1"), ("cancer" OR "carcinoma" OR "tumor" OR "sarcoma"), AND ("clinical outcome" OR "prognosis" OR "survival"). An additional manual search of references lists of enrolled literature was also screened for pertinent articles.
Inclusion and exclusion criteria

All included studies were evaluated by two independent authors, and discrepancies were resolved by the third investigator. Rigorous inclusion and exclusion criteria were adopted in the current study. Specifically, inclusion criteria were as following: (1) articles assessing the prognostic role of OIP5-AS1 in any type of human cancers; (2) clinical-pathological characteristics including OS were reported; (3) patients were categorized according to OIP5-AS1 expression levels; (4) data could be extracted directly or measured indirectly through the survival curve;

Meanwhile, studies were excluded if they were: (1) nonhuman studies; (2) reviews, editorials, correspondence or case reports without original data; (3) data not available; (4) duplicate publications.

Data extraction and quality assessment

Extracted information was as following: first author, publication year, country, tumor type, sample size, follow-up months, detection method, and survival analysis. Data were directly extracted from the enrolled studies. If only survival curves were provided in certain studies, the survival rates were indirectly extracted from the plots using Engauge Digitiser (Version 4.1) [38]. The quality of eligible studies was evaluated by Newcastle-Ottawa Scale (NOS).

Validation of data in the cancer genome atlas (TCGA)

Gene Expression Profiling Interactive Analysis (GEPIA) was adopted to further validate the differential expression pattern of OIP5-AS1 between tumor and normal samples among multiple cancers in TCGA dataset. In addition, the association between OIP5-AS1 expression and OS and disease-free survival (DFS) were plotted as Kaplan–Meier (K–M) curve as previously described [39].

Data synthesis and statistical analysis

All the analyses were carried out by using RevMan (Version 5.3) and Stata (Version 13.0). The heterogeneity among all studies was measured by Q-test and $I^2$ statistics. Fixed-effect model was applied to analyze data with low heterogeneity ($I^2 \leq 50\%$ or $p \geq .05$). Otherwise, a random-effect model was employed for analysis when heterogeneity was high. Begg’s test and funnel plot were used for detection of publication bias. Besides, sensitivity analysis was utilized by omitting the study one by one to evaluate the credibility of pooled results.

Results

Selection and description of included studies

The initial literature research of articles containing potentially relevant IncRNA OIP5-AS1 and cancer data in PubMed ($n = 34$), Web of science ($n = 28$), and Cochrane Library identified 62 publications (Figure 1). 26 duplications were initially excluded and the remained studies were screened for titles, and abstracts. Eleven studies were further excluded. Among them, two were reviews or abstracts without original data. Five were data from database and four were studies irrelevant with cancer. Additionally, 14 studies were excluded after full-text screening, mainly owing to data without clinical analysis or unable to extract. Finally, a total of 11 eligible studies met the selection criteria and exhibited OS with available hazard ratios (HRs) and 95% confidence intervals (CIs), or other clinical characteristics including age, gender, tumor size, clinical stages, and lymph node metastasis (LNMs).

The included investigations were published between 2018 and 2019. Moreover, most of them were performed in China except one in Iran and one in India. All studies containing 713 patients and eight cancerous types, including osteosarcoma, lung cancer, bladder cancer, cervical cancer, breast cancer, oral cancer, melanoma and hepatoblastoma. OIP5-AS1 expression was detected by qRT-PCR among all studies.
from 5 to 8. The details of included studies were characterized in Table 1.

**Association with prognostic significance and OIP5-AS1 expression levels**

Eight included studies were analyzed in pooled OS analysis through the OIP5-AS1 low expression versus high expression. The pooled HR and 95% CI was 0.48 (0.35–0.64) under the fixed effect model ($I^2 = 22.2\%$, $p = .253$), indicating the high OIP5-AS1 expression predicted unfavorable OS (Table 2). Besides, three subgroup analyses were further performed by dividing the studies based on the sample size (<80 and ≥80), cancer type (osteosarcoma, lung cancer, and others) and follow-up months (≥60 and <60). The stratified analysis revealed that all the subgroup did not alter the prognostic value of OIP5-AS1 in cancer patients (Figure 2(A–C)). The pooled HRs and 95% CIs were extracted and the details were presented in Table 2.

**Association between OIP5-AS1 expression levels and other clinical characteristics**

Five items of clinical characteristics including age, gender, tumor size, clinical stages and LNM were analyzed to explore their association with OIP5-AS1 among selected studies. For age, three subgroup analysis were performed according to the different cut-off values (Odds ratio, OR = 0.96, 95% CI: 0.60–1.55) for <50 vs. ≥50 and (OR = 1.15, 95% CI: 0.55–2.42) for <60 vs. ≥60; (OR = 1.63, 95% CI: 0.51–5.18) for <18 vs. ≥18) (Figure 3(A)). However, the summarized results revealed that there were no significant evidence between OIP5-AS1 and age. Likewise, the similar relevance was found between OIP5-AS1 and gender (OR = 1.22, 95% CI: 0.77–1.94) (Figure 3(B)) as well as tumor size (OR = 1.84, 95% CI: 0.82–4.17) (Figure 3(C)). Furthermore, seven studies were included to analyze the association between OIP5-AS1 expression and clinical stages (Figure 3(D)). Of note, the pooled results demonstrated that high expression level of OIP5-AS1 predicted advanced clinical stage (OR = 2.12, 95% CI: 1.06–4.23). In terms of LNM, only three studies were included, and the pooled OR and 95% CI were 2.49 (0.87–7.15), which suggested that OIP5-AS1 expression was not correlated with risk of LNM (Figure 3(E)). Whereas, more studies is needed to confirm the relevance among the OIP5-AS1 expression and all the clinical characteristics. The pooled ORs with corresponding 95% CIs and heterogeneity were summarized in Table 3.

**Evaluation of publication bias and sensitivity analysis for OS**

Funnel plots for OS illustrated symmetrical distribution, implicating that there was no obvious publication bias (Figure 4). Moreover, Begg’s and Egger’s test ($p = .711$ and $p = .19$) also showed no evidence of publication bias in the multivariate analysis of OS. Sensitivity analysis revealed that the pooled result was stable (Figure 5).

**Correlation between OIP5-AS1 expression and prognostic features in TCGA pan-cancer dataset**

TCGA pan-cancer dataset was explored to further validate the correlation between the OIP5-AS1 expression and
prognostic features in different types of cancers. Aberrant expression levels of OIP5-AS1 between cancerous and normal tissue were found in sarcoma (SARC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ), and liver hepatocellular carcinoma (LIHC) (Figure 6(A,B)). In addition, associations between OIP5-AS1 expression and OS and disease-free survival (DFS)

Figure 3. Association between OIP5-AS1 expression and other clinical parameters. Forest plots exhibit the association between OIP5-AS1 expression levels and other clinical features, including age (A), gender (B), tumor size (C), clinical stages (D) and lymph node metastasis (E).
were investigated and plotted by using K–M curve, in which showed that high OIP5-AS1 expression was significantly associated with worse OS ($p = .0033$) (Figure 6(C)), but not DFS ($p = .43$) (Figure 6(D)).

**Discussion**

Recently, IncRNA has been shown to participate in the initiation, development and progression in different cancers and has raised researchers’ interest in last consecutive years. Among them, some IncRNAs including CCAT2, SNHG16, and GIHC, could function as tumor oncogenes and facilitate tumorigenesis or tumor progression [40–42], while other IncRNAs such as BLACAT1, NORAD, NEF are well established as tumor suppressors [43–45].

OIP5-AS1 is a novel identified IncRNA transcript located on chromosome 15q15.1 with 1894 nt in length, and is abundantly expressed in the cytoplasm [17]. OIP5-AS1 was discovered in multiple carcinomas, and considered as a cancer-associated IncRNA. In osteosarcoma, high expression of OIP5-AS1 was closely associated with patients’ poor prognosis. Furthermore, Dai et al. found that mechanistically silenced OIP5-AS1 could repress cell proliferation, promote apoptosis, and induce G0/G1 cycle arrest both in vitro and in vivo [26,27]. Finally, Song et al. reported that OIP5-AS1 was notably overexpressed in chemo-resistant osteosarcoma cell lines, and knockdown of OIP5-AS1 could alleviate chemoresistance by downregulation of multiple drug resistance-related factors [25,26]. Besides, two studies conducted in China demonstrated that OIP5-AS1 expression was significantly upregulated and associated with tumor size and tumor growth speed in lung adenocarcinoma and squamous cell lung cancer [5,28]. On the contrary, Esfandi et al. showed that OIP5-AS1 expression was obviously downregulated in NSCLC in Iranian patients [35]. In cervical cancers, clinical study revealed that enhanced OIP5-AS1 expression was closely correlated with advanced clinical stage, LNM and poor OS. Consistently, function assay showed that overexpression of OIP5-AS1 promoted cell viability, colony formation, migration and invasion in vitro [30,46]. Arunkumar et al. showed that OIP5-AS1 overexpression was strongly correlated with enhanced cancer stemness and poor clinical outcome in undifferentiated oral tumors [20]. Moreover, knockdown of OIP5-AS1 also displayed oncogenic functions in breast cancer, glioma, bladder cancer and hepatoblastoma, as resulted in inhibition of cell viability, proliferation, metastasis and EMT, induced cell cycle arrest and apoptosis, leading to tumor regression and extended survival [21,29,31,33]. By contrast, Zou et al. reported that OIP5-AS1 expression was reduced in radio-resistant CRC cell lines when compared with parental cells [24]. Additionally, Yang et al. showed the evidence that loss of OIP5-AS1 function facilitate cell proliferation, cycle progression and suppression of apoptosis in multiple myeloma [23].

However, results from above-mentioned studies should be interpreted with caution due to the limited sample size and discrete outcomes. Thus a meta-analysis with all eligible studies is warranted. To our best of knowledge, this study was the first meta-analysis to elaborate the prognostic and clinicopathologic significance of OIP5-AS1 in human cancers. The pooled results revealed that promoted OIP5-AS1 expression was remarkably related with poor OS. Subgroup analysis by sample size, tumor type or follow-up time did not alter the
predictive value of OIP5-AS1 on OS. Moreover, OIP5-AS1 expression levels were significantly correlated with advanced clinical stage, rather than age, gender, and tumor size. Meanwhile, only three studies reported the role of OIP5-AS1 in LNM and the pooled association was not significant.

Furthermore, the sensitivity analysis and publication bias assessment indicated that our meta-analysis was credible. The molecular regulation involved in the cancer development may further elucidate the underlying mechanisms of interaction between altered OIP5-AS1 levels and poor clinical outcomes.

**Figure 6.** The expression pattern of OIP5-AS1 in cancers and prognostic value of OIP5-AS1 on clinical outcomes in TCGA pan-cancer dataset. The box plots showed the expression pattern of OIP5-AS1 in cancerous tissues and normal tissues (A,B). The Kaplan Meier-plotters revealed the association between OIP5-AS1 expression levels and overall survival (C)/disease-free survival (D) in TCGA pan-cancer dataset.
outcomes (Table 4). It has been well-established that antisense transcript involved in transcriptional regulation of the expression of corresponding gene [10]. In a study by Wang et al., OIP5-AS1 expression was positively correlated with OIP5 expression in bladder cancer tissues. Consistently, in vitro assay showed that downregulation of OIP5-AS1 significantly decrease both mRNA and protein levels of OIP5 [29]. Another underlying regulatory mechanism for IncRNA is the potential function as ceRNA to sponge miRNA, and subsequently modulate target genes. For instance, Deng et al. found that OIP5-AS1 could sponge miR-448 and thereby target and affect the expression of Bcl-2 in lung adenocarcinoma [5]. Meanwhile, Zhang et al. showed that knockdown of OIP5-AS1 could upregulate miR-186a-5p and downregulate target gene-ZEB1 in hepatoblastoma [21]. Another study by Zou et al. demonstrated that OIP5-AS1 could regulate DYRK1A gene expression through miR-369-3p [24]. More recently, Wang et al. reported that overexpression of OIP5-AS1 interacted with miR-378a-3p, and subsequently strongly upregulated CDK4/CDK6 expression, resulting in oncogenic phenotype in lung cancer [28]. Moreover, OIP5-AS1 was found to be involved in pivotal signaling pathways in cancers. For example, knockdown of OIP5-AS1 could suppress PI3K/AKT/mTOR pathway in osteosarcoma [26]. Whereas, OIP5-AS1 insufficiency could activate PTEN/PI3K/AKT pathway in multiple myeloma [23].

It should be noted that there are still several potential limitations worth considering in our study. Firstly, only eleven studies were enrolled, and only eight studies on OS were included in this meta-analysis. Therefore, the total sample size was still comparatively small, and may lead to possible publication bias. Secondly, all selected studies were from Asia, including nine from China, one from India and one from Iran, therefore the results should be interpreted with caution and need further validation in other ethnic populations. Thirdly, there was a lack of sufficient studies concerning other prognostic markers including DFS and distant metastasis. Finally, some HRs with corresponding 95%CIs were measured from K–M curves, which may introduce possible bias.

In conclusion, the high expression of OIP5-AS1 is markedly correlated with unfavorable OS outcome and advanced clinical stage, implicating that OIP5-AS1 may be a novel biomarker in predicting clinical outcomes in several human cancers. However, additional multi-center studies with large sample size are still in need to validate the results in this study.

Disclosure statement
The authors declare no conflicts of interest in this work.

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