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Review Article

Elevated expression of long noncoding RNA UCA1 can predict a poor prognosis: a meta-analysis

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Abstract: Background: UCA1 (Urothelial cancer associated 1), a long non-coding RNA (lncRNA), has been reported to be aberrantly regulated in a wide range of cancers. This meta-analysis was performed to explore the potential value of UCA1 as a biomarker for cancer prognosis. Methods: We searched the electronic databases PubMed and Web of Science (up to Jan 20, 2016) in attention to collect all relevant researches to identify the association of lncRNA UCA1 with overall survival (OS) and lymph node metastasis (LNM). Results: Our findings revealed that high levels of UCA1 expression could predict poor OS in multiple cancers (pooled HR: 1.719, 95% CI: 1.429-2.066, $P<0.001$). Subgroup analyses by cancer type and survival analysis indicated that UCA1 had a reliable prognostic value with multivariate analysis. However, we could not draw a definite conclusion that there's significant association between UCA1 expression and lymph node metastasis (pooled OR: 1.81, 95% CI: 0.95-3.44, $P=0.070$) owing to the limited size of samples. Conclusions: This meta-analysis showed that overexpression of UCA1 might potentially serve as a reliable biomarker for poor prognosis in different types of cancers.

Keywords: UCA1, lncRNA, metastasis, prognosis, survival, meta-analysis

Introduction

LncRNAs (non-coding RNAs >200 nucleotides) are a class of RNAs lacking an open reading frame. They are evolutionarily conserved and aberrantly expressed under different pathophysiological conditions [1, 2]. Moreover, recent studies have confirmed that these kinds of RNAs are critical to a wide range of cellular processes, such as cell proliferation, invasion and metastasis [3]. Consequently, a large number of researches were conducted to identified the associations between lncRNAs and different types of cancers, such as lung, prostate, bladder, kidney, gastric cancer and so on [4-6]. The distinctive expression profiles of lncRNAs in various cancers indicated this class of molecules can be used for tumor diagnosis and prognosis [7-9].

Urothelial carcinoma-associated 1 (UCA1) is a lncRNA isolated from transitional cell carcinoma (TCC) cell lines, and cloned full-length cDNA of UCA1 gene is 1442 bp. Further researches identified that UCA1 was significantly overexpressed in transitional cell carcinoma (TCC), which promoted tumorigenic potential of TCC, and this difference could be used as a biomarker in the diagnosis and prognosis of bladder cancer [10, 11]. Now elevated expression of UCA1 has been observed in various tumors [12-20]. Therefore, UCA1 might be feasible as a prognostic biomarker for multiple cancers. To explore the correlation of UCA1 with tumor prognosis and metastasis, we conducted this quantitative meta-analysis.

Materials

Search strategy and selection criteria

We searched the electronic databases PubMed and Web of Science (up to Jan 20, 2016). The following search terms were used: "UCA1" or "Urothelial carcinoma-associated 1" and "cancer" or "tumor" or "neoplasm". This meta-analysis collected all relevant researches and explored the association of lncRNA UCA1 with

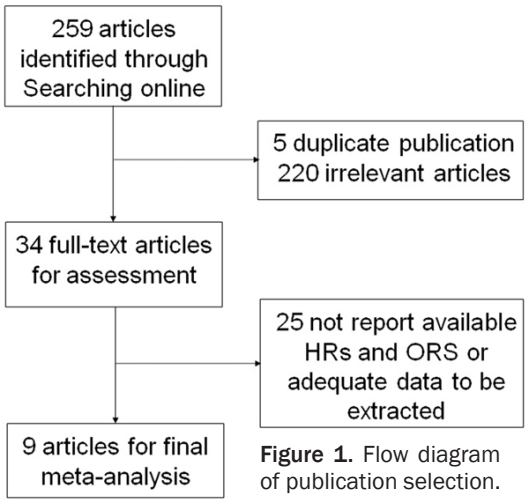

Figure 1. Flow diagram of publication selection.

overall survival (OS) and lymph node metastasis (LNM). Nine studies were applicable for analysis, which included 852 patients. Inclusion criteria were the following: (1) articles investigating the relation of UCA1 and cancer patients; (2) the expression levels of UCA1 in primary tumor tissues were measured; (3) patients were divided into high and low expression groups; (4) relevant clinicopathologic characteristics were described. Exclusion criteria were the following: (1) editorials, letters, expert opinions, reviews and case reports. (2) studies without usable data; (3) duplicate publications.

Data extraction

Tao Chen and Peng Yang extracted data independently from the feasible studies, and disagreements were resolved by discussion with a third investigator. The following information was recorded: the first author, year of publication, country, number of patients, tumor type, detection method of UCA1, cut-off values, survival analysis method, the sources of HRs (95% CI), number of high UCA1 expression group and low expression group, number of patients with LNM in each group. In one study, we extracted the relevant numerical value to extrapolate HRs with their 95% CIs from the Kaplan-Meier survival curve using Engauge Digitizer version 4.1 [21], and others' HRs could be extracted directly from data in the text.

Statistical analysis

The effect of UCA1 on survival outcome was evaluated by the HRs (95% CIs), and the relationship between UCA1 and LNM was presented as the ORs (95% CIs). The I^2 statistic was used to assess statistical heterogeneity among studies. The random-effects model was used if there was significant heterogeneity between studies (I^2>50% or P<0.05). Otherwise, fixed-effects model was chosen [22, 23]. Subgroup analysis was conducted with stratification by cancer type and survival analysis. We also performed sensitivity analysis to evaluate the stability of the results. The presence of publication bias was estimated by using funnel plots, Begg's test and Egger's test (P<0.05 represents significant) [24]. Statistical analyses of HRs for OS, and the odds ratios for LNM were calculated by Stata 12.0 (Stata Corporation, College Station, Texas, USA).

Results

Characteristics of eligible studies

A total of 259 articles were obtained by searching from PubMed and Web of Science databases. Out of these, 225 articles were excluded due to duplicate publications and irrelevant contents. After full-text reading remaining 34 articles, another 25 articles lacking available HRs and ORs (95% CI) or adequate data were excluded. Finally, 9 articles were included in the meta-analysis [12-20]. **Figure 1** showed the flow diagram of the literature research process. The main characteristics were summarized in **Table 1**. Among these 9 studies, all of them came from China. Six different types of cancers were evaluated, including 2 non-small cell lung cancer (NSCLC), 2 gastric cancer (GC), 2 hepatocellular carcinoma (HCC), 1 esophageal squamous cell carcinoma (ESCC), 1 colorectal cancer (CRC) and 1 prostate cancer (PC). All the diagnoses of LMN were based on pathology examination. In these studies, three methods were used to classify the low and high groups: (1) the level of UCA1 expression measured by qRT-PCR was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the cut-off value was mean value of UCA1 levels. (2) the level of UCA1 expression measured by qRT-PCR was normalized to β-actin, and the cut-off value was in relation to the Youden index. (3) the level of UCA1 expression measured by qRT-PCR was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and the cut-off value was median value of UCA1 levels. HRs (95% CIs) were directly extracted from 7 studies, while 1 study was calculated from survival curves.

Table 1. Characteristics of UCA1 studies included in the meta-analysis

First author	Year	Country	Cancer type	Total number	UCA1 expression				UCA1 detection method	Cut-off	Outcome	Survival analysis	HR estimate
					High with LMN	High without LNM	Low with LMN	Low without LNM					
Ma [13]	2014	China	ESCC	90	22	19	12	37	qRT-PCR	Mean	OS	Multivariate, univariate	Reported
HAN [17]	2014	China	CRC	80	17	20	18	25	qRT-PCR	Mean	-	-	-
Chen [16]	2015	China	NSCLC	60	26	10	8	16	qRT-PCR	Median	OS	Multivariate, univariate	Reported
Zheng [19]	2015	China	GC	112	35	21	37	19	qRT-PCR	Mean	OS	Multivariate, univariate	Reported
Nie [18]	2015	China	NSCLC	112	14	25	21	52	qRT-PCR	Youden index	OS	Multivariate, univariate	Reported
Gao [12]	2015	China	GC	20	-	-	-	-	qRT-PCR	Median	OS	Multivariate, univariate	Reported
Wang [15]	2015	China	HCC	98	-	-	-	-	qRT-PCR	Median	OS	Multivariate, univariate	Reported
Na [14]	2015	China	PC	40	-	-	-	-	qRT-PCR	Median	OS	Univariate	Survival curve
Yang [20]	2015	China	HCC	240	-	-	-	-	qRT-PCR	Median	OS	Univariate	Reported

HR: hazard ratio; OS: overall survival; ESCC: esophageal squamous cell carcinoma; CRC: colorectal cancer; NSCLC: non-small cell lung cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; PC: prostate cancer; LNM: lymph node metastasis.

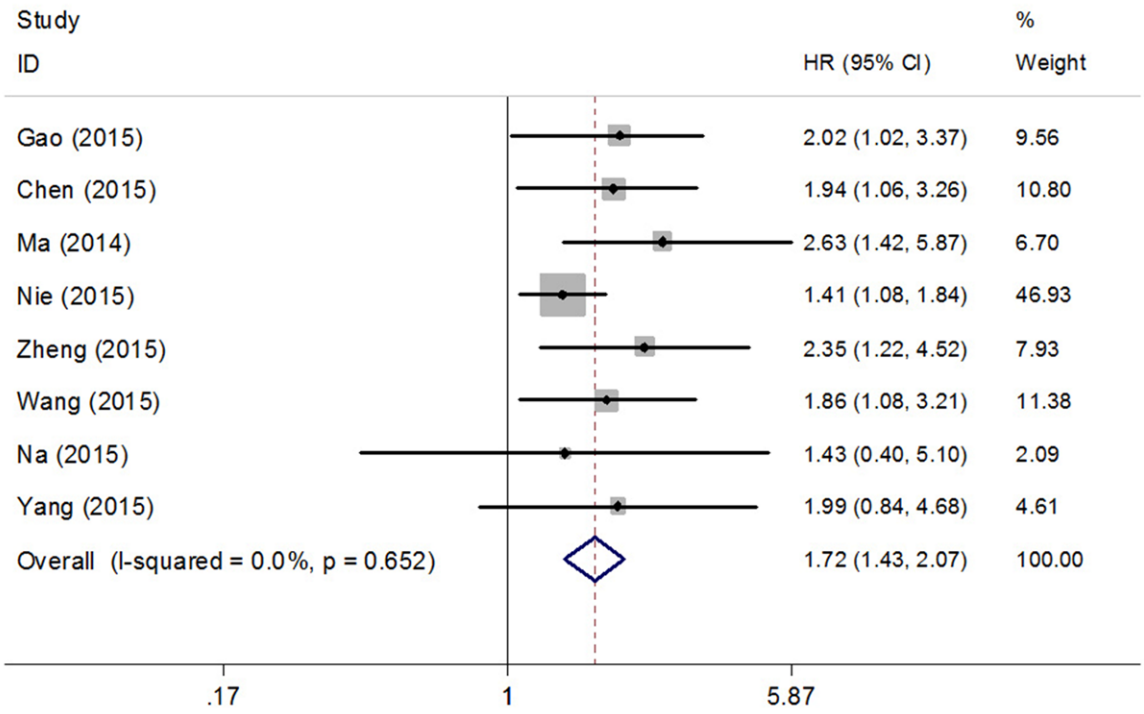

Figure 2. Forest plots for relationship between UCA1 expression and OS.

Relationship between UCA1 and OS

To investigate the relationship between UCA1 expression and cancer progression, 772 patients from 8 studies were included in this meta-analysis of overall survival. The result revealed that high level of UCA1 expression could predict poor OS in multiple cancers (pooled HR: 1.719, 95% CI: 1.429-2.066, P<0.001, **Figure 2**) by adopting a fixed-effects model without significant heterogeneity (I^2<0.1%, P=0.652).

Subsequently, we performed subgroup analysis based on cancer type and survival analysis to evaluate the association between UCA1 expression and OS (**Figures 3** and **4**). We examined the effect of the cancer type among the studies and found that UCA1 overexpression was related to the worse OS both in digestive system (HR=2.119, 95% CI: 1.585-2.834, P<0.001; I^2<0.1%, P=0.949) and nondigestive system (HR=1.493, 95% CI: 1.177-1.894, P=0.001; I^2<0.1%, P=0.604). Next, we examined the effect of analysis model and found that univariate analysis had no relevance to OS in patients (HR=1.792, 95% CI: 0.880-3.651, P=0.108; I^2<0.1%, P=0.675), and significant correlation was observed in subgroup of multivariate analysis (HR=1.713, 95% CI: 1.416-2.073, P<0.001; I^2<0.1%, P=0.432). Fixed-effects model was used for these two subgroup analyses considering that no significant heterogeneity between subgroups and within subgroups was observed.

Relationship between UCA1 and lymph node metastasis

Five studies reported the number of patients with LNM based on different UCA1 expression levels in a total of 454 individuals. The random-effects model was adopted for the significant heterogeneity (I^2=61.5%, P=0.035, **Figure 5**). Analysis showed a pooled OR of 1.810 with 95% CI 0.954–3.436 (P=0.070). Considering the small sample size, there's no sufficient evidence to prove that UCA1 expression was correlated to LNM.

Sensitivity analysis and publication bias

Sensitivity analysis indicated that the association between UCA1 expression and OS was not significantly influenced by omitting any individual article (**Figure 6**). Visual inspection of the Begg's funnel plot indicated an asymmetry (**Figure 7**). The P-value of Egger's test was

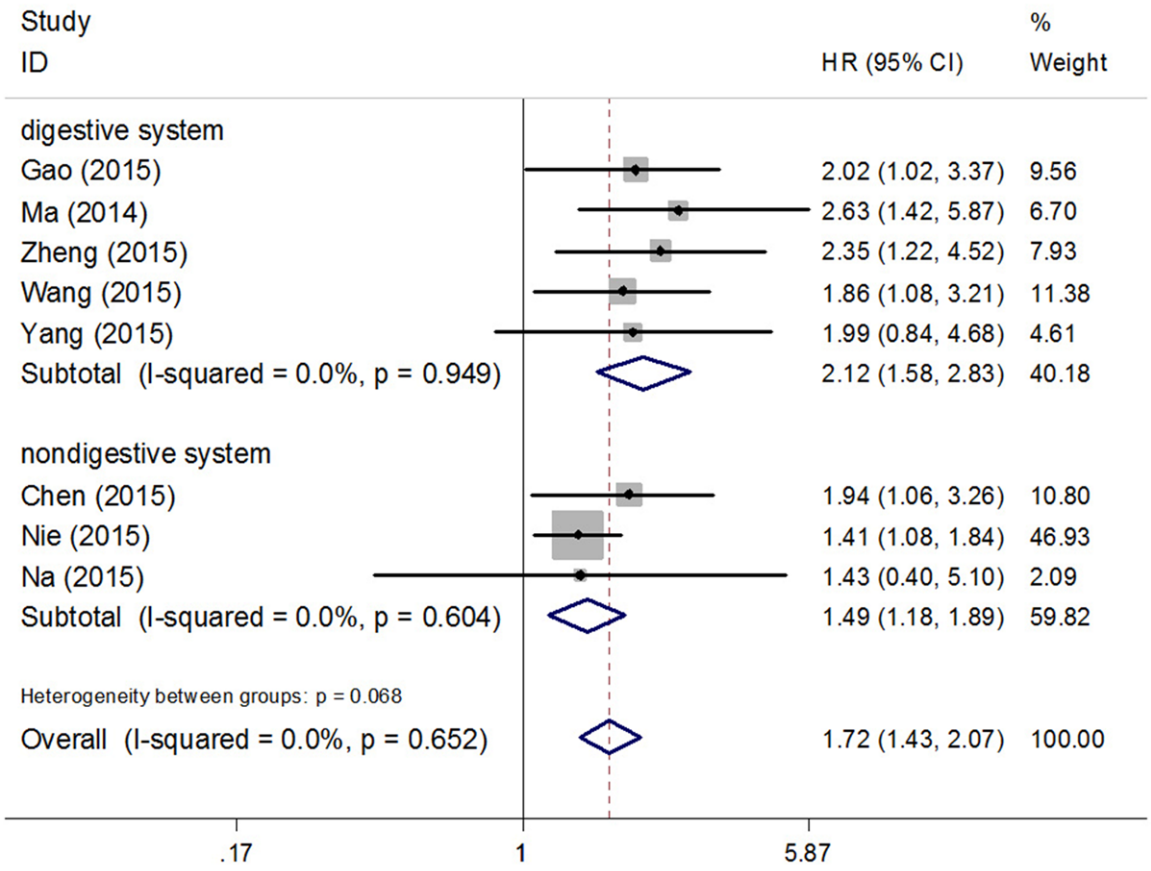

Figure 3. Forest plots for relationship between UCA1 expression and OS with subgroup analysis based on cancer type.

0.047, indicating there were publication biases exiting in our analysis.

Discussion

Recent studies have identified that lncRNAs were aberrantly expressed in different types of cancers. It was demonstrated by further clinical researches that lncRNAs were associated with cancer initiation and progression [25]. Several well-known lncRNAs such as HOTAIR and MALAT1 have been analyzed systematically to summarize their roles in cancer prognosis [26, 27]. Previous studies have showed UCA1 expression could regulate cancer cell physiological processes and was associated with poor survival outcome of cancer patients. Limited by the size of sample, there have been many controversies about the prognostic role of UCA1 in cancers. We believed that this meta-analysis was the first to investigate the relationship between lncRNA UCA1 and the clinical prognosis in human cancers. A total of 9 papers comprising 852 patients were included into this meta-analysis. We found that UCA1 expression was associated with a poorer prognosis (OS) in patients with different types of cancers.

Then we conducted subgroup analysis to further identify the specific association between UCA1 and OS. The results of subgroup analysis indicated that high UCA1 expression was significantly interrelated to poor OS when the HR was extracted from multivariate analysis rather than univariate analysis. The potential explanation could be that univariate analysis did not control the confounding factors. In cancer type group, we found that the predictive significance of UCA1 in OS was more remarkable in patients with digestive system cancer than in those with non-digestive system carcinoma, without significant heterogeneity between and within these two subgroups. This finding suggested that

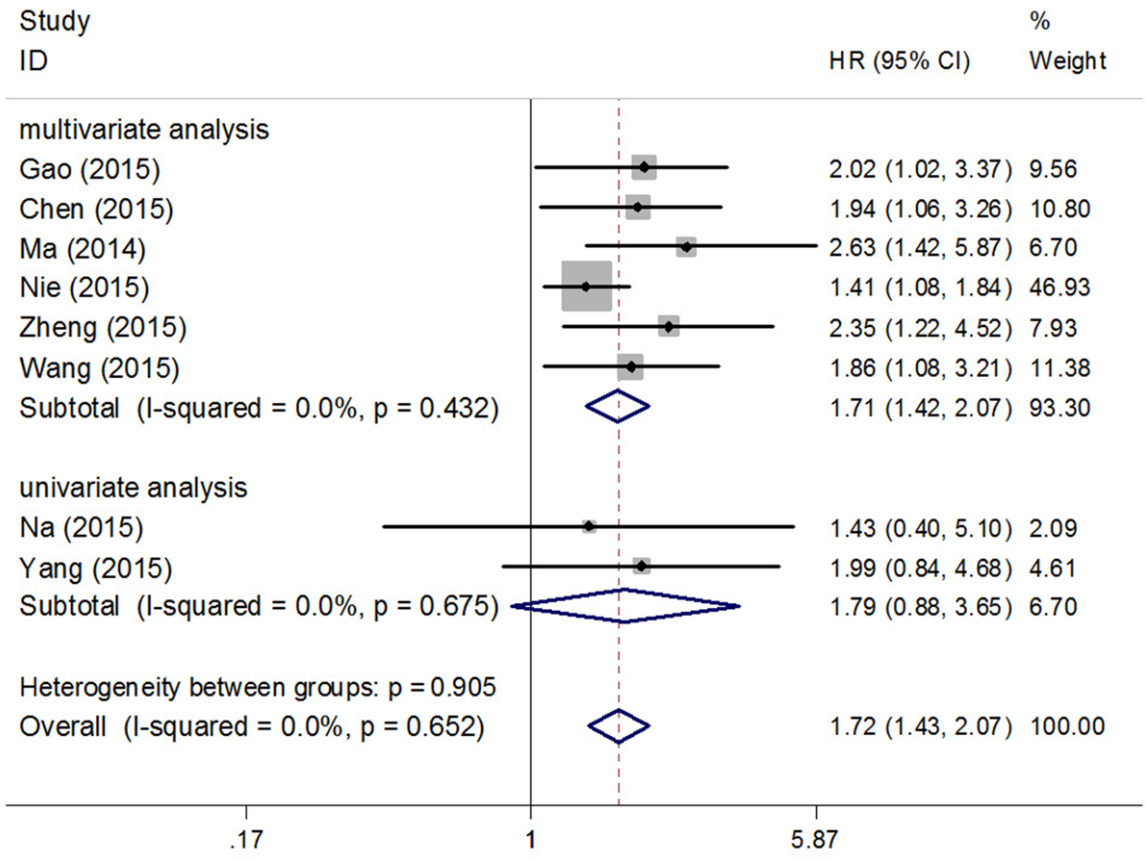

Figure 4. Forest plots for relationship between UCA1 expression and OS with subgroup analysis based on survival analysis.

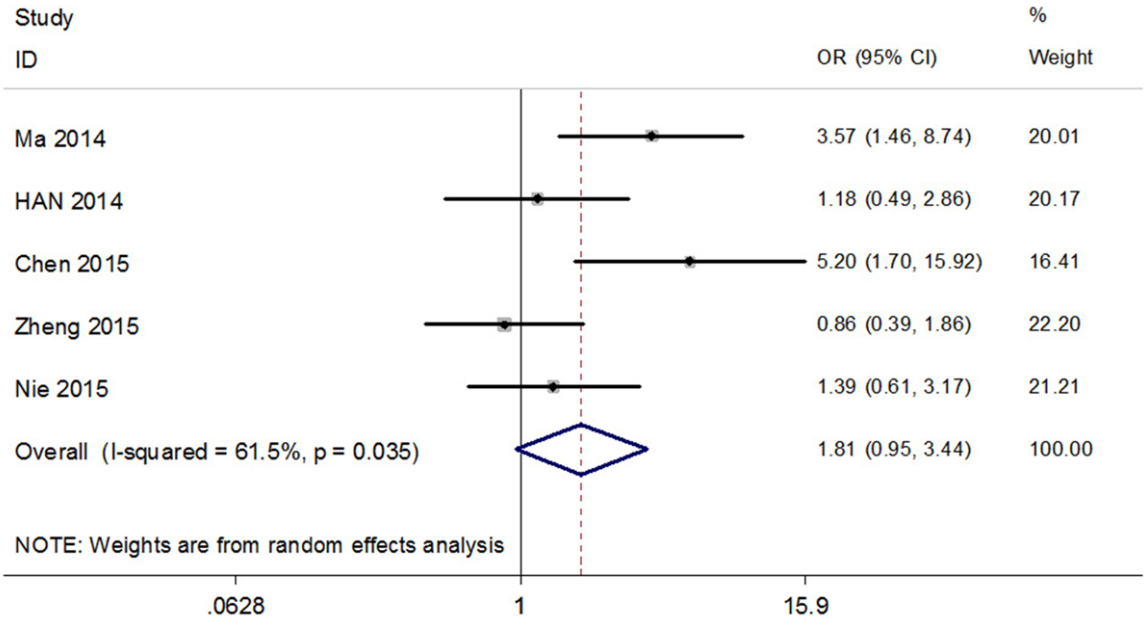

Figure 5. Forest plots for relationship between UCA1 expression and LNM.

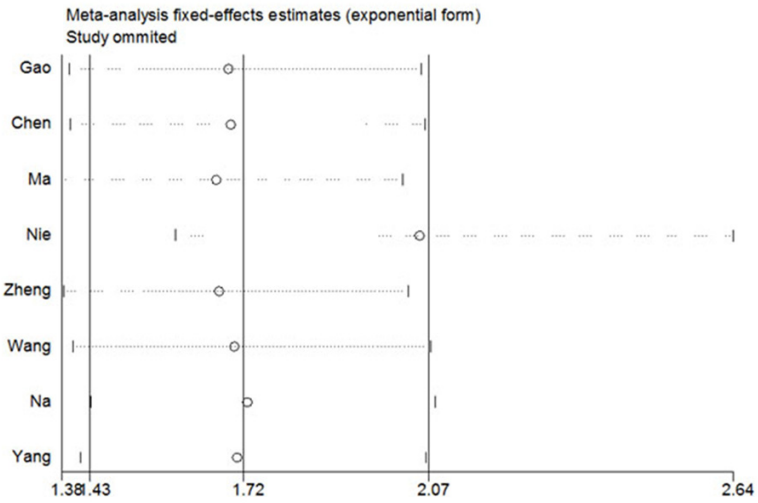

Figure 6. Sensitivity analysis of the pooled HRs of UCA1 expression and OS for the included studies.

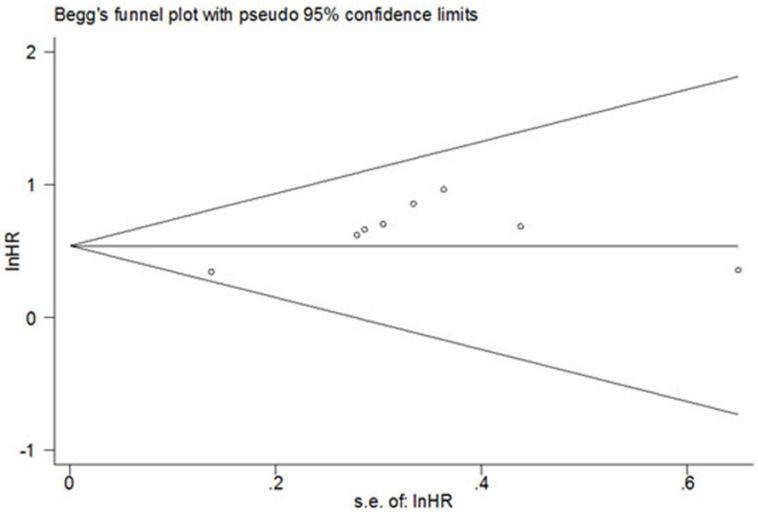

Figure 7. Begg's funnel plot to explore publication bias of the included studies between UCA1 and OS.

UCA1 expression might be more meaningful in predicting OS of patients with digestive system carcinoma than those with non-digestive system cancer. Since UCA1 overexpression promoted cancer cell invasion and migration including bladder cancer [10], melanoma cancer [28], tongue squamous cell carcinoma [29] and ovarian cancer cell [30], we estimated ORs in 5 studies with available data regarding the independent prognostic role of UCA1 in lymph node metastasis. Considering the limited number of relevant studies, we could not draw a definite conclusion that there's no relationship between UCA1 expression and LNM, as more studies with large sample size were needed. In addition, further relevant clinical researches should be conducted to confirm the role of UCA1 expression level in lymph node metastasis, distant metastasis, clinical stage, tumor size, histological differentiation and other clinical characteristics.

In this meta-analysis, visual inspection of Begg's funnel plot showed an asymmetry and Egger's test also indicated the existence of publication bias. The asymmetry of funnel plot was possibly caused by insufficient number of trials, which might cause a small-study effect. However, it should be emphasized that there were several limitations in our study. Firstly, the cut-off values dividing the UCA1 expression varied in different studies. Secondly, we calculated one of the HRs according to survival curve, which might generate inaccurate results. Thirdly, most of the included studies reported significant results instead of publishing nonsignificant results. Fourth, we only recruited English language papers. Last but not least, these studies estimated in our analysis were restricted to China patients, which might prevent us from obtaining more comprehensive results.

In conclusion, we have demonstrated that high UCA1 expression was significant correlated with poor OS (pooled HR: 1.719, 95% CI: 1.429-2.066, $P<0.001$) in many cancer types. Further studies regarding the association between clinicopathological features and UCA1 expression level are required to explore its clinical application value.

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Disclosure of conflict of interest

None.

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