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Review Article

Long non-coding RNA UCA1 as a prognostic marker in digestive cancer: a meta-analysis

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Abstract: Long noncoding RNA (lncRNA) UCA1 has been reported to be upregulated in digestive cancers, but its clinical relevance has not yet been established. This meta-analysis summarizes the potential prognostic value of UCA1 in various digestive cancers. A quantitative meta-analysis was performed through a systematic search in PubMed, EMBASE, Web of Science, Cochrane library for eligible studies on the prognostic effect of UCA1 in digestive cancers. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to summarize the strength of the link between UCA1 and its clinical prognosis. Twelve eligible studies with a total of 1237 patients were included in our study. A significant association was observed between UCA1 abundance and poor overall survival (OS) of patients with digestive cancers, and the pooled hazard ratio (HR) was 2.02 (95% CI: 1.70-2.39). Sensitivity analysis conformed the reliability of our findings. Subgroup analysis shows that difference in cancer type and detection method did not alter the overall predictive value of lncRNA UCA1 on poor prognosis in investigated cancers. This meta-analysis indicated that UCA1 abundance may serve as a novel predictive factor for poor prognosis in patients with various digestive cancers.

Keywords: UCA1, LncRNA, digestive cancers, prognosis, meta-analysis

Introduction

Digestive cancer has been the leading cause of cancer related death worldwide and constitutes a major public health problem worldwide [1]. Despite recent advances in treatment of surgery, chemotherapy and radiotherapy, survival rates of digestive cancers remain in a narrow range of 25% to 30% in most countries [2]. Therefore, it is of great importance to identify applicable prognostic biomarkers that may not only improve the poor prognosis but also provide novel therapeutic targets. Cancers in digestive system can be mainly divided into esophageal cancer (EC), gastric carcinoma (GC), colorectal carcinoma (CRC), gallbladder carcinoma (GBC), hepatocellular carcinoma (HCC) and pancreatic cancer (PC). According to global cancer statistics in 2012, HCC and GC are identified as the second and third most frequently diagnosed cancers among men in less developed countries. And EC caused 400,200 deaths in 2012 worldwide, while there were 1.4 million cases of CRC patients and 693,900 deaths occurred due to CRC [3].

Digestive cancers are multifactorial diseases caused by complex interactions between various genetic and environmental factors [4]. Allelic variations in oncogenes are candidate genetic risk factors that may alter the onset and outcome of digestive cancers [5]. With the emergence of high throughput RNA sequencing (RNA-Seq) technologies, an increasing number of investigators are focusing on non-coding RNAs (ncRNAs). LncRNA pervasively transcribed in the genome is defined as a non-protein-coding RNA with a molecule longer than 200 nucleotides in length participates in a variety of biologic processes such as proliferation, apoptosis and migration [6, 7]. Increasing evidence has confirmed that dysregulations of lncRNAs was associated with the modulation of proliferation and invasion of tumors and contribute to the progression and metastasis of human tumors [8, 9]. One example of such an oncogenic lncRNA is urothelial

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

First author	Year	Region	Cancer type	Sample size (n)	UCA1 High	UCA1 Low	Tumor stage (I/II/III/IV)	Follow-up (months)	Preoperative treatment	Criterion of high expression	Detection method	Outcome measures	Multivariate analysis	HR (OS)	NOS
Li JY	2014	China	ESCC	90	41	49	39/51 (I-II/III-IV)	Median 43	None	Mean expression	qRT-PCR	OS	U+M	2.63 (1.42, 5.87)	7
Chen DT	2015	USA	PC	63	NR	NR	I-II	Median 21	NR	Median dichotomized PC1 score	Affymetrix 2.0 microarray	OS	U+M	2.76 (1.15-6.61)	6
Ping Chen	2016	China	PC	128	64	64	70/58 (I-II/III-IV)	Over 60	None	Mean expression	qRT-PCR	OS	U+M	1.688 (1.073-2.451)	7
Shang C	2016	China	GC	77	NR	NR	NR	Over 60	None	NR	qRT-PCR	DFS	U+M	2.54 (1.09, 5.92)	8
Gao JF	2015	China	GC	20	17	3	NR	1-40	None	NR	qRT-PCR	OS	U+M	2.02 (1.02, 4.00)	8
Zheng Q	2015	China	GC	112	56	56	39/73 (I-II/III-IV)	Over 60	None	Mean expression	qRT-PCR	OS,DFS	U+M	2.53 (1.22, 4.53)	8
Wang F	2015	China	HCC	98	49	49	43/55 (I-II/III-IV)	Over 60	None	Mean expression	qRT-PCR	OS	U+M	1.94 (1.06, 3.55)	7
Yang ZJ	2015	Korea	HCC	240	NR	NR	NR	NR	NR	Median value	Illumina expression beadchip	OS,DFS	U+M	1.99 (0.84-4.69)	8
Ni BB	2015	China	CRC	54	27	27	35/19 (I-II/III-IV)	Over 50	NR	Mean expression	qRT-PCR	OS	U+M	3.10 (1.17, 8.22)	8
Bian ZH-1	2016	China	CRC	90	45	45	37/53 (I-II/III-IV)	Over 60	NR	Median expression	qRT-PCR	OS	U+M	2.395 (1.044, 5.495)	7
Bian ZH-2	2016	China	CRC	105	NR	NR	NR	Over 60	NR	Median expression	qRT-PCR	OS	U+M	1.71 (1.21-2.40)	7
Han Y	2014	China	CRC	80	37	43	43/37 (I-II/III-IV)	Mean 42.6	NR	Mean value	RT-PCR	OS	U	2.12 (1.13, 5.27)	8
Tao K	2015	China	CRC	80	20	60	44/36 (I-II/III-IV)	Over 60	None	According to the fourth quartile of the expression level	qRT-PCR	OS	U+M	2.00 (1.00, 4.00)	7

Abbreviations: NR: not reported, U: univariate, M: multivariate, OS: overall survival, DFS: disease-free survival, CRC: colorectal cancer, ESCC: esophageal squamous cell carcinoma, GC: gastric cancer, HCC: hepatocellular carcinoma, Pancreatic cancer: PC, RT-qPCR: real-time quantitative PCR.

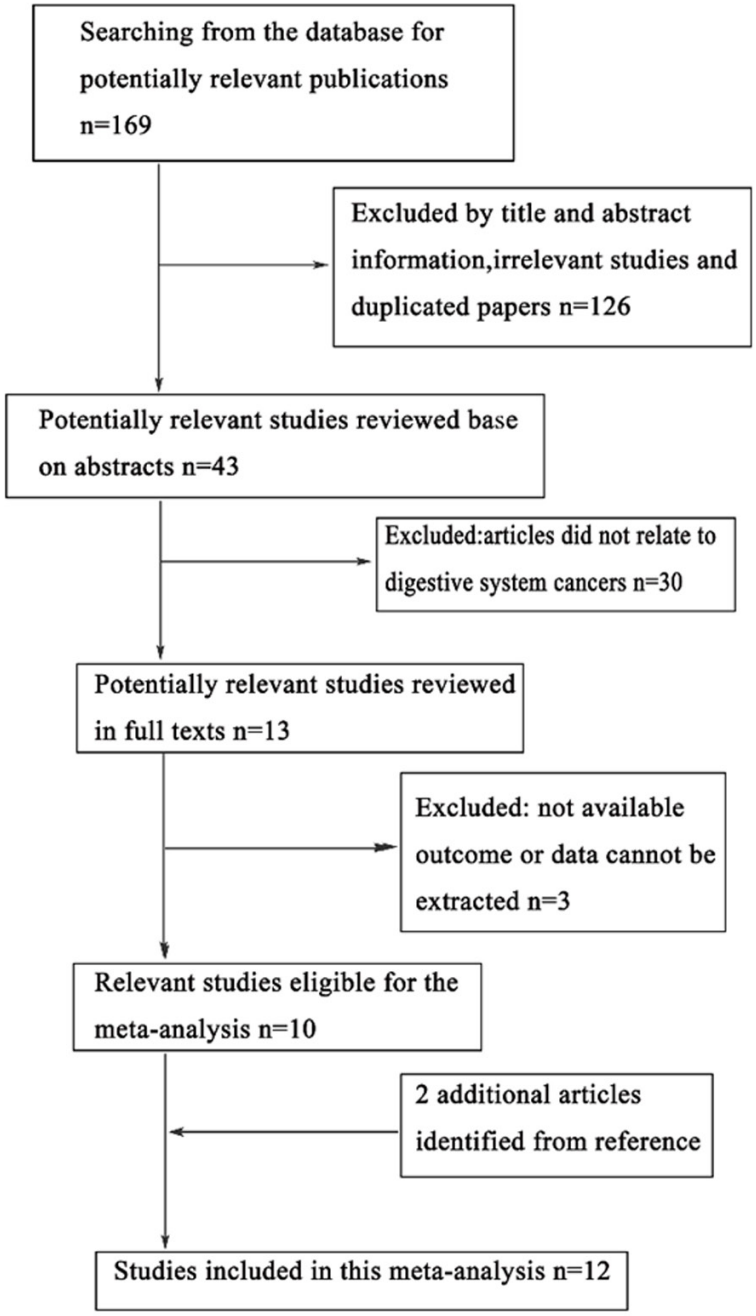

Figure 1. Flow chart of the study search and selection.

cancer associated 1 (UCA1). UCA1 was first discovered as a novel noncoding RNA gene dramatically up-regulated in bladder transitional cell carcinoma using reverse transcription-PCR by Wang in 2006 [10], located at the human chromosome 19p13.12, has been proved to be involved in the regulation of embryonic development and bladder cancer invasion and progression [11].

The oncogenic activity of UCA1 had been reported in several kinds of human cancers including bladder cancer, gastric cancer, lung cancer and so on [12-15]. Studies revealed that the upregulation of lncRNA-UCA1 in several types of tumor tissues, including tongue squamous cell carcinoma, melanoma, and esophageal squamous cell carcinoma, is statistically correlated with lymph node metastasis [14-16]. In gastric cancer, high lncRNA-UCA1 expression correlated with tumor invasion depth [13]. However, the function of most lncRNAs in gastric cancer and their clinical significance remain incompletely understood.

Materials and methods

Search strategy

A systematic literature search of PubMed, EMBASE, Web of Science and Cochrane library was conducted. The literature covered was restricted to publications in English. The following search terms were used: UCA1 or urothelial carcinoma associated 1, urothelial cancer associated 1, UCA1, lncRNA UCA1, Long non-coding RNA UCA1, long non coding RNA UCA1. The literature search stopped on May 25th, 2017. In addition, a recursive search of the reference articles of included studies was conducted manually to identify possibly relevant articles. Studies were included or excluded based on the consensus between two authors (Chenchen Liu and Xiangyu Liu) and when necessary with the assistance of Lili Zhou. All selections were performed in duplicate.

Selection criteria and quality assessment

Two investigators (Lili Zhou and Yuanyuan Ding) independently assessed all the eligible studies and extracted the data. We included studies that met the following inclusion cri-

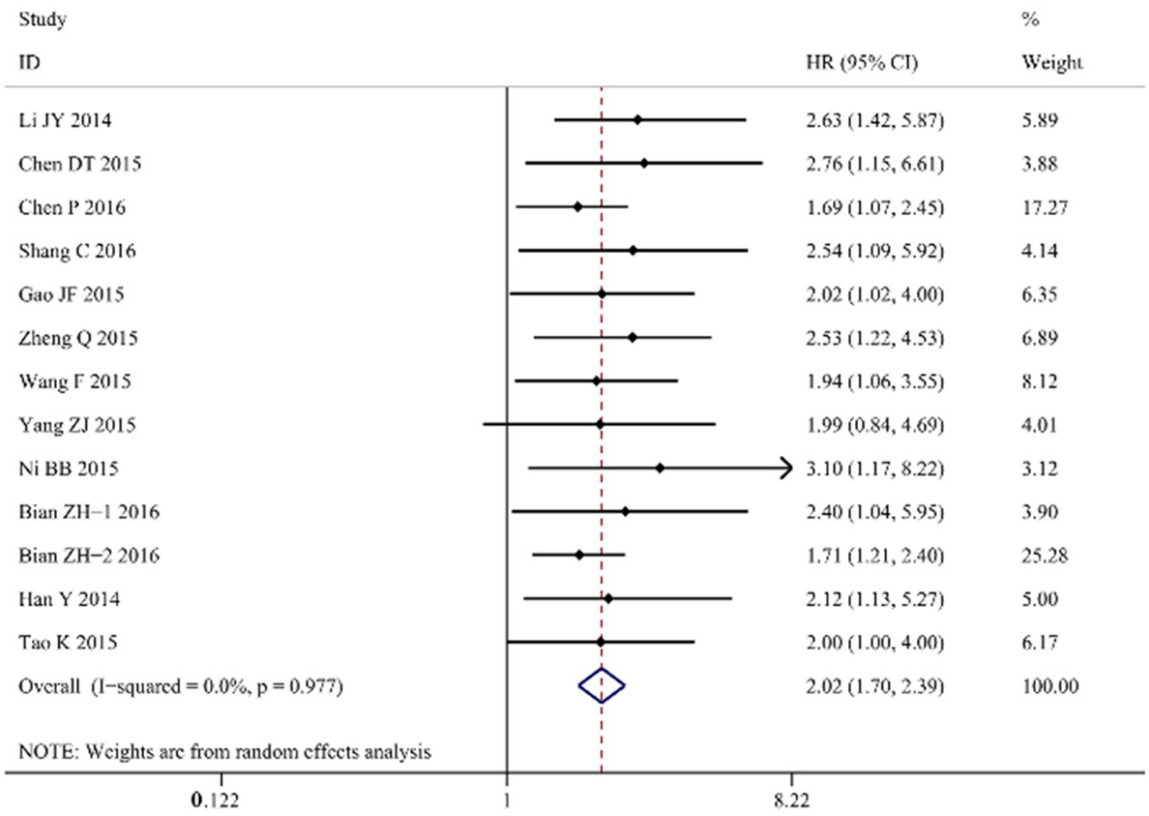

Figure 2. Forest plot for the correlation between UCA1 expression and poor prognosis (OS) of digestive cancer patients.

teria: 1) digestive cancers was studied; UCA1 expression was explored in human tissue using quantitative PCR or microarray expression analysis; 2) the relationship between UCA1 expression and survival was examined; 3) statistically acceptable methods of data collection and analysis; 4) hazard ratios (HRs) for survival rates and their 95% confidence intervals as well as those with enough information for calculating these data; 5) full manuscript publication or abstract with enough information in English language. Animal studies and single case reports were excluded.

We assessed the quality of all studies under the criteria of Newcastle-Ottawa, which included selection (4 points), comparability (2 points), and outcome (3 points) with a score range of 0-9. The NOS assigns a maximum of 4 questions for selection, a maximum of 2 questions for comparability, and a maximum of 3 questions for exposure/outcome, with a maximum 1 point for each question. Points were awarded only when the data was explicitly stated. Therefore, a higher scores denotes better quality, with 9 points being the highest quality. The final decision and interpretation was based on consensus of two authors (Lili Zhou and Yuanyuan Ding) and when necessary with the assistance of Wen Li. All selections were performed in duplicate. All eligible studies were scored in **Table 1**, with a higher score indicating a better methodological quality.

Data extraction

The two investigators (Chenchen Liu and Xiangyu Liu) extracted data independently and discrepancies in interpretation were resolved by consensus. Relevant studies were reviewed in full to ensure suitability according to the predefined inclusion and exclusion criteria. For each study, the following characteristics of the individual research articles were collected: author name, year of publication, country in which study participants were enrolled, tumor type, number of patients, clinical stage of tumor, cut-off values, study design, follow-up, overall survival (OS), methods, treatment data, HRs of elevated UCA1 for overall OS and DFS as well as their 95% CIs and *p* values.

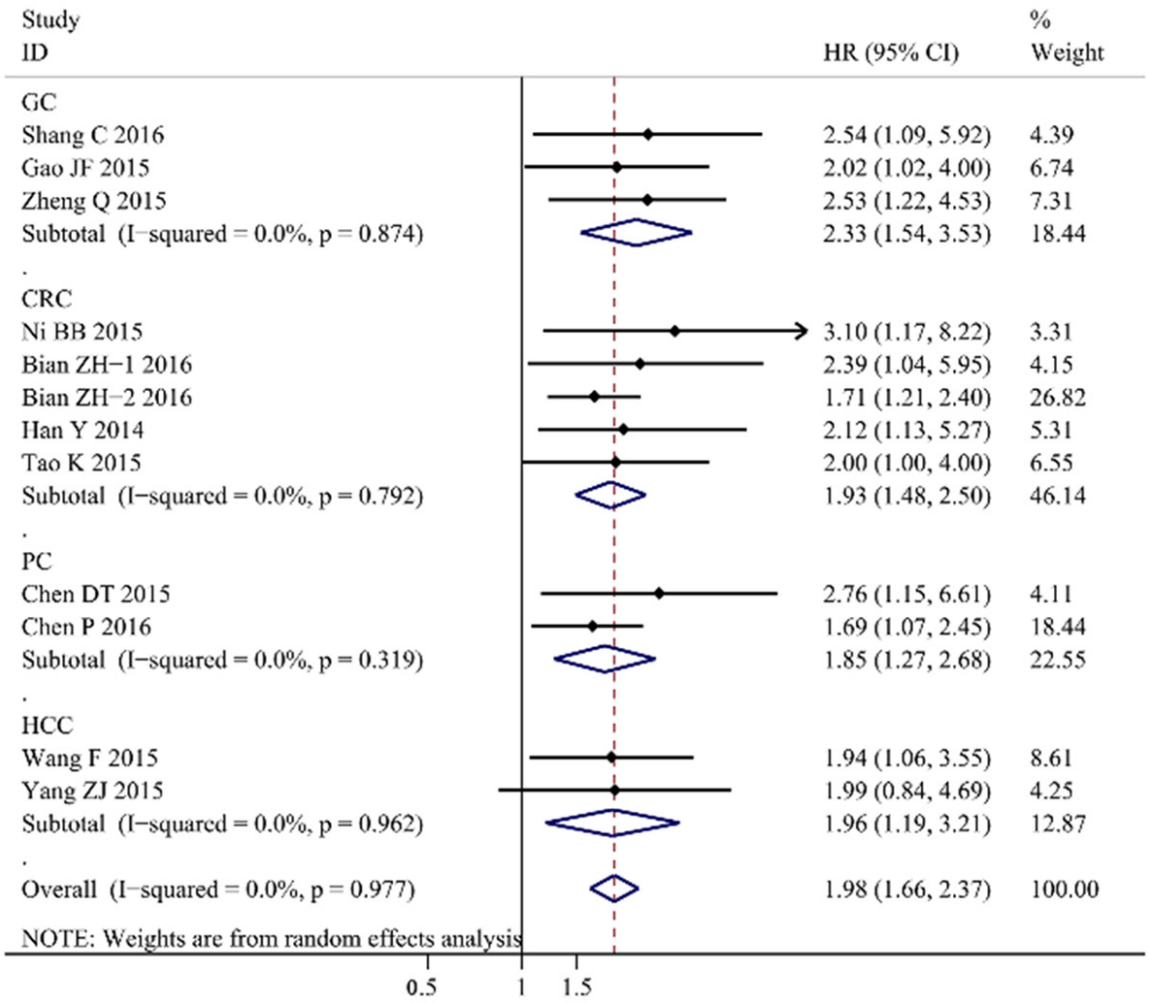

Figure 3. Forest plot of subgroup analysis showed the correlation of UCA1 expression with poor prognosis in different cancers.

We used three methods to obtain the HRs. For method 1, the HRs were obtained directly from studies. For method 2, according to the primary survival date, we calculated the HRs and 95% CIs by univariate analysis with Stata 12.0 software. For method 3, the HRs were extracted from Kaplan Meier curves, the HR estimate was reconstructed by extracting several survival rates at specified times from the survival curves using the Engauge Digitizer software [16-19].

Statistical analysis

The current meta-analysis was performed using the Stata 12.0 software. The heterogeneity between studies was determined with the Chi square-based Q test and I^2 statistics. A *p* value less than 0.05 for the Q test and I^2 value above 50 % were considered to be significantly heterogeneous, thus the random effects model was adopted, and otherwise the fixed model was applied. Potential publication bias was assessed with a funnel plot and Egger test. We utilized one-way sensitivity analysis to evaluate the stability of the meta-analysis by sequentially excluding one study each time to test the robustness of the main results. A *p* value less than 0.05 was considered statistically significant.

Results

The baseline characteristics of the included studies were summarized in ***Table 1***

The initial search identified 169 citations, the titles and abstracts were then reviewed, and

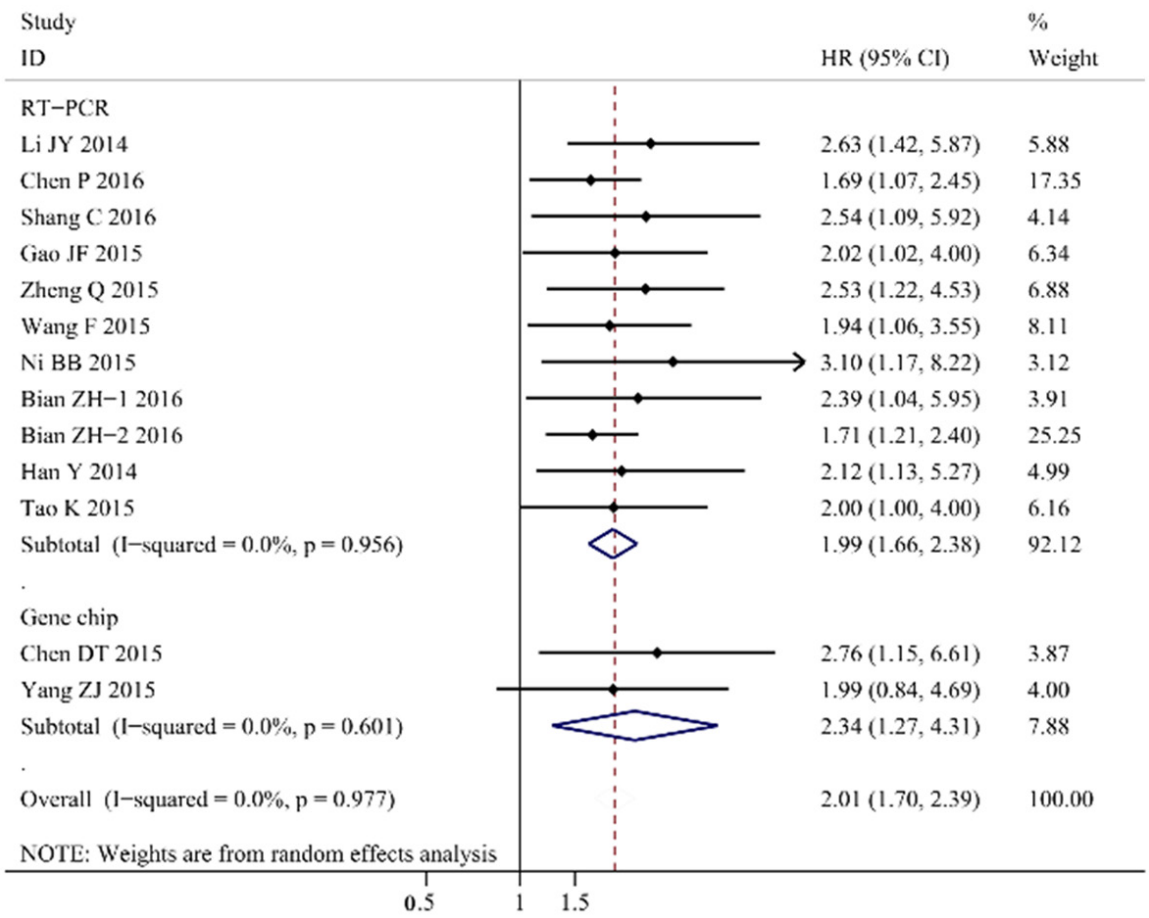

Figure 4. Forest plot of subgroup analysis showed the correlation of UCA1 expression with poor prognosis with different detection methods.

126 irrelevant studies and duplicates were excluded. After further inspection of the abstracts, 30 papers that did not investigate digestive cancers were excluded. 13 papers were considered of potential value and the full text of these 13 articles was retrieved for detailed evaluation. After further evaluation, 3 of them were subsequently excluded from the metaanalysis because of insufficient data to estimate HRs for further analysis. A recursive search of the reference articles of included studies was conducted manually to identify possibly relevant articles. Finally, according to the criteria for selection, a total of 12 studies comprising 1237 digestive cancer patients were included in the meta-analysis [13, 15, 20-29] (**Figure 1**). Of the 12 studies, there are 1, 2, 3, 2 and 4 studies concerned esophageal squamous cell carcinoma (ESCC) [20], pancreatic cancer (PC) [15, 21], gastric cancer (GC) [13, 22, 23], hepatocellular carcinoma (HCC) [24, 25] and colorectal cancer (CRC) [26-29], respectively. Ten studies were conducted in China, one in Korea and one in America (**Table 1**). Quantitative reverse transcription-polymerase chain reaction (RT-PCR) was used in 10 studies to detect the UCA1 expression, Illumina expression beadchip was used in 1 study, and Affymetrix 2.0 microarray was used in 1 study.

Association between UCA1 and patient survival in different types of digestive cancers

There was no significant heterogeneity among the studies (I^2=0%, p=0.549), and we used the random-effects model to calculate the pooled HR (**Figure 2**). Eleven studies reported the overall survival (OS), one study reported disease-free survival (DFS) and two studies reported both parameters, and in our meta-analysis we choose OS as the main parameter. A significant association was observed between UCA1 and OS in digestive cancer pa-

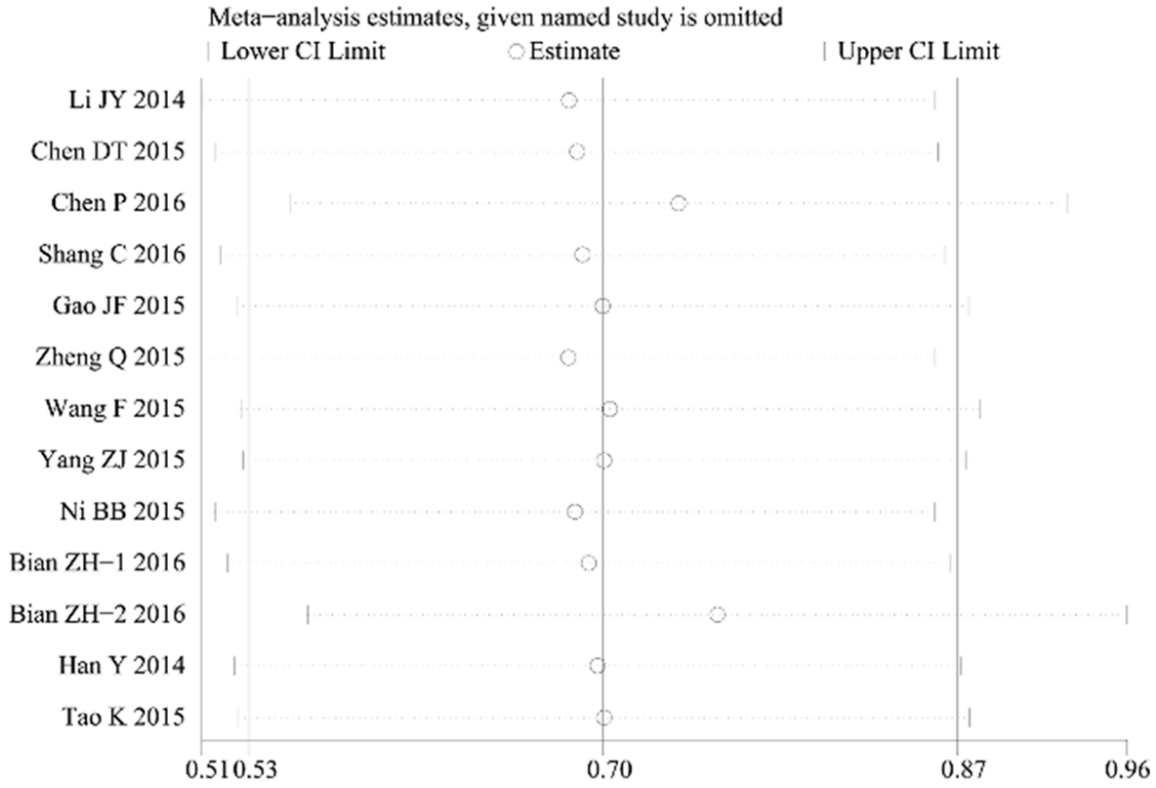

Figure 5. Sensitivity analysis of the included studies for the association between UCA1 expression and overall survival.

tients (pooled HR 2.02, 95% CI: 1.70-2.39) (**Figure 2**). The results showed that patients with high UCA1 expression were more likely to have significant shorter OS. And we further divided patients into different groups under the criteria of cancer type and methods of detecting UCA1. Results shows that the pooled HR for GC, CRC, PC, HCC were 2.33 (95% CI 1.54-3.53), 1.93 (95% CI 1.48-2.50), 1.85 (95% CI 1.27-2.68), 1.96 (95% CI 1.66-2.37), respectively (**Figure 3**). When it comes to different kinds of detection methods, the pooled HRs for RT-PCR and gene chip were 1.99 (95% CI 1.66-2.38), 2.34 (95% CI 1.27-4.32), respectively (**Figure 4**). There was no significant heterogeneity observed in both subgroup analysis. Collectively, this meta-analysis showed that UCA1 was an independent prognostic factor for digestive cancers.

Sensitivity analysis

Sensitivity analysis was performed to examine the effect of each single study on the overall meta-analysis results by omitting one study at a time in the total population. Results showed that exclusion of any individual study did not change the pooled HR significantly, indicating that the pooled HR of OS was reliable (**Figure 5**).

Publication bias

In this meta-analysis, Egger's *p* value tests were used to assess the potential publication bias statistically. The funnel plots were unsymmetrical (**Figure 6A**). And significant publication bias was found across the studies, with *p* value of 0.000 for Egger test (**Figure 6B**). Therefore, we speculate the results of our meta-analysis should be taken critically and carefully.

Discussion

Digestive system cancers, being the leading cause of morbidity and mortality worldwide, constitute a major public health problem. Owing to lack of reliable tools for early detection, most patients are diagnosed at a late stage an d have poor prognosis. Given this, it is necessary

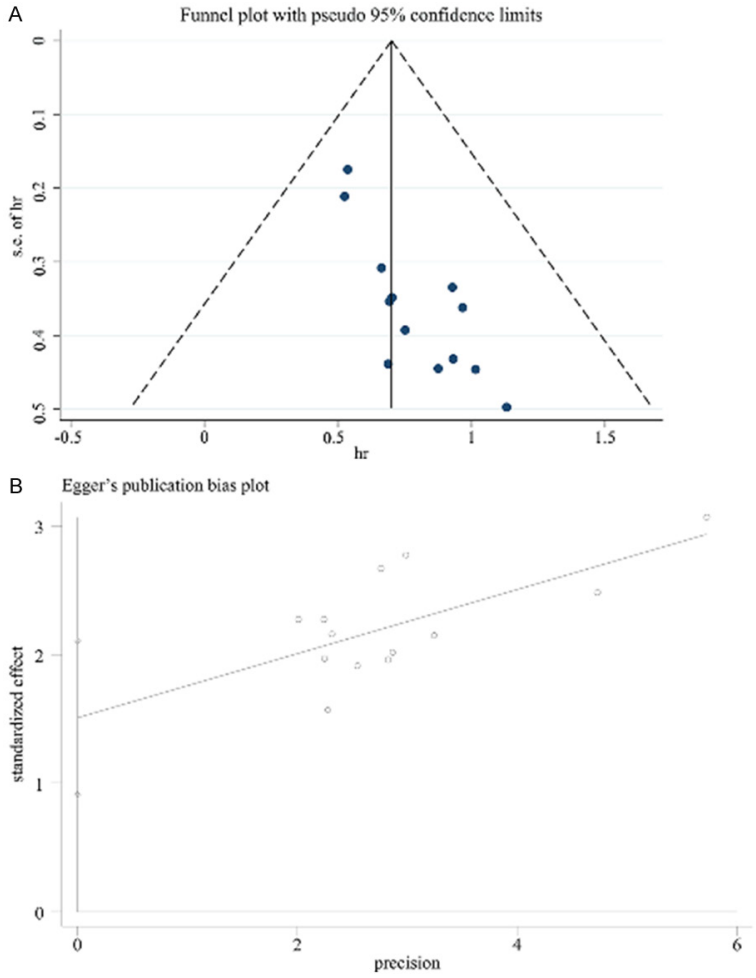

Figure 6. Funnel plot analysis (A) and Begg's test (B) of potential publication bias.

and essential to identify biomarkers, which could improve the diagnosis and therapy by providing more precise and valuable information.

Recent studies suggest that lncRNAs are involved in the modulation of several signaling pathways, acting as oncogenes or tumor suppressors during tumorigenesis [11, 12]. UCA1 was a long intergenic ncRNA which was first discovered in bladder cancer in 2006 [10]. UCA1 has been recently found to be up-regulated in several cancers, contributing to tumor proliferation, apoptosis, metastasis and survival, thus affecting their malignant potential. Importantly, UCA1 has been considered as a promising diagnostic marker and potential therapeutic target for human cancers [13, 14]. The mechanism of regulatory activity of UCA1 in digestive cancer invasion and metastasis has been explored in several cancer types. Studies show that UCA1 could promote the migration and invasion of pancreatic cancer cell via dysregulations of matrix metalloproteinases (MMPs) [30, 31]. Wang F. found that UCA1 could facilitate HCC cell growth and metastasis through the inhibition of miR-216b and activation of the FGFR1/ERK signaling pathway [24]. In colorectal cancer upregulation of UCA1 is associated with tumor progression through targeting miR-204-5p [27]. Recently, several studies have investigated the clinicopathological value of UCA1 expression in digestive cancer. However, due to the limited numbers of studies and sample sizes, the prognostic role of UCA1 expression in digestive cancer was not well established. Besides, some new studies have been conducted regarding this aspect. Hence, we carried out this meta-analysis to further clarify the clinical significance of UCA1 expression in digestive cancers.

Our meta-analysis using a detailed search strategy and selection criteria, included 12 studies with a total of 1237 patients, provided convincing evidence that UCA1 expression is predictive of poor tumor survival, suggesting that UCA1 may be used as a negative, unfavorable prognostic marker for digestive cancers. The combined results indicated that increased UCA1 expression was associated with a shorter OS in digestive cancer patients. A shorter overall survival time was observed in the patients of high UCA1 expression compared with those of low UCA1 expression. Subgroup analysis including cancer type, detection method showed that these factors did not alter the predictive value of UCA1 on poor prognosis among the investigated cancers and no evidence of statistically significant heterogeneity existed across the studies. Additionally, pub-

lication bias exist in our study despite the fact that stable results were revealed in sensitivity analysis. There might be some explanations for this. First, our data collection may be incomplete because data from non-English language papers was not included. Second, most of the included studies reported positive results due to the fact that null results are generally less likely to be published. Third, we only included studies with sufficient data to calculate the pooled HRs, omitting those with insufficient information for combined HRs. Thus, our results might overestimate the predictive significance of UCA1 in prognosis of digestive system malignancies to some extent.

Nevertheless, it should be emphasized that there are several limitations in our study due to the discrete data across studies. First, not all the HRs are provided by the primary articles and we calculated some of them by reconstructing survival curves, making the HRs less accurate. Second, most of patients included in the meta-analysis were from Asia, and only one study was from USA, and thus our results may just represent patients from Asia.

In conclusion, our study revealed that UCA1 might be a novel predictive factor for assessing poor prognosis in different types of digestive cancers. Subgroup analysis shows that difference in cancer type and detection method did not alter the overall predictive value of lncRNA UCA1 on poor prognosis in investigated cancers, despite the fact that the link of strength varies among different cancer types and detection methods. However, considering the above limitations above, larger-size, multi-center and higher-quality studies with a unified criterion for determining UCA1 expression are necessary to validate the results in this study.

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Disclosure of conflict of interest

None

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