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# Long Noncoding RNA UCA1 Overexpression Is Associated with Poor Prognosis in Digestive System Malignancies: A Meta-analysis

Fei-tao SHI, Li-dong CHEN, Lian-feng ZHANG#
*Department of Gastroenterology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*



**Summary**: Long noncoding RNA (lncRNA) urothelial carcinoma associated 1 (UCA1) has been reported to be highly expressed in many kinds of cancers. This meta-analysis summarized its potential prognostic value in digestive system malignancies. A meta-analysis was performed through a comprehensive search in PubMed, EMBASE, the Cochrane Library, Web of Science and Chinese National Knowledge Infrastructure (CNKI) for suitable articles on the prognostic impact of UCA1 in digestive system malignancies from inception to June 27, 2019. Pooled hazard ratios (HRs) with 95% confidence interval (95%CI) were calculated to summarize the effect. Sixteen studies were included in the study, with a total of 1504 patients. A significant association was observed between UCA1 abundance and poor overall survival (OS), and shorter disease-free survival (DFS) for patients with digestive system malignancies, with pooled HR of 2.07 (95%CI: 1.74–2.47), and of 2.50 (95%CI: 1.62–3.86). Subgroup analysis and sensitivity analysis suggested the reliability of our findings. It is suggested that UCA1 abundance may serve as a reliable predictive factor for poor prognosis in patients with digestive system malignancies.
**Key words**: long noncoding RNAs; urothelial carcinoma associated 1; prognosis; digestive system tumor; meta-analysis

The digestive system malignancies are becoming a major public health problem and the main causes of morbidity and mortality worldwide[1]. With the rapid development of treatment of malignancies, such as surgery, chemotherapy and radiotherapy, the diagnosis and prognosis of tumors are still extremely optimistic. As finding molecular targets for digestive system treatment might help improve the survival of patients with the fatal disease, many studies have attempted to identify new potential biomarkers for early diagnosis, more accurate prognosis prediction, and specific therapeutic target[2].

Long noncoding RNAs (LncRNAs) are a class of regulatory RNAs that are longer than 200 nucleotides[3–5]. They control gene expression level in the form of RNA in a variety of levels, but have no coding protein function. It has been proved that lncRNA plays an vital role in chromosome inactivation[6], splicing regulation of cell differentiation[7] and mRNA degradation and translation[8]. Numerous complex human diseases, particularly cancers, are related to abnormal lncRNA expression[9, 10]. Thus, lncRNAs have opened a new field of cancer genomics.

Urothelial carcinoma associated 1 (UCA1) is a highly abundant and ubiquitously expressed long non-coding RNA, which belongs to the human endogenous retrovirus H (HERV-H) family[10–12]. UCA1 consists of three exons with 1.4 kb in length, and it is markedly expressed in bladder transitional cell carcinoma[13]. A large number of articles have proved that the expression of lncRNA-UCA1 is higher in bladder cancer tissues than in adjacent normal tissues[14, 15]. It has been suggested that UCA1 expression may play an important prognostic role in all kinds of digestive system malignancies, such as esophagus cancer (EC)[13], gastric cancer (GC)[16, 17], colorectal cancer (CRC)[18, 19], and hepatocellular carcinoma (HCC)[20]. Therefore, we conducted a systematic review and quantitative meta-analysis to determine whether UCA1 can be used as a putative biomarker in digestive system malignancies.

## 1 MATERIALS AND METHODS

### 1.1 Study Strategy

Following the standard guidelines for the review of the meta-analysis and systematic review of prognostic studies of tumor markers at present[21, 22], three authors (Shi FT, Chen LD, and Zhang LF) obtained relevant articles for this review. Articles up to June 26, 2019, which related to the lncRNA UCA1 serving as a putative biomarker for prognosis of digestive system,

Fei-tao SHI, E-mail: shifeitao28@126.com
#Corresponding author, E-mail: zhanglianfengzzu@163.com

were searched in the following research databases, including PubMed, EMBASE, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Web of Science. The search strategy used both free-text words and MeSH terms to develop the abundance of the search. The search strategy was as follows: #1 UCA1 OR urothelial carcinoma associated 1; #2 cancer OR tumor OR carcinoma OR neoplasm; #3 prognosis OR survival OR clinical outcome OR mortality; #4 digestive system neoplasms OR esophageal OR colorectal OR gastric OR hepatocellular OR liver OR pancreatic. #5 #1 AND #2 AND #3 AND #4.

**1.2 Study Selection**

Three investigators independently assessed all the eligible studies and extracted the data. Inclusion criteria were as follows: (1) articles investigating the roles of UCA1 in the digestive system; (2) the expression levels of UCA1 in primary cancerous tissues detected by PCR; (3) the relationship between UCA1 expression and survival; (4) describing the related clinicopathologic parameters; (5) studies containing sufficient data for the computation of odds ratios (OR), hazard ratios (HRs) and corresponding 95% confidence intervals (CI). The exclusion criteria were as follows: (1) the molecular structure and function of UCA1 were investigated; (2) animal studies, expert opinions, duplicate publications and single case reports; (3) studies without usable data.

**1.3 Data Extraction**

The three investigators (Shi FT, Chen LD, Zhang LF) extracted data independently and reached an agreement according to the inclusion and exclusion criteria above. For each study, the following characteristics of the individual research articles were collected: first author, year of publication, study location, cancer type, total number of patients, age, percentage of male patients, clinical stage of tumor, duration of follow-up (months), preoperative treatment, cut-off values, overall survival (OS), detection methods, disease-free survival (DFS), etc.

**1.4 Quality Assessment of Primary Studies**

The methodological quality of each study was evaluated independently by three investigators using the Newcastle-Ottawa Scale (NOS)[23]. A NOS score of 0–3, 4–6, and 7–9 respectively represents low, moderate, and high methodological quality.

**1.5 Statistical Analysis**

We obtained the reported HRs or RRs directly from the publications. All statistical analyses were done using Stata SE12.0 (Stata Corporation). The $Q$ test and $I^2$ statistics were used to determine the heterogeneity among included studies[24, 25]. $P$ value less than 0.10 for $Q$ test indicated significant heterogeneity[26]; for $I^2$, cut-off value of 25%, 50%, and 75% divided heterogeneity into four levels: insignificant heterogeneity, low heterogeneity, moderate heterogeneity, and high heterogeneity[24]. The fixed-effect model was used to pool the results if $I^2$<50%, otherwise the random-effect model was chosen[26]. The presence of publication bias was evaluated by using Begg's funnel plots[27] and Egger's test[28]. Once publication bias was detected, the nonparametric trim and fill method[29] was used to estimate hypothetical "missing" studies and their HRs with 95%CI, and to evaluate whether these hypothetical "missing" studies may significantly alter the general results or not. By comparing the HRs of digestive system malignancies between high UCA1 expression group and low UCA1 expression group, we tried to make a thorough inquiry on the relationship between UCA1 expression levels and prognosis of digestive system tumors.

## 2 RESULTS

**2.1 Included Studies and Characteristics**

As shown in the flow chart (fig. 1), according to the criteria for selection, 15 articles with 16 studies were eligible for analysis[13, 16–20, 30–38]. The characteristics of included studies were presented in table 1. Among these studies, a total of 1504 patients were included, with a maximum sample size of 240 and a minimum sample size of 20 patients. Fourteen studies came from China[13, 16–19, 30, 32–38], and the rest 2 studies[20, 31] came from USA and Korea. The majority of included studies had a prospective design and used qRT-PCR for the detection of UCA1 expression levels. A total of 6 different types of cancer were involved in these studies, including CRC ($n$=6)[18, 19, 30, 35, 38], GC ($n$=3)[16, 17, 34], HCC ($n$=2)[20, 37], EC ($n$=2)[13, 36], pancreatic cancer (PC, $n$=2)[32, 33], and pancreatic ductal adenocarcinoma (PDAC, $n$=1)[31]. Patients in 10 studies[13, 16, 17, 19, 20, 32–35, 37] received no preoperative treatment, and the rest 6 studies[18, 30, 31, 36, 38] did not report this information. Fifteen studies[13, 17–20, 30–38] evaluated OS, and rest 3 studies[16, 17, 20] reported DFS. The average NOS score was 7.31, with 13 studies[13, 16–20, 32–35, 37, 38] scored 7–9, and 3 studies[30, 31, 36] scored 6.

**2.2 Association between UCA1 Expression and OS in Digestive System Malignancies**

The association between UCA1 expression and OS was reported in 15 studies[13, 17–20, 30–38] with a total of 1427 patients involved. There was no significant heterogeneity among the studies ($I^2$=0.0%, $P$=0.974), and the fixed-effects model was adopted to pool the result (fig. 2). Overall, a significant association was observed between UCA1 expression and OS (pooled HR=2.07, 95% CI: 1.74–2.47) (fig. 2). The overall result indicated that patients with high UCA1 expression were more likely to have significantly shorter OS.

Additionally, results for subgroup analysis according to cancer type, location, preoperative treatment, cut-off value, detection method, multivariate

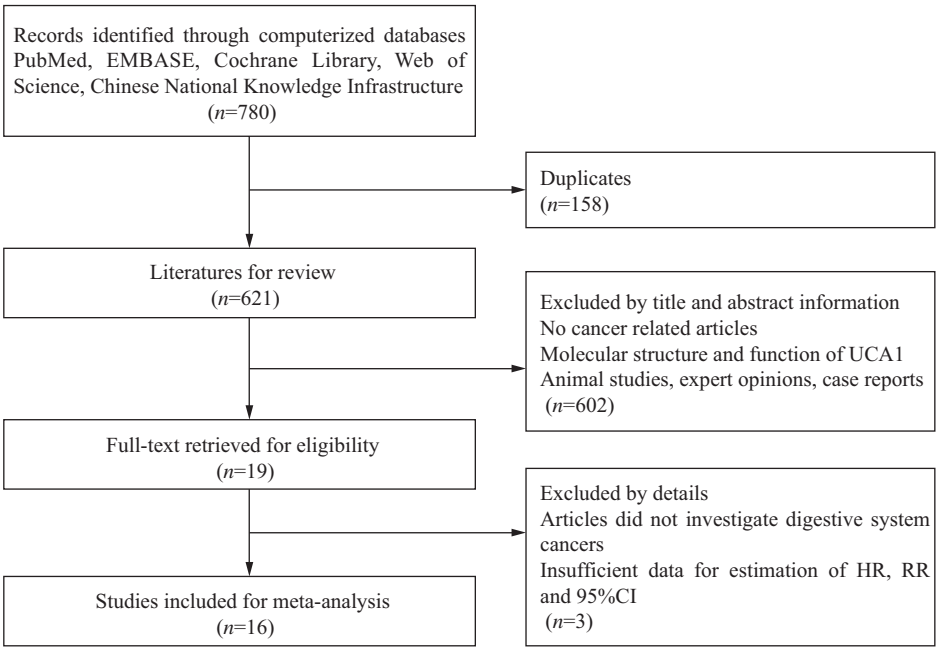


**Fig. 1** Flowchart presenting the steps of literature search and selection

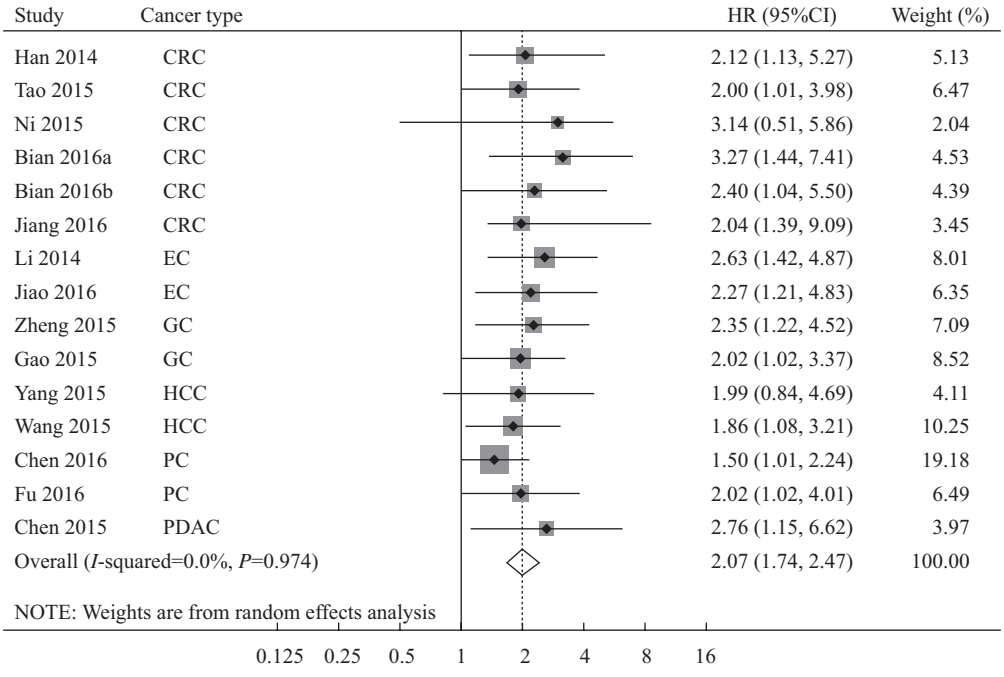


**Fig. 2** Forest plot for the association between UCA1 expression and the overall survival of patients with digestive system malignancies (pooled HR=2.01, 95%CI: 1.74–2.47); Bian 2016a: Subgroup 1; Bian 2016b: Subgroup 2

analysis, and study quality were shown in table 2. The pooled HR values of each subgroup were generally similar to those of overall results and greater than 1. The negative effect of elevated UCA1 expression on OS was observed in patients with CRC (HR=2.36, 95%CI: 1.68–3.32), EC (HR=2.46, 95%CI: 1.56–3.90), GC (HR=2.16, 95%CI: 1.39–3.36) , HCC (HR=1.90, 95%CI: 1.20–3.00) , PC (HR=1.62, 95%CI: 1.15–2.28), and PDAC (HR=2.76, 95%CI: 1.15–6.62) (table 2).

### 2.3 Association between UCA1 Expression and DFS in Digestive System Malignancies

Three studies[16, 17, 20] with 429 patients were included for analysis of association between UCA1 expression and DFS. The fixed-effects model was used in the meta-analysis considering that no significant

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

| Study | Location | Design | Sample size | Age | Gender (men%) | Cancer type | Tumor stage | Follow-up (months) | Preoperative treatment | Cut-off value | Detection method | Survival analysis | Multivariate analysis | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Han 2014 | China | Prospective | 80 | 55 | 49 | CRC | I -IV | Mean 42.6 | NA | Mean | qRT-PCR | OS | No | 7 |
| Li 2014 | China | Prospective | 90 | 60 | 55.6 | EC | I -IV | Median 43 | None | Median | qRT-PCR | OS | No | 7 |
| Yang 2015 | Korea | Prospective | 240 | 53 | 82.9 | HCC | I -IV | >60 | None | Mean | Illumina expression beadchip | OS, DFS | OS-no, DFS-yes | 7 |
| Wang 2015 | China | Prospective | 98 | NA | 86.7 | HCC | I -IV | >60 | None | Median | qRT-PCR | OS | Yes | 8 |
| Zheng 2015 | China | Prospective | 112 | NA | 57.1 | GC | I -IV | >60 | None | Median | qRT-PCR | OS, DFS | Yes | 8 |
| Gao 2015 | China | Prospective | 20 | NA | NA | GC | I -IV | NA | None | NA | qRT-PCR | OS | Yes | 7 |
| Tao 2015 | China | Prospective | 80 | 65.1 | 60 | CRC | I -IV | >60 | None | Fourth quartile | qRT-PCR | OS | Yes | 7 |
| Chen 2015 | USA | Retrospective | 63 | 68 | 52.4 | PDAC | I - II | Median 21 | NA | Mean+2 standard deviation | Affymetrix 2.0 microarray | OS | No | 6 |
| Ni 2015 | China | Prospective | 54 | NA | 72.2 | CRC | I -IV | >50 | NA | Median | qRT-PCR | OS | Yes | 7 |
| Jiang 2016 | China | Prospective | 121 | NA | 53.7 | CRC | I -IV | 1–60 | None | Median | qRT-PCR | OS | Yes | 8 |
| Fu 2016 | China | Prospective | 80 | 65 | 56.3 | PC | I -IV | >40 | None | Median | qRT-PCR | OS | Yes | 8 |
| Chen 2016 | China | Prospective | 128 | NA | 61.7 | PC | I -IV | 1–60 | None | Mean | qRT-PCR | OS | Yes | 9 |
| Shang 2016 | China | Prospective | 77 | 60.4 | 50.6 | GC | I -IV | >60 | None | Mean | qRT-PCR | DFS | Yes | 8 |
| Bian 2016a | China | Prospective | 90 | NA | 54.4 | CRC | I -IV | >60 | NA | Median | qRT-PCR | OS | Yes | 8 |
| Bian 2016b | China | Prospective | 105 | NA | NA | CRC | I -IV | >60 | NA | Median | qRT-PCR | OS | No | 6 |
| Jiao 2016 | China | Retrospective | 66 | NA | 54.5 | EC | I -IV | 1–30 | NA | Median | qRT-PCR | OS | No | 6 |

CRC: colorectal cancer; EC: esophageal carcinoma; HCC: hepatocellular carcinoma; GC: gastric cancer; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; OS: overall survival; DFS: disease-free survival; qRT-PCR: quantitative real-time-polymerase chain reaction; NA: not available; Bian 2016a: Subgroup 1; Bian 2016b: Subgroup 2

heterogeneity was detected among the studies ($I^2$=0.0%, $P$=0.992) (fig. 3). The pooled result confirmed a significant association between UCA1 expression and DFS (pooled HR=2.50, 95%CI: 1.62–3.86) (fig. 3), suggesting that patients with high UCA1 expression had significantly poor DFS. For the 2 studies on GC, negative effect of elevated UCA1 expression on DFS was observed in patients with GC (HR=2.55, 95%CI: 1.51–4.28).

### 2.4 Sensitivity Analysis

Sensitivity analysis was conducted to examine the effect of a single study on the overall meta-analysis results by omitting one study in turn. The re-pooled HR of OS, and DFS for patients with digestive system malignancies, respectively ranged from 2.03 (95%CI: 1.70–2.43) to 2.24 (95%CI: 1.84–2.72), and 2.40 (95%CI: 1.09–5.27) to 2.55 (95%CI: 1.33–4.97), none of the results were significantly altered each time (fig. 4 and 5).

### 2.5 Publication Bias

For meta-analysis of the association between UCA1 expression and OS, significant publication bias was detected by the Egger's test ($P$=0.042), and the shape of Begg's funnel plot was asymmetric (fig. 6A). The "fill and trim" method identified hypothetical 7 "missing" studies, and the estimated pooled HR with fixed-effect model ($I^2$%=0.0%, $P$=0.907) was 1.83 (95%CI: 1.57–2.12), which did not markedly differ from the general results (fig. 6B). For meta-analysis of the association between UCA1 expression and DFS, the Begg's funnel plot (fig. 7) and the Egger's test ($P$=0.764) both revealed no publication bias.

## 3 DISCUSSION

This meta-analysis systematically reviewed and examined the association of lncRNA UCA1 expression and its prognostic role in digestive system malignancies. A total of 16 studies comprising 1504 patients were included in this meta-analysis. It was demonstrated that UCA1 expression was associated with a poorer prognosis in patients with different types of digestive system malignancies. The above findings suggest that UCA1 expression might be more meaningful in predicting OS or DFS of patients with digestive system carcinoma than those with non-digestive system cancer. Both subgroup analysis and sensitivity analysis were performed in the current study, enhancing the statistical power of the findings from this meta-analysis.

LncRNAs are conserved ncRNAs of more than 200 nt in length, and have no protein coding capacity[39]. They are demonstrated to be closely correlated with various biological processes[40–42], such as chromosome inactivation, splicing regulation of cell differentiation and mRNA degradation and translation. Besides their role in normal cellular physiology, evidence has linked

**Table 2 Subgroup analysis of association between UCA1 expression and OS**

| Variables | No. of studies | No. of patients | HR (95%CI) | Model | $I^2$ % | *P* value |
|---|---|---|---|---|---|---|
| Total | 15 | 1427 | 2.07 (1.74, 2.47) | FEM | 0.0 | 0.974 |
| Cancer type | | | | | | |
| CRC | 6 | 530 | 2.36 (1.68, 3.32) | FEM | 0.0 | 0.944 |
| EC | 2 | 156 | 2.46 (1.56, 3.90) | FEM | 0.0 | 0.756 |
| GC | 2 | 132 | 2.16 (1.39, 3.36) | FEM | 0.0 | 0.738 |
| HCC | 2 | 338 | 1.90 (1.20, 3.00) | FEM | 0.0 | 0.896 |
| PC | 2 | 208 | 1.62 (1.15, 2.28) | FEM | 0.0 | 0.461 |
| PDAC | 1 | 63 | 2.76 (1.15, 6.62) | NA | NA | NA |
| Location | | | | | | |
| China | 13 | 1124 | 2.05 (1.71, 2.46) | FEM | 0.0 | 0.950 |
| Others | 2 | 303 | 2.34 (1.27, 4.32) | FEM | 0.0 | 0.601 |
| Design | | | | | | |
| Prospective | 13 | 1298 | 2.03 (1.69, 2.45) | FEM | 0.0 | 0.953 |
| Retrospective | 2 | 129 | 2.45 (1.42, 4.21) | FEM | 0.0 | 0.731 |
| Preoperative treatment | | | | | | |
| None | 9 | 969 | 1.93 (1.57, 2.36) | FEM | 0.0 | 0.974 |
| NA | 6 | 458 | 2.54 (1.80, 3.57) | FEM | 0.0 | 0.938 |
| Cut-off value | | | | | | |
| Mean | 3 | 448 | 1.66 (1.20, 2.31) | FEM | 0.0 | 0.668 |
| Median | 9 | 816 | 2.31 (1.81, 2.93) | FEM | 0.0 | 0.983 |
| Others | 3 | 163 | 2.15 (1.44, 3.21) | FEM | 0.0 | 0.820 |
| Detection method | | | | | | |
| qRT-PCR | 13 | 1124 | 2.05 (1.71, 2.46) | FEM | 0.0 | 0.950 |
| Others | 2 | 303 | 2.34 (1.27, 4.32) | FEM | 0.0 | 0.601 |
| Multivariate analysis | | | | | | |
| Yes | 9 | 783 | 1.95 (1.58, 2.41) | FEM | 0.0 | 0.842 |
| No | 6 | 644 | 2.37 (1.74, 3.22) | FEM | 0.0 | 0.993 |
| Study quality | | | | | | |
| High | 12 | 1193 | 2.02 (1.67, 2.44) | FEM | 0.0 | 0.932 |
| Moderate | 3 | 234 | 2.43 (1.54, 3.83) | FEM | 0.0 | 0.942 |

HR: hazard ratio; CI: confidence interval; FEM: Fixed-effect model; CRC: colorectal cancer; EC: esophageal carcinoma; HCC: hepatocellular carcinoma; GC: gastric cancer; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; OS: overall survival; DFS: disease-free survival; qRT-PCR: quantitative real-time-polymerase chain reaction; NA: not available

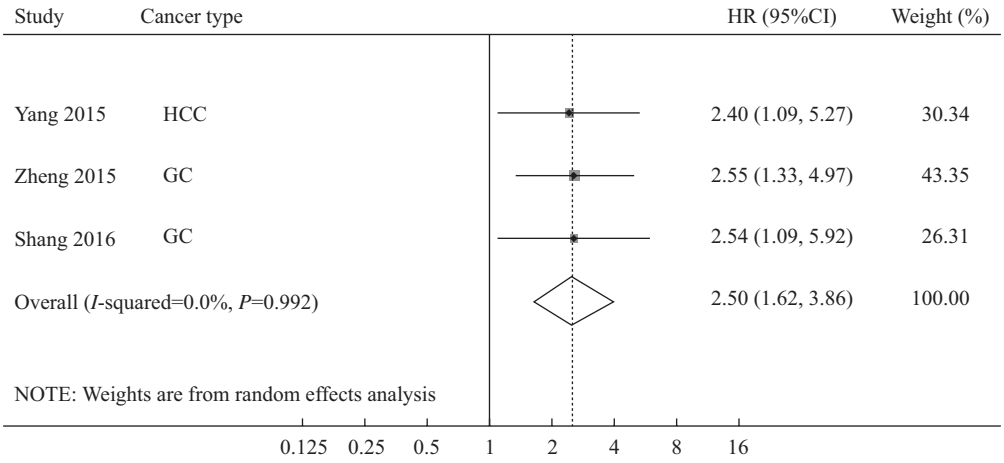


**Fig. 3** Forest plot for the association between UCA1 expression and the disease-free survival of patients with digestive system malignancies (pooled HR=2.50, 95% CI: 1.62–3.86)

lncRNA expression and functions to digestive cancer development and progression[43]. Thus, lncRNAs have opened a new field of cancer genomic.

UCA1, consisting of three exons with 1.4 kb in length, is an lncRNA originally identified in bladder transitional cell carcinoma[44]. As its first description in 2006, some reports have shown that lncRNAs play important roles in many physiological and pathological

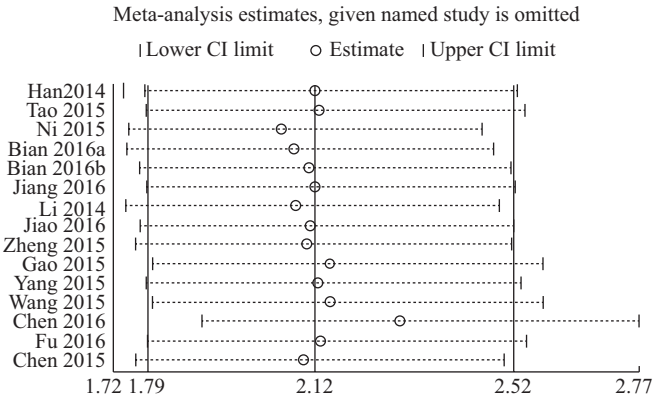


**Fig. 4** Sensitivity analysis of HR for association between UCA1 expression and overall survival

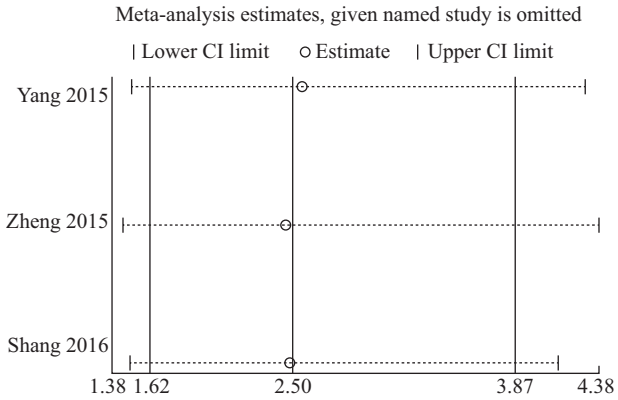


**Fig. 5** Sensitivity analysis of HR for association between UCA1 expression and disease-free survival

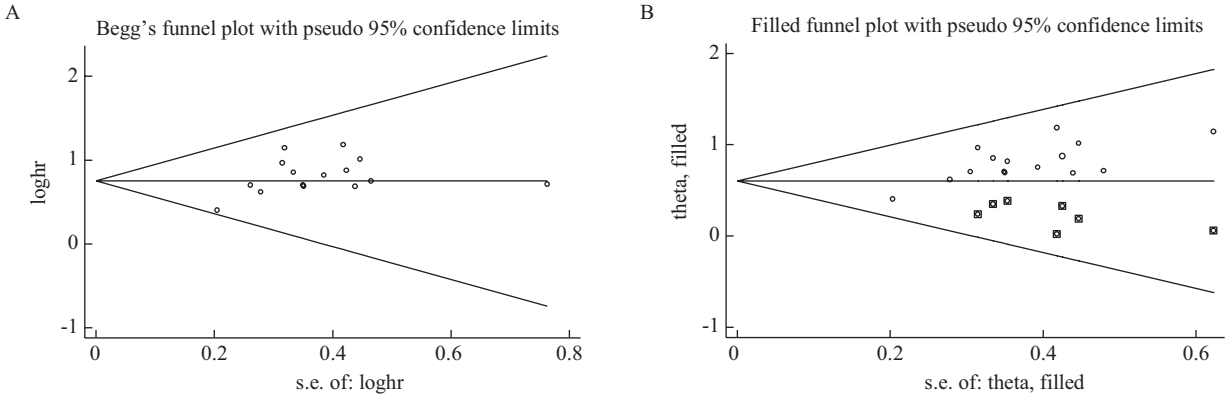


**Fig. 6** Funnel plot of HR for association between UCA1 expression and overall survival
A: Begg's funnel plot; B: Filled funnel plot with "trim-and-fill" method

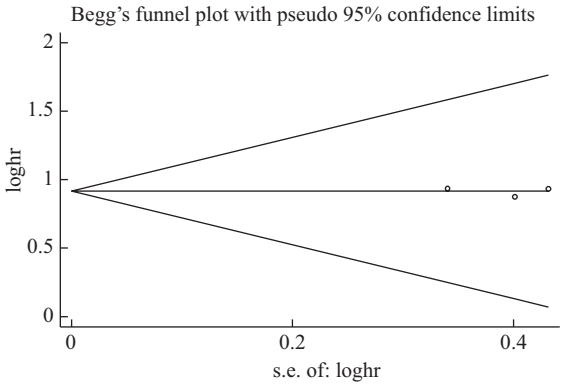


**Fig. 7** Funnel plot of HR for association between UCA1 expression and disease-free survival

processes, particularly in carcinogenesis[14]. And several articles have confirmed UCA1 to be a biomarker for urothelial carcinoma and is highly expressed in other cancers[13]. It is worth noting that many literatures have inspected that lncRNA UCA1 plays a vital role in deregulated expression in digestive system cancers[18, 34].

This meta-analysis provided evidence that UCA1 overexpression is associated with poor prognosis in patients with different types of digestive system cancers. Compared to patients with low UCA1 expression, patients with high UCA1 expression may suffer shorter OS, which was accordantly observed in patients with CRC, EC, GC, HCC, and PC. Meanwhile, though only 3 studies[16, 17, 20] reported the association between UCA1 expression and DFS in digestive system malignancies, it was also indicated that high UCA1 expression was associated with poorer DPS in patients with GC and HCC. Therefore, UCA1 could be applied as an appropriate prognostic marker for different types of digestive system cancers.

The included studies varied in different aspects, such as cancer type, study location, and preoperative treatment. The variation of studies may bring about heterogeneity which reduces the reliability of result of this meta-analysis. However, no statistically significant heterogeneity was found across studies. Meanwhile, results from subgroup analysis according to cancer type, location, preoperative treatment, cut-off value, detection method, multivariate analysis, and study quality, and from sensitivity analysis suggested that the overall results were rather robust.

Several limitations of this meta-analysis should be emphasized. First, because the sample size of included

studies ranged from 20 to 240, with an average sample size of 94, larger-size and better design studies are necessary to confirm the present findings. Second, most included studies were conducted in China, the findings from this study may not be well suitable for other ethnic groups, more studies concerning patients from other ethnic groups are needed. Third, the cut-off value of high and low UCA1 expression varied in different studies. It was difficult to reach a consensus value. Fourth, the treatment protocols are different in the various studies, and these differences might have an impact on survival and thus result in some heterogeneity. Fifth, publication bias was detected among studies, though the nonparametric trim and fill method was used and had indicated no significant impact from publication bias to general results, the potential overestimation of HRs may still exist because of the limited sum number of included studies. Thus, the significant association between UCA1 overexpression and poor prognosis in digestive system malignancies should be confirmed in further studies.

In conclusion, our study found that UCA1 might be a novel predictive factor for assessing poor prognosis in different types of digestive system malignancies. Future well designed studies are needed to confirm the present findings.

**Conflict of Interest Statement**

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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