Original Paper

The Value of lncRNA HULC as a Prognostic Factor for Survival of Cancer Outcome: A Meta-Analysis

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Key Words

lncRNA • HULC • Overall survival

Abstract

Aims: Growing evidence from recent studies has shown that lncRNA HULC plays a role in the development of multiple carcinomas. This meta-analysis aimed to analyze available data to identify the prognostic value of HULC in multiple tumors. **Methods:** A systematic search was performed by using PubMed (medline), Embase, ISI Web of Knowledge, Springer, the Cochrane Library, Scopus, BioMed Central, ScienceDirect, Wanfang, Weipu, and China National Knowledge Internet (CNKI) computerized databases from inception to Nov 30, 2016. The quality of the publications was assessed according to the critical review checklist of the Dutch Cochrane Centre proposed by MOOSE and PRISMA. Pooled hazard ratios (HR) with 95% confidence interval (95% CI) were calculated to summarize the effect. **Results:** A total of ten studies with 1077 cancer patients were pooled in the present meta-analysis to evaluate the prognostic value of HULC in multiple tumors. High expression levels of HULC were demonstrated to be associated with poor overall survival (OS) (HR=2.44, 95%CI: 1.96-3.03, $P=0.000$). Subgroup analysis showed that cancer type (digestive or non-digestive disease), residence region (China), sample size (more or less than 100) and follow-up months (more or less than 60) did not alter the predictive value of HULC on OS in various cancers. Additionally, increased HULC expression was found to be moderately associated with tumor stage and progression (III/IV vs. I/II: HR=1.59, 95% CI: 1.31-1.92, $P<0.00001$). Furthermore, elevated HULC expression significantly predicted distant metastasis (HR=3.90, 95% CI: 1.89-8.02, $P=0.0002$) and lymph node metastasis (HR=2.04, 95% CI: 1.03-4.05, $P=0.04$) respectively. No significant heterogeneity was observed among studies except lymph node metastasis. **Conclusion:** The results indicate that HULC expression level is an independent prognostic biomarker for unfavorable OS and metastasis in general tumors.

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Introduction

Cancer is becoming the leading cause of mortality and morbidity for human health over the past decade [1]. According to 2014 Cancer Statistics, an estimated 1,665,540 new cancer

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cases and 585,720 cancer deaths are projected to occur in the United States [2]. To date, the mechanisms of oncogenesis and tumor progression have not been fully clarified and the widely used prognostic markers are still tumor node metastasis (TNM) stage and grade, histological differentiation grade, and tumor size etc. Thus, many scientists are devoted to identify new potential biomarker for forecasting prognosis and predicting the therapeutic efficacy for cancer patients to improve their survival status [3, 4].

Non-coding RNAs refer to different types of RNA which can not produce biologically meaningful RNA transcripts, usually including small interfering RNA (short interfering RNA, siRNA), PIWI-interacting RNA (piRNA), microRNA (miRNA) and long noncoding RNAs (lncRNAs) etc. [5, 6]. Recent articles have indicated that at least 95% of the human genome undergoes transcription to a huge array of RNA species and most of them are longer than 200 nucleotides [7]. Mounting evidence links expression changes of lncRNAs with complex diseases such as cancer. The dysregulation suggests that lncRNAs emerge as vital modulators in carcinomas and thus further emphasize the potential role of lncRNAs in tumorigenesis and tumor progression [8-10].

Highly up-regulated in liver cancer (HULC), as one of the most up-regulated ncRNAs, was first identified from an HCC-specific gene expression profiling [11, 12]. Recently, many observations indicate that the striking promoted expression pattern was associated with worse survival and high risk of cancer metastasis in patients with various carcinomas [13, 14]. However, most individual studies assessing the implications of HULC levels in cancer have been limited by small sample sizes and the controversial results. Therefore, a comprehensive meta-analysis of all eligible articles was performed to further evaluate the clinical feasibility of HULC as a novel biomarker candidates as well as useful insights into the tumor clinicopathological features.

Material and Methods

Search strategy and Literature selection

Up to November 30, 2016, potential eligible literatures which evaluated the lncRNA HULC as a putative biomarker for the prognosis and metastasis of various tumors, were searched in several computerized databases, including PubMed, Embase, Cochrane Library, ScienceDirect, BioMed Central, Springer, ISI Web of Knowledge, together with three Chinese databases: China National Knowledge Internet (CNKI), Wanfang and Weipu databases. The searched terms in variably combinations were listed as follows: ("long noncoding RNA-, lnc RNA-, highly up-regulated in liver cancer, HULC,") and ("cancer" or "carcinoma" or "tumor" or "neoplasm") and ("prognosis" or "prognostic" or "survival" or "metastasis"). The reference lists of primary literatures were manually searched for additional relevant articles.

Inclusion and exclusion criteria

Inclusion criteria are as following: 1) Articles investigating the expression pattern of HULC in any malignant tumor; 2) Definite diagnosis or histopathology confirmed for patients with cancer; 3) Sufficient data for the computation of hazard ratio (HR) and corresponding 95% confidence intervals (CI); 4) Studies with enough information to construct the 2×2 contingency Table.

Exclusion criteria are as following: 1) Studies investigating the molecular structure and functions of HULC or literatures not pertinent to the HULC; 2) Studies of non dichotomous HULC expression and absence of survival outcome; 3) Duplicate publications as well as multiple duplicate data in the different works, excluding earlier and smaller sample data; 4) Correspondences, animal experiments, letters, editorials, expert opinions, talks, reviews and case reports without original data.

Data extraction and Quality Assessment

Two investigators (XC and YYZ) extracted all the essential information from identified articles independently. According to the inclusion and exclusion criteria, the following information from each enrolled study was extracted: (1) first authors, publication year, study population, patients and controls size, tumor type, follow-up month; (2) HULC assessment method and specimen; (3) HR and their 95%

CI of HULC value for overall survival (OS), distant metastasis (DM) or lymph node metastasis (LNM). If any essential information were not available from the original article, best efforts were made to contact the corresponding author to obtain the missing data. If only Kaplan–Meier curves were provided in some studies, the survival rates were extracted from the graphical survival plots and the calculated HR and 95% CI was determined as the published methods [15, 16]. As shown in supplementary materials (Checklist Table 5 and Table 6), all the included publications were evaluated based on the critical checklist of the Dutch Cochrane Centre proposed by MOOSE and PRISMA.

Statistical analysis

The present analyses were performed using Stata SE12.0 (Stata Corporation) and RevMan5.1 software. The impact of HULC expression on clinical prognosis and metastasis was described as HR and corresponding 95% CI. The combined effect size (ES) was considered as HR and should be statistically significant when the 95% CI did not overlap with 1. Heterogeneity across the enrolled studies was quantified with the I^2 statistics. The fix-effects model with the inverse variance method was conducted to analyze the relationship between HULC expression and clinical outcomes when calculated $I^2 < 50\%$ [17, 18]. Probable publication bias was displayed not only by constructing a funnel plot, but also conducting Begg's test with rank correlation method and Egger's bias indicator test with linear regression method respectively [19–21]. P values < 0.05 was considered statistically significant.

Results

Included literatures

A total of 257 studies were retrieved from an initial online literature search that related to the prognosis and metastasis of HULC and cancer. After carefully screening the titles and abstracts, 234 articles were excluded according to the inclusion and exclusion criteria. For the remaining potential candidate studies, 23 articles were further reviewed of the full texts, 1 study was excluded as the specimen sources was not clearly described, 12 studies were then excluded because HULC was not a dichotomic variable in the original studies. As shown in Fig 1, the selection process with specification was presented by a flow diagram. Ultimately, the present meta-analysis was conducted for the remaining 10 articles.

Fig. 1. Flow diagram of the study search and selection process.

Table 1. Summary of the ten included studies. Study design is described as retrospective (R); PC, Pancreatic cancer; OSA, osteosarcoma; GC, gastric cancer; LBL, large B-cell lymphoma; CC, cervical cancer; DM, distant Metastasis; LNM, Lymph Node Metastasis; VM, Vascular metastasis

Study	Origin of population	Study design	Disease	No. of patients	Stage	HULC assay	Survival analysis	Metastasis analysis	Hazard ratios	Follow-up Months
Peng et al 2014 [22]	China	R	PC	304	NA	qRT-PCR	OS	LNM/VM	HR/K-M	60
Sun et al 2015 [13]	China	R	OSA	78	IIA/IIIB-III	qRT-PCR	OS	DM	HR/K-M	60
Jin et al 2016 [23]	China	R	GC	100	I/II/III/IV	qRT-PCR	OS	LNM/DM	HR/K-M	30
Li et al 2016 [24]	China	R	HCC	38	I-II/III-IV	qRT-PCR	OS/RFS	DM	K-M	60
Peng et al 2016 [25]	China	R	LBL	142	I-II/III-IV	qRT-PCR	OS/PFS	NA	HR/ K-M	60
Uzan et al 2016 [26]	Brazil	R	OSA	33	I-II/III-IV	qRT-PCR	OS/EFS	DM	K-M	60
Wang et al 2016 [27]	China	R	CC	244	IIb-IIIa/Ib-IIa	qRT-PCR	OS	LNM	HR/K-M	60
Zhang et al 2016 [28]	China	R	GC	42	NA	qRT-PCR	OS	NA	K-M	60
Xie et al 2013 [29]	China	R	HCC	30	I-II/III-IV	qRT-PCR	NA	NA	NA	NA
Li et al 2015 [30]	China	R	HCC	66	I/II/III/IV	qRT-PCR	NA	NA	NA	NA

Fig. 2. Forest plot for the association between HULC expression with overall survival (OS).

Characteristics of the enrolled studies

The main features of the 10 enrolled articles are summarized in Table 1 [13, 22-30]. These studies were published between 2013 and 2016 with sample sizes ranging from 30 to 304. All of the 1077 patients were divided into two groups (high and low expression of HULC) according to the qRT-PCR measurement results. Nine of ten studies were from China and the patients were 6 types of carcinomas, including hepatocellular carcinoma, gastric cancer, pancreatic cancer, osteosarcoma, cervical cancer and large B-cell lymphoma. Of note, the median value was selected as the cut-off value in most articles.

HULC and main outcome

The fix effects model was used to analysis the pooled HR and its 95% CI because no obvious heterogeneity among those 8 studies which involved in OS analysis ($I^2 < 50\%$). According to meta result in multivariate analysis, enforced HULC expression was predictive of unfavorable OS in various carcinomas (HR=2.44, 95%CI: 1.96-3.03, $P=0.000$) (Fig. 2).

Afterwards the stratified analyses were performed by factor of country, cancer type, sample size and follow-up month to further analyze the clinical features of HULC (Table 2). For studies evaluating OS in different types of cancer, the results suggested that promoted HULC levels could estimate worse outcome in digestive system or non-digestive system malignancies, with the pooled HR of 2.57 (95% CI: 1.96-3.38, $P=0.000$), and 2.21 (95% CI: 1.54-3.17, $P=0.000$) respectively (Fig. 3A). A significant unfavorable association between HULC and OS of cancer patients was detected in China (HR=2.41, 95%CI: 1.93-3.01, $P=0.000$) (Fig. 3B). Subsequently, we found that neither sample size nor follow up month alter the predictive value of HULC on the OS for all involved cancers (Fig. 3C and 3D). No significant heterogeneity was detected across studies within the subgroups.

Fig. 3. Stratified analyses for the association between HULC expression with overall survival (OS). (A) Subgroup analysis of HRs of OS by factor of cancer type. (B) Subgroup analysis of HRs of OS by factor of residence region. (C) Subgroup analysis of HRs of OS by factor of sample size. (D) Subgroup analysis of HRs of OS by factor of follow up months.

Table 2. Subgroup analysis of the pooled HRs of overall survival with over-expressed HULC in patients with cancer

Subgroup analysis	No. of studies	No. of patients	Pooled HR (95% CI)		Heterogeneity (Fix)	
			Fix	p Value	I ² (%)	p Value
Region						
China	7	948	2.41(1.93, 3.01)	0.000	0%	0.916
Type of cancer						
Digestive system	4	484	2.57 (1.96, 3.38)	0.000	0%	0.828
Non-Digestive system	4	497	2.21 (1.54, 3.17)	0.000	0%	0.818
Sample size						
≥100	4	790	2.46 (1.89, 3.20)	0.000	0%	0.584
<100	4	191	2.37 (1.61, 3.51)	0.000	0%	0.963
Follow-up months						
≥60	7	881	2.48 (1.96, 3.13)	0.000	0%	0.913

Fig. 4. Forest plot for the association between HULC expression with TNM stage (III/IV vs. I/II).

As shown in Fig. 4, increased HULC expression was found to be moderately associated with tumor stage and progression (III/IV vs. I/II: HR=1.59, 95% CI: 1.31-1.92, $P < 0.00001$).

Table 3. Characteristics of studies included in the LNM meta-analysis

Study	No. of patients	Method	HULC Metastasis	High Total	HULC Metastasis	Low Total
Peng et al. 2014 [22]	304	qRT-PCR	157	212	23	92
Jin et al. 2016 [23]	100	qRT-PCR	34	48	25	52

Table 4. Characteristics of studies included in the DM meta-analysis

Study	No. of patients	Method	HULC Metastasis	High Total	HULC Metastasis	Low Total
Sun et al. 2015 [13]	78	qRT-PCR	16	39	5	39
Jin et al. 2016 [23]	100	qRT-PCR	9	48	2	52
Li et al. 2016 [24]	38	qRT-PCR	8	23	1	15

Fig. 5. Forest plot for the association between HULC expression with DM (A) and LNM (B).

Fig. 6. Funnel plot of the publication bias for OS.

Fig. 7. Sensitivity of HULC expression for OS.

Overall, the pooled HRs revealed that HULC expression might be served as an unfavorable independent prognostic biomarker in various types of cancers.

HULC and metastasis

The characteristics of the involved studies which evaluating the association between HULC levels and cancer metastasis were summarized in Table 3 and 4. A fix model was performed to calculate the pooled HR and its 95% CI when there is no obvious heterogeneity between studies ($I^2 < 50\%$). As shown in Fig. 5, elevated HULC expression significantly predicted DM (HR=3.90, 95% CI: 1.89-8.02, $P=0.0002$) and LNM (HR=2.04, 95% CI: 1.03-4.05, $P=0.04$) respectively.

Publication bias

The potential publication bias of the present meta-analysis was evaluated by a funnel plot, Begg's test and Egger's test. No evidence of publication bias in the multivariate analysis

Table 5. MOOSE checklist

Reporting of background should include	
Problem definition	Background (Page 3)
Hypothesis statement	Background (Page 3)
Description of study outcome(s)	OS, RFS, PFS, EFS, LNM, VM, DM
Type of exposure or intervention used	Various cancer (Page 3)
Type of study designs used	Meta-analysis (Page 3)
Study population	Global (Page 3)
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Investigator (Page 4)
Search strategy, including time period included in the synthesis and keywords	Search strategy and selection criteria (Page 4)
Effort to include all available studies, including contact with authors	We contact authors and searched reference lists and citations (Page 4)
Databases and registries searched	Methods (Page 3)
Search software used, name and version, including special features used (eg, explosion)	IE 10
Use of hand searching (eg, reference lists of obtained articles)	Search strategy and selection criteria (Page 4)
List of citations located and those excluded, including justification	Flow diagram in Figure 1. (Page 5)
Method of addressing articles published in languages other than English	Search strategy and selection criteria (Page 4)
Method of handling abstracts and unpublished studies	Method (Page 4)
Description of any contact with authors	Method (Page 4)
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Method (Page 4)
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Methods (Page 4)
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Methods (Page 4)
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Methods (Page 4)
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Methods (Page 4)
Assessment of heterogeneity	Methods (Page 4)
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods (Page 4)
Provision of appropriate tables and graphics	Methods and Results (Page 4)
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Figure 2, 3, 4, 5 and 6
Table giving descriptive information for each study included	Table 1
Results of sensitivity testing (eg, subgroup analysis)	Meta-analysis (Page 6)
Indication of statistical uncertainty of findings	Discussion (Page 6)
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Results (Page 5)
Justification for exclusion (eg, exclusion of non-English-language citations)	Discussion (Page 6)
Assessment of quality of included studies	Quality Assessment (Page 4)
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Discussion (Page 7)
Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Discussion (Page 7)
Guidelines for future research	Discussion (Page 8)
Disclosure of funding source	Grant Support (Page 9)

of OS for Begg's and Egger's test. ($P=0.23$ and $P=0.45$), and the shapes of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 6).

Sensitivity analysis

The stability of the crude results was evaluated by sensitivity analysis. The results suggested that the conclusions are stable because the pooled HR was not significantly affected by the exclusion of any single study (Fig. 7).

Discussion

LncRNAs were defined as transcriptional noise in the past decades because most of them produced from intergenic and intronic regions of the genome and lack protein coding

Table 6. PRISMA checklist

TITLE The Value of lncRNA HULC as a Prognostic Factor for Survival of Cancer Outcome: A Meta-Analysis			
Section/topic	#	Checklist item	Reported on page #
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	5

capability [5, 31]. In recent years, tremendous contributions were made by scientists to the discovery that lncRNAs regulate the target gene expression and act as oncogenic or tumor suppressors [32-34]. With the rapid development of high-throughput genome-wide analysis technology, lncRNAs have been proposed as promising biomarkers for early detection and accurate prognosis for various carcinomas [35, 36].

As one of the promising novel biomarkers with high accuracy prognostic value for cancer patients, HULC has been noted to associate with diverse cellular processes, including migration, invasion, proliferation, differentiation, and apoptosis and are thereby prone to be involved in the tumorigenesis and progression [12, 14, 37, 38]. For example, HULC has been demonstrated to regulate hepatocellular cancer (HCC) proliferation through a miR-9-mediated RXRA signaling pathway or suppressing the expression of tumor suppressor p18 [39, 40]. Additionally, HULC may function as a competing endogenous RNA (ceRNA) in HCC that binds to and reduces the expression of a number of miRNAs. The reduction of miR-220a-3p and miR-372 leads to tumor progression through the miR-200a-3p/ZEB1 and miR-372/PRKACB signaling pathway respectively [24, 41]. Though a large number of studies have explored HULC interaction partners and molecular functions in various tumors, the mechanisms underlying HULC and tumor progression are still elusive.

Emerging evidence is encouraging that high expression of HULC serves as a convinced poor prognosis in several types of cancers, such as hepatocellular carcinoma, gastric cancer, pancreatic cancer, osteosarcoma, cervical cancer and large B-cell lymphoma. According to the urgently needed of potential prognostic biomarkers for individual therapy to the high-risk cancer patients, we firstly performed the present comprehensive and detailed meta-analysis to investigate the clinical prognostic role of HULC with a variety of carcinomas. Ten studies including 1077 patients were pooled in this study, and the results indicate that elevated HULC expression was significant correlated with poor prognosis, progression, DM and LNM in patients with various types of cancer. The analysis showed a pooled HR was 2.44 (95% CI: 1.96-3.03, $P=0.000$), 1.59 (95% CI: 1.31-1.92, $P<0.00001$), 3.90 (95% CI: 1.89-8.02, $P=0.0002$) and 2.04 (95% CI: 1.03-4.05, $P=0.04$) for OS, progression, DM and LNM respectively.

Nevertheless, it should be noted that there are several limitations of this study should be discussed. First, some of the HR were calculated by reconstructing survival curves rather than directly obtained from the primary studies. Second, cut off definition were not reported in some studies, and those reported were different in each study, which might weaken the reliability of our conclusion. In addition, the major patients included in our study were most from China and only one study was from Brazil. Because of this, our finding may just represent patients from Asia. After full texts of involved articles were reviewed, cancerous tissues were examined to determine HULC expression level in most cases, while serum samples were tested in one study. Of note, different specimen sources might be a further bias of the study. Finally, sample size of the study is too small. Only 10 studies with 1077 patients were included in the present meta-analysis. Therefore, we strongly suggest conducting more larger-size and better design studies to confirm our results.

In aggregate, even some limitations mentioned above, it was preliminarily concluded that promoted HULC may be considered as a credible unfavorable prognostic factor in human cancers. In the future, well designed larger-sample studies will be necessary to verify and strengthen the prognostic role of HULC in neoplasm patients.

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Disclosure Statement

The authors declare that there are no competing interests to disclose.

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