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ORIGINAL ARTICLE

The Significance of Long Non-coding RNA HULC in Predicting Prognosis and Metastasis of Cancers: a Meta-Analysis

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Abstract Long non-coding RNAs (lncRNAs) have been demonstrated that they not only play important roles in tumorgenicity but also associate with cancer prognosis. Recently, highly up-regulated in liver cancer (HULC) is abnormally expressed in liver cancer and other cancers, and participated in cancers progression; however, it is unclear whether its expression is associated with prognosis. Here, we performed a meta-analysis and systematic review to evaluate the prognostic value and metastasis of HULC in various cancer patients. The meta-analysis was performed using a systematic search of PubMed, Web of Science, ScienceDirect and Wiley Online Library database to eligible studies. The pooled hazard ratios (HRs) with a 95% confidence interval (95% CI) were calculated to assess its prognosis and metastasis in human cancer. A total of 1134 patients from 11 studies were included. The results indicated that overexpression of HULC was associated with poor overall survival (OS) (HR = 1.89, 95% CI: 1.32–2.47). Furthermore, subgroup analysis showed that cancer type (digestive system cancer or non-digestive system cancers) and sample size (more or less than 100) significantly associated between HULC and OS. In addition, overexpression of HULC expression was significantly associated with metastasis in cancers (HR = 2.67, 95% CI: 0.94–4.39). The meta-analysis indicated that lncRNA HULC could serve as a new molecular marker for cancer prognosis and metastasis.

Keywords lncRNA · HULC · Neoplasms · Prognosis · Metastasis · Meta-analysis

Introduction

With the rising in the incidence and mortality of cancers, cancer is becoming a major public health problem [1]. Early detection, diagnosis and treatment of cancers are the major strategies to reduce mortality and improve survival. However, the current status of cancer is that the 5-year survival rate is still low in many types of human cancers. Thus, it is important to identify the new potential diagnostic and prognosis tumor markers to help early prevention and treatment of cancers [2–4].

Long non-coding RNAs (lncRNAs) are the RNA molecules larger than 200 nucleotides and cannot code any proteins [5]. LncRNAs participate in the body's health physical function mainly through epigenetics, transcription and post-transcriptional regulation of gene expression levels [6, 7]. In recent years, tons of studies have shown that lncRNA is closely related to tumor biology, and can be used as markers in prognosis of cancer patients [8]. LncRNA HULC is a 500 nt-nucleotide-long lncRNA located on chromosome 6p24.3, a specific and over-expressed in liver cancer [9]. Furthermore, lncRNA HULC was found to be closely related to the development and progression of liver cancer. In addition, abnormal expression of HULC was also associated with the development of other malignancies,

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including osteosarcoma [10], cervical cancer [11], colorectal cancer [12] and so on [13, 14].

However, many articles only assess the role of HULC in a particular tumor prognosis or metastasis respectively, and there is no systematic meta-analysis of the association of HULC with the prognosis of cancer patients, and the effect of HULC on the outcome of cancer patients remains unclear, thus, we collected all relevant articles and carried out a quantitative meta-analysis to explore the relationship between HULC expression levels with prognosis and metastasis in cancers.

Materials and Methods

Literature Search

Potential qualified studies were searched and collected in databases including PubMed, Web of Science, ScienceDirect and Wiley Online Library, and the deadline of published paper was January 8, 2017. All the publication language was limited to English. The keywords for the search in these databases included: "HULC", "long non-coding RNA HULC", "lncRNA HULC", "cancer", "tumor", "carcinoma" and "neoplasm". The above searches were carried out by two investigators independently.

Inclusion and Exclusion Criteria

The following are criteria for the inclusion: (1) studies were to investigate the role of HULC in various cancers; (2) associations of HULC expression with prognosis; (3) the expression level of HULC in primary cancerous tissue was determined by qRT-PCR; (4) patients were divided into two groups according to the expression level of HULC; (5) articles containing sufficient data for the computation of hazard ratios (HRs) and corresponding 95% confidence intervals (CI).

The exclusion criteria are included as follows: (1) studies without usable data; (2) duplicated publications; (3) studies only investigated the molecular structure and functions of HULC; (4) letters, reviews, case reports and expert opinions.

Data Extraction and Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) contains selection, outcome and comparability, with a score range of 0–9. Two investigators (YY, Ding and C, Sun) assess the quality of each study independently. All study and information data were screened and extracted by two independent investigators (YY, Ding and C, Sun). The following information was extracted from each of the standards-compliant studies: first author, year, country, ethnicity, tumor type, sample size, detection method, HR, outcome, cutoff value and NOS. If the full text only provides survival curves, no HR values is listed, the survival curve data is obtained from the GetData Graph Digitizer software (http://getdata-graphdigitizer.com/) and the hazard ratios (HRs) with 95% confidence intervals (95% CI) are estimated according to the method introduced by Tierney et al. [15].

Statistical Methods

The meta-analysis was performed with using Stata12 (Stata Corp, College Station, Texas). All P values were two-sided, and $P < 0.05$ was considered as statistically significant. Statistical heterogeneity among the studies was tested by Cochran Q test and I^2 statistic. If heterogeneity was significant (Cochran Q test: P value ≤ 0.05 or $I^2 \geq 50\%$), the random-effects model was used to estimate the pooled HR, and if not, the fixed-effects model was used. Publication bias was tested with Begg's and Egger's tests.

Results

Characteristics of Included Studies

As shown in Fig. 1, according to the criteria for selection, a total of eleven studies were identified as eligible, including a total of 1134 patients, and the patient's sample size ranges from 33 to 304 with the median value of 78. The publication times of the eleven studies ranged from 2014 to 2016. Ten of eleven studies from China and one from Brazil, nine types of human cancer were digestive system cancers including pancreatic cancer, colorectal cancer(CRC), gastric cancer(GC), hepatocellular carcinoma(HCC), and non-digestive system cancers containing cervical cancer, osteosarcoma, diffuse large B-cell lymphoma (DLBCL), triple-negative breast cancer (TNBC), glioma. The levels of HULC expression were detected by quantitative real-time PCR (qRT-PCR). Among the eleven studies, seven studies directly showed HR and 95% CI for OS, the remaining four studies were calculated from the original data. Moreover, four studies directly showed HR and 95% CI for metastasis. Main information of the studies was shown in Table 1.

The Association between HULC Expression Levels and Survival in Different Types of Cancers

We performed a cumulative meta-analysis to assess the effect of up-regulation of HULC for OS in the patients with cancer. As shown in Table 2. In the OS group, a total of eleven studies including 1134 patients were recruited to assess the effect of HULC in nine types of cancers. We pooled hazard ratios (HRs) and the respective 95% confidence interval (CI) to estimate its prognosis. It was indicated that overexpression of

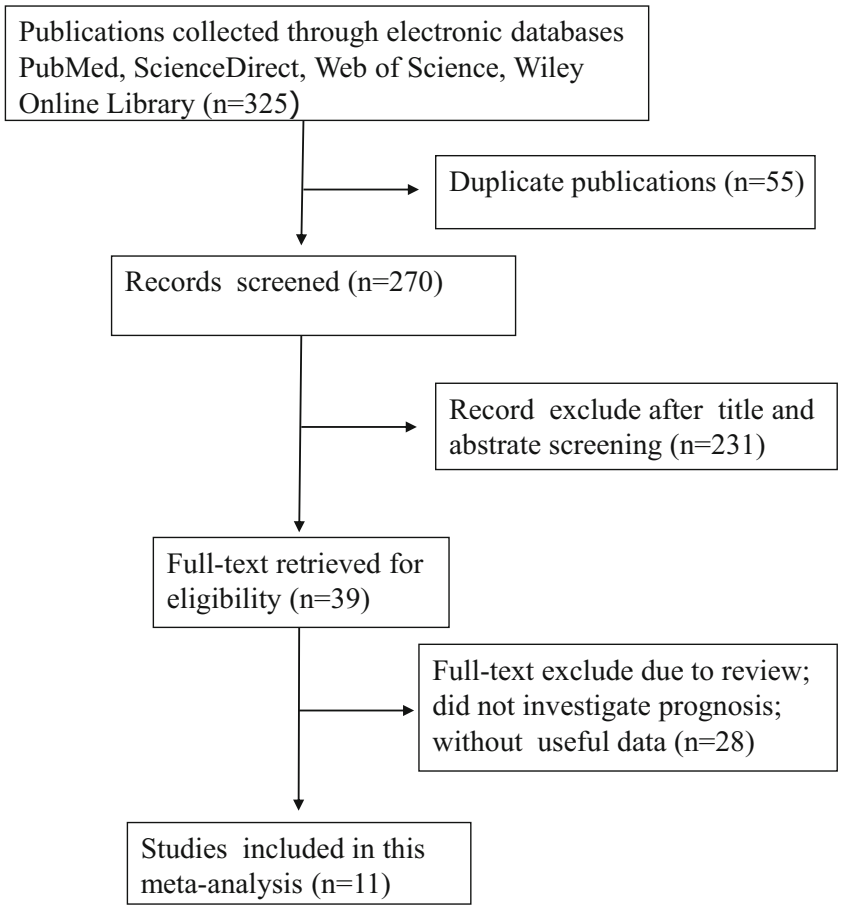

Fig. 1 Literature search and screening process

HULC predicted a poor outcome for OS in nine types of cancers (HR = 1.89, 95% CI: 1.32–2.47) with no heterogeneity (I^2 = 0.0%, $P_{heterogeneity}$ = 0.912) (Fig. 2). Furthermore, we also performed a subgroup analysis to examine the effect of cancer type and sample size on OS and the extent of impact. Due to the different types of cancer patients, we divided cancer patients into two groups with or without digestive system cancer patients. The results shown that HULC overexpression presented poor OS in both studies of digestive system (HR = 2.09, 95% CI:0.81–3.37; fixed-effects model) and non-digestive system cancer patients (HR = 1.84, 95% CI:1.20–2.49; fixed-effects model) (Fig. 2a). Meanwhile, with 100 patients as a threshold, the sample size was divided into 2 categories, the results of overexpressed HULC in predicting

Table 1 Characteristics of patients in different studies

First author	Year	Country	Ethnicity	Tumor type	Sample size	Detection method	HR	Outcome	Cutoff value	NOS
Li [28]	2016	China	Asian	HCC	38	qRT-PCR	Estimated	OS	7	7
Yan [29]	2016	China	Asian	Glioma	70	qRT-PCR	Reported	OS	NA	6
Shi [13]	2016	China	Asian	TNBC	96	qRT-PCR	Reported	OS	median	8
WANG [11]	2016	China	Asian	Cervical cancer	244	qRT-PCR	Reported	OS	median	8
Yang [12]	2016	China	Asian	CRC	35	qRT-PCR	Estimated	OS	2.23	6
Jin [30]	2016	China	Asian	GC	54	qRT-PCR	Estimated	OS	NA	6
Maciel [24]	2016	Brazil	South America	Osteosarcoma	33	qRT-PCR	Estimated	OS	0.000048	7
Peng [14]	2016	China	Asian	DLBCL	142	qRT-PCR	Reported	OS	NA	7
Sun [10]	2015	China	Asian	Osteosarcoma	78	qRT-PCR	Reported	OS	median	8
Li [25]	2016	China	Asian	HCC	40	qRT-PCR	Reported	OS	median	8
Peng [31]	2014	China	Asian	Pancreatic cancer	304	qRT-PCR	Reported	OS	NA	8

HR, Hazard ratios; *OS*, Overall survival; *CRC*, Colorectal cancer; *GC*, Gastric cancer; *TNBC*, Triple-negative Breast Cancer; *HCC* Hepatocellular carcinoma; *DLBCL* Diffuse large B-cell lymphoma; *qRT-PCR*, quantitative real-time PCR; *N/A* Not available

Table 2 Meta-analysis results of subgroups in the OS group

Subgroup	No. of study	HR (95%CI)	*P*-value	Model	Heterogeneity	
					I^2(%)	P
OS	11	1.89 (1.32–2.47)	0.000	Fixed	0%	0.912
Caner types						
Digestive system cancers	5	1.05 (0.33–1.78)	0.001	Fixed	0%	0.956
Non-digestive system cancers	6	2.09(0.81–3.37)	0.000	Fixed	0%	0.565
Sample sizes						
≥ 100	3	1.60 (0.86–2.34)	0.000	Fixed	0%	0.377
<100	8	2.33 (1.42–3.23)	0.000	Fixed	0%	0.990

HR, Hazard ratios; *CI*, Confidence interval; *OS*, Overall survival; The fixed effects model was employed when the P-value for heterogeneity test > 0.05

poor OS was shown that in studies including <100 patients (HR = 2.33, 95% CI: 1.42–3.23; fixed-effects model) as well as those with ≥ 100 patients (HR = 1.60, 95% CI: 0.86–2.34; fixed-effects model) (Fig. 2b).

The Association between HULC Expression Levels and Metastasis in Different Types of Cancers

Among the eleven studies, four studies directly reported HRs for metastasis, 722 patients were recruited to assess the effect of overexpression of HULC on metastasis in four types of cancers, including TNBC, osteosarcoma, pancreatic cancer, cervical cancer. The pooled HR*s* with 95% CI revealed a significant association in metastasis incidence between high and low HULC expression group (HR = 2.67, 95% CI: 0.94–4.39) with heterogeneity (I^2 = 71.4%, $P_{heterogeneity}$ = 0.015) (Fig. 3). Due to the heterogeneity, we also performed a sensitivity analysis, after excluding the Wang study [11], the observed heterogeneity disappeared and the results did not change. The results demonstrated that overexpression of HULC significantly predicted a higher incidence of metastasis in patients with cancer.

Publication Bias and Sensitivity Analysis

In order to assess whether publication bias, we used Begg's funnel plots and Egger's test to assess this meta-analysis, and the results of Begg's test (P = 0.484) and Egger's test (P = 0.738) revealed no publication bias for OS. Begg's funnel plot showed no evidence of obvious asymmetry for OS (Fig. 4). As the number of included studies and cases was limited (n = 4), publication bias was not analyzed in metastasis.

Discussion

Cancer is a serious threat to human health and life of the disease, and the incidence of cancer gradually increased [16]. The ultimate possible outcome of most cancer patients is the extensive metastasis of cancer and shorter survival time. Tumor metastasis and OS are important survival index, showing a special prognostic significance. Therefore, early prediction is particularly important. At present, as a hotspot in cancer research, molecular biomarkers play a key role in the prediction and treatment of cancer, lncRNAs may also represent potential biomarkers for the prediction of cancer. LncRNAs are widely involved in the biological function including cell differentiation, proliferation, growth, mobility, apoptosis, cancer initiation and progression, and the currently known lncRNAs, such as HOTAIR, MALAT1 play a very important role in tumor formation, invasion and metastasis [17, 18].

HULC, a newly discovered lncRNA, was originally discovered through the use of hepatocellular carcinoma-specific gene libraries and cDNA microarrays in 2007, which is located at 6p24.3. Although HULC is the first to be found in liver cancer and named, many studies have shown that HULC abnormal regulation is associated with other types of cancer prognosis, while involved in cancer cell proliferation [19], invasion [20] as well as apoptosis [21]. Lots of efforts have been made to understand the functional role of HULC in cancer progression [22–24], but the underlying molecular mechanisms of HULC involved cancer progression are largely unclear. In recent years, there are many important findings that HULC could sequestere miR-107 and promote tumor angiogenesis in liver cancer via miR-107/E2F1/SPHK1 signaling [22]. HULC was also found to regulates the phosphorylation of the YB-1 protein with certain oncogenic mRNAs through the ERK pathway, and leads to tumor progression [25]. Furthermore, HULC acts as an oncogenic role in hepatocarcinoma cells and leads to abnormal lipid metabolism through signaling pathways involving miR-9, PPARA and ACSL1, thereby enhances the proliferation of hepatoma cells [23]. These results suggest that abnormal expression of HULC relates to the process of tumors, and HULC may serve as a promising biomarker and potential therapeutic target in cancers. Therefore, through the meta-

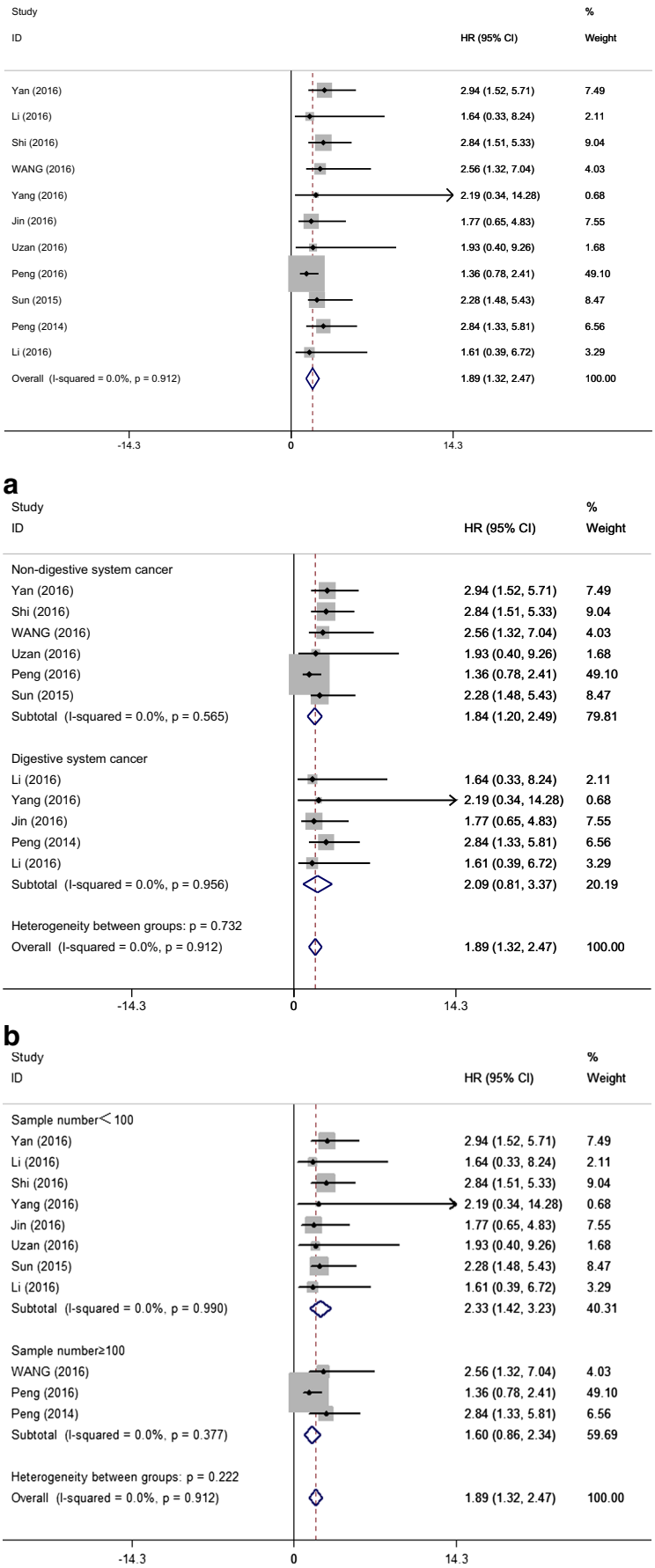

Fig. 2 Forest plot of HRs for the associate ion between high HULC expression and overall survival (OS) in cancer patients. **a** Subgroup analysis of HRs of OS by factor of cancer type. **b** Subgroup analysis of HRs of OS by factor of sample size

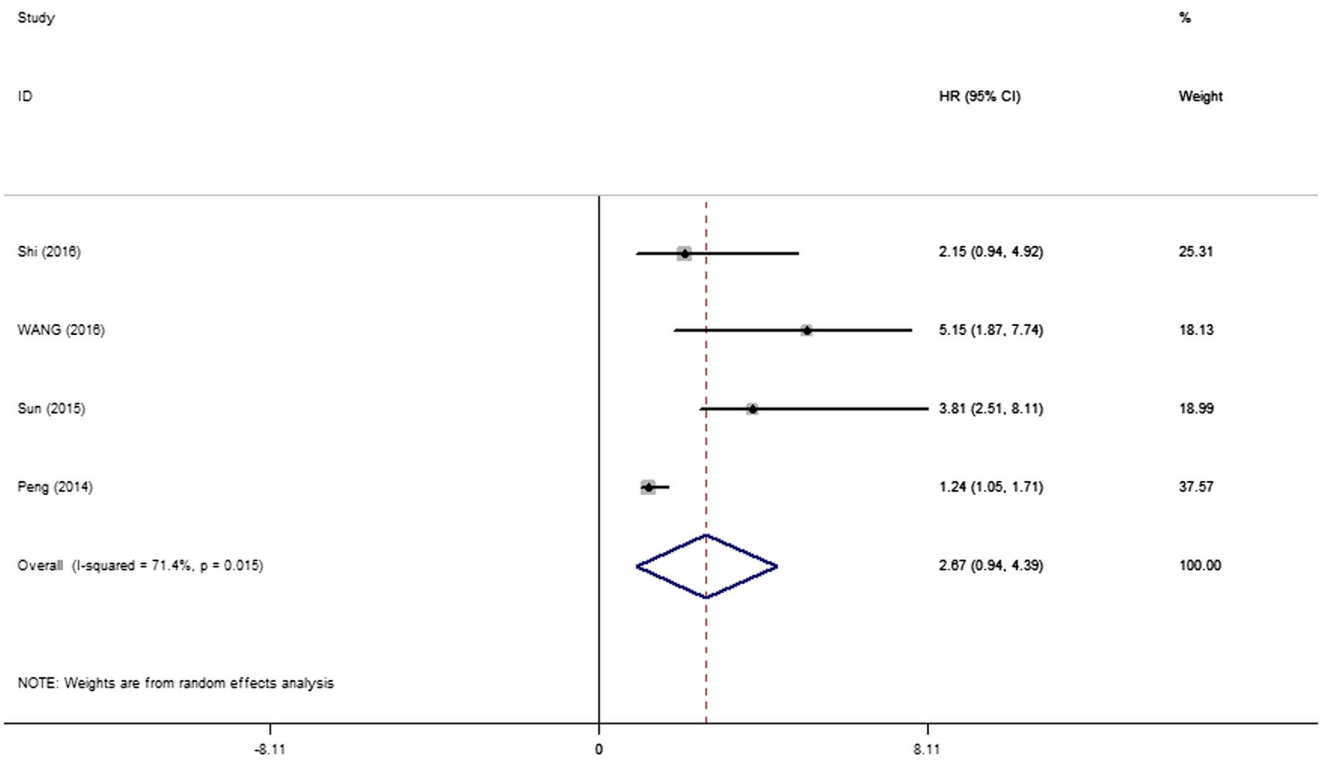

Fig. 3 Forest plot of HRs for the association between high HULC expression and metastasis in cancer patients

analysis of the HULC study, we hope to elucidate the relationship between HULC and prognosis, better help us understand the pathogenesis of HULC in tumor, enrich our understanding of HULC, and then better guide the practice of clinical practice in the future.

In this meta-analysis, data screening was conducted through a series of selection criteria, which eventually included eleven studies on nine categories of malignancies for a total of 1134 patients, and evaluated the role of HULC in the prognosis of cancer through context. The combined results indicated that high HULC expression significantly predicted poor OS. Furthermore, the similar results were observed in subgroup analysis stratified by cancer type and sample size. Only Maciel [24] and Peng's [14] study provided raw data on event-free survival (EFS) and progression-free survival (PFS), because of the sample size limited,we have not analysis the relationships between high HULC expression and EFS or PFS, but, these studies suggested the prognostic role of

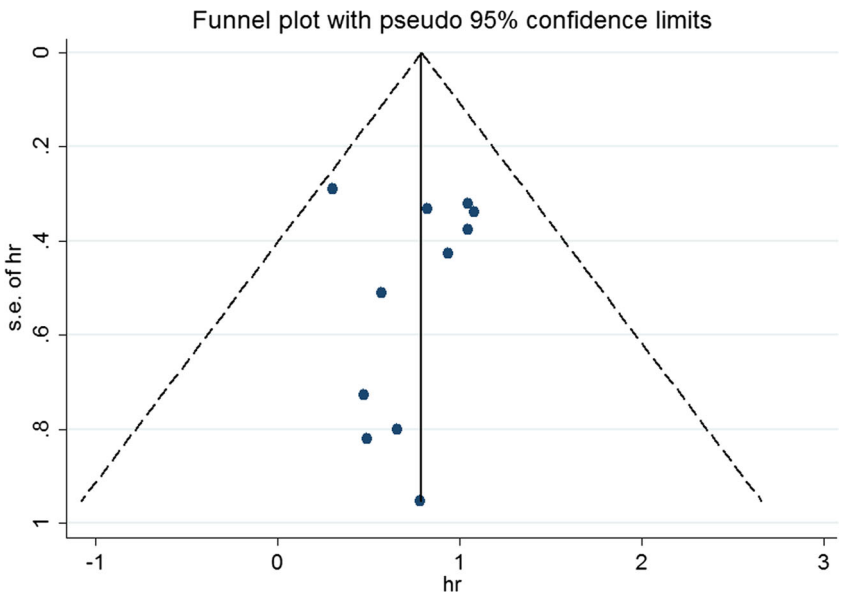

Fig. 4 Funnel plot of the publication bias for the analysis of HULC in OS in the different types of cancers

HULC for EFS as well as PFS in these cancer patients. Furthermore, overexpression of HULC is associated not only with poor survival but also with higher incidence of metastasis. In spite of the heterogeneity of the meta-analysis for metastasis is obvious, which may be related to the sample selection and sample size. Most studies, like cui [23] and yu [26] regarded HULC as a tumor-promoting indicator, and HULC upregulation was negatively correlated with OS, but, yang's [27] study showed that HULC upregulation in tumor tissue was positively correlated with HCC survival by preliminary analysis from gene expression. We did not include this study in the meta-analysis, mainly it does not meet the inclusion criteria 3, and the article is inconsistent with other approaches in research.

Conclusion

To sum up, this is the first meta-analysis showing that overexpression of HULC is a predictor of poor prognosis and higher incidence of metastasis in cancer patients. However, this meta-analysis has some limitations, the main limitation of which is that most of our patients in the study are Asian. Thus, our findings may represent patients from Asia. Another limitation is that not all of the studies reported the cut-off values, making it difficult to reach a consensus value. Beyond that, individual studies on the prognosis of HULC were based on gene expression levels, these articles were not included in this meta-analysis, which may lead to the potential bias, and therefore need to be better designed. Finally, all the studies were retrospective studies, with a relatively small sample size, and the number of studies in each cancer type is limited, these need to be conducted larger-size to confirm our results in the future.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that there is no conflict of interests regarding the publication of this paper.

Abbreviations *HR*, hazard ratios; *CI*, confidence interval; *OS*, overall survival; *CRC*, colorectal cancer; *GC*, gastric cancer; *TNBC*, triple-negative breast cancer; *HCC*, hepatocellular carcinoma; *DLBCL*, diffuse large B-cell lymphoma; *EFS*, event-free survival; *PFS*, progression–free survival

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