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REVIEW

Expression level and clinical significance of SNHG1 in human cancers: a meta-analysis

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Background: As reported by numerous research studies, the expression levels of *SNHG1* (small nucleolar RNA host gene 1) are increased in different kinds of tumours, revealing that *SNHG1* is likely to perform a crucial function in cancer prevalence and progression. Moreover, a mounting degree of evidence suggests that increased *SNHG1* expression also has an association with poor medical outcomes among cancer patients.

Materials and methods: Collection of qualifying research studies was performed through the retrieval of keywords in PubMed and Web of Science, up to March 20, 2018. This quantitative meta-analysis was carried out using Stata SE12.0 software and aimed at exploring the connection between the expression level of *SNHG1* and clinicopathology.

Results: Ten research studies, involving an aggregate of 715 patients, met the inclusion criteria. As suggested by the findings of the current meta-analysis, with regard to prognosis, the patients with high expression of *SNHG1* had poorer overall survival (OS) (HR =3.36, 95% CI: 2.42, 4.67) and, with regard to their clinicopathology, increased *SNHG1* was associated with advanced TNM stage (RR =1.88, 95% CI: 1.58, 2.24), poorly differentiated histological grade (RR =1.38, 95% CI:1.09, 1.76), and positive lymph node metastasis (RR =1.80, 95% CI: 1.42, 2.29).

Conclusion: As revealed by this meta-analysis, elevated *SNHG1* expression is typical in various types of cancer. In addition, elevated *SNHG1* expression is likely to function as an advanced predictive element of poor prognosis and lymph node metastasis in various cancer types. Nonetheless, to date, it remains essential to carry out larger-size and better-designed research studies for the confirmation of our findings.

Keywords: SNHG1, cancer, prognosis, meta-analysis

Introduction

Long noncoding RNAs (lncRNAs) represent a large family of RNAs without protein-coding capability that are characterized by a length of more than 200 nucleotides and the lack of an identifiable open reading frame (ORF).[1–6] As revealed by the research to date, upregulation of some lncRNAs is evident in several cancer tissues and cell lines, in comparison to the tissues surrounding the cancer and normal cell lines, respectively. Additionally, some of these lncRNAs have pro-oncogenic potential; conversely, some others are reported to have low expression levels and tumour-suppressive functions.[7–10]

Among the lncRNAs, the small nucleolar RNA host gene 1 (*SNHG1*; also known as *UHG*, *U22HG*, *lncRNA16*, *LINC00057*, and *NCRNA00057*) has garnered our attention. Specification of *SNHG1* mechanisms extends our understanding of invasive pathophysiology. Additionally, overexpression of *SNHG1* is reported to be a predictor

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of oncogenesis in patients with many kinds of cancer, including oesophageal squamous cell carcinoma,[11] lung squamous cell carcinoma,[12] hepatocellular carcinoma,[13,14] colorectal cancer[15,16] and gastric cancer.[17]

As revealed by the growing number of research studies, *SNHG1* is likely to perform the function of a diagnostic and a prognostic biomarker with regard to the cancers stated above. For the purpose of validating its clinical relevance as a biomarker or therapeutic target, it was deemed quite necessary to investigate whether *SNHG1* expression level is associated with pathological features. The current research study is aimed at carrying out a meta-analysis of this association in human cancers.

Materials and methods

Literature search strategies

Independent identification of the relevant literature was performed by two scholars with the use of both PubMed and Web of Science. The relevant literature reported the connection between *SNHG1* expression level and pathological attributes in human cancers. The literature search strategy included a combination of keywords ("*SNHG1*", "*LINC00057*", "*lncRNA16*", "cancer or carcinoma or tumour or neoplasm", and "pathology"). In addition, the references of attained literature were also examined for the identification of additional relevant studies.

Inclusion and exclusion criteria

The research studies involved in this analysis were required to satisfy the inclusion criteria listed here: 1) reported expression levels of *SNHG1*, as determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR); 2) put forward the decision; 3) segregated the patients into high and low expression groups with the help of definite criteria for *SNHG1* expression levels; 4) reported data associated with the clinicopathological attributes of the patients, and at a minimum, one of the following pathological features: TNM stage, histological grade, lymph node metastasis, distant metastasis, and overall survival information; and 5) utilized a case-control or cohort study design.

Research studies were not included in the analysis if they met any of the exclusion criteria listed here: 1) stated recurring research reports or studies that included patients who were reported in a former research study; 2) provided insufficient statements of the data; 3) employed nonhuman specimens; 4) were reviews, together with letters, unpublished data, and commentaries; and 5) were reports that were not published in the English language.

Assessment of the quality of the research studies was performed by two scholars by going through the title, abstract, and complete text of each report while referencing the inclusion and exclusion criteria.

Literature screening and data extraction

Independent collection of the data was performed by two investigators (Yang Yu and Jian Yang), in accordance with both the inclusion and exclusion criteria, and after resolving any conflicts with the help of a consensus or talks with a third scholar (Shengquan Yang) prior to the performance of the analysis. Data extraction from the literature included the following: first author, publication year, country of data source, kind of cancer, number of patients placed in both the high and low *SNHG1* expression cohorts, the *SNHG1* expression level identification methodology, and the cut-off approximations for *SNHG1* expression levels.

Quality assessment

Assessment of the quality of the involved research studies was performed with the help of the Newcastle-Ottawa Scale standard that assessed selection (four points), comparability (two points), and outcome (three points) and had a score ranging between 0 and 9. Each of the qualifying studies was scored in Table 1, with a higher score suggesting better methodological quality.

Statistical analysis

Cochran's Q and Chi-square-based I^2 tests were used for the determination of the heterogeneity among the involved research studies. Homogeneity tests were carried out using a significance level of $\alpha = 0.1$. *P*-values <0.1 were regarded as being statistically significant, whereas I^2 values >50% implied heterogeneity among the research studies. Analysis of the homogeneous data was carried out with the use of a fixed effects framework; otherwise, a random effects framework was used for the analysis. Statistical analyses, together with the assessment of publication bias and Begg's methodology, was carried out using StataSE 12.0 (Stata Corp LP, College Station, Texas, USA).

Results

Data selection and characteristics

Ten research studies that involved an aggregate of 715 patients showed agreement with the inclusion criteria.

Table 1 Characteristics of the included studies

Author name (year)	Country	Cancer type	Total number	High	Low	Cutoff (high/low)	Detection method	Quality score
Jiandong Wang (2017 May)	China	Osteosarcoma	44	27	17	Mean	qRT-PCR	7
Hong-Yan Zhang (2017 March)	China	Lung squamous cell carcinoma	62	36	26	Mean	qRT-PCR	6
Hui Zhang (2016 December)	China	Hepatocellular carcinoma	122	70	52	Mean	qRT-PCR	6
Min Zhang (2016 February)	China	Hepatocellular carcinoma	82	41	41	Median	qRT-PCR	6
Tian Tian (2017 December)	China	Colorectal cancer	82	41	41	Median	qRT-PCR	8
Yijun Zhang (2017 December)	China	Esophageal squamous cell carcinoma	72	38	34	Mean	qRT-PCR	6
Yongbo Hu (2017 July)	China	Gastric cancer	50	–	–	–	qRT-PCR	6
Yun Cui (2017 January)	China	Non-small cell lung cancer	68	34	34	Median	qRT-PCR	8
Yuping Zhu (2017 December)	China	Colorectal cancer	108	54	54	Median	qRT-PCR	8
Zhe Jiang (2017 November)	China	Osteosarcoma	25	19	6	Mean	qRT-PCR	6

Abbreviation: qRT-PCR, quantitative reverse transcription polymerase chain reaction.

Each and every research study originated from China; two were studies of colorectal cancer, two were studies of hepatocellular carcinoma, two were studies of lung cancer, two were studies of osteosarcoma, and the remaining two were studies of oesophageal squamous cell carcinoma and gastric cancer. QRT-PCR was used for detecting *SNHG1*, on the basis of which, categorization of the patients into groups of high and low *SNHG1* expression was performed. The mean and median were employed as the cut-off values for estimating for the *SNHG1* expression level. A summary of the attributes of the involved research studies is provided in Table 1, whereas the flowchart of the study search, together with the selection process, is presented in Figure 1.

Association between SNHG1 expression and pathological features

TNM stage

Eight research studies reported a link between *SNHG1* expression and TNM stage (III/IV versus I/II). There was no statistically significant ($P>0.05$, $I^2=0.00\%$) heterogeneity among the research studies; accordingly, the fixed-effects framework was applied for the calculation of the accumulated pooled RR, together with its 95% CI, which reached statistical significance [RR =1.88, 95% CI (1.58, 2.24), $P<0.001$] (Figure 2, Table 2). This suggests that a high *SNHG1* expression level has a link with advanced TNM phase.

Histological grade

Reports from an aggregate of 4 research studies revealed the association between *SNHG1* expression and histological grade. Statistically significant ($P>0.05$, $I^2=0.00\%$) heterogeneity among the research studies was not observed; accordingly, the fixed-effects framework was applied for the calculation of the accumulated RR, together with its 95% CI, which exhibited a statistically significant difference [RR =1.38, 95% CI (1.09, 1.76), $P<0.01$] (Figure 3, Table 2). This suggested that high *SNHG1* expression was associated with a higher risk of poorly differentiated histological grade.

Lymph node metastasis

Reports from an aggregate of 5 research studies suggested a connection between *SNHG1* expression and lymph node metastasis. Statistically significant ($P>0.05$, $I=0.00\%$) heterogeneity was not observed among the studies; accordingly, the fixed-effects framework was applied for the calculation of the accumulated RR, together with its 95%

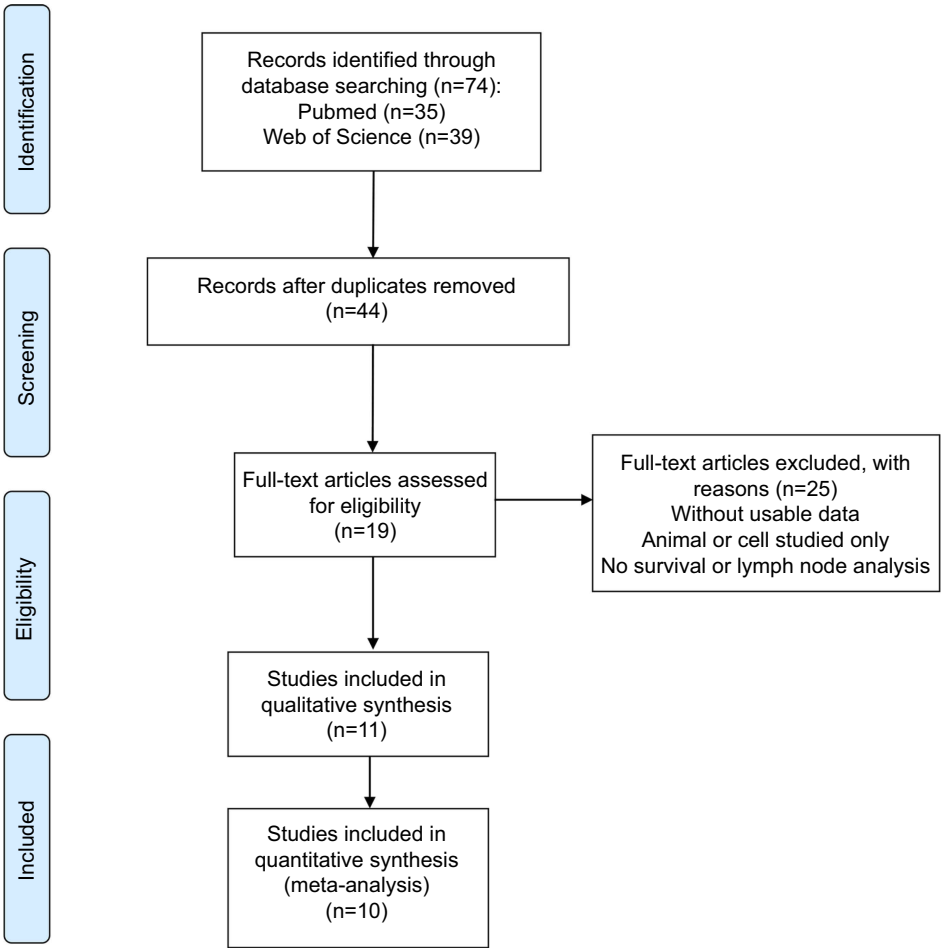

Figure 1 Flowchart of selecting studies for inclusion.

CI, which reached statistical significance [RR =1.8, 95% CI (1.42, 2.29), $P<0.001$] (Figure 4, Table 2). This association illustrates the fact that the cohort with the high *SNHG1* expression level exhibited a higher risk of lymph node metastasis compared with the cohort with the low *SNHG1* expression levels.

Distant metastasis

Reports from 3 research studies revealed a link between *SNHG1* expression level and distant metastasis. Statistically significant ($P>0.05$, $I=0.00\%$) heterogeneity among the research studies was not observed; accordingly, the fixed-effects framework was applied for the calculation of the accumulated RR, together with its 95% CI, which did not reach statistical significance [RR =1.29, 95% CI (0.80, 2.08), $P>0.05$] (Figure 5, Table 2). This result highlights that *SNHG1* expression levels have no correlation with distant metastasis. The reasons behind the inexistence of any correlation could include that the number of patients registered in some of the research works was comparatively smaller; moreover, not every kind of cancer was studied, and no consensus on the cut-off for making a distinction between a high or low *SNHG1* expression level was observed. As such, future studies comprising larger samples of patients are going to be needed; moreover, the cut-off value for making a distinction between high or low *SNHG1* expression level requires consistency as well.

Association between SNHG1 expression and survival in different types of cancers

In total, 5 research studies comprising 352 patients were employed for the assessment of the impact of *SNHG1* overexpression on OS in various cancers (Table 3). Moreover, it was highlighted that augmented *SNHG1* expression forecasted a weak performance for OS in the involved cancer types [pooled HR=3.36, 95% CI

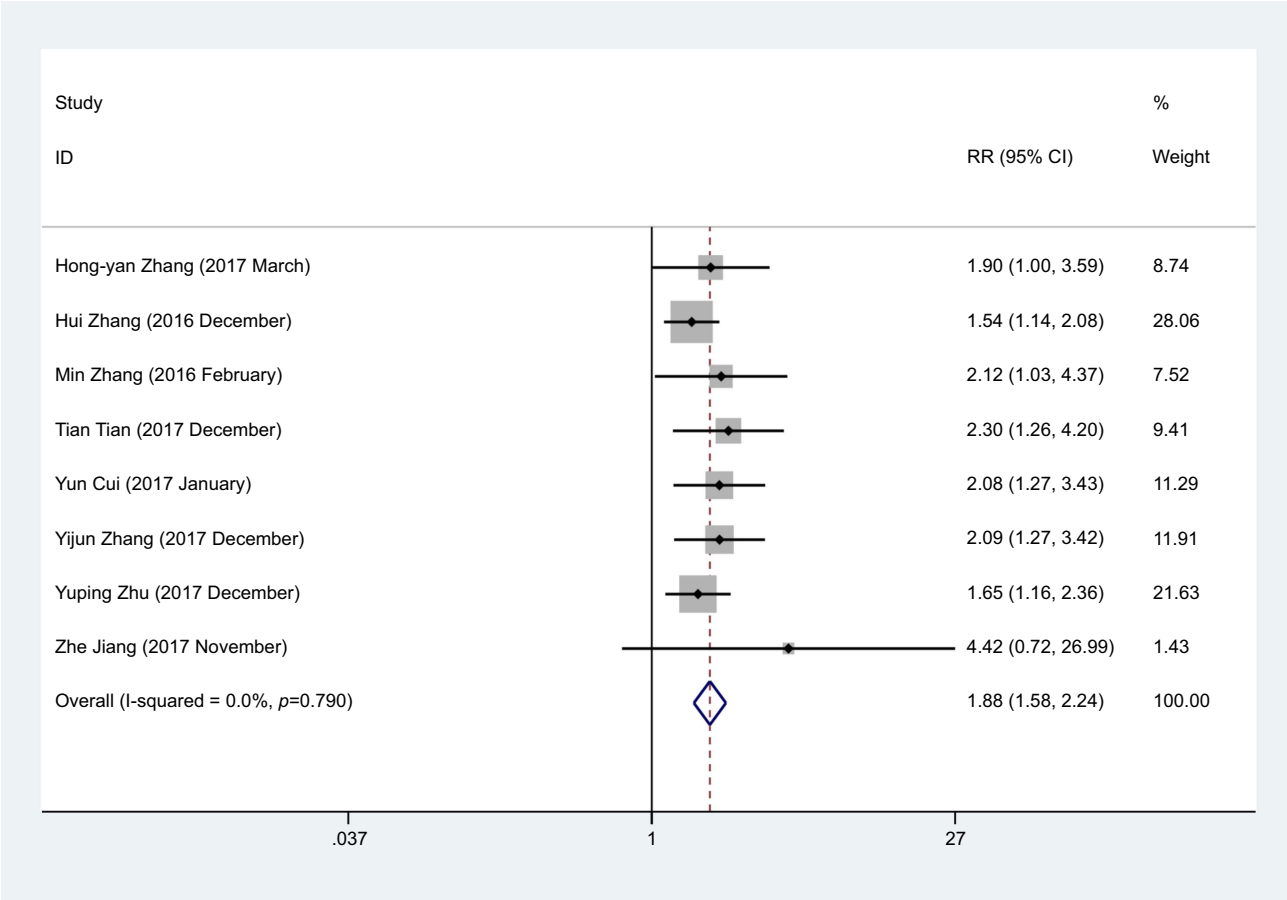

Figure 2 Forest plot for the association between *SNHG1* expression and TNM stage in human cancers.

Table 2 Meta analysis results for the association of over-expressed *SNHG1* with clinicopathological parameters

Clinicopathological parameters	Studies (n)	Number of patients	RR (95% CI)	*P*-value	Heterogeneity		
					I^2	P_h	Model
TNM stage (III/IV vs I/II)	8	621	1.879 (1.579, 2.237)	0.000	0.00%	0.790	Fixed effects
Histological grade (poorly/others vs well/moderately)	4	330	1.384 (1.090, 1.757)	0.008	0.00%	0.507	Fixed effects
Lymph node metastasis (+ vs –)	5	335	1.799 (1.416, 2.285)	0.000	0.00%	0.702	Fixed effects
Distant metastasis (+ vs –)	3	312	1.288 (0.798, 2.079)	0.300	40.6%	0.186	Fixed effects

(2.42, 4.67), $P<0.001$], with heterogeneity ($I^2=57.3\%$, $P>0.05$). In addition, a subgroup analysis was also performed on the basis of the aggregate number of each study concerned. A substantial connection between *SNHG1* overexpression and poor OS in the research studies with aggregate numbers below 80 patients was noted [pooled HR =2.55, 95% CI (1.52, 4.26)) (Figure 6). In comparison with the low *SNHG1* expression cohort, the high *SNHG1* expression group exhibited a statistically significant decline in OS, in addition to being correlated with worse survival.

Assessment of publication bias

Due to the small number of research studies included, analysis of publication bias was not possible for TNM

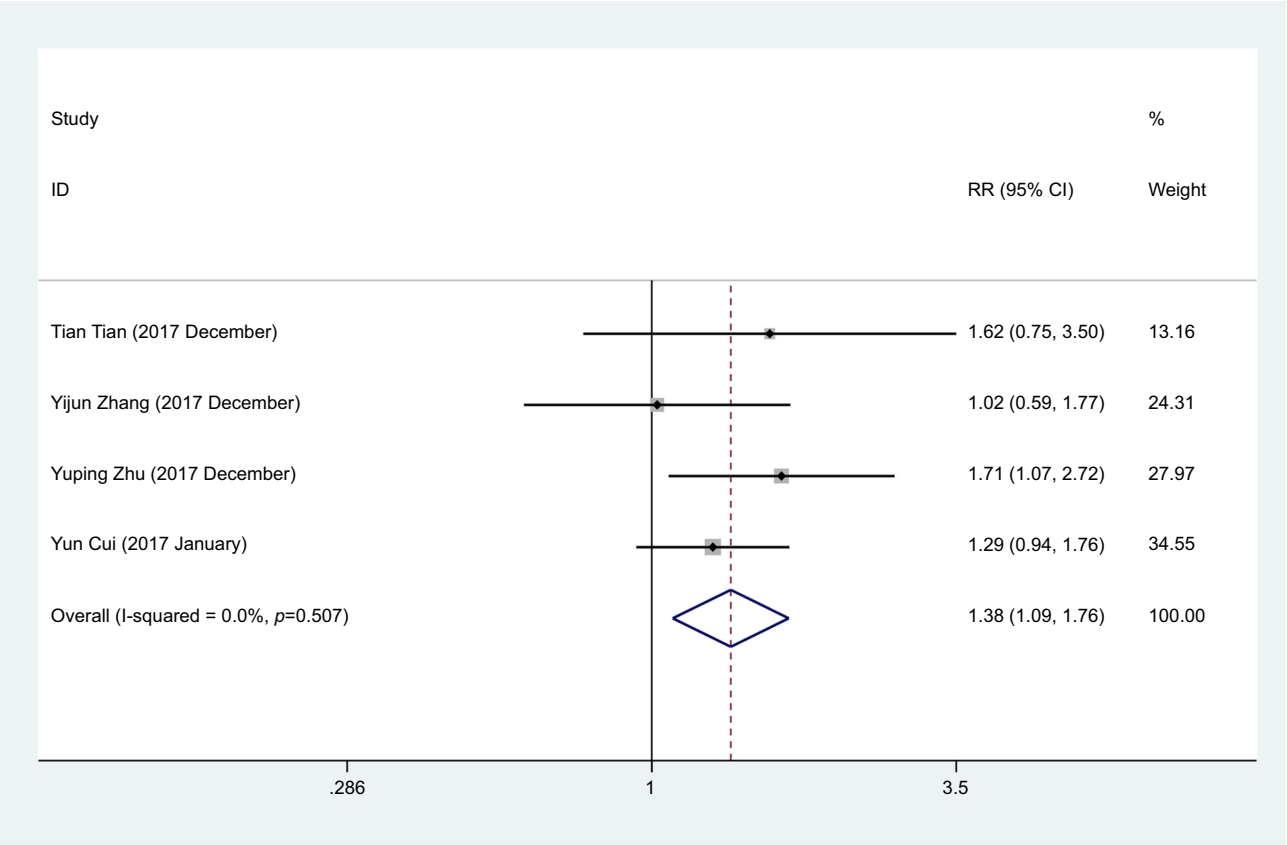

Figure 3 Forest plot for the association between *SNHG1* expression and histological grade in human cancers.

phase, histological grade, lymph node metastasis, or distant metastasis.

Discussion

To date, deregulation of lncRNAs has been observed in numerous human cancers. Additionally, deregulation of lncRNAs has been linked to cancer proliferation by acting as a regulator in alternative splicing and translation, by promoting steadiness of the host mRNAs with the help of post-transcriptional phenomena, or by acting as the scaffolding or instructions for regulating protein-protein or protein-DNA interactions.[18,19]

The current meta-analysis was aimed at investigating the link between *SNHG1* expression levels and pathological attributes observed in human cancers. In total, 715 patients from 10 research studies were eventually included. The fixed-effects framework was applied for the assessment of TNM stage and histological grade, lymph node metastasis, and distant metastasis. Consequently, the cohort with the high *SNHG1* expression level exhibited a higher risk of advanced TNM stage, poorly differentiated grade and lymph node metastasis compared to the low *SNHG1* expression level group. In addition, in regard to prognosis, the patients with high expression of *SNHG1* experienced relatively short overall survival.

Nonetheless, this research study has some limitations: (1) each and every involved research study originated from China and no patients from any other country were included; (2) the number of patients registered in some of the research studies was comparatively smaller and not all the cancer types were studied; (3) no consensus was reached regarding the cut-off level for making a distinction between a high or low *SNHG1* expression level; (4) no cohort studies observed met the inclusion criteria. High-quality studies with large sample sizes are necessary for the confirmation of these results.

To summarize, with regard to the clinicopathology, high expression levels of *SNHG1* had a close association with advanced TNM stage, poorly differentiated grade, and lymph node metastasis. In addition, with regards to prognosis, the patients having a high expression level of *SNHG1* experienced relatively poor overall survival (OS). Notably, *SNHG1* is capable of acting as a biomarker of poor prognosis for patients with cancer.

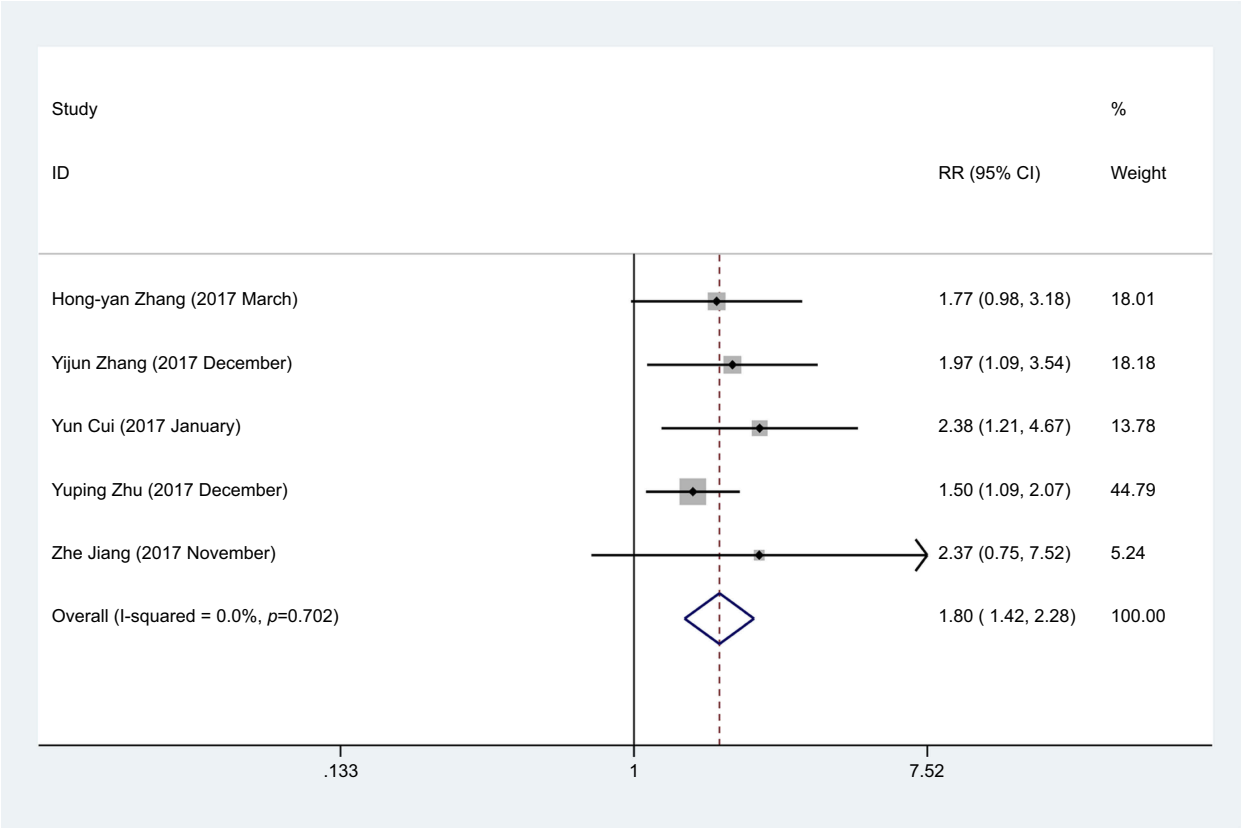

Figure 4 Forest plot for the association between *SNHG1* expression and lymph node metastasis in human cancers.

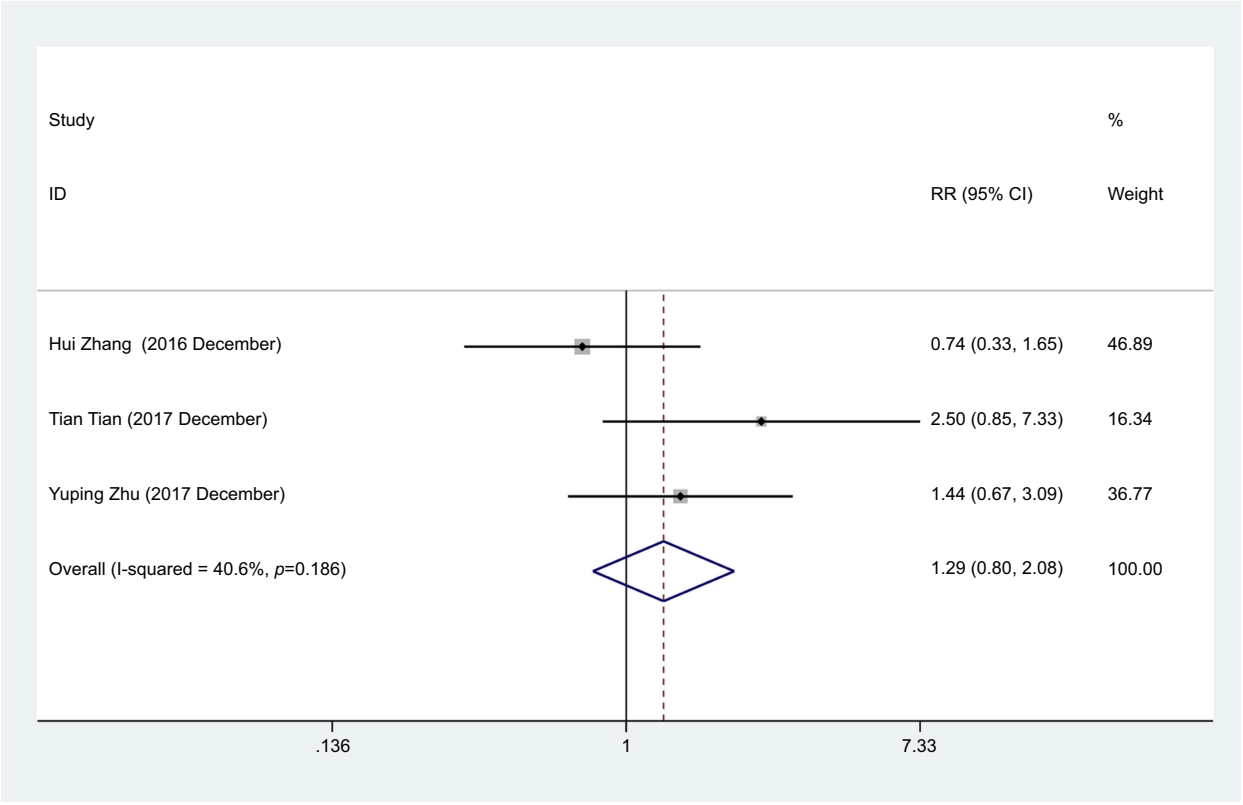

Figure 5 Forest plot for the association between *SNHG1* expression and distant metastasis in human cancers.

Table 3 Characteristics of the overall survival of the included studies

Author name (year)	Country	Cancer type	Survival analysis	HR statistic	HR (95% CI)	Follow-up months	Outcome
Jiandong Wang (2017 May)	China	Osteosarcoma	Univarite	Survival curves	1.41 (0.50, 4.00)	60	OS
Min Zhang (2016 February)	China	Hepatocellular carcinoma	Univarite	Survival curves	1.92 (0.86, 4.35)	60	OS
Yongbo Hu (2017 July)	China	Gastric cancer	Univarite	Survival curves	3.92 (1.91, 8.06)	60	OS
Yun Cui (2017 January)	China	Non-small cell lung cancer	Univarite	Survival curves	1.89 (0.79, 6.25)	60	OS
Yuping Zhu (2017 December)	China	Colorectal cancer	Univarite	Data in paper	5.41 (2.47, 6.71)	60	OS

Abbreviation: OS, overall survival.

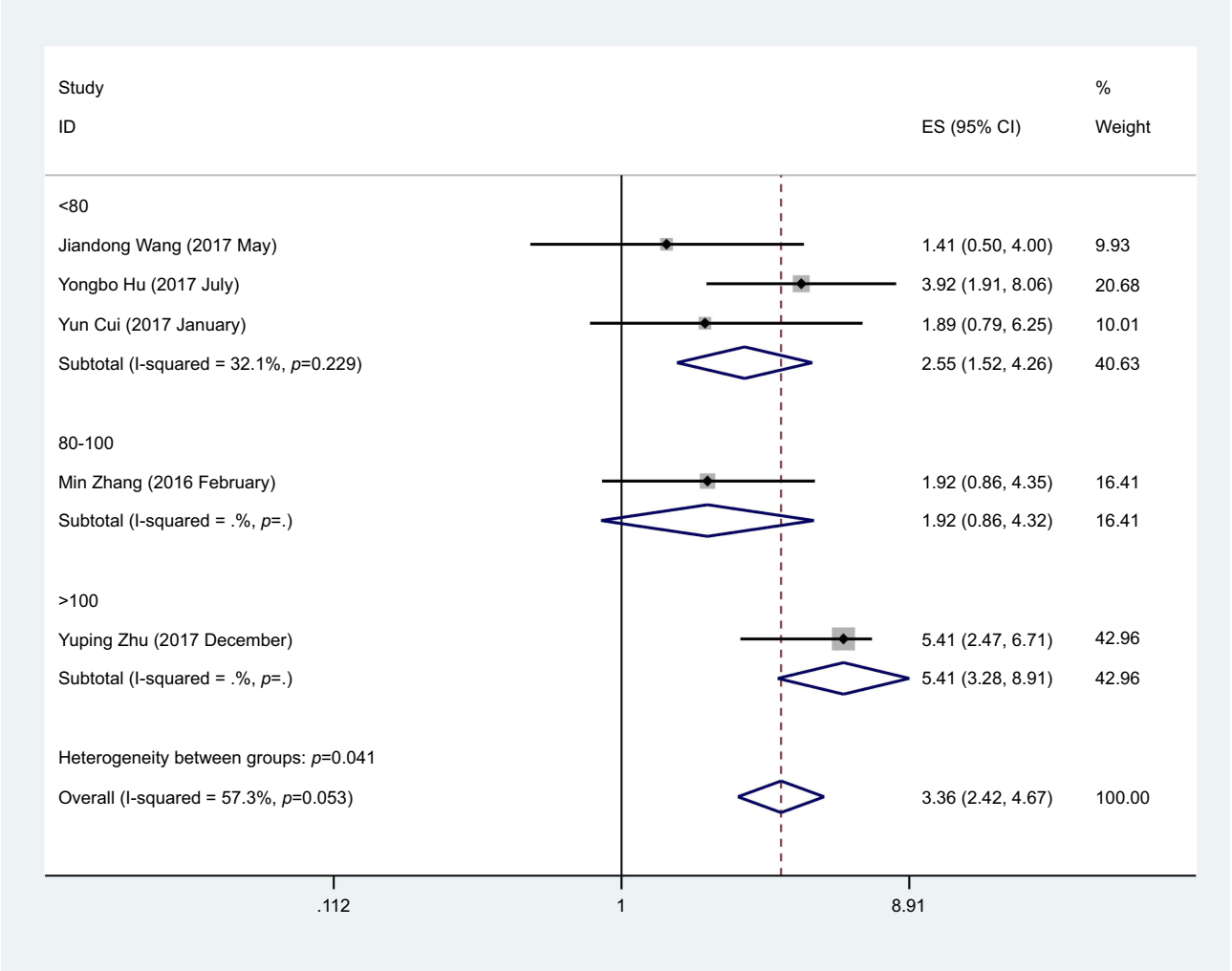

Figure 6 Meta-analysis for the pooled HRs of overall survival in patients with various cancers.

Conclusion

This meta-analysis discovered that augmented *SNHG1* expression is common in a number of different kinds of cancer and has a likelihood of acting as an innovative predictive element of poor prognosis and lymph node metastasis in various cancers. Nonetheless, it is still deemed essential to

carry out research studies with a larger sample size, and with an improved design, for the confirmation of our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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