Systematic Review and Meta-Analysis

Medicine®

OPEN

Prognostic value of long noncoding RNA ROR in patients with cancer in China

A systematic review and meta-analysis

Shuai Li, MD[a], Xin-Can Yue, MD[a], Chao-Yan Sun, MD[a], Hai-Yan Qin, MD[a], Xiao-Yang Zhang, MD[b,*]

Abstract

Background: For cancer, it is common that there is usually a dysregulation of the long noncoding RNA regulator of reprogramming (LncRNA ROR). To illustrate the application of LncRNA ROR, which serves as the prognostic marker for the malignant tumors, it is of great importance to conduct a meta-analysis.

Methods: There were 3 databases being applied. The data used were collected before January 5, 2018. These 3 databases include the OVID, PubMed, and Science databse. To further explore the association between the expression and survival of LncRNA ROR, it calculated the 95% confidence intervals (CIs) and hazard ratios (HRs). Meanwhile, the odds ratios (ORs) have been calculated for the evaluation of the correlation between the pathological and expression parameters of LncRNA ROR.

Results: There were 8 researches participated by 720 patients. According to the HR, it has been implied that there was a high LncRNA ROR expression related with the weak disease-free survival (DFS) (HR = 3.48, 95% CI, 2.24–5.41) and overall survival (OS) (HR = 2.47, 95% CI, 1.76–3.47) among the cancer patients with none dramatic heterogeneity. There was also a correlation among lymph node metastasis (OR = 5.38, 95% CI, 2.21–13.12), high tumor stage (OR = 3.80, 95% CI, 1.95–7.41), and larger tumor size (OR = 4.43, 95% CI, 1.26–15.51).

Conclusions: Thus, it can be predicted about the lymph node metastasis and high tumor stage, larger tumor size, DFS, and poor OS based on the high LncRNA ROR. This suggests that high LncRNA ROR can be used as a new indicator of poor prognosis in cancer.

Abbreviations: CC = colon cancer, CI = confidence interval, GAPDH = glyceraldehyde-3-phosphate dehydrogenase, GBC = gallbladder cancer, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, HTS = high tumor stage, LncRNA ROR = long non-coding RNA regulator of reprogramming, LNM = lymph node metastasis, LTS = larger tumor size, NSCLC = nonsmall cell lung cancer, OR = odds ratio, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma, PHG = poor histological grade, RCC = renal cell carcinoma.

Keywords: LncRNA, metastasis, neoplasms, prognosis, ROR

1. Introduction

Based on the recent report, it has been found that 17 million new cancer cases occurred in the United States during 2017, ascribing to the death of 600,000 people.[1] However, the 5-year survival rate of the majority of the cancer is still not high. There are many scientists exploring new biomarkers to decide or diagnose prognosis of cancer.

The transcribed RNA molecules refer to the long noncoding RNAs (LncRNAs) which do not have the meaningful open reading frame and also possess many significant functions, taking the epigenetic, transcriptional, and posttranscriptional regulation as the examples. These molecules are >200 nucleotides in length.[2,3] In addition, seemingly, there is a correlation between LncRNA and different types of cancer.[4–7] For example, there are some LncRNAs that are of great importance in cancer cell proliferation, invasion, and metastasis.[8,9] This demonstrates that this can be an important marker for the cancer prognosis.[10]

The long noncoding RNA regulator of reprogramming (LncRNA ROR) serves as a type of LncRNA, which was identified as a significant regular of the reprogramming of the differentiated cells for the induced pluripotent stem cells (iPSCs).[11] LncRNA ROR is located at 18q21.31 in chromatin, and also called lincRNA-ST8SIA3. For the highly expressed embryonic stem cells (ESCs), there was also high expression of LncRNA ROR. For the embryonic cells, the LncRNA ROR also has a high expression, the regulation of which is through the pluripotency transcription factors (taking the Nanog, Oct4, Sox2

Editor: Hua Yang.

This article was supported by the Youth Fund Project of the Zhoukou Central Hospital (No. QN-2017-B015).

The authors have no conflicts of interest to disclose.

[a] Department of Intensive Care Unit of Neuroscience, [b] Department of Neurosurgery, Zhoukou Central Hospital, Zhoukou, Henan Province, People's Republic of China.

[*] Correspondence: Xiao-Yang Zhang, Department of Neurosurgery, Zhoukou Central Hospital, East Section of Renmin Road, Zhoukou, Henan 466000, People's Republic of China (e-mail: zhangxiaoyang208@163.com).

Medicine (2019) 98:21(e15758)

Received: 10 July 2018 / Received in final form: 2 April 2019 / Accepted: 26 April 2019

http://dx.doi.org/10.1097/MD.0000000000015758

as examples).[12] It has been revealed from the study that LncRNA ROR serves as a strong negative regulator of p53 responding to the damage of DNA.[13] In addition, it has been reported that LncRNA ROR has a correlation with multiple tumor biological parameters, such as tumor growth, metastasis, and invasion.[14–16] Apart from the fact that LncRNA ROR serves as a regulatory molecule for many biological processes of cancer, it still remains to be elucidated about the implied systems of its contribution to the carcinogenesis. There are abundant researches that have been constrained by the discrete outcomes and sample size so far. Consequently, we conducted an update meta-analysis to decide LncRNA ROR's prognostic value of the cancer patients.

2. Materials and methods

2.1. Literature collection

Based on the standard guidelines of the meta-analyses,[17] there were 2 authors carried out a systematic exploration about some online databases independently to explore the articles that are related with LncRNA ROR, which serves as a prognostic biomarker for the patients' survival who suffer from cancer. It has been updated on January 5, 2018. The literature search was conducted by both the MESH strategy and also the text word with the terms of "prognosis" or "prognostic," "tumor" or "cancer," "neoplasm" or "carcinoma," "CTD-2526M8.1 or LincRNA-ST8SIA3," "noncoding RNA" or "long intergenic noncoding RNA." There was adjustment of the strategies according to differences of the databases. During the retrieval process, there was a manual research conducted by applying the reference lists of related researches to engage the eligible researches. All the analyses were conducted on the basis of the prior published researches. Therefore, it did not require patient consent or ethical approval.

2.2. Study selection

There were 2 scholars evaluating all these included researches. Meanwhile, they also extracted the data independently. This inclusion process should follow the standards as given: the correlation between survival and expression of LncRNA ROR was evaluated in various human tumors; it measured the expression levels of LncRNA ROR of the human tumor tissue; there were 2 groups of patients based on the LncRNA ROR's expression level; the histological and pathological examinations confirmed all the tumors; and the pathological and survival parameters, taking the lymph node metastasis, histological grade, tumor stage, and tumor size have been analyzed regarding the LncRNA ROR expression.

The following standards have been excluded: expert and editorial opinions and reviews; animal and non-English researches; researches about the molecular functions and structure of LncRNA ROR only; and database analysis with none original statistics.

2.3. Date extraction

There was an independent examination of the statistics of the original articles. There were 2 reviewers extracting them from the original articles. During the literature evaluation process, there was a disagreement between the 2 reviewers. This issue has been finally solved via the third party. The following statistics were collected from the aspects: the detection method of LncRNA ROR, the reference gene of LncRNA ROR, 95% CI of elevated LncRNA ROR for overall survival (OS), hazard ratio (HR), high tumor stage (HTS) and lymph node metastasis (LNM), poor histological (differentiation) grade (PHG), the number of patients with larger tumor size (LTS), sample size, tumor type, country, publication year, and surname of the author.

2.4. Statistical methods

It applied the STATA version 12.0 to analyze the statistics. In addition, it also conducted the Q and I^2 tests to evaluate the heterogeneity. It is indicated from the test results that there was strong heterogeneity in this study ($I^2 \geq 50\%$, and $P < .1$).[18,19] Based on the outcomes of the heterogeneity analysis, it was suggested to adopt a random- or a fixed-effect model. It also should adopt the random model when the studies had a strong heterogeneity.

There were some evaluations made in the research regarding the potential publication bias of the Begg's funnel plot and Egger's test. It was suggested that there should be an extraction of the aggregated odds ratios (ORs) by the researchers. It should adopt the crude ones when it could obtain the HRs directly from the publication.

For the prediction of the HR, Kaplan–Meier curves have been used for the extraction of the survival information if the 95% CI and HR have not been directly reported from the researches.[20] To make a summary regarding the survival outcome, both the log HR and SE should be applied. Besides, both OR and 95% CI have been combined to evaluate about the correlation between LncRNA ROR and clinicopathological parameters, taking the LTS, HTS, PHG, and LNM as examples.

3. Results

3.1. Studies characteristics

Figure 1 presents the details regarding the screening process. Based on the inclusion and exclusion standards, there were supposed to be 720 patients being included and also 8 researches.[21–28] In addition, the features of the 8 researches have been summarized in Table 1, including the meta-analysis. The subjects' number in the 8 researches ranged between 30 and 229, the average of which is 90.

During 2016 and 2017, these researches have been published and then implemented in China. Among these 8 researches, there were 2 focused on pancreatic ductal adenocarcinoma (PDAC),[21,22] and one each on hepatocellular carcinoma (HCC),[23] nonsmall cell lung cancer (NSCLC),[24] renal cell carcinoma (RCC),[25] gallbladder cancer (GBC),[26] colon cancer (CC),[27] and gastric cancer (GC).[28]

Every clinicopathologiacl parameter relied on pathology. It has been found that the LncRNA ROR's reference genes were inconsistent, such as GAPDH[23–28] and β-actin[21].

3.2. Association between the LncRNA ROR expression level and survival

A cumulative meta-analysis has been conducted to evaluate the function of LncRNA ROR for the OS of the patients who have cancer. In addition, all engaged the researches[21–28] with 720 patients who reported about the correlation between LncRNA

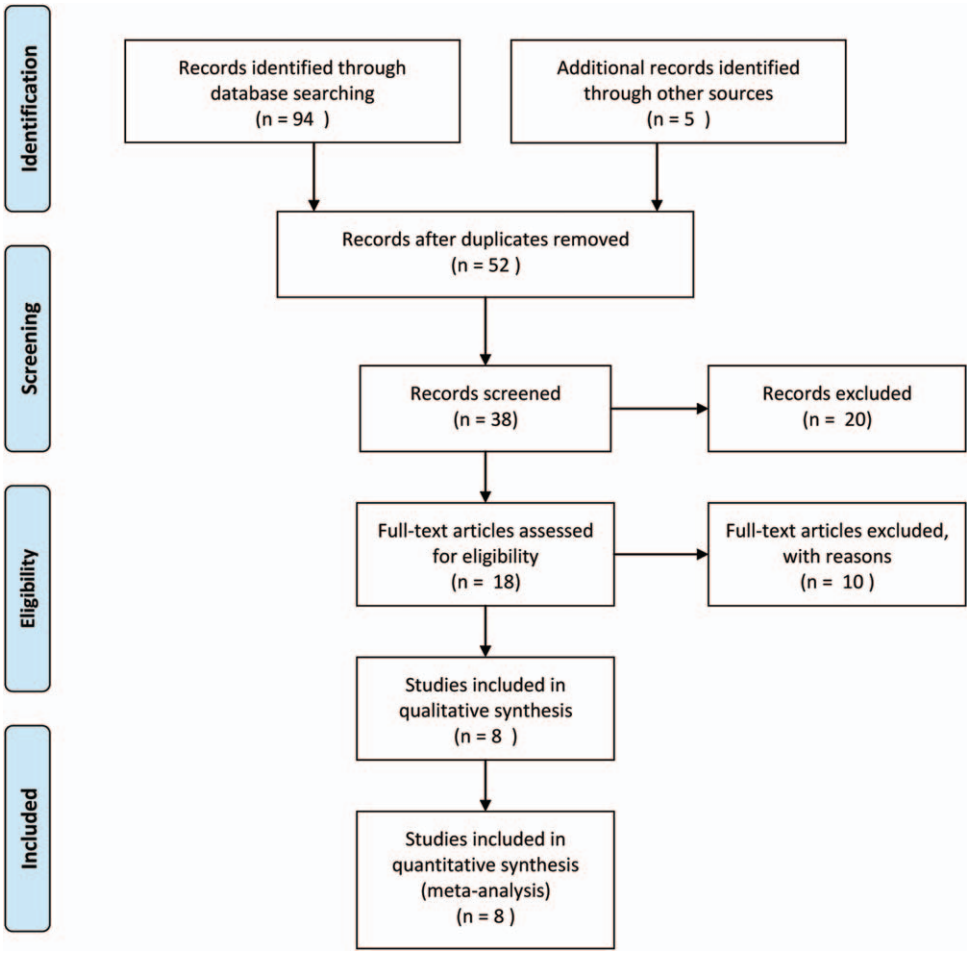

Figure 1. Flowchart showing the steps of study selection in this meta-analysis.

ROR and OS. It applied the random-effects model due to the strong heterogeneity among the studies ($I^2 = 55.3\%$, $P_Q = 0.028$). It has been found there was a strong correlation between the OS and LncRNA ROR among the cancer patients (pooled HR = 2.47, 95% CI, 1.76–3.47; Fig. 2).

A cumulative meta-analysis was conducted to decide the function of LncRNA ROR among 377 cancer patients having DFS in the eligible 3 researches.[23,24,27] It has been revealed from the statistical analyses that there was a correlation between DFS and LncRNA ROR (pooled HR = 3.48, 95% CI, 2.24–5.41; Fig. 3). There was none strong heterogeneity being found among the researches ($I^2 = 0.0\%$, $P_Q = 0.607$).

There was strong LncRNA ROR expression being demonstrated from this result, which might be associated with shorter

Table 1

The basic information and data of all included studies in the meta-analysis.

					LncRNA ROR expression												
					High expression					Low expression							
Study	Year	Region	Tumor type	Sample size	Total	LTS	PHG	HTS	LNM	Total	LTS	PHG	HTS	LNM	Analysis (OS)	HR (95% CI) high/low	Reference gene	Method
Fu[21]	2017	China	PDAC	81	41	—	—	—	—	40	—	—	—	—	Multivariate	1.76 (1.08–2.88)	β-actin	PCR
Gao [22]	2016	China	PDAC	61	31	16	12	10	8	30	7	10	8	7	Multivariate	3.52 (1.86–6.66)	—	PCR
Li [23]	2017	China	HCC	88	44	20	—	26	26	44	14	—	8	11	Multivariate	2.47 (1.41–4.33)	GAPDH	PCR
Qu [24]	2017	China	NSCLC	229	113	63	—	42	37	116	76	—	27	21	Multivariate	2.983 (1.442–8.792)	GAPDH	PCR
Shi[25]	2017	China	RCC	36	18	17	—	13	—	18	5	—	4	—	Multivariate	2.67 (1.03–6.92)	GAPDH	PCR
Wang[26]	2016	China	GBC	30	14	11	9	10	11	16	5	7	8	3	Multivariate	2.67 (1.14–6.21)	GAPDH	PCR
Zhou[27]	2016	China	CC	60	32	—	10	26	29	28	—	11	4	3	Multivariate	7.22 (2.43–17.43)	GAPDH	PCR
Zou[28]	2016	China	GC	135	68	55	40	46	49	67	16	11	30	21	Multivariate	1.44 (1.21–2.32)	GAPDH	PCR

The dashes represent no data.

PDAC = pancreatic ductal adenocarcinoma, HCC = hepatocellular carcinoma, NSCLC = nonsmall cell lung cancer, RCC = renal cell carcinoma, GBC = gallbladder cancer, CC = colon cancer, GC = gastric cancer, LTS = lager tumor size, HTS = high tumor stage, PHG = poor histological grade, LNM = lymph node metastasis, OS = overall survival, HR = hazard ratio, GAPDH = glyceraldehyde-3-phosphate dehydrogenase.

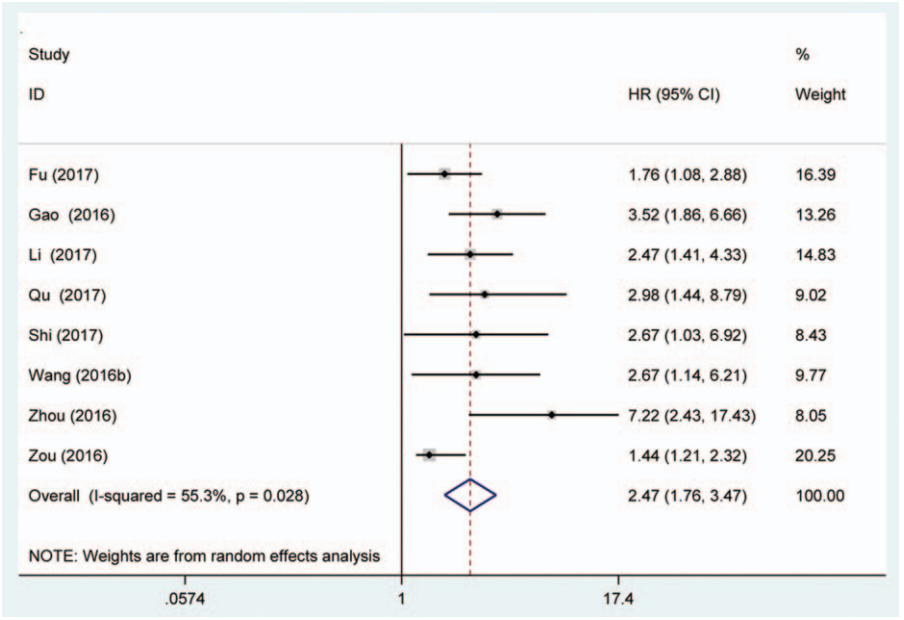

Figure 2. Forest plot reflecting the association between OS and LncRNA ROR expression level in cancer.

DFS and OS among the cancer patients. Therefore, it has been found that LncRNA ROR served as an independent element for the survival rate of the patients with cancer.

3.3. Association between the LncRNA ROR expression level and LTS

Figure 4 presented the association between the LTS and the LncRNA ROR. There were 6 researches,[21–26,28] with 579 patients claimed the connection between the number of cancer patients with LTS and the LncRNA ROR expression levels. It has been shown there was strong heterogeneity in these researches. It also applied the random-effects model ($I^2 = 89.6\%$, $P_Q = 0.000$).

It has been shown a pooled OR = 4.43 in the analysis (95% CI, 1.26–15.51; high vs low LncRNA ROR expression). Consequently, the patients suffering from LTS have increased dramatically among the high LncRNA ROR expression group. It has been revealed from the result that the patients having high LncRNA ROR expression level might suggest an increased chance of LTS.

3.4. Association between the LncRNA ROR expression level and HTS

These 7 eligible researches[22–28] included 639 patients to examine the connection between the HTS and LncRNA ROR

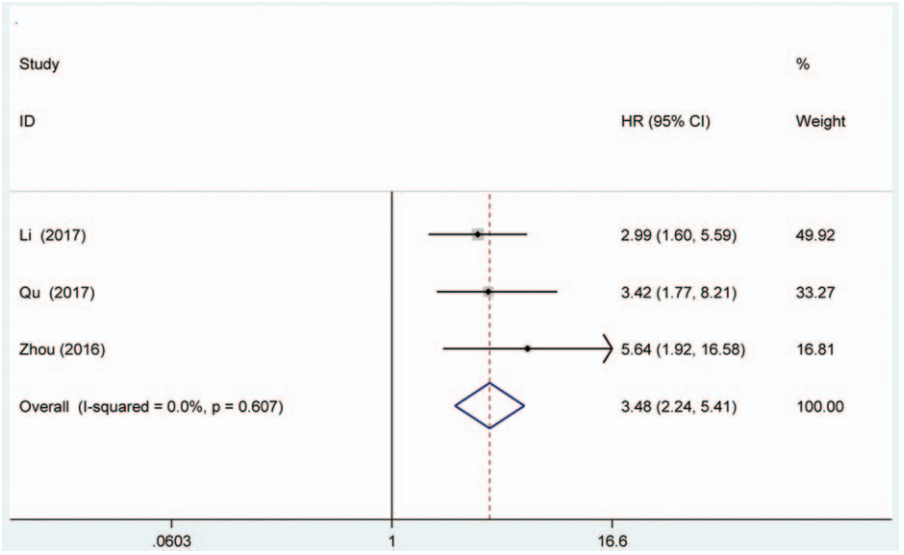

Figure 3. Forest plot showing the association between DFS and LncRNA ROR expression level in cancer.

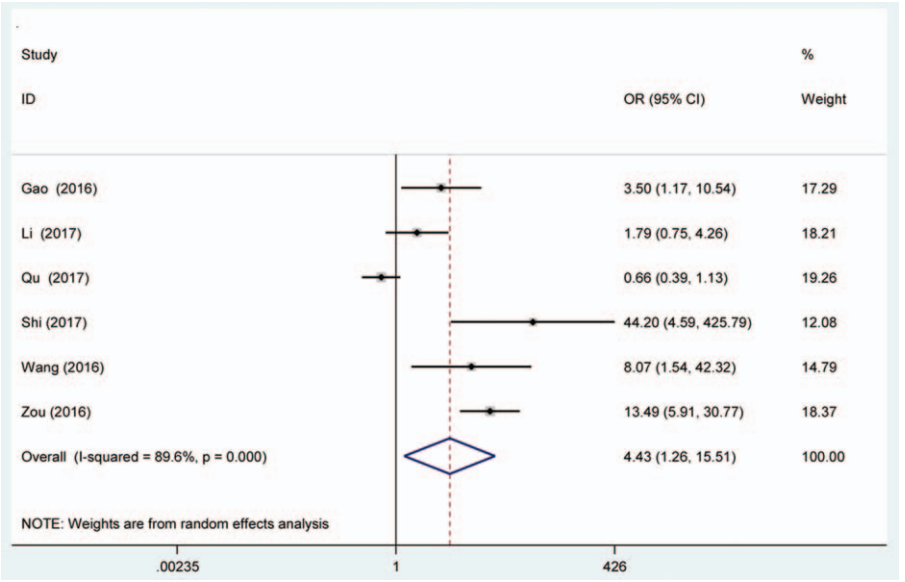

Figure 4. Forest plot showing the association between LTS and LncRNA ROR expression level in cancer.

expression levels in the meta-analysis. The random-effects model has been applied for the detection of strong heterogeneity ($I^2=67.5\%$, $P_Q=0.005$). It has found a strong association between the HTS in cancer patients and high LncRNA ROR expression level (pooled OR = 3.80, 95% CI, 1.95–7.41; Fig. 5).

Based on the results of the analysis, there was a dramatic increase of HTS in the high LncRNA ROR expression group in compression with the low LncRNA ROR expression group. It has been shown from the results that there was a strong correlation between HTS and LncRNA ROR expression for the patients with cancer.

3.5. Association between the LncRNA ROR expression level and PHG

These 4 eligible researches[22,26–28] included 286 patients in total, the data of whom have been collected and analyzed. There was a strong heterogeneity among these researches ($I^2=78.3\%$, $P=.003$). The pooled OR has been calculated through the random-effects model with corresponding 95% CI. There was 2.02 OR (95% CI, 0.64–6.34; Fig. 6), which was expressed as high LncRNA ROR expression group versus low LncRNA ROR expression group.

Based on the results, none great differences were shown in the PHG incidence between these 2 groups. It required to have

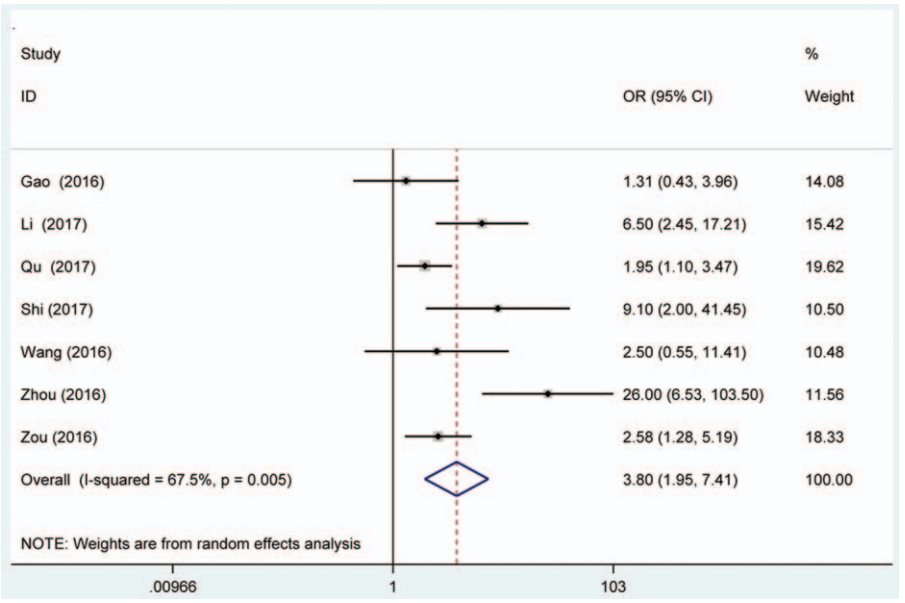

Figure 5. Forest plot showing the correlation between HTS and LncRNA ROR expression level in cancer.

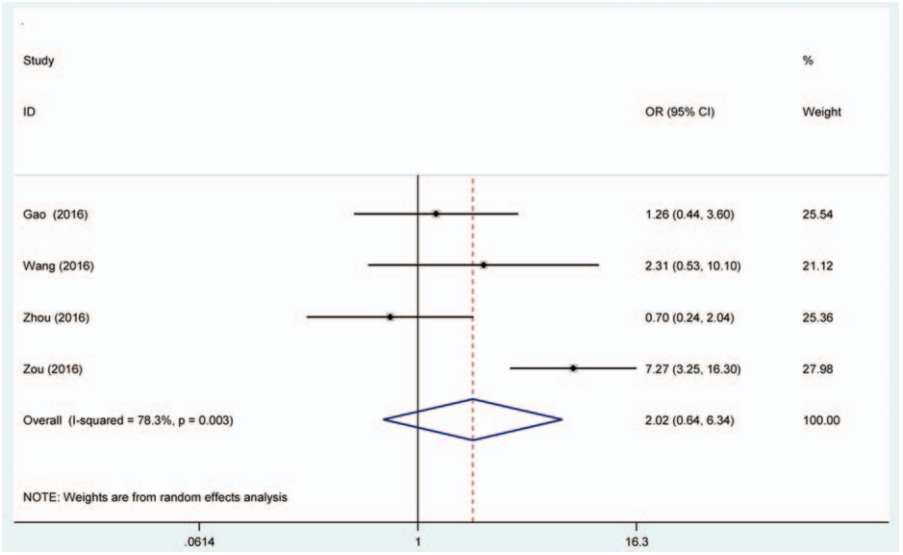

Figure 6. Forest plot reflecting the correlation between PHG and LncRNA ROR expression level in cancer.

additional researches to verify the correlation between PHG and LncRNA of the patients with cancer.

3.6. Association between the LncRNA ROR expression level and LNM

There were altogether 603 patients having cancer based on 6 eligible researches,[22–24,26–28] the data of whom have been collected and also analyzed. It applied the random-effects model for strong heterogeneity (I^2=78.6%, P_Q=0.000). There was 5.38 of OR, which was expressed as high LncRNA ROR expression group versus low LncRNA ROR expression group (Fig. 7). Based on the result, dramatic differences existed in the LNM incidence among these 2 groups. It has been shown from the results that there was a strong association between LNM and high LncRNA ROR.

3.7. Publication bias

Besides, the Egger's test and Begg's funnel plot have been constructed for the assessment of the publication bias. It has been shown from the results that there was no evidence of apparent asymmetry for OS ($P>|t|$=0.108; Fig. 8A), DFS ($P>|t|$=0.296; Fig. 8B), LTS ($P>|t|$=0.133; Fig. 8C), HTS ($P>|t|$=0.518; Fig. 8D), PHG ($P>|t|$=0.210; Fig. 8E) and LNM ($P>|t|$=0.300; Fig. 8F).

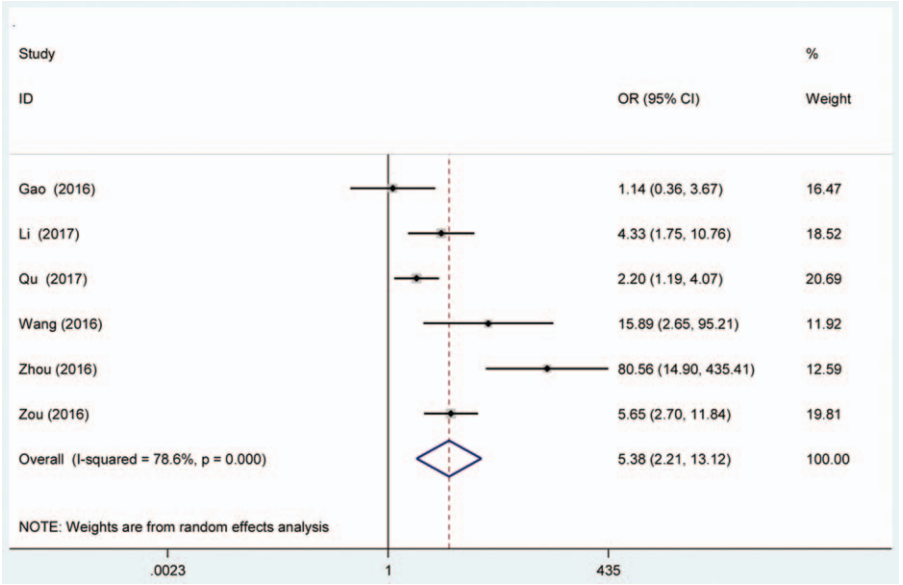

Figure 7. Forest plot reflecting the correlation between LNM and LncRNA ROR expression level in cancer.

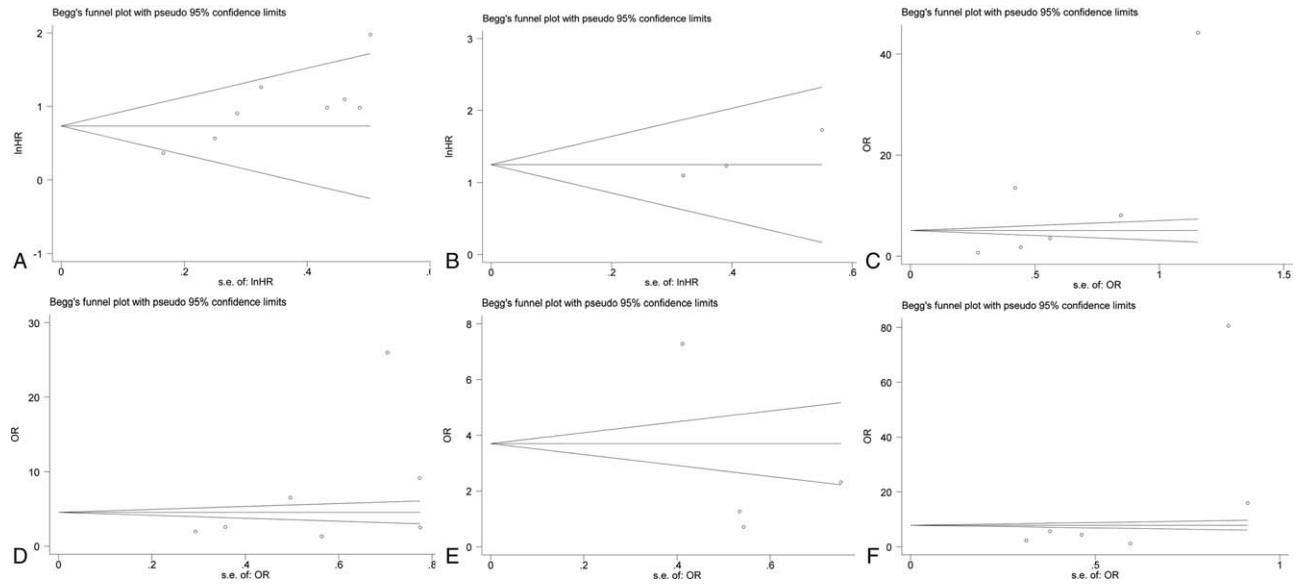

Figure 8. Begg's publication bias plots evaluating the relationship between lncRNA ROR expression level and OS (A), DFS (B), LTS (C), HTS (D), PHG (E), and LNM (F).

4. Discussion

Human health is seriously threatened by the cancer. There has been a gradual increase of the incidence of cancer recently.[1] It still remains uncertain about the exact system of the metastasis among the cancer patients despite the fact that the metastasis' occurrence actually is an important index for the poor prognosis.[29,30] At present, it is of great importance to identify the molecular markers to make a prediction about the tumor metastasis as it is of great importance for the prediction and treatment cancer.[31,32] LncRNAs serve as those types of molecular markers, the influence of which can impact both the occurrence and development of the tumor, which has been assumed to have the potential of the easy biomarkers' collection for the monitoring and diagnosing tumors.[33]

It has been shown from prior studies that LncRNA ROR serves as an important oncogene for various cancer types, such as gastric cancer, gallbladder, NSCLC, hepatocellular carcinoma, and pancreatic ductal adenocarcinoma.[21–28] It has been confirmed from recent progress that there was upregulation of the LncRNA ROR in the gallbladder carcinoma tissues, through the over-expression of which it can promote and foresee the tumor cell invasion, migration, and proliferation.[26] It has been reported by Arunkumar et al that there might be a correlation between the poor prognosis of the patients having oral cancer and LncRNA ROR overexpression.[34]

After exploring the TCGA database, it has been found that there were dramatic differences in terms of the LncRNA ROR expression between the paired normal tissues and various tumor samples, particularly in testicular germ cell tumors, ovarian serous cystadenocarcinoma, head and neck squamous cell carcinoma, esophageal carcinoma and liver hepatocellular carcinoma. It has been found that there were 0.4% patients have LncRNA ROR deletion or amplification among 32,471 patients having multiple tumors in the TCGA database. In addition, LncRNA-ROR can serve as the ceRNA, the over-expression of which can lead to the negative regulation between the miRNAs and also the corresponding genes. We searched for articles published on lincRNA-ROR and miRNA, and we found that the relevant miRNAs have miR-34, miR-133, miR-205, and miR-145.[12,22,35–39] Besides, the location of LncRNA-ROR serves as the binding site for the pluripotency transcription factors, such as Nanog, Sox2, and Oct4. Therefore, these transcription factors can control the LncRNA-ROR expression. The number of the iPSC colonies can be decreased by LncRNA-ROR.[39]

It has been shown that LncRNA ROR serves as an important prognostic factor for the patients with cancer. Currently, it still remains unknown about the underlying systems of how the LncRNA ROR impacts the cancer. This thesis also presents a research about the clinicopatholgic significance and prognostic value of LncRNA ROR.

There were 8 eligible researches collecting altogether 720 patients' data in the research. It applied a fixed-effect model and random-effects model based on the outcomes of the heterogeneity analysis. It has been found that a poor prognosis was indicated by the high LncRNA ROR expression in patients with cancer. Through the combination of the HRs with the Cox multivariate analyses, there was a strong difference in OS between the low and high expression groups of LncRNA ROR.

It has been found that there was a strong correlation between the cancer and the LncRNA ROR. Besides, there was also a strong correlation between the LNM, HTS, LTS of the cancer patients, and high LncRNA ROR. Combined together, it has been suggested from these findings that LncRNA ROR might be applied as a significant prognostic biomarker of poor results in the majority of the cancers.

5. Limitations

During the interpretation process of the conclusions of the current meta-analysis, it is of great importance to take several constraints into consideration. First, the statistics of the meta-analysis might not be applicable for all the nations considering

the included researches were conducted in China. Besides, apart from the best effort exerted to explore for all the related researches, only 8 researches were finally registered in this study. The stringency of the conclusions, therefore, has been reduced. In the third place, the standards of the internal control and high expression of LncRNA ROR have been different in all the reaches. It was difficult to acquire the same value. Finally, cancer prognosis can be impacted by many other factors, taking the therapies and comorbidities as examples. However, information was inaccessible in the analyzed enrolled articles, which thus became a disadvantage of the systematic meta-analysis and review. Thus, it required to have additional well-designed and high-quality reaches to verify the importance of LncRNA ROR in cancer.

6. Conclusion

To conclude, there is a strong correlation between poor LTS, HTS, LNM, DFS, OS, and high levels of LNCRNA ROR expression. As a result, applying LncRNA ROR is promising for the evaluation of the prognosis and metastasis for the cancer patients.

Author contributions

SL and XCY search the electronic databases of Pubmed, OVID, and Web of Science. SL and CYS evaluated all of the included studies and extracted the data independently. SL and HYQ extracted and examined the data from the original articles independently. XYZ resolved the disagreements in the literature assessment and XYZ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Data curation: Shuai Li, Xin-Can Yue.

Investigation: Shuai Li, Chao-Yan Sun, Hai-Yan Qin, Xiao-Yang Zhang.

Writing – original draft: Xiao-Yang Zhang.

Writing – review and editing: Xiao-Yang Zhang.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[2] Johnsson P, Lipovich L, Grander D, et al. Evolutionary conservation of long non-coding RNAs: sequence, structure, function. Biochim Biophys Acta 2014;1840:1063–71.

[3] Fan YH, Fang H, Ji CX, et al. Long noncoding RNA CCAT2 can predict metastasis and poor prognosis: A meta-analysis. Clin Chim Acta 2017;466:120–6.

[4] Li T, Chen Y, Zhang J, et al. LncRNA TUG1 promotes cells proliferation and inhibits cells apoptosis through regulating AURKA in epithelial ovarian cancer cells. Medicine (Baltimore) 2018;97:e12131.

[5] Zhou Y, Wang DL, Pang Q. Long noncoding RNA SPRY4-IT1 is a prognostic factor for poor overall survival and has an oncogenic role in glioma. Eur Rev Med Pharmacol Sci 2016;20:3035–9.

[6] Liu H, Chen P, Jiang C, et al. Screening for the key lncRNA targets associated with metastasis of renal clear cell carcinoma. Medicine (Baltimore) 2016;95:e2507.

[7] Li T, Xiao Y, Huang T. HIF1alphainduced upregulation of lncRNA UCA1 promotes cell growth in osteosarcoma by inactivating the PTEN/AKT signaling pathway. Oncol Rep 2018;39:1072–80.

[8] Liu J, Liu L, Wan JX, et al. Long noncoding RNA SNHG20 promotes gastric cancer progression by inhibiting p21 expression and regulating the GSK-3beta/beta-catenin signaling pathway. Oncotarget 2017;8:80700–8.

[9] Guan ZB, Cao YS, Li Y, et al. Knockdown of lncRNA GHET1 suppresses cell proliferation, invasion and LATS1/YAP pathway in non small cell lung cancer. Cancer Biomark 2018;21:557–63.

[10] Du Z, Fei T, Verhaak RG, et al. Integrative genomic analyses reveal clinically relevant long noncoding RNAs in human cancer. Nat Struct Mol Biol 2013;20:908–13.

[11] Loewer S, Cabili MN, Guttman M, et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. Nat Genet 2010;42:1113–7.

[12] Wang Y, Xu Z, Jiang J, et al. Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal. Dev Cell 2013;25:69–80.

[13] Zhang A, Zhou N, Huang J, et al. The human long non-coding RNA-RoR is a p53 repressor in response to DNA damage. Cell Res 2013;23:340–50.

[14] Zhan HX, Wang Y, Li C, et al. LincRNA-ROR promotes invasion, metastasis and tumor growth in pancreatic cancer through activating ZEB1 pathway. Cancer Lett 2016;374:261–71.

[15] Chen Y, Peng Y, Xu Z, et al. LncROR promotes bladder cancer cell proliferation. Migration, and epithelial-mesenchymal transition. Cell Physiol Biochem 2017;41:2399–410.

[16] Shi H, Pu J, Zhou XL, et al. Silencing long non-coding RNA ROR improves sensitivity of non-small-cell lung cancer to cisplatin resistance by inhibiting PI3K/Akt/mTOR signaling pathway. Tumour Biol 2017;39: 1010428317697568.

[17] Altman DG, McShane LM, Sauerbrei W, et al. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. PLoS Med 2012;9:e1001216.

[18] Xu J, Zhang FQ, Pei J, et al. Acupuncture for migraine without aura: a systematic review and meta-analysis. J Integr Med 2018;16:312–21.

[19] Sun DW, Zhang YY, Sun XD, et al. Prognostic value of cytokeratin 19 in hepatocellular carcinoma: a meta-analysis. Clin Chim Acta 2015;448:161–9.

[20] Fan Y, Yan T, Chai Y, et al. Long noncoding RNA HOTTIP as an independent prognostic marker in cancer. Clin Chim Acta 2018;482:224–30.

[21] Fu Z, Li G, Li Z, et al. Endogenous miRNA Sponge LincRNA-ROR promotes proliferation, invasion and stem cell-like phenotype of pancreatic cancer cells. Cell Death Discov 2017;3:17004.

[22] Gao S, Wang P, Hua Y, et al. ROR functions as a ceRNA to regulate Nanog expression by sponging miR-145 and predicts poor prognosis in pancreatic cancer. Oncotarget 2016;7:1608–18.

[23] Li C, Lu L, Feng B, et al. The lincRNA-ROR/miR-145 axis promotes invasion and metastasis in hepatocellular carcinoma via induction of epithelial-mesenchymal transition by targeting ZEB2. Sci Rep 2017;7:4637.

[24] Qu CH, Sun QY, Zhang FM, et al. Long non-coding RNA ROR is a novel prognosis factor associated with non-small-cell lung cancer progression. Eur Rev Med Pharmacol Sci 2017;21:4087–91.

[25] Shi J, Zhang W, Tian H, et al. LncRNA ROR promotes the proliferation of renal cancer and is negatively associated with favorable prognosis. Mol Med Rep 2017;16:9561–6.

[26] Wang SH, Zhang MD, Wu XC, et al. Overexpression of LncRNA-ROR predicts a poor outcome in gallbladder cancer patients and promotes the tumor cells proliferation, migration, and invasion. Tumour Biol 2016;37:12867–75.

[27] Zhou P, Sun L, Liu D, et al. Long non-coding RNA lincRNA-ROR promotes the progression of colon cancer and holds prognostic value by associating with miR-145. Pathol Oncol Res 2016;22:733–40.

[28] Zou Z, Ding Q, Li JP, et al. Overexpression of lincRNA-ROR predicts poor prognosis in patients with gastric cancer. Int J Clin Exp Pathol 2016;9:9467–72.

[29] Chen X, Pei Z, Peng H, et al. Exploring the molecular mechanism associated with breast cancer bone metastasis using bioinformatic analysis and microarray genetic interaction network. Medicine (Baltimore) 2018;97:e12032.

[30] Hong L, Wang S, Li W, et al. Tumor-associated macrophages promote the metastasis of ovarian carcinoma cells by enhancing CXCL16/CXCR6 expression. Pathol Res Pract 2018;214:1345–51.

[31] Mirzaei H, Gholamin S, Shahidsales S, et al. MicroRNAs as potential diagnostic and prognostic biomarkers in melanoma. Eur J Cancer 2016;53:25–32.

[32] Fan YH, Ye MH, Wu L, et al. Overexpression of miR-98 inhibits cell invasion in glioma cell lines via downregulation of IKKepsilon. Eur Rev Med Pharmacol Sci 2015;19:3593–604.

[33] Qi P, Du X. The long non-coding RNAs, a new cancer diagnostic and therapeutic gold mine. Mod Pathol 2013;26:155–65.

[34] Arunkumar G, Deva Magendhra Rao AK, Manikandan M, et al. Expression profiling of long non-coding RNA identifies linc-RoR as a

prognostic biomarker in oral cancer. Tumour Biol 2017;39: 1010428317698366.
[35] Eades G, Wolfson B, Zhang Y, et al. lincRNA-RoR and miR-145 regulate invasion in triple-negative breast cancer via targeting ARF6. Mol Cancer Res 2015;13:330–8.
[36] Zhou X, Gao Q, Wang J, et al. Linc-RNA-RoR acts as a "sponge" against mediation of the differentiation of endometrial cancer stem cells by microRNA-145. Gynecol Oncol 2014;133:333–9.
[37] Jiang F, Zhou X, Huang J, et al. Non-coding RNA-ROR mediates the reprogramming in cardiac hypertrophy. PLoS One 2016;11:e0152767.
[38] Hou P, Zhao Y, Li Z, et al. LincRNA-ROR induces epithelial-to-mesenchymal transition and contributes to breast cancer tumorigenesis and metastasis. Cell Death Dis 2014;5:e1287.
[39] Pan Y, Li C, Chen J, et al. The emerging roles of long noncoding RNA ROR (lincRNA-ROR) and its possible mechanisms in human cancers. Cell Physiol Biochem 2016;40:219–29.