Clinicopathological and prognostic significance of long non-coding RNA-ROR in cancer patients
A systematic review and meta-analysis

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Abstract

Background: Accumulating studies have focused on the clinicopathological and prognostic roles of large intergenic noncoding RNA regulator of reprogramming (lincRNA-ROR) in cancer patients. However, the results were controversial and unconvincing. Thus, we performed a meta-analysis to assess the associations between lincRNA-ROR expression and survival and clinicopathological characteristics of cancer patients.

Methods: Hazard ratios for overall survival and disease-free survival with their 95% confidence intervals were used to evaluate the role of lincRNA-ROR expression in the prognosis of cancer patients. Risk ratios with their 95% confidence intervals were applied to assess the relationship between lincRNA-ROR expression and clinicopathological parameters.

Results: A total of 18 articles with 1441 patients were enrolled. Our results indicated that high lincRNA-ROR expression was significant associated with tumor size, TNM stage, clinical stage, lymph metastasis, metastasis and vessel invasion of cancer patients. There were no correlations between high lincRNA-ROR expression and age, gender, infiltration depth, differentiation, serum CA19–9 and serum CEA of cancer patients. In addition, high lincRNA-ROR expression was associated with shorter Overall survival and disease-free survival on both univariate and multivariate analyses. Meanwhile, there were no obvious publication bias in our meta-analysis.

Conclusions: LincRNA-ROR expression was associated with the clinicopathological features and outcome of cancer patients, which suggested that lincRNA-ROR might serve as a potential biomarker for cancer prognosis.

Ethical approval: Since this study is on the basis of published articles, ethical approval and informed consent of patients are not required.

Abbreviations: 95% CIs = 95% confidence intervals, DFS = disease-free survival, HRs = hazard ratios, LincRNA-ROR = Large intergenic noncoding RNA regulator of reprogramming, OS = overall survival.

Keywords: cancer, expression, large intergenic noncoding RNA regulator of reprogramming, meta-analysis, prognosis
1. Introduction

Long non-coding RNAs (lncRNAs) are defined as over 200-nucleotide RNA molecules in length without the capacity of protein-coding, including antisense lncRNA, intronic transcript lncRNA, large intergenic noncoding RNA (lincRNA), promoter associated lncRNA and UTR associated lncRNA. Recently, it is well known that lncRNAs have played significant roles in many pathological processes and human diseases. In particular, numerous lncRNAs have been verified as critical regulatory molecules in the development and progression of many cancers.

As a member of lncRNAs, lincRNA regulator of reprogramming (lincRNA-ROR) was first proven in induced pluripotent stem cells, where it was regulated by the crucial pluripotency factors including Oct4, Sox2, and Nanog. More and more studies have paid attention to the relationship between lincRNA-ROR and tumors. Recent data have indicated that lincRNA-ROR was involved in a variety of cancers, such as colorectal cancer, breast cancer, esophageal squamous cell carcinoma and oral cancer. In addition, abnormal expression of lincRNA-ROR was closely associated with the prognosis and clinicopathological characteristics of patients with cancer. However, the results were still inconsistent. For example, some evidences supported that lincRNA-ROR high expression was correlated with larger tumor size, higher TNM stage, the present of lymph metastasis and vessel invasion. Nevertheless, several reports have indicated the opposite results. The study by Zhu et al. indicated that the relationships between lincRNA-ROR expression and TNM stage or lymph metastasis or metastasis of tumor patients were not statistically significant. The study by Wang et al. showed that the relationship between lincRNA-ROR expression and clinical stage was not statistically significant. The study by Gao et al. indicated that the relationships between lincRNA-ROR expression and TNM stage or lymph metastasis of tumor patients were not statistically significant. Therefore, we carried out this meta-analysis to evaluate the value of lincRNA-ROR in the prognosis and clinicopathological characteristics of patients with cancer.

2. Methods

This study was performed on the basis of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

2.1. Literature searches

PubMed, Web of Science, Cochrane Library, Wanfang Data, and China National Knowledge Infrastructure were applied to select articles up to March 11, 2019. The following terms were used in the literature searching: “cancer” or “sarcoma” or “tumor” or “neoplasm” and “lincRNA-ROR” or “lincRNA-ROR” or “lincRNA ROR” or “lincRNA ROR” or “long non-coding RNA regulator of reprogramming” or “large intergenic non-coding RNA regulator of reprogramming” and “prognosis” or “survival” or “outcome” or “recurrence.”

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies were investigated the relationship between lincRNA-ROR and prognosis or clinicopathological characteristics of patients with cancer; (2) availability of information on outcome or clinicopathological parameters; (3) literatures have sufficient data to assess hazard ratios (HRs) or risk ratios, and corresponding 95% confidence intervals (95% CIs); (4) studies were published in the English or Chinese language. In addition, the exclusion criteria were as follows: (1) literatures were reviews, letters, or case reports; (2) studies without survival or other clinicopathological parameters; (3) studies were used in other languages instead of English or Chinese.

2.3. Data Extraction and quality assessment

Two investigators (Deqing Luo and Hui Liu) extracted the data independently and assessed study quality. Disagreements were resolved by a third senior author (Zunxian Huang). The following data were extracted: the first author’s name, publication year, research region, histological type, detection method, cut-off value, sample size, high lincRNA-ROR expression case, high lincRNA-ROR expression rate, follow-up time, outcome, and analysis method. The quality of each included study was assessed by the Newcastle-Ottawa Scale (NOS, 0–9). If the NOS score was more than 6, the study was considered as high quality.

2.4. Statistical methods

Statistical analyses in this study were carried out using STATA 12 software (STATA Corp., College Station, TX). Risk ratios and corresponding 95% CIs were used to assess the correlation between lincRNA-ROR expression and clinicopathological parameters. The association between lincRNA-ROR expression and prognosis was determined by calculating HRs and corresponding 95% CIs, which could be obtained from the original text or Kaplan–Meier survival curves. Subgroup analyses were conducted according to histological type, case, follow-up or quality. Standard Cochran’s Q test and I² statistics were used to describe heterogeneity in this meta-analysis. If I² was more than 50%, we performed the random effects model, otherwise the fixed effect model was used (I² < 50%). Sensitivity analysis was used to assess the stability of the results, when the study was removed one by one. Begg’s and Egger’s tests were used to calculate publication bias. A P value < 0.05 was considered statistically significant. The weights and sample sizes used were linearly related.

3. Results

3.1. Study selection

A total of 267 studies were initially found from the database search. After removing 35 duplicate articles, 232 studies were further evaluated by the titles and abstracts. Then, 57 studies were remained for further evaluation by browsing full texts. Finally, 18 articles were eligible for this meta-analysis. The flow diagram of the literature searches and screening process was shown in Figure 1.

3.2. Characteristics of the studies

A total of 18 articles with 1441 patients were enrolled in this meta-analysis. Among them, 14 articles with 1130 patients were reported the relationship between lincRNA-ROR expression and clinicopathological parameters of cancer patients.
The clinicopathological characteristics of the included studies was shown in Supplemental Table 1, http://links.lww.com/MD2/A267. In addition, 14 articles with 1197 patients were investigated the association between lincRNA-ROR expression and prognosis of cancer patients. The basic characteristics of the studies was shown in Table 1. All of studies were from Asian, and were performed quantitative real-time PCR (qRT-PCR) to detect the lincRNA-ROR expression. 14 studies were investigated the information of overall survival (OS), 4 studies were reported the information of disease-free survival (DFS). In term of histological type, 9 studies were digestive cancer including 2 colorectal cancer, 2 esophageal squamous cell carcinoma, 2 pancreatic cancer, 1 hepatocellular cancer, 1 gastric cancer, and 1 gallbladder cancer, 5 studies were other cancers including 2 non-small-cell lung cancer, 1 osteosarcoma, 1 breast cancer and 1 renal cancer. The sample size of the studies was range from 30 to 229. The follow-up time was from 24 to 120 months. Moreover, 11 studies were high quality, and 3 studies were low quality.

3.3. Relationship between lncRNA-ROR expression and clinicopathological features

To investigate the role of lincRNA-ROR expression as a biomarker in cancer, we explored the association between lincRNA-ROR expression and clinicopathological features. A total of 14 articles with 1197 patients were included in this meta-analysis, and the results were shown in Table 2. On evaluating the data, a significant correlation was found between high lincRNA-ROR expression and tumor size (RR = 1.82; 95% CI: 1.10–3.04; \(P = .021\); Fig. 2A), TNM stage (RR = 1.55; 95% CI: 1.29–1.88;
P \leq .001; Fig. 2B), clinical stage (RR = 2.10; 95% CI: 1.20–3.67; P = .009; Fig. 2C), lymph metastasis (RR = 1.55; 95% CI: 1.25–1.94; P < .001; Fig. 2D), metastasis (RR = 1.65; 95% CI: 1.26–2.16; P < .001; Fig. 2E), and vessel invasion (RR = 1.87; 95% CI: 1.42–2.47; P < .001; Fig. 2F). Meanwhile, high lincRNA-ROR expression was not associated with age (RR = 0.93; 95% CI: 0.81–1.07; P = .310; Supplemental Figure 1A, http://links.lww.com/MD2/A264), differentiation (RR = 1.15; 95% CI: 0.80–1.65; P = .445; Supplemental Figure 1C, http://links.lww.com/MD2/A263), tumor size (cm) (>5 vs \leq 5) (RR = 1.01; 95% CI: 0.82–1.24; P = .93; Supplemental Figure 1D, http://links.lww.com/MD2/A263), and tumor size (cm) (<6 vs \geq 6) (RR = 0.98; 95% CI: 0.77–1.24; P = .41; Supplemental Figure 1E, http://links.lww.com/MD2/A263), and tumor size (cm) (\leq 5 vs >5) (RR = 1.02; 95% CI: 0.80–1.32; P = .84; Supplemental Figure 1F, http://links.lww.com/MD2/A263).

3.4. Prognostic Value of lncRNA-ROR Expression for OS
A total of 14 articles with 1197 patients were investigated the association between lincRNA-ROR expression and OS of cancer patients. Our results indicated that high lincRNA-ROR expression was associated with poor OS on both univariate and multivariate analysis (HR = 2.45, 95% CI: 1.90–3.16, P < .001; Table 2). Meanwhile, high lincRNA-ROR expression was associated with poor OS on both univariate and multivariate analysis (HR = 2.45, 95% CI: 1.90–3.16, P < .001; Table 2). To detect the source of heterogeneity for OS with univariate and multivariate analyses, subgroup analyses were performed according to histological type, the number of cases, the time of follow-up and quality. As shown in Table 3, the correlation between lincRNA-ROR expression and OS of cancer patients with univariate analysis was present in all subgroups including digestive cancer (HR = 2.70, 95% CI: 1.85–3.94, P < .001, Supplemental Figure 2A, http://links.lww.com/MD2/A264), other cancer (HR = 2.12, 95% CI: 1.24–2.47; P < .001, Fig. 2F).

### Table 1
Basic characteristics of the included studies.

| Study Year | Region       | Histological type                      | Detection method | Cut-off value | Case (n) | High expression (n) | High expression (%) | Follow-up (mo) | NOS score | Quality | Outcome | Analysis |
|------------|--------------|----------------------------------------|------------------|---------------|-----------|---------------------|--------------------|---------------|-----------|---------|---------|----------|
| Chen 2019  | Asian        | colorectal cancer                      | qRT-PCR          | mean          | 79        | 43                  | 54.4               | 60            | 7         | High    | OS      | MA       |
| Fei 2018   | Asian        | osteosarcoma                           | qRT-PCR          | mean          | 48        | 26                  | 54.2               | 60            | 7         | High    | OS      | UA       |
| Fu 2017    | Asian        | pancreatic cancer                      | qRT-PCR          | NA            | 81        | 41                  | 50.6               | 60            | 6         | High    | OS      | UA       |
| Gao 2015   | Asian        | pancreatic cancer                      | qRT-PCR          | NA            | 61        | 31                  | 50.8               | 45            | 4         | Low     | OS      | UA       |
| Hou 2018   | Asian        | breast cancer                          | qRT-PCR          | mean          | 94        | 35                  | 37.2               | 60            | 7         | High    | OS      | UA       |
| Li 2017    | Asian        | HCC                                    | qRT-PCR          | median        | 88        | 44                  | 50.0               | 60            | 7         | High    | OS/DFS  | UA       |
| Liu 2017   | Asian        | ESCC                                   | qRT-PCR          | NA            | 120       | 64                  | 53.3               | 60            | 6         | High    | OS/DFS  | UA/MA    |
| Qu 2017    | Asian        | NSCLC                                  | qRT-PCR          | median        | 229       | 113                 | 49.3               | 60            | 7         | High    | OS/DFS  | UA/MA    |
| Wang 2018  | Asian        | gallbladder cancer                     | qRT-PCR          | NA            | 60        | 32                  | 53.3               | 80            | 8         | High    | OS/DFS  | UA/MA    |
| Zhou 2019  | Asian        | colon cancer                           | qRT-PCR          | median        | 135       | 68                  | 50.4               | 120           | 7         | High    | OS/DFS  | UA/MA    |
| Shi 2017   | Asian        | renal cancer                           | qRT-PCR          | NA            | 96        | –                   | –                  | 50            | 4         | Low     | OS      | UA       |
| Li 2017    | Asian        | ESCC                                   | qRT-PCR          | NA            | 36        | 18                  | 50.0               | 24            | 6         | High    | OS      | UA       |
| Wang 2016  | Asian        | gallbladder cancer                     | qRT-PCR          | NA            | 30        | 14                  | 46.7               | 36            | 6         | High    | OS      | UA       |
| Xia 2017   | Asian        | NSCLC                                  | qRT-PCR          | median        | 40        | –                   | –                  | 60            | 4         | Low     | OS      | UA       |
| Zhou 2016  | Asian        | carcinoma                              | qRT-PCR          | median        | 60        | 32                  | 53.3               | 80            | 8         | High    | OS/DFS  | UA/MA    |
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### Table 2
The analysis for lincRNA-ROR and the clinicopathological characteristics of patients with cancer.

| Clinicopathological features | Number of studies | Number of case (n) | lincRNA-ROR high expression (n) | Pooled data | Test for heterogeneity |
|------------------------------|-------------------|--------------------|---------------------------------|-------------|-----------------------|
| Age (<60 vs \geq 60)         | 9                 | 794                | 408                             | RR = 0.93   | 0.81–1.07             | P-value = .310     | Chi2 = 7.50 | .484 | 0.0    |
| Gender (male vs female)      | 14                | 1130               | 583                             | RR = 0.99   | 0.88–1.12             | P-value = .925     | 7.78        | .858 | 0.0    |
| Tumor size (cm) (\geq 5 vs <5) | 5             | 425                | 224                             | RR = 1.82   | 1.10–3.04             | P-value = .021     | 22.42       | <.001 | 82.2   |
| Infiltration depth (T3/T4 vs T1/T2) | 4             | 309                | 165                             | RR = 1.32   | 0.87–2.00             | P-value = .197     | 10.57       | .014 | 71.6   |
| Differentiation (poor vs well/moderate) | 7            | 467                | 249                             | RR = 1.15   | 0.80–1.65             | P-value = .445     | 22.84       | <.001 | 73.7   |
| TNM stage (I/II vs III)      | 10                | 968                | 504                             | RR = 1.55   | 1.29–1.88             | <.001              | 21.47       | .011 | 58.1   |
| Clinical stage (I/II vs III) | 2                 | 66                 | 33                              | RR = 2.10   | 1.20–3.67             | <.001              | 0.41        | .523 | 0.0    |
| Lymph metastasis (yes vs no) | 10                | 956                | 495                             | RR = 1.55   | 1.25–1.94             | <.001              | 24.51       | .004 | 63.3   |
| Metastasis (yes vs no)       | 7                 | 641                | 334                             | RR = 1.65   | 1.26–2.16             | <.001              | 16.98       | .009 | 64.7   |
| Vessel invasion (yes vs no)  | 3                 | 227                | 119                             | RR = 1.87   | 1.42–2.47             | <.001              | 0.54        | .763 | 0.0    |
| Serum CA19–9 (positive vs negative) | 3            | 200                | 106                             | RR = 0.84   | 0.63–1.12             | P-value = .241     | 1.48        | .477 | 0.0    |
| Serum CEA (positive vs negative) | 2             | 139                | 75                              | RR = 0.90   | 0.80–1.24             | P-value = .514     | 0.77        | .380 | 0.0    |

CI = confidence interval, RR = risk ratio.
1.56–2.88, *P* < .001, Supplemental Figure 2A, http://links.lww.com/MD2/A264), smaller cases (n < 80) (HR = 3.20, 95% CI: 2.07–4.95, *P* < .001, Supplemental Figure 2B, http://links.lww.com/MD2/A264), larger cases (n ≥ 80) (HR = 2.10, 95% CI: 1.60–2.74, *P* < .001, Supplemental Figure 2B, http://links.lww.com/MD2/A264), shorter follow-up time (n < 60) (HR = 3.35, 95% CI: 2.35–4.77, *P* < .001, Supplemental Figure 2C, http://links.lww.com/MD2/A264), longer follow-up time (n ≥ 60) (HR = 2.21, 95% CI: 1.65–2.95, *P* < .001, Supplemental Figure 2C, http://links.lww.com/MD2/A264), high quality (HR = 2.33, 95% CI: 1.79–3.05, *P* < .001, Supplemental Figure 2D, http://links.lww.com/MD2/A264), and low quality (HR = 3.64, 95% CI: 1.92–6.88, *P* < .001, Supplemental Figure 2D, http://links.lww.com/MD2/A264). Moreover, lincRNA-ROR expression was correlation with OS of cancer patients on multivariate analysis in all subgroups including digestive cancer (HR = 3.73, 95% CI: 2.85–4.88, *P* < .001, Supplemental Figure 2D, http://links.lww.com/MD2/A264).
95% CI: 1.51–9.22, \( P = .004 \), Supplemental Figure 2E, http://links.lww.com/MD2/A264), other cancer (HR = 2.98, 95% CI: 1.21–7.37, \( P = 1.21–7.37 \), Supplemental Figure 2E, http://links.lww.com/MD2/A264), smaller cases (n < 80) (HR = 7.17, 95% CI: 4.07–12.65, \( P < .001 \), Supplemental Figure 2F, http://links.lww.com/MD2/A264), and larger cases (n ≥ 80) (HR = 2.18, 95% CI: 1.20–3.98, \( P = .011 \), Supplemental Figure 2F, http://links.lww.com/MD2/A264).

3.5. Prognostic Value of lncRNA-ROR Expression for DFS
Meanwhile, 4 articles with 497 patients were detected the association between lincRNA-ROR expression and DFS of cancer patients. Our results indicated that high lincRNA-ROR expression was associated with shorter DFS on both univariate analysis (HR = 2.47, 95% CI: 1.45–4.23, \( P < .001 \), heterogeneity: random-effects model: \( \chi^2 = 14.71, I^2 = 79.6\% \), \( P = .002 \), Fig. 4A) and multivariate analysis (HR = 3.41, 95% CI: 2.22–
5.23, \(P < .001\); heterogeneity: random-effects model: \(\chi^2 = 1.10, I^2 = 0\%, P = .578\), Fig. 4B). Moreover, subgroup analysis was performed according to histological type, the number of cases, and the time of follow-up. As shown in Table 4, the correlation between lncRNA-ROR expression and DFS of cancer patients with univariate analysis was present in all subgroups including digestive cancer (HR = 2.96, 95% CI: 1.24–7.07, \(P = .015\), Supplemental Figure 3A, http://links.lww.com/MD2/A265), other cancer (HR = 1.82, 95% CI: 1.42–2.65, \(P = .002\), Supplemental Figure 3A, http://links.lww.com/MD2/A265), smaller cases (\(n < 100\)) (HR = 4.38, 95% CI: 1.28–15.01, \(P = .019\), Supplemental Figure 3B, http://links.lww.com/MD2/A265), larger cases (\(n \geq 100\)) (HR = 1.66, 95% CI: 1.30–2.13, \(P < .001\), Supplemental Figure 3B, http://links.lww.com/MD2/A265), shorter follow-up time (\(n \leq 60\)) (HR = 1.76, 95% CI: 1.40–2.21, \(P < .001\), Supplemental Figure 3C, http://links.lww.com/MD2/A265), and longer follow-up time (\(n > 60\)) (HR = 8.51, 95% CI: 3.73–19.42, \(P < .001\), Supplemental Figure 3C, http://links.lww.com/MD2/A265). In addition, lncRNA-ROR expression was correlation with DFS of cancer patients on multivariate analysis in all subgroups including digestive cancer (HR = 3.45, 95% CI: 1.97–6.04, \(P < .001\), Supplemental Figure 3D, http://links.lww.com/MD2/A265), other cancer (HR = 3.42, 95% CI: 1.59–7.36, \(P = .002\), Supplemental Figure 3D, http://links.lww.com/MD2/A265), smaller cases (\(n < 100\)) (HR = 5.64, 95% CI: 1.92–16.57, \(P = .002\), Supplemental Figure 3E, http://links.lww.com/MD2/A265), larger cases (\(n \geq 100\)) (HR = 3.10, 95% CI: 1.94–4.94, \(P < .001\), Supplemental Figure 3E, http://links.lww.com/MD2/A265), shorter follow-up time (\(n \leq 60\)) (HR = 3.10, 95% CI: 1.94–4.94, \(P < .001\), Supplemental Figure 3F, http://links.lww.com/MD2/A265), and longer follow-up time (\(n > 60\)) (HR = 5.64, 95% CI: 1.92–16.57, \(P = .002\), Supplemental Figure 3F, http://links.lww.com/MD2/A265).

### 3.6. Test of heterogeneity

Galbraith plots were performed to explore the potential sources of heterogeneity. As shown in Figure 5A, the studies by Zhou et al and Liu et al might have mainly contributed to heterogeneity in OS data with univariate analysis. After omitting the two studies, the statistical significance of the pooled HRs was not obviously altered, but \(I^2\) decreased from 58.5% to 20.4% (data not shown). Similarly, the studies by Zou et al might be the main source of heterogeneity in OS data with multivariate analysis (Fig. 5B, from \(I^2 = 83.7%\) to \(I^2 = 27.4%\), data not shown). As shown in Figure 5C, the studies by Zhou et al might have mainly contributed to heterogeneity in DFS data with univariate analysis (from \(I^2 = 79.6%\) to \(I^2 = 0\%\), data not shown). Furthermore, there was no obvious heterogeneity in DFS data with multivariate analysis (Fig. 5D, \(I^2 = 0\%)\).

### 3.7. Sensitivity analysis and publication bias

We further evaluated the robustness of the results by removing studies at a time. As shown in Figure 6A, the results of OS with univariate analysis was also stable. And excluding one study did not have an obvious effect on the conclusion of OS with multivariate analysis apart from a single study from Zou et al that was the major source of heterogeneity (Fig. 6B). Moreover, our results indicated that the findings of DFS with both univariate and multivariate analyses were reliable and robust (Fig. 6C and D). In addition, Begg and Egger tests were used to assess potential publication bias. As shown in Table 5 and Supplemental Figure 4A-4D, http://links.lww.com/MD2/A266, there were no significant publication bias in our meta-analysis of OS and DFS with both univariate and multivariate analyses (All \(P \geq .05\)).
4. Discussion

LincRNA-ROR has been proved to play critical role in the regulation of gene transcription and translation, epigenetic and other cellular activities.\[30\] Moreover, lincRNA-ROR may be considered as oncogene or tumor suppressor involving in the development and progression of cancers.\[31\] Emerging evidence indicated a strong association between lincRNA-ROR and various cancers.\[6\] However, the effect of lincRNA-ROR on the prognosis of cancer was unclear. Although two meta-analyses have reported the relationship between lincRNA-ROR expression and the outcome in human cancer,\[32,33\] there were some shortcomings. The numbers of enrolled studies for analyzing lincRNA-ROR expression in OS or clinicopathological features of cancer patients were less than or equal to ten, it need more studies to further estimate the above association. Moreover, they were lack of the evaluation on the DFS with multivariate analysis. Hence, it is necessary to update the meta-analyses.

In this meta-analysis, a total of 18 articles with 1441 patients were enrolled. Our results indicated that high lincRNA-ROR expression was significant associated with tumor size, TNM
### Table 4
The subgroups analysis for lincRNA-ROR and DFS in cancer patients.

| Subgroups          | Number of Studies | Case (n) | High expression (n) | High expression (%) | Pooled Data | Test for Heterogeneity |
|--------------------|-------------------|----------|---------------------|---------------------|-------------|------------------------|
|                    |                   |          |                     |                     | HR          | 95% CI                 | P-value | P-value | I² (%) |
| Univariate analysis|                   |          |                     |                     |             |                        |         |         |        |
| Histological type  |                   |          |                     |                     |             |                        |         |         |        |
| Digestive cancer   | 3                 | 268      | 140                 | 52.2                | 2.96        | 1.24–7.07              | .015    | .001    | 86.2   |
| Other cancer       | 1                 | 229      | 113                 | 49.3                | 1.82        | 1.25–2.65              | .002    | –       | –      |
| Case (n)           |                   |          |                     |                     |             |                        |         |         |        |
| < 100              | 2                 | 148      | 76                  | 51.4                | 4.38        | 1.28–15.01             | .019    | .015    | 83.0   |
| ≥ 100              | 2                 | 349      | 177                 | 50.7                | 1.66        | 1.30–2.13              | <.001   | .531    | 0.0    |
| Follow-up (mo)     |                   |          |                     |                     |             |                        |         |         |        |
| ≤ 60               | 3                 | 437      | 221                 | 50.6                | 1.76        | 1.40–2.21              | <.001   | .426    | 0.0    |
| > 60               | 1                 | 60       | 32                  | 53.3                | 8.51        | 3.73–19.42             | <.001   | –       | –      |
| Multivariate analysis|                 |          |                     |                     |             |                        |         |         |        |
| Histological type  |                   |          |                     |                     |             |                        |         |         |        |
| Digestive cancer   | 2                 | 180      | 96                  | 53.3                | 3.45        | 1.97–6.04              | <.001   | .295    | 8.9    |
| Other cancer       | 1                 | 229      | 113                 | 49.3                | 3.42        | 1.59–7.36              | .002    | –       | –      |
| Case (n)           |                   |          |                     |                     |             |                        |         |         |        |
| < 100              | 1                 | 60       | 32                  | 53.3                | 5.64        | 1.92–16.57             | .002    | –       | –      |
| ≥ 100              | 2                 | 349      | 177                 | 50.7                | 3.10        | 1.94–4.94              | <.001   | .751    | 0.0    |
| Follow-up (mo)     |                   |          |                     |                     |             |                        |         |         |        |
| ≤ 60               | 2                 | 349      | 177                 | 50.7                | 3.10        | 1.94–4.94              | <.001   | .751    | 0.0    |
| > 60               | 1                 | 60       | 32                  | 53.3                | 5.64        | 1.92–16.57             | .002    | –       | –      |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, LincRNA-ROR = Large intergenic noncoding RNA regulator of reprogramming.

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**Figure 5.** Galbraith plots of studies evaluating the associations between lncRNA-ROR expression and prognosis including OS with univariate (A) and multivariate (B) analyses, and DFS with univariate (C) and multivariate (D) analyses.
stage, clinical stage, lymph metastasis, metastasis and vessel invasion of cancer patients. There were no correlations between high lincRNA-ROR expression and age, gender, infiltration depth, differentiation, serum CA19–9 and serum CEA of cancer patients. In addition, high lincRNA-ROR expression was associated with shorter OS and DFS on both univariate and multivariate analyses. Meanwhile, there were no obvious publication bias in our meta-analysis.

Recently, more and more researchers have paid increasing attention to the functional mechanisms of lincRNA-ROR. On one hand, as a typical lncRNA, lincRNA-ROR can maintain stem cell pluripotency and trigger the epithelial-mesenchymal transition (EMT) by interacting with miRNAs. It is reported that lincRNA-ROR regulates the expression of core transcription factors and differentiation-related miRNAs involving in human embryonic stem cell self-renewal.[34] Moreover, lincRNA-ROR induces EMT by regulation the degradation of microRNA-205 target genes ZEB2 in breast cancer.[35] On other hand, lincRNA-ROR mediates multiple signaling pathways involving in the growth and progression of various tumors. Research indicated that lincRNA-ROR promoted the proliferation, migration and invasion of breast cancer by regulating the TGF-β pathway.[36] Moreover, lincRNA-ROR activates MAPK/ERK signaling and increases estrogen-independent growth of breast cancer.[37]

Although some evidences have achieved in our study, this meta-analysis had several limitations. Firstly, all enrolled studies were from Asian, and further studies from other populations are required to evaluate the association. Secondly, there were some heterogeneity in our meta-analysis, which is probably caused by one or two studies. Hence, larger studies with high quality are needed. Thirdly, sensitivity analyses indicated that the association between lincRNA-ROR expression and OS with multivariate analysis was not robustly stable due to a single study from Zou et al that was the major source of heterogeneity. Finally, due to the limit of number, DFS analysis should also be investigated in further studies with larger sample sizes.

**Table 5**

| Outcome               | P value of Begg test | P value of Egger test |
|-----------------------|----------------------|-----------------------|
| Overall survival      |                      |                       |
| Univariate analysis   | .272                 | .075                  |
| Multivariate analysis | .624                 | .060                  |
| Disease-free survival |                      |                       |
| Univariate analysis   | .089                 | .051                  |
| Multivariate analysis | .117                 | .105                  |

LincRNA-ROR = Large intergenic noncoding RNA regulator of reprogramming.
5. Conclusions
In conclusion, our results indicated that high lncRNA-ROR expression predicts poor prognosis in cancer, including OS and DFS with univariate and multivariate analyses. Furthermore, lncRNA-ROR expression was significant associated with tumor size, TNM stage, clinical stage, lymph metastasis, metastasis, and vessel invasion of cancer patients. This meta-analysis suggested that lncRNA-ROR might be regarded as a potential molecular biomarker for predicting the prognosis of cancer patients.

Author contributions
Deqing Luo contributed to the design of experiments. Limin Yang, Le Yu, Yijin Chen, and Zunxian Huang collected and analyzed the data. Deqing Luo wrote the manuscript. Hui Liu reviewed the manuscript and supervised this work. All authors read and approved the final manuscript.

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References
[1] Tsai MC, Spitele RC, Chang HY. Long intergenic noncoding RNAs: new links in cancer progression. Cancer Res 2011;71:3–7.
[2] Esteller M. Non-coding RNAs in human disease. Nat Rev Genet 2011;12:861–74.
[3] Maruyama R, Suzuki H. Long noncoding RNA involvement in cancer. BMB Rep 2012;45:604–11.
[4] Amaral PP, Clark MB, Gascoigne DK, Dinger ME, Mattick JS. lincRNAdb: a reference database for long noncoding RNAs. Nucleic Acids Res 2011;39:D146–51.
[5] 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.
[6] Pan Y, Li G, 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.
[7] Thiele JA, Hosek P, Královcova E, et al. lncRNAs in non-malignant tissue have prognostic value in colorectal cancer. Int J Mol Sci 2018;19:9.
[8] Eades G, Wolfson B, Zhang YS, Li Q, Yao Y, Zhou Q. lincRNA-RoR and miR-145 regulate invasion in triple-negative breast cancer via targeting ARF6. Mol Cancer Res 2015;13:338–48.
[9] Saberi R, Malakootian M, Balalaee B, et al. Linc-ROR and its spliced variants 2 and 4 are significantly up-regulated in esophageal squamous cell carcinoma. Iran J Basic Med Sci 2016;19:1131–5.
[10] Arunkumar G, Rao A, Manikandan M, et al. Expression profiling of long non-coding RNA identifies linc-Ro as a prognostic biomarker in oral cancer. Tumour Biol 2017;39:4.
[11] Chen Y, Peng Y, Xu Z, et al. lincRNAR promotes bladder cancer cell proliferation, migration, and epithelial-mesenchymal transition. Cell Physiol Biochem 2017;41:2399–410.
[12] Zou ZW, Ding Q, Li PD, et al. Overexpression of lincRNA-ROR predicts poor prognosis in patients with gastric cancer. Int J Clin Exp Pathol 2016;9:467–72.
[13] Cheng F, Wang Y, Zeng C, Ou B. Expression and clinical significance of lincRNA-ROR in serum and tissues of colorectal cancer patients. Med J Southwest Natl Def 2019;29:62–5.