Research article

# Prognostic significance of non-coding RNAs related to the tumorigenic epithelial-mesenchymal transition (EMT) process among ovarian cancer patients: A systematic review and meta-analysis

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## ARTICLE INFO

## ABSTRACT

*Introduction:* Ovarian cancer is the seventh most prevalent cancer among women. It has high mortality and morbidity and imposes a great burden on healthcare systems worldwide. Unraveling the mechanisms behind the Epithelial-Mesenchymal Transition and finding a panel for predicting the prognosis of the disease may help find the appropriate treatment approaches for the management of the disease. The overarching aim of this systematic review was to define a panel of different types of EMT-associated non-coding RNAs (ncRNAs) with significant prognostic value in all types of ovarian cancers.
*Methods:* We searched PubMed, Web of Science, Scopus, and Embase till Jun 2024 to retrieve relevant papers. Two independent reviewers screened papers, and discrepancies were resolved by consensus. Publications related to the dysregulation of different types of ncRNAs, including microRNAs, lncRNAs, and circRNAs, only in patients with ovarian cancer were included. The participation of ncRNAs in epithelial-mesenchymal transformation should be assessed via methods evaluating different EMT-related proteins. To assess the quality and risk of bias for the included case-control and cohort studies, refined Newcastle-Ottawa Scale (NOS) and Quadas-2 were recruited. A bivariate meta-analysis was performed to analyze extracted data.
*Results:* A total of 37 studies with overall 42 non-coding RNAs (15 microRNA, 24 long non-coding RNAs, and 3 circular RNAs) were entered into the analysis. Overall diagnostic odds ratio for ncRNAs in lymph node metastasis, distant metastasis, TNM stage, and clinical stage were 4.19,

3.80, 6.52, and 3.97, respectively. Also, a hazard ratio of 1.39 (P = 0.32) for overall survival was observed. Bioinformatic analyses on the Pan-cancer database demonstrated a significant correlation between low expression of miRNA and high expression of lncRNAs with poor prognosis of ovarian cancer.

*Conclusion:* Based on the results, the defined panel of ncRNAs can properly predict prognostic factors related to EMT in ovarian cancer without involving potentially invasive methods.

## 1. Introduction

Ovarian cancer (OC) is one of the most prevalent gynecological malignancies and accompanies a poor prognosis and a high mortality rate. It has a five-year survival rate of less than 45 % and is considered the leading lethal malignancy among gynecological cancers [1,2]. OC is known as a cancer with asymptomatic, inconspicuous, and hidden growth with delayed symptom onset, and it is usually diagnosed in advanced stages, which limits recruiting the possible treatment methods [3]. High rates of metastasis, invasion into adjacent tissues, and resistance to conventional therapies contribute to the high mortality rate and poor prognosis of this cancer [4]. Early diagnostic tests of OC (e.g., measurement of serum cancer antigen 125 (CA125) and transvaginal ultrasonography) are not specific, effective, and sensitive enough for early detection and do not significantly contribute to improving clinical outcomes [5]. Therefore, finding diagnostic and prognostic approaches is one of the most important challenges and necessities. Determining mechanisms that result in these features of OC and providing prognostic panels may decrease the burden of the disease and increase overall survival.

Epithelial-mesenchymal transition (EMT) is a molecular process in which cells undergo specific changes, including losing their cell-to-cell adhesion, acquiring more mobility and stem cell-like properties, and transforming from an epithelial to a mesenchymal cell type. EMT has been shown to play an important role in cancer metastasis, invasion, and cellular resistance to chemotherapy. Blocking EMT to reduce tumorigenesis is considered a key adjuvant strategy for OC treatment [6]. During the EMT process, the expression of E-cadherin as an epithelial marker decreases, while mesenchymal markers, such as N-cadherin, increase. Several studies have investigated different mediators and pathways contributing to EMT, and non-coding RNAs (ncRNAs) have been shown to play roles in the induction or suppression of EMT [7–9].

The ncRNAs are RNA transcripts that do not encode proteins and were assumed to be by-products with no important biological functions. NcRNAs comprise various types, including housekeeping (e.g., transfer RNAs, ribosomal RNAs, and small nucleolar/nuclear RNAs) and regulatory ncRNAs (e.g., small interfering RNAs, Long non-coding RNAs (lncRNAs), microRNAs, and circular RNAs (circRNAs)). Housekeeping ncRNAs are known to be stably expressed genes supporting cell life activity, while regulatory ncRNAs participate in biological processes. Abnormalities in ncRNA regulatory networks can interfere with normal cell functions and are closely associated with pathological changes, occurrence and, or progression of various diseases, drug resistance, and multiple malignancies, including OC, which may become more aggressive in response to these different types of ncRNAs [7,10–15]. For instance, overexpression of MIR503, a tumor suppressor in cancers, suppresses the tumorigenic ability of OC, impairing the proliferation, EMT, and invasiveness and facilitating cell apoptosis [16]. Furthermore, long intergenic ncRNA LINC00665 is upregulated in OC, which targets and inhibits miR-181a-5p while upregulating FHDC1 expression [17]. Although the mechanisms by which ncRNAs participate in cancer progression are not fully understood, numerous reports have elucidated their role in the EMT process as a known mechanism affecting malignant cell growth or spread [18].

Moreover, multiple ncRNAs have been shown to have prognostic values for this cancer. The role of ncRNA downregulation and upregulation in the EMT process and metastasis in the OC has been investigated in several studies. Also, it has been shown that they could predict the stemness of cancer stem cell proliferation, metastasis, apoptosis, and chemotherapy resistance. Although there have been some review papers on the role of ncRNAs in OC, to the best of our knowledge, there has not been a comprehensive systematic review and meta-analysis outlining the significance of EMT-related ncRNAs in the prognosis of OC [9,19–26]. Here, we have gathered all the published data and conducted a thorough systematic review and meta-analysis of the EMT-associated ncRNAs that have prognostic and diagnostic value, as well as provided mechanistic information about OC. In this review, we focused on different types of OC, including epithelial ovarian cancer (EOC), high-grade serous ovarian cancer (HGSOC), and ovarian serous carcinomas (OSC).

## 2. Methods

### 2.1. Study protocol and search strategy

A systematic search of the literature was performed to retrieve papers discussing the prognostic value of ncRNAs related to EMT in OC patients. We developed a specific search strategy for each of the Embase, PubMed, Scopus, and Web of Science databases using the keywords (("Ovarian" OR "Ovary") and ("cancer*" OR "Neoplasm*" OR "Ovarian Neoplasm*")) and ("Metasta*" OR "EMT" OR "Epithelial-Mesenchymal transition" OR "Epithelial-Mesenchymal transformation" OR "Epithelial Mesenchymal*") and (("RNA and Untranslated") OR ("Noncoding" and "RNA") OR ("Non-coding" and "RNA*") OR "ncRNA*" OR "MicroRNA*" OR "miRNA*" OR "miR" OR ("Long Noncoding" and "RNA*") OR ("long" and "non" and "coding" and "RNA*") OR "lncRNA*" OR ("long non-coding RNA*") OR "ceRNA*" OR ("competing endogenous RNA*") OR "LINC RNA*" OR "circRNA*" OR ("Circular" and "RNA*")), and the relevant MeSH terms. The detailed search strategy for each database is available in Supplementary Table 1.

The searches were not restricted to the title/abstract or specific languages. We applied the search terms to all fields by considering papers published from 2000 to Jun 13, 2024. The search result of each database was collected in a library. Then, retracted articles and duplicates were removed. This systematic review is based on the PRISMA statement [27]. The methodology of this study was registered in PROSPERO (Registration No. CRD42022304776).

## 2.2. Data management, screening, and detailed review

Two reviewers (SNS and SM) independently screened the title and abstract of the studies acquired from the previous step based on the defined inclusion and exclusion criteria. Disagreements were resolved by consulting with the third reviewer (ASK). In the title/abstract screening stage, conference abstracts, duplicate papers, letters, reviews, and editorial publications were excluded. Eligible articles were necessarily related to EMT, ncRNAs, and OC. Otherwise, they were excluded and classified as "not related to the topic" publications. Furthermore, papers that had not discussed prognosis and overall survival (OS) in their abstracts were not excluded at this stage, and a decision about them was taken during the full-text review.

In the detailed review step, the full text of the included papers was screened to check if the documents meet the study's inclusion criteria and have enough data to proceed with further steps. The evaluation of ncRNAs and their correlation with EMT and the evaluation of the prognostic role of the assessed ncRNAs were the essential factors reviewers appraised. Other exclusion criteria were case series, case reports, interventional and bioinformatics papers, cell line research, and animal studies lacking human samples. To be included, intervention-free samples must have been obtained from human OC patients, regardless of their disease stage, who did not suffer from other diseases or had not received medication therapies.

## 2.3. Data extraction

SNS and SM extracted the following data from the eligible articles: first author, publication year, country, study design, sample type, the number of cases and controls, ncRNA detection method, cancer stage, age-related information of controls and patients (mean, minimum, maximum, and standard deviation [SD]), type and name of the ncRNAs, the number of patients with upregulated and downregulated ncRNAs, p-value, prognosis levels (poor or good), the oncogenic or tumor-suppressive role of the ncRNAs, target genes and molecular mechanism of ncRNAs, type of OC, the number of patients with or without lymph node or distant metastasis regarding expression levels of ncRNAs, the number of patients with different clinical stages and TNM stages in both high and low expression levels of target ncRNA, hazard ratio (HR) and confidence of interval (CI) of both univariate and multivariate analysis of OS and progression-free survival (PFS). In case the needed data was not available in the paper or its supplementary material, the corresponding author(s) were contacted to obtain the needed data.

## 2.4. Quality assessment

To assess each included article's validity, quality, and risk of bias, case-control and cohort studies were evaluated based on the Newcastle-Ottawa Scale (NOS) [28]. We refined NOS questions and scores according to our study and defined the total validity score ranging from a minimum of 0 to a maximum of 8. The maximum scores of four, two, and two have been awarded to the three characteristics of each study: selection, comparability, and outcome, respectively. There was a consensus on considering papers with a total score of $\geqslant 5$ as high-quality studies. Moreover, The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist was recruited to assess the risk of bias [29].

## 2.5. Statistical analysis

True positive (TP), true negative (TN), false positive (FP), and false negative (FN) rates were directly extracted from the included studies or were calculated based on the reported sensitivity, specificity, and prevalence. TP, TN, FP, and FN values were used to calculate the pooled effect size of ncRNAs expression in cancerous tissue for predicting TNM staging, clinical staging, lymph node metastasis (LNM), and distant metastasis (DM) as factors, predicting the severity and prognosis of OC. A univariate meta-analysis was conducted to compute the overall sensitivity, specificity, and diagnostic odds ratio (DOR) for the mentioned variables. The ncRNAs were only included in the meta-analysis if their effect had been reported as significantly positive. A generalized linear mixed model (GLMM) with log transformation was used for a random-effect univariate meta-analysis of sensitivity and specificity. An inverse variance model was used for a random-effect univariate meta-analysis of DOR. Continuity correction for studies containing zero cell counts was performed via the method introduced by Weber et al. [30]. Cochrane's Q test and $I^2$ were used to assess the heterogeneity between studies, and a P-value of lower than 0.1 was considered significant. Subgroup analysis was performed based on the type of ncRNAs (microRNA, lncRNA, and circRNA) if there were at least two groups with at least two studies in each group. Furthermore, to find the best ncRNAs panel for predicting the prognosis of OC, based on the primary analysis, the effects of the ncRNAs with low expression were adjusted to improve the power of the model.

Bivariate meta-analysis fitted to logit-transformed sensitivities and false positive rates (FPRs) using the Reitsma et al. approach, and variance components were calculated using the restricted maximum likelihood (REML) method [31]. The summary receiver operating curve (SROC) was used to visualize the summary of the diagnostic performance of the included studies. The area under the SROC (AUSROC) and its CI were calculated by bootstrapping (2000 iterations) [32]. The heterogeneity was evaluated by the visual symmetry of the SROC and the correlation between logit-transformed sensitivity and specificity. Additionally, the Holling sample size adjusted

method was used for calculating the $I^2$ estimate of heterogeneity, and $I^2$ over 75 %, 25–75 %, and under 25 % were considered high, moderate, and low heterogeneity [33,34]. Deek's funnel plot asymmetry test assessed the publication bias; a *P*-value <0.1 was considered significant. Meta-regression was performed for the type of ncRNAs.

Moreover, a meta-analysis was performed for the HR of OS of OC as a predictor of prognosis for ncRNAs. The natural logarithm of HR was used as the effect size, and the REML method was used to calculate the variance components. Subgroup analysis was performed for the type of ncRNAs. Cochrane's Q test and $I^2$ were used to evaluate heterogeneity. Egger's test was used to assess the asymmetry of the funnel plot. Generally, *P*-values <0.05 were considered significant, and all reported CIs are 95 % CI. All analyses were performed via the R programming language, V4.2.1, using "mada," "meta," "metafor," "dmetar," and "dmetatools" packages [32,35–38].

### 2.6. Bioinformatics analysis

Further analysis was conducted to find a probable correlation between the obtained data from this meta-analysis and existing datasets. We used TCGA data from the Pan-cancer database. The purpose of applying the Pan-cancer database was to validate our discoveries. We re-evaluated the OS impact of the differential expression of the microRNAs and lncRNAs in OC patients compared with healthy women using the Kaplan–Meier (K-M) plotter (https://kmplot.com/analysis/) [39]. It could be noted that the K-M plot visualization was performed based on the auto-select cut-off values [40].
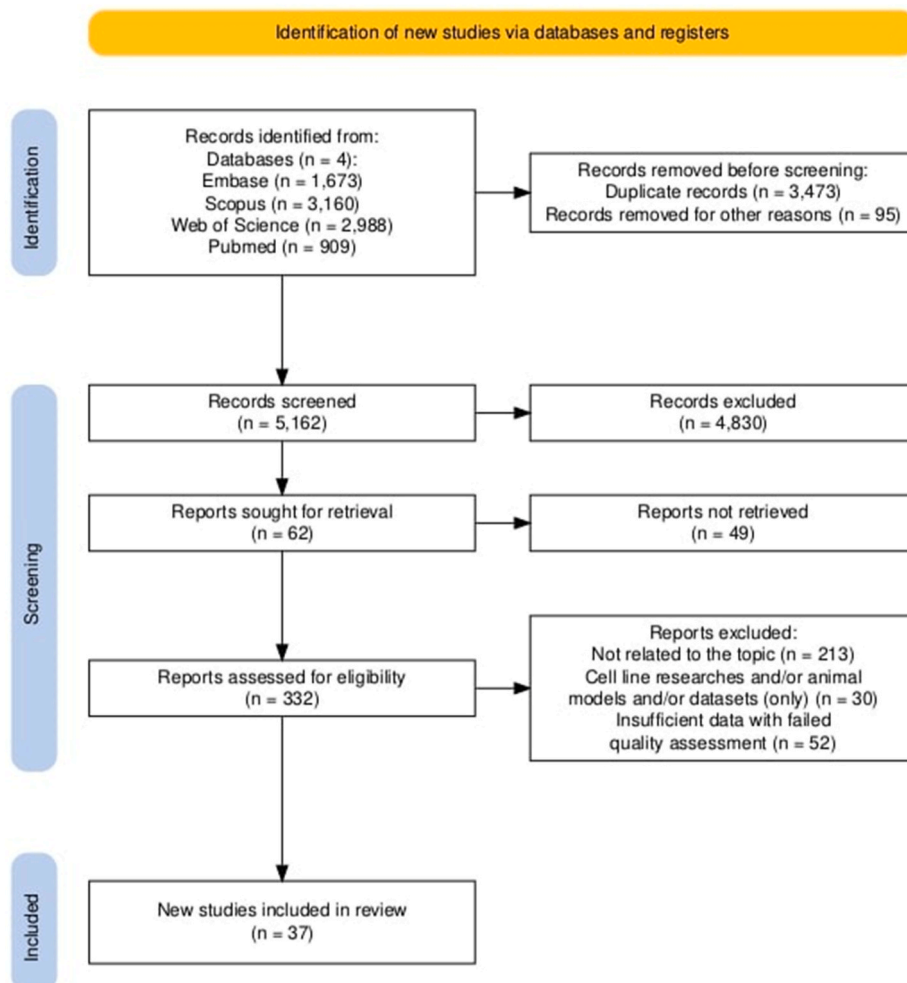


**Fig. 1. PRISMA flow diagram of the systematically reviewed papers with differential ncRNAs expression in OC patients**. Initial searches in four databases resulted in 8730 articles. After removing 3473 duplicated and 95 retracted articles, 5162 papers were selected to be screened based on title/abstract and be categorized based on the defined exclusion/inclusion criteria. 332 included articles were grouped based on full-text screening. Finally, 37 studies were identified as eligible for our meta-analysis.

## 3. Results

### 3.1. Study selection

Searching four databases, collecting the results of each search to a single library, omitting duplicate publications, and screening abstracts resulted in the retrieval of 332 studies. Following that, full-text reviewing led to the selection of 37 eligible articles for meta-analysis [41–77]. During the detailed review step, fifty-two articles were excluded due to insufficient data and failure to receive an appropriate score in the validity assessment, despite having all the inclusion criteria required for acceptance. The selection process with the exclusion reason of the articles was briefly characterized in Fig. 1.

### 3.2. Study characteristics and quality assessment

A total of fifteen microRNAs (miR-506 [41], miR-26b [51], miR-216a [42], miR-532 [53], miR-3064 [53], miR-616 [64], miR-219a-5p [63], miR-214 [73], miR-196-5p [62], miR-99a [56], miR-18a [69], miR-126 [70], miR-489 [57], miR-98-5p [59], and miR-488 [44]), twenty-four lncRNAs (HOTAIR [50], CCAT1 [60], HOXD-AS1 [61], ADAMTS9-AS2 [72], MEG3 [63], PVT1 [73], DQ786243 [74], GAS5 [62], LncARSR [54], FLVCR1-AS1 [55], TC0101441 [58], FAM83H-AS1 [65], HOXB-AS3 [66], LINC-PINT [76], NEAT1 [52], SNHG20 [75], MAFG-AS1 [68], DSCR8 [59], LINC01094 [77], E2F4as [43], DNM3OS [45], LINC01969 [46], SRA [48], and HCG18 [49]), and three circRNAs (Circ_100395 [67], Circ_0000745 [47], and CircAGFG1 [71]) were evaluated in the included publications. The detection method of the target ncRNAs was quantitative real-time polymerase chain reaction (qRT-PCR) in almost all studies. Overall, the studies carried out their research on 5207 clinical samples, including 2086 control and 3121 OC patient tissue samples. The main characteristics of the included studies are described in Table 1.

Among the 37 included primary studies for meta-analysis, seventeen got a score of 5 [41–44,47–49,52,53,64,72–78], ten got a score of 6 [45,50,51,54–59,71], eight got a score of 7 [60–63,65–68], and two got a score of 8 [69,70] in the refined NOS quality assessment. The quality assessment results have been summarized in Table 2. Moreover, the risk of bias assessment via QUADAS-2 has been shown in Fig. 2A and B.

### 3.3. Diagnostic accuracy of ncRNAs for LNM in OC

In the univariate analysis of DOR, the overall effect for ncRNAs in LNM was 4.5 (95%CI, 3.39–5.99; *P*-value <0.0001). The heterogeneity was moderate, with an $I^2$ of 24 % (*Q*, 31.38; *P*-value 0.14). The subgroup analysis demonstrated that overall, DOR in microRNA and lncRNA was 4.67 (95%CI, 2.48–8.81; *P*-value <0.0001) and 4.44 (CI, 3.15–6.25; *P*-value <0.0001), respectively. Heterogeneity was moderate in both subgroups ($I^2$, 35 %; *Q*, 10.79; *P*-value 0.15 and $I^2$, 26 %; *Q*, 20.32; *P*-value 0.16 for microRNA and lncRNA, respectively). There was only one study that examined the effects of circRNA, so the subgroup analysis was not applicable to this ncRNA. The subgroup difference was insignificant ($X^2$, 0.02; *P*-value, 0.99). The forest plot for DOR univariate meta-analysis has been depicted in Fig. 3A. Publication bias was not significant, with a P-value of 0.71. Fig. 4D shows Deek's funnel plot for DOR. Univariate analysis for sensitivity and specificity demonstrated an overall sensitivity of 72 % and specificity of 64 %, with moderate heterogeneity for both sensitivity and specificity (Fig. 3B).

The bivariate scatter plot shows the data are generally concentrated around the center with low dispersion (Fig. 4A). A bivariate meta-analysis demonstrated that the overall sensitivity was 0.71 (95%CI, 0.65–0.77; intercept *P*-value <0.001; between-studies standard deviation [SD], 0.51) and the overall specificity was 0.63 (95%CI, 0.57–0.68; intercept *P*-value <0.001; between-studies SD, 0.45). The total AUC was 0.72 (95%CI, 0.66–0.75). The overall DOR, LR$^+$, and LR$^-$ were 4.19 (95%CI, 3.13–5.47), 1.91 (95% CI, 1.67–2.19), and 0.46 (95%CI, 0.38–0.55), respectively. The bivariate meta-analysis result has been shown as SROC and bagplot in Fig. 4B and C. The SROC was symmetrical, and the correlation coefficient between logit-transformed sensitivity and specificity was negative (r, −0.70), showing low heterogeneity. Also, the Holling sample size adjusted $I^2$ was 1.5–1.7 %. The log-likelihood for the model goodness-of-fit was 31.74.

### 3.4. Diagnostic accuracy of ncRNAs for DM in OC

The univariate analysis demonstrated an overall DOR of 3.86 (95%CI, 2.47–6.03 and *P*-value <0.0001) with a moderate heterogeneity ($I^2$, 65 %; *Q*, 33.80; *P*-value <0.01). The subgroup analysis demonstrated no significant difference between subgroups ($X^2$, 1.97; *P*-value, 0.37). The overall DOR was 4.65 (95%CI, 2.20–9.84; *P*-value <0.0001),2.74 (95%CI, 1.56–4.82; *P*-value <0.001), and 5.63 (95%CI, 1.86–17.06; *P*-value <0.01) in miRNA, lncRNA, and circular RNA, respectively (Fig. 5A). The heterogeneity was high in the miRNA subgroup ($I^2$, 77 %; *Q*, 21.79; *P*-value <0.01), moderate in the lncRNA subgroup ($I^2$, 51 %; *Q*, 8.18; *P*-value, 0.09), and low in the circular RNA subgroup ($I^2$, 0 %; *Q*, 0.26; *P*-value, 0.61). The publication bias was high (*P*-value <0.001). Deek's funnel plot has been depicted in Fig. 6D. Overall sensitivity and specificity in univariate analysis were 73 % and 58 %, respectively, with moderate heterogeneity in both analyses (Fig. 5B).

The scatter plot demonstrated that the data are not centered and have dispersion (Fig. 6A). The bivariate meta-analysis demonstrated total sensitivity and specificity of 0.73 (95%CI, 0.66–0.78; intercept *P*-value, <0.001; between-studies SD, 0.38) and 0.58 (95% CI, 0.52–0.64; intercept *P*-value <0.01; between-studies SD, 0.29), respectively. The overall AUC was 0.67 (95%CI, 0.56–0.74). The total DOR, LR$^+$, and LR$^-$ in the bivariate meta-analysis were 3.80 (95%CI, 2.38–5.75), 1.75 (95%CI, 1.44–2.10), and 0.47 (95%CI, 0.36–0.61), respectively. The SROC and bag plot for the bivariate meta-analysis has been depicted in Fig. 6B and C. The SROC did not

**Table 1**

Main characteristics of the included studies for meta-analysis.

| First Author | Year | Country | Type of ncRNA | Name of ncRNA | Detection Method | Sample Size (case/control) | Expression Levels (Up/Down) | Target Gene(s) | Type of OC | Molecular Mechanism | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lin J | 2015 | China | MicroRNA | miR-26b | qRT-PCR | 97/- | 48/49 | KPNA2 | EOC | MiR-26b inversely correlates with the expression of KPNA2 that downregulates OCT4 and Vimentin and conversely upregulates E-cadherin. | [51] |
| Liu H | 2017 | China | MicroRNA | miR-216a | qRT-PCR | 87/25 | 44/43 | PTEN | – | MiR-216a directly targets PTEN and inhibits the PTEN/AKT pathway, which promotes EMT and metastasis of OC cells. | [42] |
| Bai L | 2017 | China | MicroRNA | miR-532 miR-3064 | qRT-PCR | 60/20 | miR-532: 0/31 miR-3064: 0/29 | hTERT | EOC | Both miR-3064 and miR-532 bind to and suppress the hTERT Leading to EMT process suppression and apoptosis induction, and the loss of these MiRs leads to OC. | [53] |
| Chen Z | 2018 | China | MicroRNA | miR-616 | qRT-PCR | 60/60 | 30/30 | TIMP2 | – | MiR-616 directly targets TIMP2, which is required for EMT process promotion. | [64] |
| Wang L | 2019 | China | MicroRNA | miR-219a-5p | qRT-PCR | 317/317 | 132/185 | EGFR | – | MiR-219a increases the expression of E-cadherin and reduces the expressions of N-cadherin. Therefore, MiR-219a prevents EMT by targeting EGFR. | [63] |
| Zhao H | 2018 | China | MicroRNA | miR-196-5p | qRT-PCR | 195/195 | 114/81 | HOXA5 | HGS-OC | MiR-196a-5p promotes EMT by targeting HOXA5, reducing E-cadherin, and increasing N-cadherin in HGSOC. | [62] |
| Chen Y | 2018 | China | MicroRNA | miR-214 | qRT-PCR | 231/58 | 101/130 | – | EOC | MiR-214 is downregulated by PVT1, which promotes EMT in EOC. | [73] |
| Zhang L | 2019 | China | MicroRNA | miR-99a | qRT-PCR | 47/47 | 23/24 | HOXA1 | – | MiR-99a directly targets HOXA1 and suppresses cell proliferation via the AKT/mTOR pathway. This microRNA also inhibits invasion-mediated EMT. | [56] |
| Zhao Y | 2020 | China | MicroRNA | miR-18a | qRT-PCR | 50/50 | 20/30 | CBX/ERK | – | MiR-18a targets and inhibits the CBX7 and ERK protein levels Promotes ERK/MAPK signaling pathway leads to suppression of the proliferation, migration, invasion, and EMT. | [69] |
| Zhang Y | 2020 | China | MicroRNA | miR-126 | qRT-PCR | 54/54 | 20/34 | EGLF7/ERK | – | MiR-126 directly targets EGFL7 and regulates the ERK/MAPK signaling pathway via suppression of ERK and participates in EMT. | [70] |
| Jiang HW | 2020 | China | MicroRNA | miR-489 | qRT-PCR | 51/51 | 20/31 | XIAP/PI3K/EMT-related genes | – | MiR-489 binds to and regulates the X-linked inhibitor of apoptosis protein (XIAP), phosphatidyl-inositol 3-kinase/protein kinase B pathway (PI3K/AKT), and EMT in OC. | [57] |
| Dong L | 2020 | China | MicroRNA | miR-98- 5p | qRT-PCR | 52/52 | 26/26 | STAT3/HIF-1α | – | Downregulation of miR-98-5p in OC tissues promotes EMT and cell growth progression of OC. | [59] |
| Guo JY | 2020 | China | MicroRNA | miR-488 | qRT-PCR | 58/- | 18/40 | CCNG, P53 | – | MiR-488 suppresses OC metastasis by reducing the expression of p53 and CCNG and blocking EMT. | [44] |
| Sun Y | 2015 | China | MicroRNA | miR-506 | ISH | 204/- | 95/102 | EMT- related genes (Vimentin/SNAI2/CDH2) | EOC | MiR-506, an EMT inhibitor, directly targets and inhibits Vimentin, SNAI2, and CDH2 expression while increasing the E-cadherin levels in EOC. | [41] |
| Chen J | 2021 | China | LncRNA | LINC01969 | qRT-PCR | 41/41 | 19/22 | miR-144-5p | – | LINC01969 sponges miR-144-5p to upregulate LARP1 and then promotes migration, invasion, EMT, and proliferation of OC cells. | [46] |
| Qiu JJ | 2014 | China | LncRNA | HOTAIR | qRT-PCR | 64/29 | 32/32 | MMPs | EOC | HOTAIR promotes EMT in EOC via MMP. | [50] |
| Cao Y | 2017 | China | LncRNA | CCAT1 | qRT-PCR | 72/72 | 36/36 | miR-152/miR-130b/ADAM17/WNT1/ | EOC | In EOC, CCAT1 is inversely associated with the activity of miR-152 and miR-130b, Which target ADAM17, | [60] |

*(continued on next page)*

**Table 1** (*continued*)

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| First Author | Year | Country | Type of ncRNA | Name of ncRNA | Detection Method | Sample Size (case/ control) | Expression Levels (Up/ Down) | Target Gene(s) | Type of OC | Molecular Mechanism | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhang Y | 2017 | China | LncRNA | HOXD- AS1 (HAGLR) | qRT-PCR | 43/43 | 22/21 | ZEB1/STAT3/ Vimentin/N-cadherin miR-133a- 3p | EOC | WNT1, STAT3, ZEB1, Vimentin, and N-cadherin, then negatively regulate the EMT process. lncRNA HOXD-AS1 promotes cell proliferation, invasion, and EMT by targeting and sponging miR-133a-3p and activates the Wnt/β-catenin pathway in EOC. | [61] |
| Wang A | 2018 | China | LncRNA | ADAMTS9-AS2 | qRT-PCR | 47/- | 24/23 | miR-182-5p | – | ADAMTS9-AS2 sponges miR-182-5p and decreases OC progression via regulating the miR182-5p/FOXF2 pathway. Low levels of ADAMTS9-AS2 are correlated with OC cell metastasis, proliferation, invasion, and EMT. MiR-182-5p directly targets FOXF2. | [72] |
| Wang L | 2019 | China | LncRNA | MEG3 | qRT-PCR | 317/317 | 136/171 | miR-219-5p | – | MEG3 regulates miR-219a-5p/EGFR axis and prevents EMT. | [63] |
| Chen Y | 2018 | China | LncRNA | PVT1 | qRT-PCR | 231/58 | 115/116 | miR-214/EZH2 | EOC | PVT1 represses miR-214 expression through interaction with EZH2. PVT1 overexpression reduces E-cadherin while elevating the expression levels of Vimentin, β-catenin, Snail, and Slug proteins, promoting EMT. | [73] |
| Yong W | 2018 | China | LncRNA | NEAT1 | qRT-PCR | 75/- | 37/38 | miR-506 | HGS-OC | NEAT1 is stabilized by LIN28B, sponges miR-506, and promotes OC progression in HGSOC. NEAT1 promotes EMT by elevating the expression of E-cadherin, whereas reducing the expression of N-cadherin, MMP9, and MMP2. | [52] |
| Yan H | 2018 | China | LncRNA | DQ786243 | qRT-PCR | 30/30 | 15/15 | miR-506 | – | DQ786243 interacts with and suppresses miR-506 and promotes OC progression through targeting CREB1. Furthermore, DQ786243 promotes EMT via downregulation of E-cadherin protein and upregulation of the Vimentin and snai2 protein levels. | [74] |
| Zhao H | 2018 | China | LncRNA | GAS5 | qRT-PCR | 195/195 | 70/125 | miR-196a- 5p | HGS-OC | GAS5 directly targets miR-196a-5p in HGSOC and prevents EMT. | [62] |
| Shu C | 2018 | China | LncRNA | LncARSR | qRT-PCR | 76/76 | 38/38 | HuR/ZEB1/ZEB2 | EOC | Overexpression of lncARSR activates the WNT/B-Catenin pathway and increases ZEB1 and ZEB2 expression by competitively binding to the miR-200 family (lncARSR acts as ceRNA for miR-200 family), thus inducing EMT. | [54] |
| Yan H | 2019 | China | LncRNA | FLVCR1- AS1 | qRT-PCR | 50/50 | 27/23 | miR-513 | OSC | FLVCR1-AS1 directly targets and downregulates miR-513, thus upregulated FLVCR1-AS1 mediates miR-513/ YAP1 axis in OSC to promote EMT, cell growth, migration, and invasion and lower apoptosis. | [55] |
| Qiu JJ | 2019 | China | LncRNA | TC0101441 (ERLNC1) | qRT-PCR | 74/20 | 37/37 | KiSS1 | EOC | TC0101441 targets and negatively regulates the KiSS1 and promotes cell migration/invasion and EMT in EOC. | [58] |
| Dou QR | 2019 | China | LncRNA | FAM83H- AS1 (IQANK1) | qRT-PCR | 80/80 | 38/42 | HuR | – | FAM83H-AS1 interacts with and stabilizes HuR and facilitates EMT. | [65] |
| Wang D | 2019 | China | LncRNA | SNHG20 | qRT-PCR | 60/15 | 38/22 | – | EOC | SNHG20 promotes EMT in EOC. | [75] |
| Zhuang XH | 2019 | China | LncRNA | HOXB-AS3 | qRT-PCR | 178/178 | 91/87 | – | EOC | HOXB-AS3, an oncogene, activates Wnt/β-catenin signaling, promotes cell proliferation, migration, invasion, and EMT, and inhibits apoptosis in EOC. | [66] |

**Table 1** (*continued*)

| First Author | Year | Country | Type of ncRNA | Name of ncRNA | Detection Method | Sample Size (case/control) | Expression Levels (Up/Down) | Target Gene(s) | Type of OC | Molecular Mechanism | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hao T | 2020 | China | LncRNA | LINC-PINT | qRT-PCR | 72/72 | 20/52 | miR-374a-5p | – | LncRNA LINC-PINT sponges miR-374a-5p, inhibits cell proliferation, migration, and EMT, and augments apoptosis in OC. | [76] |
| Bai Y | 2021 | China | LncRNA | MAFG-AS1 (MILIP) | qRT-PCR | 75/75 | 37/38 | miR-339-5p | – | MAFG-AS1 recruits and upregulates NFKB1 by binding to miR-339-5p. This leads to higher levels of IGF1 and promotes EMT and cell migration/invasion. | [68] |
| Dong L | 2020 | China | LncRNA | DSCR8 | qRT-PCR | 52/52 | 26/26 | miR-98- 5p | – | Overexpression of DSCR8 in OC tissue leads to cell proliferation, invasion, and EMT while inhibiting apoptosis. Overexpressed DSCR8 positively regulates the expression of hypoxia-inducible factor 1 alpha (HIF-1α) and STAT3 and participates in miR-98-5p downregulation. | [59] |
| Xu J | 2020 | China | LncRNA | LINC01094 | qRT-PCR | 93/93 | – | miR-577 | – | LINC01094 directly targets and inhibits miR-577 and promotes cell proliferation, migration, invasion, and EMT. MiR-577 targets LRP6, Wnt2b, and β-catenin and regulates the Wnt/β-catenin pathway. | [77] |
| Park SA | 2020 | Korea | LncRNA | E2F4as | qRT-PCR | 108/32 | 78/30 | – | – | E2F4as promotes cell proliferation, invasion, and EMT migration and decreases apoptosis. | [43] |
| He L | 2021 | China | LncRNA | DNM3OS | qRT-PCR | 49/18 | 25/24 | miR-193a-3p/EMT -related genes | – | DNM3OS interacts with miR-193a-3p and increases the expression of MAPK3K3 by repressing miR-193a-3p. Overexpression of DNM3OS augments OC EMT, proliferation, cell migration, invasion, and the expression of N-cadherin protein and impedes the E-cadherin levels. | [45] |
| Kim LK | 2021 | South Korea | LncRNA | Lnc-SRA | qRT-PCR | 101/63 | 66/35 | E-cadherin/β-catenin/ N-cadherin/Snail/ HES1/Vimentin/ NOTCH/NICD/P300 | | LncRNA SRA regulates OC progression through NOTCH signaling and EMT. | [48] |
| Zhang F | 2022 | China | LncRNA | HCG18 | qRT-PCR | 30/30 | 15/15 | miR-29a/b | EOC | LncRNA-HCG18 stimulates the NF-κB pathway-mediated EMT, proliferation, and migration of EOC cells by acting as a ceRNA of miR-29a/b, which upregulates TRAF4/5 expression levels. Overexpression of HCG18 reduces E-cadherin while increasing the protein levels of MMP2, MMP9, and Vimentin. | [49] |
| Li X | 2020 | China | CircRNA | Circ_100395 | qRT-PCR | 60/60 | 30/30 | miR-1228 | – | CircRNA_100395 negatively associates with miR-1228 and exerts its inhibitory activity against cell growth, cell proliferation, and metastasis of OC cells by regulating the miR-1228/p53/EMT pathway. | [67] |
| Wang S | 2021 | China | CircRNA | Circ_0000745 | qRT-PCR | 50/50 | 24/26 | miR-3187- 3p | – | Circ_0000745 targets and inhibits miR-3187-3p and promotes phosphorylation of the PI3K/AKT pathway via stabilizing ERBB4. Circ_0000745 facilitates EMT by enhancing the expression of Vimentin and Snail and reducing the expression of E-cadherin. MiR-3187-3p inhibits ERBB4 and blocks Circ_0000745. | [47] |
| Luo J | 2024 | China | CircRNA | CircAGFG1 | qRT-PCR | 30/30 | 15/13 | miR-409-3 p | – | CircAGFG1 promotes EMT, proliferation, and invasion/migration of the OC by targeting miR-409-3p, elevating the zinc finger E-box binding homeobox 1 (ZEB1) expression. | [71] |

**Table 2**
NOS scores for included studies.

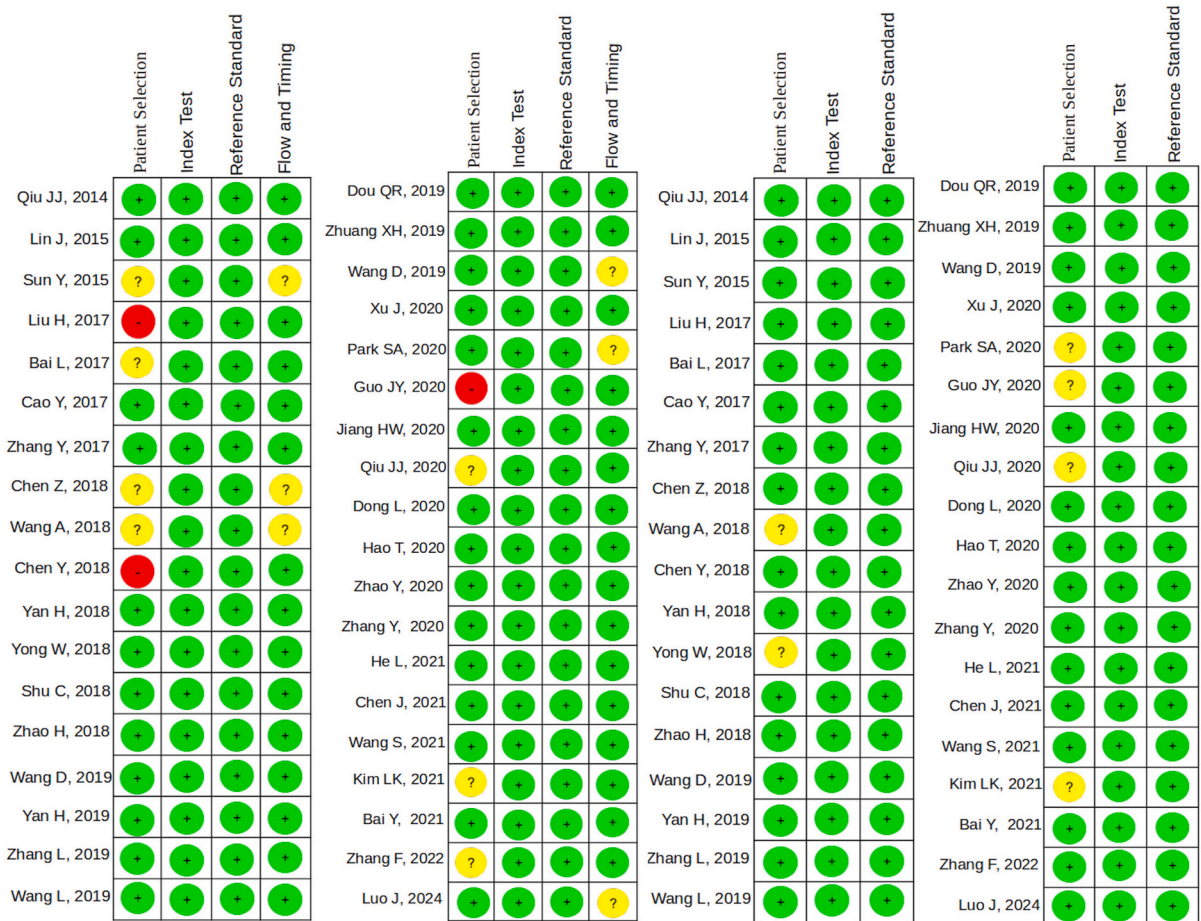| First Author (Year) | #1 | #2 | #3 | #4 | #5 | #6 | #7 | #8 | T | First Author (Year) | #1 | #2 | #3 | #4 | #5 | #6 | #7 | #8 | T |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhang Y (2020) | * | * | * | * | * | * | * | * | 8 | Qiu JJ (2014) | * | * | – | – | * | * | * | * | 6 |
| Zhao Y (2020) | * | * | * | * | * | * | * | * | 8 | Zhang F (2022) | * | * | – | – | * | * | – | * | 5 |
| Bai Y (2021) | * | * | * | – | * | * | * | * | 7 | Chen J (2021) | – | * | * | – | * | * | – | * | 5 |
| Li X (2020) | * | * | * | – | * | * | * | * | 7 | Wang S (2021) | – | * | * | – | – | * | * | * | 5 |
| Zhuang XH (2019) | * | * | * | – | * | * | * | * | 7 | Kim LK (2021) | * | * | – | – | * | * | – | * | 5 |
| Dou Q (2019) | * | * | * | – | * | * | * | * | 7 | Xu J (2020) | * | * | * | – | – | * | – | * | 5 |
| Wang L (2019) | * | * | * | – | * | * | * | * | 7 | Guo JY (2020) | – | * | – | – | * | * | * | * | 5 |
| Zhao H (2018) | * | * | * | – | * | * | * | * | 7 | Park SA (2020) | – | * | – | – | * | * | * | * | 5 |
| Zhang Y (2017) | * | * | * | – | * | * | * | * | 7 | Hao T (2020) | – | * | * | – | * | * | – | * | 5 |
| Cao Y (2017) | * | * | * | – | * | * | * | * | 7 | Wang D (2019) | – | * | * | – | * | * | – | * | 5 |
| Luo J (2024) | * | * | – | – | * | * | * | * | 6 | Wang A (2018) | * | * | – | – | * | * | – | * | 5 |
| He L (2021) | – | * | * | – | * | * | * | * | 6 | Yong W (2018) | * | * | * | – | – | * | – | * | 5 |
| Jiang HW (2020) | – | * | * | – | * | * | * | * | 6 | Yan H (2018) | – | * | * | – | * | * | – | * | 5 |
| Dong L (2020) | * | * | * | – | * | * | – | * | 6 | Chen Y (2018) | * | * | – | – | * | * | – | * | 5 |
| Qiu JJ (2020) | * | * | – | – | * | * | * | * | 6 | Chen Z (2018) | * | * | – | – | * | * | – | * | 5 |
| Yan H (2019) | * | * | * | – | * | * | – | * | 6 | Liu H (2017) | * | * | – | – | * | * | – | * | 5 |
| Zhang L (2019) | – | * | * | – | * | * | * | * | 6 | Bai L (2017) | * | * | – | – | * | * | – | * | 5 |
| Shu C (2018) | – | * | * | – | * | * | * | * | 6 | Sun Y (2015) | * | * | * | * | – | – | – | * | 5 |
| Lin J (2015) | * | * | – | – | * | * | * | * | 6 | Selection: #1, #2, #3, and #4/Comparability: #5 and #6/Outcome: #7 and #8/T: total score | | | | | | | | | |
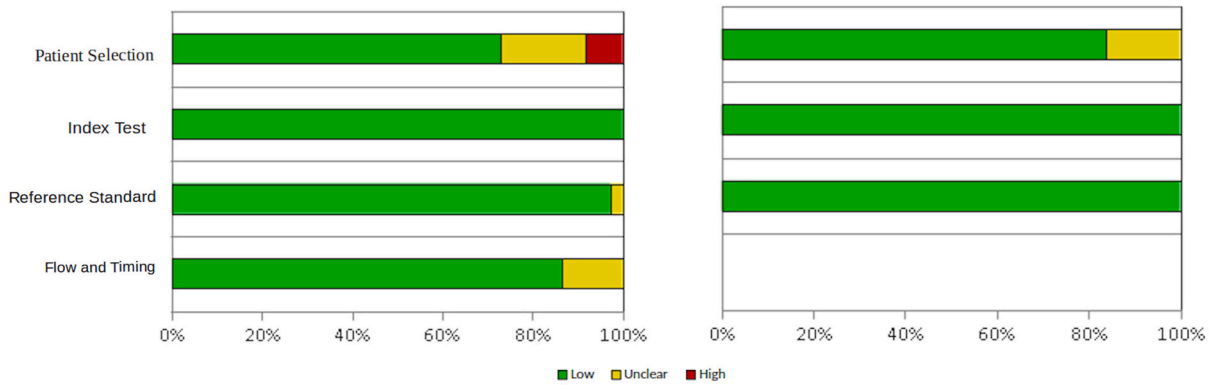
**Fig. 2. (A)** Risk of bias assessment via QUADAS-2 for included studies, low-risk (green), high-risk (red), and unclear (Yellow) for each domain, including patient selection, index test, reference standard, and flow and timing. **(B)** Concerns regarding applicability.

seem symmetrical, and the correlation coefficient between the logit-transformed sensitivity and specificity was positive (r, 0.29), implicating potential heterogeneity in the model. The Holling sample size adjusted $I^2$ was 3.2–3.4 %. The log-likelihood for the goodness-of-fit of the model was 22.21.
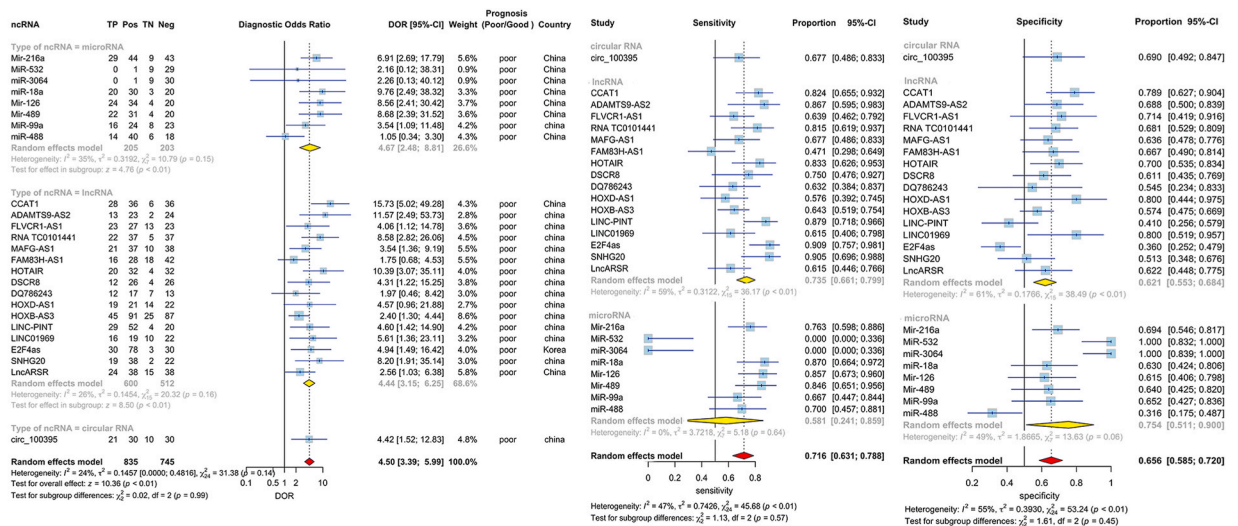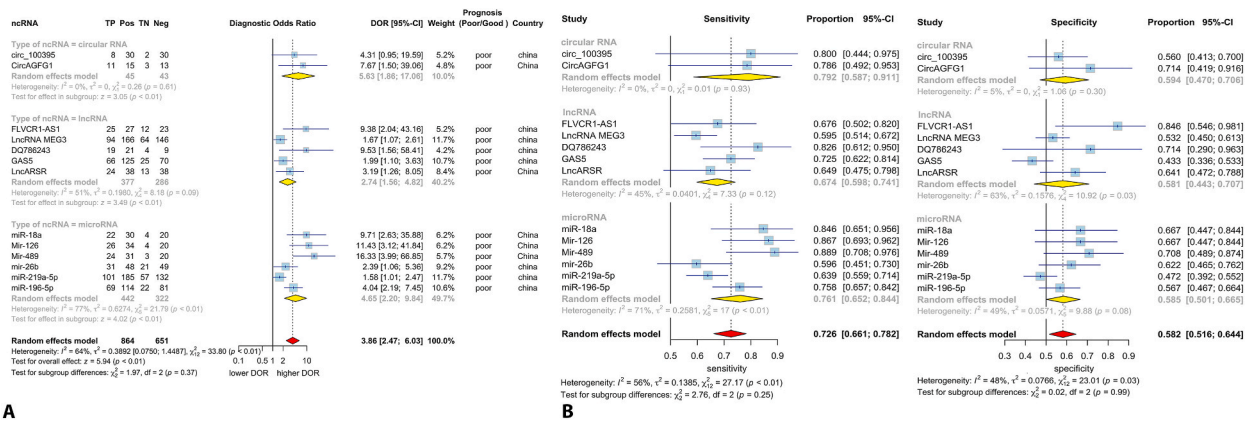
**Fig. 3. Univariate meta-analyses of ncRNAs in LNM. (A)** Univariate forest plots for LNM show an overall DOR of 4.5 with no significant difference between subgroups (P = 0.99) **(B)** Univariate forest plots show sensitivity and specificity of 0.72 and 0.66, respectively.
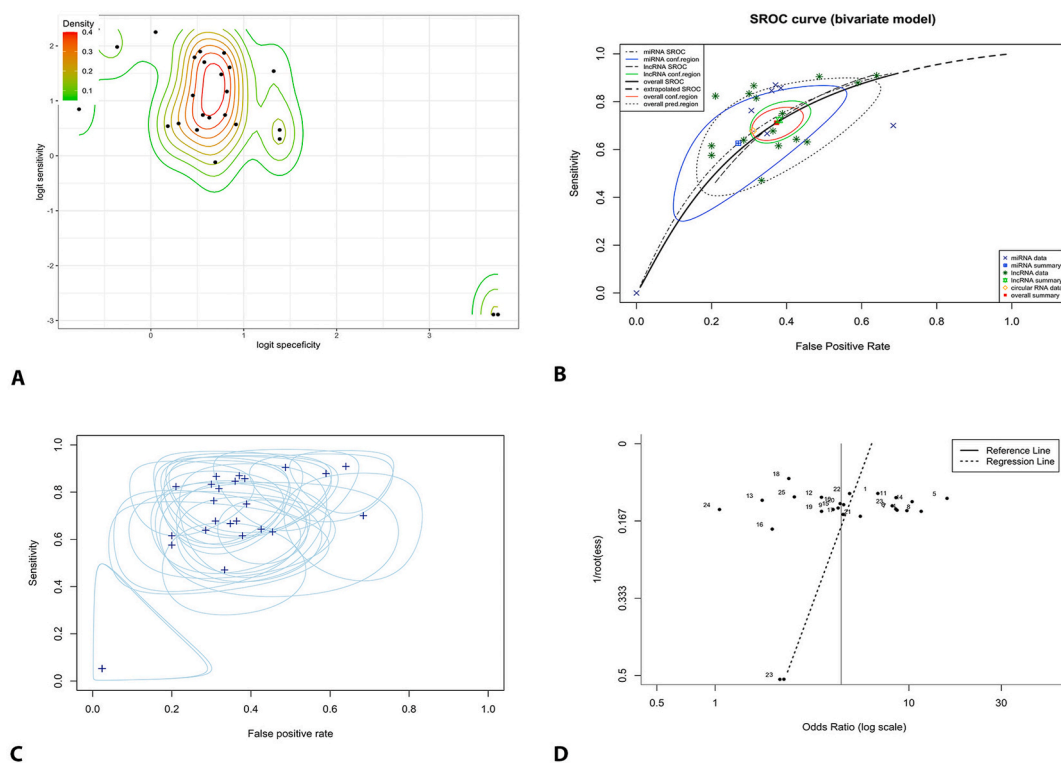


**Fig. 4. Bivariate meta-analysis of ncRNAs in LNM. (A)** Scatter plot of logit sensitivity and specificity shows low data dispersion **(B)** SROC for bivariate meta-analysis shows an overall AUC of 0.72 **(C)** Ellipse plot for bivariate meta-analysis. **(D)** Deek's funnel plot shows no publication bias.

### 3.5. Diagnostic accuracy of ncRNAs for TNM staging in OC

The total DOR was 5.69 in univariate analysis (95%CI, 3.26–9.94; *P*-value <0.0001), and the heterogeneity was low (*I*$^2$, 16 %; *Q*, 5.95; *P*-value, 0.31). The subgroup analysis for the type of the ncRNAs demonstrated no significant difference between subgroups (*X*$^2$, 3.18; *P*-value, 0.07) with a DOR of 7.74 in the miRNA subgroup (95%CI, 4.18–14.35; *P*-value <0.0001) and 3.11 in the lncRNA

**Fig. 5. Univariate meta-analysis of ncRNAs in DM.** **(A)** Univariate forest plots for DM show an overall DOR of 3.86 with no significant difference between subgroups (P = 0.37) **(B)** Univariate forest plots show sensitivity and specificity of 0.73 and 0.58, respectively.
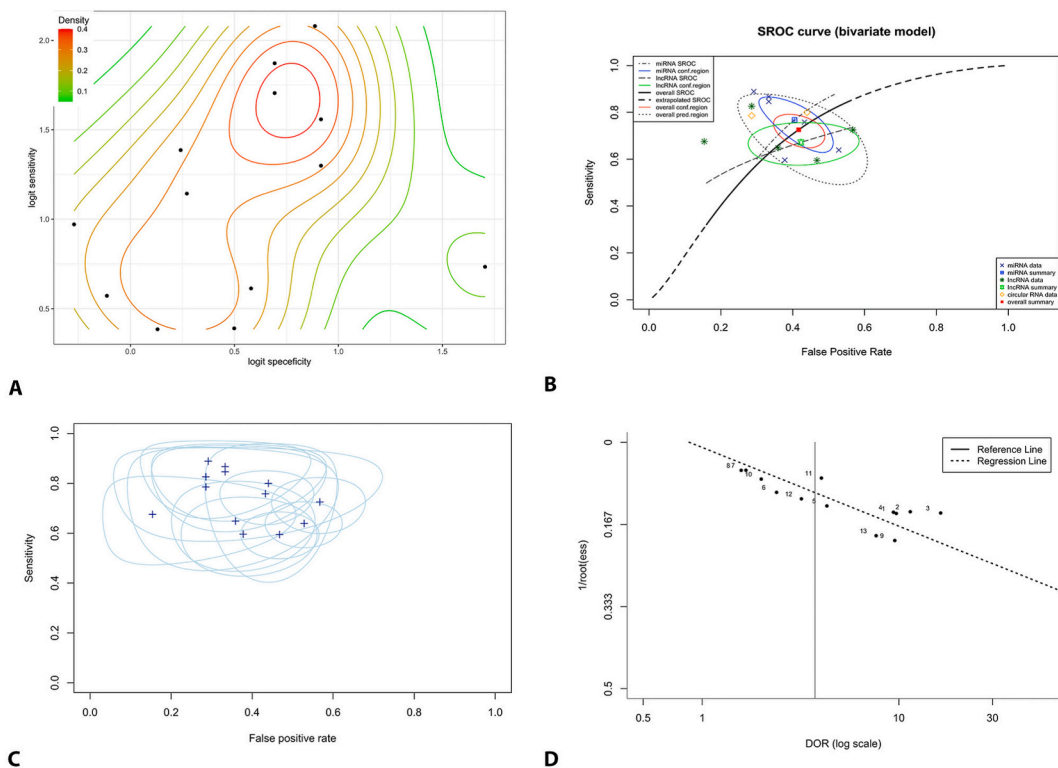


**Fig. 6. Bivariate meta-analysis of ncRNAs in DM.** **(A)** Scatter plot of logit sensitivity and specificity shows that the data are dispersed **(B)** SROC for bivariate meta-analysis shows an overall AUC of 0.67 **(C)** Ellipse plot for bivariate meta-analysis. **(D)** Deek's funnel plot shows presence of publication bias.

subgroup (CI, 1.41–6.86; *P*-value <0.01). The forest plot for univariate DOR meta-analysis has been demonstrated in Fig. 7A. The heterogeneity in both subgroups was low ($I^2$, 0 %; *Q*, 2.5; *P*-value, 0.47 for miRNA and $I^2$, 0 %; *Q*, 0.27; *P*-value, 0.60 for lncRNA). The publication bias was low (*P*-value, 0.40), and Deek's funnel plot is demonstrated in Fig. 8D. In univariate analysis, the overall sensitivity was 76 % with moderate heterogeneity, and the overall specificity was 67 % with low heterogeneity, Fig. 7B.

The scatter plot of logit-transformed sensitivity and specificity demonstrated that the data are dispersed (Fig. 8A). Pooled effects of 0.75 (95%CI, 0.65–0.84; intercept *P*-value <0.001; between studies SD, 0.43) and 0.67 (95%CI, 0.58–0.74; intercept *P*-value <0.001; between-studies SD, 0.06) were observed for sensitivity and specificity, respectively. SORC and ellipse plots for the bivariate meta-analysis have been shown in Fig. 8B and C, respectively. The overall AUC was 0.69 (95%CI, 0.63–0.83). Moreover, the overall DOR, LR$^+$, and LR$^-$ were 6.52 (95%CI, 3.27–11.60), 2.29 (95%CI, 1.79–3.01), and 0.37 (95%CI, 0.24–0.54). The SROC plot was
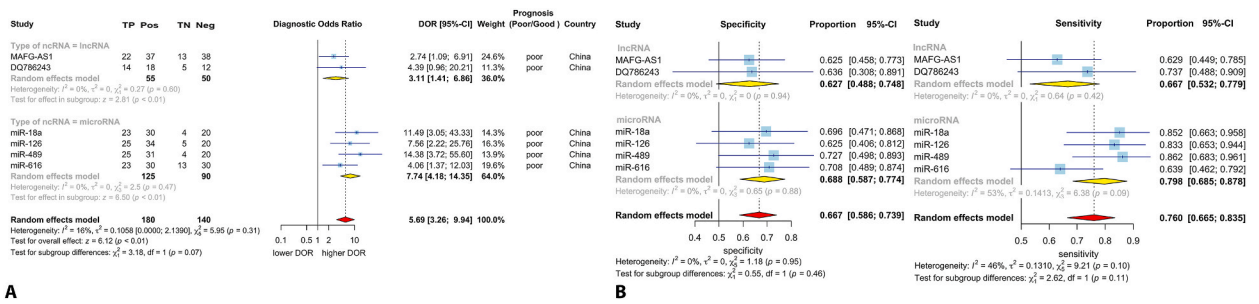
**Fig. 7. Univariate meta-analysis of ncRNAs in TNM stage. (A)** Univariate forest plots for TNM show an overall DOR of 3.86 with no significant difference between subgroups (P = 0.37) **(B)** Univariate forest plots show sensitivity and specificity of 0.67 and 0.76, respectively.
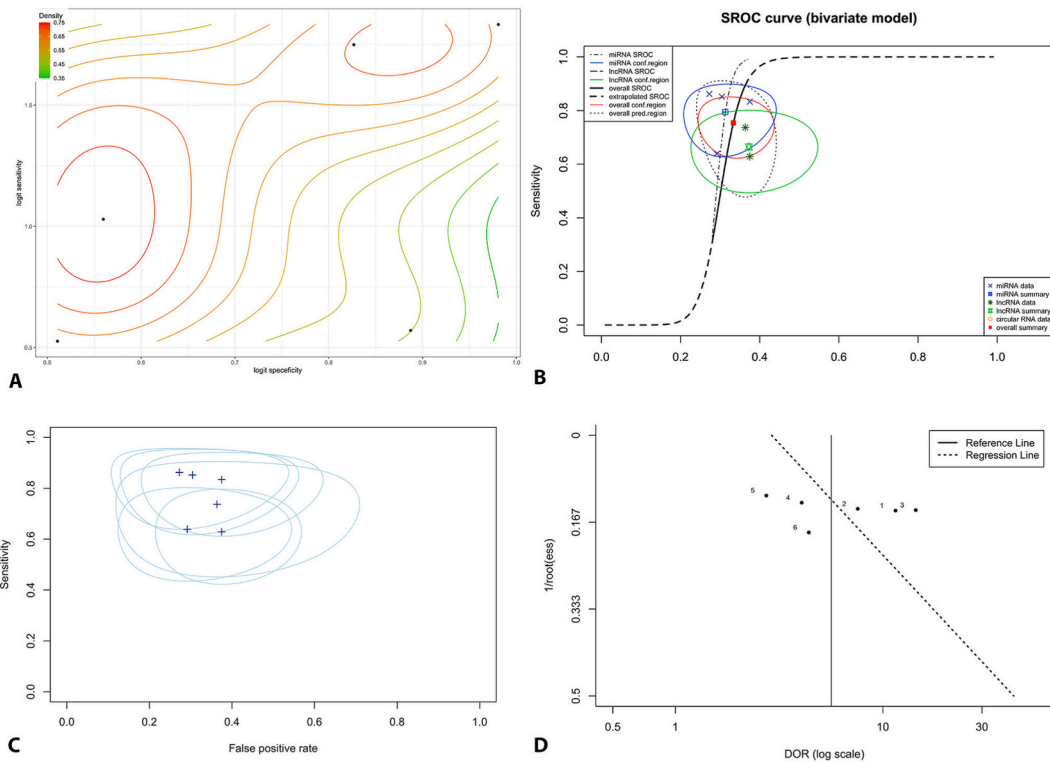


**Fig. 8. Bivariate meta-analysis of ncRNAs in TNM stage. (A)** Scatter plot of logit sensitivity and specificity shows that the data are dispersed **(B)** SROC for bivariate meta-analysis shows an overall AUC of 0.69 **(C)** Ellipse plot for bivariate meta-analysis. **(D)** Deek's funnel plot shows no publication bias.

asymmetric, and the correlation coefficient between the logit-transformed sensitivity and the specificity was positive, which may show potential heterogeneity in the bivariate model. Also, the $I^2$ estimate based on the Holling sample size adjusted method was 1.7–1.8 %. The log-likelihood ratio for the goodness-of-fit of the model was 12.23.

### 3.6. Diagnostic accuracy of ncRNAs for clinical staging in OC

Based on the primary univariate analysis, the overall univariate DOR of the ncRNA panel for clinical staging was 3.97 with 95%CI, 3.18–4.96, and *P*-value <0.0001. Heterogeneity was moderate, with $I^2$ equal to 45.2 % (*Q*, 56.58; *P* < 0.01). In miRNA, lncRNA, and circular RNA subgroups, the DOR was 3.62 (95%CI, 2.77–4.73; *P*-value <0.0001), 3.90 (95%CI, 2.48–5.35, *P*-value <0.0001), and 6.04 (95%CI, 2.22–16.45; *P*-value <0.001), respectively. The forest plot for univariate DOR meta-analysis has been shown in Fig. 9A. The heterogeneity was moderate in miRNA ($I^2$, 41 %; *Q*, 18.67; *P*-value, 0.07), lncRNA ($I^2$, 49 %; *Q*, 31.63; *P*-value <0.01), and circular RNA ($I^2$, 45 %; *Q*, 3.61; *P*-value, 0.16) subgroups. The difference between the subgroups was insignificant ($X^2$, 0.98; *P*-value, 0.61). The publication bias was significant based on Deek's method (*P*-value <0.01). The funnel plot has been demonstrated in Fig. 10D. The
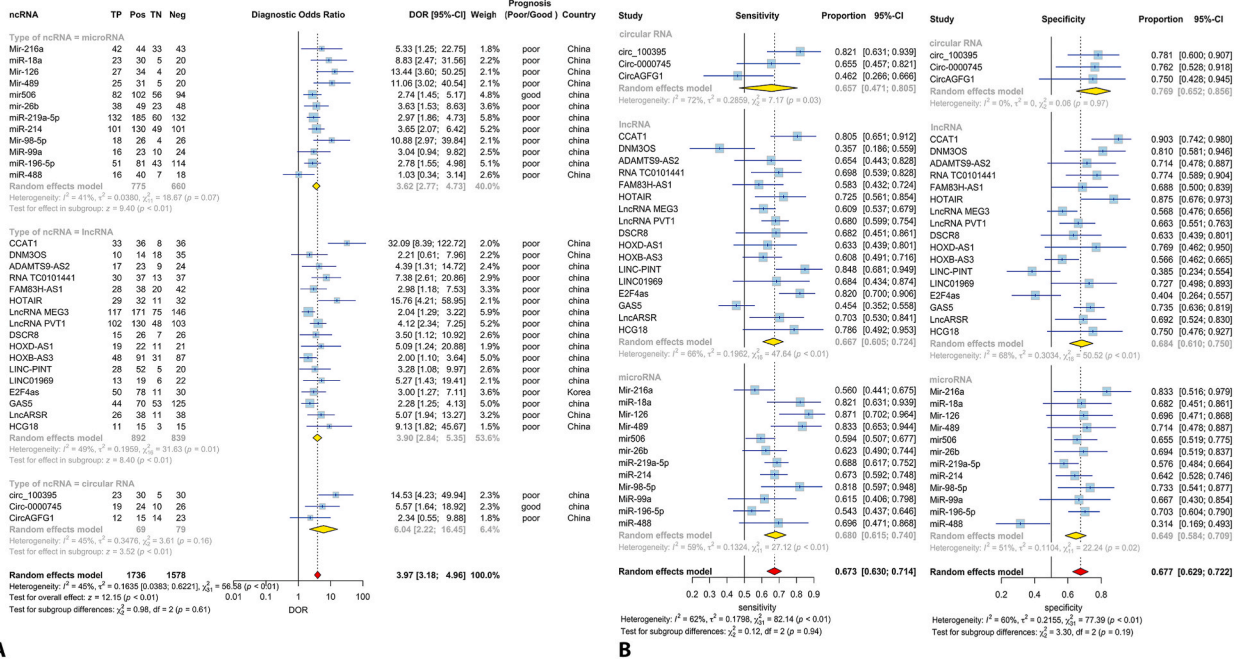
**Fig. 9. Univariate meta-analysis of ncRNAs in clinical stage. (A)** Univariate forest plots for the clinical stage show an overall DOR of 3.97 with no significant difference between subgroups (P = 0.61) **(B)** Univariate forest plots show sensitivity and specificity of 0.67 and 0.68, respectively.
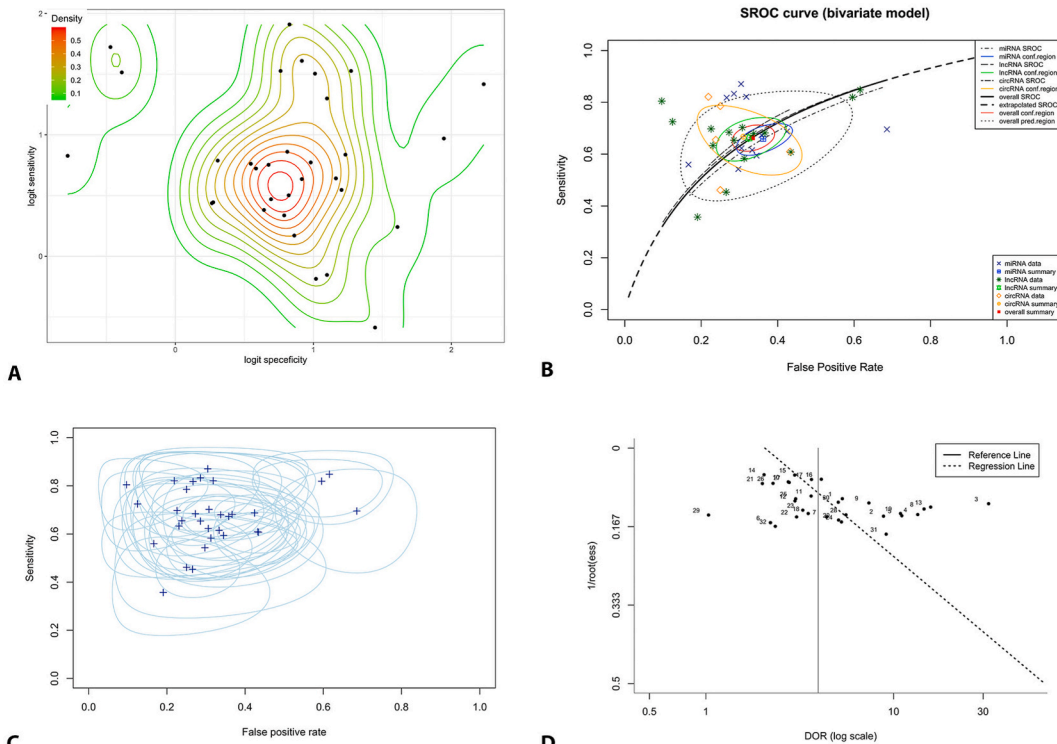


**Fig. 10. Bivariate meta-analysis of ncRNAs in clinical stage. (A)** Scatter plot of logit sensitivity and specificity shows low data dispersion **(B)** SROC for bivariate meta-analysis shows an overall AUC of 0.71 **(C)** Ellipse plot for bivariate meta-analysis. **(D)** Deek's funnel plot shows the presence of publication bias.

univariate analysis demonstrated that the overall sensitivity and specificity were 67 % and 68 %, respectively, with moderate heterogeneity in both groups (Fig. 9B).

The scatter plot demonstrated relatively centered data with low dispersion (Fig. 10A). The overall sensitivity and specificity were 0.66 (95%CI, 0.62–0.70; intercept P-value <0.001; between-studies SD, 0.43), 0.67 (CI, 0.62–0.71; intercept P-value <0.001; between-studies SD, 0.40), respectively in bivariate meta-analysis. The total AUC was 0.71 (CI, 0.67–0.73). The SROC and ellipse plots are depicted in Fig. 10B and C, respectively. Overall, DOR, LR$^+$, and LR$^-$ were 3.97 (95%CI, 3.11–4.98), 1.99 (CI, 1.75–2.27), and 0.51 (CI, 0.45–0.57), respectively. The symmetric SROC curve and negative correlation between sensitivity and specificity (r, −0.15) show small heterogeneity. Additionally, Heterogeneity was low based on the Holling sample size adjusted $I^2$ estimate of 1.9–2.0 %. The log-likelihood for the goodness-of-fit of the model was 45.96.

### 3.7. Meta-analysis of HR to evaluate the value of ncRNAs in predicting OC prognosis

A total of 10 ncRNAs were included in an overall survival (OS) HR meta-analysis, of which 6 belong to the lncRNA subgroup and 4 belong to the miRNA subgroup. A random-effect meta-analysis demonstrated no significant overall effect (HR, 1.39; 95%CI, 0.67–2.84; P-value, 0.32). Overall heterogeneity was significant, with an $I^2$ of 91.2 % (Q, 102.26; P-value <0.0001). The subgroup analysis demonstrated that overall HR in the miRNA subgroup was 0.92 (95%CI, 0.24–3.59; P-value, 0.91), and in the lncRNA, a subgroup was 1.82 (95%CI, 0.81–4.09; P-value, 0.14). The difference between subgroups was not significant ($X^2$, 0.72; P-value, 0.40). Heterogeneity within the subgroups was significant ($I^2$, 94 %; Q, 48.25; P-value <0.01 and $I^2$, 90 %; Q, 48.63; P-value <0.01 for miRNA and lncRNA groups, respectively). The forest plot for HR is shown in Fig. 11A. Egger's test demonstrated no significant publication bias (P-value, 0.72). The funnel plot is depicted in Fig. 11B.

### 3.8. Outcomes validation based on bioinformatics analysis

The prognostic value of the obtained microRNAs and lncRNAs were re-analyzed based on the OS in OC patients, applying the Pan-cancer miRNA and Pan-cancer RNA-seq data, respectively. OS analysis of microRNAs resulted in the identification of a correlation between poor prognosis and high levels of hsa-miR-216a (HR = 1.68), hsa-miR-3064 (HR = 1.43), hsa-miR-489 (HR = 1.7), hsa-miR-488 (HR = 1.61), and hsa-miR-196a (HR = 1.44). However, low levels of hsa-miR-532 (HR = 0.75), hsa-miR-219a (HR = 0.65), hsa-miR-18a (HR = 0.78), and has-miR-98 (HR = 0.73) were related to poor OS of OC patients. Combining the results using the mean expression of the whole target microRNAs represented that the correlation between low expression levels of total microRNAs and poor OS prognosis was significant (log Rank P = 0.017). K-M plots for microRNAs have been shown in Fig. 12a-j. Furthermore, OS analysis of lncRNAs recognized the elevated expression of lncRNAs, including HOTAIR (HR = 1.81), NEAT1 (HR = 1.4), GAS5 (HR = 1.5), HOXB-AS3 (HR = 1.58), DSCR8 (HR = 1.33), and LINC01969 (HR = 1.66), and decreased expression of lncRNAs, involving CCAT1 (HR = 0.54), FLVCR1- AS1 (HR = 0.76), and HCG18 (HR = 0.67), as indicators of poor prognosis in OC patients. Total lncRNAs OS analysis revealed a close correlation (log Rank P = 0.017) between high levels of the whole selected lncRNAs with poor prognosis of OC (Fig. 13a-j). P-values for ncRNAs OS have been provided in Supplementary Table 2.

## 4. Discussion

To our knowledge, this study is the first systematic review conducted to define the designation of ncRNAs in OC prognosis and EMT. Our results provide information on the importance and applicability of ncRNAs in predicting clinical stage, DM and LNM, and TNM stage of OCs. The current meta-analysis demonstrates that ncRNAs could be appropriate markers for predicting factors related to OC prognosis, including TNM staging, clinical staging, LNM, and DM; overall DOR for them were 6.52, 3.97, 4.19, and 3.8, respectively.
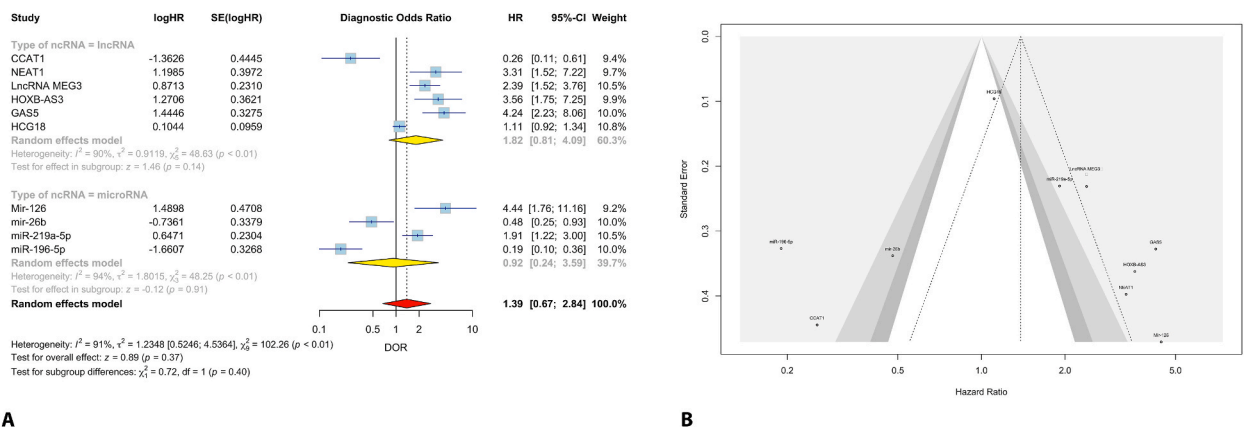


**Fig. 11. Meta-analysis for OS. (A)** The forest plot for overall survival shows an HR of 1.39 with no subgroup difference (P = 0.40) **(B)** The Funnel plot for OS shows no significant publication bias.
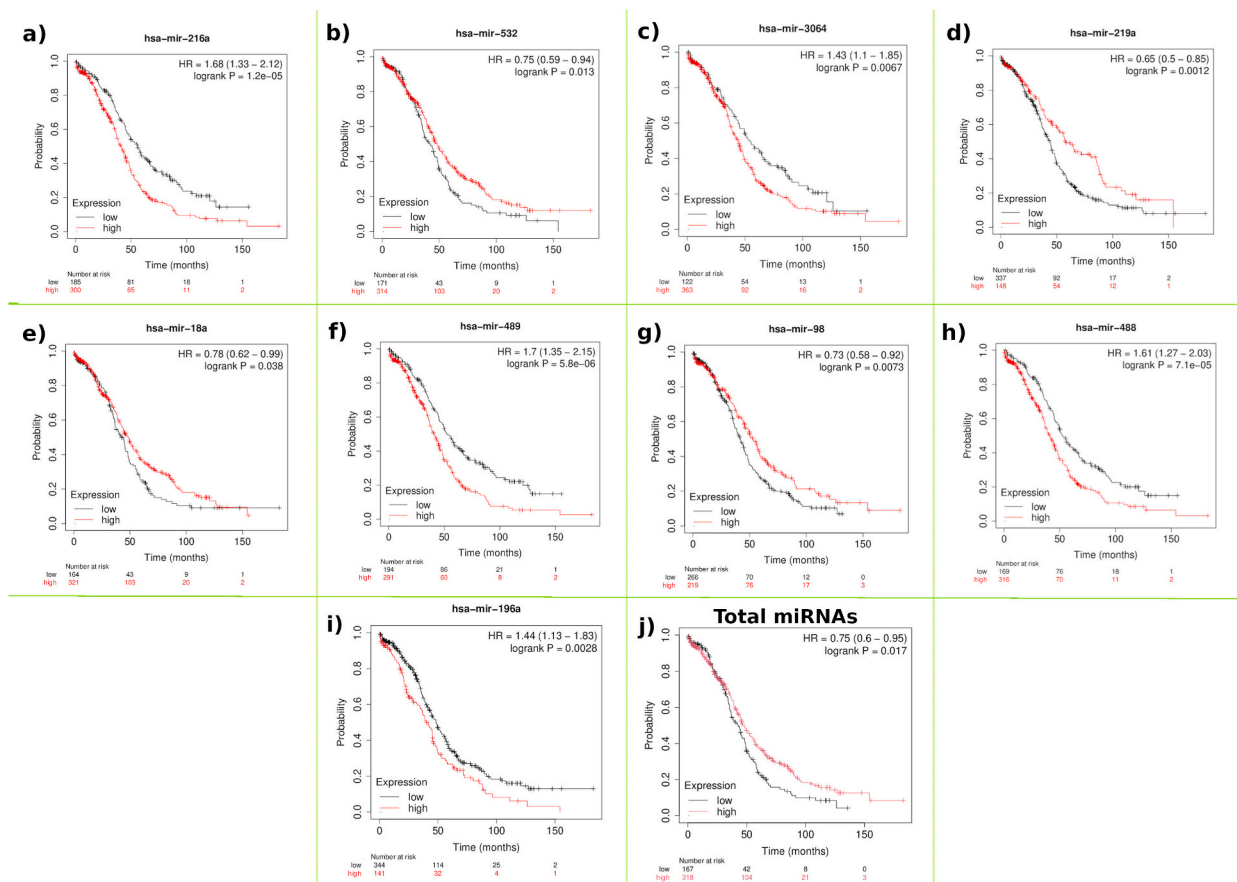
**Fig. 12. K-M plots for microRNAs based on Pan-cancer miRNA**. High levels of miR-3064, miR-216a, miR-489, miR-196a, and miR-488 and low expression of miR-532, miR-18a, miR-219a, and has-miR-98 are shown to be correlated with poor prognosis of OC. Low levels of whole microRNAs are associated with poor OS.

The HR of the high-expression ncRNA group to the low-expression ncRNA group was insignificant.

OC, the most lethal gynecological malignancy, is predicted to increase in cases and deaths annually. Commonly used OC tumor markers, such as CA125, lack enough specificity and sensitivity and are unsatisfying for OC detection in early-stage and all subtypes. Serum and ascites levels of most kallikrein-related peptidases (KLK) family members that are noticeably overexpressed in OC tissues elevate due to protease secretion. KLK could serve as a potential biomarker and is adopted as a complementary tool along with CA125 for OC diagnosis, and its upregulation is associated with aggressive tumor phenotypes. However, DNA methylation patterns, micro-RNAs, and circulating tumor cells are identified as promising biomarkers with early detection possibilities and better diagnostic accuracy [79–81]. Small ncRNAs (sncRNAs) play critical roles in gene regulation, and a combination of different types of sncRNA indicates OC development with early diagnosis benefits [82]. LncRNAs are considerably specific for each tumor origin, substantially stable in body fluids involving urine, whole blood, serum, and saliva, and easily detectable employing molecular techniques such as qRT-PCR, RNA-sequencing, and microarray hybridization [83].

Many studies have shown the dysregulation of ncRNAs in cancer. MicroRNAs target transcription factors to control the EMT process of tumor cells in different types of cancers [84]. MiR-148b is upregulated in 92.21 % of OC samples and could be used as competent diagnostic biomarkers for early-stage detection [85]. Distinct expression of plasma microRNAs can serve as highly sensitive and specific diagnostic markers for endometriosis-related OC [86]. Significant upregulated VPS13C-has-circ-001567 is positively associated with OC stage, LNM, cell proliferation, and invasion while reducing apoptosis and E-cadherin levels [87]. Overexpression of lncRNA CTBP1-AS2 and PTEN leads to a decreased proliferation of OC cells and miR-216a expression [88]. Based on the study by Zhonghua Chen et al. [89], the mean serum level of miR-125b in EOC patients was significantly reduced compared to control groups. Decreased levels of miR-125b are beneficial diagnostic markers and are accompanied by a poor prognosis for EOC patients.

Several studies have investigated the roles of ncRNAs in OC. Circulating ncRNAs contribute to cell migration, invasion, metastasis, and recurrence of OC [90]. MiR-146a and miR-150 stimulate cell survival and promote drug resistance [91]. Higher expression levels of lncRNA SNHG3 in OC tissues are positively associated with LNM, clinical stages, poor prognosis, and higher increased levels of invasion-related protein CyclinD1, CDK1, MMP9, and MMP3 [92]. LncRNA-MALAT1 negatively regulates miR-503-5p expression by increasing proliferation and decreasing OC cell apoptosis via the JAK2-STAT3 pathway [93]. Overexpression of lncRNA AB073614 is
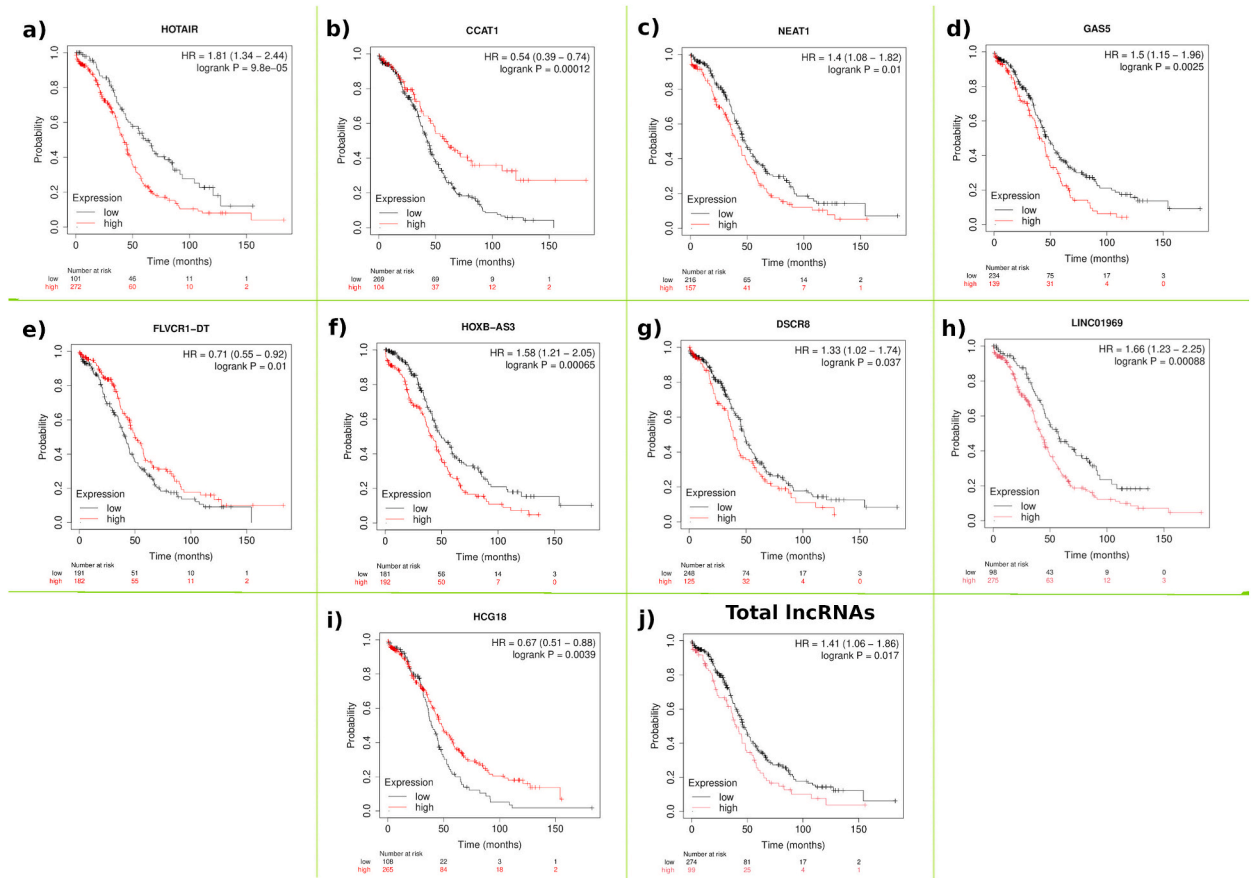
**Fig. 13. K-M plots for lncRNAs based on Pan-cancer RNAseq data.** High levels of HOTAIR, GAS5, NEAT1, HOXB-AS3, LINC01969, and DSCR8, low levels of expression of CCAT1, HCG18, and FLVCR1- AS1, and high levels of whole lncRNAs are correlated with poor OS of OC patients.

significantly associated with tumor size, clinical stage, lymph node invasion, and shorter survival rate of EOC patients. Therefore, AB073614 can be a prognostic biomarker and a potential treatment target for EOC [94].

Among the different roles ncRNAs participate in, some ncRNAs play a critical role in EMT-related mechanisms. MiR-26b expression is attenuated in OC tissues. Therefore, the suppressive activity of miR-26b on its target molecule, ERα, would be diminished, which leads to enhancing EMT, invasion, and cell proliferation [95]. Downregulation of miR-214-3p in HGSOC leads to upregulation of its target genes, including MUC16 and MMP7, in tumor tissue, resulting in its participation in the EMT process. MiR-214-3p expression is directly correlated with progesterone receptor protein and negatively correlated with CDK6 and MAPK1 [96]. LncRNA-CCAT1 acts as an oncogene in OC by contributing to TGFβ1-induced EMT via the miR-490-3p/TGFβR1 axis [97]. HOXD-AS1 is overexpressed in EOC and directly binds and targets miR-186-5p, resulting in upregulation of PIK3R3 and promoting EMT, cell invasion, and migration [98]. Upregulation of NEAT1 in OC results in miR-1321 downregulation and TJP3 upregulation, thus promoting OC invasion and metastasis [99]. The overexpression of lncRNA MEG3, DNM3OS, and MIAT in OC results in the regulation of the EMT-related gene pathways. Although upregulation of DNM3OS remarkably correlates with reduced OS for OC patients, MIAT or MEG3 levels lack correlation with survival [100].

There are numerous reviews about the different roles of ncRNAs in OC. Circulating ncRNAs contribute to cell migration, invasion, metastasis, and recurrence of OC [90]. lncRNAs H19, XIST, and LSINCT are involved in the development of OC occurrence, cell growth and proliferation, invasion, and metastasis. These mentioned lncRNAs have diagnostic and prognostic values [101]. CircRNAs are responsible for adjusting cell proliferation in OC, and their aberrant expression promotes the initiation and progression of this cancer [102]. Abnormal expression of microRNAs takes part in OC initiation, proliferation, chemotherapy resistance, and survival [103]. Investigating specific roles of ncRNAs, Luo et al. [104], Ning et al. [105], and Seyed Hosseini et al. [106] focused on the survival value of dysregulated lncRNAs. Ferreira et al. focused on microRNAs and their chemotherapy-related response, diagnosis, and prognosis [106] roles. Despite the existence of a review on the diagnostic and prognostic roles of circRNAs in OC, there were no systematic reviews and meta-analyses on this topic [107]. Identifying both the prognostic and diagnostic roles of all existing studies on EMT-related ncRNAs in OC, we did not narrow our investigation to a specific ncRNA type (e.g., lncRNAs, microRNAs, circRNAs) or subtype. At the end of the eligibility surveying step, a total of 15 microRNAs, 24 lncRNAs, and 3 circRNAs were identified for assessing the correlation of their dysregulated expression and different characteristics, including clinical stages, TNM stages, LNM, and DM. To

assess the DOR and effectiveness of the target ncRNAs in the diagnosis and prediction of OC, we initiated with univariate analysis, provided a panel of ncRNAs, and then performed a bivariate analysis.

Going beyond the primary univariate analysis, we defined an adjusted panel of ncRNAs for each of the LNM, TNM staging, DM, and clinical staging items, which are all related to the prognosis assessment of OC. Our panel for prognosis evaluation based on LNM consists of eight microRNAs, including miR-216a [42], miR-3064 [53], miR-532 [53], miR-18a [69], miR-489 [57], miR-126 [70], miR-99a [56], and miR-488 [44], sixteen lncRNAs, involving, CCAT1 [60], ADAMTS9-AS2 [72], FLVCR1-AS1 [55], TC0101441 [58], MAFG-AS1 [68], FAM83H-AS1 [65], HOTAIR [50], DSCR8 [59], DQ786243 [74], HOXD-AS1 [61], HOXB-AS3 [66], LINC-PINT [76], E2F4as [43], SNHG20 [75], LINC01969 [46], and LncARSR [54], and one circRNA called circ_100395 [67]. After adjusting the ncRNA panel, the overall diagnostic and prognostic effectiveness elevated in both whole-panel and subgroup analysis of three differentiated types of ncRNAs. However, lncRNAs were identified as more robust predictors compared to microRNAs for LNM. Since circ_100395 was the only representative of circRNAs for LNM items, the subgroup analysis was not executed for this type of ncRNA and cannot separately be assumed as a proper prognostic indicator of OC. The ncRNAs panel for DM comprises six microRNAs, five lncRNAs, and two circRNAs. Meanwhile, the microRNAs subgroup, involving miR-489 [57], miR-18a [69], miR-126 [70], miR-26b [51], miR-219a-5p [63], and miR-196-5p [62] was a considerably valuable diagnostic factor compared to the lncRNAs subgroup, consisting FLVCR1-AS1 [55], DQ786243 [74], GAS5 [62], LncARSR [54], and MEG3 [63]. Based on statistical outcomes, the circRNAs subgroup (circ_100395 [67] and CircAGFG1 [71]) accounted for the second most effective predicting factors among two other types of ncRNAs. However, due to the limited number of this ncRNA type that inhibits precisely evaluating their effectiveness, this subgroup cannot be separately recognized as a valuable marker for our purpose. Furthermore, for a more comprehensive assessment of results accuracy, $LR^-$ and $LR^+$ were calculated together. Totally, the current study discovered that the defined panel of ncRNAs, which are EMT-related ncRNAs, were significantly associated with both DM and LNM. According to the previous papers, the EMT process can take part in the metastasis and invasion of cancer [108,109]. With high enough overall sensitivity, specificity, and accuracy, our results demonstrated that the EMT-related ncRNA panels play significant roles as efficient predictors of DM and LNM in OC.

Recruiting the same approach to appraise the significance of ncRNAs for clinical stages led to defining a panel consist of twelve microRNAs (miR-126 [70], miR-216a [42], miR-18a [69], miR-99a [56], miR-489 [57], miR-506 [41], miR-26b [51], miR-219a-5p [63], miR-214 [73], miR-488 [44], miR-98-5p [59], and miR-196-5p [62]), seventeen lncRNAs (CCAT1 [60], DNM3OS [45], ADAMTS9-AS2 [72], TC0101441 [58], GAS5 [62], FAM83H-AS1 [65], HOTAIR [50], HOXD-AS1 [61], PVT1 [73], E2F4as [43], MEG3 [63], DSCR8 [59], HOXB-AS3 [66], LINC-PINT [76], lncARSR [54], LINC01969 [46], and HCG18), and three circRNAs (circ_100395 [67], circ_0000745 [47], CircAGFG1 [71]). Although the entire defined panel for clinical stages served as a significant predicting factor of OC, the lncRNAs subgroup displayed better prognostic effectiveness in comparison to the microRNAs and circRNAs subgroups. The defined panel for TNM item encompasses miR-126 [70], miR-18a [69], miR-489 [57], miR-616 [64], DQ786243 [74], and MAFG-AS1 [68]. Four microRNAs included in this panel are more likely to predict the TNM stages in OC patients.

Along with the univariate analysis, the bivariate meta-analysis was performed to reduce the high percentage of heterogeneity shown in the univariate analysis, which was represented by the natural discrepancies between various studies. This type of analysis reduced data heterogeneity and data dispersion, resulting in a more symmetrical SROC curve and increasing the AUC of the SROC curve.

In addition to the mentioned analysis, a meta-analysis based on HR was implemented to assess the OS and prognostic effectiveness of the included ncRNAs. The total HR of high-expressing ncRNAs compared to low-expressing groups was not significant.

Based on the validation of significant ncRNAs in our meta-analysis using previously existing data in Pan-cancer, the acquired lncRNAs and microRNAs have differential expression in OC patients compared with healthy women. Therefore, these ncRNAs could be indicators of poor OS prognosis in OC patients.

Our study encompasses limitations. Some previous studies with similar objectives did not report the risk ratio of the effect of the ncRNAs in their evaluation of OC prognosis. Additionally, we could not gain access to the full text of some papers found relevant in title-abstract screening despite contacting their authors. Moreover, we had expected to reconstruct the survival data from K-M graphs using the "Guyot algorithm." However, neither of the K-M curves of eligible articles reported the "number at risk" data, which is an indispensable element for retrieving HR and CI. Furthermore, initial OC diagnostic tests are not specific and sensitive enough, have particular limitations, and are ineffective in the early detection of OC. The obtained ncRNA panels from this study can predict ovarian cancer more specifically and sensitively. These ncRNAs can serve as therapeutic targets for specific clinical purposes. However, more studies are needed to discover a non-invasive panel for early detection based on serum or plasma.

## 5. Conclusion

In conclusion, this systematic review and meta-analysis provide gathered information on the prognostic implications of EMT-related ncRNAs in OCs of all types. Our results suggest that panels of ncRNAs could effectively predict factors related to the EMT process and prognosis of OC, including LNM, DM, clinical staging, and TNM staging.

**Ethics approval and consent to participate**

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and material

All data are available upon reasonable request.

## Competing interests

The authors declare that they have no conflicts of interest to disclose regarding this study.

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## CRediT authorship contribution statement

**Alireza Soltani Khaboushan:** Writing – review & editing, Validation, Project administration, Methodology, Formal analysis, Data curation. **Seyedeh Nazanin Salimian:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Saghar Mehraban:** Writing – review & editing, Writing – original draft, Methodology. **Afshin Bahramy:** Visualization, Validation, Project administration, Methodology, Formal analysis. **Narges Zafari:** Writing – review & editing, Writing – original draft, Project administration, Methodology. **Abdol-Mohammad Kajbafzadeh:** Visualization, Validation, Resources. **Joshua Johnson:** Validation, Supervision, Investigation. **Masoumeh Majidi Zolbin:** Writing – review & editing, Visualization, Supervision, Project administration.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35202.

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