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Prognostic value of long non-coding RNAs in triple negative breast cancer

A PRISMA-compliant meta-analysis

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Abstract

Background Triple-negative breast cancer (TNBC) is the most aggressive and lethal subtype of breast cancer. Accumulating evidence showed long non-coding RNAs (lncRNAs) are abnormally expressed in TNBC and could be valuable prognostic tools for TNBC patients. This study aims to research the prognostic value of lncRNAs in TNBC, using the meta-analysis method.

Methods We performed a detailed literature search on Pubmed, Scopus, and Web of Science for studies on the prognostic value of lncRNAs in TNBC. The meta-analysis method was used to determine the relationship between lncRNAs expression and survival of TNBC patients.

Results A total of 2803 TNBC patients and 24 lncRNAs from 27 different articles were included in the present study. Subgroup analysis demonstrated that overexpression of lncRNAs in a group that is upregulated in TBNC showed a significant association with poor overall survival (HR = 1.86, 95%CI = 1.45–2.27, I^2 = 41.9%) and disease-free survival (HR = 1.85, 95%CI = 1.37–2.33, I^2 = 0%). Conversely, overexpression of lncRNAs in a downregulation group was markedly related to good overall survival (HR = 0.60, 95% CI = 0.43–0.77, I^2 = 28.6%). Moreover, expression of lncRNA SNHG12, MALAT1, HOTAIR, HIF1A-AS2, HULC, LINC00096, ZEB2-AS1, LUCAT1, and LINC000173 showed a marked correlation with positive lymph node metastasis (LNM), while lncRNA MIR503HG, GAS5, TCONS_l2_00002973 showed the opposite effect. High expression level of MALAT1, HIF1A-AS2, HULC, LINC00096, ADPGK-AS1, ZEB2-AS1, LUCAT1 were positively correlated with distant metastasis (DM), while lncRNA MIR503HG showed the opposite effect. In addition, the mechanisms of lncRNAs in TNBC were summarized.

Conclusions This meta-analysis demonstrated that abnormally expressed lncRNA were significantly associated with the survival of TNBC patients and may serve as biomarkers and therapeutic targets for TNBC prognosis.

Abbreviations: DFS = disease-free survival, lncRNAs = long non-coding RNAs, OS = overall survival, TNBC = Triple-negative breast cancer.

Keywords: biomarkers, breast cancer, long noncoding RNA, meta-analysis, prognosis

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1. Introduction

Breast cancer is the most frequent cause of death in women worldwide.[1] With regard to the pathology-based biomarkers, breast cancer can be classified into 4 intrinsic subtypes: luminal A, luminal B, epidermal growth factor receptor 2 enriched and Triple negative breast cancer (TNBC). TNBC, which is characterized by a lack of estrogen receptor, progesterone receptor and epidermal growth factor receptor 2 expression, accounts for approximately 15% to 20% of all new cases.[2] TNBC is considered to be the most aggressive and lethal type of breast cancer among the subtypes. Patients with TNBC have shorter disease-free survival (DFS) and overall survival (OS) compared to those diagnosed with hormone receptor-positive tumors.[3] Furthermore, despite their high chemo-sensitivity, the median survival of patients with metastatic disease rarely exceeds 12 months.[4] In the last decades, few effective prognostic markers and targeted therapeutic drugs were developed for TNBC. For these reasons, TNBC remains a major therapeutic challenge that is highly threatening to patient outcomes.

long non-coding RNAs (LncRNAs) are defined as non-protein-coding RNA transcripts with more than 200nt nucleotides in length. There is abundant evidence demonstrating that lncRNAs could be key regulators of various cellular processes, interacting with other components such as proteins, other species of RNA

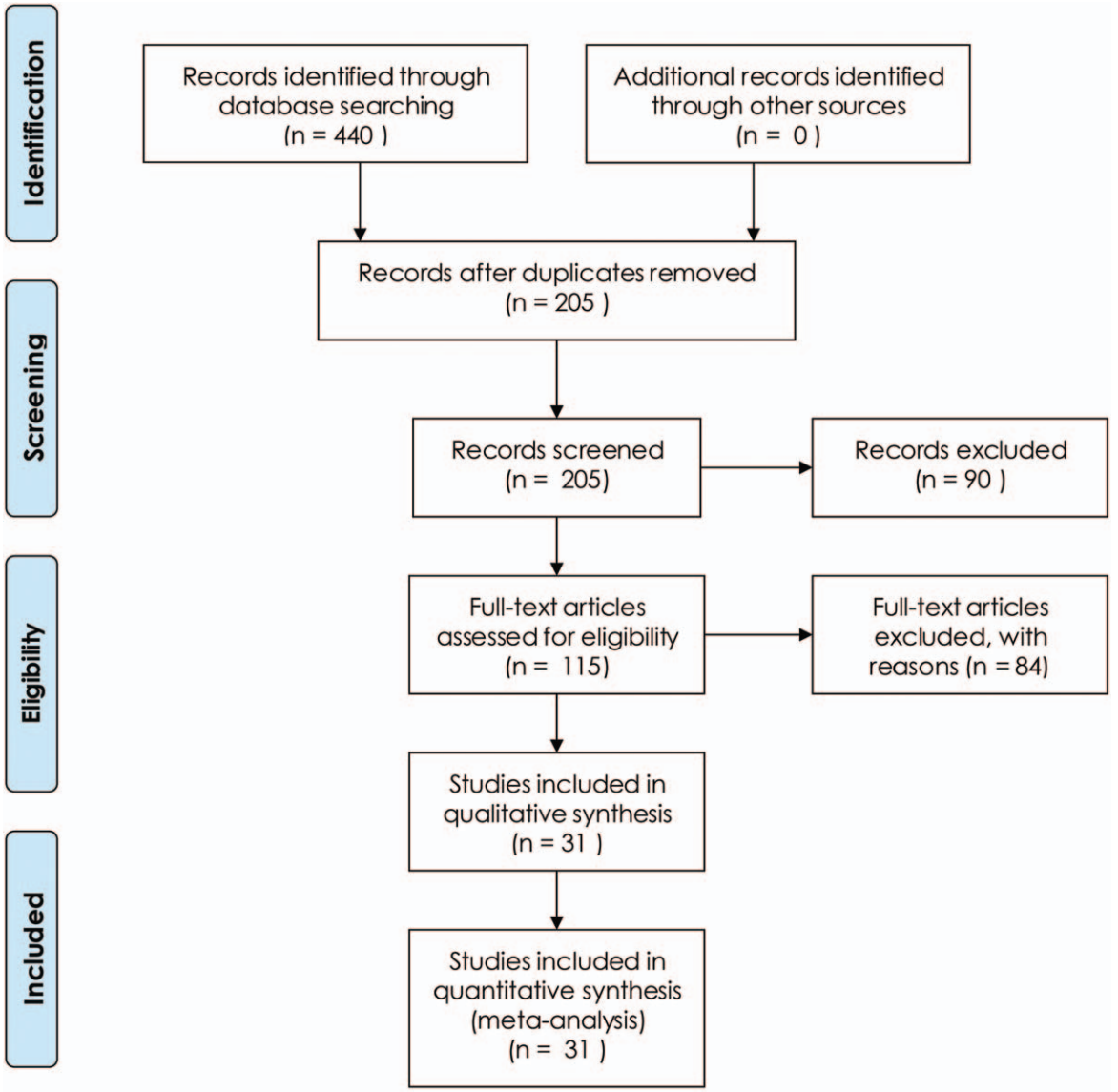

Figure 1. Flow diagram of this systematic review and meta-analysis.

and DNA,[5] participating in diverse cellular process from normal development to cancer.[6] Many studies have suggested that the abnormal expression of lncRNAs is correlated with breast cancer metastasis and progression.[7] Recent research showed that lncRNAs differ dramatically in expression across the different breast cancer subtypes.[8] Therefore, it is of great clinical value to search for biomarkers to predict the prognosis of TNBC, which could help improve the therapeutic approach. Moreover, lncRNAs which negatively correlate with the survival of patients could also be promising targets in TNBC. Overall, we herein undertake a comprehensive meta-analysis according to standard methods to evaluate the value of lncRNAs in the prognosis of TNBC.

2. Methods

2.1. Literature search and selection

We conducted a systematic literature search of online databases, including PubMed, Web of Science, and Scopus from inception to December 2019, to identify all potential original studies in English. The search terms and relative variants were as follows: (long non-coding RNA OR lncRNA) AND (triple-negative breast cancer) AND (prognosis OR prognostic OR survival OR outcome OR mortality). We also reviewed the references of included articles to identify additional studies. All the analyses were conducted based on the prior published articles. Therefore, patient consent or ethical approval are not necessary.

All the search results were evaluated independently by 2 of the authors. The inclusion criteria were as follows:

(1) study population: TNBC patients who had a definite diagnosis by pathologic examinations;
(2) intervention: studies evaluating the prognostic significance of lncRNA signature in TNBC;
(3) outcomes measure: the survival results were estimating the HR with 95% CI for OS, progression free survival, DFS or disease-specific survival.

Table 1

Characteristics of studies in this meta-analysis.

Study	Year	Country	LncRNA	Total number	Detection method	Cut-off	LncRNA						Survival analysis	Multivariate analysis	HR (95% CI)
							High	Low	LNM (H)	LNM (L)	DM (H)	DM (L)			
Bamodu OA	2016	China	KDM5B	270	Immunohistochemical staining	NA	133	137					OS	yes	1.68 (1.02–2.75)
Beltrán-Anaya FO	2018	Mexico	LncKLHDC7B	122	Microarray Analysis	fold change and P value	60	62					OS	NA	0.46 (0.15–1.39)
Collina F	2018	Italy	HOTAIR	163	RNA In Situ Hybridization Assay (RNA ISH).	NA	47	116	26	44	8	22	OS	NA	3.28 (1.14–9.44)
													DFS	NA	2.34 (1.56–3.51)
Fan HJ	2020	China	LINC00173	84	qRT-PCR	median	48	36	20	6			OS	NA	1.74 (1.38–2.19)
													RFS	NA	1.60 (1.19–2.15)
Fu J	2019	China	MIR503HG	94	qRT-PCR	mean	47	47	15	36	1	12	OS	yes	0.43 (0.22–0.84)
Hua KY	2020	China	HOST2	40	qRT-PCR	mean	16	24					OS	NA	4.04 (2.90–5.63)
Jin C	2015	China	MALAT1	139	qRT-PCR	median	69	70			17	31	NA	NA	NA
Li SQ	2018	China	GAS5	103	qRT-PCR	median	50	53	20	32			OS	NA	0.49 (0.25–0.93)
Liang HG	2019	China	HOTAIR	84	qRT-PCR	Youden index	40	44					OS	NA	1.57 (0.63–3.91)
Liu RL	2019	China	LINC00511	87	qRT-PCR	median	44	43	15	26	12	24	OS	NA	2.04 (1.21–3.45)
													DFS	NA	1.99 (1.19–3.31)
Mou EX	2019	China	LUCAT1	94	qRT-PCR	median	47	47	31	18	33	17	OS	YES	2.02 (0.39–10.54)
Shi F	2016	China	HULC	96	qRT-PCR	Median	48	48	34	8	8	1	OS	YES	2.84 (1.15–5.33)
Song X	2019	China	NEF	64	qRT-PCR	mean	34	30					OS	NA	0.51 (0.19–1.35)
Tang JM	2018	China	DANCR	60	qRT-PCR	median	30	30					OS	NA	1.79 (0.62–5.16)
Tao WY	2019	China	DANCR	57	qRT-PCR	mean	25	32					OS	NA	1.61 (0.46–5.67)
Tian YY	2019	China	LINC00096	90	Microarray Analysis	Fold change and P value	50	40	26	8	17	4	NA	NA	NA
Wang DF	2019	China	MAPT-AS1	60	qRT-PCR	mean	18	42					DFS	NA	0.91 (0.33–2.51)
Wang KN	2018	China	AWPPH	68	qRT-PCR	median	34	34			12	14	OS	NA	1.64 (0.75–3.57)
Wang OC	2017	China	SNHG12	102	qRT-PCR	median	51	51	37	27	4	5	NA	NA	NA
Wang PS	2017	China	linc-ZNF469–3	233	qRT-PCR	NA	65	168					OS	NA	1.64 (1.08–2.48)
													DFS	NA	1.63 (1.06–2.50)
Wang YF	2018	China	HIF1A-AS2	86	qRT-PCR	median	43	43	32	18	8	0	OS	YES	2.23 (1.04–4.79)
Xu ST	2017	China	ANRIL	37	qRT-PCR	mean	21	16	9	6	5	4	OS	NA	2.18 (0.73–6.50)
Yan JQ	2019	China	TCONS_l2_00002973	96	qRT-PCR	median	48	48	30	41			OS	NA	0.44 (0.03–6.90)
Yang F	2018	China	ARNILA	88	qRT-PCR	mean	49	39					PFS	YES	2.72 (1.26–5.70)
Yang J	2019	China	POU3F3	56	qRT-PCR	Youden index	30	26					OS	NA	1.22 (0.40–3.76)
Yang JH	2019	China	ADPGK-AS1	74	qRT-PCR	median	37	37	13	15	26	11	OS	NA	1.33 (0.18–9.80)
Zhang GX	2019	China	ZEB2-AS1	98	qRT-PCR	median	49	49	33	18	29	16	OS	NA	3.54 (2.15–5.84)
Zhang HW	2019	China	NAMPT-AS	64	qRT-PCR	median	36	28					OS	YES	6.0 (1.48–24.32)
													RFS	YES	6.87 (2.21–21.39)
Zhang KM	2018	China	AFAP1-AS1	238	qRT-PCR	mean	132	106	67	50	2	2	OS	NA	1.78 (0.80–3.96)
													DFS	NA	1.41 (0.58–3.39)
Zheng SP	2019	China	GAS5	156	qRT-PCR	NA	69	87					OS	NA	0.74 (0.60–0.92)
Zuo YG	2017	China	MALAT1	43	qRT-PCR	median	21	22	12	5	8	2	OS	NA	2.85 (1.12–7.26)

DFS = disease-free survival, HR = hazard ratios, OS = overall survival, lncRNAs = long non-coding RNAs, PFS = progression-free survival, qRT-PCR = quantitative real-time PCR, RFS = relapse-free survival.

Studies not fitting the above inclusion criteria as well as abstracts from conferences, non-comparative studies, review articles, case reports, commentary articles, studies in a different language than English were excluded.

2.2. Data extraction and quality assessment

Data extraction and the evaluation of literature quality were conducted independently by 2 reviewers . The following information was retrieved: researched lncRNA, first author name, publication year, country/ethnicity, sample size, follow-up time, cutoff value, detection method, HR with 95% CI for OS, DFS, progression free survival, disease-specific survival. If HR and 95% CI were not directly shown in the paper, data were extracted from survival curves.[9] For quality assessment of included studies, the modified Newcastle-Ottawa Scale was used to assess all the included studies. Any disagreement was resolved by a third reviewer.

2.3. Statistical analysis

All statistical analysis was performed using STATA, verson 12.0 (Stata Corporation, College Station, TX). HR and 95% CI were obtained from each study. If the HRs could be obtained directly from the studies, we used crude ones. Otherwise, we extracted the survival information from the Kaplan-Meier survival curves using the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) to estimate the HRs and 95%CI according to the method described in the previous study.[10] A test of heterogeneity of combined HRs was conducted using Cochran Chi-square test and the test of inconsistency index (I^2). I^2 values over 50% were considered to suggest significant heterogeneity. If $I^2 > 50\%$, a random-effects model was used to pool the results; if $I^2 < 50\%$ a fixed-effects model was used. The meta-analysis results were displayed as forest plots. For publication bias, all included studies were assessed by using the Funnel plot test and Egger liner regression test recommended for enumeration data. P-value $< .05$ was considered statistically significant (2-sided).

Table 2

Quality assessment of eligible studies (Newcastle-Ottawa Scale).

	Selection			Comparability			Outcome		
Study	Adequacy of case definition	Number of case	Representativeness of the cases	Ascertainment of exposure	Ascertainment of detection method	Ascertainment of cut-off	Assessment of outcome	Adequate follow-up	Total
Bamodu OA (2016)	1	1	1	1	1	0	1	1	7
Beltrán-Anaya FO (2018)	1	1	1	1	1	1	1	1	8
Collina F (2018)	1	1	1	1	1	0	1	1	7
Fan HJ (2020)	1	1	1	1	1	1	1	1	8
Fu J (2019)	1	1	1	1	1	1	1	1	8
Hua KY (2020)	0	1	1	1	1	1	1	1	7
Jin C (2015)	0	1	1	1	1	1	0	0	5
Li SQ (2018)	1	1	1	1	1	1	1	1	5
Liang HG (2019)	1	1	1	1	1	1	1	1	8
Liu RL (2019)	0	1	1	1	1	1	1	1	7
Mou EX (2019)	0	1	1	1	1	1	1	1	7
Shi F (2016)	0	1	1	1	1	1	1	1	7
Song X (2019)	1	1	1	1	1	1	1	1	8
Tang JM (2018)	0	1	1	1	1	1	1	1	7
Tao WY (2019)	0	1	1	1	1	1	1	1	7
Tian YY (2019)	0	1	1	1	1	1	0	0	5
Wang DF (2019)	0	1	1	1	1	1	1	1	7
Wang KN (2018)	1	1	1	1	1	1	1	1	8
Wang OC (2017)	1	1	1	1	1	1	0	0	6
Wang PS (2017)	1	1	1	1	1	0	1	1	7
Wang YF (2018)	1	1	1	1	1	1	1	1	8
Xu ST (2017)	1	0	1	1	1	1	1	1	7
Yan JQ (2019)	0	1	1	1	1	1	1	1	7
Yang F (2018)	0	1	1	1	1	1	1	1	7
Yang J (2019)	1	1	1	1	1	1	1	1	8
Yang JH (2019)	0	1	1	1	1	1	1	1	7
Zhang GX (2019)	0	1	1	1	1	1	1	1	7
Zhang HW (2019)	0	1	1	1	1	1	1	1	7
Zhang KM (2018)	0	1	1	1	1	1	1	1	7
Zheng SP (2019)	0	1	1	1	1	0	1	1	6
Zou YG (2017)	1	0	1	1	1	1	1	1	7

3. Results

3.1. Study selection and quality assessment

As shown in Fig. 1, a total of 31 articles published between 2015 and 2020 with 3146 TNBC patients were included in this meta-analysis. The 27 relevant lncRNAs were as follows: LINC00096,[11] SNHG12,[12] TCONS_l2_00002973,[13] MALAT1,[14,15] KDM5B,[16] ANRIL,[17] AFAP1-AS1,[18] ARNILA,[19] AWPPH,[20] DANCR,[21,22] GAS5,[23,24] ZEB2-AS1,[23,24] ADPGK-AS1,[26] POU3F3,[27] HIF1A-AS2,[28] MAPT-AS1,[29] NEF,[30] LUCAT1,[31] LINC00511,[32] HOTAIR,[33,34] MIR503HG,[35] LncKLHDC7B,[36] HULC,[37] linc-ZNF469–3,[38] NAMPT-AS,[39] LINC00173,[40] and HOST2.[41] Among the included studies, 29 studies were conducted in China, while the other 2 were performed in Mexico and Italy, respectively. 6 studies reported HRs directly. More details are shown in Table 1. Additionally, all included studies were considered high quality because of the Newcastle-Ottawa Scale scores were more than 5 for each study (Table 2).

3.2. The relationship between lncRNAs and patient survival

LncRNA TCONS_l2_00002973, GAS5, NEF and MIR503HG were downregulated in TNBC tissues and acted as cancer suppressors, while the remaining 23 lncRNAs were upregulated in cancer tissues and promoted TNBC progression. The subgroup analysis suggested that high expression levels of lncRNAs in the upregulation subgroup were significantly related to poor OS (pooled HR = 1.86, 95%CI = 1.45–2.27, I^2 = 41.9%, Fig. 2). In contrast, increased levels of GAS5, NEF and MIR503HG were favorable factors in OS (pooled HR = 0.60, 95%CI = 0.43–0.77, I2 = 28.6%, Fig. 2). We also found that high expression levels of AFAP1-AS1, LINC00511, HOTAIR, linc-ZNF469–3 were markedly associated with DFS (pooled HR = 1.85, 95%CI = 1.37–2.33, I2 = 0%, Fig. 3).

3.3. The relationship between lncRNAs and clinicopathological outcomes

The results indicated that SNHG12, MALAT1, HOTAIR, HIF1A-AS2, HULC, LINC00096, ZEB2-AS1, LUCAT1, and LINC000173 exhibited a notable correlation with positive LNM (SNHG12: OR = 2.35, 95%CI (1.03–5.36); MALAT1: OR = 4.53, 95%CI (1.21–16.96); HOTAIR: OR = 2.03, 95%CI (1.02–4.03); HIF1A-AS: OR = 4.04, 95%CI (1.62–10.08); HULC: OR = 12.14, 95%CI (4.55–32.41); LINC00096: OR = 4.33, 95%CI (1.67–11.24); ZEB2-AS1: OR = 3.55, 95%CI (1.54–8.17); LUCAT1: OR = 3.12, 95%CI (1.34–7.25); LINC000173: OR = 3.57, 95%CI (1.25–10.18); Fig. 4). In contrast, MIR503HG, GAS5 and TCONS_l2_00002973 were favorable factors for LNM (MIR503HG: OR = 0.14, 95%CI (0.06–0.36);

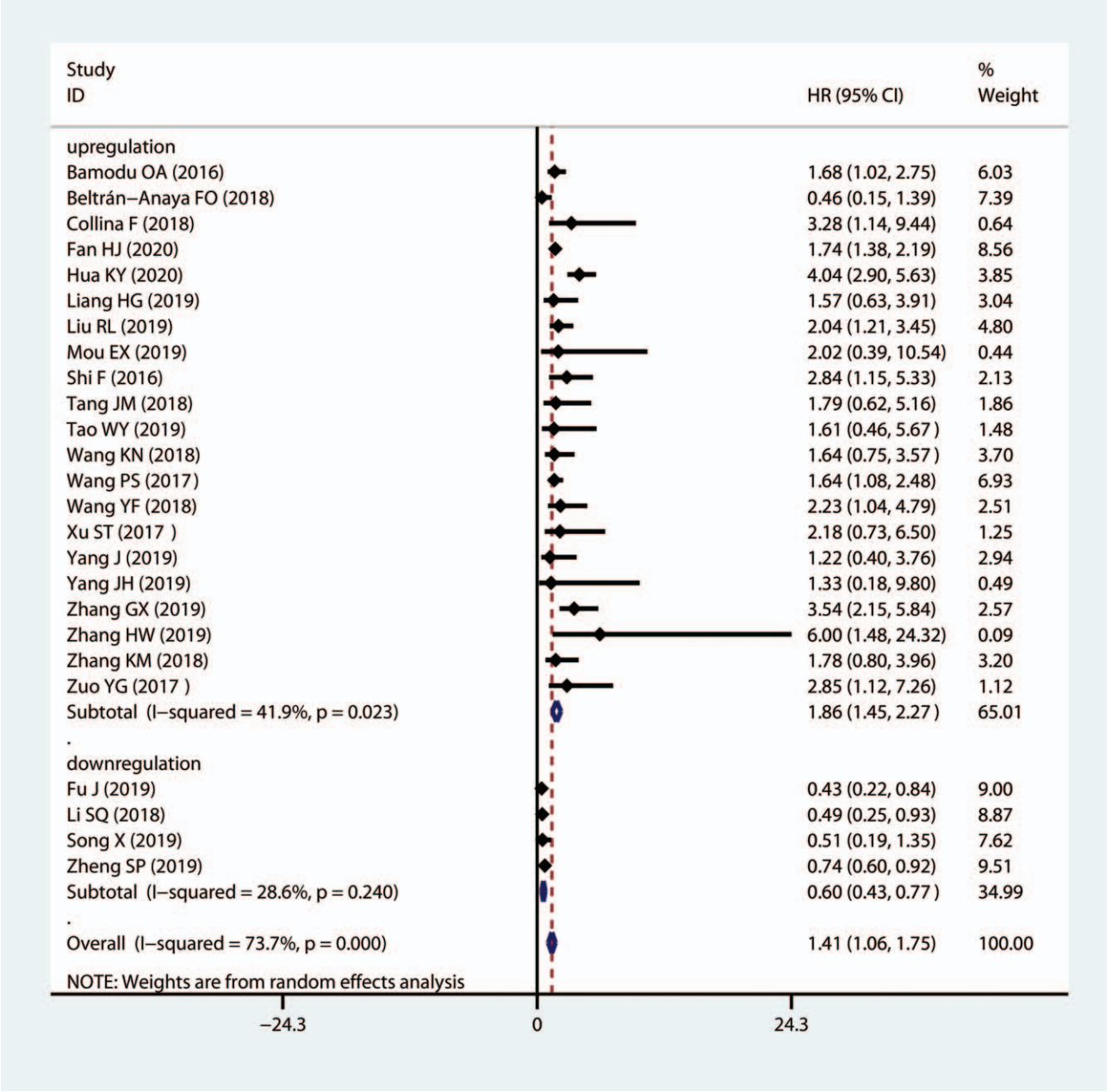

Figure 2. Forest plots of subgroup analysis of OS by lncRNA expression in TNBC tissues. lncRNAs = long non-coding RNAs, TNBC = Triple-negative breast cancer.

GAS5: OR1 = 0.44, 95%CI (0.20–0.96), OR2 = 0.74, 95%CI (0.60–0.92); TCONS_l2_0000297: OR = 0.28, 95%CI (0.11–0.77). Furthermore, seven lncRNAs (MALAT1, HIF1A-AS2, HULC, LINC00096, ADPGK-AS1, ZEB2-AS1, LUCAT1) were unfavorable factors for DM, while MIR503HG showed a negative association with DM in TNBC (Fig. 5).

3.4. Publication bias and sensitivity analysis

Begg funnel plots seemed to have a symmetric distribution of the included studies (Fig. 6A). We used Begg and Egger test to evaluate the publication bias of the lncRNAs and OS, and the results of both tests exhibited no significant publication bias for the HR of OS (Egger test: $P = .502$ and Begg test: $P = .375$). Sensitivity analysis was used to evaluate the stability and reliability of the results of lncRNAs and OS by removing each eligible study, and the result was not significantly affected (Fig. 6B). The results showed that there was no change in the combined HRs after excluding research data of one study.

3.5. Action mechanism of lncRNAa in TNBC

In addition, we concentrated on potential targets and pathways of the included lncRNAs in TNBC, as presented in Table 3. 12 lncRNAs were reported to involve in tumor progression by regulating miRNAs, including LINC00096, MALAT1, KDM5B,

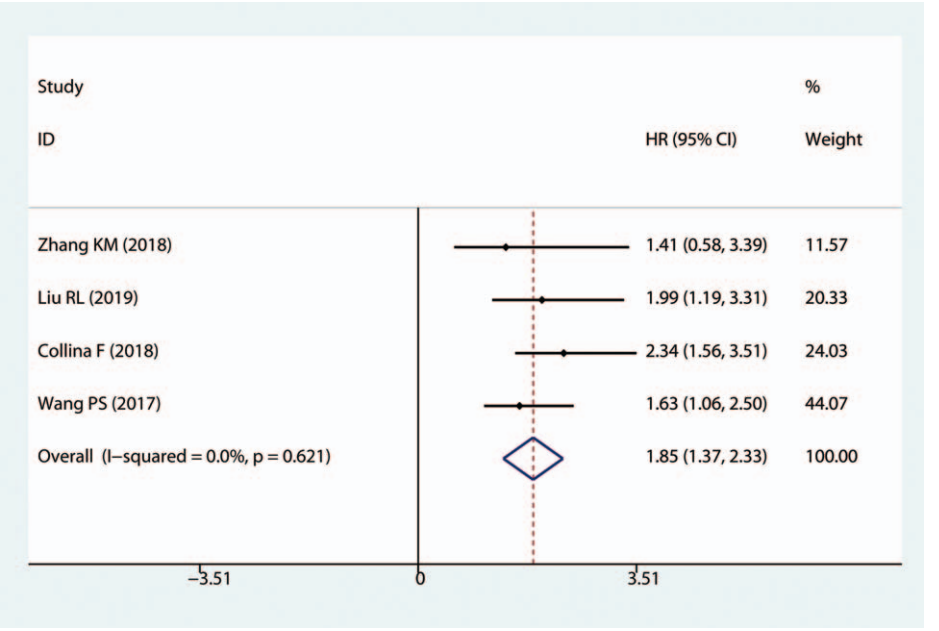

Figure 3. Forest plots of the HRs for the association between lncRNA expression and DFS in TNBC tissues. HR = hazard ratio, lncRNAs = long non-coding RNAs, DFS = disease-free survival, TNBC = Triple-negative breast cancer.

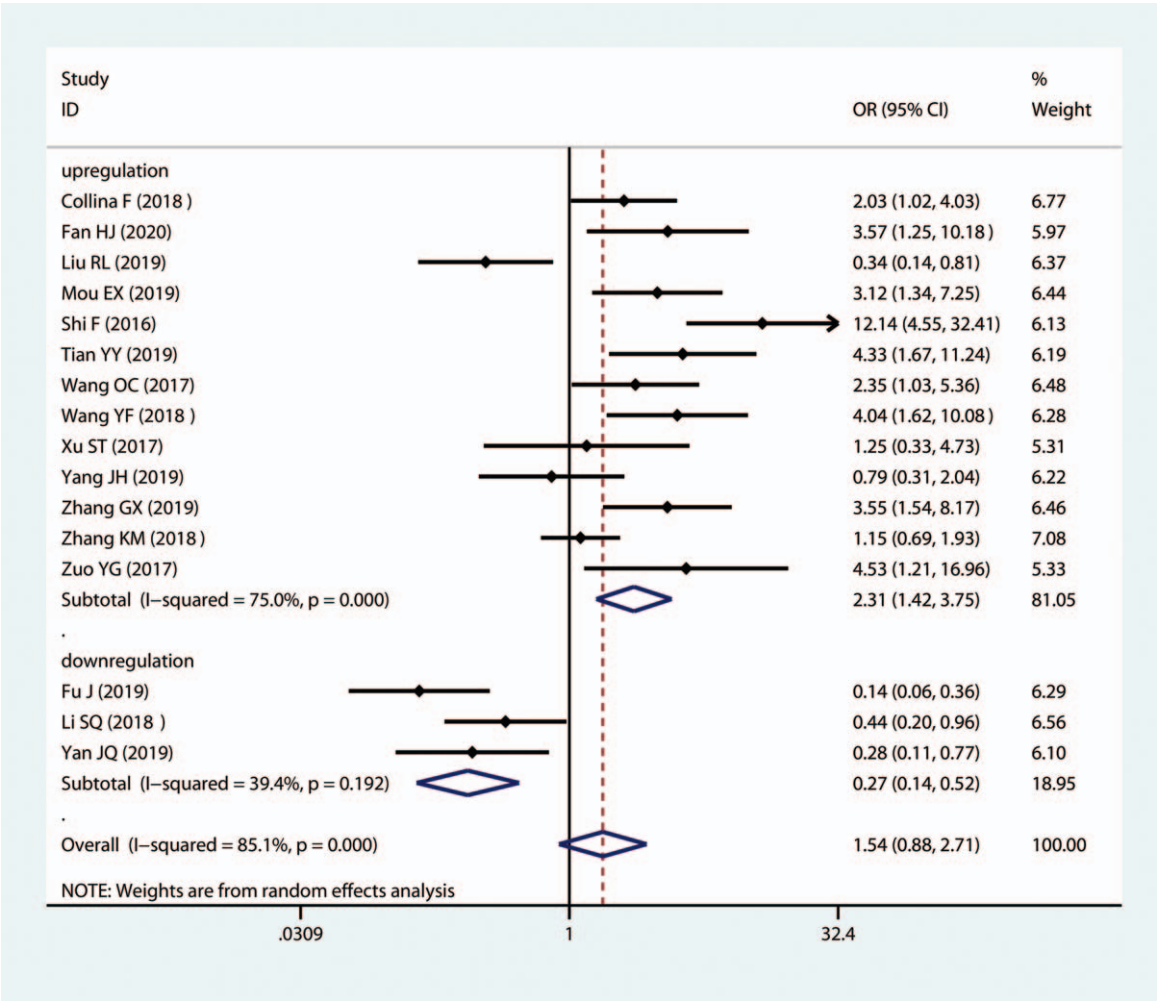

Figure 4. Forest plots of the association of high lncRNA expression with LNM. lncRNAs = long non-coding RNAs.

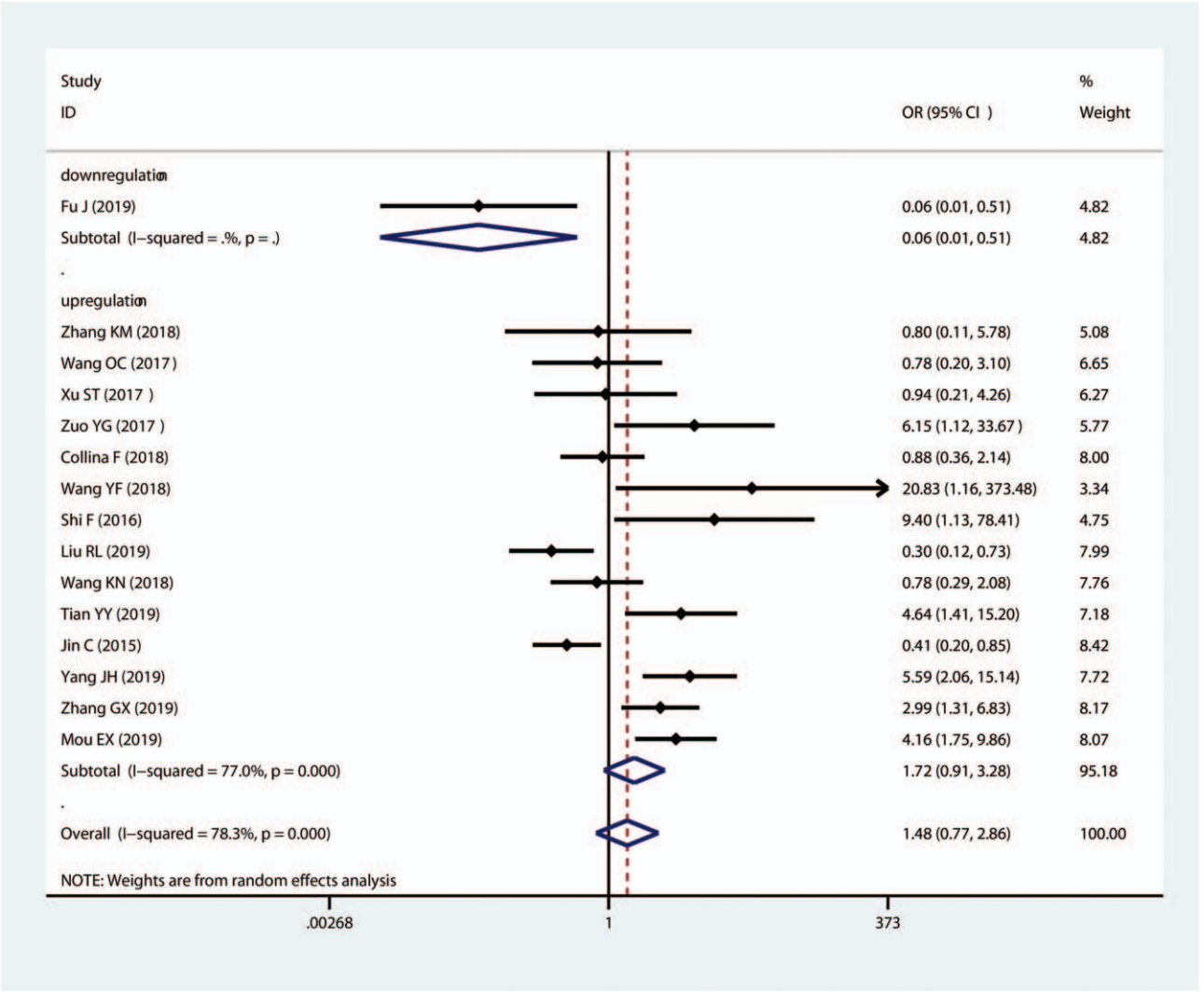

Figure 5. Forest plots of the association of high lncRNA expression with DM. lncRNAs = long non-coding RNAs.

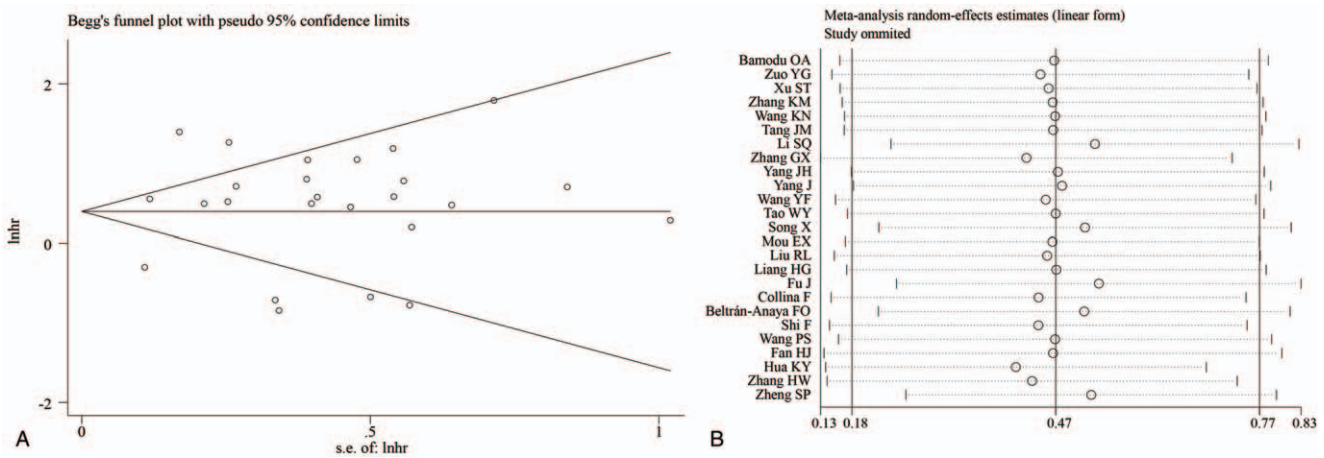

Figure 6. Tests for publication bias (A) and sensitivity analysis (B).

Table 3

Summary of lncRNAs with their potential targets and pathways.

LncRNA	Expression	Potential target	Pathway	Reference
ADPGK-AS1	Upregulation	miR-3196	↑proliferation, migration, induced epithelial-mesenchymal transition (EMT) process; ↓apoptosis;↓miR-3196;↑OTX1	(Yang et al, 2019)
AFAP1-AS1	Upregulation	Wnt/beta-Catenin Signaling Pathway	↑proliferation and invasion, ↓apoptosis; ↑C-myc and epithelial-mesenchymal transition-related molecules	(Zhang et al, 2018)
ANRIL	Upregulation	miR-199a	↑proliferation; ↓apoptosis; ↓miR-199a	(Xu et al, 2017)
ARNILA	Upregulation	miR-204	↑epithelial-mesenchymal transition (EMT), invasion and metastasis; ↓miR-204; ↑Sox4	(Yang et al, 2018)
AWPPH	Upregulation	frizzled homolog 7 (FZD7)	↑proliferation; ↑FZD7	(Yang et al, 2018)
DANCR	Upregulation	miRNA-216a-5p; RXRA	↑proliferation and invasion; ↓miRNA-216a-5p; bound with RXRA; ↑PIK3CA	(Tang et al, 2018; Tao et al, 2019)
GAS5	Downregulation	miR-196a-5p; miR-378	↓proliferation;↑apoptosis	(Li et al, 2018; Zheng et al, 2019)
HIF1A-AS2	Upregulation	NA	↑migration and invasion	(Wang et al, 2019)
HOST2	Upregulation	let-7b	↑proliferation and migration	(Hua et al, 2020)
HOTAIR	Upregulation	NA	↑migration and invasion	(Liu et al, 2019)
HULC	Upregulation	MMP-2 /MMP-9	↑metastasis through MMP-2 and MMP-9	(Shi et al, 2016)
KDM5B	Upregulation	miR-448	↑migration, invasion and clonogenic capacity	(Jin et al, 2016; Zuo et al, 2017)
LINC00096	Upregulation	miR-383–5p	↑proliferation and invasive; ↓miR-383–5p; ↑RBM3	(Tian et al, 2019)
LINC00173	Upregulation	miR-490–3p	↑proliferation, colony formation, and invasion	(Fan et al, 2020)
LINC00511	Upregulation	Snail	↑proliferation and invasion; interacting with Snail	(Liu et al, 2019)
linc-ZNF469–3	Upregulation	miR-574–5p	↑invasion and stemness properties, metastasis; miR-574–5p-ZEB1 axis	(Wang et al, 2018)
LncKLHDC7B	Upregulation	NA	↑apoptosis, ↓migration and invasion	(Beltran-Anaya et al, 2019)
LUCAT1	Upregulation	miR-5702	↓apoptosis, ↑proliferation and migration; ↓miR-5702	(Mou et al, 2019)
MALAT1	Upregulation	miR-129–5p, miR-1	↑proliferation, migration, and invasion	(Jin et al, 2016; Zuo et al, 2017)
MAPT-AS1	Upregulation	NA	NA	(Wang et al, 2019)
MIR503HG	Downregulation	miR-103	↓migration and invasion;↓miR-103; ↑OLFM4 axis	(Fu et al, 2019)
NAMPT-AS	Upregulation	miR-548b-3p	promote tumor progression and metastasis	(Zhang et al, 2019)
NEF	Downregulation	miRNA-155	↓migration and invasion	(Song et al, 2019)
POU3F3	Upregulation	caspase 9	↑proliferation;↓apoptosis;↓caspase 9	(Yang et al, 2019)
SNHG12	Upregulation	MMP13	↑proliferation, apoptosis, migration	(Wang et al, 2017)
TCONS_l2_00002973	Downregulation	NA	↓proliferation; ↓apoptosis	(Yan et al, 2019)
ZEB2-AS1	Upregulation	ZEB2	↑proliferation and metastasis; ↑ZEB2	(Zhang et al, 2019)

lncRNAs = long non-coding RNAs.

ANRIL, ARNILA, DANCR, GAS5, ADPGK-AS1, NEF, LUCAT1, MIR503HG, linc-ZNF469–3, HOST2, LINC00173, and NAMPT-AS. Among them, 3 lncRNAs (GAS5, NEF and MIR503HG) downregulate in TNBC tissue to inhibit cell proliferation, migration and invasion, as well as promoting apoptosis, and the other 12 lncRNAs upregulate in TNBC cells to show the same effect. In addition, 7 lncRNAs (SNHG12, AFAP1-AS1, AWPPH, DANCR, ZEB2-AS1, POU3F3, LINC00511, HULC) enhance cancer cell proliferation, migration and invasion by regulating relevant proteins. The molecular mechanism of TCONS_l2_00002973, HIF1A-AS2, MAPT-AS1, HOTAIR, LncKLHDC7B in TNBC remain to be revealed.

4. Discussion

TNBC is the most aggressive subtype of breast cancer with high proliferative and metastatic phenotypes. About 30% of TNBC patients experience a rapid relapse in the first 3 years after standard adjuvant chemotherapy.[42] Few treatment options are available because of an absence of the more common molecular targets in breast cancer. Therefore, there is an urgent need to identify efficient biomarkers that could better stratify TNBC patients with regard to their risk of recurrence and survival, and also could provide new clues for therapeutic targets.[43]

A comprehensive analysis on 7256 RNA-sequencing libraries comprising the tumor tissues, normal samples, and cell lines, showed that 68% of the total transcribed genes are represented by lncRNAs.[44] Over the past few years, emerging evidences have suggested that lncRNAs are expressed aberrantly in various types of human cancers, such as colorectal, prostate, breast, liver, brain cancer, renal, and bladder cancer.[45] LncRNAs could function as key players in epigenetic, transcriptional or post-transcriptional gene regulation and they are associated with multiple cell processes, including proliferation, invasion, differentiation, migration. Meanwhile, abundance of tumor-associated lncRNAs were found to play a vital role in breast cancer tumorigenesis and metastasis.[11] Importantly, some of tumor-associated lncRNAs have been demonstrated to regulate TNBC pathogenesis.[11] Additionally, many lncRNAs travel in different bodily fluids and can be used as non-invasive cancer biomarkers.[34]

To validate the accuracy of the reported lncRNAs as prognostic molecular markers for TNBC, we systematically meta-analyzed the available studies on lncRNAs and evaluated the value of lncRNAs as prognostic markers for TNBC. Our research is the first report focusing on this clinical association, in which 31 studies were analyzed and 27 types of lncRNAs involved in the survival analysis of TNBC were compared.

In this meta-analysis, the results showed down-regulated expression of TCONS_l2_00002973, GAS5, NEF and MIR503HG were favorable factors for OS of TNBC patients, and elevated expression of the other 23 lncRNAS were associated with poor DFS and RFS of TNBC patients. For those lncRNAs with upregulated expression, patients with high levels of lncRNAs had a 1.86-fold higher risk of poor OS, a 1.85-fold higher risk of DFS when compared with those with low expression levels of lncRNAs. This suggests great potential of using lncRNA for future clinical applications to early diagnose and treat high risk TNBC.

The ceRNA hypothesis, originally proposed by Pandolfi et al, indicates that lncRNAs can function as a competing endogenous RNAs (ceRNAs) that sequesters miRNAs to block the repression of miRNAs on target mRNAs.[46] Most of aberrant expression lncRNAs modulated TNBC tumorigenesis through acting as molecular 'sponge' for miRNAs, and the target miRNAs included miR-383–5p, miR-129–5p, miR-1, miR-448, miR-199a, miR-204, miRNA-216a-5p, miR-196a-5p, miR-3196, miRNA-155, miR-5702, miR-103, miR-574–5p, miR-378, let-7b, miR-490–3p, and miR-548b-3p. Notably, it was reported that DANCR bound with RXRA and increased its serine 49/78 phosphorylation via GSK3beta, led to the activation of PIK3CA transcription, and subsequently promoted PI3K/AKT signaling and TNBC tumorigenesis.[21] Additionally, lncRNA ZEB2-AS1 activated the epithelial mesenchymal transition through the PI3K/Akt/GSK3beta/Zeb2 signaling pathway.[25] Recent study confirmed the function of LINC00511 to maintain the stability of Snail by impeding its ubiquitination and degradation by the BTRC E3 ubiquitin protein to decrease TNBC cell growth and invasion.[32] Although many molecular mechanisms of abnormal expression lncRNAs in TNBC have been revealed, it remains further studies to thoroughly understand the mechanism and function of lncRNAs in TNBC.

Several potential limitations in this study should be considered. First, a specific definition of the cutoff value of lncRNA expression level should be required, while the studies did not use the same cutoff value and some of them even did not report the value. This very likely contributed to some of the observed heterogeneity. Second, HRs and 95% CIs that were extracted from Kaplan-Meier curves in several studies might be the cause of some imprecisions. Third, only English papers were included in our meta-analysis, which may exclude some relevant articles. Additionally, unpublished articles of negative results also might cause a publication bias. Therefore, our research might overstate the prognostic value of lncRNA in TNBC patients.

5. Conclusions

In summary, this meta-analysis indicated that there was a significant association between expression of lncRNAs and prognosis, as well as clinicopathological characteristics in TNBC patients. However, well-designed studies with larger sample sizes are required to confirm the prognostic value of lncRNAs in TNBC patients, and to discover the molecular mechanism.

Author contributions

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