BMJ Open Influence of dysregulated expression of circular RNA on the diagnosis and prognosis of breast cancer in Asia: a meta-analysis study

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ABSTRACT

Objective Recent studies have reported a correlation between non-coding RNAs such as circular RNAs (circRNAs) and clinical value of various cancers. However, the diagnostic and prognostic role of circRNA in breast cancer remains controversial.

Design Systematic review and meta-analysis.

Methods Diagnostic efficacy was estimated by sensitivity, specificity and area under the curve (AUC). Pooled HRs with 95% CIs estimated overall survival (OS), and ORs with 95% CIs investigated clinical features.

Results By searching PubMed, Embase, Web of Science, CNKI and Cochrane Library, we obtained a total of 29 studies with 4405 patients. A shorter survival time was associated with high expression levels of tumour-promoter circRNAs (OS: HR=2.43, 95% CI 2.20 to 2.92, $p<0.001$), and tumour-suppressor circRNAs were related to a favourable prognosis (OS: HR=0.32, 95% CI 0.23 to 0.44, $p<0.001$). Furthermore, high expression levels of oncogenic circRNAs were associated with poor clinical outcomes; tumour-suppressor circRNAs showed the opposite result. As for the diagnostic role, the outcome indicated an AUC of 0.82 (95% CI 0.78 to 0.85), with 85% sensitivity and 86% specificity to distinguish patients with breast cancer from healthy controls.

Conclusion Dysregulated expression of circRNA was related to diagnosis and prognosis in breast cancer, which indicated it might be a novel biomarker and a target of therapy for breast cancer.

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INTRODUCTION

In the twenty-first century, breast cancer is one of the malignant cancers in developed and developing countries.^{1 2} Mortality from breast cancer ranked third in all cancers in 2018, according to the latest data from Global Cancer Statistics.³ Currently, owing to the increasing incidence of breast cancer, new methods are needed to improved diagnostic accuracy and therapeutic effect of breast cancer. Therefore, many researchers spend significant effort searching for novel biomarkers which predict the progression

Strengths and limitations of this study

- This study reported the guidelines of the Meta-analysis Of Observational Studies in Epidemiology group and Preferred Reporting Items for Systematic reviews and Meta-analysis statement.
- Analyses have been undertaken respecting potential sources of known statistical heterogeneity.
- This meta-analysis to describe on the association of circular RNAs expression with breast cancer prognosis and diagnostic features, which indicated it might be a novel biomarker and target of therapy for breast cancer.
- The variability in methods of assessing risk and reporting of frequency of risk characteristics limited analyses.

of breast cancer, in terms of early diagnosis, prognosis and treatment.

Circular RNAs (circRNAs) are a special kind of endogenous non-coding RNAs, with a closed covalent ring structure connecting 3' and 5' ends.^{4 5} They are also competitive RNAs that, along with long-chain non-coding RNAs, co-regulate microRNAs.⁶ CircRNA participates in the growth and development of cancer, diabetes, nervous system disorders, cardiovascular diseases, and other diseases through various biological roles, such as sponge action, protein translation and binding protein action.⁷⁻⁹ Recently, a growing number of studies showed that numerous circRNAs have been discovered and have a close relation with the development of breast cancer.⁴ It is well known that the function of circRNA has great potential in metastasis, invasion, initiation and carcinogenesis of breast cancer. However, the role of circRNA in breast cancer remains controversial based on existing research. Therefore, we conducted this meta-analysis to summarise their diagnostic and prognostic role in breast cancer.

MATERIALS AND METHODS

Search strategy

Based on the guidelines of the Meta-analysis Of Observational Studies in Epidemiology group and Preferred Reporting Items for Systematic Reviews and Meta-analysis ¹⁰, we searched the Web of Science, EMBASE, PubMed, Cochrane Library and CNKI databases up to 1 August 2020. The searching items were: ('circRNA' or 'circular RNA' or 'has_circ') and ('breast cancer' or 'breast neoplasms' or 'mammary cancer' or 'breast tumour'). To avoid missing documents, we manually screened the reference lists of the retrieved articles.

Eligibility criteria

Eligible articles conformed to the following criteria: (1) The subjects were patients with breast cancer confirmed by histopathological diagnosis and the clinical data were complete; (2) The article evaluated the relationship between circRNA expression and clinicopathological features, diagnosis and prognosis; and (3) It was a case-control study. The exclusion criteria were: (1) The subjects of the study were not human; (2) The publication was not a primary research publication (eg, a review, correspondence, repeated publication, conference summary). (3) There were no data available in the article.

Quality assessment

The quality of primary diagnostic studies was assessed by the QUADAS-2 tool. The QUADAS tool consists of four key domains, including patient selection, index test, reference standard and flow of patients. The answer of risk for bias could be rated as 'no' (0 points), 'yes' (one point) or 'unclear' (0 points).¹¹ The Newcastle-Ottawa Scale was used to evaluate the quality of case-control studies from three aspects: selection, comparability and results.¹² Publications below six points were considered as low quality; high quality was above six points.

Data extraction

Two researchers (FL, HZ) separately evaluated the suitability of all retrieved studies and extracted the relevant data. The two researchers contacted a third researcher (XW) when there was a disagreement. The following data were extracted: (a) Title, first author, ethnicity, year of publication, cancer type, patient size, circRNA signature, follow-up (months); (b) Expression status of circRNA, pooled HRs, detection methods, overall survival (OS) and their corresponding 95% CIs; (c) Sensitivity, specificity and area under the curve (AUC) of circRNAs for diagnosis; (d) Clinical data with age, menopause, tumour size, TNM stage, lymph node metastasis, oestrogen receptor, progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2).

Statistical analysis

HRs and 95% CIs were used to estimate OS. Sensitivity, specificity and AUC were involved in the diagnostic analysis. Clinical parameters were assessed using ORs and 95% CIs. Heterogeneity was assessed by the χ^2 test and I^2 index.

High heterogeneity was judged with an I^2 value $>50\%$. Subgroup and sensitivity analyses were performed to investigate potential sources of heterogeneity when $I^2 >50\%$. Publication bias was evaluated quantitatively using Deek's funnel plot, Begg's tests and Egger's tests. Statistical analyses were performed by Revman V.5.3 and Stata V.15.1 software (Stata Corporation, College Station, Texas, USA).

Patient and public involvement

No patients or the public were involved in the research.

Ethics approval statement

This study did not involve human participants.

RESULTS

Selection of studies

A total of 366 articles were initially obtained from the databases and other sources based on keywords (figure 1). Among these articles, 186 duplicate articles were removed, and 180 articles remained. By looking through titles and abstracts, 65 articles were left for further full-text review. We then reviewed the full texts of these articles carefully and excluded an additional 36 articles. Finally, 29 articles^{13–41} were included in this meta-analysis, including 21 studies for clinicopathological feature,^{15–35} 8 for diagnosis^{13–17} and 26 for prognosis.^{17–41}

Characteristics of included studies and quality assessment

The study characteristics are shown in tables 1–2. A total of 4405 patients with breast cancer from Asia were collected from the 29 included articles. The publication years ranged from 2017 to 2020. The follow-up period varied from 40 months to 200 months. According to their function in breast cancer, 24 circRNAs were recognised as tumour promoters/upregulated and 11 were tumour suppressors/downregulated. With the QUADAS-II criteria, the scores of all diagnostic researches were ≥ 4 (online supplemental figure 1). Assessed by the Newcastle-Ottawa Scale, the points of the prognostic trials were ≥ 6 (table 3). The scores suggested that all of the included articles are of high quality.

Overall survival

The OS was reported in 27 studies. Elevated expression of tumour-suppressor circRNAs was related to a favourable prognosis (HR=0.32, 95% CI 0.23 to 0.44, $p<0.001$) (figure 2). A fixed-effect model was applied because there was low heterogeneity ($I^2=0\%$, $p=0.429$). Conversely, high expression of tumour-promoter circRNAs was associated with an unfavourable prognosis (HR=2.43, 95% CI 2.20 to 2.92, $p<0.001$) (figure 3). There was no significant heterogeneity ($I^2=0\%$, $p=0.791$), so the fixed-effect model was performed for this analysis as well.

Diagnostic analysis

The outcomes of pooled sensitivity and specificity were shown in figure 4. The summary estimates are as follows:

Figure 1 Data acquisition and screening flow chart. circRNA, circular RNA.

specificity, 0.76 (95% CI 0.62 to 0.86) ; sensitivity, 0.75 (95% CI 0.66 to 0.82); negative likelihood ratio, 0.33 (95% CI 0.21 to 0.50); positive likelihood ratio, 3.10 (95% CI 1.80 to 5.60); and overall diagnostic OR, 10.0 (95% CI 4.0 to 26.0). Besides, a summary receiver operator characteristic curve was carried out in [figure 5](#) and AUC was 0.82 (95% CI 0.78 to 0.85). A significant heterogeneity

was detected in the pooled sensitivity ($I^2=86.07\%$) and specificity ($I^2=85.35\%$). To explore the potential source of heterogeneity, we did subgroup analysis according to sample size, year, ethnicity, expression state of circRNA. Finally, sample size was the main source of heterogeneity. As shown in online supplemental figure 2, the heterogeneity was reduced in the pooled sensitivity ($I^2=2.46\%$) and

Table 1 Main characteristics of studies for diagnostic analysis

Study	Year	circRNA signature	Sample size		Detection methods	Expression status	Diagnostic power		
			Case	Control			Sen	Spe	AUC
Zheng <i>et al</i> ¹⁷	2020	circSEPT9	60	60	qRT-PCR	Upregulated	0.750	0.633	0.711
Yi <i>et al</i> ¹⁵	2020	circ-1073	112	112	qRT-PCR	Downregulated	0.924	0.973	0.989
Li <i>et al</i> ¹³	2019	circ-VRK1	350	163	qRT-PCR	Downregulated	0.617	0.791	0.720
Yin <i>et al</i> ¹⁶	2018	hsa_circ_0001785	57	17	qRT-PCR	Upregulated	0.786	0.756	0.771
Yin <i>et al</i> ¹⁶	2018	hsa_circ_0108942	57	17	qRT-PCR	Upregulated	0.815	0.504	0.701
Yin <i>et al</i> ¹⁶	2018	hsa_circ_0068033	57	17	qRT-PCR	Downregulated	0.732	0.578	0.619
Lü <i>et al</i> ¹⁴	2017	hsa_circ_006054	51	51	qRT-PCR	Upregulated	0.650	0.690	0.710
Lü <i>et al</i> ¹⁴	2017	hsa_circ_100219	51	51	qRT-PCR	Upregulated	0.690	0.710	0.780

AUC, area under the receiver operator characteristic curve; circRNA, circular RNA; qRT-PCR, quantitative real-time PCR; sen, sensitivity; spe, specificity.

Table 2 Main characteristics of studies for prognostic analysis

Study	Ethnicity	Year	Sample type	Patient size	circRNA signature	Follow-up (months)	Cancer type	Expression status	Survival	Detection methods
Tang <i>et al</i> ²¹	Asian	2019	Tissue	240	circKIF4A	125	TNBC	Upregulated	OS/DFS	qRT-PCR
Xu <i>et al</i> ²³	Asian	2019	Tissue	107	circTADA2A-E6	100	BC	Downregulated	OS/DFS	qRT-PCR
Xu <i>et al</i> ²³	Asian	2019	Tissue	107	circTADA2A-E5/E6	100	BC	Downregulated	OS/DFS	qRT-PCR
Chen <i>et al</i> ¹⁸	Asian	2018	Tissue	240	circEPST11	125	TNBC	Upregulated	OS/DFS	qRT-PCR
Yang <i>et al</i> ²⁵	Asian	2019	Tissue	57	circ_0103552	60	BC	Upregulated	OS	qRT-PCR
Yang <i>et al</i> ²⁶	Asian	2019	Tissue	80	circAGFG1	160	TNBC	Upregulated	OS	qRT-PCR
Xie <i>et al</i> ²²	Asian	2019	Tissue	51	hsa circ 0004771	100	BC	Upregulated	OS	qRT-PCR
Xu <i>et al</i> ²⁴	Asian	2018	Tissue	76	circ_0005230	60	BC	Upregulated	OS	qRT-PCR
Zeng <i>et al</i> ²⁷	Asian	2018	Tissue	165	circANKS1B	100	TNBC	Upregulated	OS	qRT-PCR
Gao <i>et al</i> ¹⁹	Asian	2018	Tissue	96	hsa_circ_0006528	90	BC	Upregulated	OS	qRT-PCR
Li <i>et al</i> ²⁰	Asian	2019	Tissue	350	Circ-VRK1	350	BC	Downregulated	OS	qRT-PCR
Liu <i>et al</i> ³³	Asian	2019	Tissue	70	circRNA_002178	40	BC	Upregulated	OS	FISH
Xiao <i>et al</i> ²⁸	Asian	2019	Tissue	136	circAHNAK1	125	TNBC	Downregulated	OS/DFS	qRT-PCR
Yan <i>et al</i> ³⁶	Asian	2019	tissue	32	hsa_circ_0072309	140	BC	Downregulated	OS	qRT-PCR
Wang <i>et al</i> ³⁵	Asian	2018	tissue	143	CircZNF609	120	BC	Upregulated	OS	qRT-PCR
Geng <i>et al</i> ³⁰	Asian	2019	tissue	32	circ_0001667	120	BC	Upregulated	OS	qRT-PCR
Zhou <i>et al</i> ³⁸	Asian	2019	tissue	150	circFBXL5	150	BC	Upregulated	OS	qRT-PCR
Cao <i>et al</i> ²⁹	Asian	2020	tissue	50	circRNF20	60	BC	Upregulated	OS	qRT-PCR
Ye <i>et al</i> ³⁷	Asian	2019	tissue	473	circFBXW7	200	TNBC	Downregulated	OS/DFS	qRT-PCR
Liu <i>et al</i> ⁴⁰	Asian	2020	tissue	65	circRNA_103809	60	BC	Downregulated	OS	qRT-PCR
Liu <i>et al</i> ³²	Asian	2020	tissue	222	circGNB1	125	TNBC	Upregulated	OS	qRT-PCR
Liang <i>et al</i> ³¹	Asian	2020	tissue	113	circCDYL	40	BC	Upregulated	OS	qRT-PCR
Zheng <i>et al</i> ¹⁷	Asian	2020	tissue	60	circSEPT9	140	TNBC	Upregulated	OS	qRT-PCR
Song <i>et al</i> ³⁴	Asian	2020	tissue	267	circHMCU	141	BC	Upregulated	OS	qRT-PCR
Xu <i>et al</i> ⁴¹	Asian	2020	tissue	150	circNFIC	160	BC	Downregulated	OS	qRT-PCR
Xing <i>et al</i> ³⁹	Asian	2020	tissue	78	circIFI30	160	TNBC	Upregulated	OS	FISH

circRNA, circular RNA; DFS, disease-free survival; FISH, fluorescence in situ hybridisation; OS, overall survival; qRT-PCR, quantitative real-time PCR; TNBC, triple negative breast cancer.

Table 3 Study quality assessed via the Newcastle-Ottawa Scale checklist

Study	Selection	Comparability	Outcome	Total score
Tang <i>et al</i> ²¹	☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆
Xu <i>et al</i> ²³	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Xu <i>et al</i> ²³	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Chen <i>et al</i> ¹⁸	☆☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Yang <i>et al</i> ²⁵	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Yang <i>et al</i> ²⁶	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Xie <i>et al</i> ²²	☆☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Xu <i>et al</i> ²⁴	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Zeng <i>et al</i> ²⁷	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Gao <i>et al</i> ¹⁹	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Li <i>et al</i> ²⁰	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Liu <i>et al</i> ³³	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Xiao <i>et al</i> ²⁸	☆☆☆	☆☆	☆☆	☆☆☆☆☆☆☆☆
Yan <i>et al</i> ³⁶	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Wang <i>et al</i> ³⁵	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Geng <i>et al</i> ³⁰	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Zhou <i>et al</i> ³⁸	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Cao <i>et al</i> ²⁹	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆
Ye <i>et al</i> ³⁷	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Liu <i>et al</i> ⁴⁰	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Liu <i>et al</i> ³²	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Liang <i>et al</i> ³¹	☆☆☆	☆☆	☆☆	☆☆☆☆☆☆☆☆
Zheng <i>et al</i> ¹⁷	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Song <i>et al</i> ³⁴	☆☆☆	☆☆	☆☆☆	☆☆☆☆☆☆☆☆
Xu <i>et al</i> ⁴¹	☆☆☆	☆☆	☆☆	☆☆☆☆☆☆☆☆
Xing <i>et al</i> ³⁹	☆☆	☆☆	☆☆	☆☆☆☆☆☆☆

Figure 2 Forest plots for overall survival according to the type of tumour-suppressor circular RNA (circRNA).

specificity ($I^2=0.00\%$) after two large sample studies were excluded. The above outcomes suggested that circRNAs might be an ideal diagnostic biomarker for breast cancer.

Clinicopathological association

Twenty-one studies were included to evaluate the relationship between circRNA expression and the clinicopathological features of patients with breast cancer. As presented in [table 4](#), prominent associations were observed. Elevated levels of tumour-promoter circRNAs were associated with adverse clinical outcomes, including tumour size (OR=2.84, 95% CI 2.07 to 3.91, $p<0.001$), TNM stage (OR=2.71, 95% CI 2.00 to 3.67, $p=0.001$), lymph node metastasis (OR=2.75, 95% CI 1.99 to 3.75, $p<0.001$), oestrogen receptor (OR=0.61, 95% CI 0.43 to 0.87, $p=0.006$) and HER2 (OR=0.60, 95% CI 0.39 to 0.93, $p=0.022$). Elevated levels of tumour-suppressor circRNAs were negatively correlated to the clinical features: age (OR=0.66, 95% CI 0.46 to 0.95, $p=0.024$), tumour size (OR=0.54, 95% CI 0.36 to 0.80, $p=0.002$), lymph node metastasis (OR=0.57, 95% CI 0.39 to 0.83, $p=0.004$), TNM

Figure 3 Forest plots for overall survival according to the type of oncogenic circular RNA (circRNA).

stage (OR=0.63, 95% CI 0.45 to 0.90, $p=0.011$) and HER2 (OR=0.50, 95% CI 0.28 to 0.89, $p=0.019$). No significant associations were found in terms of menopause or PR ($p>0.05$).

Publication bias

Judged by Deeks' funnel plot, there was no evidence of publication bias ($p=0.66$) in the diagnostic analysis (online supplemental figure 3). Begg's funnel plot (online supplemental figure 4, $p=0.983$) and Egger's test (online supplemental figure 5, $p=0.937$) indicated that there was no clear publication bias in the analysis

Figure 4 Forest plot of sensitivity and specificity of circular RNAs (circRNAs) for the diagnosis of breast cancer.

Figure 5 The summary receiver operator characteristic (SROC) curve. AUC, area under the ROC curve; ROC, receiver operator characteristic.

of circRNAs in terms of OS. These outcomes indicated that circRNAs are likely to be a favourable diagnostic and prognostic biomarker for breast cancer.

DISCUSSION

Up to now, plenty of predictors have been found and applied in the diagnosis and prognosis of breast cancer, including oestrogen receptor, HER2, BRCA and miRNA. Recently, circRNAs have been widely recommended due to their high conservation, high stability, high expression and specificity.^{5 6} CircRNA is recognised as a novel biomarker which has the potential to play a significant role in the development of breast cancer. For instance, Huang *et al*¹² and Huang *et al*¹³ have summarised that circRNAs may act as important biomarkers for diagnosis and prognosis in lung cancer and osteosarcoma, respectively, by meta-analysis. Research into the role of circRNAs in breast cancer is increasing, but the clinical value of circRNAs is debatable. Current research discovered that circRNAs correlated with small tumour size, longer survival time and acted as antioncogenes in breast cancer. Whereas, more research proved that circRNAs might function as a vital oncogene for breast cancer.¹⁻⁹ Based on clinical research, we conducted this meta-analysis to summarise the diagnostic and prognostic role of circRNA in breast cancer.

A total of 29 articles with 4405 patients with breast cancer in Asia were included in this study. According to circRNAs' function in breast cancer, we divided circRNAs into two groups. Some circRNAs such as circEPSTI1 were markedly upregulated in breast cancer and were considered as tumour-promoter circRNAs (tables 1-2). It is

Table 4 Clinical characteristics of circRNAs in breast cancer

	Tumour suppressor			Tumour promoter		
	OR	95% CI	P value	OR	95% CI	P value
Age (>50/≤50) (years)	0.66	0.46 to 0.95	0.024	1.09	0.82 to 1.44	0.543
Menopause (Y/N)	0.87	0.52 to 1.46	0.612	1.14	0.87 to 1.51	0.335
Tumour size (>2cm vs ≤2 cm)	0.54	0.36 to 0.80	0.002	2.84	2.07 to 3.91	0.000
TNM stage (III+IV/I+II)	0.63	0.45 to 0.90	0.011	2.71	2.00 to 3.67	0.000
Lymph node metastasis (Y/N)	0.57	0.39 to 0.83	0.004	2.75	1.99 to 3.75	0.001
Oestrogen receptor (positive/negative)	1.54	0.86 to 2.77	0.149	0.61	0.43 to 0.87	0.006
PR (positive/negative)	1.09	0.62 to 1.90	0.760	0.89	0.63 to 1.26	0.517
HER-2 (positive/negative)	0.50	0.28 to 0.89	0.019	0.60	0.39 to 0.93	0.022

The results are in bold if $p < 0.05$.

circRNA, circular RNA; HER-2, human epidermal growth factor receptor-2; N, no; PR, progesterone receptor; Y, yes.

interesting that in breast cancer, no matter whether it is upregulation or downregulation, different biomarkers have the same effect through various mechanisms. For example, circSEPT9 is able to regulate expression of the leukaemia inhibitory factor (LIF) via sponging miR-637 and activating the LIF/Stat3 signalling pathway involved in progression of triple negative breast cancer (TNBC),¹⁷ besides, circEPSTI1 binds to miR-4753 and miR-6809 as a miRNA sponge to regulate BCL11A expression and affect TNBC proliferation and apoptosis.¹⁸ Opposite to this, the others were identified as tumour-suppressor circRNAs when circRNAs were downregulated in breast cancer (tables 1–2); hsa_circ_0068033 exerts biological functions by sponging miR-659,¹⁶ but circAHNAK1 acted as a miR-421 competitive endogenous RNA to attenuate the inhibitory effect of miR-421 on its target gene RAS1.²⁸ In pooled analysis, high expression levels of oncogenic circRNAs were significantly associated with poor prognoses, whereas, evaluated tumour-suppressor circRNAs predicted favourable OS. Moreover, our study showed an AUC of 0.82, with 75% sensitivity and 76% specificity, suggesting that circRNAs are good diagnostic markers for breast cancer. In terms of clinical features, evaluated oncogenic circRNA was also significantly related to bigger size of the tumour, higher rates of lymph node metastasis and higher TNM stage. Antioncogenic circRNA was opposite (table 4).

Despite the promising data, there are some limitations to our study. First, all the patients in our study were selected from an Asian population. Patients from other regions, such as Europe, were not included. The results of this study should be interpreted with caution. Second, the sample size in this study was small and more high-quality clinical studies are needed.

CONCLUSION

Dysregulated expression of circRNA was related to diagnosis and prognosis in breast cancer, which indicated it

might be a novel biomarker and target of therapy for breast cancer.

Contributors Methodology: FL; XW; HZ. Formal analysis and investigation: FL; XW. Writing—original draft preparation: FL; XW. Writing—review and editing: FW. Funding acquisition: FW. Resources: FW. Supervision: HZ. HZ is the paper's guarantor.

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