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Current evidence on circRNAs as potential theranostic markers for detecting chemoresistance in breast cancer: a systematic review and meta-analysis

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This study assessed the value of circRNAs (circular RNAs) as prognostic markers in BC (breast cancer). We searched pertinent studies on the PubMed, Embase, and Web of Science online databases published according to PRISMA guidelines. A random-effects model for meta-analysis was used to assess the combined effect size of the HRs (hazard ratios) of the included studies. The heterogeneity test used Cochran's *Q*-test and I^2 statistics. Thirty of the 520 trials retrieved were included in the systematic review. A total of 11 chemotherapeutic agents were used in the included studies. A total of 30 studies on 30 circRNAs were included in the systematic review. Of the 30 relevant circRNAs, 28 were upregulated and two were downregulated in breast cancer versus normal samples, and both were associated with increased drug resistance. Nine of 30 studies were used for the meta-analysis. The results of the meta-analysis showed that the groups with circRNA upregulation and circRNA downregulation showed the same prognostic risk (HR = 1.37, 95% CI: 0.80–2.36, I^2 = 63.7%). The results of subgroup analysis showed that both upregulated circRNAs (HR = 2.24, 95% CI: 1.34–3.75, I^2 = 0%) and downregulated circRNAs (HR = 0.61, 95% CI: 0.45–0.83, I^2 = 0%) were associated with poor BC prognosis. Collectively, the results of all relevant articles collected indicated that circRNAs showed good potential as possible clinical biomarkers of chemoresistance in BC patients.

Abbreviations

CircRNAs	Circular RNAs
BC	Breast cancer
CI	Confidence interval
HR	Hazard ratio
PRISMA	Preferred items for systematic reviews and meta-analyses
RT-PCR	Real-time reverse transcription-polymerase chain reaction
MiRNA	MicroRNA
OS	Overall survival

Currently, the incidence of BC ranks second-highest among that of cancers worldwide, with 2,261,419 cases every year[1]. The incidence of BC is increasing year by year, and the age of onset is decreasing. Exploring new molecular markers of BC is beneficial for predicting prognosis accurately and monitoring curative effects. Therefore, finding an effective, rapid, noninvasive and specific marker is urgent and is crucial for the diagnosis, prognosis evaluation and drug resistance evaluation of BC[2,3].

The choice of drugs for BC patients varies according to individual circumstances[4]. To date, the main treatments for BC are surgery, radiotherapy and chemotherapy[5]. Chemotherapy is a standard method for BC treatment[6]. There are many commonly used chemotherapy drugs for BC, including anthracyclines (doxorubicin, epirubicin, doxorubicin liposomes, etc.), paclitaxel drugs (paclitaxel, docetaxel, paclitaxel liposomes, and nab-paclitaxel) and fluorouracil (5-FU, capecitabine). In addition, there are targeted drugs such as trastuzumab and

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pertuzumab[7,8] for BC. However, patients are developing resistance to conventional drugs. Chemotherapy resistance is one of the main reasons for clinical treatment failure and poor prognosis in BC patients[9]. This resistance might be due to alterations in several main regulatory pathways, such as *PI3K/AKT*[10–12]. Recently, some studies have found that certain circRNAs are strongly associated with resistance to a number of anticancer drugs, ranging from traditional chemotherapy drugs to targeted and immunotherapy drugs[13–17].

CircRNAs are endogenous RNAs characterized by a covalent ring structure. Compared with other RNAs, circRNAs are less abundant, but circRNAs exhibit the advantage of high tissue specificity[18]. Recently, many researchers have indicated that certain circRNAs in different tumors might play essential roles in tumor cell proliferation, metastasis and drug resistance[19]. Several studies have suggested that circRNAs affect the development of drug resistance and prognosis of BC patients. Upregulated or downregulated circRNAs are involved in tumor growth and drug resistance, affecting the prognosis of breast cancer patients. Liang et al. showed that circKDM4C could inhibit BC proliferation and doxorubicin resistance in vitro, and this circRNA is a tumor suppressor in BC[20]. Wang et al. found that miR-142 regulated the *WWP1* and *PI3K/AKT* genes[10]. Circ-WAC could act as a sponge for miR-142 and decrease the inhibitory effect of miR-142 on its target *WWP1*. In addition, if triple-negative breast cancer patients expressed a high level of miR-142, their overall survival time was longer than that of other patients with low miR-142 expression. Additionally, Yang et al. showed that circ-CDR1as was involved in breast carcinogenesis and sensitivity to cisplatin in vivo. Knockdown of circ-CDR1as might increase the sensitivity of drug-resistant BC cells by reducing REGγ expression by eliminating the competition of miR-7[21]. Some articles have reported an association between changes in circRNAs and changes in drug resistance status in BC[11,20–32]. However, no article has summarized the specific mechanisms and modalities of circRNAs involved in BC drug resistance.

In the related meta-analysis, the involvement of circRNAs in BC was included, and we investigated the undiscovered prognostic value of circRNAs in BC. Several studies found that the expression of certain circRNAs was associated with increased drug resistance and a poor prognosis in BC patients[10,22,23,32]. Preclinical and clinical observational studies have shown that circRNA expression profiles can help identify patients at possible high risk for chemotherapy-resistant BC[11,33]. Therefore, we attempted to conduct a comprehensive systematic review and meta-analysis of published studies on circRNA-mediated chemoresistance in BC.

Materials and methods

Registration. We have registered the protocol on PROSPERO. Our registration number is CRD42022295180.

Data search strategy. We searched all relevant articles through the PubMed, Embase, and Web of Science online databases that were published before 13 October 2022. The following entry words were used: (1) "Breast Neoplasms" or "Breast Cancer" or "BC." (2) "RNA, Circular" or "circRNAs" or "hsa circ"; (3) "Resistance, Drug" or "Drug resistance" or "chemoresistance.". The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct search strategies.

Inclusion and exclusion criteria. The selection criteria for inclusion in the literature were as follows: (1) studies that involved the effect of circRNAs on drug resistance or drug sensitivity in BC; (2) studies that collected clinical samples or involved in vitro preclinical analysis; and (3) studies that involved the effect of circRNA on the prognosis of BC. The criteria for exclusion were as follows: (1) duplicate studies; (2) reviews, editorials, opinions, case studies, and reports; unpublished materials, uninterpretable data, conference proceedings, or theses; (3) articles without complete information; (3) studies that did not indicate whether circRNA expression was upregulated or downregulated; (4) studies that did not include specific drug resistance changes; and (5) studies in languages other than English.

Data extraction. Two researchers (Z.Z. and H.J.) extracted the data independently. When necessary, divergences were resolved by a third investigator (J.X.). The extracted information was as follows: (1) first author, publication year, circRNA, number of patients, detection methods for circRNAs, HR, CI; (2) follow-up time and outcomes; and (3) clinicopathological features, including TNM stage and T classification. When the results were not directly shown in the articles for HRs and 95% CIs, survival data were extracted from Kaplan−Meier plots using Engauge Digitizer 4.1 software. The Excel program file of Tierney et al[34]. was then be used to calculate the HRs and 95% CIs.

Quality assessment. Two independent investigators (Z.Z. and H.J.) used the Newcastle Ottawa Scale (NOS) to assess the quality of the articles for meta-analysis. If one study had a total score of > 6 points, it was considered high quality. When necessary, divergences were resolved by a third investigator (J.X.).

Statistical analysis. Statistical analysis was performed using Stata 15.0. Data in the form of Kaplan−Meier survival curves were converted to HRs and 95% CIs. Pooled outcome data were generated for forest plots to assess the prognostic value of circRNAs in BC. Heterogeneity tests were obtained by Cochran's Q test and Higgins I^2. According to the rule, a random-effects model was used to generate pooled results if the I^2 value was > 50%, and a fixed-effects model was used if the I^2 value was < = 50%. A p value < 0.05 was used to determine statistical significance.

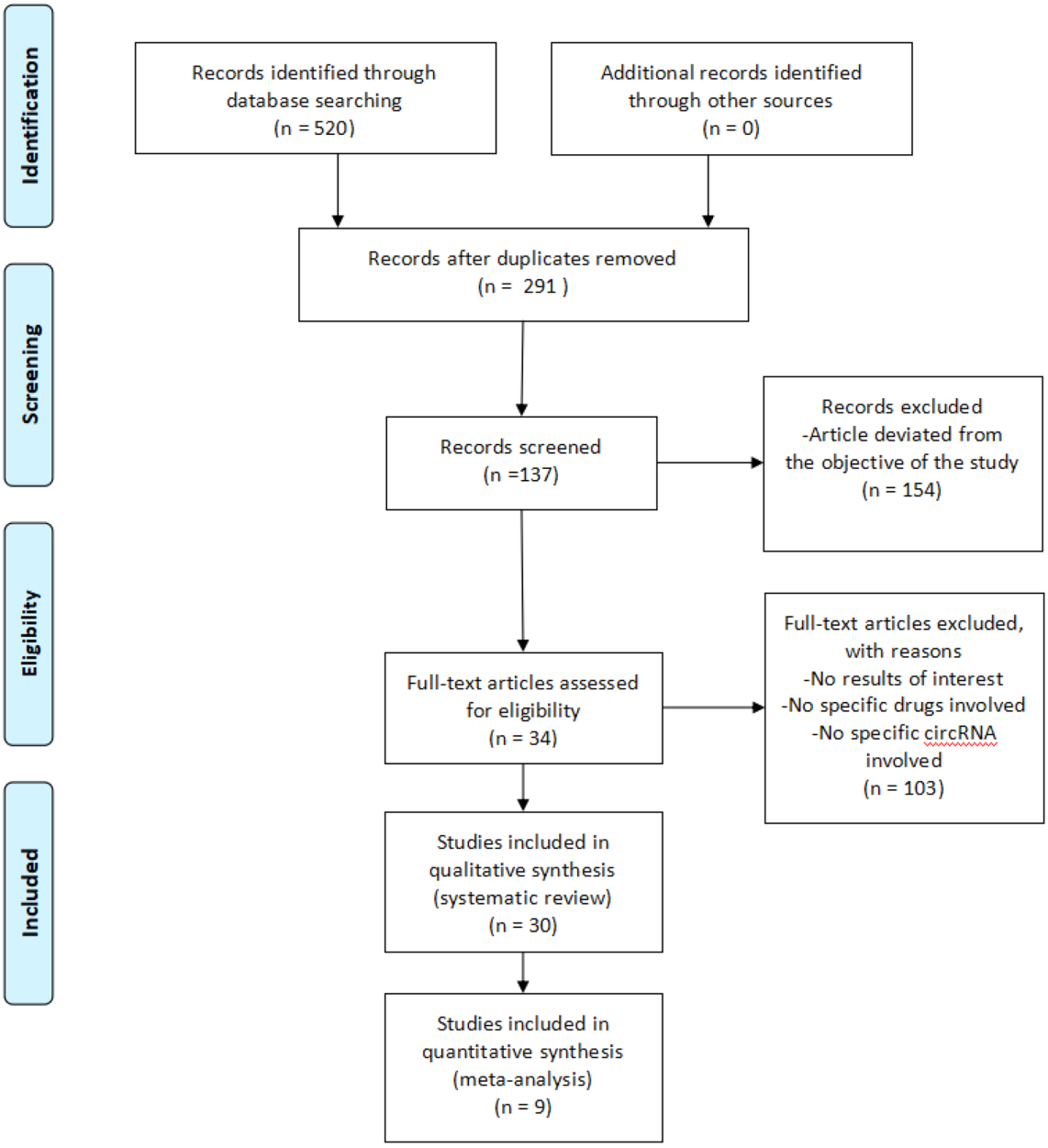

Figure 1. Flowchart of trial selection.

Results

Selection of studies. Figure 1 shows a flowchart for study selection. Through the search strategy, 520 articles were identified from PubMed, Embase, and Web of Science. After deduplication, screening criteria were used to review 291 potentially eligible studies. A careful selection of 137 articles was made by finalizing 34 full-text studies with available information according to PRISMA guidelines. Of these 34 articles, four studies were excluded since they were about other cancers. After multistep screening, the remaining 30 articles were used for systematic reviews[10–12,20–32,35–47], of which nine were used for meta-analysis.

Study characteristics and quality assessment. All included studies were collected until 13 October 2022 (the details of the description of the 30 included studies are shown in supplemental appendix 1). The 11 chemotherapy drugs used in the studies included 5-FU, lapatinib, adriamycin, doxorubicin, paclitaxel, cisplatin, monastrol, tamoxifen, docetaxel, trastuzumab, and oxaliplatin. Of these, paclitaxel is the most commonly used chemotherapeutic agent in clinical practice, while lapatinib and oxaliplatin are the least used. A total of 2077 BC tissue samples were included in the analysis. Seven of 30 studies documented clinical stage, including 187 in stage I, 464 in stage II, and 211 in stage III. Thirty studies used reverse transcription-polymerase chain reaction (RT−qPCR) to detect circRNA, and only one study used the raw sequencing reads. Nine studies with survival curves were included in the meta-analysis, containing a total of 1962 individuals.

Downregulated			Upregulated		
Drug	CircRNA	Pathway or associated protein/axis	Drug	CircRNA	Pathway or associated protein/axis
Doxorubicin	circ-LARP4	miR-761/p53, p21	5-FU	circ-CDR1as	CCNE1
	circ-KDM4C	miR-548p/PBLD axis		circ-FBXL5	HMGA2
			Lapatinib	circ-MMP11	miR-153-3p/Anillin axis
			Adriamycin	circ-0006528	MAPK and PI3K/AKT
				circ-0001667	NCOA3
				circ-0006528	miR-1236-3p/CHD4 axis
				circ-0085495	miR-873-5p/integrinβ1 axis
				circ-0044556	miR-145/NRAS axis
			Doxorubicin	circ-UBE2D2	miR-512-3p/CDCA3 axis
				circ-0092276	miR-348/ATG7 axis
			Paclitaxel	circ-RNF111	E2F3
				circ-ABCB10	Let-7a-5p/DUSP7 axis
				circ-WAC	WWP1, PI3K/AKT
				circ-HIPK3	HK2
				circ-AMOTL1	AKT
				circ-0006528	miR-1299/CDK8 axis
			Cisplatin	circ-CDR1as	miR-7/REGγ
				circUBAP2	miR-300/ASF1B axis chaperone/PI3K/AKT/mTOR axis
			Monastrol	circ-MTO1	TRAF4/Eg5 axis
			Tamoxifen	circ-0025202	miR-197-3p/HIPK3 axis
				circTRIM28	miR-409-3p/HMGA2 axis
				circMET	miR-204/AHR
				circ-0097922	miR-876-3p/ACTN4 axis
				circ-0025202	miR-182-5p/FOXO3a Axis
			Docetaxel	circ-EPHA3.1/circ-EPHA3.2/circ-ABCB1	PI3K-AKT/AGE-RAGE
			Trastuzumab	circCDYL2	HER2
				circ-0001598	miR-1184/PD-L1
			Oxaliplatin	circFAT1	miR-525-5p/SKA1 axis

Table 1. Genetic pathways, proteins or axes involved in BC drug resistance.

Preclinical and clinical investigation of circRNA expression. A total of 17 different cell lines were used in 30 studies to explore circRNA expression and its association with drug resistance and associated pathways or proteins/axes. MCF-7 was the most commonly used cell line, while the U343 and U251 cell lines were the least commonly used. The experimental methods used in these studies include western blot, transfection and vector construction, flow cytometry, Transwell, ELISA, cytotoxicity assay, dual-luciferase reporter assay, RNA pull-down, RIP assay, IHC assay, RNase R treatment assay, 5-ethynyl-2′-deoxyuridine (EdU) assay, fluorescence in situ hybridization (FISH) assay, exosome tracing and blockade of exosome secretion.

After excluding duplicate circRNAs, our systematic review included a total of 30 different circRNAs, 28 of which were associated with increased drug resistance and a poor prognosis in breast cancer patients when their expression was upregulated, while only 2 were associated with increased drug resistance and a poor prognosis in breast cancer patients when their expression was downregulated.

BC chemoresistance and drug-regulated genetic pathways. In these 30 studies, a total of 32 circRNAs were reported, and excluding duplicate circRNAs, a total of 30 circRNAs were reported, and these circRNAs led to resistance to 11 drugs through 28 pathways or associated proteins/axes. (Table 1).

Findings of prognosis analysis. Nine circRNAs were used for meta-analysis. Seven circRNAs were upregulated, and two were downregulated (Table 2 demonstrates details of prognostic research). The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included research (Table 3). The results showed that they all qualified for meta-analysis. The results of the meta-analysis showed that both the upregulated and downregulated groups were at risk for poor prognosis (HR = 1.37, 95% Cl: 0.80–2.36, $I^2 = 63.7\%$). There was significant heterogeneity between the studies. Therefore, we classified all circRNAs into "enhanced resistance"-related circRNAs and "attenuated resistance"-related circRNAs according to the expression of circRNAs. Subgroup analysis was performed according to the upregulation or downregulation of circRNAs. Interestingly, the heterogeneity was significantly reduced after performing a subgroup analysis (Fig. 2), which suggested that circRNAs could be used to determine the prognosis of BC patients (upregulated circRNAs (HR = 2.24, 95% Cl: 1.34–3.75, $I^2 = 0\%$)

Author	Year	Country	CircRNA	Cancer type	High	Low	Methods	Regulation	follow up (month)	HR	CI
Wu et al.[22]	2021	China	circ-MMP11	BC	27	21	RT−qPCR	Upregulated	60	2.43	0.79–7.49
Dou et al.[23]	2020	China	circ-UBE2D2	BC	33	33	RT−qPCR	Upregulated	60	2.39	0.9–6.32
Wang et al.[26]	2021	China	circ-WAC	BC	45	45	RT−qPCR	Upregulated	80	2.44	0.57–10.5
Hao et al.[10]	2021	China	circ-0006528	BC	32	31	RT−qPCR	Upregulated	60	2.46	0.47–12.5
Zhang et al.[20]	2020	China	circ-LARP4	BC	142	141	RT−qPCR	Downregulated	60	0.51	0.22–1.15
Liang et al.[32]	2019	China	circ-KDM4C	BC	474	587	RT−qPCR	Downregulated	150	0.65	0.41–1.03
Yang et al.[40]	2022	China	circTRIM28	BC	32	32	RT−qPCR	Upregulated	60	1.84	0.15–5.18
Ling et al.[43]	2022	China	circMET	BC	64	63	RT−qPCR	Upregulated	120	1.74	0.35–8.67
Huang et al.[47]	2022	China	circ-0025202	BC	50	50	RT−qPCR	Upregulated	80	2.34	0.57–9.51

Table 2. Basic features of studies for prognostic analysis.

Author/Year	①	②	③	④	⑤	⑥	⑥	⑧	Total points
Wu et al. 2021[22]	1	1	1	1	1	1	1	0	7
Dou et al. 2021[23]	1	1	1	1	1	1	1	0	7
Zhang et al. 2019[26]	1	1	1	1	1	1	1	1	8
Wang et al. 2021[10]	1	1	1	1	1	1	1	0	7
Liang et al.2019[20]	1	1	1	1	1	1	1	1	8
Hao et al. 2021[32]	1	1	1	1	1	1	1	0	7
Yang et al.2022[40]	1	1	1	1	1	1	1	1	8
Ling et al.2022[43]	1	1	1	1	1	1	1	1	8
Huang et al.2022[47]	1	1	1	1	1	1	1	1	8

Table 3. Quality assessment of included studies using the Newcastle Ottawa Scale checklist. ① Adequacy of case definition ② Number of cases ③ Representativeness of the cases ④ Ascertainment of relevant cancers ⑤ Ascertainment of detection method ⑥ CircRNA expression ⑦ Assessment of outcome ⑧ Adequate follow-up.

and downregulated circRNAs (HR = 0.61, 95% Cl: 0.45–0.83, $I^2 = 0\%$) were associated with poor BC prognosis.). All four circRNAs in the upregulated group were highly expressed in tumor tissues, and they affected gene pathways that promoted drug resistance in breast cancer cells, while the two circRNAs in the downregulated group were expressed at low levels in tumor tissues and affected gene pathways that inhibited proliferation, metastasis and drug resistance in breast cancer cells.

Sensitivity analysis and publication bias. We also performed a sensitivity analysis for OS. No significant changes were observed compared to previous results after each study was removed (Fig. 3). In addition, we used funnel plots to assess publication bias. Each dot represents one study. Nine studies fell within the 95% confidence interval. The reason for the poor symmetry may be due to the inconsistent effect of circRNAs in the upregulated and downregulated groups (Fig. 4). Finally, we performed Begg's test, which showed $P = 0.004$ (< 0.05), and Egger's test suggested publication bias, which may be because far more circRNAs were upregulated than downregulated among the nine circRNAs (Fig. 5).

Discussion

Studies have shown that abnormal circRNA expression is important in tumor cell proliferation, metastasis and cancer recurrence in BC patients[10–12,20–32,35–39]. Many studies have also confirmed that several specific circRNAs are consistently expressed in human tissues and blood. Therefore, circRNAs have the chance to be excellent biomarkers for BC diagnosis, prognosis and drug resistance assessment[3,33,48,49].

Some studies have concentrated on the effects of circRNAs on chemoresistance in breast, cervical[50], colorectal[51,52], gastric[53,54], lung[55], oral[56], ovarian[57], pancreatic[58] and prostate[59] cancers. In this study, we collected relevant articles before 25 October 2021 and conducted a systematic review and meta-analysis, hoping to find clues about the value of circRNAs as biomarkers for BC prognosis. In the systematic review, studies incorporating 30 circRNAs, including 28 upregulated circRNAs and two downregulated circRNAs, were included. Most studies investigated only one circRNA, while only one study focused on more than one circRNA[12]. Our systematic

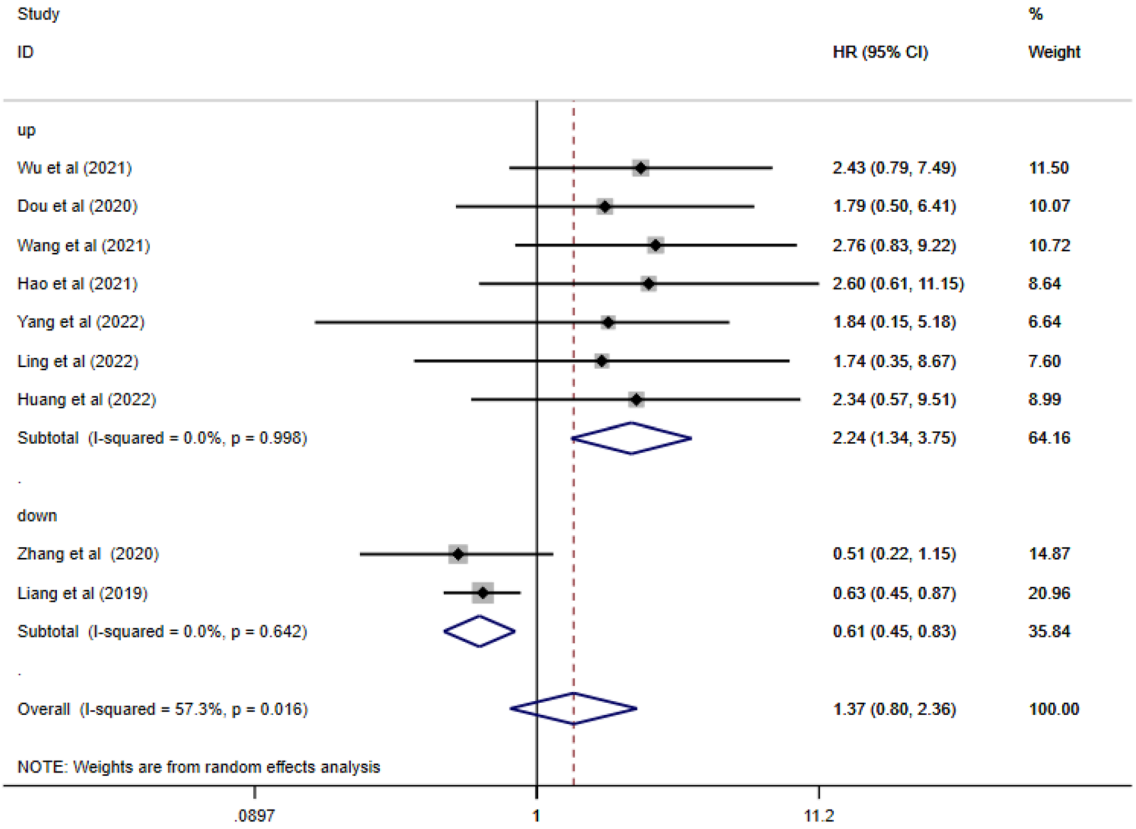

Figure 2. Pooled HRs for the overall survival of patients in the included studies.

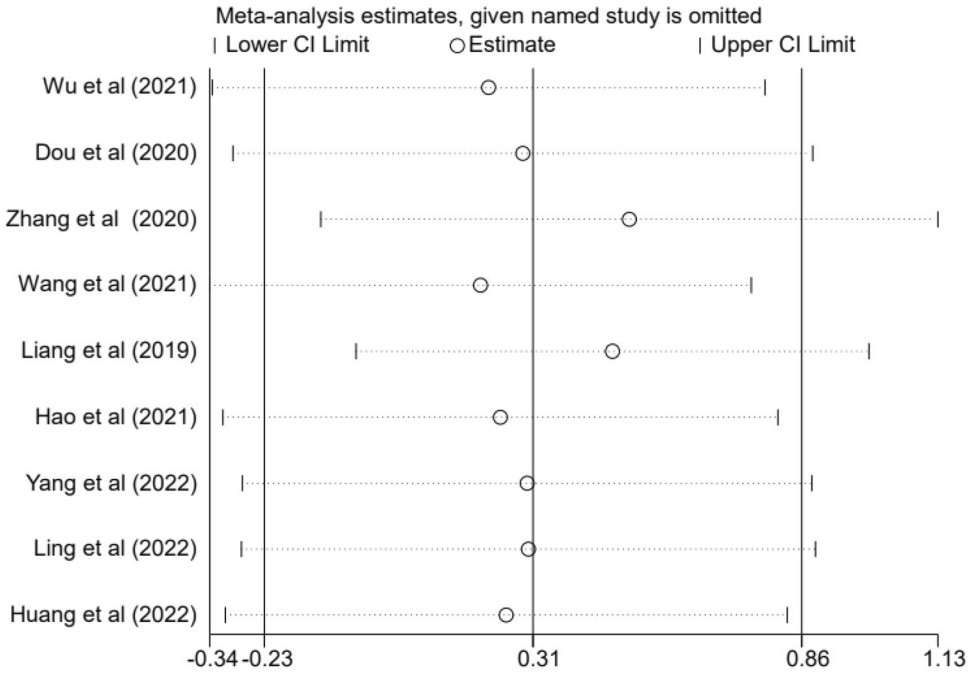

Figure 3. Sensitivity analysis for the involved studies.

review focused on pharmacological modulation pathways, including *MAPK, PI3K/AKT*, *AKT* and *AGE-RAGE,* in BC chemotherapy resistance and sensitivity.

Several studies have shown that target genes of upregulated circ-00006528 play a role in the *MAPK* and *PI3K/AKT* gene pathways. Further validation showed that the expression of circ-0006528 showed a negative correlation

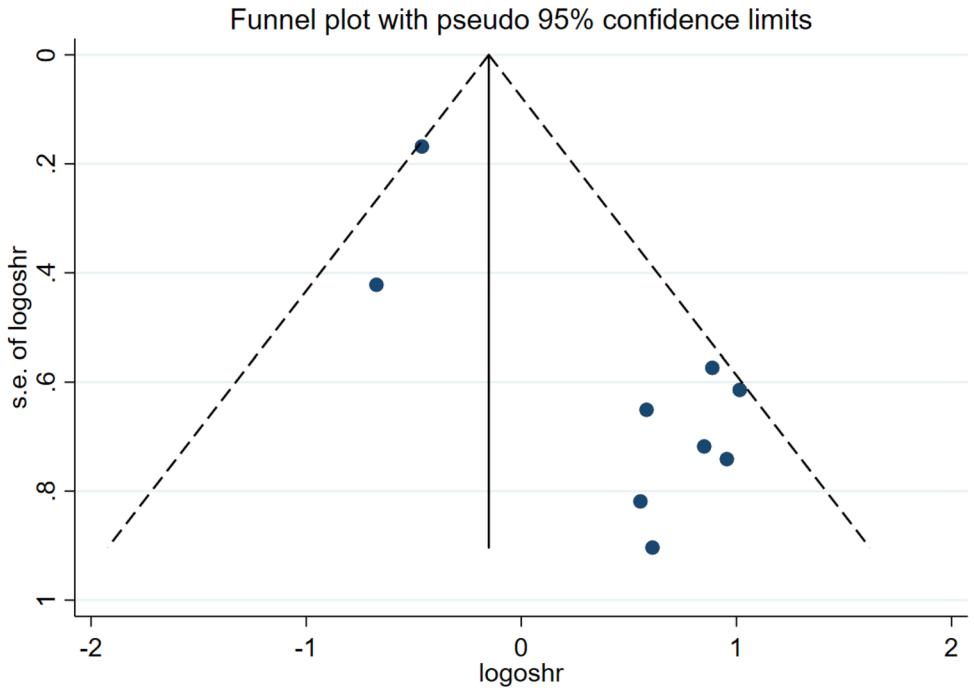

Figure 4. Funnel plot of publication bias related to the association between the expression of circRNAs and the prognosis of patients with BC.

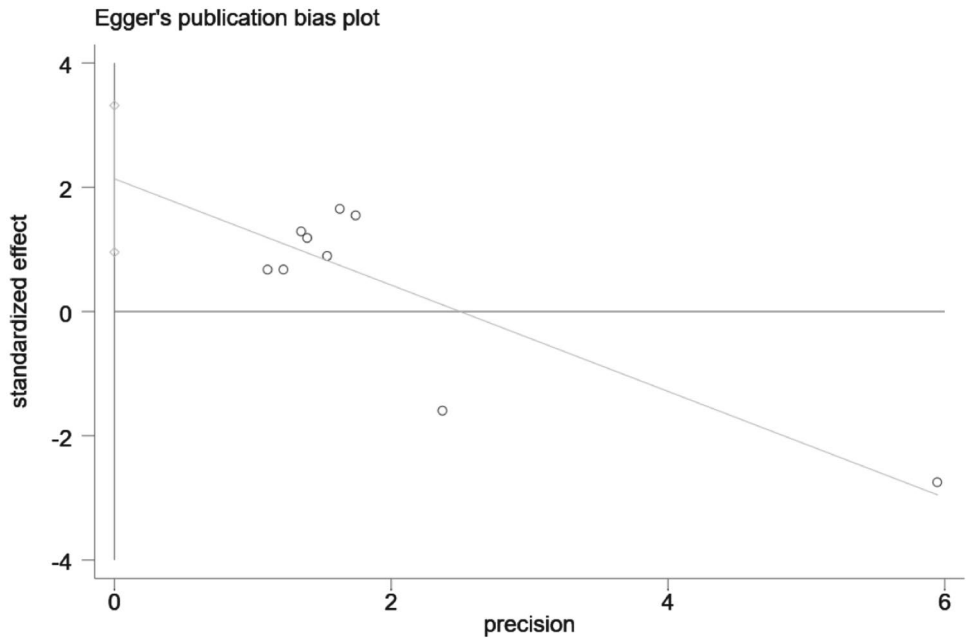

Figure 5. Egger's test for publication bias.

with miR-7-5p in adriamycin resistance. Another study showed a significant increase in both phosphorylated and total *AKT* protein in some circ-AMOTL1-overexpressing cells, suggesting that *AKT* might be a key factor in adjusting the resistance effect. Thus, circ-AMOTL1 affected the expression of proapoptotic (*BAX* and *BAK*) and antiapoptotic (BCL-2) factors associated with *AKT*[59]. This suggested that circ-AMOTL1 might be important in paclitaxel resistance in BC cells by affecting the *AKT* pathway, promoting antiapoptotic proteins and inhibiting proapoptotic proteins. In addition, data from a study showed that circ-ABCB1, circ-cEPHA3.1 and circ-EPHA3.2 might sponge several significantly expressed miRNAs related to drug resistance through the *PI3K-AKT* and AGE signaling pathways and lead to doxorubicin resistance[59]. They also found that the expression of RNA molecules

transcribed from this region might be due to DNA amplification in doxorubicin-treated cells. These results are beneficial for subsequent research on the mechanisms of drug resistance in BC.

Nine circRNAs related to prognosis were included in the meta-analysis and were critical to the development of drug resistance. Among them, seven were upregulated (circ-MMP11, circ-WAC, circ-UBE2D2, circ-0006528, circTRIM28, circCDYL2, circ-0001598), and two were downregulated (circ-LARP4, circ-KDM4C). Certain cancer-related genes could increase susceptibility to breast cancer, leading to poorer survival rates. In our analysis, the results showed that the overall HR (95% CI) of upregulated circRNAs was 2.24 (1.34, 3.75), and that of downregulated circRNAs was 0.61 (0.45, 0.83), suggesting that both upregulated circRNAs and downregulated circRNAs could predict poorer cancer prognosis. It is worth noting that if circRNAs could be used as prognostic biomarkers of breast cancer, their clinical application prospects would be very broad. Other typical clinical indicators of tumor status are susceptible to change, but the expression of circRNAs is stable[60]. Steps should be taken to comprehensively assess the role of circRNAs as biomarkers for BC prognosis and drug-resistance assessment.

Some shortcomings must be acknowledged. First, in our study, all of the samples we collected were from Asian populations. Samples collected from a single source may not be able to distinguish between regional and racial differences and ethnic differences. Second, the method used to detect circRNAs was RT−PCR, except for one study that used raw sequencing reads. The relative homogeneity of the methods used to detect circRNAs may affect the value of the assay results. Third, the meta-analysis involved a relatively small sample size and was limited by the number of available articles. In addition, the number of studies included in the meta-analysis was so low that the results of publication bias using funnel plots may not be meaningful.

Overall, circRNAs, as stably expressed molecules, are expected to be biomarkers for breast cancer prognosis. The relationship between circRNA expression and breast cancer features needs to be further investigated, and the practical value of circRNAs in evaluation BC drug resistance and prognosis needs to be further explored.

Conclusion

Currently available evidence suggests that circRNAs might be considered potential prognostic biomarkers for BC patients and that there is a significant association between the expression of circRNAs and the prognosis of breast cancer patients. We anticipate that our findings might contribute to BC treatment.

Data availability

Data are available in a public, open access repository. The corresponding author of this paper can provide relevant information supporting the conclusions of this study if needed.

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Author contributions

Z.Z. and H.J. had complete authority over all data in the study, and They ensured the integrity of the article and the quality of the data in each section. J.L. and B.L. proposed this research idea. Z.Z. and H are writing the manuscript. J.X. was responsible for data interpretation. X.J. provides administrative, technical, and logistical support.

Competing interests

The authors declare no competing interests.

Additional information

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