REVIEW ARTICLE

Diagnostic value of circular RNAs as promising hematological biomarkers in acute myeloid leukemia: A systematic review and meta-analysis

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Despite significant advancements in the diagnosis and treatment of acute myeloid leukemia (AML), patients still face poor diagnosis with unsatisfactory survival, so it is imperative to explore novel diagnostic biomarkers to improve early detection and treatment outcomes. Thus, here, the potential role of circular RNAs (circRNAs) in AML diagnosis is reviewed. PubMed, Scopus, WOS, ProQuest databases, and Google Scholar search engines were searched for studies published through March 2023. The results were assessed using the modified method of GRADE assessment. The sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (AUC) were combined to investigate the diagnostic role of circRNAs in AML. The number of studies included in this systematic review and meta-analysis was 18. For the diagnostic value of circRNAs in AML, the pooled SEN, SPE, PLR, and NLR were 0.85 (95% confidence interval [CI]: 0.80–0.89), 0.85 (95% CI: 0.82–0.88), 5.74 (95% CI: 4.49–7.33), and 0.18 (95% CI: 0.13–0.24), respectively. Furthermore, the pooled DOR and AUC were 32.71 (95% CI: 20.09–53.24) and 0.91 (95% CI: 0.88–0.93), respectively. Furthermore, through subgroup analysis, it is better to have a sample size above 120 and a control/patient ratio above 50%. In addition, Deek's funnel plot demonstrated nonconsiderable publication bias (P = 0.65). Finally, according to the GRADE assessment for diagnostic tests, the certainty of evidence regarding sensitivity and specificity was moderate. Our systematic review and meta-analysis suggest the analysis of circRNAs expression as promising and valuable biomarkers related to the diagnosis of AML and also can be helpful in the diagnosis of AML patients as a noninvasive and low-cost method.

Key words: Acute myeloid leukemia, circular RNA, diagnose, meta-analysis, noncoding RNAs, systematic review

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INTRODUCTION

Hematological malignancies happen when cells in the lymphatic system and bone marrow change into cancerous cells. The prevalence of acute myeloid leukemia (AML) is high, and it has some characteristics such as high and abnormal proliferation and incomplete differentiation of myeloid cells, which leads to clonal and abnormal accumulation of blast cells in the bone marrow, peripheral blood, and rarely in organs. Genetic heterogeneity is an essential point in AML,[1] and the prevalence of AML is higher in the elderly compared to the young.[2,3] AML diagnosis is done by different methods, including observing chromosomal abnormalities in karyotype analysis, observing extramedullary tissue infiltrate, as well as with the help of flow cytometry, antibodies, immunophenotyping, the presence of ≥20% of blasts in the peripheral blood

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or bone marrow, or checking myeloperoxidase activity to determine the myeloid origin of the blasts. Despite the progress that has been made to treat AML, in most cases, recurrence and death of patients also occur.[4]

High-throughput sequencing data prove that about 98% of the human genome is made up of noncoding DNA sequences. The majority of the whole human transcriptome remains untranslated and is called noncoding RNAs,[5] and they have a covalently closed loop structure due to the phosphodiester bond between the 3′ and 5′ ends. Due to lack of 3′ polyadenyl tail and 5′ cap, circular RNAs (circRNAs) are conserved from ribonuclease (RNase) activity, so they are more stable than linear messenger RNAs. CircRNAs have various functions in the intracellular process and can have tumor suppressor or oncogene roles, which exert this effect directly or indirectly on the transcription and expression of genes involved in tumorigenesis, metastasis, drug resistance, etc.[6,7] For example, sponging circRNAs with various microRNAs alters microRNA-mediated gene expression or sponging with proteins such as RNA-binding proteins (RBPs) affects their functions.[6] In addition, the role of circRNAs in the pathogenesis and progression of hematopoietic abnormalities and the importance of aberrant expression of numerous circRNAs in leukemogenesis have been proven by various investigations.[5] Furthermore, various studies have proven the role of circRNAs in the diagnosis of AML. For example, Li *et al*. investigated the circRNAs expression profile in cytogenetic normal AML patients compared with healthy controls and figured out that 317 circRNAs were downregulated, whereas 147 circRNAs were upregulated. Their unique finding was hsa_circ_0004277, in which expression was significantly downregulated in AML patients, whereas after complete remission, the expression of hsa_circ_0004277 increased again and showed the same expression level as healthy controls; in the postremission stage and in cases of recurrence, the expression was downregulated again.[8]

Hence, finally, early diagnosis of AML can help with better treatment, prognostication, and raising the survival rate. On the other hand, the limitations of conventional diagnostics, such as high costs, insufficient sensitivity and specificity, and low efficiency in forecasting and diagnosis, reveal the necessity of finding new diagnostic methods and reliable biomarkers.[9] Furthermore, the abundance of circRNAs in blood and body fluids, tissue-specific expression of circRNAs, low-cost examination, and their stability against destructive factors such as RNase make circRNAs suitable options to become new diagnostic biomarkers in AML.[5,6,10] Thus, the purpose of this systematic review and meta-analysis is to investigate the role of circRNAs in the diagnosis of AML and the clear prospects that exist can provide more motivation and clues for further studies.

METHODS

Eligibility criteria

We performed a systematic review, registered on PROSPERO (ID: CRD42023399733). This study was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11] The inclusion criteria were: (a) AML patients were diagnosed by the gold standards; (b) the studies that had provided data relevant to the diagnostic role of circRNAs in AML patients, such as sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC) values; and (c) the number of patients and healthy people who had reported. The exclusion criteria were: (a) studies without a complete paper, insufficient data, or just employing an in-silico methodology were not accepted; (b) review studies; (c) sufficient data could not be obtained from studies (directly or indirectly) in the form of 2 × 2 table; (d) study subjects that were not AML patients (studies worked on animals or cell lines); and (e) due to language limitations, only English-language articles (at least in the abstract) were considered for the review.

Information sources

According to the PRISMA Statement,[11] the Web of Science, Scopus, PubMed, ProQuest databases, and Google Scholar search engines were searched for studies published through March 2023 based on the diagnostic role of circRNAs in AML. And also, Grey literature sources such as allconferences.com, conferencealerts.com, and oatd.org were searched. Furthermore, all included studies were examined in their reference lists.

Search strategy

By using the Medical Subject Heading (MeSH) and non-MeSH keywords based on our research question, the strategy search formula was written. The following keywords were used: #1 "RNA, Circular" or "CircRNAs" or "Closed Circular RNA" or "Circular RNA*;" and #2 "Leukemia, Myeloid, Acute" or "Acute Myeloid Leukemia" or "Leukemias, Acute Myeloid." The strategy search formula was (#1 AND #2) [Supplementary Data 1, the full text of search strategies for all databases].

Selection process

After studies were extracted from databases, duplicate studies were eliminated. In the next step, screening the title and abstract of articles to determine potentially relevant studies for this systematic review was performed by two researchers (A.A. and Y.M.). Then, the studies' full text was independently assessed by two researchers to verify whether these are qualified to be included according to the inclusion and exclusion criteria. To find

consensus on every disagreement when researchers were not sure whether a study should be included, the project manager (M.R.) advised the team. Initial screening of the extracted articles was performed using the web-based software Rayyan.[12]

Data collection process

Based on the data extraction checklist, the data extraction of the included articles was performed separately by three researchers (A.A, Y.M, and Z.H), and if there were irresolvable disagreements, the final decision was made by the fourth researcher (M.R). The WebPlotDigitizer 4.6 software was used to indirectly extract the data from ROC curves. However, before the indirect extraction of the data, the corresponding authors of the included studies were contacted three times (by E-mail) to obtain information.

Data items

Researchers extracted the data by using a prespecified form. The general data that were extracted were: the first's author, the name of the circRNAs, study date, country, sample type, sample size (patients and healthy people), the control gene, methods for circRNAs analysis (techniques), differences in circRNAs expression (oncogene or tumor suppressor), and so on. The specific data that were extracted for diagnostic meta-analysis were: the required information was directly or indirectly extracted to form 2 × 2 table, such as sensitivity (Sen), specificity (Spe), true positive (TP), true negative (TN), false positive (FP), false negative (FN), and so on.

Quality and risk of bias assessment

To ensure that no studies were missed, MESH words were used. The risk of bias was examined by two reviewers (A.A and Y.M), and discrepancies were resolved by consensus with the project manager (M.R). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used for the assessment of quality and the avoidance of bias in our review.[13] With the QUADAS-2 tool, four key domains were evaluated, including patient selection, index test, reference standard, flow, and timing. Also based on the QUADAS II tool, each article receives a maximum of 7 points [Figure 1].

In addition to the certainty of the evidence, the results were assessed using the modified method of GRADE assessment for diagnostic tests.[14] Certainty of evidence show confidence than the effect size. The certainty of evidence includes several domains such as study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias [Supplementary Table 1 to description of the GRADE framework was used]. Based on the certainty of the evidence, the results of the meta-analysis are classified as high, moderate, low, or very low certainty of the evidence. High certainty means higher confidence than the estimated effect, which indicates a close association between the true effect and the estimated effect. Moderate certainty means moderately confident than the estimated effect that shows the estimate of the effect is likely to be close to the true effect, but there is also a possibility that it is substantially different. Low certainty means lower confidence than the estimated effect; actually, the true effect might be substantially different from the estimate of the effect. Very low certainty means less confidence than the estimated effect, meaning that the true effect is likely to be substantially different from the estimate effect.[14,15]

Statistical analysis

The data extracted from the studies meeting the inclusion criteria were combined. For diagnostic analysis, the numbers of TP, FP, FN, and TN were calculated from the included studies, and finally, the pooled sensitivity, specificity, AUC, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), 95% confidence intervals (95% CIs), AUC, and heterogeneity were evaluated. The AUC values and their association with diagnostic accuracy are the following: 0.9–1.0: excellent, 0.8–0.9: very good, 0.7–0.8: good, 0.6–0.7: sufficient, 0.5–0.6: bad, and <0.5: test not useful, and also, good diagnostic tests have PLR >10 and NLR <0.1.[16,17]

Due to methodological heterogeneity in the primary study, the random effects model (REM) was used.[18] The Chi-square test and the I^2 statistic were utilized to assess the between-study heterogeneity. If an I^2 value was < 50%, it was considered to have no significant heterogeneity. To assess the potential source of heterogeneity, prior subgroup analysis (mentioned in the protocol of Prospero, such as expression status and sample type) and *post hoc* subgroup analysis were conducted according to similar features of the included studies, and sensitivity analysis of all the included studies was carried out to find the effect of each article on the final effect of the meta-analysis results. Publication bias was examined quantitatively using Deek's funnel plot. In this study, meta-analysis was performed with STATA version 14.2 (Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP) and Meta-Disc software version 1.4 (Clinical BioStatistics Unit-Hospital Ramon y Cajal, Madrid, Spain). P <0.05 was considered statistically significant.

RESULTS

Study selection

The PRISMA flow diagram[11] of the study selection process is shown in Figure 2. A total of 1049 studies were extracted from the mentioned databases. At first, 204 articles were removed due to duplication. The title and abstract of 845 articles were initially screened by two researchers and 768

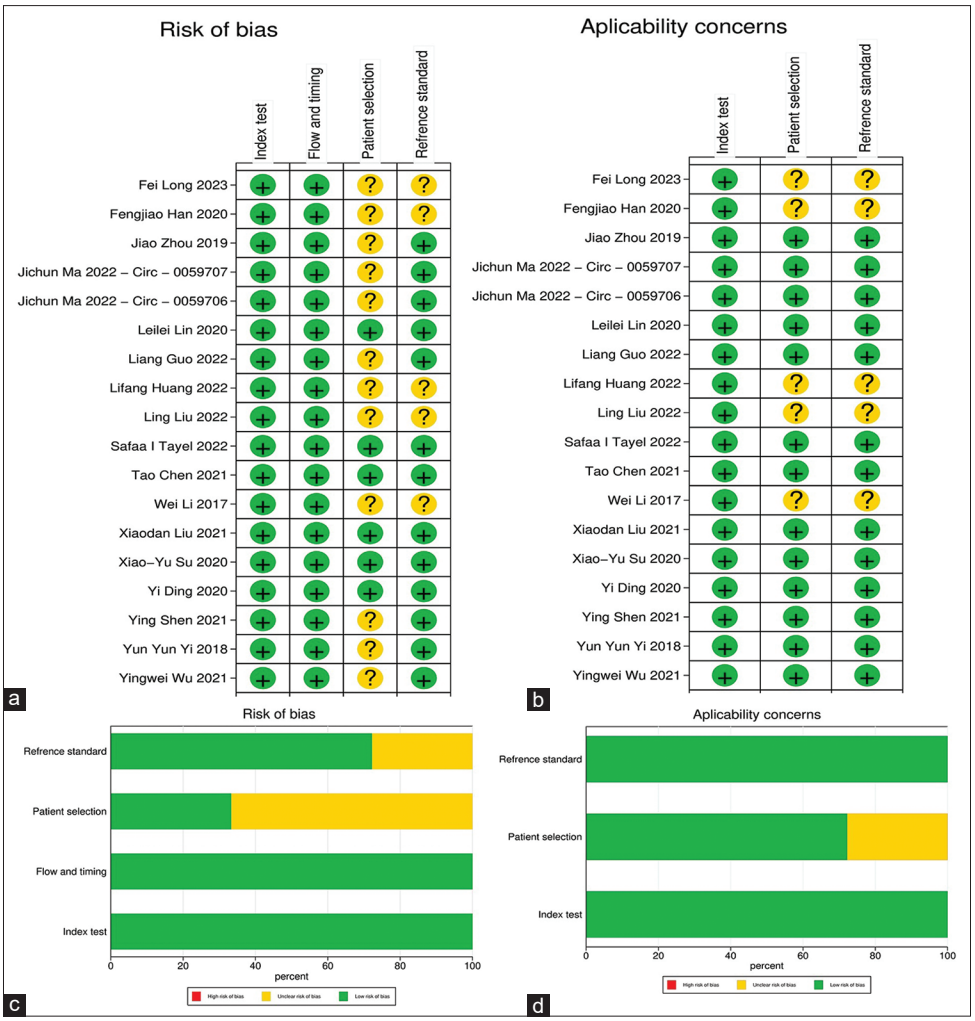

Figure 1: Quality assessments by the QUADAS II. Each bias risk item for included studies (a) and the percentages (c), each bias risk in applicability concerns item for the studies (b) and the percentages (d)

of them were excluded due to incompatibility with the inclusion and exclusion criteria. In the next step, 77 studies were selected for full-text examination; 2 full-text studies were not retrieved, and 57 studies were excluded for the reasons described in Figure 2. Finally, the number of articles included in the diagnostic meta-analysis was 18.[8,19-35]

Study characteristics

All the included articles were published between 2017 and 2023 and included 1644 patients with AML and 718 controls. The study population was mostly Chinese except for one article that had an Egyptian population.[32] Changes in the expression of circRNAs in some studies were measured by the microarray method, and finally, for confirmation, the qRT-PCR method was used. A total of 18 different circRNAs were examined. In the studies of Tayel *et al*.[32] and Ding *et al*.,[20] 3 and 9 circRNAs along with different expression and various diagnostic accuracy were measured, respectively. To avoid multiplicity,[36] from each of these studies, one circRNA with high accuracy was selected to perform diagnostic meta-analysis.

Results of syntheses

Diagnostic value of circular RNAs in acute myeloid leukemia patients

The features of the included diagnostic studies are indicated in Table 1. After diagnostic meta-analysis, the evaluation of results showed that diagnostic indicators such as the overall Sen, Spe, PLR, and NLR were 0.85 (95% CI: 0.80–0.89), 0.85 (95% CI: 0.82–0.88), 5.74 (95% CI: 4.49–7.33), and 0.18 (95% CI: 0.13–0.24), respectively [Figure 3a-d]. Furthermore, the pooled DOR and the area under the summary ROC (SROC) curve of circRNAs to differentiate AML from healthy control were 32.71 (95% CI: 20.09–53.24) and 0.91 (95% CI: 0.88–0.93), respectively [Figure 4a and b].

Clinical application

To assist professionals in clinical decision-making, Fagan's nomogram to assess the association between the posttest probabilities of disease in patients with AML and the likelihood ratio based on Bayes' theorem was drawn [Supplementary Figure 1a]. Furthermore, the likelihood ratio scattergram [Supplementary Figure 1b] and the

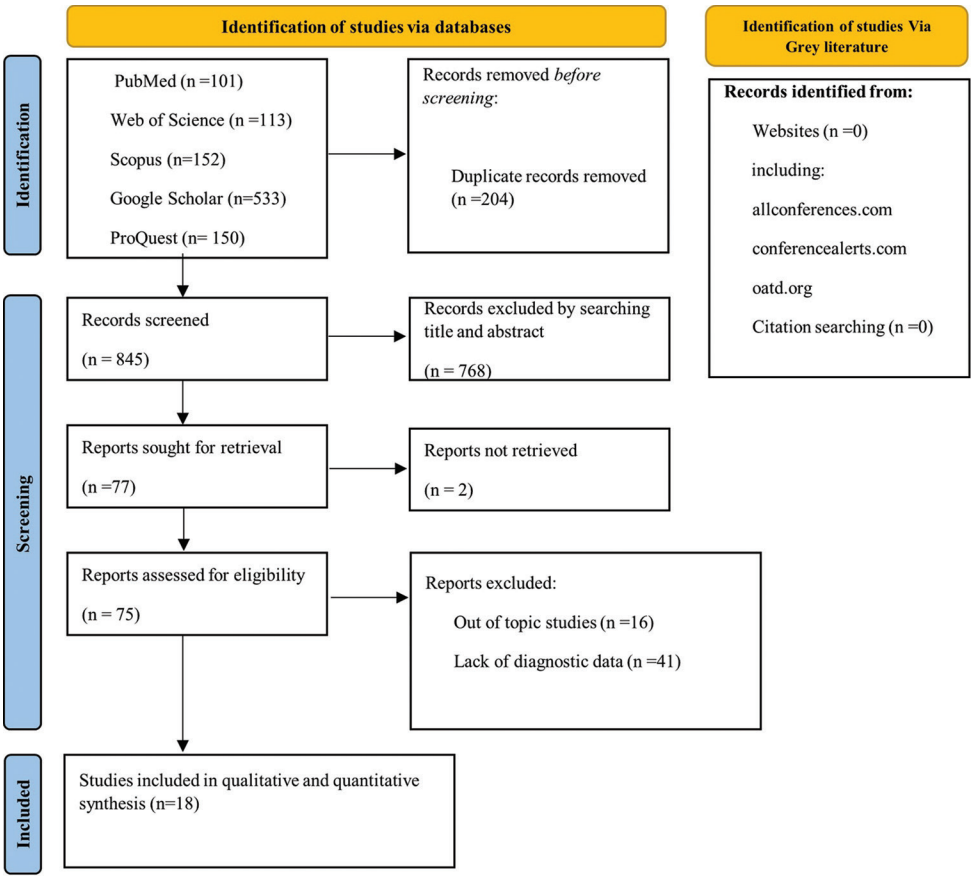

Figure 2: The PRISMA flow diagram for the study selection process

probability modifying plot [Supplementary Figure 1c] have been shown.

Subgroup analysis

To reduce and spot the heterogeneity between studies, subgroup analysis according to expression status (upregulation vs. downregulation), gene control (GAPDH vs. non-GAPDH), sample size (interquartile range <120 vs. ≥120), and control/patient ratio (<50% vs. ≥50%) was conducted [Table 2]. The results indicated that studies with upregulation of circRNAs had higher specificity (0.86 vs. 0.81), AUC (0.91 vs. 0.89) and lower sensitivity (0.83 vs. 0.89) and DOR (28.73 vs. 31.39) than studies with downregulation of circRNAs. Based on the type of gene control, results showed that all diagnostic parameters in studies with GAPDH control were better than studies with non-GAPDH control, with sensitivity, specificity, PLR, NLR, DOR, and AUC (0.86 vs. 0.83), (0.86 vs. 0.83), (6.17 vs. 4.80), (0.16 vs. 0.20), (30.68 vs. 22.32), and (0.93 vs. 0.89), respectively. In addition, studies with the ratio of control to patient ≥50% revealed a higher sensitivity (0.86 vs. 0.85), specificity (0.88 vs. 0.82), PLR (6.88 vs. 4.65), NLR (0.16 vs. 0.18), DOR (39.78 vs. 23.61), and AUC (0.93 vs. 0.86) than the studies with the ratio of control to patient <50%. On the other hand, subgroup analysis based on sample size indicated that studies with a sample size of <120 had higher diagnostic indices than studies with a sample size ≥120, which makes the results in this subgroup seem like overestimation [Supplementary Figures 2a-c and 3a-b]. Meanwhile, according to Penny Whiting's study,[37] which focuses on exploring the subjective rating in quality assessment of articles based on QUADAS, it does not recommend using scoring systems for subgroup analysis; so, we have also refrained from subgroup analysis of articles based on quality scores.

Sensitivity analysis

The goodness-of-fit and bivariate normality showed that the random effects bivariate model was suitable for sensitivity analysis [Figure 5a and b]. Influence analysis [Figure 5c] ascertained that the studies of Huang *et al.*[23] and Chen and Chen[19] were the important studies that could affect the results, as shown in Table 2, the exclusion of these two studies did not considerably affect our results. Furthermore, outlier detection revealed that no primary studies would substantially affect the heterogeneity of our study [Figure 5d].

Publication bias

Deek's funnel plot was performed to assess publication bias. P =0.65 in our results showed a symmetrical funnel

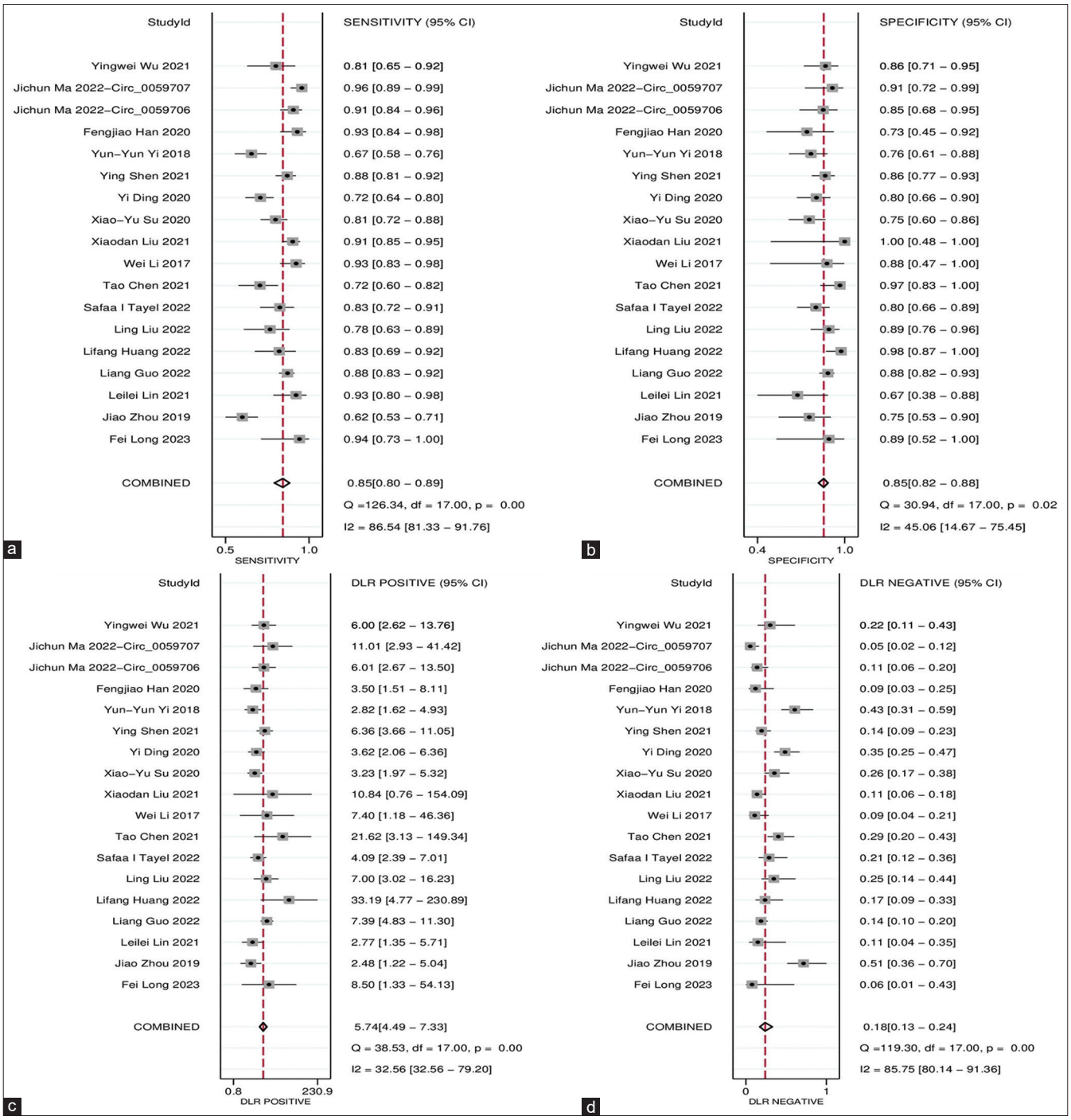

Figure 3: Forest plots of the pooled sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d) in the diagnostic value meta-analysis

shape and recommended that publication bias was non-considerable [Supplementary Figure 4].

GRADE assessment

The modified method of GRADE assessment for diagnostic tests was used to evaluate the certainty of the evidence.[14] The GRADE assessment showed that the certainty of evidence regarding sensitivity and specificity was moderate. The scoring method and the results are shown in Table 3.

DISCUSSION

AML is the most common type of acute leukemia in adults and also occurs in children and adolescents.[4,38] Today, AML diagnostics relies on cytomorphology of blood or bone marrow, flow cytometry, cytogenetics, and molecular genetics.[39] Despite the development of research in the field of early diagnosis of leukemia as well as the progress

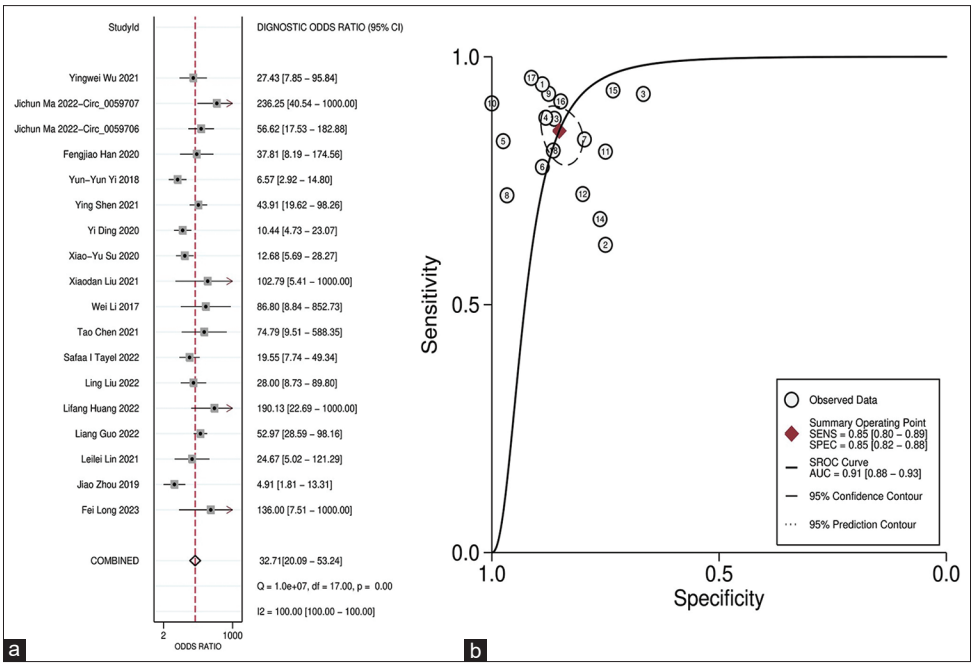

Figure 4: Forest plots of the diagnostic odds ratio (DOR) (a) and, the summary receiver operating characteristic curve (b) in diagnostic value meta-analysis

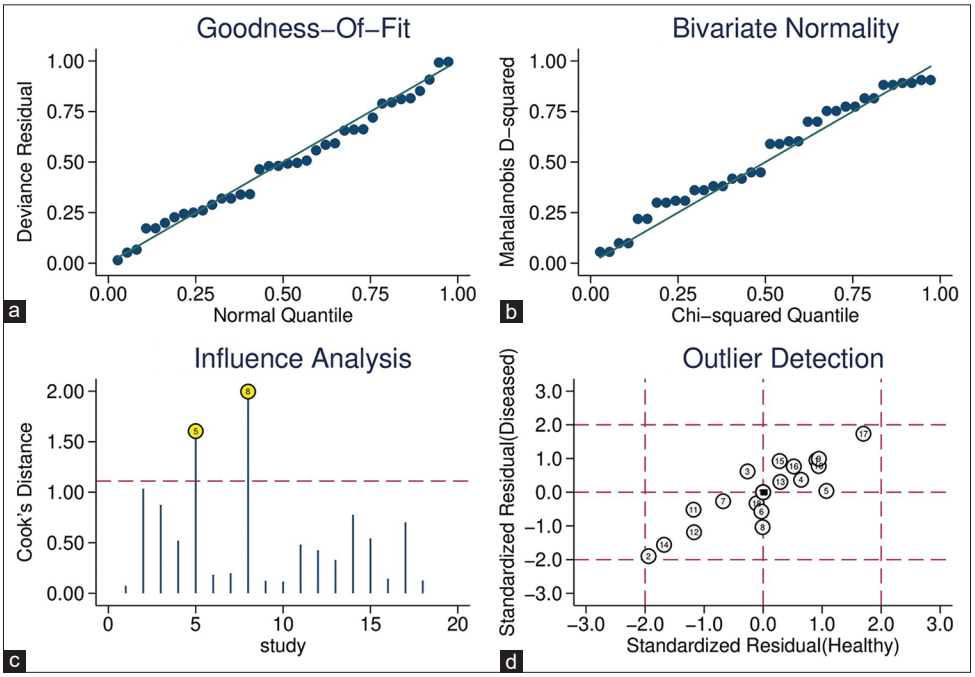

Figure 5: Goodness-of-fit (a), Bivariate normality (b), Influence analysis (c), Outlier detection (d) for diagnostic studies

of treatments, patients with AML have poor overall survival (OS) rates.[39,40]

CircRNAs are noncoding RNAs that are essential in the development and progression of AML.[6] circRNAs play different roles in cellular functions by regulating the gene expression involved in various leukemogenesis pathways, such as proliferation, cell cycle transition, adhesion, migration, and apoptosis.[6] Furthermore, due to their circular structure, they are highly stable in tissues and bodily fluids, and because of this distinctive feature, circRNAs can be considered promising diagnostic biomarkers in AML.[5,41] Furthermore, many primary and secondary studies have investigated the diagnostic accuracy of circRNAs in AML and other cancers. For example, in a systematic review and meta-analysis that was performed by Wang *et al*., the diagnostic role of circRNAs in renal cancer with an AUC of 0.89 was shown.[42] Furthermore, Chen *et al*. in their

Table 1: Main characteristics of the diagnostic studies

Study	Country	Year	CircRNAs (*n*=18)	AML samples size	Control samples size	Sample type	Control gene	Method	Cut off value	Diagnostic indexes			Quadas score
										AUC	Sensitivity	Specificity	
Fei Long	China	2023	Circ-ZBTB46	18	9	BM	GAPDH	Microarray qRT-PCR	-	0.97	0.94	0.89	3
Jiao Zhou	China	2019	Circ-Foxo3	116	24	BM	ABL	qRT-PCR	0.233	0.63	0.62	0.75	6
Leilei Lin	China	2021	Circ-PLXNB2	40	15	BM	GAPDH	Microarray qRT-PCR	-	0.85	0.92	0.68	7
Liang Guo	China	2022	Circ-0079480	236	160	Pb	-	qRT-PCR	-	0.93	0.88	0.88	6
Lifang Huang	China	2022	Circ-NFIX	47	40	BM	GAPDH	qRT-PCR	-	0.93	0.83	0.97	3
Ling Liu	China	2022	Circ-0044907	45	45	BM	GAPDH	qRT-PCR		0.94	0.78	0.89	3
Safaa I Tayel	Egypt	2022	Circ-0075001	66	54	Pb	GAPDH	qRT-PCR	>1.16	0.85	0.83	0.80	7
Tao Chen	China	2021	Circ-PVT1	68	30	BM	GAPDH	qRT-PCR	2.077	0.92	0.72	0.97	7
Wei Li	China	2017	Circ-0004277	67	8	BM	GAPDH	Microarray qRT-PCR	-	0.96	0.93	0.87	3
Xiaodan Liu	China	2021	Circ-RNF220	149	5	Pb	GAPDH	Microarray qRT-PCR	9.295	0.96	0.90	0.97	7
Xiao-Yu Su	China	2020	Circ-0002232	115	48	BM	ABL	qRT-PCR	0.165	0.85	0.81	0.76	7
Yi Ding	China	2020	Circ-ANXA2	130	50	BM	GAPDH	Microarray qRT-PCR	-	0.83	0.72	0.80	7
Ying Shen	China	2021	Circ-ANAPC7	144	80	BM	β-actin	qRT-PCR	-	0.91	0.87	0.87	6
Yun-Yun Yi	China	2018	Circ-VIM	113	42	BM	ABL	qRT-PCR	-	0.74	0.67	0.76	6
Fengjiao Han	China	2020	Circ-0001947	59	15	BM	GAPDH	Microarray qRT-PCR	-	0.89	0.93	0.73	3
Jichun Ma	China	2022	Circ-0059706	100	33	BM	ABL	qRT-PCR	0.254	0.92	0.91	0.86	6
Jichun Ma	China	2022	Circ-0059707	94	23	BM	ABL	qRT-PCR	-	0.98	0.95	0.92	6
Yingwei Wu	China	2021	Circ-0009910	37	37	BM	ABL	qRT-PCR	-	0.92	0.81	0.86	6

AML=Acute myeloid leukemia; AUC=The area under the receiver operating characteristic curve; BM=Bone marrow; Pb=Peripheral blood; qRT–PCR=Quantitative reverse transcription polymerase chain reaction

meta-analysis indicated the diagnostic accuracy of circRNAs as novel biomarkers with an AUC of 0.83 in gastric cancer.[43] Meanwhile, we showed in a previous meta-analysis the potential role of circRNAs as diagnostic biomarkers in hematological malignancy of multiple myeloma with a pooled AUC of 0.86.[44] Hence, our focus in this systematic review and meta-analysis was to investigate the diagnostic value of circRNAs in AML, which are PCR-based molecular genetics tests, and finally, this diagnostic value can be useful in the early diagnosis of AML and treatment process.

In this diagnostic meta-analysis, the pooled sensitivity and specificity were 0.85 and 0.85, respectively, which show the high ability of this test for the diagnosis of patients with AML and patients without AML. As an essential index in diagnostic meta-analysis, DOR displays that the odds of a positive test in patients are higher than the odds of a positive test in people without disease and so higher DOR is related to better diagnostic value.[45] In our study, the pooled DOR was 32.71, which suggests circRNAs are potential diagnostic index for recognizing AML patients from healthy controls. The ROC curve and the AUC reflect the efficacy of the diagnostic test and the larger AUC shows a higher diagnostic value.[16] The pooled AUC of circRNAs in AML was 0.91, which indicates circRNAs have excellent diagnostic accuracy in identifying patients with AML. In this meta-analysis, circRNAs had different DORs; Circ-0059707 (DOR = 236), Circ-NFIX (DOR = 190), and Circ-ZBTB46 (DOR = 136) had the highest DOR, while Circ-Foxo3 had the lowest DOR = 4.

Clinical application is one of the most important features of new diagnostic biomarkers. PLR and NLR and posttest probabilities are useful indexes for medical professionals because they provide information about the likelihood that a patient with a positive or negative test actually has AML or not. Likelihood ratio is a vigorous parameter that can indicate increasing or decreasing the probability of disease. Pooled PLR 5.74 indicates 5-fold increase in the likelihood of AML in the patient with a positive result, while NLR 0.18 shows 5.5-fold decrease in the likelihood of AML in the patient with a negative result. According to the result of the likelihood ratio, there is a moderate shift in the probability of the disease.[17] Furthermore, Fagan nomogram was used to express the posttest probabilities of disease in the AML patients. If the circRNAs test is positive and the prior probability of AML is 70% (prevalence in the study population of this meta-analysis), in this case, the posttest probability of AML would reach 93%, and if the circRNAs test is negative, this would mean that the posttest probability of AML would drop to 29%.

The results of the subgroup analysis are shown in Table 2. Regarding the effects of sample size on statistical power,

Table 2: Subgroup analysis for diagnostic meta-analysis

Subgroups	Number of studies	Sensitivity (95% CIe)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	I^2%	AUC (95% CI)
Total study included	18	0.85 (0.80–0.89)	0.85 (0.82–0.88)	5.74 (4.49–7.33)	0.18 (0.13–0.24)	32.71 (20.09– 53.24)	100	0.91 (0.88–0.93)
Outliers excluded (two study)	16	0.86 (0.81–0.90)	0.84 (0.80–0.87)	5.39 (4.23–6.87)	0.17 (0.12–0.24)	31.79 (18.61–54.30)	100	0.90 (0.87–0.92)
Expression status								
Up regulation	12	0.83 (0.78–0.87)	0.86 (0.82–0.90)	6.03 (4.52–8.03)	0.20 (0.15–0.26)	28.73 (16.44–50.2)	63	0.91 (0.88–0.93)
Down regulation	6	0.89 (0.78–0.94)	0.81 (0.73–0.88)	4.76 (3.03–7.48)	0.14 (0.07–0.29)	31.39 (10.51–93.75)	76.9	0.89 (0.86–0.91)
Gene control								
GAPDH	10	0.86 (0.80–0.90)	0.86 (0.77–0.92)	6.17 (3.73– 10.19)	0.16 (0.11–0.24)	30.68 (17.10–55.06)	31.6	0.93 (0.90–0.95)
Non-GAPDH	7	0.83 (0.73–0.90)	0.83 (0.76–0.88)	4.80 (3.18–7.26)	0.20 (0.11–0.35)	22.32 (9.45–52.72)	80.1	0.89 (0.86–0.91)
Sample size								
<120	9	0.89 (0.82–0.93)	0.88 (0.80–0.93)	7.44 (4.56–12.14)	0.13 (0.05–0.20)	48.67 (27.99–84.65)	0.5	0.94 (0.92–0.96)
≥120	9	0.82 (0.75–0.87)	0.83 (0.77–0.87)	4.70 (3.40–6.48)	0.22 (0.15–0.32)	19.20 (10.03–36.77)	77.8	0.89 (0.85–0.91)
Control/patient ratio								
<50	11	0.85 (0.77–0.91)	0.82 (0.76–0.86)	4.65 (3.41–6.34)	0.18 (0.11–0.29)	23.61 (11.83–47.14)	68.8	0.86 (0.83–0.89)
≥50	7	0.86 (0.83–0.88)	0.88 (0.84–0.90)	6.88 (5.34–8.87)	0.16 (0.13–0.20)	39.78 (26.43–59.87)	9.2	0.93 (0.91–0.95)

PLR=Positive likelihood ratio; NLR=Negative likelihood ratio; DOR=Diagnostic odds ratio; AUC=The area under the receiver operating characteristic curve; CI=Confidence interval

studies with larger sample size reported reliable results, whereas studies with smaller sample size overestimated the results.[46] In our study, sample size categorization based on data distribution, as was expected, shows that studies with sample size "<120" magnify results compared to studies with sample size "≥120" [Supplementary Figure 2c]. In addition, subgroup analysis based on the control/patient ratio indicates that more reliable results are observed in the presence of a control/patient ratio higher 50% than a ratio lower 50% [Supplementary Figure 2d]. Furthermore, subgroup analysis in studies with sample size "≥120" based on the control/patient ratio shows more reliable results, which confirm the previous finding [Supplementary Figure 3a]. Furthermore, in the gene control subgroup, the results show that using GAPDH gene control had better results compared to nonGAPDH gene control [Supplementary Figure 2b]. On the other hand, subgroup analysis in studies with GAPDH gene control based on sample size shows that among the 10 studies with GAPDH gene control, 7 studies had sample size "<120," so there is no significant difference in the use of different gene controls [Supplementary Figure 3b]. The results of the sensitivity analysis and publication bias suggested that the homogeneity of our data is adequate and the pooled results are reliable. Regarding the recommendations presented by Whiting *et al*.,[37] we have opted not to categorize the articles based on their quality score. This decision ensures that the quality assessment process remains unbiased and avoids potential pitfalls associated with subjective scoring systems and also enhances the reliability, validity, and conclusions of our findings. In relation to the design of the primary studies, all of the included studies in our article were cross-sectional studies with a case–control population selection. Considering the article by Mathes and Pieper[47] that discusses the categorization of diagnostic studies, there are concerns that our primary studies might have inherent biases in their design and overestimate the results. Hence, finally, based on the GRADE assessment for our results, the certainty of evidence regarding sensitivity and specificity for cross-sectional studies with case–control selection patients was moderate. In addition, the findings of the studies conducted by Xu *et al*.,[48] Zhang *et al*.,[49] and Li *et al*.[9] in AML patients similar to our findings demonstrate promising results regarding the diagnostic value of microRNAs as one of the noncoding RNAs. This similarity reinforces the use of noncoding RNAs as valuable indicators for diagnosing AML.

Recommendation

Totally based on the evidence in our meta-analysis, to achieve reliable results in diagnostic tests of AML, our recommendation is a sample size above 120 and a control/patient ratio above 50%. According to the article by Mathes and Pieper,[47] the design of studies evaluating diagnostic

Table 3: Scoring method and the results of GRADE assessment

Domains of GRADE assessment	Study design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Summary of finding	
							Effect size (95% CI)	Certainty of evidence
Diagnostic parameters (number of studies)								
Sensitivity	Cross-sectional study with case-control selection patients[a]	No problem[b]	No problem[c]	No problem[d]	No problem[e]	No problem[f]	0.83 (0.77–0.88)	⨁⨁⨁◯ moderate
Specificity	Cross-sectional study with case-control selection patients	No problem	No problem	No problem	No problem	No problem	0.85 (0.81–0.88)	⨁⨁⨁◯ moderate

[a]A type of cross-sectional study design for diagnostic accuracy studies; [b]Based on the five main QUADAS2 questions, it wasn't possible to downgrade the quality of the evidence; [c]Based on the similarity in patient's population, diagnostic test, comparison test in included studies, it wasn't possible to downgrade the quality of the evidence; [d]Despite varying degrees of heterogeneity, it wasn't possible to reduce the quality of the evidence by finding explainable inconsistency; [e]According to a sufficient number of studies and narrow confidence interval, it wasn't possible to downgrade the quality of the evidence; [f]The possibility of publication bias wasn't considerable to downgrade the quality of evidence. CI=Confidence interval; GRADE=Grading of recommendations assessment, development, and evaluation

accuracy should be cross-sectional with a cohort selection to prevent overestimation of the results. By employing cross-sectional design and cohort selection, we can overcome some of the limitations associated with cross-sectional design and case–control selection. The design of cross-sectional with cohort selection allows for the collection of data related to exposure (index test) and outcome (diagnosis) variables over time and providing a stronger basis for establishing causal relationships and reducing the potential for bias. In addition, using cohort population selection can enhance the generalizability of the findings, as it involves following a representative sample of individuals from a defined population. This approach allows for more accurate estimation of the diagnostic value and provides more robust foundation for drawing conclusions and making clinical recommendations. Therefore, it is recommended that future research in this area consider employing prospective cohort studies with a population selection strategy, such as the Cochrane methodology, to ensure more valid and reliable results in evaluating diagnostic accuracy.[47,50,51] Finally, according to the quality control of the studies, it is suggested that the authors clearly state the criteria for diagnosing patients (for example, based on WHO or FAB) and the criteria for exclusion of patients when writing articles.

Limitations of the review

With all efforts, this meta-analysis still had the following limitations: first, some primary studies did not provide clear data to form 2 × 2 table, so we reclaimed the necessary data from the ROC curve, which may have caused bias (despite sending emails to the authors three times to receive information). Second, the studies were mostly from China, which may limit the generalizability of these findings and lead to bias. Third, cutoffs were not accessible to examine threshold effects. Fourth, heterogeneity is still a vital issue, although we performed various subgroup analyses to explore possible sources. Fifth, articles with positive results are more likely to be published, which may increase overall diagnostic accuracy; finally, the sixth reason is that, due to the linguistic restrictions, we only included studies with the English language (at least in the abstract), which may have affected our results.

CONCLUSION

Considering the spread of AML in all over the world, early and comprehensive diagnosis of AML helps in effective treatment management, reduction of costs, and mortality. Hence, our systematic review and meta-analysis suggest measuring the changes in the expression of circRNAs as promising and valuable biomarkers related to the diagnosis of AML.

Ethics approval and consent to participate

IR.ZUMS.BLC.1402.024.

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Conflicts of interest

There are no conflicts of interest.

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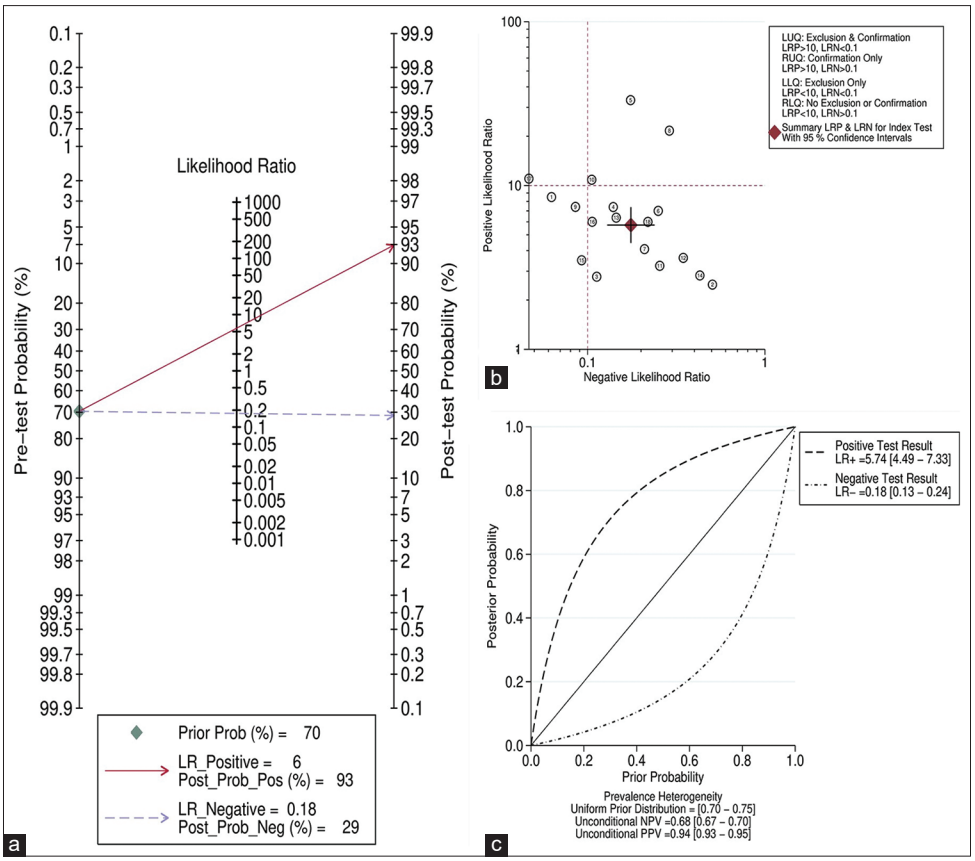
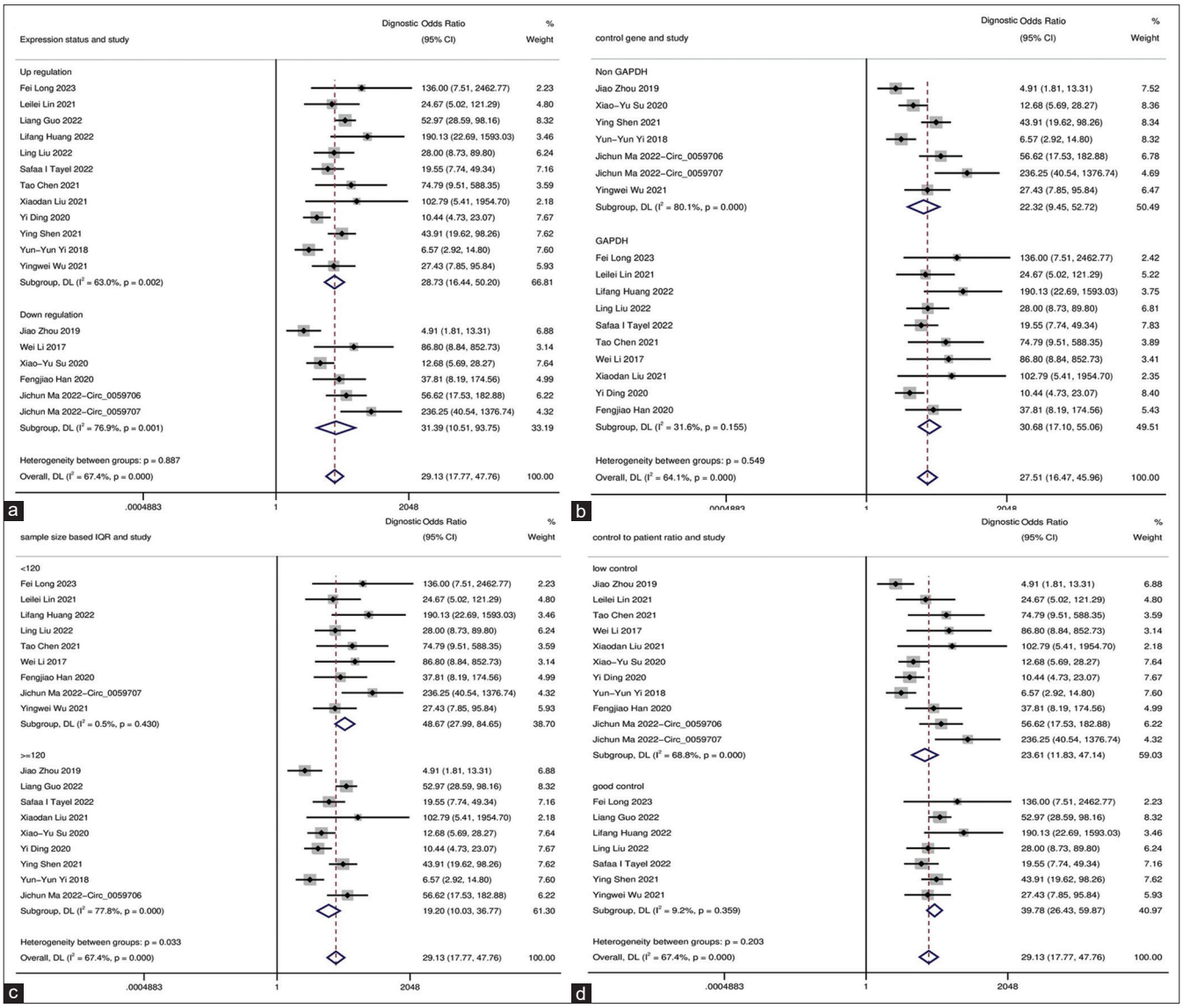
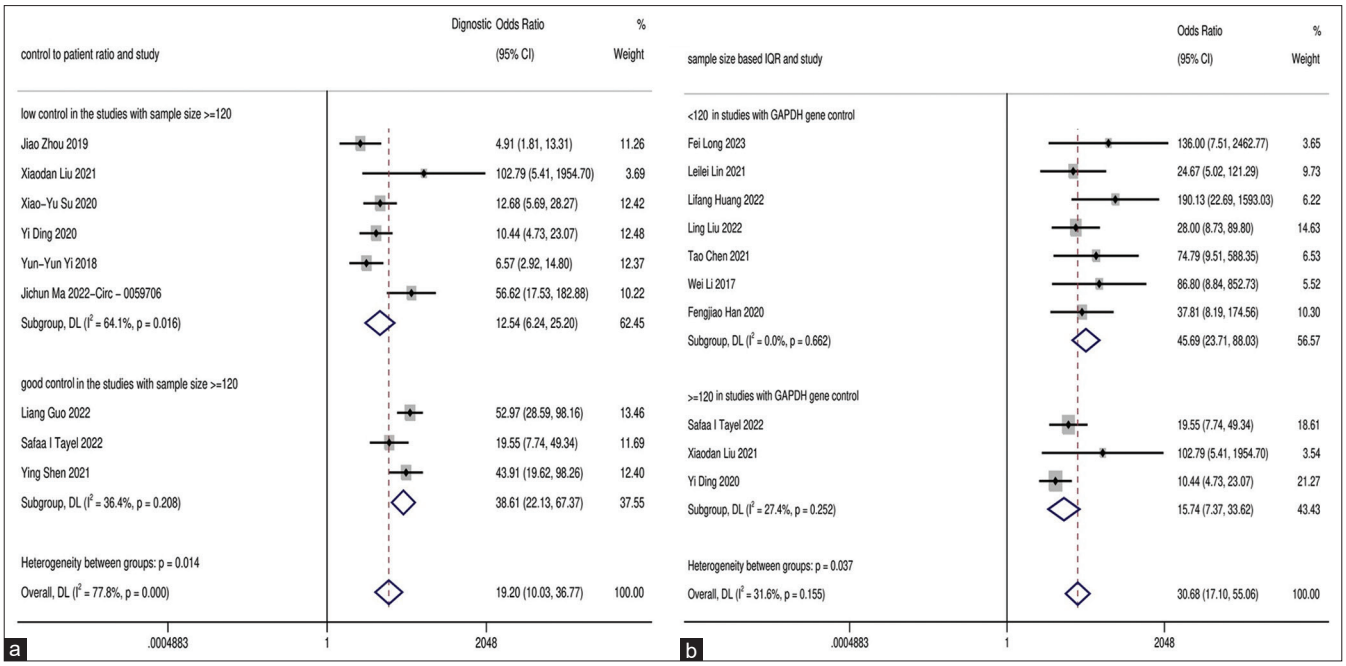


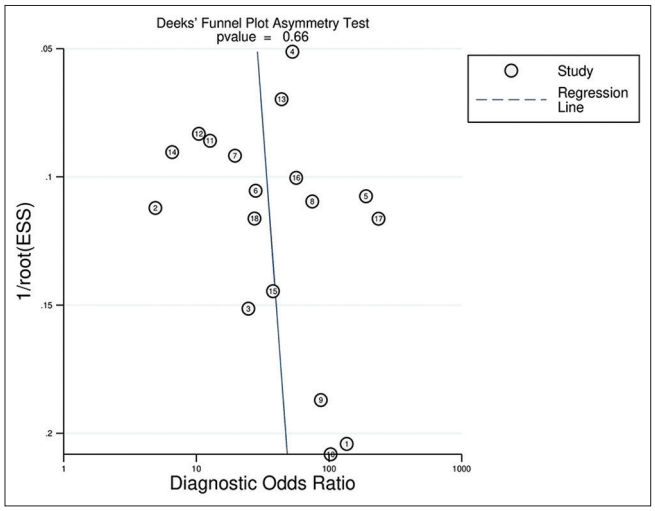
Supplementary Figure 1: Fagan's nomogram to describe the value of circRNAs on the diagnosis of AML (a), Likelihood ratio scattergram (b), Relationship between pre- and posttest probability based on the likelihood of a positive (above diagonal line) or negative (below diagonal line) test (c)



Supplementary Figure 2: Forest plots of Subgroup analysis based on DOR. Expression status subgroup (a), Gen control subgroup (b), Sample size subgroup (c), C/P ratio subgroup (d)



Supplementary Figure 3: Forest plots of Subgroup analysis based on DOR. Subgroup analysis in studies with sample size ">=120" based on C/P ratio (a) and subgroup analysis in studies with GAPDH gene control based on sample size (b)



Supplementary Figure 4: Deek's funnel plot to evaluation publication bias for diagnostic studies

Supplementary Table 1: Description of the GRADE framework

Study design	Point	Explanations
Cross-sectional study with cohort selection patients	+4	
Cross-sectional study with case-control selection patients	+2	
Risk of bias		
No problems	0	1. Was a consecutive or random sample of patients enrolled? 2. Were the index test results interpreted without knowledge of the results of the reference standard? 3. Is the reference standard likely to correctly classify the target condition? 4. Were the reference standard results interpreted without knowledge of the results of the index test? 5. Were all patients included in the analysis?
Problem with 1 or 2 elements	−1 (serious)	
Problem with more 2 elements	−2 (very serious)	
Indirectness		
No problems	0	Dissimilarity in patient population, diagnostic test, comparison test
Problem with 1 element	−1 (serious)	
Problem more 1 element	−2 (very serious)	
Inconsistency		
0%–50%	0	For accuracy studies unexplained inconsistency in sensitivity, specificity or likelihood ratios can lower the quality of evidence No points are deducted if heterogeneity factors are found*
50%–75%	−1 (serious)	
>75%	−2 (very serious)	
Imprecise		
Number of studies 5 or more than 5 and narrow 95% CI	0	For accuracy studies wide CIs and low number of studies for estimates of test accuracy, rates can lower the quality of evidence
Number of studies <5 and wide 95% CI	−1 (serious)	
Number of studies <3 and wide 95% CI	−2 (very serious)	
Publication bias		
Nonsignificant *P* value	0	Evaluation of publication bias based on Deek's funnel plot
Significant *P* value	−2 (very serious)	

Score 4=High certainty of evidence; Score 3=Moderate certainty of evidence; Score 2=Low certainty of evidence; Score 1=Very low certainty of evidence. CI=Confidence interval; GRADE=Grading of recommendations assessment, development and evaluation

SUPPLEMENTARY DATA 1: SEARCH STRATEGY FORMULA: (#1 AND #2)

SUPPLEMENTARY DATA

Search syntax for PubMed

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Search syntax for Scopus

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Search syntax for Web of Science

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Search syntax for Poquest

TI, AB, SU("RNA, Circular" OR "CircRNAs" OR "Closed Circular RNA" OR "Circular RNA, Closed" OR "RNA, Closed Circular" OR "Circular RNA*" OR "RNAs, Circular" OR "circRNA" OR "Circular Intronic RNA" OR "Intronic RNA, Circular" OR "RNA, Circular Intronic" OR "ciRNA" OR "hsa circ")

TI, AB, SU("Leukemia, Myeloid, Acute" OR "Acute Myeloid Leukemia*" OR "Leukemias, Acute Myeloid" OR "Myeloid Leukemias, Acute" OR "ANLL" OR "Leukemia, Acute Myelogenous" OR "Leukemia, Acute Myeloid" OR "Leukemia, Myeloblastic, Acute" OR "Leukemia, Myelocytic, Acute" OR "Leukemia, Myelogenous, Acute" OR "Leukemia, Nonlymphoblastic, Acute" OR "Leukemia, Nonlymphocytic, Acute" OR "Myeloblastic Leukemia, Acute" OR "Acute Myeloblastic Leukemia*" OR "Leukemia, Acute Myeloblastic" OR "Leukemias, Acute Myeloblastic" OR "Myeloblastic Leukemias, Acute" OR "Myelocytic Leukemia, Acute" OR "Acute Myelocytic Leukemia*" OR "Leukemia, Acute Myelocytic" OR "Leukemias, Acute Myelocytic" OR "Myelocytic Leukemias, Acute" OR "Myelogenous Leukemia, Acute" OR "Myeloid Leukemia, Acute" OR "Nonlymphoblastic Leukemia, Acute" OR "Acute Nonlymphoblastic Leukemia*" OR "Leukemia, Acute Nonlymphoblastic" OR "Leukemias, Acute Nonlymphoblastic" OR "Nonlymphoblastic Leukemias, Acute" OR "Nonlymphocytic Leukemia, Acute" OR "Acute Nonlymphocytic Leukemia*" OR "Leukemia, Acute Nonlymphocytic" OR "Leukemias, Acute Nonlymphocytic" OR "Nonlymphocytic Leukemias, Acute" OR "Acute Myelogenous Leukemia*" OR "Leukemias, Acute Myelogenous" OR "Myelogenous Leukemias, Acute" OR "Myeloid Leukemia, Acute, M1" OR "Leukemia, Myeloid, Acute, M1" OR "Acute Myeloid Leukemia without Maturation" OR "Leukemia, Myeloid, Acute, M2" OR "Myeloid Leukemia, Acute, M2" OR "Acute Myeloid Leukemia with Maturation")