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REVIEW

Prognostic value of circular RNAs expression and their correlation with clinicopathological features in acute myeloid leukemia: a systematic review and meta-analysis

Yasin Mirazimi[1] · Amir Hossein Aghayan[1] · Amir Atashi[2] · Davood Mohammadi[3] · Mohammad Rafiee[4,5]

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Abstract

Acute myeloid leukemia (AML) prognosis is affected by unique factors to each individual and studies have indicated that dysregulated expression of circRNAs may serve as prognostic biomarkers for AML. Therefore, we conducted this study to assess the prognostic value of circRNAs expression and it's correlation with clinicopathological features. Comprehensive search was conducted in WOS, Scopus, PubMed, Google Scholar, ProQuest, and grey literature. The certainty of evidence was assessed using the modified GRADE approach for prognostic and clinicopathological meta-analysis. The hazard ratio (HR) was employed to assess the prognostic value of dysregulated expression of circRNAs in patient survival, while the risk ratio (RR) was utilized to analyze the correlation between circRNAs and clinicopathological features. Our results demonstrated that dysregulation of circRNAs expression was associated with poor prognosis related to overall survival (OS) indicator (HR:2.05; 95%CI: 1.75–2.40) and also related to non-OS indicators such as (EFS, LFS, RFS, and DFS) (HR:2.09, 95%CI: 1.47–2.97). Priori and post-hoc subgroup analysis was conducted to describe variables that potentially affected heterogeneity and effect size. We also evaluated the association between dysregulated expression of circRNAs and 19 clinicopathological parameters. Our results show that there is significant relationship between the dysregulated expression of circRNAs and the mentioned parameters: type M6 vs. other types (RR:1.51, 95% CI:1.12–2.03), FLT3-ITD mutation (RR:1.17, 95%CI: 1.00-1.36), and risk status (RR:1.35, 95% CI: 1.13–1.60). This systematic review and meta-analysis suggest that the investigation of circRNAs expression changes can serve as valuable biomarkers for the assessment of prognosis in AML patients.

Keywords CircRNA · AML · Prognosis · Non-coding RNAs · Meta analysis · Survival · Treatment · Recommendation

Abbreviations

AML	Acute myeloid leukemia
HR	Hazard ratio
RR	Risk ratio
OS	Overall Survival
PFS	Progression-free survival
LFS	Leukemia-free survival
EFS	Event-free survival

Yasin Mirazimi and Amir Hossein Aghayan contributed equally to this work.

✉ Mohammad Rafiee
M.rafiee911@gmail.com

[1] Student Research Committee, Department of Medical Laboratory Sciences, School of Paramedical Sciences, Zanjan University of Medical Sciences, Zanjan, Iran

[2] Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Shahroud University of Medical Sciences, Shahroud, Iran

[3] Department of Medical Genetics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[4] Department of Medical Laboratory Sciences, School of Paramedical Sciences, Zanjan University of Medical Sciences, Zanjan, Iran

[5] Department of Medical Laboratory Sciences, School of Paramedicine, Hamadan University of Medical Sciences, Hamadan, Iran

DFS Disease Free Survival
CIs Confidence intervals

Introduction

Leukemia is one of the major groups of hematological malignancies with malignant transformation of the cells in the bone marrow. Acute myeloid leukemia (AML) is the most common acute leukemia in adults [1, 2] and it is characterized by high and abnormal proliferation and incomplete differentiation of myeloid cells. Following these features, adverse outcomes such as clonal accumulation of blast cells in the peripheral blood, bone marrow and rarely in organs are observed in AML patients. This aberrant accumulation of blast cells prevents the production of healthy and normal white blood cells in the bone marrow. Bone marrow failure can result in leukocytosis with anemia and thrombocytopenia. Moreover, different clinical symptoms such as Fever, fatigue, headache and weight loss are possible in AML patients; ignoring the mentioned symptoms and neglecting the treatment can result in death in a few months by bleeding or infection as secondary complications [3, 4]. In most cases, AML occurs as a de novo malignancy in previously healthy people [3], but it can have other reasons, such as previous exposure to chemotherapy drugs, radiotherapy for the treatment of other cancers or history of underlying hematological disorders [5]. Genetic heterogeneity is one of the most important points about AML malignancy [6]. Chromosomal abnormalities such as inversion, translocation, and deletion are common in AML [6]. However, approximately 50% of patients exhibit a normal karyotype. In such cases, molecular changes, including mutations, play a crucial role in leukemogenesis and predicting prognosis [3]. Based mostly on cytogenetic data, the 5-year overall survival rate of AML patients is split into three groups: favorable (55%), intermediate (24–42%) and poor (11%) [7]. The presence of myeloid blasts in the peripheral blood or bone marrow, flow cytometry and immunophenotyping, extramedullary tissue infiltration, karyotype analysis ar and presence of specific genetic mutations, are diagnostic methods for AML. Despite significant progress in AML treatment, allogeneic stem cell transplantation in eligible patients and chemotherapy with cytarabine and anthracycline are the main methods of treatment. However in most cases, relapse and death of patients have been reported [3].

Advances in high throughput sequencing indicate that about 2% of the human genome is made up of coding DNA sequences; thus, the vast majority of the human genome could be transcripted into RNAs that remain untranslated and are called Non-coding RNAs(ncRNAs) [8]. Based on their functions, ncRNAs are divided into regulatory and housekeeping groups which, the first of group includes long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) [9]. CircRNAs have covalently closed loop structure with phosphodiester bonds between the 3′ and 5′ ends and lack of 5′cap and 3′ polyadenyl tail conserves them from ribonuclease (RNase) activity; thus, they are more stable compared to linear messenger RNAs (mRNAs) [8–11]. The four main biological functions of circRNAs consist of: First, circRNAs act as a protein adaptor for interaction with RNA binding proteins (RBPs) and their effect on gene regulatory functions. Second, circRNAs act as miRNA sponges. They can bind to miRNAs and regulate miRNA-mediated gene activity. Third, circRNAs act as protein translators. New researches show that circRNAs can encode proteins. For example, circ-ZNF609 could be translated into proteins and control myoblasts proliferation and fourth, circRNAs act as transcriptional regulators. Intron-containing circRNAs regulate RNA polymerase II and promote maternal gene expression [12]. CircRNAs can have tumor suppressor or oncogenic roles and their aberrant expression is effective in tumorigenesis, metastasis and drug resistance in various cancers [10].The role of circRNAs in the pathogenesis of hematopoietic malignancies and leukemogenesis has been proven in various studies [13].

Continuous monitoring of AML patients, whether before or after treatment, leads to an improved prognosis, better treatment and finally higher survival rate. Therefore, according to the significant features and benefits of circular RNAs, it is possible to identify them as new prognostic factors. Many studies have investigated the role of circRNAs as new prognostic factors. For example, Yi et al. showed that circ-VIM can act as a prognostic marker and its high expression is associated with shorter leukemia-free survival and overall survival in AML patients [14]. Another study predicted that has-circ-0004520 modulates the expression of vascular endothelial growth factor A (VEGFA), which results in angiogenesis in AML-EMI [1]. Extramedullary Infiltration (EMI) in AML is associated with poor prognosis and is known by the accumulation of blasts in extramedullary places such as the liver, central nervous system, skin and spleen [12]. Furthermore, the study of Hongli Chen et al. indicated that circ-ANAPC7 sponging with the miR-181 family and dysregulated their biological functions, which finally worsens the prognosis in AML patients [15]. On the other hand, in AML the information provided by Clinicopathological parameters plays a key role in understanding the disease status and predicting treatment outcomes. It is important to consider the significance of these parameters when diagnosing AML and predicting treatment results, as it helps determine the appropriate strategies for patient care. By examining these parameters, we can improve the accuracy of diagnosis and identify suitable treatment approaches

and ultimately leading to better clinical outcomes for individuals with AML. The evaluation of Clinicopathological parameters encompasses factors like the patient's age, type of leukemic cells, blast cell ratio and chromosomal abnormalities, all of which contribute to predicting treatment outcomes and patient survival.

Finally, based on the mentioned examples and other reasons such as tissue-specific expression and abundance in blood and other body fluids, non-invasive and cost-effective examination can be considered for circRNAs as new suitable prognostic biomarkers in AML patients [8, 10, 11]. So, this study aims to investigate the role of circRNAs in the prognosis of AML patients and their correlation with their clinicopathological features.

Methods

Eligibility criteria

According to the registered protocol (PROSPERO ID: CRD42023399738), we accomplished a systematic review and meta-analysis. This study was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. The inclusion criteria were: (A) case-control and cohort study design; (B) confirmation of AML diagnosis was reported for all patients; (C) the studies have provided data (directly or indirectly extracted) relevant to the expression of circRNAs and prognostic and clinicopathological parameters of the patient with AML; (D) the studies that have analyzed the effects of circRNAs on the therapy response or progression of patients with AML. 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) studies that have worked on animals; (D) Considering the language limitations, only articles in English (at least in the abstract) were considered for this review.

Information sources

The WOS, Scopus, PubMed, Google Scholar, and ProQuest databases were searched, and studies were extracted up to March 2023. Also, grey literature sources such as allconferences.com, conferencealerts.com, and oatd.org were searched. Further, all references to the included studies were reviewed.

Search strategy

Using Medical Subject Headings (MeSH) and non-MeSH keywords, a strategy search formula was developed based on our research question (PICO). The 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) (the full text of search strategies for all databases can be found in supplementary data S1).

Selection process

Following the extraction of studies from databases, duplicate studies were removed. Initial screening of articles for inclusion or exclusion by using the title and abstract information was done by two researchers (A.A and Y.M). Then, the full text of the studies was independently assessed by two researchers to verify whether they qualified to be included according to the inclusion and exclusion criteria mentioned in Sect. 2.1. When researchers were uncertain whether to include the study, the project manager (M.R) consulted with the team to find a consensus. Initial screening was performed on the extracted articles using the web-based software Rayyan [17].

Data collection process

In order to extract data from the included articles, three researchers (A.A, Y.M and D.M) independently conducted their tasks, and if there were unresolvable disagreements, the final decision was made by fourth researcher (M.R). In order to indirectly extract the data from Kaplan Meier curves for prognostic meta-analysis, the WebPlotDigitizer 4.6 software was used and also the methods described by Tierney to indirectly calculate HR and 95% CI was used [18]. To obtain information, the corresponding authors of the included studies were contacted three times (by email) prior to the indirect extraction of data.

Data items

By using a pre-specified form, three researchers extracted the required data. The general data that were extracted were: (1) study characterization, including the first author's name, the name of the circRNAs, study date, country, and year; (2) sample type, sample size (patients and healthy people), the control gene, possible intervention, and follow-up criteria; (3) methods for circRNAs analysis (techniques); (4) Differences in circRNAs expression (upregulation or downregulation); (5) the effects of the circRNAs on the cell biology, microRNA sponging, and so on. (6) the effects of the circRNAs on survival indicators such as OS, LFS, RFS, and so on; (7) the effects of the circRNAs on the treatment response. The specific data that were extracted for

prognostic meta-analysis includes the following: hazard ratio (HR) with 95% confidence interval (CI) for survival indicators (if reported in the article), follow-up time, and survival outcome. Finally, for the meta-analysis of clinicopathological features, the specific data were extracted from the clinicopathologic characteristics tables and are as follows: Gender, risk status, French-American-British (FAB) classification, and different cytogenetic abnormalities and mutations.

Bias assessment

MESH words were used to ensure that no study was missed. Two reviewers (A.A. and Y.M.) reviewed the risk of bias, and discrepancies were resolved by consensus with the project manager (M.R.). The risk of bias assessment was done based on the Newcastle-Ottawa Scale (NOS) checklist for cohort and case-control articles [19] (see supplemental file S2, NOS bias assessment). According to the NOS checklist, each article receives a maximum of 9 points, and the NOS checklist evaluates three domains: selection, comparability, and outcome (cohort studies) or exposure (case-control studies). Each domain is awarded a maximum of one star within the selection and outcome/exposure categories. A maximum of two stars can be given for comparability.

In addition, the certainty of evidence was assessed for the results using the modified method of GRADE assessment for prognostic and clinicopathological meta-analysis [20]. Certainty of evidence shows more 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 (see supplemental file S3 for description of the GRADE framework used). Based on the certainty of the evidence, our meta-analysis results are classified as high, moderate, low, or very low. High certainty means high confidence in the estimated effect, which indicates a close association between the true effect and the estimated effect. Moderate certainty means being moderately confident about the estimated effect, which shows that 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 low confidence in the estimated effect; in fact, the true effect might be substantially different from the estimate of the effect. Very low certainty means little confidence in the estimated effect, meaning that the true effect is likely to be substantially different from the estimate of the effect [20, 21].

Statistical analysis

The data from studies that met the inclusion criteria were synthesized. For prognostic analysis, the hazard ratio (HR) and 95% CIs were combined to investigate the effect of circRNAs on survival indicators. For clinicopathological meta-analysis, the risk ratio (RR) and 95% confidence intervals (CIs) were used to analyze the correlation between circRNAs and clinicopathological features in AML patients. As the primary study was methodologically heterogeneous, HR and RR values were combined by using the Random Effects Model (REM) [22]. It was determined that the magnitude of association between the study variables and the dysregulated expression of circRNAs and its interpretation area for the prognostic index (HR) and clinicopathologic characteristics index (RR) were the following: 1 to 1.21: trivial (inconsiderable); 1.22 to 1:85: small; 1:86 to 2:99: moderate; 3 or more: large [23]. In order to assess heterogeneity between studies, we used the chi-square test and the I^2 statistic. It was considered heterogeneous if the I^2 value was over 50%. For the purpose of assessing the potential sources of heterogeneity for prognostic meta-analysis, priori (as specified in the Prospero protocol, such as expression status, sample size, and follow-up time) and post-hoc subgroup analysis was performed based on the similarity between the included studies. Furthermore, sensitivity analysis of all the included articles were conducted in order to determine the influence of each article on the final effect of the meta-analysis. Publication bias was examined using the funnel plot, Egger's and Begg's tests, and the Trim and Fills method. STATA version 14.2 was used for the meta-analysis, and it was considered statistically significant if the p-value was less than 0.05.

Results

Study selection

The process of study selection based on the PRISMA flow diagram [16] is shown in Fig. 1. A total of 1049 studies were extracted from the mentioned database. Initially, 204 duplicate articles were removed. After two researchers initially screened 845 titles and abstracts, 768 were excluded because they were not compatible with the inclusion and exclusion criteria. Next, 77 studies were selected for full-text examination. 2 full-text studies could not be retrieved, and 17 studies were excluded as a result of the reasons outlined in Fig. 1. Finally, the number of articles included in the qualitative synthesis was 58 [14, 15, 24–79], and the number of articles included in the quantitative synthesis meta-analysis was 21 [14, 24, 26–33, 35, 36, 38–40, 42, 43, 49–52]. Of these, 20 articles were associated with the prognostic meta-analysis [14, 24, 26–33, 35, 38–40, 42, 43, 49–52] and 14 cohort articles were associated with the clinicopathological meta-analysis [14, 24, 26–33, 35, 36, 38, 39].

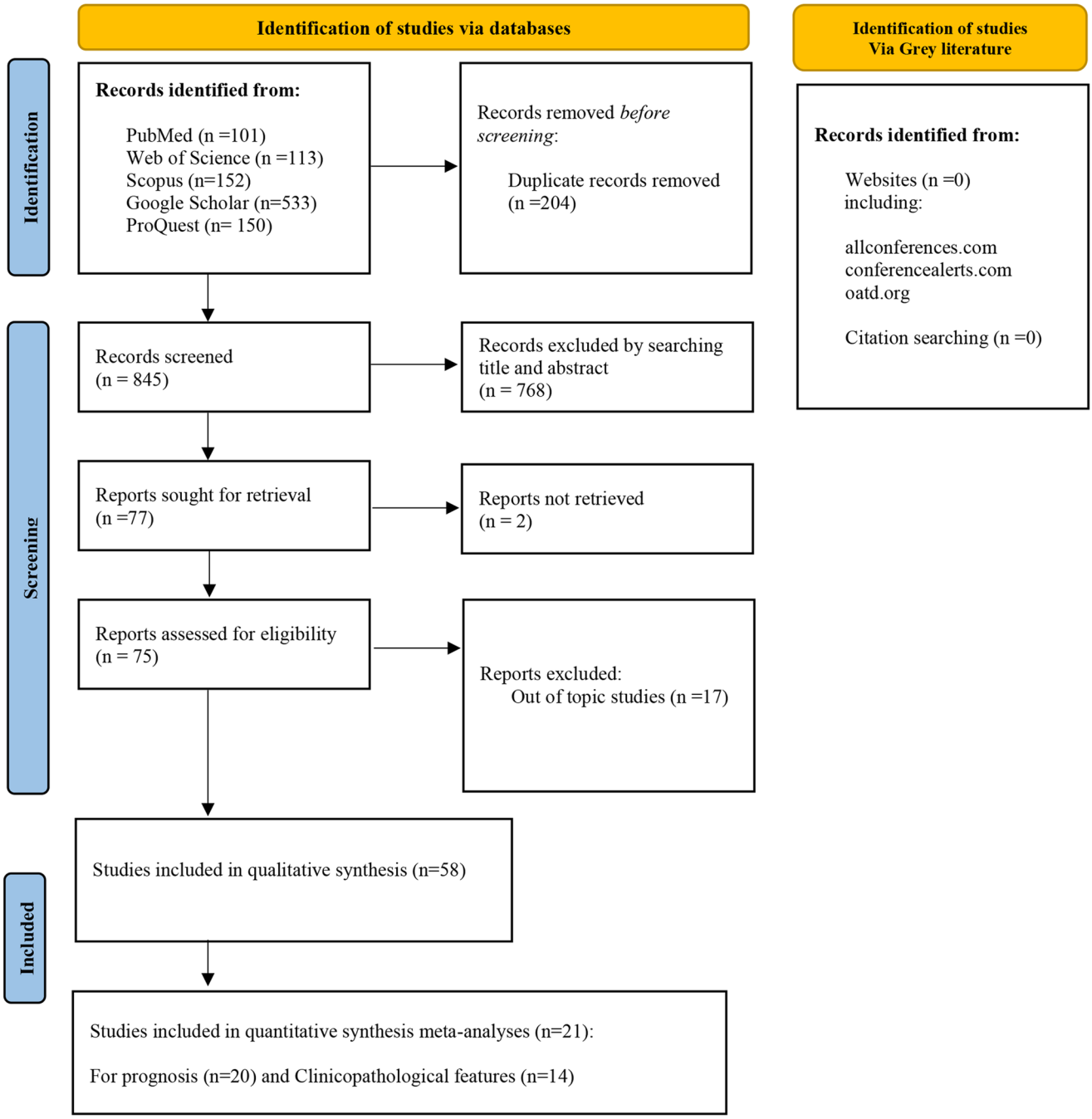

Fig. 1 The study selection processes based on the PRISMA flow diagram

Study characteristics

All the articles included in the qualitative synthesis were published between 2017 and 2023 and included 3243 patients with AML and 2188 controls. For prognostic meta-analysis, the study population was exclusively Chinese, and for clinicopathological meta-analysis, the majority of the study population was Chinese, with the exception of one article with an Egyptian population [36]. Table (1) indicates the features of the 58 included studies for qualitative synthesis, such as the role of circRNAs in cell biology function and their relationship with various microRNAs, as well as the effect of circRNAs on survival, response to treatment, and so on. In some studies, changes in circRNAs expression were measured using microarrays and confirmed using qRT-PCR. In 45 studies, circRNAs had upregulation expression, and in 13 studies, circRNAs had downregulation expression. In cohort studies, the minimum follow-up period was

Table 1 The of circrnas' role in the development of MM and the impact on survival and therapy response

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Fei Long [48]	Circ- ZBTB46	ZBTB46	Chr 20	up regulation	tumorigenesis / cell proliferation/ cell Cycle progression/ ferroptosis	Circ-ZBTB46 promotes cell proliferation by sponge miR-326 as a cell proliferation inhibitor	-	CircZBTB46 Protects AML Cells against ferroptosis which is a type of cell death. Ferroptosis is widely involved in therapy resistance
Fengjiao Han [45]	Circ-0001947	-	-	down regulation	cells proliferation/ apoptosis	Circ-0001947 sponging with miR-329-5p that inhibits the proliferation and promotes apoptosis	-	The effect of chemotherapy on circ-0001947 causes the over expression of circ-0001947 in the CR stage
Jiao Zhou [42]	Circ-Foxo3	Foxo3	-	down regulation	apoptosis	low level of circfoxo3 down regulated foxo3 and inhibits these pro apoptotic factors such as (Bim/Bad), Fas and TNF	Patients with high level of foxo3 expression had longer LFS time than low level patients.	Patients with high level of Foxo3 are more sensitive to chemotherapy drugs. After standard chemotherapy, patients with high level of Foxo3 expression lived longer than those with low level
Jichun Ma [31]	Circ-0059706	ID1[7]	-	down regulation	cell growth/ apoptosis	Circ-0059706 inhibits cell growth and increases apoptosis in leukemia by sponge miR-326	OS of patients with high circ-0059706 expression was significantly longer than that of those with low expression	Circ-0059706 had no value for predicting CR

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Jichun Ma [30]	circ −0059707	ID1[7]	-	down regulated	cell growth/ apoptosis	The Circ-0059707 inhibits cell growth and promotes apoptosis by up regulating miR-1287-5P	OS of patients in the high-circ-0059707 expression group is significantly longer than that of patients with low expression	There are no significant differences in CR rates between the high and the lowcirc-0059707 expression groups
Leilei Lin [26]	Circ-PLXNB2 (Circ-00125)	PLXNB2	Chr22	up regulation	cell proliferation/ migration/ apoptosis	Circ-PLXB2 increases the level of PLXNB2 and anti-apoptotic factors such as BCL2, cyclin D1 and decreases the level of apoptotic factors such as BAX	Patients with AML in the circPLXNB2 high group has a remarkably shorter OS and LFS than patients with AML in the circPLXNB2 low group	-
Liang Guo [24]	Circ-0079480	-	Chr7	up regulation	tumor progression	Circ-0079480 promotes tumor progression through the miR-654-3p/ HDGF regulatory axis	High serum circ-0079480 level is significantly associated with shorter OS and RFS in AML patient	Level of circ-0079480 is significantly lower among AML patients undergoing treatment, particularly in individuals that achieve CR, suggesting that serum circ-0079480 can be assesses as a biomarker associated with patient therapeutic responsiveness
Lifang Huang [46]	Circ-NFIX	-	-	up regulation	cell growth/ progression/ apoptosis	Circ-NFIX can be increase proliferation and apoptosis of AML cells by targeting the miR-876-3p/TRIM31 axis	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Ling Liu [28]	Circ- 0044907	-	-	up regulation	cell proliferation/ apoptosis	Circ-0044907 absorbs miR-186-5p to block the inhibiting impact of miR-186-5p on KIT, thus promoting AML progression.	AML patients with high expression of circ_0044907 in BM has a significantly shorter OS	-
Xiaodan Liu [29]	Circ-RNA220	RNA220	Chr 1	up regulation	cell proliferation/ apoptosis	Circ-RNA220 may function as an endogenous miR-30a sponge to inhibit its activity, which results in increased cell proliferation through targeting	-	Circ-RNA220 expression decreased dramatically in patients who achieve CR after treatment
Xiao-Yu Su [35]	circ-0002232	PTEN	Chr 10	down regulation	-	-	Circ-0002232 low group has significantly longer OS compared with circ-0002232high group in whole AML	There are no significant discrepancies between the group with low expression of circ-0002232 and group with high expression of circ-0002232
Yi Ding [44]	Circ-ANXA2	-	-	down regulation	cell proliferation/ apoptosis	circ-ANXA2 sponging with miR-23a-5p and miR-503-3p to promoting proliferation and decrees apoptosis in AML cell line	circ-ANXA2 high expression is correlated with shorter OS and EFS in AML	circ-ANXA2 knockdown increased chemosensitivity to cytarabine and daunorubicin in AML cell line
Ying Shen [34]	Circ-ANAPC7 (Circ-101141)	ANAPC7	Chr 12	down regulation	-	-	The expression level of circ-ANAPC7 is not related to OS and DFS of AML patients	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Yun-Yun Yi [14]	Circ-VIM	Vimentin	-	up regulation	tumor progression	Circ-VIM may accelerate the progression of AML by up regulating the expression of VIM genes through certain miRNAs and the Pol II transcription	Over expressed Circ-VIM is associated with shorter OS and LFS in whole-cohort AML	There is no significant difference in complete remission rate between Circ-VIM low patients and Circ-VIM high patients after induction therapy
Safaa ITayel [36]	Circ-0075001	-	-	up regulation	-	-	Group with high expression of circ-0075001 has significantly short OS	Univariate analysis revealed that over expression of circ-0075001 can predict CR achievement
Tao Chen [43]	Circ-PVT1	PVT1	Chr 8	up regulation	-	-	High expression of circ-PVT1 is correlated with shorter EFS and OS in AML patients	High expression of circ-PVT1may reduce the sensitivity of AML cell lines to chemotherapy
Wei Li [47]	Circ-0004277	WDR37	Chr 10	down regulation	-	-	-	Significant increase of circ-0004277 expression in CR stage compared with AML patient without prior treatment
Hong Li [61]	Circ-POLA2	-	-	up regulation	maturation/cells proliferation	Circ-POLA2 promotes cell proliferation by suppressing the production of mature miR-34a	The patients with higher expression levels of circ-POLA2 have lower OS rate	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Lai Yi [75]	Circ-PTK2	-	-	up regulation	Cell proliferation/ Apoptosis	Circ-PTK2 promotes the proliferation and hampers the apoptosis of AML cells through targeting miR-330-5p/ FOXM1 axis	AML patients with high expression of circ-PTK2 have shorter survival time compared with those with low expression of circ-PTK2	-
Lei Ping [32]	Circ-0009910	-	Chr 1	up regulation	cell proliferation/ apoptosis	knockdown of circ0009910 inhibits AML cell proliferation and induces apoptosis through increasing miR-20a-5p	the patients with high expression of circ-0009910 have shorter OS rate than those with low expression of circ-0009910	-
Ting Xiong [51]	Circ-SPI1 (Circ-0000303)	-	-		cell proliferation/ apoptosis/ differentiation	-	There is no correlation between EFS and circ-SPI1 expression at baseline, while low circ-SPI1 expression after induction therapy is linked with longer EFS in AML patient	Low circ-SPI1 expression at baseline shows a correlation trend with CR. Whereas reduced circ-SPI1 expression after induction therapy is associated with CR
Wu Zijuan [40]	Circ-KEL	-	-	up regulation	Cell proliferation/ apoptosis	Circ-KEL sponging with miR-335-5p and regulate LRG1, which their association to cell proliferation and cell apoptosis	patients with high circ-KEL expression have significantly worse OS	-
Jinghan Wang [50]	Circ-0075451	GMDS [8]	Chr 6	up regulation	a unique metabolic feature	Circ-0075451 can directly bind to miR-330-5p and miR-326, thereby affecting the expression of PRDM16	Circ-0075451 causes the poor survival	-

Table 1 (continued)

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Yuanyuan Lin [27]	Circ-TASP1 (Circ-406083)	TASP1	Chr 20	up regulation	cell proliferation/ apoptosis/ tumor progression	knockdown of circ-TASP1 inhibits proliferation and induces apoptosis by modulating miR-515-5p/HMGA2 pathway and Wnt/β-catenin signaling	high levels of circ-TASP1 leads to poor survival of patients with AM	knockdown of circ-TASP1 in mice can significantly reduce tumor growth, indicating that circTASP1 can be considered as a potential therapeutic target for children's AML and save more lives
Zhen Shang [33]	Circ-001215	RNF220	Chr 1	up regulation	cell proliferation/ apoptosis/	Circ-0012152 knockdown suppresses cell proliferation and promotes death by targeting SOX12 mediated by miR-625-5p in AML cells	the overall survival rate of high circ_0012152 group is significantly lower than that of low circ_0012152 group	-
Yao Liu [67]	Circ-0004277	-	-	down regulation	tumor progression	Circ-0004277 suppresses the progression of AML via miR-134-5p/SSBP2 axis	-	-
Di Wang [37]	Circ-0009910	-	-	up regulation	cell proliferation/ apoptosis/ cell cycle	Circ-0009910 knockdown restricts AML cell proliferation, arrests cell cycle, and augments apoptosis by up regulating miR-5195-3p.	Circ-0009910 up regulation is also associated with shorter survival of AML patients	-
Qinghua Li [62]	Circ-0005774	-	Chr 10	up regulation	cell proliferation/ apoptosis/ cell cycle	blocking circ-0005774 and/or over expressing miR-192e5p can be enhance apoptosis or another mechanism	-	-
D.M. YUAN [76]	Circ-0004136	-	-	up regulation	cell proliferation	Circ-0004136 promotes the proliferation of AML by sponging miR-142	-	-
Hongli Chen [15]	Circ-ANAPC7 (Circ-101141)	ANAPC7	-	up regulation	-	Sponging with miR-181 family	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Hongqiong Fan [58]	Circ-100,290	-	-	up regulation	proliferation/ apoptosis	Circ-100,290 sponging with miR-203 and regulate the proliferation and apoptosis of AML cells and can accelerates cell proliferation and inhibits cell apoptosis by regulating cyclin D1, CDK4, Bcl-2	-	-
Juan Tong [69]	Circ-0000005	-	-	up regulation	Proliferation/migration/ invasion/apoptosis	Circ-0000005 sponging with miR-139-5p and repressing expression of miR-139-5p, and Tspan3 negatively regulates by miR-139-5p	-	-
Rong Zhang [78]	Circ-RNF13 (Circ-0001346)	RNF13[9]	chr3	up regulation	Proliferation/migration/ invasion/apoptosis	downregulation of circRNF13 can inhibit the proliferation and promote the early apoptosis by activating Caspase 3/7 and miRNA-1224-5p regulates the function of circRNF13	-	-
ShanshanGuo [59]	Circ-0012152	-	-	up regulation	-	Circ-0012152 can be modulating miR-491-5p/ EGFR/MAPK1 or miR-512-3p/EGFR/MAPK1 axis	-	-
Yarong Wu [72]	Circ-ATAD1	-	-	up regulation	cell proliferation	As a nucleus specific circRNA in AML, modulates AML cell proliferation by downregulation miR-34b via methylation.	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Xiaoyan Hu [60]	Circ-KCNQ5 (Circ-0004136)	KCNQ5[10]	-	up regulation	cell proliferation/ apoptosis	Circ-KCNQ5 sponging to miR-622 and inhibits miR-622 expression. miR-622 regulates RAB10 and circ-KCNQ5 bound to miR-622 to increase the expression of RAB10. MiR-622 inhibits AML cell proliferation and induces cell apoptosis.	-	-
Lingyan Zhang [77]	Circ-0000370	FLI-1	-	up regulation	cell viability/ apoptosis	Circ-0000370 increases cell viability and inhibits apoptosis of FLT3-ITD-positive acute myeloid leukemia cells by regulating miR-1299 and S100A7A	-	-
Shifang Dong [57]	Circ-DLEU2 (Circ-0000488)	-	-	up regulation	proliferation/migration/ invasion/apoptosis	Increased expression of Circ-DLEU2 induces cell proliferation, migration and invasion, and induces cell apoptosis through the miR-582-5p/COX2 axis. Also, miR-582-5p leads to decreased expression of Bcl-2 and increased level of Bax.	-	-
Wei Chang [55]	Circ-SFMBT2 (Circ-0017639)	SFMBT2[11]	-	up regulation	proliferation/ migration/invasion /glycolysis / induced apoptosis	circ-SFMBT2 sponging with miR-582-3p, and miR-582-3p targets ZBTB20.Also, circ-SFMBT2 leads to decreased levels of in Cyclin D1 and MMP9 and a significant increase in Bax level	-	-
Wen Liu [66]	Circ-CRKL	CRKL[12]	-	Downregulation	proliferation	Circ-CRKL inhibits AML cells proliferation by sponging miR-196a-5p/ miR-196b-5p to affect p27 expression.	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Zewen Zhang [41]	CircRNF220 (Circ-0012152)	RNF220[13]	chr1	up regulation	cell development/ apoptosis	Circ-RNF220 effects on miR-330-5p/SOX4 axis. glucose consumption and lactate production suppress by circRNF220 level inhibition, means that circRNF220 might block the glycolytic process in AML cell progression	-	-
Yi Xiao [73]	Circ-0002483	PTK2[14]	-	up regulation	proliferation/ apoptosis	Circ 0002483 interacts with miR-758-3p/MYC axis and also, down-regulation of circ 0002483 induces reduction of Bcl-2 and elevation of Bax and C-caspase 3/ Pro-caspase 3.	-	-
Yanyan Wang [71]	Circ-RAD18	-	-	up regulation	cell progression/ apoptosis	Circ-RAD18 positively modulated PRKACB expression via targeting miR-206 in AML cells. Down regulation of Circ-cRAD18 also induces the apoptosis of AML cells, along with the elevation of Bax and c-caspase-3 and the reduction of Bcl-2	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Xiaoling Wang [70]	Circ-SPI1	SPI1	chr11	up regulation	myeloid differentiation/proliferation/apoptosis	Circ-SPI1 contributes to myeloid differentiation of AML cells by interacting with the translation initiation factor eIF4AIII to antagonize expression of PU.1 at the translation level. And also, circSPI1 induces the proliferation and apoptosis by interacting with miR-1307-3p, miR-382-5p, and miR-767-5p. BCL2, CDK6, and p-ERK1/2, which involves in apoptosis, decreased upon circSPI1 knockdown.	Expression of HSPA8 is positively correlates with circSPI1 expression. HSPA8 is essential for the survival of AML cells	-
Yingwei Wu [39]	Circ-0009910	-	-	up regulation	proliferation/ sphere formation/ autophagy/ apoptosis	Circ-0009910 can be modulating expression of B4GALT5 and activating the PI3K/AKT signaling pathway via sponging miR-491-5p in AML cells.	the overall survival rate of high circ-0009910 group is distinctly lower than that of low circ-0009910 group	-
Ting Zhang [79]	Circ-0058058	-	-	up regulation	cell proliferation/migration/ / invasion/ apoptosis	Circ 0058058 interacts with miR-4319/EIF5A2 axis. miR-4319 has an anticancer role by inhibiting the expression of EIF5A2	-	-
Qidong Ye [52]	Circ-0003602 (Circ-SMARCC1)	-	chr3	up regulation	Proliferation/migration/ invasion/ apoptosis	Circ-0003602 interacts with miR-502-5p/ IGF1R axis. miR-520-5p inhibitor leads to a significant increase in IGF1R protein levels	patients with high expression of circ-0003602 shows shorter survival time compared to those with low expression of circ-0003602	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Jing Liu [65]	Circ-0003256	CIT [15]	-	up regulation	cell Proliferation/ apoptosis	Circ-0003256 Contains Functional Binding Sites for miR-582-3p. Protein kinase cAMP-activated catalytic subunit beta (PRKACB) is a functionally downstream target of miR-582-3p	-	-
Jing Bi [53]	Circ-0004136	KCNQ5[10]	-	up regulation	cell viability/ cell cycle progression/ migration / invasion/ apoptosis	Exosomal circ-0004136 enhances the progression of pediatric acute myeloid leukemia depending on the regulation of miR-570-3p/tetraspanin 3(TSPAN3) axis	-	-
Nianxue Wang [38]	Circ-0040823	-	-	Downregulation	cell Proliferation / apoptosis	sponging with miR-516b, thereby diminishing the regulatory effect of miR-516b on PTEN. circ-0040823 induces cell apoptosis and G0/G1 arrest in leukemia cells so High Circ-0040823 level also leads to markedly reduce expressions of cyclins and Bcl-2, and unregulated Bax and cleaved caspase 3 in AML cells.	high expression of circ-0040823 shows significantly improved overall and disease-free survival compared with the "low circ-0040823" group	-
Shufen Li [63]	Circ-HIPK2	HIPK2	-	Downregulation	differentiation	Circ-HIPK2 might contribute to APL differentiation by sponging miR-124- 3p to restore the protein level of CEBPA	-	circ-HIPK2 is require for ATRA-induced differentiation of APL cells.

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Jiufang Cao [54]	Circ-0094100	-	-	up regulation	cell viability / cell cycle /apoptosis	Circ-0094100 positively modulates ATP1B1 expression by sponging miR-217	-	Rapamycin inhibits AML cell viability and cell cycle process and induces apoptosis via regulation of the circ-0094100/miR-217/ATP1B1 axis. Rapamycin treatment markedly reduces circ_0094100 expression in AML cell.
JIE DING [56]	Circ-NPM1 (Circ-0075001)			up regulation	cell proliferation/migration/ invasion / cell cycle arrest	Circ-NPM1 modulates miR-345-5p/ FZD5 axis.		circNPM1 might be an effective regulator of ADM chemoresistance in AML cells. circNPM1 silence can be strengthen the effects of ADM, leading to further cell proliferation, migration and invasion inhibition, apoptosis promotion and cell cycle arrest
Feng Xue [74]	Circ-0035381	PIGB	-	up regulation	proliferation, Apoptosis//Mitochondrial Damage/ autophagy	Circ-0035381 regulating miR-582-3p/ YWHAZ axis. Circ-0035381 knockdown evidently suppresses autophagy by decreasing the value of LC3II/I and the protein level of Beclin1 and also represses cell proliferation and promoted cell apoptosis and mitochondrial damage.	-	-

Table 1 (continued)

Author's name	CircRNAs	Gen Symbol	Chr[1]	Expression status	Impact on functions of cells or biological role	Mechanism	Impact on survival (OS[2], PFS[3], LFS[4], EFS[5], DFS[6]and so on)	Impact on therapy response
Guoqiang Lin [64]	Circ-0003420	-	-	Downregulation	replication/ apoptosis	Circ-0003420 targets the mRNA of insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1). down-regulation of IFG2BP1 in response to circ-0003420 overexpression induces cell apoptosis and suppressed the expression of HOXB1, MYB, and ALDHA1A1	-	-
Susanne Lux [68]	Circ-BCL11B	BCL11B[16]	-	up regulation	cell proliferation	Knockdown of circ-BCL11B has a negative effect on leukemic cell proliferation and result to in increased cell death of leukemic cells.	-	-
Hong Li [25]	Circ-EHBP1	-	-	up regulation	apoptosis	High expression of CircEHBP1 increased premature miR-129 level but decreased mature miR-129 Level.	-	Altered gene expression is more obvious in ADR resistant group than in ADR sensitive group. CircE-HBP1 suppresses ADR-induced cell apoptosis and attenuates the enhancing effects of miR-129 on cell apoptosis.
Xian-Fu Sheng [49]	Circ-PVT1	PVT1	chr8	up regulation	Cell viability/ migration/ apoptosis	CircPVT1 may exert an oncogenic role by stabilizing the expression of c-Myc protein and its downstream target CXCR4 expression.	Higher expression of circPVT1 is related to shorter OS and RFS in AML patients	-

[1]Chromosome; [2]Overall survival;[3]Progression-free survival;[4]Leukemia-free survival; [5] event-free survival;[6]Disease Free Survival; [7] Inhibitor of DNA binding 1; [8]GDP-mannose 4,6-dehydratase; [9] RING finger protein 13; [10] Potassium Voltage-Gated Channel Subfamily Q Member 5; [11]Scm like with four mbt domains 2; [12]V-Crk Avian Sarcoma Virus CT10 Oncogenic Homolog-Like; [13]Ring Finger Protein 220; [14]Protein tyrosine kinase 2; [15] Citron rho-interacting serine/threonine kinase; [16]T-cell transcription factor gene B cell CLL/lymphoma 11B; [17]Plasmacytoma Variant Translocation 1

50 months, and the maximum was 100 months. In the study of Safaa I Tayel [36], three circRNAs were measured along with different expression levels and varied clinicopathological characteristics; therefore, to avoid multiplicity [80], only one circRNA (Circ-0075001) was chosen for clinicopathological meta-analysis.

Results of syntheses

Prognostic value of circrnas in AML patients

In the prognostic meta-analysis, 1758 AML patients from 20 primary studies were included, and the main features of these studies are shown in Table 2. 18 studies reported an overall survival (OS) indicator, and the pooled results related to the OS indicator demonstrated that dysregulation of circRNAs expression were associated with a poor prognosis (HR = 2.05; 95% CI: 1.75 to 2.40) in patients with AML (Fig. 2A). Also, $I^2 = 15.7\%$ in the OS indicator showed that heterogeneity between studies was non-considerable. In addition, 8 studies reported non-OS indicators such as (EFS, LFS, RFS, and DFS). The pooled results related to non-OS indicators revealed that dysregulation of circRNAs expression were associated with shorter EFS/LFS/RFS/DFS than the normal expression of circRNAs (HR = 2.09, 95% CI = 1.47–2.97) (Fig. 2B). Also, $I^2 = 59.7\%$ in non-OS indicators showed that heterogeneity between studies was considerable.

Subgroup analysis The results of subgroup analysis for both OS and non-OS indicators are shown in Table 3. Subgroup analysis for the OS indicator was performed based on expression status (Upregulation vs. Downregulation), gene control (GAPDH vs. non-GAPDH), follow-up time (<=60 vs. >60), sample size distribution (<=60 vs. >68), and extraction method (Direct vs. Indirect) (Fig. 3A-E). According to subgroup analysis results, an obvious difference was observed in the results of sample size and control gene that seems to have been overestimated. Also, subgroup analysis for non-OS indicators was conducted based on sample size (<74 vs. >=74) and extraction method (Direct vs. Indirect) (Table 3) (Fig. 4A-C). The result of HR in studies with sample size >= 74 was 2.69 (95% CI: 1.22–5.94) whereas the result of HR in studies with a sample size < 74 was 1.79 (95% CI: 1.26–2.56). Studies with direct extraction indicated a higher HR (2.71 vs. 1.81) than studies with indirect extraction.

The clinicopathological significance of circrnas in AML patients

For clinicopathological meta-analysis, in 14 cohort primary studies, the association between dysregulated expression of circRNAs and clinicopathological parameters such as Gender, Risk status, French–American–British (FAB) classification, Different Cytogenetic abnormalities and Mutations were investigated (Table 4). Parameters with at least five studies were included in the clinicopathological meta-analysis. In the French–American–British (FAB) classification, type M6 vs. other types showed significant associations with dysregulated expression of circRNAs (RR: 1.51, 95%CI: 1.12–2.03) (Fig. 5A), while other types of this classification weren't related to dysregulated expression of circRNAs. The results for different cytogenetic abnormalities and mutations showed a relationship between dysregulated expression of circRNAs and the FLT3-ITD mutation (RR: 1.17, 95%CI: 1.00-1.36) (Fig. 5B), while there was no significant relationship between dysregulated expression of circRNAs and other mutations. Furthermore, a significant relationship was observed between dysregulated expression of circRNAs and Risk status (RR: 1.35, 95%CI: 1.13–1.60) (Fig. 5C). Also, dysregulated expression of circRNAs wasn't linked to Gender (RR: 1.03, 95%CI: 0.93–1.14) (Fig. 5D) (Figures related to other parameters are available in supplementary data S4/Figs. 1 and 2).

Publication bias evaluation

The funnel plot, Egger's and Begg's tests, and trim and fill method were performed to assess publication bias. For prognostic meta-analysis, the results of the funnel plot pattern (asymmetric distribution) (Fig. 6A), Begg's test (P-value = 0.001), Egger's test (P-value = 0.005) (Fig. 6B), as well as the results of the trim and fill method (Fig. 6D), indicated considerable publication bias for the OS indicator. Also, the results of Begg's test (P-value = 0.009), Egger's test (P-value = 0.006) (Fig. 6C), and the results of the trim and fill method (Fig. 6E) showed considerable publication bias for non-OS indicators. As is shown in Table 4, for clinicopathological meta-analysis, Begg's and Egger's tests showed that type of M2 (FAB classification), CEBPA mutation, DNMT3A mutation, and NPMI mutation had obvious publication bias, and also that only Egger's tests for type of M6 (FAB classification) showed publication bias. Meanwhile, other clinicopathological parameters had low publication biases.

Table 2 Main characteristics of the prognostic studies

Author's name	Country	Year	CircRNAs	Expression status	Gene Control	AML[a] patiens size	Sample type	Detection method	Survival outcome	Survival indicator		HR Extraction	Follow up*	NOS[e]
										HR[c] (95% CI[d])	*P* value			
Jiao Zhou [42]	China	2019	Circ-Foxo3	Down regulation	ABL	122	BM[f]	qRT-PCR	OS[b]	1.039 (0.65–1.66)	0.873	Direct	60	8
Jichun Ma [31]	China	2022	Circ-0059706	Down regulation	ABL	57	BM	qRT-PCR	OS	1.890 (0.97–3.66)	0.059	Direct	100	8
Jichun Ma [30]	China	2022	Circ_0059707	Down regulation	ABL	58	BM	qRT-PCR	OS	2.0 (0.95–4.16)	0.065	Direct	60	9
Jinghan Wang [50]	China	2021	Circ-GMDS (Circ-0075451)	up regulation	β-actin	218	BM	microarray qRT-PCR	OS	1.706 (1.19–2.43)	0.003	Direct	90	8
Lei Ping [32]	China	2019	Circ-0009910	up regulation	β-actin	70	BM	microarray qRT-PCR	OS	2.38 (1.13–4.97)	0.021	Indirect	80	8
Leilei Lin [26]	China	2021	Circ-PLXNB2 (Circ-0001257)	up regulation	GAPDH	40	BM	microarray qRT-PCR	OS	2.60 (1.06–6.35)	0.0364	Indirect	50	7
									LFS[h]	2.56 (1.04–6.26)	0.0393			
Liang Guo [24]	China	2022	Circ-0079480	up regulation		236	PB[g]	qRT-PCR	OS	1.76 (1.27–2.39)	<0.05	Indirect	60	9
									RFS[i]	1.34 (1-1.78)	<0.05			
Ling Liu [28]	China	2022	Circ-0044907	up regulation	GAPDH	45	BM	qRT-PCR	OS	2.18 (1.20–4.33)	<0.05	Indirect	60	8
Tao Chen [43]	China	2021	Circ-PVT1	up regulation	GAPDH	68	BM	qRT-PCR	EFS[k]	1.379 (1.01–1.88)	0.043	Direct	60	7
Ting Xiong [51]	China	2022	Circ-SPI1	up regulation	GAPDH	80	BM	qRT-PCR	OS	2.698 (1.03–7.03)	0.042	Direct	60	8
									EFS	1.878 (0.93–3.78)	0.078			
Wu Zijuan [40]	China	2021	Circ-KEL	up regulation	GAPDH	116	BM	qRT-PCR	OS	1.93 (1.22–3.03)	<0.01	Indirect	80	8
Xian-Fu Sheng [49]	China	2023	Circ-PVT1	up regulation	GAPDH	23	BM	qRT-PCR	OS	3.43 (1.15–10.24)	0.027	Indirect	50	7
									RFS	2.62 (1.01–6.80)	0.047			
Xiaodan Liu [29]	China	2021	Circ-RNF220 (Circ-0012152)	up regulation	GAPDH	149	BM PB	microarray qRT-PCR	RFS	5.749 (1.21–27.10)	0.027	Direct	60	7
Xiao-Yu Su [35]	China	2020	Circ-0002232	Down regulation	ABL	88	BM	qRT-PCR	OS	1.817 (1.02–3.22)	0.041	Direct	70	8
Yuanyuan Lin [27]	China	2021	Circ-TASP1	up regulation	GAPDH	60	PB	microarray qRT-PCR	OS	4.50 (2.03–9.95)	0.0002	Indirect	80	8
Yun-Yun Yi [14]	China	2018	Circ-VIM	up regulation	ABL	113	BM	qRT-PCR	OS	3.206 (1.83–5.60)	0.001	Direct	84	8
									LFS	7.023 (2.69–18.28)	0.001			
Zhen Shang [33]	China	2021	Circ-0012152	up regulation	GAPDH	60	BM	qRT-PCR	OS	3.57 (1.53–8.26)	0.003	Indirect	60	8
Qidong Ye [52]	China	2022	Circ-0003602	up regulation	GAPDH	50	BM	qRT-PCR	OS	2.43 (1.08–5.44)	0.0315	Indirect	60	6
Yingwei Wu [39]	China	2021	Circ-0009910	up regulation	β-actin	37	BM	qRT-PCR	OS	2.45 (1.02–5.83)	0.0438	Indirect	60	8
Nianxue Wang [38]	China	2021	Circ-0040823	Down regulation	GAPDH	68	PB	microarray qRT-PCR	OS	2.27 (1.08–4.74)	0.029	Indirect	80	8
									DFS[m]	2.28 (1.13–4.57)	0.020			

[a] Acute myeloid leukemia; [b] Overall survival; [c] Hazard ratio; [d] 95% confidence interval; [e] Newcastle-Ottawa Scale; [f] Bone marrow; [g] Peripheral blood

[H] Leukemia-free survival; [I] relapse-free survival; [k] event-free survival; [m] Disease Free Survival

[*] Months

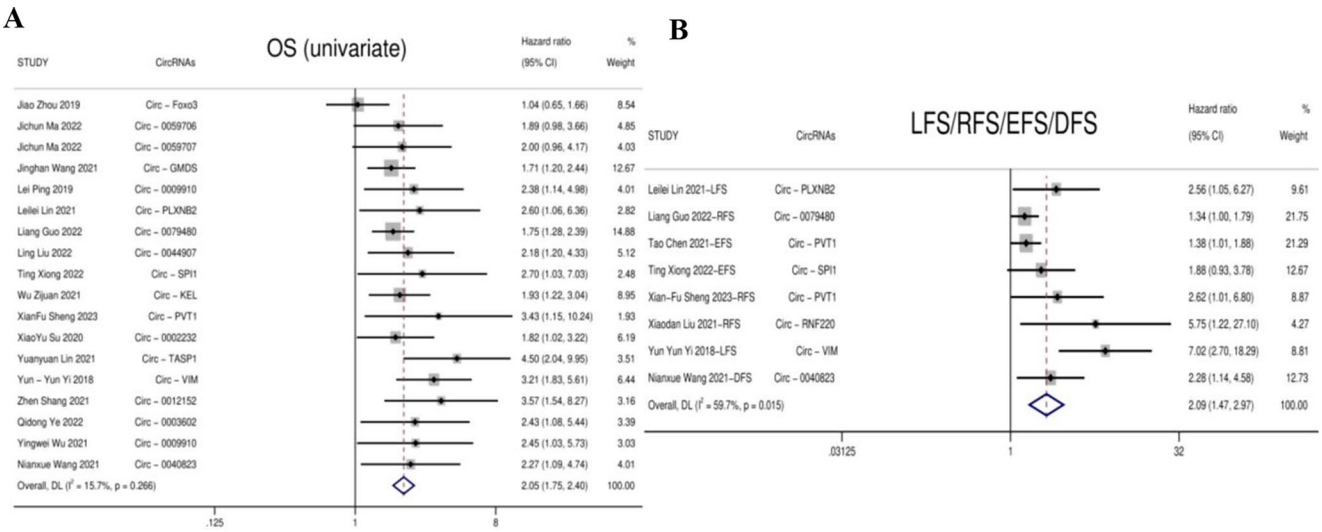

Fig. 2 Forest plots for the prognostic value of circRNAs in AML patients. Prognostic value of circRNAs related to overall survival (OS) indicator (**A**) and Prognostic value of circRNAs related to non-OS indicators (**B**)

Table 3 The subgroup analysis for OS indicator and non-OS indicators

Subgroups For OS indicator	No. of studies	Hazard Ratio (95% CI)	I^2%	Subgroups For Non-OS indicators	No. of studies	Hazard Ratio (95% CI)	I^2%
Total study included	18	2.05(1.75–2.40)	15.7	**Total study included**	8	2.09 (1.47–2.97)	59.7
Expression status:	7	2.07 (1.75–2.45)	0.0	**Non-OS indicator**:	2	4.18 (1.56–11.22)	56.1
Up regulation	11	1.93 (1.40–2.67)	42.7	LFS	3	2.10 (0.98–4.50)	58.4
Down regulation				RFS	2	1.45 (1.09–193)	0.0
				EFS	1	2.28 (1.14–4.58)	--
				DFS			
Sample size:	10	2.52 (1.97–3.22)	0.0	**Sample size**:	4	1.79 (1.26–2.56)	24.0
<=68	8	1.84 (1.48–2.28)	35.3	<74	4	2.69 (1.22– 5.94)	77.7
>68				>=74			
Extraction method:	7	1.84 (1.39–2.76)	41.3	**Extraction method**:	4	2.71 (1.25–5.88)	76.2
Direct	11	2.20 (1.82–2.64)	0.0	Direct	4	1.81 (1.23–2.67)	34.1
Indirect				Indirect			
Gene Control:	9	2.51 (1.96–2.44)	0.0				
GAPDH	9	1.83 (1.49–2.23)	24.7				
Non - GAPDH							
Follow up– time:	10	1.98 (1.56–2.53)	23.5				
<=60	8	2.14 (1.74–2.63)	8.8				
>60							

Sensitivity analysis

The one-out remove method was used for sensitivity analysis, which evaluates the influence of individual studies on the effect size. The one-out remove method showed that removing any of the primary studies had no significant effect on the pooled results (Fig. 7A). Furthermore, for non-OS indicators, the trim and fill method indicated that four studies were added, whereas publication bias had no impact on the results (Fig. 6E). Also, the one-out remove method showed that the study of Yun-Yun YI [14] can change the overall effect of circRNAs on the combination of HRs but has no significant impact (Fig. 7B). Also, sensitivity analysis for clinicopathological parameters demonstrated that the study of Yuanyuan Lin [27] in the CEBPA mutation parameter and the study of Xiao-Yu Su [35] in the t (15;17) parameter can have an effect on the pooled results. Further analysis revealed that the exclusion of the Xiao-Yu Su [35] study doesn't change the pooled results of the t (15;17) parameter, but the exclusion of the Yuanyuan Lin [27] study makes the CEBPA mutation parameter significant with (RR = 1.21 95%CI: 1.04–4) and reduced heterogeneity between studies (I^2 = 0%) (Figures related to sensitivity analysis for clinicopathological parameters are available in supplementary data S4/Figs. 3 and 4, and 5).

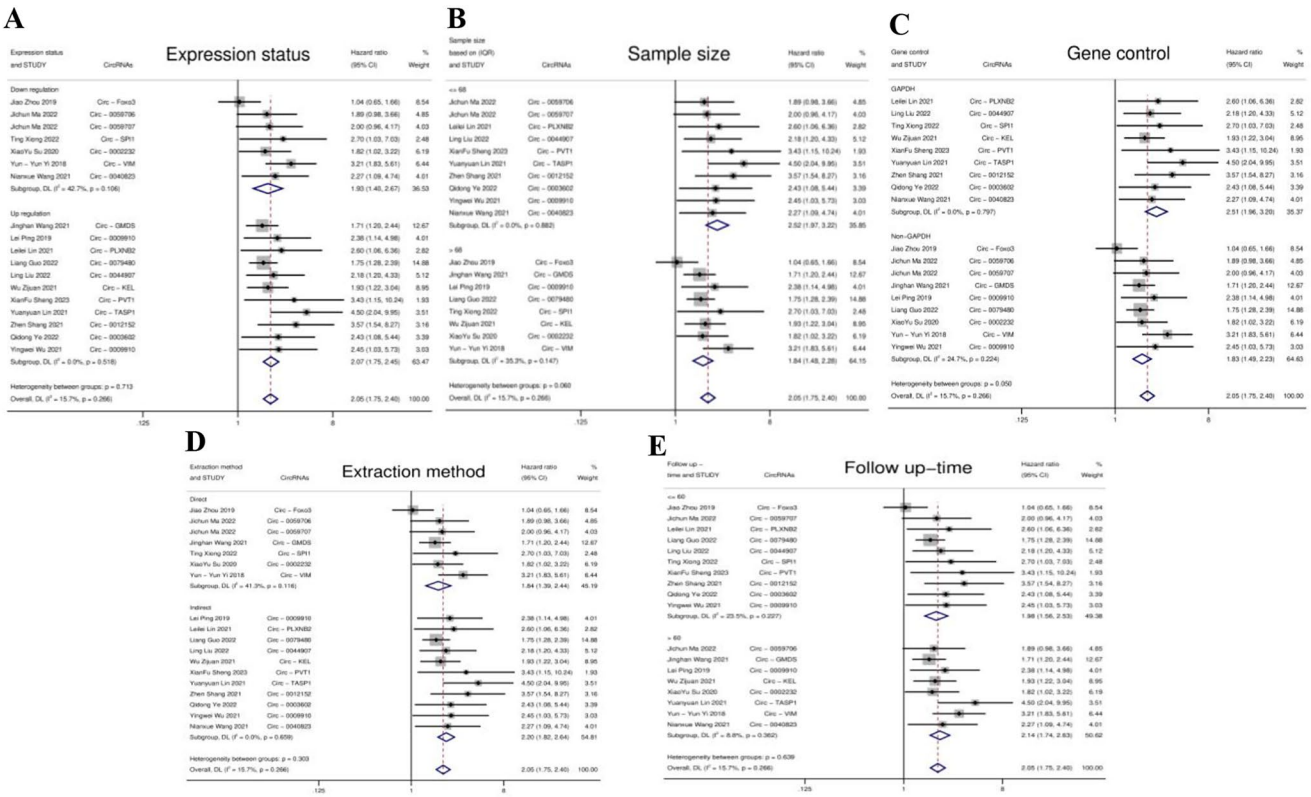

Fig. 3 Forest plots of subgroup analysis for overall survival (OS) indicator. Subgroup analysis based on expression status (**A**), subgroup analysis based on Sample size (**B**), subgroup analysis based on Gene control (**C**), subgroup analysis based on Extraction method (**D**), subgroup analysis based on Follow up– time (**E**)

GRADE assessment

The modified method of GRADE assessment was used to appraise the certainty of evidence for prognostic and clinicopathological meta-analysis [20]. According to the results of the GRADE assessment for prognostic meta-analysis, moderate certainty of evidence related to pooled results of OS and non-OS indicators was observed (the scoring method and the results are shown in Table 5). In addition, the results of the GRADE assessment for clinicopathological meta-analysis are shown in Table 4. For significant clinicopathological parameters, high certainty of evidence for results of FLT3-ITD and risk status parameters and low certainty of evidence for type of M6 were obtained (the scoring method and the results of GRADE assessment for clinicopathological meta-analysis are available in supplementary data S5).

Discussion

Acute myeloid leukemia (AML) is a heterogeneous disease with a highly variable prognosis [81]. Despite the advances in research into blood cancer and treatment, patients with AML still experience a poor overall survival rate [82]. The 5-year survival rate for AML patients is still below 50% in adults and is drastically lower in elderly individuals [83]. For example, the typical survival of patients aged 65 and over is less than 12 months [84]. For patients with acute myeloid leukemia, selecting appropriate prognostic factors is essential for predicting the course of the disease, selecting the treatment, and monitoring the response to treatment [85]. An assessment of the prognosis of patients with AML is based on their cytogenetic abnormalities, gene mutations, age, white blood cell count and etc [81]. Recent studies have gradually explored non-coding RNA's role in AML. As is demonstrated in Table 1, circRNAs have various functions in intracellular processes (proliferation, apoptosis, metastasis, cell cycle regulation, and so on) by sponging with miRNAs and other ways. Due to their impact on the survival rate, trend of treatment, and their circular structure (highly stable in tissues and bodily fluid), circRNAs can be considered novel prognostic biomarkers in AML. So, our attention in this systematic review and meta-analysis was to investigate the prognostic value of circRNAs in AML and to find the correlation between circRNAs and patients clinicopathological features, which can finally be useful in the prognosis and treatment process of AML patients. From 58 primary studies, we extracted descriptive information

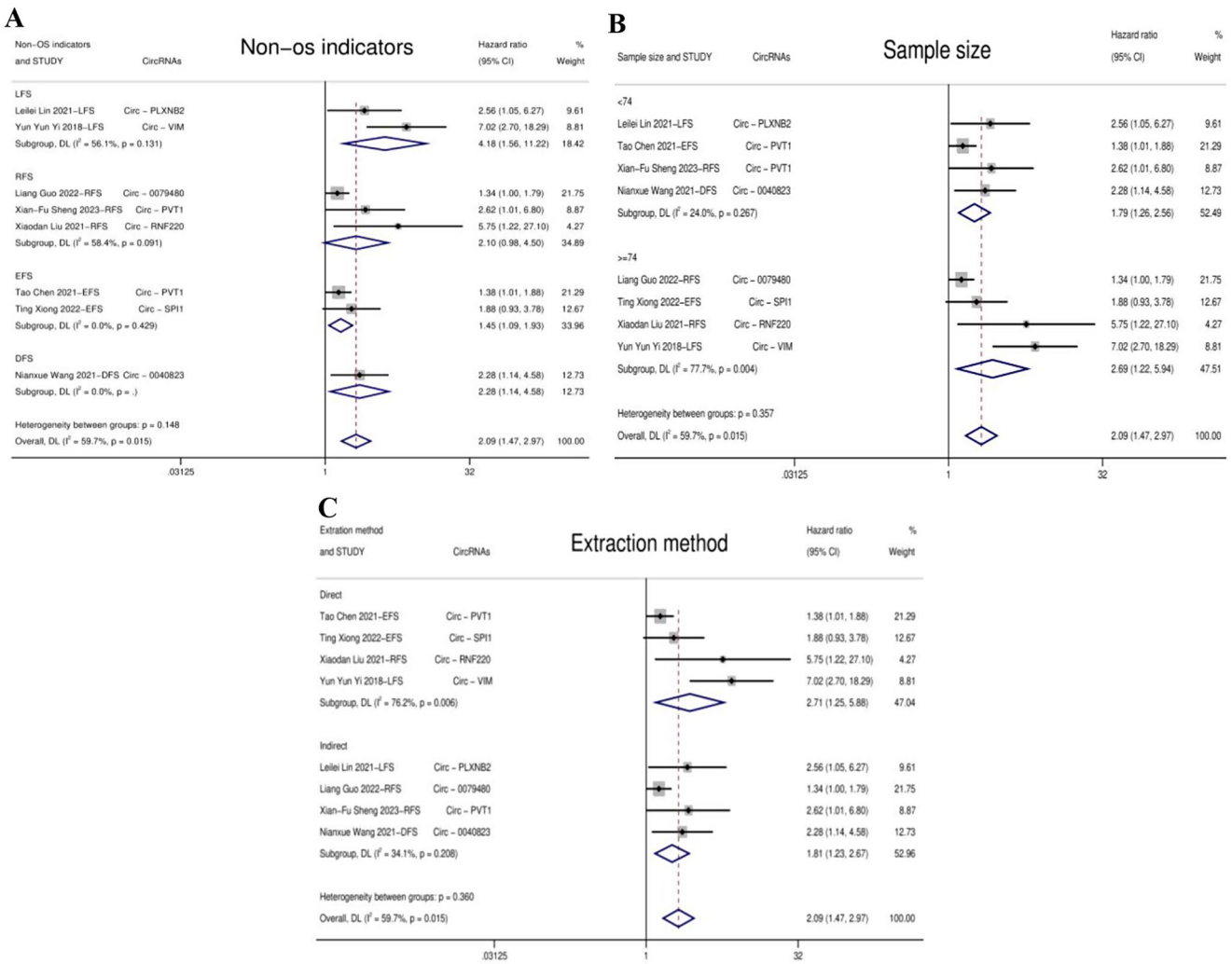

Fig. 4 Forest plots of subgroup analysis for non-OS indicators. Subgroup analysis based on non-OS indicators (**A**), subgroup analysis based on Sample size (**B**), subgroup analysis based on Extraction method (**C**)

regarding circRNAs function for our systematic review and meta-analysis. Among the primary studies, 20 studies provided prognostic information, and 14 cohort studies provided clinicopathological information. The results of our study indicated that dysregulation of circRNAs expression in AML patients is associated with poor prognosis related to OS indicator as well as non-OS indicators (HR = 2.05 and HR = 2.09, respectively). The interpretation areas [23] suggest that these relationships are moderate, and based on the GRADE assessment [20, 21], the relationships are moderately certain. The results of our study emphasize, as in other articles [9, 10, 86, 87], the prognostic role of circRNAs in blood cancers such as AML. As well, other systematic reviews and meta-analysis (like our previous study) demonstrate the prognostic value of circRNAs in variety of diseases [87–90]. Moreover, based on Tables 1 and 2 and HR data, over-expressed circTASP1, and under-expressed Circ-0040823 are significantly correlated with poor OS and dysregulated expression of these circRNAs are associated with the greatest the HR in AML patients.

Although we conducted a comprehensive search that included various databases as well as grey literature, publication bias still exists within our article, and language limitations or negative results bias (studies with negative results that weren't published) might contribute to this bias [91]. In order to reduce heterogeneity in the prognostic meta-analysis and to identify relationships between subgroups for both OS and non-OS, subgroup analysis was conducted. There was no significant difference between the subgroups in terms of expression status, follow-up time, and extraction method in terms of OS indicator. Based on subgroup analysis for the OS indicator, it was determined that studies with <=68 patients overestimated the hazard ratio results. On the other hand, overestimation of the result in the GAPDH subgroup related to the OS indicator was due to the use of this control gene in studies with small sample sizes, so choosing

Table 4 Association between circrnas and clinicopathological features of AML

Clinicopathologic parameter	No. of studies	No. of patients	Effect size			I2 (%)	Publication bias		Certainty of evidence
			Risk Ratio	95%CI	*P*-value		Begg's test	Egger's test	
Gender	13	1211	1.03	0.93–1.14	0.628	0.0	0.669	0.844	High
FAB classification:	12	897	1.15	0.98–1.35	0.079	0.0	0.373	0.391	High
M1 vs. non-M1	12	897	0.87	0.70–1.08	0.215	57.8	**0.034***	**0.002***	Moderate
M2 vs. non-M2	11	857	1.10	0.96–1.25	0.163	0.0	0.119	0.051	High
M3 vs. non-M3	12	897	1.08	0.91–1.29	0.383	34.6	0.837	0.687	High
M4 vs. non-M4	12	897	1.19	0.96–1.48	0.110	47.8	0.537	0.358	High
M5 vs. non-M5	12	469	**1.51**	1.12–2.03	**0.006***	0.0	0.386	**0.043***	low
M6 vs. non-M6									
Risk status (Poor/Good)	11	1034	**1.35**	1.13–1.60	**0.001***	50.0	0.436	0.391	High
Cytogenetic Abnormalities	7	564	1.01	0.88–1.15	0.932	0.0	0.368	0.280	High
and Mutations:	7	564	1.05	0.81–1.35	0.723	17.0	0.764	0.730	Moderate
Normal cytogenetic	8	572	1.03	0.79–1.34	0.841	35.2	**0.035***	**0.058***	low
Complex cytogenetic	6	439	1.01	0.79–1.29	0.926	0.0	**0.060***	**0.029***	low
CEBPA	8	570	**1.17**	1.00–1.36	**0.050***	0.0	0.386	0.465	High
DNMT3A	6	425	1.18	0.84–1.67	0.339	0.0	0.260	0.320	Moderate
FLT3-ITD	5	429	1.07	0.79–1.45	0.682	0.0	0.462	0.259	Moderate
IDH 1 / 2	5	383	0.98	0.71–1.34	0.877	0.0	0.462	0.530	Moderate
KIT	7	491	1.08	0.93–1.26	0.318	0.0	**0.072***	**0.013***	Moderate
N/K RAS	6	504	1.18	0.99–1.42	0.066	0.0	0.452	0.408	High
NPMI	5	465	1.10	0.85–1.40	0.472	29.4	0.221	0.027*	low
t (8; 21)									
t (15; 17)									

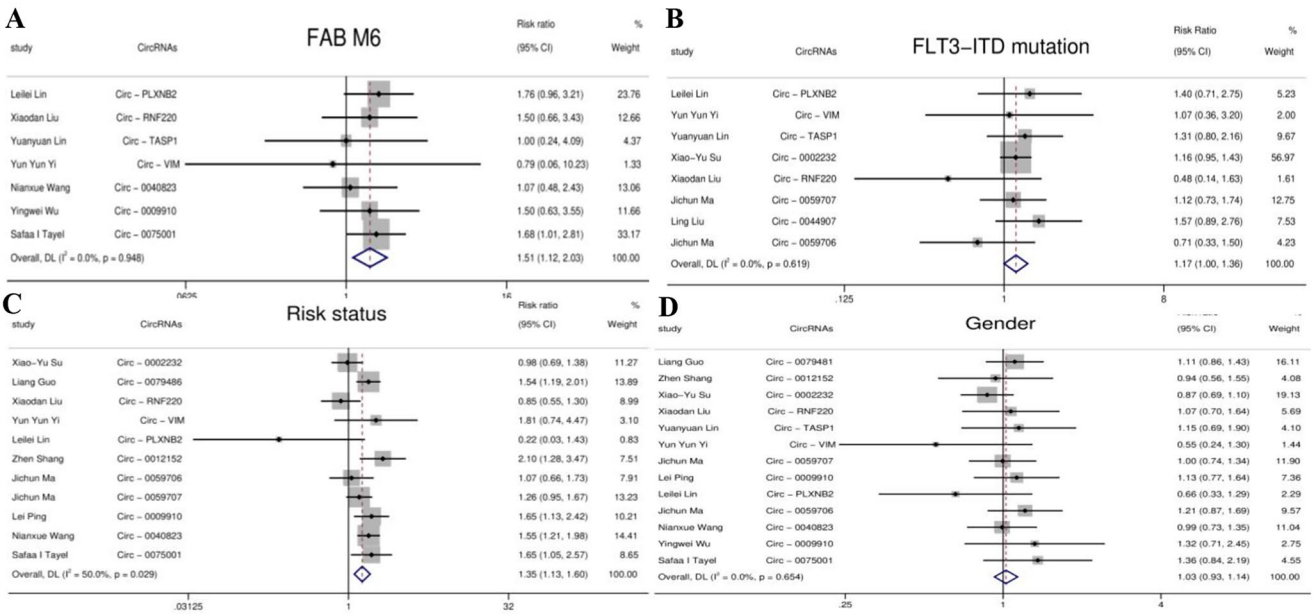

Fig. 5 Forest plots of FAB M6 (**A**), FLT3-ITD mutation (**B**), Risk status (**C**), Gender (**D**) in the clinicopathological features association analysis with circRNAs in AML patients

a larger sample size for more reliable results was recommended. Also, based on the results of subgroup analysis for the non-OS indicators, we can say that the circRNAs' prognostic power can be increased when the information is directly extracted from the study and when the sample size is >=74 people.

In the clinicopathological meta-analysis, the risk ratio index was used as a more reliable indicator than the odds ratio, so only cohort studies were included in the meta-analysis [92]. Among the clinicopathological parameters, M6 type (FAB classification), FLT3-ITD mutation, and risk status were associated with dysregulation of circRNA expression, whereas others were not. The significant association of

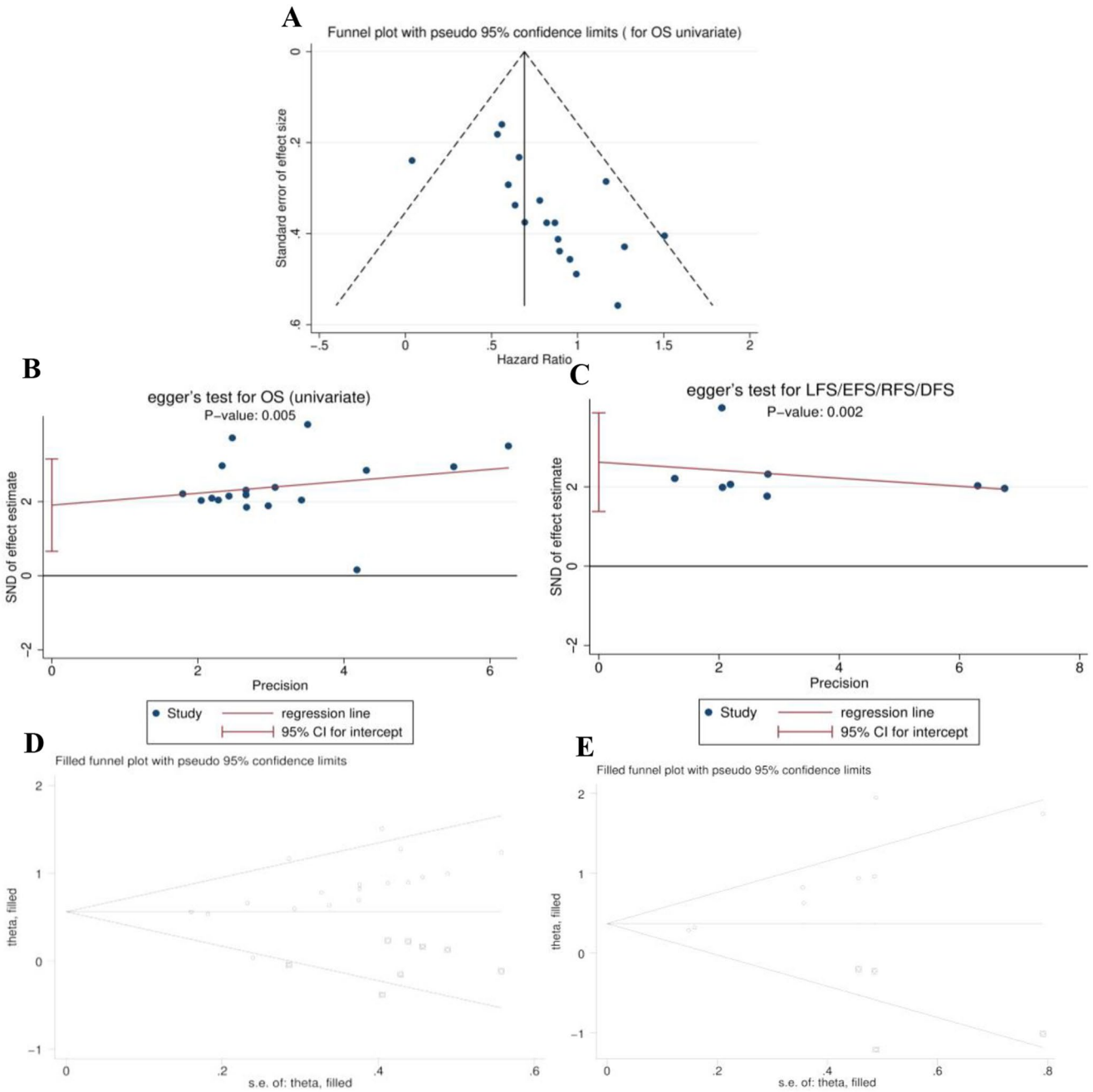

Fig. 6 Publication bias evaluation for prognostic studies. Funnel plot (**A**), Egger's test (**B**) and Trim and fill method (**D**) for overall survival (OS) indicator. Egger's test (**C**) and Trim and fill method (**E**) for non-OS indicators

FLT3-ITD with dysregulated expression of circRNAs can be attributed to the distinct role of FLT3-ITD mutation (is a well-established driver mutations and leading to abnormal cell proliferation and resistance to apoptosis) in the pathogenesis of AML. Indeded unlike to the other mutations in this study, FLT3-ITD mutation in AML can be have a more pronounced effect on dysregulated expression of circRNAs. Therefore, due to the importance of FLT3-ITD mutation and the various treatment methods based on FLT3-ITD mutation targeting, future studies can more accurately evaluate the relationship between FLT3-ITD mutation and dysregulated expression of circRNAs. According to the areas of interpretation [23], the results of M6 (classified by FAB), risk status, and FLT3 mutation, respectively, demonstrated small, small, and trivial associations with circRNA expression dysregulation. Also, based on the GRADE assessment [20, 21], the results indicated a high level of certainty regarding

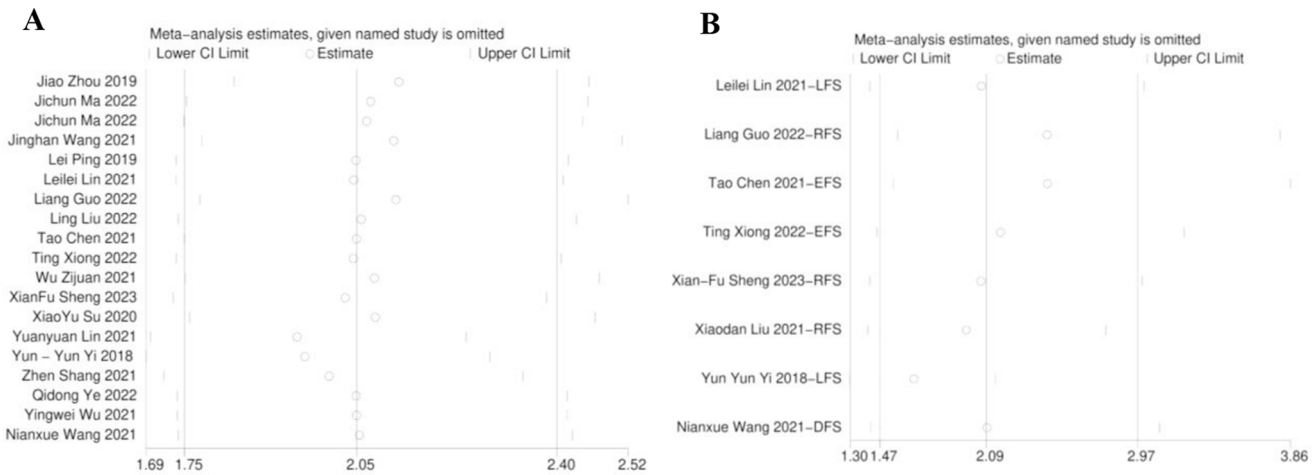

Fig. 7 One-out remove method Sensitivity analysis. Sensitivity analysis for overall survival (OS) indicator (**A**) and Non-OS indicators (**B**)

Table 5 GRADE assessment for prognostic meta-analysis

Domain of Grade assessment	Study design	Risk of bias	Indirectness	inconsistency	imprecision	Publication Bias	Summary of finding	
							Hazard Ratio (95% CI)	Certainty of evidence
prognostic parameters: (No of studies)								
Overall Survival (18 studies)	Cohort	No Problem	No Problem	No Problem	No Problem	Serious	2.05 (1.75 – 2.40)	⨁⨁⨁◯ Moderate
Non- Overall Survival indicators (8 studies)	Cohort	No Problem	No Problem	No Problem	No Problem	Serious	2.09 (1.47 – 2.97)	⨁⨁⨁◯ Moderate

FLT3-ITD mutations and risk status, while the M6 subtype (FAB classification) exhibited a low level of evidence certainty.

Future perspectives and strategies

This study focuses on the prognostic value of dysregulated expression of circRNAs. While well-established cytogenetic abnormalities along with common mutations like FLT3, NPM1, and others, continue to be central to prognosis assessment, our findings highlight that circRNAs can also demonstrate significant prognostic properties. These dysregulated expression of circRNAs could serve as valuable components in prognostic models alongside other established factors and contributing to a more accurate and comprehensive evaluation of AML patient prognosis. Similar to how genetic

mutations and cytogenetic abnormalities are incorporated into clinical practice to predict patient outcomes, circRNAs due to their stability in bodily fluids and their regulation of key cellular processes, could be integrated into clinical models for early diagnosis and treatment monitoring. Evaluating the expression of circRNAs in clinical settings could help identify high-risk patients, allowing for more tailored and effective treatments. Moreover, expression of circRNAs could be explored for the development of novel therapeutic strategies, such as circRNA-targeted therapies, to improve outcomes for AML patients.

Recommendation

Our advice to the authors of prognostic studies is to report HR in order to improve the quality of their work and not rely solely on survival analysis based on Kaplan-Meier. Also, the authors of primary studies that investigate the role of clinicopathological features should not only report P-value; thay can also report OR or RR indices for better understanding based on the type of study.

Conclusion

The spread of AML in different societies, incidence at different ages, and diverse pathophysiology lead to the complexity of treating patients. Therefore, determining the factors that are related to the prognosis of patients can play a significant role in the management of the treatment and survival of patients. Therefore, in this systematic review and meta-analysis, we showed the value of circRNAs in patients with AML as novel prognostic factors. And also, it was indicated that dysregulation of circRNAs expression can be associated with some clinicopathological features of patients with AML and can be used as new biomarkers for the investigation of treatment effectiveness.

Limitations of the review

This study faced the following limitations: First, some primary studies did not report clear data for prognostic meta-analysis, despite sending emails three times to the corresponding authors to receive information. The necessary data was extracted from the Kaplan-Meier curve, which may have caused bias. Second, for meta-analysis, studies were mostly from China, which may limit the generalizability of these findings and lead to bias. Third, heterogeneity is still a vital issue, although to explore possible sources, various subgroup analysis were carried out. Fourth, rather than focusing on the clinical significance of circRNAs in AML, the majority of the studies included focused on the functions of circRNAs, and for this reason, the inclusion and exclusion criteria of patients, treatment procedures, and follow-up procedures are not clearly specified in the text of the article.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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