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Review Article

Identification of circRNA biomarkers in osteosarcoma: An updated systematic review and meta-analysis

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ABSTRACT

Circular RNAs (circRNAs) play a crucial role in cancer development and progression. This study aimed to identify potential circRNA biomarkers for osteosarcoma. Articles published from January 2010 to September 2023 were searched across eight databases to compare circRNA expression profiles in osteosarcoma and control samples (human, animal and cell lines). Meta-analysis was conducted under a random effects model. Subgroup analysis of circRNAs in different samples and tissues was performed. Diagnostic value was evaluated using receiver operator characteristic curves. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis explored functions of circRNA host genes. A circRNA-miRNA-mRNA axis depicted the regulatory mechanism in osteosarcoma. Among 1356 circRNAs with differential expression were identified across 226 original studies, only 74 were reported in at least three published sub-studies. Meta-analysis identified 58 dysregulated circRNAs (52 upregulated and 6 downregulated). Eleven circRNAs consistently showed dysregulation in tissues and cell lines, with hsa_circ_0005721 showing potential as a circulating biomarker in osteosarcoma. Sensitivity analysis demonstrated 97 % consistency. The overall area under the curve was 0.87 (95 % CI, 0.83–0.89). GO and KEGG enrichment analyses revealed host gene involvement in cancer. The circRNA-miRNA-mRNA axis revealed the regulatory axis and interactions within osteosarcoma specifically. This study demonstrates circRNAs as potential diagnostic biomarkers for osteosarcoma. Consistently reported dysregulated circRNAs are potential biomarkers in osteosarcoma pathogenesis, with hsa_circ_0005721 as a potential circulating biomarker for diagnosis and treatment.

1. Introduction

Osteosarcoma originates from bone-forming mesenchymal stem cells and is the most prevalent primary malignant bone tumor which holds the third position among the most prevalent cancers in adolescence [1,2]. Typically found near the growth plates of the metaphysis in long bones, particularly in the femur and tibia. It is characterised by its marked aggressiveness and a heightened propensity for lung metastasis [3,4]. Despite improvements in prognosis through the implementation of chemotherapy since the late 1970s, the survival rates for metastatic cases have not shown significant improvement [5,6]. Therefore, it is essential to investigate novel biomarkers and explore molecular mechanisms to identify potential therapeutic targets for osteosarcoma. Numerous studies have been conducted on the genetic biomarkers in osteosarcoma, with circular RNAs (circRNAs) emerging as substantial contributors to the development of osteosarcoma [7].

CircRNAs represent a recently discovered group of endogenous non-coding RNAs characteristic by a closed-loop structure formed through a process as back-splicing [8]. The closed-loop structure provides resistance to Ribonuclease R, endowing circRNAs with remarkable stability

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and an average half-life of more than 48 h, significantly longer than that of mRNA (less than 20 h) [9,10]. CircRNAs can be broadly categorized into three types: exonic circRNAs (ecircRNAs) derived from back-spliced exons, exon-intron circRNAs (EIciRNAs) generated from both exons and introns, and circular intronic RNAs (ciRNAs) formed by intron lariats [11]. While most ecircRNAs are localized in the cytoplasm, EIciRNAs and ciRNAs predominantly reside in the nucleus [12]. CircRNAs take part in a wide range of biological processes, and several regulatory functions have been identified, including binding to microRNA (miRNA), influencing RNA transcription and translation, and interacting with proteins [8,13]. The central concept is that circRNAs function as competing endogenous RNAs (ceRNAs) by acting as miRNA sponges to modulate target genes [14,15].

An increasing body of evidence suggests that circRNAs play a pivotal role in the onset and progression of a range of diseases, including cardiovascular diseases, diabetes, and cancer [16–18]. Multiple studies have reported differential circRNA expression and their role in the advancement of osteosarcoma [19–21]. However, identifying potential circRNA biomarkers including tissue-specific circRNAs remains challenging. This is due to variations in profiling platforms, detection methods, and inconsistent findings across studies. While previous meta-analyses have demonstrated the potential of circRNAs as biomarkers for osteosarcoma in diagnosis, prognosis, and treatment response [22–24], there is lack of focus on the expression profiles of consistently reported circRNAs. Therefore, this meta-analysis aims to compare circRNA expression profiles between osteosarcoma and control samples, identifying consistently dysregulated circRNAs that hold promise as potential biomarkers for osteosarcoma.

2. Methods

2.1. Protocol and registry

The established protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) at https://www.crd.york.ac.uk/prospero/(ID: CRD42022356757).

2.2. Search strategies

To explore the association between circRNA expression and osteosarcoma, articles published between January 2010 and September 2023 were searched in four English databases (PubMed, EMBASE, Cochrane Library, Web of science) and four Chinese databases (Wanfang, Sinomed, CNKI, Vip). The following search terms were used: “osteosarcoma” or “osteosarcoma tumor” or “osteogenic sarcoma” or “skeletal sarcoma” or “osteoid sarcoma” or “malignant sarcoma of osteoid”; “circular RNA” or “circRNA” or “closed circular RNA” or “circular intronic RNA” or “ciRNA” or “circular ribonucleic acid”; “expression” or “profile” or “profiling”.

2.3. Study selection

The study selection process is outlined in Fig. 1. Two investigators independently screened the titles and abstracts of records retrieved from

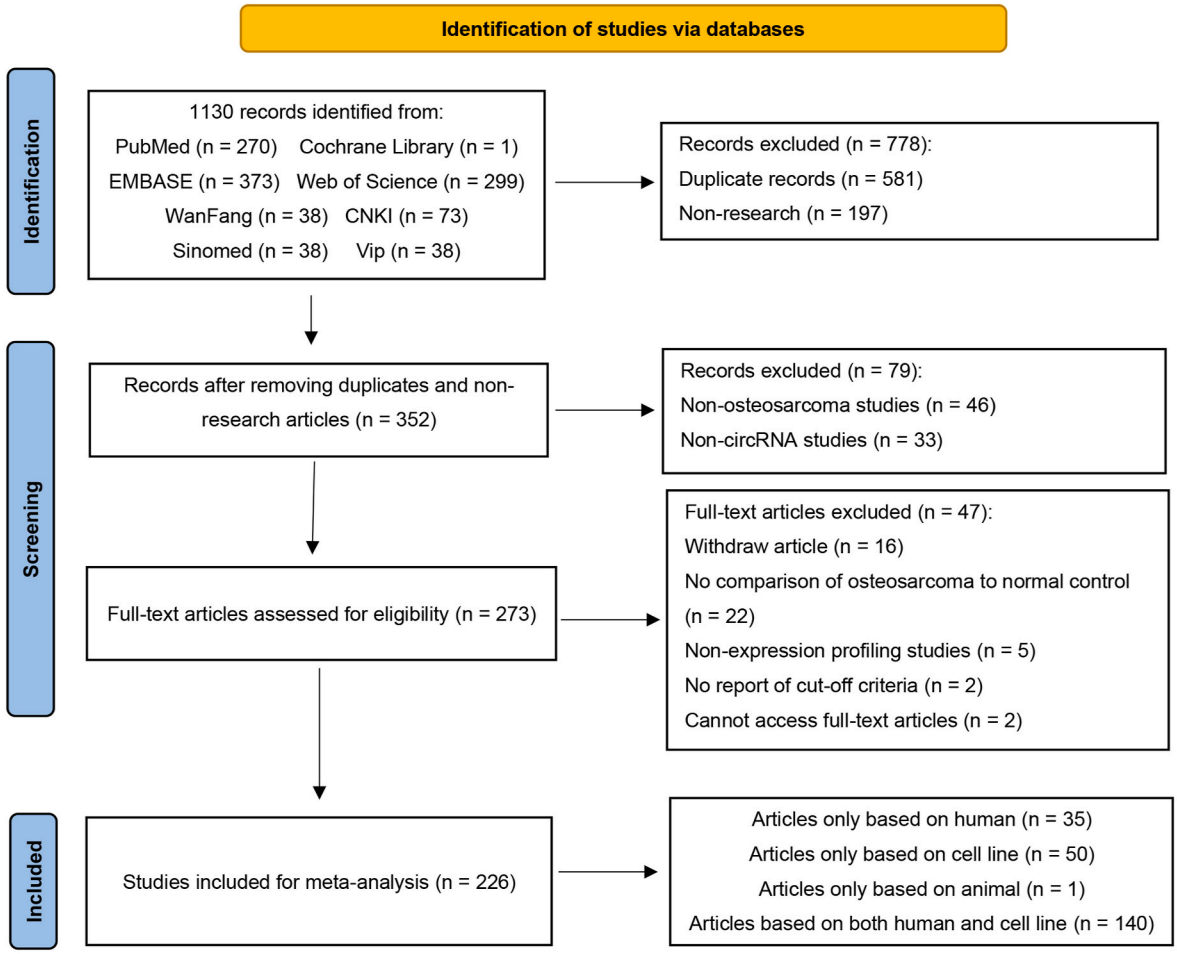

Fig. 1. Flow diagram of selection process. The process of study selection including identification, screening and inclusion steps are showed in the flow diagram. Out of the 1130 records identified, 226 studies were included.

the eight electronic databases to determine eligibility; the full text of the article was evaluated if the content was not clear from the abstract. Disagreements in study inclusion were resolved through consensus, and when no consensus was reached it was resolved by a third author (H.W.). Eligible studies had to meet the following inclusion criteria: 1) circRNA differential expression studies; 2) comparing osteosarcoma and control samples; 3) using RNA-Seq or circRNA microarray or qRT-PCR; 4) reporting cut-off criteria of differentially expressed circRNAs; and 5) reporting sample sizes. The exclusion criteria included 1) systematic review and/or meta-analysis; and 2) abstracts, meeting reports and/or congress reports.

2.4. Data extraction and quality assessment

Data extraction was independently performed by one investigator (C. Z.), whilst another investigator (K.W.) checked the extracted information. The following items were collected from the full text and supplementary information of eligible studies: first author, publication year, tissue type, sample size, circRNA expression profiling platform, cut-off criteria of upregulated and downregulated circRNAs and fold changes (if available). All inconsistencies were resolved by investigators. A standardised circRNA nomenclature has yet to be established, and it is common to encounter multiple names corresponding to the same circRNA. The circRNA alias used in circBase have been wildly adopted in most circRNA databases. Therefore, we chose to convert circRNA names with their corresponding circBase alias by cross-referencing circRNA databases mentioned in the literature or Gene Expression Omnibus (GEO) platforms. In this paper, the quality assessment of the reviewed studies was conducted using a five-domain scale: encompassing experiment design, sample characteristics, description and representation of case and control, platform annotation, and raw data processing [25]. Disagreements in quality assessment were resolved by consensus.

2.5. Meta-analysis

We analyzed the extracted data using a random effects model. The findings related to the dysregulated circRNAs in osteosarcoma were presented in the form of $\log_e$ odds ratios (lnORs) along with their corresponding 95 % confidence intervals (CIs), and the *P*-values were adjusted using Bonferroni corrections.

2.6. Subgroup analysis

CircRNAs exhibited differential expression among different biological samples and tissues, resulting in corresponding heterogeneity. Subgroup analyses were performed based on biological samples (tissues and cell lines) and tissue types (musculoskeletal tissue and blood).

2.7. Sensitivity analysis

We conducted sensitivity analysis to evaluate the robustness of our results by excluding studies with small sample sizes of less than 30.

2.8. Diagnostic accuracy analysis

We summarized the overall diagnostic accuracy of circRNAs to estimate their feasibility as biomarkers in osteosarcoma. This evaluation considered parameters including sensitivity, specificity, true positive (TP), false positive (FP), false negative (FN), true negative (TN), and area under the curve (AUC).

2.9. Bioinformatics analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were applied to anticipate the likely functions of genes corresponding to differentially expressed circRNAs in our meta-analysis. GO enrichment analysis was used to predict potential functions in three categories: biological process (BP), molecular function (MF), and cellular component (CC). KEGG analysis was used to identify potential pathways. The regulatory network involving circRNA, miRNA, and mRNA in osteosarcoma was established using Cytoscape software.

2.10. Statistical analysis

R software, along with packages (Metafor, ggplot) and Stata17 software were used for data analysis. Adjusted *P*-values less than 0.05 were considered statistically significant. Heterogeneity was assessed using Higgins' $I^{2,}$ with values greater than 50 considered statistically significant. Potential circRNA biomarkers were evaluated based on consistent reporting in multiple samples at least three times and were ranked according to the following criteria: (1) *P*-value; (2) number of consistent reports; and (3) lnOR values.

3. Results

3.1. Characteristics of included studies

The selection process for the studies included in this research is presented in Fig. 1. A total of 1130 records were identified from 8 databases, and 226 articles met the eligibility criteria. Among these studies, 35 focused on human circRNA expression profiles, 50 focused on circRNA expression profiles in cell lines, 140 reported both human and cell line expression profiles, and 1 study was based on an animal model. The number of dysregulated circRNAs ranged from 1 to 489, with 20 studies providing information on fold changes. Detailed characteristics of the human, animal, and cell line circRNA expression profiles are shown in Table S1 and Table S2. The details of the quality assessment are summarized in Table S3. Among the included studies, most did not report raw data and sufficient information about sample-sample relationships. Consequently, one low-quality article was excluded.

3.2. Differentially expressed CircRNAs

Of the 1356 differentially expressed circRNAs reported in the 226 original studies comparing osteosarcoma samples with control samples, only 74 circRNAs were reported in at least three sub-studies, however some of them showed inconsistent findings. Among these 74 circRNAs, 58 showed statistically significant dysregulation (52 upregulated and 6 downregulated). The results of the overall analysis and overlapping circRNAs were summarized in Fig. 2. The most commonly reported upregulated circRNA was hsa_circ_0001821 (adjusted $P < 0.0001$), consistently reported as upregulated in 11 sub-studies. The most downregulated circRNA was hsa_circ_0001910, reported in 5 sub-studies with an adjusted $P < 0.001$. Detailed results are presented in Table S4.

3.3. Subgroup analysis

Subgroup analysis of biological samples revealed 25 statistically significant circRNAs in tissue samples (Table S5) and 18 in cell samples (Table S6). Among the dysregulated circRNAs, hsa_circ_0016347, hsa_circ_0085539, hsa_circ_0004846, circUBAP2, hsa_circ_0001461, hsa_circ_0005909, hsa_circ_0009112, hsa_circ_0051079, hsa_circ_0001721, hsa_circ_0020378, hsa_circ_0001821 were reported consistently upregulated in both biological samples (Fig. 2). Among these circRNAs, hsa_circ_0051079, hsa_circ_0001721, hsa_circ_0020378 and hsa_circ_0001821 were detected in both musculoskeletal tissue and blood.

Further subgroup analysis focused on musculoskeletal tissue and blood, from which CircRNAs were extracted. A total of 618 circRNAs were reported in musculoskeletal tissue from various studies, with 27 reported in at least three sub-studies. Among these 27 circRNAs, 22 showed statistically significant dysregulation (20 upregulated and 2 downregulated) (Table S7). In blood samples, 506 circRNAs were

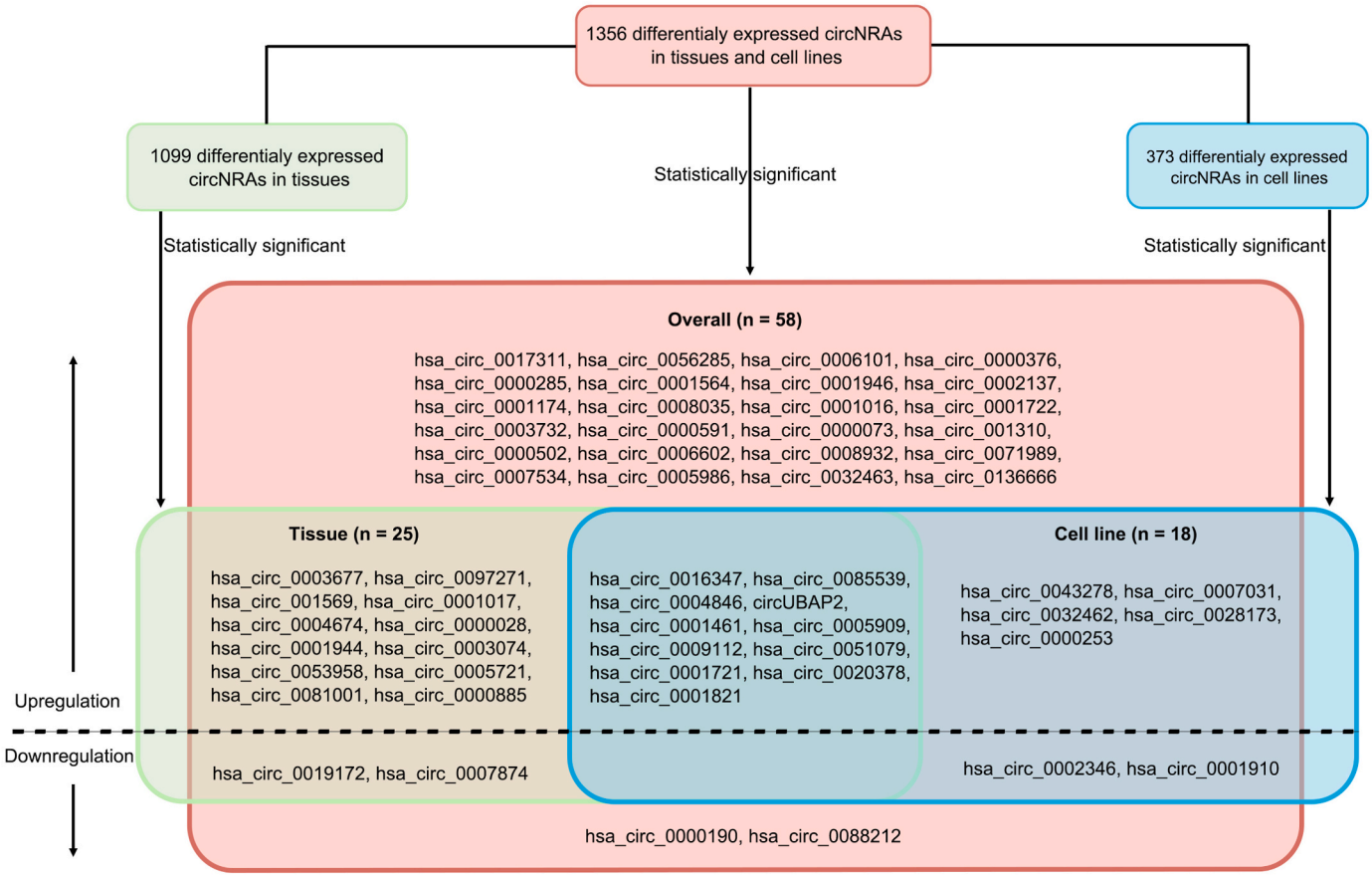

Fig. 2. The Venn diagram summarizes the results of the overall analysis and overlapping circRNAs in tissues and cell lines.

reported, but only 1 circRNA (hsa_circ_0005721) was reported in at least two sub-studies, consistently showing upregulation in musculoskeletal tissue (Table S8). Due to the limited number of studies on circRNAs in tissues other than musculoskeletal tissue and the presence of only one study focusing on circRNA in an animal model of osteosarcoma, the identification of species-specific and tissue specific circRNAs has not been established.

3.4. Sensitivity analysis

Due to the considerable diversity in sample size among the included studies, a sensitivity analysis was conducted to investigate whether sample size influenced the overall analysis. In this analysis, we excluded those eligible studies with sample sizes less than 30. A total of 34 circRNAs exhibited significantly differentially expressed, with 29 upregulated and 5 downregulated (Table S9). Thirty-three circRNAs (97 %) consistently showed differential expression in both the overall analysis and sensitivity analysis, while only 1 circRNA (circHIPK3) was not significantly dysregulated in the overall analysis. These results suggest that the pooled outcomes of circRNA studies were relatively robust. Furthermore, the fact that many studies with small sample sizes primarily concentrate on cell lines implied a notable and consistent dysregulation of circRNAs during cell line validation.

3.5. Diagnostic accuracy analysis

The evaluation of the diagnostic efficacy of circRNAs in osteosarcoma encompassed 22 studies, which collectively involved 1908 samples (Table S10). The meta-analysis results indicated a combined sensitivity was 0.78 (95 % CI, 0.71–0.83) and specificity of 0.82 (95 % CI, 0.76–0.87) (Fig. 3a). Additionally, an AUC of 0.87 (95 % CI, 0.83–0.89) was revealed by the summary receiver operating characteristic (SROC) curve (Fig. 3b). The funnel plot analysis revealed no evidence of publication bias ($P = 0.39$; Fig. 3c). These findings indicate that circRNAs have the potential to serve as biomarkers for osteosarcoma.

3.6. Bioinformatics analysis

Comprehensive bioinformatics analysis was conducted on the host genes of the 645 differently expressed circRNAs. GO and KEGG analyses were performed to gain insights into the potential functions and pathways associated with these circRNAs. The top 10 disease-related GO processes identified included protein serine/threonine kinase activity, protein serine kinase activity, protein phosphatase binding, p53 binding, histone methyltransferase activity, histone H3 methyltransferase activity, guanyl-nucleotide exchange factor activity, GTPase regulator activity, ATP hydrolysis activity and 1-phosphatidylinositol-3-kinase activity (Fig. 4a). Furthermore, the top 10 disease related KEGG pathways comprised of the VEGF signaling pathway, thyroid hormone signaling pathway, proteoglycans in cancer, phospholipase D signaling pathway, FoxO signaling pathway, focal adhesion, ErbB signaling pathway, cellular senescence, cell cycle and adherens junction (Fig. 4b). In addition, we reviewed the regulatory role of circRNAs in the pathogenesis of osteosarcoma, including their involvement in processes such as proliferation, apoptosis, glycolysis, migration, invasion, metastasis, epithelial-mesenchymal transition (EMT), and chemoresistance (Table S11). Most of the studies focused on the circRNA-miRNA-mRNA axis as the primary regulatory mechanism, and the networks involving circRNA-miRNA-mRNA interactions were established to enhance our comprehension of the regulatory roles of circRNAs in osteosarcoma (Fig. 5).

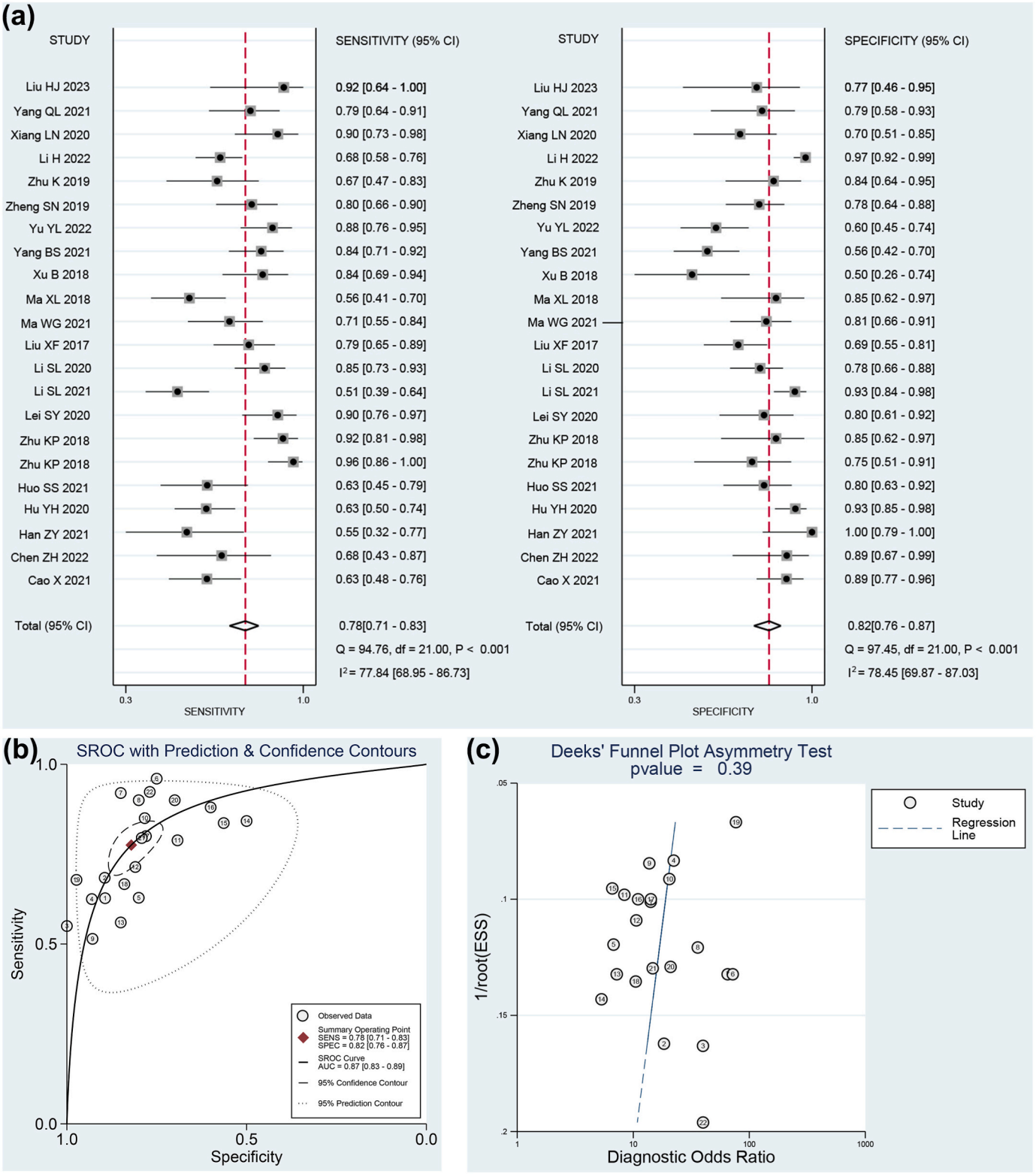

Fig. 3. **(a)** The forest plot of sensitivity and specificity of circRNAs in the diagnosis of osteosarcoma. **(b)** The summary receiver operator characteristic plot of circRNAs in diagnosis of osteosarcoma. **(c)** The funnel plot for publication bias.

4. Discussion

Osteosarcoma is the most prevalent malignant bone tumor with a poor prognosis, predominantly affecting adolescents requiring aggressive surgery and cytotoxic chemotherapy. CircRNAs are a novel class of non-coding RNAs that have been implicated in the initiation and progression of cancer. Previous systematic reviews have conducted meta-analyses to assess the diagnostic and prognostic significance of dysregulated circRNAs in osteosarcoma [22–24]. A recent review reported the link between circRNA circ_0002052 and the overall survival of osteosarcoma patients [22], but the findings regarding its dysregulation were inconsistent [26–29]. While numerous circRNAs have been

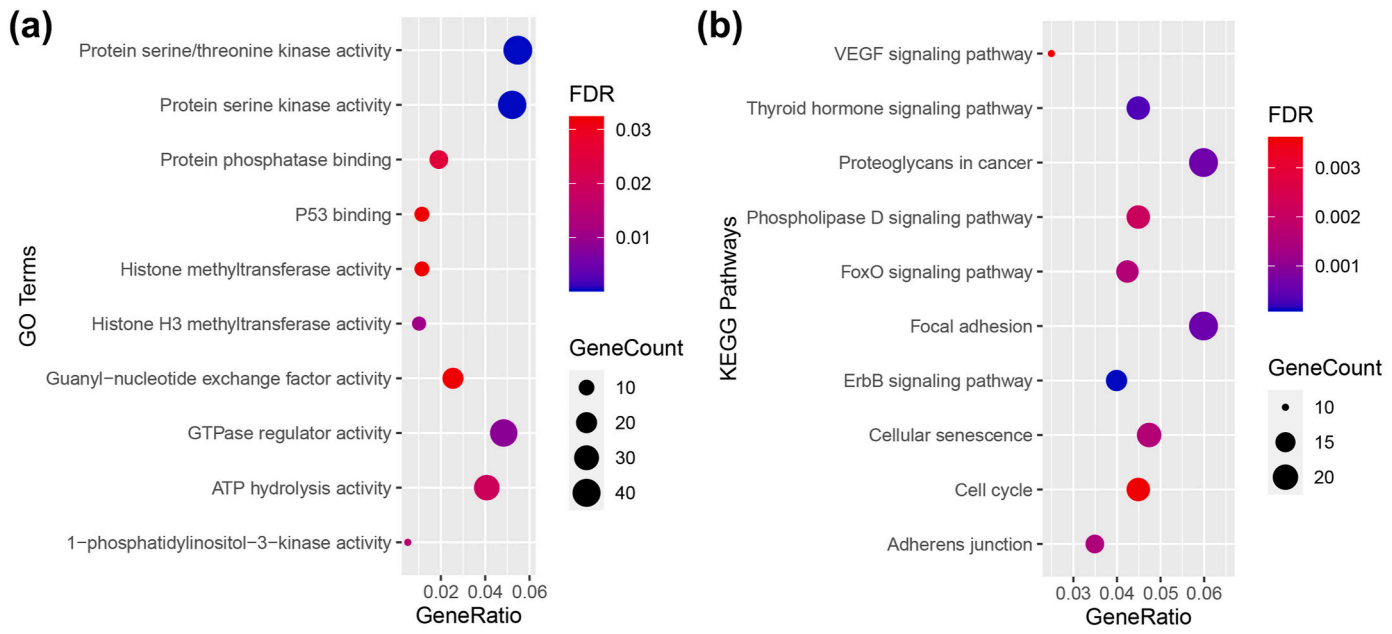

Fig. 4. **(a)** The bubble plot of top 10 enriched GO terms for host genes of differentially expressed circRNAs. **(b)** The bubble plot of top 10 enriched KEGG pathways for host genes of differentially expressed circRNAs related to cancer development. FDR, false discovery rate.

identified as differentially expressed, only a subset of them may truly serve as specific biomarkers in osteosarcoma. Our study is the first to identify specific circRNAs as potential biomarkers for osteosarcoma by analyzing circRNA expression profiling in human samples, animal models, and cell lines. We identified 58 circRNAs (52 upregulated and 6 downregulated) as potential targets for osteosarcoma diagnosis and treatment. Among these, 11 circRNAs (hsa_circ_0016347, hsa_circ_0085539, hsa_circ_0004846, circUBAP2, hsa_circ_0001461, hsa_circ_0005909, hsa_circ_0009112, hsa_circ_0051079, hsa_circ_0001721, hsa_circ_0020378, hsa_circ_0001821) consistently recurred in both tissue and cell lines. Hsa_circ_0001821, being the most consistently reported circRNA, detected in both musculoskeletal tissue and blood, and holds promise as a valuable biomarker for osteosarcoma detection. Additionally, hsa_circ_0005721 recurred in the tissue subgroup analysis. CircRNAs exhibit characteristics of stability and accumulation over time, with tissue or developmental stage-specific expression [30]. If differentially expressed circRNAs in circulating blood can serve as biomarkers, a minimally invasive approach for diagnosing osteosarcoma would be highly beneficial. These findings suggest that circRNAs may hold potential as biomarkers for osteosarcoma, although further studies are needed to identify tissue-specific circRNAs.

It is important to note that only one study reported dysregulation in circRNA in osteosarcoma using an animal model, specifically a porcine model. In this model, a novel circRNA called circTP53 was identified, which exhibited tissue-specific upregulation in bone and promoted the proliferation of osteosarcoma cells [31]. Given that the porcine model carried an oncogenic $TP53^{R167H}$ mutation, which is orthologous to the human $TP53^{R175H}$ mutation, circTP53 may have a potential regulatory role in humans. Furthermore, exploring the relationship between *TP53* isoforms and circTP53 could provide insight into the biogenesis of circTP53, thereby enhancing our understanding of the mechanisms underlying circRNAs generation from parental genes.

Previous studies have reported that circXPO1 and circKCNH1 can promote the proliferation of osteosarcoma by regulating their host genes, demonstrating a positive correlation between circRNA expression and that of the parental gene [32,33]. To gain a better understanding of the potential functions of dysregulated circRNAs, we performed bioinformatics analysis, including GO enrichment analysis and KEGG pathway analysis. The GO enrichment analysis showed that dysregulated circRNAs significantly impact cell growth, proliferation, apoptosis, differentiation, survival, motility, and metabolism, which are crucial in the tumorigenesis and development of osteosarcoma. The results of the KEGG pathway analysis identified several important signaling pathways, including focal adhesion, which plays a critical role in cell migration, invasion, and angiogenesis during cancer progression [34,35]. The FoxO signaling pathway is involved in key cellular processes in cancer, such as cell differentiation, proliferation, apoptosis, DNA damage, and repair [36]. The VEGF signaling pathway has been linked to cancer growth and spread through the abnormal activation of cell growth, migration, differentiation, and vascular permeability [37]. These findings suggest that the host genes of dysregulated circRNAs can influence the occurrence and development of osteosarcoma through multiple functions. However, the regulatory mechanisms between circRNAs and their host genes remain unclear and warrant further exploration.

Many studies have reported the regulatory role of the circRNAs identified in this study. For example, hsa_circ_0001821, a 410 nucleotide circRNA originating from exon 2 of the oncogene gene *PVT1* located on chromosome 8q24 [38], promotes the invasion of osteosarcoma by inhibiting miR-205-5p, miR-526b, and miR-26b-5p thereby upregulating *c-FLIP*, *FOXC2*, and *CCNB1*, respectively [39–41]. Hsa_circ_0001821 can also regulate *ABCB1* to increase the resistance of osteosarcoma to doxorubicin and cisplatin [42]. Moreover, overexpression of hsa_circ_0001821 enhances doxorubicin resistance through the miR-137/TRIAP1 axis [43]. Hsa_circ_0001821 is one of the most consistently reported upregulated circRNAs, and our meta-analysis also confirmed the identification of this circRNA. Hsa_circ_0005721, detected in peripheral blood, is closely related to osteosarcoma. Two previous studies indicated that hsa_circ_0005721 in blood could be a promising minimally invasive biomarker with diagnostic potential for distinguishing osteosarcoma from healthy individuals and patients with benign bone tumors [44,45]. Moreover, the regulatory mechanism of hsa_circ_0005721 in the proliferation, apoptosis and metastasis of osteosarcoma can be attributed to its upregulation of *TEP1* via miR-16-5p [46]. Most studies have focused on the function of circRNAs as ceRNAs that regulate mRNAs by sponging miRNAs. The constructed network reveals that a specific circRNA can regulate downstream mRNAs via multiple miRNAs. For example, hsa_circ_0001721 can regulate

Fig. 5. The circRNA-miRNA-mRNA regulatory network. The circular nodes (pink) represent circRNA, square nodes (blue) represent miRNA, diamonds (yellow) represent mRNA.

expression of *GAB1*, *MAPK7*, and *E2F2* by sponging miR-520a-3p, miR-372-3p, and miR-198, respectively, to facilitate osteosarcoma progression [47–49]. Furthermore, a specific miRNA can be regulated by multiple circRNAs, subsequently affecting target mRNAs. For example, hsa_circ_0017311, hsa_circ_0000006, and hsa_circ_0000253 can sponge miR-578 to promote malignant behavior in osteosarcoma by regulating *LDHA*, *VEGF*, and *TGFβ2,* respectively [50–52]. In addition to acting as miRNA sponges, hsa_circ_0002402 has been reported to interact with

the c-Myc protein to regulate energy metabolism in osteosarcoma [53]. However, further research is needed to explore the additional biological roles of circRNAs in osteosarcoma, including translation into proteins and regulation of alternative splicing or transcription.

We evaluated the diagnostic efficacy of circRNAs in osteosarcoma. The SROC analysis revealed a combined AUC of 0.87 for circRNAs in osteosarcoma, indicating a favorable diagnostic accuracy, in line with previous studies [23]. However, the clinical application of circRNAs encounters challenges due to the regulatory and degradation mechanisms governing the accumulation of circRNA during exosomal formation in exosomal circRNA derived from tissues or blood. Additionally, the clinical application of circRNAs presents challenges related to the detection of circRNA with low abundance and the accurate assessments of circRNA expression [30]. Moreover, the assessment was based on multiple studies on circRNAs, each with a limited sample size. Our study suggests that future investigations should focus on hsa_circ_0001821 and hsa_circ_0005721 in patients with osteosarcoma.

There are several limitations to this study. The inconsistency in circRNA naming conventions resulted in variations in circRNA IDs among the included studies. While the majority of the included studies aligned circRNA names with the aliases used in circBase, it's worth noting that in some articles, aliases remained unidentified. It is expected that a consensus circRNA nomenclature will be established in the near future. Furthermore, all studies except one on an animal model were conducted in China, which may lead to population bias.

5. Conclusions

In conclusion, this study successfully identified 58 dysregulated circRNAs, shedding light on their potential roles in osteosarcoma. Among these circRNAs, several showed specific dysregulation in musculoskeletal tissue, suggesting their involvement in the development and progression of osteosarcoma. Notably, hsa_circ_0005721 emerged as a promising blood biomarker for osteosarcoma, offering the potential for minimally invasive diagnosis and targeted therapy. These findings provide valuable insight into the diagnostic and therapeutic landscape of osteosarcoma, highlighting the significance of circRNAs as potential biomarkers. Further research and validation studies are warranted to fully understand the clinical implications and exploit the therapeutic potential of these circRNAs in the management of osteosarcoma.

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CRediT authorship contribution statement

Chunbin Zhou: Writing – original draft, Visualization, Software, Funding acquisition, Formal analysis, Data curation. **Lois Balmer:** Writing – review & editing, Validation, Supervision. **Manshu Song:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Gehendra Mahara:** Writing – review & editing. **Kezhou Wu:** Validation, Investigation. **Wei Wang:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization. **Hu Wang:** Writing – review & editing, Validation, Supervision, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

circRNA	circular RNA
ecircRNA	exonic circRNA
EIciRNA	exon-intron circRNA
ciRNA	circular intronic RNA
miRNA	microRNA
ceRNA	competing endogenous RNA
GEO	Gene Expression Omnibus
lnOR	$\log_e$ odds ratio
CI	confidence interval
TP	true positive
FP	false positive
FN	false negative
TN	true negative
AUC	area under the curve
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
BP	biological process
MF	molecular function
CC	cellular component
SROC	summary receiver operating characteristic
EMT	epithelial-mesenchymal transition

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ncrna.2024.01.007.

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