Non-coding RNAs as potential biomarkers in osteosarcoma

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Osteosarcoma (OS) is a primary solid malignant tumor that occurs most frequently in the metaphysis of long bones. More likely to happen to children and adolescents. OS has high mortality and disability rate. However, the etiology and pathogenesis of OS have not been fully understood till now. Due to the lack of effective biomarkers, OS cannot be precisely detected in the early stage. With the application of next-generation and high-throughput sequencing, more and more abnormally expressed non-coding RNAs (ncRNAs) have been identified in OS. Growing evidences have suggested the ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), have played an important role in the tumorigenesis and progression of OS. Thus, they can be served as novel biomarkers for diagnosis, treatment and prognosis. This review summarized the application of ncRNA as biomarkers in OS in detail, and discussed the limitation and future improvement of the potential biomarkers.

KEYWORDS
osteosarcoma, non-coding RNAs, biomarker, diagnosis, treatment, prognosis

Introduction

Osteosarcoma (OS), as a common kind of primary malignant tumor of bone, has a high mortality (Cersosimo et al., 2020), accounting for about 2.4% of children with malignant tumors and 20% of all primary bone cancers. Depending on statistics, there are about 800 new cases in the United States each year, among which about 50% are children and adolescents (Ward et al., 2014). Studies have shown that the incidence of OS in men is higher than that in women, which is 1.27 times that of women. (Lee J. A. et al., 2021). OS occurs in the epiphysis of long bones more frequently, such as the proximal tibia, distal femur, proximal humerus, and other parts of the fastest growing bone (Zhao et al., 2018). OS has a high disability and mortality, and is prone to metastasis (Zheng et al., 2020). The prognosis of patients with early metastasis are very poor, the 5-year survival rate of patients with metastasis is lower than 20% (Thanindratarn et al., 2019). However, the early symptoms of OS are not typical, it was usually in the late stage when found even with metastasis, resulting in the high mortality rate. Early diagnosis and treatment are very important for the prognosis of OS. With the continuous improvement of the diagnosis
and treatment methods, a variety of therapies have emerged, including targeted therapy and immunotherapy, which have effectively reduced the overall mortality of the patients. Nevertheless, the prognosis is still far from ideal. Therefore, it is urgent to carry out in-depth research on the related molecular mechanisms of the occurrence and development. By looking for new and effective biomarkers for detection, diagnosis, therapy and prognosis, the disability rate and mortality rate can be reduced in some extent, so as to prolong the survival time of the patients.

There are a wide kinds of tumor markers. At present, the discovered species include nucleic acid, protein, glucose, small molecular metabolites, cytokines, circulating tumor cells (CTCs), and so on, which play an important role in the diagnosis, treatment and prognosis of tumors. In the past few decades, bioinformatics has provided new ideas for the functions of early diagnosis and treatment with its advantages of simplicity, non-invasive and high efficiency, further play an important role in early diagnosis and prognosis evaluation. Compared with protein biomarkers, ncRNAs tumor markers have the advantage of replicability, stable expression, less affected by in vivo and in vitro stimulation. In clinic, the commonly used ncRNAs tumor markers of OS include microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) (Inamoto et al., 2018; Yang et al., 2021). Biomarkers have become a new potential due to their advantages of easy sample acquisition, less trauma to the human body, higher sensitivity and specificity. These biomarkers have played significant roles in non-invasive diagnosis and detection during the occurrence, development and prognosis of tumor. Non-coding RNA (ncRNAs), because of its own advantages, has become a major participant in tumor markers, such as in hepatocellular carcinoma, lung cancer, breast cancer, et al. (Wong et al., 2018; Iqbal et al., 2019; Shen et al., 2020).

At present, the researches focused on ncRNAs tumor markers and relevant action pathways have revealed the important roles in the occurrence, metastasis and prognosis. These biomarkers can help to determine the accuracy of the diagnosis, decide on the appropriate treatment time, make personalized treatment plans, and explore new therapeutic targets. Many ncRNAs biomarkers and corresponding protein products have been reported to be upregulated or under-expressed in OS, such as miR-223 (Xu et al., 2013), COP9 signalosome subunit 3 (COPS3) (Zhang et al., 2018), IncRNA small nuclear RNA host gene 4 (IncRNA SNHG4) (Xu R et al., 2018), miR-142 (Shabani et al., 2019), etc. Although the reports on types and functions of ncRNAs in OS are still limited, they might express some diagnostic, stage, treatment and prognosis targets. ncRNAs such as miRNAs, IncRNAs, circRNAs studied before were summarized in this review. miRNA is a small ncRNA molecule, which mainly regulates gene expression by degrading mRNA or inhibiting the translation process after transcription. The discovery of IncRNA mainly comes from microarray technology, the second generation high-throughput transcriptome sequencing technology, single cell sequencing technology, etc., and plays an important role in maintaining the activities of living cells. circRNA is a wide range of ncRNA that is stable in nature, highly conservative and specific. In this paper, by searching the relevant databases, we searched the ncRNA related to the occurrence and development of OS, and expounded its role in the occurrence and development of OS. The specific literature screening process is shown in Figure 1. The specific roles of some of the relevant ncRNAs are presented in Table 1.

In this review, the roles of ncRNAs who had the potential as biomarkers in the diagnosis, stage, treatment, and prognosis of OS were discussed in depth, which has great potential to provide reference for relevant studies.

### Diagnostic biomarkers

Diagnosing OS at the early stage can cure diseases faster and earlier, significantly improve the prognosis of patients. Abnormal expression of ncRNA biomarkers can be used as potential biomarkers for diagnosis of OS. For miRNAs, there were significant differences in serum and plasma levels of miR-21 between patients with OS and healthy people, which found can be used as biomarkers of OS. Studies have shown that miR-21 was over-expressed in OS tissues and cell lines, and it had great potential as a biomarker for OS diagnosis. Cong et al. (2018) found that the serum miR-124 level in patients with OS was significantly lower than that in the periostitis group and the healthy control group. The level of miR-124 normalized after tumor resection, and the area under the area under curve (AUC) for serum miR-124 was 0.846, with sensitivity of 79.8% and specificity of 86.0%, which proved that miR-124 had the potential to be the biomarker for diagnosis of OS. Wang et al. (2014) found that compared with the corresponding para-carcinoma tissue, the miR-143 level significantly decreased in OS, which proved that miR-143 can be used as diagnostic biomarker of OS.

Fraxetin (FXT), had been reported to be associated with the development of various tumors (Yao et al., 2022). Through examining the expression of FTX in 25 OS and the adjacent tissues, Huang et al. (2020) found that FTX were significantly upregulated in OS tissues, and knocking out FTX gene could inhibit the survival rate, invasion, and migration force of OS cells, as well as promote the apoptosis of OS cells. LncRNA can not only directly regulate OS cells, but also affect the growth, proliferation, apoptosis and invasion of OS cells through the regulation of mRNA or miRNA, playing a key regulatory role in the occurrence and development of OS. The research studied by Li et al. (2017) found that IncRNA can be regulated in the occurrence and development of OS by competing endogenous RNAs (ceRNA), Wnt/β-Catenin and other pathways. In short,
IncRNA can be served as biomarkers for early screening of OS, but their specificity and sensitivity need to be further verified clinically.

When it comes to circRNAs, recently more and more studies have shown that circRNAs can be used as a kind of biomarkers in the early diagnosis of OS, with high accuracy and specificity. Zhou et al. (2018) reported that circ_0008717 owned high expression in OS tissues, compared with the corresponding paracancerous tissues (Figure 2). Molecular sponge could bind to miR-203 to exert its carcinogenic effect. Its AUC was 0.782 (95% CI: 0.682–0.862), sensitivity was 0.80, and specificity was 0.73, which could be used as a potential biomarker for the diagnosis of OS. The commonly used biomarkers for clinical OS diagnosis are serum alkaline phosphatase (AKP) and lactate dehydrogenase (LDH), but the comparison of diagnostic efficacy between these biomarkers and OS biomarkers has not been reported. Lei and Xiang (2020) found that hsa_circ_0003074 was highly expressed in plasma of OS patients and had a high efficacy in distinguishing OS patients from healthy volunteers, with the AUC of 0.93, higher than LDH (AUC = 0.83) and alkaline phosphatase (ALP) (AUC = 0.88). Thus, circRNAs also had the potential to be a diagnostic biomarker, which need further studies.

FIGURE 1
Flow chart of literature selection and collection.
| Tumor biomarker | Deregulation | Genes/proteins affected | OS cases | Controls | Observation in OS | Ref |
|----------------|-------------|-------------------------|----------|----------|-------------------|-----|
| circ_0008717   | Overexpression | miR-203/Bmi-1          | 45       | 45       | Correlation with the patient's poor prognosis and lung metastasis | (Zhou et al., 2018; Lei and Xiang, 2020) |
| circ_CDR1as    | Overexpression | CDR1as/miR-7            | 38       | 18       | Associated with tumor size, Enneking staging, and distant metastasis | Xu R et al. (2018) |
| circ_TADA2A    | Overexpression | miR-203a-3p            | 10       | 10       | Related to migration, invasion and proliferation | Wu et al. (2019) |
| circ_001617     | Overexpression | miR-78/TCF4/Wnt/β-catenin | 51       | 51       | Related to cell resistance and growth | Guan et al. (2021) |
| circ_000502    | Overexpression | miR-1238               | 63       | 63       | Relate to tumor proliferation, migration, invasion and apoptosis | Qi et al. (2018) |
| circ_MTO1      | Low-expression | miR-630               | 44       | 44       | Associated with Enneking stage and/or pathological fracture, as well as neoadjuvant treatment | Shi et al. (2021) |
| circ_0008932   | Overexpression | miR-145-5p            | 50       | 50       | Closely related to the proliferation, migration, invasion and apoptosis of OS cells | Cao and Shu (2021) |
| circ_PVT1      | Overexpression | Gene ARCB1            | 80       | 20       | Increased risk for chemotherapy resistance | Kun-Peng et al. (2018) |
| circ_LRP6      | Overexpression | KLF2/APC              | 50       | 50       | Associated with proliferation, migration, invasion and apoptosis | Zheng et al. (2019) |
| circ_001621    | Overexpression | miR-578/CDK4/MMP9     | 30       | —        | Related to proliferation and migration | Ji et al. (2020) |
| circ_001721    | Overexpression | miR-569 and miR-599   | 52       | 52       | Closely relate to that poor prognosis and clinical severity of the patient | Li et al. (2019) |
| circ_hsa_circ_0003074 | Overexpression | —                     | 60       | 60       | Closely related to clinical characteristics, such as tumor size, lung metastasis, enneking stage, and chemotherapy resistance | Lei and Xiang (2020) |
| circ_0081001   | Overexpression | miR-494-3p/TGM2       | 35       | 28       | Can affect tumor metastasis and chemotherapy sensitivity | Wei et al. (2021) |
| circ_0007534   | Overexpression | Bcl-2/caspase-3       | 57       | 57       | Relate to that proliferation, migration, invasion and apoptosis of tumor cells | Li and Li (2018) |
| circ_001569    | Overexpression | miR-185-5p/FLOT2      | 20       | 20       | Related to proliferation, migration, invasion, EMT, tumor size, Enneking stage (or TNM stage), and lung metastasis | Xiao et al. (2020) |
| has_circ_0009910 | Overexpression | miR-449a/IL6R         | 30       | 30       | Promote OS cell growth and inhibiting apoptosis | Deng et al. (2018) |
| circ_UAP2      | Overexpression | miR-504p/1HMGA2       | 42       | 42       | Associated with OS cell proliferation, invasion and migration, and negatively correlated with overall survival | Ma et al. (2021) |
| circ_HIPK3     | Overexpression | miR-637/HDAC4         | 12       | 12       | Has a positive correlation with that total survival time of the patient | Wen et al. (2021) |
| circ_0021347   | Low-expression | B7-H3                | 35       | 35       | Negatively correlated with TNM staging, positively correlated with patient survival, and negatively correlated with B7-H3 | Wang et al. (2019) |
| hasa_circ_0000658 | Low-expression | miR-1227/IRF2        | 60       | 60       | Differentiation grade and distant metastasis | Jiang and Chen (2021) |
| miR-21-5p      | Overexpression | Wnt/β-catenin/PTEN/Akt | 1        | 1        | Positively correlated with the differentiation grade and distant metastasis of the tumor | Wu H et al. (2021) |
| miR-124        | Low-expression | —                     | 114      | 50       | Lower 5-year survival and disease-free survival | Cong et al. (2018) |
| miR-21         | Overexpression | —                     | 65       | 30       | Might be a good candidate for a therapeutic target, and a potential biomarker for the prediction of chemotherapeutic sensitivity and prognosis | Yuan et al. (2012) |
| miR-21         | Overexpression | —                     | 94       | 94       | Correlated with the pathological stage, tumor grade, and lung metastasis | Zhao H et al. (2019) |
| miR-21         | Overexpression | —                     | 69       | 69       | Closely related to the therapeutic effects of OS, and can be used as a potential biomarkers and | Hua et al. (2017) |

(Continued on following page)
| Tumor biomarker | Deregulation | Genes/proteins affected | OS cases | Controls | Observation in OS | Ref |
|-----------------|-------------|-------------------------|----------|----------|-------------------|-----|
| miR-143         | Overexpression | ERK/MAPK                | 2        | —        | Related to tumor invasiveness | Wang et al. (2014) |
| miR-100         | Low-expression | P53R/AKT7/MAPK/ERK/IGFIR | 20       | 20       | Associated with tumor proliferation, migration, invasion and chemotherapy resistance | Liu et al. (2016) |
| miR-140         | Low-expression | HDAC4                   | 10       | —        | Overexpression of miR-140 inhibits the proliferation and invasion of OS cells, and promotes their apoptosis | Song et al. (2009) |
| miR-217         | Low-expression | SIRT1                   | 42       | 37       | Relate to OS cell proliferation, migration and invasion | He et al. (2019) |
| miR-646         | Low-expression | FGF2                    | 64       | 64       | Relate to OS cell proliferation, migration and invasion | Sun et al. (2015) |
| miR-223         | Low-expression | —                       | 112      | 50       | Related to the metastasis of OS and could be used as a potential diagnostic and prognostic biomarker | Dong et al. (2016) |
| miR-382-5p      | Low-expression | VEZF1                   | 20       | 20       | Affect OS cell proliferation, migration, aggregation, invasion, apoptosis | Wu Z et al. (2021) |
| miR-191         | Overexpression | checkpoint kinase 2      | —        | —        | Affect OS cell proliferation | Huang et al. (2015) |
| miR-143-3p      | Low-expression | FOSL2/MAPK7             | 20       | 20       | Related to OS cell proliferation, migration and invasion | Sun et al. (2018) |
| miR-145         | Low-expression | MMP16/VEGF              | 31       | 35       | Affect that invasion and migration of OS cells | Chen et al. (2015) |
| miR-145-5p      | Low-expression | E2F transcription factor 3 | 20     | 10       | Affect the proliferation and progression of tumor cells | Li H et al. (2020) |
| miR-335         | Low-expression | SNIP1                   | 37       | 37       | Related to the migration and invasion of tumor cells | Xie et al. (2019) |
| miR-221         | Overexpression | PTEN/PI3K/akt            | 108      | 108      | Associated with overall survival and its high expression predicts a poor prognosis | Yang et al. (2015) |
| miR-106a        | Overexpression | VNN2                    | 18       | 18       | Can regulate the proliferation and invasion of OS cells | Chen et al. (2018) |
| miR-210         | Overexpression | FGFRL1                  | 54       | 54       | Associated with larger tumor volumes, poor preoperative chemotherapy response, metastases | Liu et al. (2018) |
| miR-27a         | Overexpression | SIRT1/Wnt/J-catenin/MAP2K4 | 166     | 60       | Associated with invasion, proliferation, metastasis | Tang et al. (2015) |
| miR-646         | Low-expression | FGF2                    | 64       | 64       | Low expression is associated with metastasis, and its overexpression inhibits cell proliferation, migration, and invasion | Sun et al. (2015) |
| miR-382-5p      | Low-expression | VEZF1                   | 20       | 20       | Related to the proliferation, invasion, migration and apoptosis of OS cells | Wu H et al. (2021) |
| miR-191         | Overexpression | checkpoint kinase 2      | —        | —        | Forced expression of miR-191 can promote the proliferation of OS cells, while miR-191 antisense oligonucleotides block cell proliferation | Huang et al. (2015) |
| miR-410         | Low-expression | VEGF                    | —        | —        | The overexpression of miR-410 exerted greater inhibition on the expression of VEGF | Chen et al. (2017) |
| miR-19a         | Overexpression | JAK2/STAT3              | —        | —        | Closely related to cell proliferation and apoptosis | Chen and Chen, (2020) |
| IncR-FTX        | Overexpression | miR-320a/TXNRD1         | 25       | 25       | Knocking out FTX can inhibit OS cell proliferation and migration, and promote apoptosis | Huang et al. (2020) |
| IncR-91H        | Overexpression | CDK4                    | —        | —        | Knock-out of 91H inhibits the occurrence of OS by inducing methylation of CDK4 promoter in vitro and in vivo | Cheng et al. (2021) |
| IncR-BCAR4      | Overexpression | —                       | 168      | 168      | Significantly correlated with the overall survival rate, clinical stage and distant metastasis | Ju et al. (2016) |
| IncR-FGFR3-AS1  | Overexpression | —                       | 62       | 62       | Related to tumor volume, Enneking staging, metastasis, and survival | Sun et al. (2016) |
| IncR-GNAS-AS1   | Overexpression | miR-490-3p              | 112      | 1        | Patients with high IncR- GNAS-AS1 expression represented shorter overall survival and was an independent prognostic predictor of OS | Mi et al. (2021) |
| Tumor biomarker | Deregulation | Genes/proteins affected | OS cases | Controls | Observation in OS | Ref |
|----------------|-------------|------------------------|---------|----------|------------------|-----|
| lncR-HIF2PUT   | Overexpression | HIF2                   | 30      | 30       | Relate to proliferation, migration and invasion of OS patients | Zhao H et al. (2019) |
| lncR-HotTIP    | Overexpression | PTBP1/KHSRP             | 20      | 20       | Relate to that proliferation, invasion and migration of OS cells | Yao et al. (2021) |
| lncR-HULC      | Overexpression | miR-372-3p/ HMGB1       | 32      | 32       | Overexpression of HULC or knockdown of miR-372-3p promotes the proliferation, migration, and invasion of OS cells and induces apoptosis | Li L et al. (2020) |
| Malat-1        | Overexpression | —                      | —       | —        | Relate to chemotherapy resistance of OS cells | Liu et al. (2021) |
| lncR-UCA1      | Overexpression | miR-513b-3p/E2F5        | —       | —        | Related to the proliferation, migration and invasion of OS cells | Zhang et al. (2021) |
| lncR-DLX6-AS1  | Overexpression | miR-641/HOXA9           | 40      | 40       | Relate to OS cell proliferation and metastasis | Zhang N et al. (2019) |
| lncR-TUSC7     | Low-expression | miR-181a/RASSF6/ miR-211 | 45      | 45       | Overexpression inhibits the proliferation, migration and invasion of OS cells, and promotes the apoptosis of cells in vitro and in vivo | Zhao et al. (2021) |
| lncR-MEG3      | Low-expression | miR-361-5p/FoxM1         | 78      | 126      | Associated with the synergistic regulation of miR-361-5p/FoxM1 on the proliferation, migration and apoptosis of OS | Li Y et al. (2020) |
| lncR-SNHG3     | Overexpression | miR-196a-5p             | 127     | 127      | Related to overall survival rate of patients and tumor size | Chen et al. (2019) |
| lncR-SNHG4     | Overexpression | miR-224-3p              | 136     | 40       | Promote tumor growth and represent a poor prognosis | Xu B et al. (2018) |
| lncR-CCAT2     | Overexpression | GSK3β/β-catenin          | 50      | 50       | Positive correlation with tumor size, stage and overall survival rate | Ruan and Zhao, (2018) |
| lncR-SOX21-AS1 | Overexpression | miR-7-5p/IRS2            | —       | —        | High expression leads to the proliferation, migration and invasion of OS cells | Chen and Chen, (2021) |
| lncR-DLX6-AS1  | Overexpression | miR-641/HOXA9           | 40      | 40       | Related to TNM stage, clinical stage and distant metastasis of OS | Zhang H et al. (2019) |
| lncR-Sox2OT-V7 | Overexpression | miR-142/miR-22           | —       | —        | Associated with chemotheray resistance | Zha et al. (2020) |
| lncR-NR-036444 | Low-expression | —                      | 60      | —        | May be used as a biomarker to distinguish the chemotheray sensitivity and judge the prognosis of OS | Zha and Zhang, (2017) |
| lncR-SNHG4     | Overexpression | miR-224-3p/ DOCK7        | 136     | 40       | Positively correlated with tumor volume and negatively correlated with overall survival rate | Xu B et al. (2018) |
| lncR-XIST      | Overexpression | miR-153-SNAI1            | 30      | 30       | Relate to migration, invasion and EMT of OS cells | Wen et al. (2020) |
| lncR-DANCR     | Overexpression | miR-149/MSI2             | 109     | 109      | Relate to TNM stage | Zhang et al. (2020) |
| lncR-FOXD2-AS1 | Overexpression | —                      | 20      | 20       | Negatively correlated with overall survival. Positive correlation with migration and invasion | Zhang N et al. (2019) |
| lncR-TTN-AS1   | Overexpression | miR-134-3p/ MBTD1        | —       | —        | Positively correlated with chemotherapy resistance and tumor volume | Fu et al. (2019) |
| lncR-BC050642  | Overexpression | c-myc                   | 97      | 97       | Related to the clinical stage and cell viability of the patient | Yang et al. (2019) |
| lncR-01614     | Overexpression | miR-520a-3p/SNX3         | 10      | 0        | Positive correlation with migration, invasion and tumor size of OS cells | Cai et al. (2021) |
| lncR-SNHG16    | Overexpression | miR-488/ITGA6            | 10      | 10       | Promoted migration, invasion and EMT of OS by sponging miR-488 to release ITGA6 | Bu et al. (2021) |
| lncR-NNT-AS1   | Overexpression | —                      | 126     | 126      | Related to the migration and invasion of tumor cells | Ye et al. (2018) |
| lncR-BCAR4     | Overexpression | GLI2-dependent gene      | 60      | 60       | Positive correlation with tumor size, migration, invasion and invasion stage. Negatively correlated with overall survival | Chen et al. (2016) |
| lncR-MALAT1    | Overexpression | miR-150-5p/ VEGFA        | —       | —        | Induction of angiogenesis | Vimalraj et al. (2021) |
| piR-39980      | Overexpression | SERPINB1/MMP-2           | 2       | —        | Positively correlated with the proliferation, migration and invasion of OS cells | Das et al. (2020) |
| hsa_piR-008613 | Low-expression | FN1 mRNA                | 2       | —        | | Cui et al. (2022) |
It can be observed that many articles have proved that ncRNAs also has the potential as a diagnostic marker. In addition to the function in diagnosis, the levels of OS ncRNAs biomarkers also play an important role in determining the disease stage of OS at diagnosis. Abnormal expression of OS related genes and biomarkers can induce the activity, proliferation and differentiation of osteoblasts. The abnormal degree can directly reflect the pathological staging of patients and affect the prognosis. Enneking staging has become an important basis of OS surgical staging which can better remind the prognosis, and help to select an appropriate treatment. However, research on the relationship between ncRNAs biomarkers and tumor staging is still very lacking. A variety of ncRNAs biomarkers are closely related to the clinical stage of Enneking and have been widely used to determine the clinical stage of OS. The more malignant the lesion is, the higher Enneking stage and higher possibility of distant metastasis the tumor have.

It was found that the expression of IncRNA GNAS antisense (IncRNA GNAS-AS1) could significantly increase in OS cells and tissues, which were positively correlated with Enneking stage and distant metastasis. Its high expression often predicted the short overall survival time (Mi et al., 2021). Through regulating miR-490-3p, IncRNA GNAS-AS1 could play a major role in cell proliferation, migration and invasion, which could be an independent prognostic predictor of OS, providing a new therapeutic strategy for OS (Mi et al., 2021). The expression of circRNA-mitochondrial tRNA translation optimization 1 (circ_MTO1) in OS is low, its expression level is significantly correlated with Enneking staging, and its high expression in the tumor meant that the Enneking staging was lower in OS patients who had better neoadjuvant chemotherapy response and longer disease-free survival (DFS) (Shi et al., 2021). Except for the above, the increased expression of circ_001569 in OS was positively related to tumor size, Enneking stage or Tumor Node Metastasis (TNM) stage and lung metastasis (Xiao et al., 2020). The results reported by Wang et al. (2019) showed that circ_0021347 was significantly downregulated in OS tissues and cell lines, negatively correlated with TNM staging and positively correlated with patient survival. circ_0021347 can target B7 Homolog3 (B7-H3), which showed a strong negative correlation with the expression of B7-H3 in OS and exerted anti-cancer effect by negatively regulating the expression of B7-H3.

### TABLE 1 (Continued) Identification of NcRNA Tumor Biomarkers analyzed in multiple studies.

| Tumor biomarker | Deregulation Genes/proteins affected | OS cases | Controls | Observation in OS | Ref |
|-----------------|-------------------------------------|----------|----------|-------------------|-----|
| IncR-NR-136400 | Low-expression TUSC5 | 4 | 3 | Positively correlated with proliferation and migration | Liu et al. (2020) |
| ceR-IGF-1 | Overexpression miR-29a/VEGF | 1 | 1 | Promote angiogenesis | Gao et al. (2016) |
| circ_0001785 | Overexpression miR-1200/HOXB2/ PI3K/Akt | — | — | Promote proliferation | Li L. et al. (2019) |
| circ_DOCK1 | Overexpression miR-339-3p/IGF1R | 70 | 70 | Increased oncogenicity in vivo and malignant transformation in vitro | Li S. et al. (2021) |
| circ_EPST1 | Overexpression miR-892b | 50 | 50 | Promote migration and invasion of OS cells | Tan et al. (2020) |
| circ_0102049 | Overexpression miR-1304-5p/ MDM2 | 76 | 76 | Positively correlated with the tumor volume and lung metastasis of the patient, and negatively correlated with the overall survival rate | Jin et al. (2019) |
| IncR-HCG9 | Overexpression miR-34b-3p/ RAD51 | 15 | 15 | Positively correlated with proliferation, migration and invasion | Wang et al. (2021) |
| IncRNA-SNHG16 | Overexpression miR-1285-3p | 50 | 50 | Positively correlated with proliferation, migration, invasion, apoptosis | Xiao et al. (2021) |
| PIK3CA | Overexpression | 59 | 63 | High expression means that patients have a higher risk of OS | He et al. (2013) |
| iNOS | Overexpression Wnt/β-Catenin | 45 | 45 | INOS is closely related to the formation of OS, and inhibition of INOS will affect the effect of β-protein | Chu et al. (2021) |
| IDH1 | Low-expression — | 44 | 16 | Upregulation can significantly reduce the invasion and migration activity of OS | Hu et al. (2014) |
| TP53 | mutated | 425 | — | Oncogenic function of mutant TP53 maintains tumor cell proliferation and growth in OS | Tang et al. (2019) |
| RECQL4 | mutated | 18 | 12 | Necessary for normal OS amplification and OS formation | Maire et al. (2009) |
| DLG2 | mutated | 31 | — | Associated with susceptibility to OS | Shao et al. (2019) |
In a word, the emergence of ncRNAs biomarkers in patients provides a reliable non-invasive method for the diagnosis and clinical staging of OS. However, when exploring new serum biomarkers in the future, the sensitivity and specificity of existing biomarkers should not be ignored, so as to provide accurate guidance information for clinical practice.

**Therapeutic biomarkers**

Neoadjuvant chemotherapy is the standard treatment at present, and its survival rate has been greatly improved. However, the survival rate of patients with lung metastasis and chemotherapy resistance is still very low. Although the introduction of neoadjuvant chemotherapy has greatly improved the 5-year survival rate of OS, a large number of patients still have poor response to chemotherapy. Even after surgical resection and chemotherapy, there still exist a high risk of local recurrence or distant metastasis, leading to poor prognosis. It is necessary to develop new therapeutic methods for OS clinically, which require us to clarify the molecular mechanisms of the pathogenesis and development of OS. The screening of new molecular markers is important for the prognosis and treatment of OS.

The ncRNAs have good stability, which can be used as potential cancer biomarkers and treatment targets (Rong et al., 2017). Previous studies have explained the mechanism of OS from multiple drug resistance-related genes, miRNAs, circRNAs and other aspects. Significant changes of miRNAs expression profile in drug-resistant OS cells indicate that miRNAs can participate in the development of drug resistance by regulating various targets and signaling pathways. The treatment based on miRNAs mainly included blocking the expression of oncogenic miRNAs and restoring the expression of tumor-inhibiting miRNAs genes. For instance, miR-21, which was highly expressed in many cancer types, had higher...
expression level in the sera of OS than that in the healthy, which has been used clinicall as a biomarker of chemotherapy sensitivity and prognosis (Yuan et al., 2012; Hua et al., 2017; Zhao H et al., 2019). Related studies have proved that transforming growth factor-β1 (TGF-β1) inhibitor treatment reduced the inhibitory effects of miR-21 knockdown on OS cell proliferation. miR-21 inhibition may inhibit OS cell proliferation by targeting PTEN and regulating the TGF-β1 signaling pathway (Hu et al., 2018). In addition, the miRNAs profile is associated with tumor response which can be a preferred tool for predicting tumor susceptibility to treatment.

With the deepening understanding of genetic biomarkers, the therapeutic effect of IncRNAs has become a hot research topic in recent years, which is superior to known protein encoded gene biomarkers in predicting drug responses. At present, the abnormal expression of IncRNAs has been found in many patients. These abnormal expressions can affect the processes of drug outflow, apoptosis, DNA repair, cell cycle, proliferation, autophagy, etc. At the same time, these abnormal expressions participate in the chemotherapy resistance of OS by regulating the expression of different target genes and related signaling pathways. Distal-less homeobox 6 antisense 1 (DLX 6-AS1), which was highly expressed in OS patients, exerted its capability of inhibiting the proliferation, invasion and metastasis of OS cells by targeting the miR-641/homeobox protein Hox-A9 (HOXA9) signaling pathway (Zhang H et al., 2019). Upregulation of SOX2 overlapping transcript lncRNA transcript variant 7 (Sox2OT-V7) in OS can directly target miR-142/miR-22 to inhibit its expression, especially in OS tissues and cell lines that were resistant to chemotherapy. When knocking out Sox2OT-V7 in OS cells, the drug-resistant U2OS/Dox cells can be re-sensitive to chemotherapy drugs (Zhu et al., 2020).

Small nucleolar RNA host genes 4 (SNHG 4) can play a role in the occurrence and development of OS through the miR-224-3p/DOCK7 pathway, which provide a new method in the treatment of OS (Xu B et al., 2018). Lee A. M. et al. (2021) identified a positive correlation between the expression of IncRNA and anti-sense non-coding RNA in the INK4 locus (ANRIL) and the resistance of two therapeutic drugs for OS, cisplatin and doxorubicin. It was found that the drug resistance of MG-63/DXR cells transfected with IncRNA NR_036444 decreased significantly, the proportion of cells in the G (1) phase increased. The proportion of cells in the later stage of apoptosis also increased, which might play an important role in regulating the drug resistance to doxorubicin, and might become a useful biomarker to evaluate chemotherapy sensitivity and predict prognosis of OS in the future (Zhu and Zhang, 2017).

CircRNAs can play positive or negative regulatory roles in the occurrence and development of OS. In the fact, circRNAs can further participate in the regulation of chemotherapy resistance and metastasis of OS through “sponging” miRNAs as a tumor activating or inhibiting factor. The treatment based on miRNAs mainly included blocking the expression of oncogenic miRNAs and restoring the expression of tumor-inhibiting miRNAs genes. The carcinogenic effects of circ_0009910 were partially dependent on the JAK2/STAT3 pathway, which was involved in the apoptosis and proliferation of cells, thus affecting the progression of OS (Richardson et al., 2010). And circ_001569 may promote resistance through the Wnt/β-catenin pathway (Wu et al., 2014).

Drug resistance is the main limiting factor for the effectiveness of cancer treatment. Some drugs can quickly relieve the tumor, but on the one hand, they can also produce resistance, thus increasing the difficulty of treatment (Vasan et al., 2019). At present, more and more ncRNAs have been found to be associated with drug resistance of OS (Raei et al., 2021). The reversal of targeted ncRNAs is likely to be a potential method for reversing drug resistance of OS, which requires us to consider how to select the key ncRNAs from a large number of candidates ncRNAs. In the future, we should actively carry out clinical trials or transformation research based on targeted ncRNAs therapy, clarify the detailed mechanism of ncRNAs in OS drug resistance, and further apply them to clinical treatment of OS.

## Prognostic biomarkers

OS has a poor prognosis due to chemo-resistance and/or metastases. ncRNAs biomarkers of OS can affect the prognosis in many ways. Clarifying the relationship between ncRNAs biomarkers and the prognosis of OS, can help to optimize the current treatment plan and choose the right time of surgery and chemotherapy.

A variety of miRNAs also have great significance for the prognosis and progression of OS. The expression of miR-140 was related to the chemotherapy sensitivity of OS xenografts, which was involved in a wide range of chemotherapy resistance mechanisms by inhibiting HDAC4-mediated decrease in cell proliferation in G (1) and G (2) stages and participating in chemotheray resistance. miR-140 could inhibit the proliferation of U2OS cells, but its inhibitory effect on MG-63 cell was weak (Song et al., 2009). miR-223 has proved to be a potential prognostic marker for a variety of cancers in the past. Recently, some scholars have observed its function in OS. They found that miR-223 may be related to OS metastasis, and it has great potential as a potential biomarker for diagnosis and prognosis of OS (AUC:0.926) (Dong et al., 2016).

LncRNAs can play important roles in drug sensitivity and cancer metastasis. lncR-BC050642 was significantly increased in OS tissues and cell lines, playing an important role in promoting the proliferation of OS cells, who can also be an independent biomarker of OS prognosis (Yang et al., 2019). In OS tissues, the significantly upregulated lncR-01614 indicated a worse prognosis for patients. After knocking out lncR-01614, the proliferation, invasion and
The early symptoms of OS are not typical. It is easy to metastasize, and the treatment often lagging behind with poor effect. Although the diagnosis and treatment of OS have made factors through Cox multivariate regression analysis. After knocking down the expression of circ_0008717, the proliferation, migration and invasion of tumor cells can be reduced, and apoptosis can be promoted (Shen et al., 2022). circ_0081001 was another potential biomarker of OS prognosis, which was selected from chemotherapy and chemotherapy-sensitive OS cell lines, showing high levels in advanced OS, chemotherapy-resistant and lung metastasis (Wei et al., 2021) (Figures 2, 3). Although some ncRNAs as prognostic biomarkers have been identified in OS, the outcome was not fully validated. As there have been some studies on the prognostic markers of OS, there is no practical application. The function of biomarkers for the diagnosis and prognosis of OS, especially patients with metastasis, may be an urgently needed tool for early diagnosis and identifying potential therapeutic targets.

## Perspectives and future opportunities

The early symptoms of OS are not typical. It is easy to metastasize, and the treatment often lagging behind with poor effect. Although the diagnosis and treatment of OS have made
continuous progress in recent years, the 10-year survival rate of patients with metastatic OS is still less than 20% (Yang et al., 2020). As a result, new early diagnosis and treatment methods of OS are urgently needed. Biomarkers refer to biochemical indicators that can mark changes or possible changes in the structure or function of systems, organs, tissues, cells, and subcellular. The development of biomarkers provides new insights for the early diagnosis and treatment of diseases, which can assist clinicians in initial diagnosis especially for patients with metastatic OS, guide the treatment method, judge disease stages, evaluate the safety and effectiveness of new drugs or therapies in target population, providing a series of key genes and approaches for elucidating the molecular mechanism of OS. Therefore, it is urgent to search for useful biomarkers and therapeutic targets for clinical application. ncRNAs can be produced in the early stage of disease, which is an important part of epigenetics research. It can be used as a key regulatory factor to regulate the expression of related genes and participate in the processes of cell development, differentiation, proliferation, transcription, post-transcriptional modification, apoptosis, and cell metabolism (de la Fuente et al., 2012). Moreover, it can naturally connect related genetic networks to affect various basic protein effect factors that drive specific cellular biological responses and determine cell fate (Wei et al., 2017). As a carcinogen or anti-cancer factor, it plays an important role in the occurrence and development of a variety of cancers, with a certain stability and richness. ncRNAs can enter the circulatory system, which is expected to become a potential biomarker of OS (Slack and Chinnaiyan, 2019).

The application of these ncRNAs in the research and development of anti-OS drugs, related therapeutic targets and biomarkers in the field of OS was discussed in detail in this paper. At present, the newly discovered tumor biomarkers are one of the hot spots in oncology research. The research on ncRNAs-encoded peptides or proteins has opened up a new research field for the diagnosis and treatment of tumors. As for OS, ncRNAs can be produced in the early stage of the disease, with certain stability and richness. When them entered the circulatory system, they can play an important role in cell function and affect its clinical manifestations to a certain extent. It is expected to become an effective diagnosis and treatment method. However, current research on ncRNAs also has the following problems. Firstly, the related research on ncRNAs and OS is limited and not in-depth. The current research mainly focuses on basic in vitro experiments. Further animal experiments and clinical trials are needed to confirm it in the future. Secondly, the targeted anticancer drugs of ncRNAs can weaken or even eliminate drug resistance of the patients, and further enhance the therapeutic effect. However, these drugs still have the disadvantages of insufficient specificity and utilization rate. The absorption and biodistribution of some drugs still need further solution. There is still a long way to go before the approval and commercialization of ncRNAs-targeted anticancer drugs. Thirdly, ncRNAs have many targets and complex regulatory networks. At present, most research on ncRNAs are independent and scattered. The lack of specificity in the diagnosis and treatment of OS targeting ncRNAs still needs to be resolved. Finally, there still exist problems such as small sample size in the current research on the relationship between ncRNAs and OS, and lacking of epidemiological evaluation and functional exploration of candidate biomarkers. Only a few ncRNAs have been fully studied, and the possibility of its clinical application is still uncertain. In addition, most ncRNAs cannot be detected by standard methods such as quantitative PCR. It is an urgent to find new detection optimization methods and advanced laboratory platform conditions.

In summary, the expression of the biomarker is significantly related to the tumor size, distant metastasis, TNM stage, and Enneking surgical stage of the patients, which has the ability to distinguish OS from the healthy. It is important to look for a reliable clinical biomarker in the field of the early diagnosis and treatment of OS. These biomarkers are helpful to clarify the molecular mechanisms related to OS, and may become new targets for OS diagnosis and treatment. The higher the level of biological evolution, the higher the proportion of ncRNAs in the genome. Constituting almost 60% of the transcriptional output in human cells, ncRNAs have been shown to regulate cellular processes and pathways in developmental and pathological contexts (Anastasiadou et al., 2018). Therefore, searching for more types of ncRNAs and its more extensive and diverse biological functions and action mechanisms are our current main tasks. The role of these ncRNAs in the proliferation, occurrence and development of OS cells should be deeply studied, so as to better predict and diagnose OS, provide meaningful theoretical guidance for individualized treatment and drug research. In the future, ncRNAs may continue to better help researchers and clinicians find molecular features, help in differential diagnosis, personalized treatment and determine prognosis et al. Although the applications of ncRNAs are still at an early stage, it deserves expectation can be put into clinical practice especially those candidates that can be readily detected. In the follow-up study, we would further verify the efficacy of diagnosis, treatment and prognosis of OS in large samples, and combine multiple ncRNAs to build a model to assist the diagnosis of clinical OS. Benign biomarkers should affect biological function of the disease, and the impact of promising ncRNA on the function of OS will be further explored. In addition, the biomarkers found in urine or blood by non-invasive procedures is ideal better than collecting tissues. Furthermore, there are great challenges associated with RNA-based therapeutics. On the one hand, RNA drugs can easily approach the targets based on nucleotide hybridization. On the other hand, the delivery method is a challenging process. As a promising new biomarker, ncRNA research is undergoing a rapid change and entering a new area of development. To keep up the pace, better techniques for the detect of new useful ncRNAs need...
to be implemented, and the evaluation of those potential biomarker should be validated in a larger sample size. In the near future, our team will still be committed to the above studies of OS. Discovering new targets by high throughput sequencing methods, and follow-up studies on pathways are our research goals which can promise the revolution of OS. It is believed that with the further popularization and deepening of research, there will be new thoughts on the early prevention, accurate diagnosis and safer and more effective treatment of OS, and further application of ncRNAs to the diagnosis and treatment of other types of cancer.

**Author contributions**

JL conceived the study. LF and ZZ conducted the study and drafted the application sections, they contributed equally to this work. YL contributed to the writing and review of the manuscript. All authors read, revised and approved the final manuscript.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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