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The role of miRNAs as biomarkers in cancer

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Abstract

MicroRNAs (miRNAs), a class of non-coding RNAs, play a critical role in regulating gene expression and have demonstrated significant potential as biomarkers in cancer research. This review explores the role of miRNAs in tumorigenesis, invasion, and metastasis, highlighting their altered regulation in various cancers, including lung, breast, liver, colorectal, and prostate cancer. miRNA expression patterns analysis helps clinicians in early cancer diagnosis, classification, and therapeutic monitoring. The stability of miRNAs in body fluids makes them ideal candidates for liquid biopsy, offering a non-invasive tool for cancer detection and prognosis assessment. Despite the promising clinical applications, challenges remain in the standardization of detection methods and integration of multi-omics data. Results are variable because different detection platforms, including qPCR, microarray and sequencing methods which have varying sensitivity and specificity. However, integrating multi-omics data comes with additional technological challenges because it calls for sophisticated bioinformatics tools to manage intricate and huge datasets. Further advancements are expected to establish miRNAs as a robust foundation for personalized cancer therapy.

Key words microRNAs, cancer biomarkers, tumorigenesis, liquid biopsy, early cancer detection, personalized therapy

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Introduction

Cancer remains one of the leading causes of death worldwide, with incidence and mortality rates rising annually [1, 2]. Despite significant advancements in modern medical technologies for cancer treatment and management, challenges persist in early detection, accurate classification, and personalized treatment. Early cancer screening is generally associated with better treatment outcomes. However, traditional diagnostic methods, such as tissue biopsy and imaging, often lack the sensitivity and accuracy needed to detect tumors at early stages. Recent advancements in molecular biology tools have led to a growing interest in the use of biomarkers in early tumor diagnosis.

As a subclass of non-coding RNAs, microRNAs (miRNAs) have shown great promise as cancer research biomarkers in recent years. miRNA molecules regulate the translation and degradation of target genes, which is vital in various biological processes, including cell division, proliferation, apoptosis, and metabolism [3]. The miRNAs are closely associated with tumorigenesis and cancer progression. Numerous studies have demonstrated that dysregulation of miRNA expression is the key factor in cancer initiation, invasion, and metastasis [4, 5]. For example, unregulated cell proliferation promotes cancer development because oncogenes such as RAS are overexpressed, while tumor suppressor miRNAs such as let-7 are down-regulated [6]. miR-21 overexpression targets apoptosis and cytoskeleton regulation-related genes, including PDCD4 and TPM1, thereby increasing the motility and invasiveness of cancer cells during the invasive phase [7, 8]. Furthermore, it has been shown that miR-10b increases the invasiveness and motility of cancer cells during metastasis by blocking HOXD10 which involve in cell adhesion and extracellular matrix organization [9]. By controlling oncogenes or tumor suppressor genes, particular miRNAs can function as oncogenic drivers or as parts of tumor-suppressive systems. For instance, Javanmardi S. discovered that miR-21 is a well-known oncogenic miRNA that is overexpressed in many types of cancer [10]. On the other hand, miR-34a is a tumor-suppressor miRNA, typically downregulated in tumor cells [11].

The biological behavior of tumors can be reflected in the expression levels of miRNAs, with significant tissue and disease specificity. Compared to conventional tissue biopsies, miRNAs provide notable technological benefits. They can be detected in bodily fluids such as blood, urine, and saliva through liquid biopsy techniques due to their exceptional stability. This offers a viable method for the non-invasive screening of cancer [12]. Furthermore, miRNAs can express a tumor's molecular features, which makes them helpful for a variety of clinical tasks, including tumor subtype identification, tumor progression prediction, and therapy response evaluation. Consequently, miRNAs have the potential to offer direction for tailored therapeutic approaches.

Shen, J. et al. study on the early detection of lung cancer showed elevated plasma levels of miR-21 and miR-210. Conversely, patients with malignant solitary pulmonary nodules (SPNs) showed significantly lower levels of miR-486-5p than patients with benign SPNs and healthy controls. Research indicates that these miRNAs can effectively distinguish between healthy individuals and lung cancer patients, demonstrating high sensitivity and specificity [13]. In breast cancer, miRNAs such as miR-155 [14, 15] and miR-21 [16] are closely associated with tumor invasiveness and metastasis. Their expression can be used as a biomarker for early diagnosis and for monitoring therapeutic responses. Furthermore, by examining miRNA expression patterns, physicians can forecast tumor recurrence rates and survival outcomes because there is a substantial correlation between miRNA expression and patient prognosis.

MiRNAs hold considerable promise for cancer treatment and diagnosis, yet several challenges hinder their practical application. One major issue is the significant heterogeneity in miRNA expression, with variations not only between patients but also within different tumor sites. Moreover, additional refining of miRNA detection techniques is needed to guarantee reproducibility and consistency of results between laboratories. A critical area for future research involves the integration of miRNA biomarkers with other omics data, including proteomics, genomes, and epigenomics [17], to improve diagnostic sensitivity and accuracy. Consequently, miRNAs have significant promise for early cancer diagnosis, diagnostic subtyping, prognostic evaluation, and tailored therapy. In summary, The rapid progress in miRNA research as tumor biomarkers, coupled with advances in detection technologies and the integration of multi-omics data, suggests the growing importance of miRNAs in clinical oncology. This study focuses on the potential of miRNAs as tumor biomarkers and their applications in early diagnosis, prognostic assessments, and therapeutic interventions.

Biological functions of miRNAs

MiRNAs, as non-coding RNAs, play a pivotal role in gene expression regulation and are integral to the intracellular gene regulatory network. They influence critical biological processes such as cell proliferation, apoptosis, invasion, metastasis, and angiogenesis, all vital to tumor development and progression. MiRNAs serve a complex and essential function in the initiation and exacerbation of tumors. In addition to helping to clarify the molecular principles behind tumor growth, a deeper comprehension and analysis of miRNA functions offer fresh viewpoints and methods for cancer diagnosis, prognosis evaluation, and tailored therapy. The biological roles of miRNAs will be expounded upon in the ensuing sections, with particular attention paid to their production and processing, modes of action, roles within normal cells, and dysregulation inside malignancies.

miRNA biogenesis and processing

The biogenesis and processing of miRNAs are complex and systematic, involving multiple stages and enzymes. The process begins with the transcription of primary miRNAs (primor-miRNAs) from the genome, typically facilitated by RNA polymerase II or III. First cleaved in the nucleus by the Drosha-DGCR8 complex, primor-miRNAs are lengthy RNA molecules with a distinctive hairpin structure. These precursor miRNAs, also known as pre-miRNAs, are roughly 70 nucleotides long [18]. These pre-miRNAs are transported to the cytoplasm by Exportin-5, where they are further processed by the enzyme Dicer into mature miRNA duplexes. One strand of the duplex (the guide strand) is loaded into the RNA-induced silencing complex (RISC), while the other strand is typically degraded [19]. Any dysregulation in this processing pathway can result in abnormal miRNA expression, subsequently affecting the regulatory functions of target genes. Such abnormalities play a significant role in the development of cancer and other diseases. For instance, impaired Drosha or Dicer function can cause widespread miRNA dysregulation and promote tumorigenesis.

Mechanism of gene regulation by miRNA

The primary function of miRNAs is to regulate gene expression by binding to target mRNAs, thereby inhibiting their translation or promoting their degradation. miRNA binding typically occurs at the 3' untranslated region (3' UTR) of the target mRNA, a process mediated by the RNA-induced silencing complex (RISC). The particular processes entail either mRNA degradation or

translational suppression [19, 20]. Important biological processes connected to metabolic control require this gene-silencing mechanism. Protein translation is prevented when miRNA attaches partial complementarity to the 3' UTR of the target mRNA, preventing ribosome recognition and binding to the mRNA. Essential biological processes linked to the regulation of metabolism include this gene-silencing mechanism [21]. miRNAs can affect gene transcription indirectly in addition to directly affecting mRNA through their regulation of transcription factors or interactions with chromatin modification complexes. Moreover, miRNAs can control histone modifications and DNA methylation, which controls epigenetic gene expression [22].

The role of miRNA in cellular physiological processes

miRNAs are crucial regulators of gene expression, influencing various cellular physiological processes, including immune response, metabolism, apoptosis, cell division, and proliferation. miRNAs can precisely regulate cell proliferation and differentiation by altering genes associated with the cell cycle and differentiation. For instance, the miR-34 family, recognized as tumor suppressor RNAs, interacts with the tumor suppressor gene p53. These results are supported by Hermeking H.'s investigation into the functions of miR-34a and miR-34b/c in apoptotic responses in tumor and normal cells [23]. Additionally, Jauhari A. investigated the role of the miR-34 family in neuronal differentiation and identified p53 as a mediator of nerve growth factor (NGF)-induced miR-34a expression, which is involved in the differentiation of PC12 cells [24]. Recent studies have also demonstrated that miR-124 exerts a significant impact on neuronal differentiation. Gu X. and colleagues outlined the role and potential mechanisms of miR-124 in neurodevelopment [25]. In apoptosis regulation, miRNAs modulate the balance between cell survival and death by targeting apoptosis inhibitors or promoters, such as BCL2 or PTEN [26]. In metabolic processes, Tsai WC et al. demonstrated miR-122's regulatory influence on liver metabolism, underscoring miRNAs' essential role in metabolic stability [27]. In the immune system, miRNAs such as miR-146a play a critical role in modulating immune cell function and inflammatory responses [28]. Overall, as key regulators of gene expression, miRNAs participate in and maintain various cellular physiological processes through intricate gene regulatory networks. Dysregulation of these networks may lead to a range of diseases, including cancer, metabolic disorders, and immune-related diseases. As research progresses, understanding miRNA functions and mechanisms offers promising avenues for novel therapeutic strategies targeting these diseases.

The role of miRNAs in tumors

The role of miRNAs in tumorigenesis

The role of miRNAs in tumorigenesis is critical, as they can function either as oncogenes (oncomiRs) promoting tumor development or as tumor suppressor miRNAs inhibiting tumor progression. In tumors, overexpressed miRNAs may contribute to cancer progression by inhibiting tumor suppressor genes, while the downregulation of other miRNAs may suppress tumor formation by inhibiting oncogene expression. For example, miR-21 is considered an oncomiR, and its overexpression has been observed in various cancers, such as lung and breast cancer. miR-21 promotes cell proliferation and anti-apoptotic capacity by targeting tumor suppressor genes such as PTEN, PDCD4, and TPM1. By suppressing PTEN, a key negative regulator of the PI3K/AKT signaling pathway, miR-21 leads to increased cell survival and growth [29]. Inhibition of PDCD4, a pro-apoptotic protein involved in programmed cell death, further enhances cancer cell resistance to apoptosis [7]. Additionally, downregulation of TPM1, a cytoskeletal protein, contributes to enhanced cell motility and invasiveness, promoting tumor progression and metastasis[8].Peralta-Zaragoza, O. discovered that miR-21 post-transcriptionally downregulates PTEN expression to promote cell proliferation and cervical cancer cell survival [30], Qi, L. et al. found that the expression of miR-21 and its targets (PTEN, PDCD4, TM1) in breast ductal carcinoma in situ and invasive carcinoma is associated with squamous atypia [31], Xu LF et al. demonstrated that miR-21 simultaneously regulates multiple processes, such as enhanced cell proliferation, apoptosis, and tumor invasiveness, by targeting PTEN, RECK, and Bcl-2 in GSQCLC, suggesting a key role in the tumorigenesis and progression of lung squamous cell carcinoma [32]. Additionally, miR-155 is highly expressed as an oncogenic miRNA in various cancers, promoting tumor cell survival and immune evasion by targeting tumor suppressor genes such as SHIP1 and SOCS1 [33]. The miR-34 family, including miR-34a, miR-34b, and miR-34c, is one of the classical tumor-suppressor miRNAs, and its expression is downregulated in numerous cancers [34]. For instance, miR-34a is associated with the p53 pathway, and the absence of miR-34a can lead to tumorigenesis [35]. Moreover, the let-7 family of miRNAs is widely involved in tumor suppression by inhibiting the expression of oncogenes such as RAS and HMGA2. Research by Yan, L. et al. showed that depletion of H19 impairs, while its overexpression enhances the motility and invasiveness of tumor cells, a phenomenon mediated by let-7-regulated metastasis-promoting genes, including Hmga2, c-Myc, and Igf2bp3 [36]. The dysregulation of these miRNAs can provide insights into the molecular mechanisms underlying tumorigenesis.

The role of miRNAs in tumor invasion and metastasis

Tumor invasion and metastasis are the leading causes of mortality in cancer patients. miRNAs play a crucial role in tumor metastasis by regulating processes such as cell migration, invasion, and epithelial-mesenchymal transition (EMT). During EMT, epithelial cells transform, losing their polarity and adhesion to become mesenchymal cells with increased migratory and invasive abilities. Aberrant expression of miRNAs influences cytoskeletal remodeling, cell adhesion, and matrix degradation, making them critical regulators of tumor invasion and metastasis. For instance, miR-221 and miR-222 are widely recognized as key miRNAs promoting tumor proliferation and invasion. miR-221 and miR-222 facilitate rapid tumor cell proliferation by inhibiting the cell cycle inhibitors p27 and p57 [37]. Furthermore, Zhang CZ et al. found that miR-221 and miR-222 target PUMA, a pro-apoptotic factor, thereby inducing glioblastoma cell survival and further enhancing cancer cell resistance [38]. These findings suggest that miR-221/222 plays a pivotal role in cell cycle regulation, apoptosis, and survival pathways.

miR-10b promotes the invasion and metastasis of breast cancer cells by upregulating the RHOC gene. RHOC, a member of the Rho GTPase family, is involved in the dynamic regulation of the cytoskeleton and cell migration. Studies have shown that miR-10b promotes cancer cell migration and invasion by inhibiting the expression of the HOXD10 gene, which in turn activates RHOC. Subsequently, research by Du, J. demonstrated differential expression of miR-10b between hepatocellular carcinoma (HCC) and adjacent non-tumor tissues, with reduced miR-10b expression in HCC being associated with venous invasion. High RHOC expression levels were also linked to venous invasion in HCC, indicating that both miR-10b and RHOC are independent predictors of invasion and metastasis in HC [39]. These findings suggest that miR-10b and RHOC are metastasis factors in breast

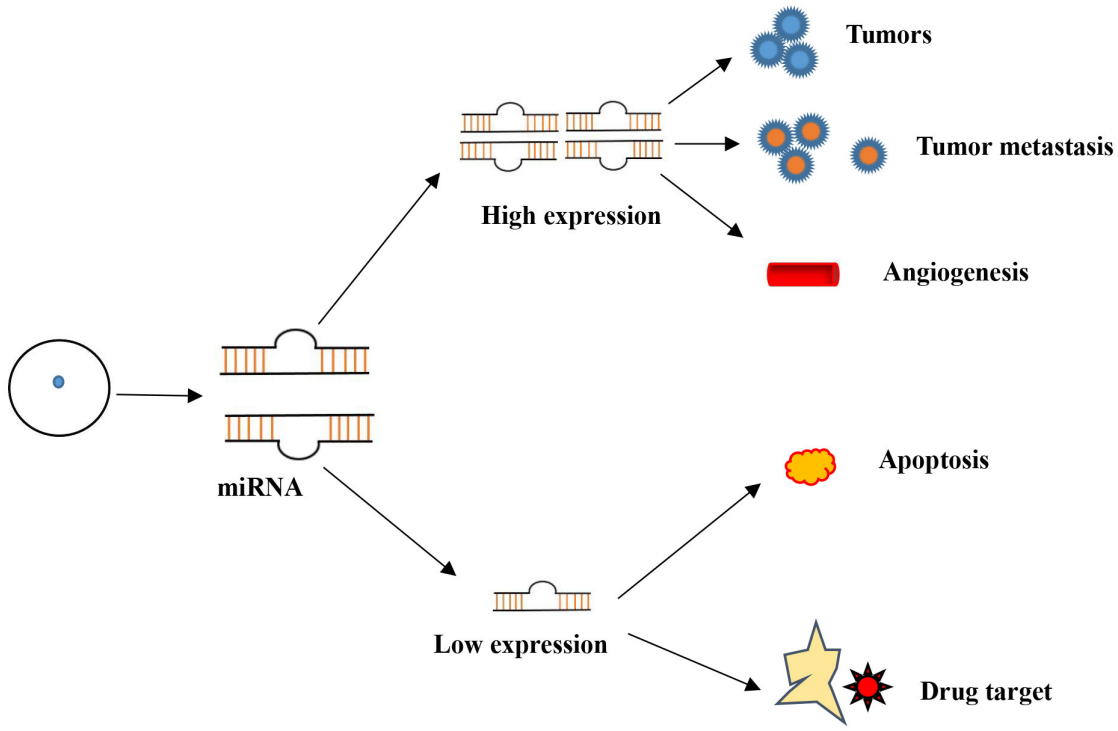

Figure 1. Schematic diagram of miRNA regulation.

cancer and play critical regulatory roles in the invasion and metastasis of liver cancer.

Huang Q. discovered that miR-373 and miR-520c enhance the migratory capacity of tumor cells by regulating genes such as CD44 and EGFR. [40]. EGFR plays a key role in cell proliferation and survival signaling pathways. CD44, a cell adhesion molecule, is crucial for maintaining interactions between tumor cells and their microenvironment. In contrast to pro-migratory miRNAs, the miR-200 family (including miR-200a, miR-200b, and miR-200c) effectively inhibits tumor metastasis by directly suppressing ZEB1 and ZEB2, thereby blocking the epithelial-mesenchymal transition (EMT) process. ZEB1 and ZEB2 downregulate E-cadherin and promote EMT, enhancing the migratory and invasive capabilities of tumor cells. Through the maintenance of E-cadherin expression, the miR-200 family efficiently inhibits the spread of cancer by maintaining epithelial phenotype [41]. Additionally, miR-31 targets genes such as RHOA and WAVE3, which are involved in cytoskeletal remodeling and cell invasion, respectively. By downregulating these genes, miR-31 curbs the invasive and migratory characteristics of tumor cells, acting as a potential metastasis suppressor in various cancers. In conclusion, miRNAs are essential for the development of tumors and their spread (**Figure 1**).

miRNAs as diagnostic biomarkers for tumor

miRNAs are an important family of non-coding RNA molecules that have shown great promise in the identification of different forms of cancer. Their capacity to remain stable in physiological fluids makes them an essential component of liquid biopsies, which are crucial for early cancer detection. The higher sensitivity and specificity of miRNAs than standard tissue biopsies make them an ideal choice. The use of miRNAs in liquid biopsies has garnered more attention in recent years, and studies have demonstrated their remarkable efficacy in the early diagnosis of many malignancies [42].

miRNA detection

Liquid biopsy, a non-invasive method, leverages biomarkers found in physiological fluids such as blood, urine, and saliva to facilitate early cancer diagnosis, monitor therapy, and evaluate recurrence. MiRNAs are a vital component of liquid biopsy because of their consistent presence in blood and other physiological fluids. The use of miRNAs has a number of benefits over traditional tissue biopsy, including non-invasiveness, high sensitivity, and great specificity. Of these, the early identification of cancer has shown considerable promise [43].

Compared to mRNA, miRNAs are highly stable and less prone to degradation by nucleases due to their ability to bind with proteins such as Argonaute or associate with microparticles. This association extends their half-life in external environments. Studies have demonstrated that miRNAs not only remain stable in plasma and serum but are also encapsulated and protected by exosomes, microvesicles, and other structures. This makes miRNAs reliable biomarkers for liquid biopsy, with potential applications in early screening and diagnosis of various cancer types. Currently, miRNAs, as biomarkers for liquid biopsy, have shown promising clinical applications in multiple cancer types. For instance, research by Porzycki P. et al. revealed an elevated level of the miR-141-3p, miR-21, and miR-375 relative expression in prostate cancer [44], closely correlating with the occurrence and progression of prostate cancer. miRNA detection not only aids in early cancer screening but also provides a basis for molecular subtyping and personalized treatment of tumors. Additionally, miRNAs are crucial in monitoring cancer recurrence and evaluating treatment efficacy. In breast cancer treatment, Müller V. et al. have found that variations in the levels of miR-21, miR-210, and miR-373 can indicate patient responses to chemotherapy and targeted therapy, showcasing the broad potential of miRNAs in cancer management

[45].

Continuous technological advancements have led to breakthroughs in miRNA detection to enhance the sensitivity and specificity of miRNA detection in liquid biopsy. Commonly used methods for miRNA analysis include qPCR, digital PCR (dPCR), and next-generation sequencing (NGS). These techniques make it possible to find incredibly low levels of miRNAs in bodily fluids, which helps with early cancer detection and diagnosis. NGS is appropriate for large-scale screening since it can produce high-throughput data and simultaneously detect many miRNAs [46, 47], while qPCR is favored for clinical testing due to its low cost and simplicity. Moreover, digital PCR offers notable advantages in terms of sensitivity and quantitative precision, particularly for detecting very low amounts of miRNAs in the blood of cancer patients. For instance, detecting miR-21 levels in the serum of colorectal cancer patients via digital PCR has been shown to enable early detection with a sensitivity exceeding 85% [48].

Application of miRNAs in early cancer detection

miRNAs play a critical role in the early detection of cancer, enhancing therapy success rates and survival outcomes due to their unique expression patterns. However, the practical application of miRNAs in clinical settings faces several challenges, including variability in miRNA expression profiles among patients, lack of standardized detection methods, and difficulties in distinguishing between normal and cancer-related miRNA changes. Additionally, the stability of miRNAs in biofluids and the reproducibility of results across different platforms remain significant hurdles to their widespread clinical use [49, 50].These patterns enable the identification of subtle pathogenic changes at the initial stages of carcinogenesis, making miRNAs excellent biomarkers for early cancer diagnosis. Through liquid biopsy, miRNAs in body fluids allow for the early identification of tumor-related gene expression changes, opening avenues for timely intervention. Research has demonstrated that miRNAs not only sensitively capture molecular changes in tumors but also distinguish between different cancer types, providing valuable insights for personalized medicine.

Breast cancer is one of the most extensively studied fields in miRNA research. Elevated levels of miR-155, miR-21, and miR-10b in the blood of patients correlate strongly with breast cancer stage, invasiveness, and prognosis [51]. Zhang J. demonstrated that miR-10b expression is associated with disease stage, survival status, and tumor size [52]. Notably, miR-21, commonly overexpressed in various cancers, has emerged as one of the widely studied oncogenic miRNAs. Furthermore, Shang C. reported that the low expression of miR-127 contributes to breast cancer migration, invasion, and tumorigenesis, making it a potential therapeutic target and prognostic biomarker for breast cancer [53]. In early screening for breast cancer, Wang F. and colleagues found that miR-155 holds potential diagnostic value for breast cancer [15]. Additionally, previous research explored serum exosomal microRNA-21 (miR-21) as a biomarker for the early detection and diagnosis of breast cancer[54]. Both miR-155 and miR-21 could serve as potential diagnostic markers, aiding in the differentiation between precancerous lesions and malignant tumors and providing clinicians with more comprehensive diagnostic information.

Lung cancer, with high incidence and mortality, has shown promise for early detection through miRNA profiling. Studies have indicated that elevated levels of miRNAs such as miR-21, miR-486, and miR-210 in plasma can aid in identifying early-stage lung cancer patients [55]. Research by Li W. suggests that miR-486 and miR-150 may serve as potential blood-based biomarkers for the early diagnosis of non-small cell lung cancer (NSCLC). Monitoring changes in miR-486 expression could provide a non-invasive method for predicting recurrence in early-stage NSCLC [56]. Compared to traditional chest X-rays and CT scans, miRNA detection can diagnose tumors at earlier stages, even in cases of low tumor burden, as aberrant miRNA expression can still be sensitively detected. Furthermore, in lung cancer detection, the overexpression of miRNAs such as miR-17-5p and miR-19a has been closely associated with early tumor progression. Studies have shown that these miRNAs can help differentiate early-stage lung cancer patients from healthy controls. Yamamoto K. et al. identified FOXP1, TP53INP1, TNFAIP3, and TUSC2 as targets of miR-19a involved in lung cancer progression [57]. miRNA detection not only facilitates early cancer diagnosis but also assists in distinguishing between benign and malignant lesions, providing additional information for cancer screening.

In prostate cancer, miR-141 and miR-21 are two widely studied miRNAs. Previous research revealed that miR-141 is significantly elevated in the plasma of prostate cancer patients [58], and its expression level has been closely associated with the pathological staging and invasiveness of the disease. Furthermore, miR-21, a well-known oncogenic miRNA, is upregulated in prostate cancer and has potential utility in early diagnosis and therapeutic monitoring. Elevated miR-21 expression serves as a biomarker for early detection of prostate cancer and as a potential marker for monitoring treatment response. Ribas J. demonstrated that increased miR-21 expression enhances the growth of CaP tumors in vivo. Additionally, quantitative reverse transcription-PCR analysis showed elevated miR-21 expression in CaP tissues compared to adjacent normal tissues, suggesting miR-21 as a contributing factor to the CaP pathogenesis [59]. Detection of these miRNAs through liquid biopsy technologies offers the potential for early, non-invasive diagnosis of prostate cancer.

Significant progress has been made in the detection of miRNAs in gastrointestinal tumors. Research indicates that miR-223, miR-17-5p, and miR-20a levels are substantially higher in gastric cancer patients, with these miRNAs' expression levels closely linked to tumor size, stage, and prognosis. Wang M. demonstrated that circulating miR-17-5p/20a levels may serve as promising non-invasive molecular biomarkers for monitoring pathological progression, prognosis prediction, and chemotherapy response in gastric cancer [60]. Li L. found that miRNA-223-3p promotes gastric cancer proliferation, invasion, and metastasis by regulating ECT2 via the Wnt/β-catenin signaling pathway [61]. Furthermore, in colorectal cancer, Liu GH. identified miR-92a and miR-21 as potential biomarkers for early diagnosis [62]. Notably, when combined with other biomarkers, such as CEA (carcinoembryonic antigen), these miRNAs significantly enhance diagnostic sensitivity and specificity, offering the potential for early cancer detection.

In summary, the specific expression of miRNAs has demonstrated significant potential for clinical applications across various cancers. The dysregulation of miRNAs in lung, breast, liver, colorectal, and prostate cancer has been extensively studied and validated. Detecting these miRNAs expression levels facilitates early cancer diagnosis, classification, and monitoring of therapeutic efficacy. The broad application prospects of miRNAs as biomarkers provide an important theoretical foundation and clinical tools for the future of personalized cancer therapy.

Application of miRNAs in tumor prognosis evaluation

Variations in miRNA expression are strongly correlated with tumor aggressiveness, recurrence rates, and patient survival, making miRNAs valuable in the assessment of cancer prognosis. Particular miRNA expression can help clinicians to more precisely forecast tumor prognosis, including patient survival, recurrence risk, and treatment response [63]. MiRNAs influence tumor prognosis primarily by regulating oncogenes and tumor suppressor genes. It can regulate the biological activities of tumor

Table 1. Application of miRNAs in tumor diagnosis and prognosis.

Tumor type	miRNA name	Main function	References
Breast cancer	miR-21, miR-210, miR-155, miR-10b	Associated with recurrence and shorter disease-free survival; related to hypoxia conditions and invasiveness; related to treatment resistance and metastasis.	[10-12], [34], [40], [44]
Colorectal cancer	miR-21, miR-31, miR-92a	Associated with recurrence and shorter disease-free survival; predicts metastasis and recurrence; early diagnosis.	[4], [43], [55], [59]
Lung cancer	miR-150, miR-210, miR-486, miR-17-5p, miR-19a	Related to tumor invasiveness, metastasis, and treatment resistance; associated with hypoxic conditions and early diagnosis.	[60-62]
Prostate cancer	miR-141, miR-221, miR-21, miR-34a	Associated with pathological staging, invasiveness, and metastasis.	[39, 40], [51, 52]
Gastric cancer	miR-21, miR-223, miR-17-5p, miR-20a	Related to recurrence and used for prognosis evaluation; associated with tumor size and staging.	[53, 54], [72]
Lymphoma	miR-155, miR-34a	Associated with invasiveness, metastasis, and treatment resistance; promotes apoptosis and inhibits proliferation.	[42], [60, 61]
Liver cancer	miR-221, miR-122, miR-224, miR-10b	Related to tumor metastasis, invasiveness, early diagnosis, and recurrence.	[15]，[64-66]
Pancreatic cancer	miR-375, miR-21, miR-196a	Related to proliferation, poor prognosis, recurrence, and metastasis risk.	[67, 68]
Bladder cancer	miR-145, miR-9, miR-100, miR-182-5p/p27	Tumor suppressor miRNAs, regulate proliferation, invasiveness, and treatment resistance.	[69-71]
Ovarian cancer	miR-200 family, miR-21, miR-199a	Inhibits EMT (epithelial-mesenchymal transition), reducing metastasis risk; associated with progression, recurrence, and poor prognosis.	[72-74]

cells, including proliferation, invasion, and metastasis, via gene modification. The overexpression of certain miRNAs may lead to enhanced tumor cell growth and inhibited apoptosis, contributing to poor prognosis. On the other hand, tumor progression and metastasis may occur from the downregulation of other miRNAs, which may compromise tumor suppression mechanisms. According to Braicu C.'s research, miRNAs play a major role in the prognosis of bladder cancer, and changes in their expression patterns have a substantial biological bearing on the molecular characteristics of the tumor [64]. Tumor heterogeneity leads to significant variations in patient prognosis, and miRNA expression profiles provide insights into the molecular characteristics and biological behavior of tumors. Detection of miRNAs can provide more personalized prognostic assessments, helping to identify patients in different risk groups.

Multiple miRNAs have been identified as strong prognostic markers in cancer. Below are several representative miRNAs and their prognostic roles:

(1) miR-21 is a well-studied oncogenic miRNA that is upregulated in various tumor types. Studies indicate that high expression of miR-21 is strongly associated with tumor aggressiveness and poor prognosis. High levels of miR-21 in colorectal, breast, and gastric cancers correlate with tumor recurrence and shorter disease-free survival. Research by Wang W. et al. suggests that miR-21 could be a valuable biomarker for predicting cancer prognosis in clinical settings [65]. Additionally, Kang W.'s study shows that high miR-21 expression predicts recurrence-free survival in stage II colorectal cancer [66]. MiR-21 also serves as a marker for predicting chemotherapy and targeted therapy responses, with changes in expression indicating patient responses to treatment. A decrease in miR-21 levels after treatment suggests a favorable prognosis, whereas sustained high levels may signal potential drug resistance or a risk of tumor recurrence.

(2) miR-155 is abnormally overexpressed in various cancers, including lymphoma and lung cancer. Studies have shown that elevated miR-155 expression is closely associated with increased tumor aggressiveness and metastatic risk, particularly in patients with poor prognosis. Van Roosbroeck K et al. identified the miR-155/TP53 feedback loop, which contributes to chemotherapy resistance [67]. Therefore, miR-155 holds significant value in predicting tumor recurrence and treatment resistance [68].

(3) miR-34a as a tumor-suppressor miRNA: Low expression of miR-34a has been observed in various tumor types, including breast cancer, lung cancer, and prostate cancer. miR-34a plays a critical role in tumor suppression by inhibiting tumor cell proliferation and inducing apoptosis. Shi Y. demonstrated that miR-34a can inhibit the growth of non-small cell lung cancer (NSCLC) [69]. Furthermore, its low expression is typically associated with poor prognosis, higher recurrence rates, and shorter survival times. Wu X. found that downregulation of miR-34a leads to head and neck cancer by upregulating the MET oncogene and modulating tumor immune evasion [70].

In conclusion, the clinical application of miRNAs is not limited to early cancer detection but also extends to serving as prognostic biomarkers, aiding in the assessment of disease progression and therapeutic response. For example, dynamic changes in the levels of miRNAs, such as miR-21 and miR-155 can be used to monitor patient response to treatment. Additional discoveries and applications are detailed in Table 1, including findings related to Liver Cancer [71-73], Pancreatic Cancer [74, 75], Bladder

Cancer [76-78], Ovarian Cancer [79-81], etc. By regularly detecting the expression of specific miRNAs during treatment, clinicians can evaluate therapeutic efficacy in real time and adjust treatment regimens accordingly. With advancements in detection technologies, the potential of miRNAs in tumor prognosis is vast, particularly in personalized therapy and monitoring tumor recurrence, where miRNAs will become crucial tools (**Table 1**).

Discussion and outlook

As an important class of non-coding RNAs, miRNAs hold tremendous potential in the initiation, progression, and treatment of tumors. Their stable presence and precise regulation of gene expression have made them a focal point of cancer research. However, despite current findings indicating the significant advantages of miRNAs in early cancer diagnosis, prognosis assessment, and personalized therapy, several challenges remain in their clinical translation.

Firstly, expression exhibits significant heterogeneity across different patients and tumor types [82]. This heterogeneity not only exists between various cancer types but also within different subtypes of the same cancer and among individual patients. For instance, there are recognized molecular subtypes of breast cancer, including triple-negative, hormone receptor-positive and HER2-positive, every one of which has unique clinical and genetic characteristics [83]. Similarly, in lung cancer, heterogeneity is observed between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), as well as among subtypes like adenocarcinoma and squamous cell carcinoma [84]. Moreover, intra-tumor heterogeneity within individual patients can lead to different clonal populations with variable drug responses, as observed in renal cell carcinoma [85]. Such variability in expression could lead to considerable differences in diagnostic and prognostic outcomes across patients. Therefore, standardizing miRNA detection and analysis methods to ensure consistency and reproducibility across different laboratories is a key challenge that needs to be addressed in future research.

Secondly, although liquid biopsy technologies are convenient and promising for miRNA clinical applications, the sensitivity and specificity of miRNA detection must be enhanced. The detection of miRNAs in liquid biopsy is limited by their low abundance and interference from the complex background in body fluids. Thus, more sensitive detection techniques are needed to accurately capture dynamic changes in miRNA levels [86]. Additionally, integrating multi-omics data (such as genomics, transcriptomics, and proteomics) to enhance the diagnostic accuracy and predictive power of miRNA detection will be a critical direction for future research.

Lastly, while numerous studies have demonstrated the potential of miRNAs in early cancer detection, prognosis evaluation, and therapeutic monitoring, their application in clinical practice requires further clinical validation and large-scale clinical trials. In the future, the continued development of high-throughput sequencing technologies and bioinformatics is likely to unveil more miRNA regulatory mechanisms, facilitating their broader clinical application.

In conclusion, the expanding technological landscape and deepening understanding of miRNA functions suggest a promising future for miRNAs in personalized cancer therapy. The enhancement of detection technologies, standardization of clinical workflows, and integration of multi-dimensional omics data are pivotal. These developments will not only strengthen the role of miRNAs in early cancer diagnosis and prognosis evaluation but also position them as significant therapeutic targets in future cancer treatments.

Conclusion

As tumor biomarkers, miRNAs have shown immense potential in cancer diagnosis, prognosis, and treatment. Their stability and specificity rendered them valuable tools for liquid biopsy, particularly demonstrating broad application prospects in the realm of early cancer detection. Future research will focus on refining miRNA detection techniques, standardizing clinical applications, and harnessing multi-omics data to improve diagnostic precision. With continuous technological advancements, the application of miRNAs in clinical oncology will expand further, providing robust support for personalized treatment and precision medicine.

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Data and materials are available on request from the authors.

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Author contributions

YFO, conceptualized, designed, conducted research, and wrote the manuscript; ZR contributed to the revision and figure production and approved the final submission.

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