Review Paper

MicroRNAs as Cancer Biomarkers: Unveiling Diagnostic and Prognostic Potential

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Abstract

MicroRNAs (miRNAs) are short, non-coding RNA molecules that play a crucial role in regulating human gene expression by influencing messenger RNA stability and translation, thus affecting around 30% of genes post-transcriptionally. They are integral to cellular functions such as cell growth, apoptosis, and differentiation. Dysregulation of specific miRNAs has been strongly implicated in the onset and progression of several cancers, including pancreatic cancer, breast cancer, ovarian cancer, and hepatocellular carcinoma (HCC). In these malignancies, altered miRNA expression profiles contribute to tumor initiation, growth, metastasis, and resistance to therapy, highlighting their value as both biomarkers and therapeutic targets. This review synthesizes evidence on the roles of key deregulated miRNAs in these cancers, linking miRNA patterns with prognosis and responsiveness to treatment. Advances in miRNA research offer new avenues for the early detection of cancer, personalized therapy, and improved outcome prediction. By clarifying the mechanisms behind miRNA dysregulation, researchers are paving the way for novel interventions that modify miRNA activity, enhancing the precision and effectiveness of cancer treatments. The ability to specifically target aberrant miRNAs holds promise for revolutionizing clinical management, potentially improving survival rates and quality of life for cancer patients. Understanding miRNAs multifaceted roles not only deepens knowledge of cancer biology but also contributes to the development of innovative diagnostic and therapeutic strategies that can transform patient care.

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1. Introduction

MicroRNAs (miRNAs) are promising candidates for cancer biomarkers because of their distinct regulatory roles, stability, and disease-specific expression patterns. They regulate roughly 30% of human gene expression at the post-transcriptional level, impacting essential cellular processes including proliferation, apoptotic cell division, and homeostasis (Condrat *et al.* 2020; Bautista-Sanchez *et al.* 2020). Specific miRNAs in cancer are frequently dysregulated, which contributes to tumor start, development, metastasis, and therapeutic resistance. Expression profiles are frequently tissue and disease-specific, making them extremely useful for differentiating cancer types and subtypes (Ali Syeda *et al.* 2020). Furthermore, miRNAs can be detected in bodily fluids such as blood, saliva, and urine, providing a minimally intrusive method for early diagnosis, prognosis, and therapy response monitoring. These traits all contribute to their growing prominence as strong molecular indicators in cancer research and therapeutic applications (Cicatiello *et al.* 2025). Cells spontaneously manufacture miRNAs, or small non-coding RNAs, from genome-encoded sequences with unique promoter regions. miRNAs are first transcribed within the nucleus as long, capped, polyadenylated precursors, known as primary miRNAs, by RNA polymerase II or III (Hudder and Novak 2008). Most eukaryotes, humans included, have microRNA, which was first recognized in the organism Caenorhabditis elegans. The formation of mature microRNA occurs via two distinct cleavage processes acting on primary miRNA (O'Brien *et al.* 2018). This mature microRNA (miRNA) binds to the RISC (RNA-induced silencing complex), serving as the effector complex. The detection of miRNAs in animal and human serum and plasma has provided evidence of their potential use as diagnostic biomarkers for a range of illnesses (Bhaskaran and Mohan 2014). Previous advancements in short interfering RNA-based therapeutic methods enabled rapid progress towards the therapeutic modulation of miRNAs. MiRNAs play a significant role in various cancer-associated mechanisms, including proliferation, cell cycle regulation, programmed cell death, discrimination, cell movement, and biochemical process (Reda El Sayed *et al.* 2021). Transcription and translation influenced by miRNAs, alters the initial state of cells and adaptive response. Using miRNA expression profiling, miRNAs that are crucial for the control of many processes, such as tissue differentiation, disease pathophysiology and organismal development could be addressed (Oliveto, Manfrini, and Biffo 2025). The discovery of the first microRNA (miRNA) in 1993 was by Victor Ambross, together with associates Rosalind Lee and Rhonda Feinbaum (Ambros 2013). To differentiate miRNA genes from their corresponding mature forms (miR), the genes are denoted in italics (e.g., mir-1) followed by a number, whereas the mature forms are written in regular font (e.g., miR-1), and notably, the mature miRNA is substantially shorter than the encoding DNA sequence (Desvignes *et al.* 2015). Northern blotting, a gold standard for miRNA detection techniques, is the most popular technique. The inhibition of translation mRNAs into protein and promotion of mRNA degradation are the well-known function of miRNA (Ye *et al.* 2019). MicroRNA (miRNA) synthesis initiates in the cell nucleus through the transcription of primary miRNA (pri-miRNA) transcripts, which typically occurs by RNA polymerase II. The DGCR8-Drosha microprocessor complex converts these lengthy, hairpin-shaped transcripts into smaller precursor miRNA (pre-miRNA) molecules (Han *et al.* 2004). The pre-miRNA is subsequently transported to the cytoplasm via Exportin-5. Eventually in the cytoplasm, the digestive enzyme Dicer cleaves the pre-miRNA to form an adult miRNA duplex, with one strand integrated into the complex that induces silencing of RNA (RISC) (Wang *et al.* 2011). Within RISC, mature miRNA directs the intricate structure to target messenger RNAs (mRNAs) by complementary base pairing, typically in the mRNA's 3' untranslated region (3' UTR). This interaction causes post-transcriptional gene silencing via mRNA degradation or translational inhibition (**Figure 1**). In cancer, miRNAs serve important regulatory roles, acting as either oncogenes (oncomiRs) or tumor suppressors. OncomiRs, such as miR-21 and miR-155, are frequently increased in malignancies and promote tumor development by the action

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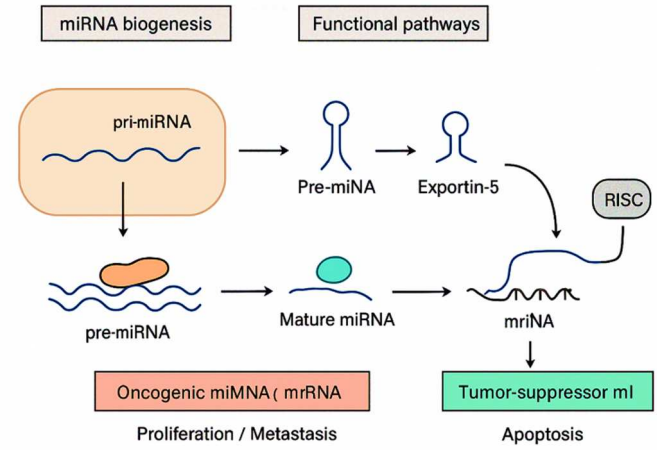

Figure 1: Schematic representation of miRNA biogenesis and Functional pathway.

of tumor suppressor genes, which increases cell proliferation, survival, metastasis, and resistance to therapies. In contrast, tumor suppressor miRNAs such as let-7 and miR-34 are typically downregulated in cancer, resulting in unregulated oncogene expression and contributing to tumor growth (Otmani and Lewalle 2021). MiRNA expression dysregulation has a major impact on characteristics of cancer such as apoptosis evasion, persistent proliferative signaling, enhanced invasiveness, and therapeutic resistance, making miRNAs interesting biomarkers and therapeutic targets in oncology (Chakrabortty *et al.* 2023). Cancer is a condition characterized by the unmanageable growth and spread of unusual cells, which can infiltrate surrounding tissues and organs, and metastasize to distant regions of the body via the bloodstream or lymphatic system leading to the emergence of secondary tumors (Brown *et al.* 2023). One third of people will experience a cancer diagnosis during their lifetime, making it a common ailment. Here, we discussed the emerging use of miRNAs as biomarkers in cancer, underscoring their transformative potential in timely diagnosis and intervention approaches.

2. Role of MiRNA in Various Cancer Types

2.1. Role miRNA in Breast cancer

Breast cancer primarily influences the female population. While 25% of cases are aggressive, defined by sluggish growth but rapid dissemination, the majority are benign and can be efficiently treated with surgery. Among the identified mature subtypes of the let-7 family in humans are let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98, and miR-202. Notably, let-7a and let-7f are derived from precursor sequences (let-7a-1, let-7a-2, let-7a-3; let-7f-1, let-7f-2) (Dziechciowska *et al.* 2023). Recent studies in tumour sample have revealed that the expression levels of several let-7 isoforms were found to be correlated with various clinical and pathological features. For example, let-7c was linked to PR status, while let-7a-3, let-7f-1, and let-7a-2 have been connected to lymph node metastasis (Wang *et al.* 2024). Additionally, let-7c and let-7d were found to be linked to a high proliferation index. The classification of breast cancer into specific subtypes based on HER2/neu or ER/PR status reveals unique miRNA expression profiles for each subtype. Since miR-155 is upregulated in breast cancer, there is a chance it could function as an oncogene (Kudela *et al.* 2020). The upregulation of miR-373 and miR-520c, which inhibits CD44 expression, promotes metastasis. ROC curve analysis revealed that the three-miRNA signature consisting of miR199a, miR29c, and miR424 provided the highest diagnostic accuracy for breast cancer patients. This signature was subsequently validated, confirming its potential utility as a biomarker for diagnosing breast cancer (Huang *et al.* 2008). Current developments in high-throughput including single-molecule technology have considerably improved our understanding of miRNA interactions and their implications in cancer biology (Rhim *et al.* 2022). Rapid sequencing methods, such as short RNA sequencing (RNA-seq), enable detailed mapping of miRNA expression and the identification of new miRNAs throughout tissues and illnesses. Microarray systems and quantitative real-time PCR (qRT-PCR) are still useful for target validation and expression assessment (Benesova, Kubista, and Valihrach 2021). To explore direct miRNA-mRNA interactions, technologies such as crosslinking immunoprecipitation (CLIP) and its variations (HITS-CLIP, PAR-CLIP, and iCLIP) are commonly used, allowing for transcriptome-wide identification of miRNA binding sites. In parallel, RNA immunoprecipitation sequencing (RIP-seq) aids in the capture of Argonaute-bound miRNA-mRNA complexes, revealing functional connections (Haecker and Renne 2014).

2.1.1. Diagnostic Biomarkers

Blood and tissues miRNA fingerprints have been demonstrated to discriminate people with breast cancer from healthy people, as well as between molecular subtypes (luminal A/B, HER2-positive, triple-negative). Their excellent stability in serum and plasma makes them useful as minimally invasive diagnostic instruments (de Miranda *et al.* 2024; van Schooneveld *et al.* 2012).

2.1.2. Disease Progression and Treatment Resistance

Specific miRNAs are associated with clinical outcomes in breast cancer. High miR-21 expression, for example, is linked to poor prognosis and chemoresistance, but enhanced miR-200 levels predict less metastatic potential and improved survival (Yan *et al.* 2008). Thus, miRNA profiles offer predictive information that goes beyond traditional clinicopathological indicators. miRNAs influence sensitivity to endocrine treatment, chemotherapy, and targeted drugs. MiR-221/222 downregulates estrogen receptor α, leading to resistance to tamoxifen (Cortellesi *et al.* 2025). Conversely, restoring miR-200c can make breast cancer cells more susceptible to treatment. These findings emphasize their relevance in treatment decision-making and therapy personalization (Othman *et al.* 2024).

2.1.3. Therapeutic potential

Preclinical investigations have shown that restoring tumor-suppressive miRNAs or blocking oncogenic miRNAs can suppress breast tumor development and spread. MiRNA mimics, anti-miRs, and nanoparticle-based delivery methods are among the strategies being investigated, with the potential to revolutionize targeted breast cancer therapy (Telkoparan-Akillilar *et al.* 2025).

2.2. Hepatocellular Carcinoma Cancer

Hepatocellular carcinoma (HCC), a primary form of liver cancer, ranks as the third leading cause of cancer-related deaths worldwide, with a significant incidence rate of among fifth of men and seventh of women. Research findings underscore the potential significance of miRNA expression in the HCC disease progression (Chidambaranathan-Reghupaty, Fisher, and Sarkar 2021). Moreover, Bead-array miRNA expression analysis emerges as a promising approach for assessing miRNA expression in extensive diagnostic trials. Tumors in hepatocellular carcinoma (HCC) shown decreased miR-26 expression compared to adjacent non-malignant tissues, suggesting its relevance to HCC (Huang *et al.* 2009). This indicates that miR-26 levels in tumors could serve as a prognostic marker and help identify patients who might benefit from adjuvant interferon alfa therapy to prevent relapse. The elevated expression of a panel comprising eight miRNAs, including miR-324-3p, miR-25-3p, miR-132-3p, miR-30a-5p, miR-185-5p, miR-20a-5p, miR-92a-3p and miR-320a, has shown potential for distinguishing HBV-related HCC patients from those who are HBV-positive but cancer-free (Ji *et al.* 2013). A panel of four microRNAs, including miR-192-5p, miR-21-5p, and miR-375, has been recognized as a biomarker for the early

detection of hepatocellular carcinoma (HCC), either individually or in conjunction with alpha-fetoprotein (AFP) (Zenlander *et al.* 2024).

2.2.1. miRNAs as Diagnostic Biomarkers

Despite their great stability in serum and plasma, circulating miRNAs have emerged as viable non-invasive biomarkers for detecting early HCC. For example, lower miR-122 levels and higher miR-21 expression can identify HCC patients from healthy people and those with chronic liver disease. The incorporation of miRNA panels into liquid biopsy platforms provides more sensitivity than traditional indicators such as AFP (Zhang *et al.* 2015).

2.2.2. Prognostic value in HCC and Therapy Resistance

Certain microRNAs are linked to tumor aggressiveness, recurrence risk, and survival outcomes. High expressions of miR-221 and miR-21 are associated with an adverse outcome and shorter life expectancy, whereas elevated miR-26 levels are associated with improved survival and better response to interferon treatment (Xue *et al.* 2014). Thus, miRNA profiles offer useful prognostic insights that go beyond established staging schemes. MiRNAs have a substantial impact on the response to chemotherapy, targeted therapy, and immunotherapy. For example, miR-122 downregulation promotes sorafenib resistance, whereas increasing its expression increases treatment sensitivity (Sareen *et al.* 2025). Similarly, changed miR-181 and miR-216 expressions are associated with susceptibility to conventional chemotherapeutics, implying that they could be used to predict treatment responses (Lei *et al.* 2022).

2.2.3. Therapeutic Potential of miRNA Modulation in HCC

Preclinical and clinical research supports the therapeutic use of miRNAs in HCC. Restoring tumor-suppressive miRNAs (e.g., miR-122 mimics) or blocking oncogenic miRNAs (e.g., antimiR-221) can help to slow tumor development, minimize metastasis, and improve therapeutic response (Hassan *et al.* 2023). Notably, miravirsen (anti-miR-122) has demonstrated clinical success in hepatitis C virus (HCV) infection, highlighting the viability of miRNA-based therapeutics in liver illnesses and their prospective application to HCC (Jopling 2010).

2.3. Role miRNAs in Ovarian Cancer

In women, Ovarian cancer comprising 4% of all cancers, and it is the foremost fatal factor among gynecologic malignancies, with approximately 75% of cases detected at an advanced level owing to the typically asymptomatic nature of early-stage disease. The significant suppression of miR-30a-5p in urine implies that this miRNA originates from ovarian serous adenocarcinoma cells. The levels of MiR-30a-5p regulation levels in urine are considered as a potential diagnostic indicator for serous ovarian adenocarcinoma (Chandra *et al.* 2019). miR-145-5p expression is significantly decreased in patients with advanced ovarian cancer (OC), correlating with the progression of the disease. The dysregulation of this microRNA is a key element in the development of OC, highlighting the critical role of miRNAs in diagnosis, treatment, and prognosis (Gorecki *et al.* 2025). Researchers found that higher levels of miR-200c in ovarian cancer patients lead to better survival rates, while miR-141 levels increase as the cancer advances, suggesting that these microRNAs may have divergent functions in cancer progression and could be valuable targets for both diagnosis and treatment (Koutsaki *et al.* 2017).

2.3.1. miRNA as Diagnostic Biomarkers

Circulatory and cellular miRNAs show great promise for non-invasive early identification of ovarian cancer, where conventional biomarkers such as CA-125 have low sensitivity and specificity. Elevated miR-200 family expression in serum, for example, has a high association with epithelial ovarian cancer and can distinguish patients from healthy people (Staicu *et al.* 2020). Multiple miRNA panels improve diagnostic accuracy, particularly for early-stage illness (Song *et al.* 2023).

2.3.2. Disease progression and Therapy resistance

Several miRNAs are associated with disease aggressiveness and patient survival. Excessive expression of miR-200c and miR-214 is linked to a bad prediction of regression, and advanced illness stage, but higher levels of miR-145 and let-7 are associated with better results. Thus, miRNA profiles provide predictive information in addition to clinical and pathological indications (Karakatsanis *et al.* 2013). Chemoresistance remains a significant barrier in ovarian cancer treatment, and miRNAs play important roles in influencing drug responsiveness. MiR-214 and miR-1307 target apoptotic pathways to increase cisplatin and paclitaxel resistance, but miR-200c or miR-199a restoration improves chemosensitivity. These findings highlight miRNA's potential as predictive indicators for treatment response (Nayak *et al.* 2025).

2.3.3. Therapeutic Potential of miRNA Modulation

Therapeutic methods targeting dysregulated miRNAs are being investigated in ovarian cancer. Preclinical models have shown that delivering tumor-suppressive miRNAs (e.g., miR-145 mimics) or inhibiting oncogenic miRNAs (e.g., antimiR-21) can reduce tumor growth, metastasis, and therapy resistance. Advances in nanoparticles and exosome-based delivery technologies provide promise for bringing miRNA-based therapeutics into clinical practice (Asl *et al.* 2023).

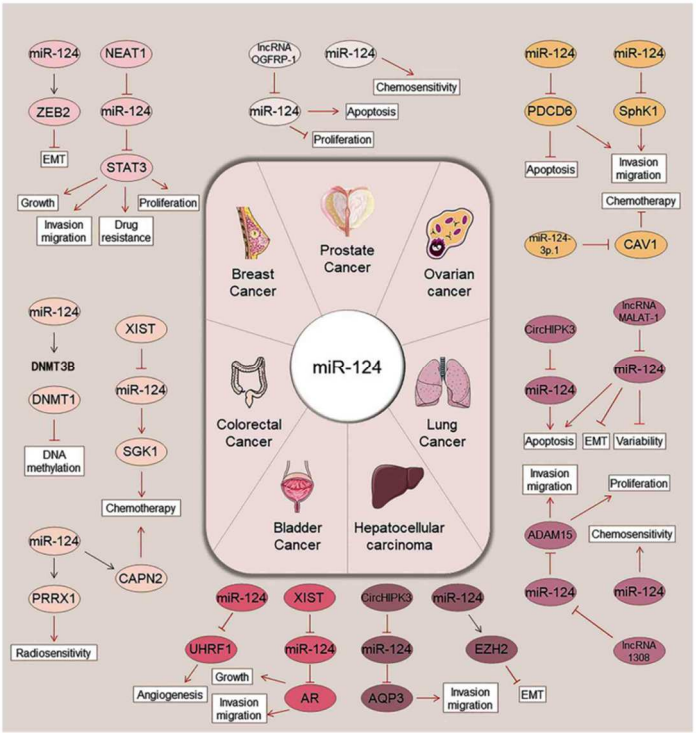

Figure 2: Cancer Specific miRNA interactions with different types of Cancer.

2.4. Role miRNAs in Pancreatic Cancer

Microarray analysis reveals miR-22, miR-885-5p and miR-642b, as promising diagnostic markers for the early detection of pancreatic cancer when blood samples of cancer patients and healthy individuals were analyzed. Blood is a convenient and preferred biological fluid for diagnosing various diseases, including pancreatic cancer. The synergy of plasma levels of miRNA-16 and miRNA-196a alongside CA 19-9 has proven to be highly effective (85.2%) in screening for early-stage pancreatic cancer (Moise *et al.* 1995). Combining heightened levels of miR-196a and miR-16 with elevated serum cancer antigen 19-9 (also known as carbohydrate antigen 19-9) levels revealed promise in

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differentiating pancreatic cancer from pancreatitis and healthy individuals, particularly for diagnosing stage 1 pancreatic cancer. A study confirmed the most differentially expressed miRNAs for distinguishing pancreatic cancer from various control groups are miR-486-5p and miR-938 (Gao, He, and Li 2014).

Table 1. Key miRNA involved in Breast, Ovarian, Pancreatic, and Hepatocellular Carcinoma (HCC)

Cancer Type	Oncogenic miRNAs (OncomiRs)	Tumor Suppressor miRNAs	Targets / Pathways	Clinical Roles
Breast Cancer	miR-21, miR-155, miR-10b, miR-221/222	let-7 family, miR-34a, miR-200 family	EMT, PI3K/AKT, apoptosis, stemness regulation	Predict therapy resistance (tamoxifen, trastuzumab, circulating biomarkers (miR-21, miR-195); potential miRNA-based therapeutics
Ovarian Cancer	miR-200 family (EMT regulation), miR-214, miR-222	miR-34 family, miR-199a	NOTCH, BCL-2, HIF-1α, angio genesis pathways	Biomarkers for stage/ prognosis (miR-200, miR-205); linked to cisplatin resistance; therapeutic delivery via nanoparticles
Pancreatic Cancer	miR-21, miR-221, miR-155	miR-34a, miR-96, miR-217	KRAS signaling, apoptosis pathways	Biomarkers for early detection (miR-1290); prognosis prediction (miR-21, miR-155); chemo resistance modulation (gemcitabine)
Hepato cellular Carcinoma (HCC)	miR-21, miR-221, miR-222	miR-122, miR-199a/b	mTOR, HIF-1α, lipid metabolism, HBV/HCV-associated signaling	Early detection (miR-122, miR-192); resistance to sorafenib; therapeutic application of miR-122 mimics (Miravirsen)

2.4.1 miRNA as Diagnostic biomarker

Early identification of pancreatic cancer remains difficult due to vague symptoms and the limited specificity of traditional indicators like CA19-9. Circulating microRNAs (miRNAs) represent promising noninvasive biomarkers, as their dysregulated expression is strongly linked with tumor initiation, progression, and therapy resistance across different cancers (Xue *et al.* 2019). For instance, elevated miR-21 and miR-210 levels, along with reduced miR-217 expression in plasma or serum, have been proposed as diagnostic markers for pancreatic ductal adenocarcinoma (PDAC). Similarly, as shown in **Figure 2**, miR-124 demonstrates cancer-type specific interactions and regulatory roles in breast, prostate, ovarian, colorectal, lung, bladder, and hepatocellular carcinomas. Combining such miRNAs into diagnostic panels significantly enhances sensitivity and specificity, particularly for detecting early-stage malignancies (Vychytilova-Faltejskova *et al.* 2015).

2.4.2 Prognostic value of miRNAs in pancreatic cancer

Several miRNAs are associated with disease aggressiveness, recurrence, and overall survival. High expressions of miR-21 and miR-155 are related to bad prognosis, quick advancement, and resistance to therapy, but restoration of miR-34a or let-7 family is associated with improved outcomes. Thus, miRNA expression profiles provide extra prognostic information beyond traditional staging schemes (Jegathesan *et al.* 2024). Chemoresistance, particularly to gemcitabine, remains a significant challenge in pancreatic cancer treatment. Dysregulated miRNAs have a major impact on medication responses. miR-21 and miR-221 overexpression confer resistance to gemcitabine by inhibiting apoptotic pathways and increasing survival signals. Re-expression of tumor-suppressive miRNAs like miR-34a or miR-200c, on the other hand, makes pancreatic cancer cells more sensitive to chemotherapy and radiotherapy, implying that they could be used as predictive indicators of treatment response (Funamizu *et al.* 2023).

2.4.3. Therapeutic potential of miRNA modulation

Pancreatic cancer therapeutic methods that target miRNAs are currently being investigated. Preclinical studies have indicated that delivering tumor-suppressive miRNAs (e.g., miR-34 mimics) or inhibiting oncogenic miRNAs (e.g., antimiR-21) can reduce tumor growth, metastasis, and therapy resistance (Martino, Tagliaferri, and Tassone 2025). Novel delivery technologies, such as lipid nanoparticles, viral vectors, and modified exosomes, are being investigated to improve the stability, tumour targeting, and clinical translation of miRNA-based therapeutics (Sanadgol *et al.* 2025). Collectively, these findings underscore the central role of miRNAs as diagnostic, prognostic, and therapeutic modulators across multiple cancer types. A summary of the key oncogenic and tumor-suppressive miRNAs in breast, ovarian, pancreatic, and hepatocellular carcinoma is provided in **Table 1**.

2.5. Clinical and Therapeutic trials on Cancer Management

MicroRNAs, being a short, regulatory RNA molecules that exert a profound impact on gene regulation after transcription. MiRNAs are associated with various cellular functions and have turned up as promising molecular markers for diagnosing cancer and treatment (Ying, Chang, and Lin 2008). miR-21, one of the most studied oncomiRs, is currently being evaluated in multiple clinical trials as a non-invasive biomarker for early detection and prognosis in breast, pancreatic, and liver cancers (e.g., NCT03334613 for pancreatic cancer). Similarly, miR-122, which plays a liver-specific regulatory role, has reached clinical trial phases in the context of hepatocellular carcinoma (HCC) (Chen, Demirkhanyan, and Gondi 2024). A therapeutic agent targeting miR-122 (Miravirsen) was initially developed for hepatitis C but has implications for HCC treatment strategies as well. In ovarian cancer, miR-200 family members are being explored as potential biomarkers for epithelial ovarian cancer in body fluids, and several platforms are under development to integrate these into liquid biopsy assays. Moreover, circulating miRNAs including miR-155 and miR-34a are being investigated for their diagnostic and therapeutic potential in breast cancer and have been included in early-phase clinical studies (van der Ree *et al.* 2014). Despite these advances, the widespread use of miRNA-based diagnostics or therapeutics in routine clinical oncology remains limited due to challenges related to standardization of detection methods, specificity/sensitivity, and delivery systems for miRNA-based drugs (Park, Kim, and Lee 2025). However, the

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consistent validation of certain miRNAs across independent cohorts and cancer types provides a strong foundation for their eventual integration into personalized cancer management strategies. These findings highlighted their importance in cancer biology which mainly involved in early diagnosis of the cancer and therefore considering it as a potential clinical tool in cancer management (Sempere, Azmi, and Moore 2021).

2.6. Advanced technologies study for miRNA interactions

Current developments in high-throughput including single-molecule technology have considerably improved our understanding of miRNA interactions and their implications in cancer biology. Rapid sequencing methods, such as short RNA sequencing (RNA-seq), enable detailed mapping of miRNA expression and the identification of new miRNAs throughout tissues and illnesses. Microarray systems and quantitative real-time PCR (qRT-PCR) are still useful for target validation and expression assessment (Hong *et al.* 2020). To explore direct miRNA-mRNA interactions, technologies such as crosslinking immunoprecipitation (CLIP) and its variations (HITS-CLIP, PAR-CLIP, and iCLIP) are commonly used, allowing for transcriptome-wide identification of miRNA binding sites. In parallel, RNA immunoprecipitation sequencing (RIP-seq) aids in the capture of Argonaute-bound miRNA-mRNA complexes, revealing functional connections (Ascano *et al.* 2012). In the meantime, CRISPR/Cas9-based functional assessment was successfully used to unravel miRNA regulatory systems and evaluate downstream targets in cancer models. Single-celled RNA sequencing (scRNA-seq) improves the accuracy of detection of cell-type-specific miRNA expressions in heterogeneous tumor environments. New innovations such as nanopore-based direct RNA sequencing, miRNA bio sensors, and microfluidic devices show promising for real-time, sensitive, and non-invasive miRNA interaction detection. In combination, these enhanced techniques not only broaden our understanding of miRNA regulatory processes but also speed up the creation of clinically useful diagnostics and therapeutic methods in oncology (Merk *et al.* 2024; Hoffmann *et al.* 2019).

2.7. Current tools and algorithms

A broad range of analytical techniques and algorithms have recently been designed to predict miRNA targets, utilizing both sequence-specific features and experimental data (Yue, Liu, and Huang 2009; Liu and Wang 2019). Conventional techniques, such as TargetScan, miRanda, and PicTar, rely on sequence compatibility between miRNAs and target mRNAs, with a focus on the "seed region" (nucleotides 2–8). These approaches use evolutionary preservation to improve forecast accuracy. Techniques such as RNAhybrid and PITA consider both thermodynamic stability and binding free energy, allowing for the evaluation of miRNA-mRNA duplex formation (Riolo *et al.* 2020). More contemporary platforms, such as DIANA-microT-CDS, miRDB, and mirTarBase, combine experimentally confirmed targets with prediction models, increasing dependability. Integration of high-throughput experimental data has also boosted target prediction; for example, starBase and doRiNA assemble CLIP-seq datasets to map miRNA-RNA interactions across the transcriptome. In addition, artificial intelligence learning and deep learning-inspired algorithms (e.g., miRAW, deepTarget) are being increasingly utilized to enhance predictive power by including complex variables such as sequencing context, secondary structure, and international trends (Tastsoglou *et al.* 2023; Paraskevopoulou *et al.* 2013). Although these tools have made significant contributions to the area, there are frequently disparities amongst prediction platforms due to differences in algorithms and input settings. As a result, integrating various prediction algorithms with experimental validation (qRT-PCR, luciferase reporter assays, and CLIP-based methods) is critical for accurately identifying physiologically relevant miRNA targets (Quillet *et al.* 2021; Riffo-Campos, Riquelme, and Brebi-Mieville 2016).

3. Discussion

In breast cancer, miRNAs act as both cancer-causing genes and tumor suppressors. Tumor-associated miRNAs such as miR-21, miR-155, and miR-10b, that promote tumor growth, invasion, and metastasis, have been extensively researched. Overexpression of miR-21 possesses established linked to resistance to commonly used medicines such as trastuzumab and tamoxifen, suggesting it a key modulator of pharmacological response (Munoz *et al.* 2023). Tumor-suppressive miRNAs, including as the let-7, miR-34a, miR-204, and miR-200 families, control EMT, embryonic development, and apoptosis pathways. Their downregulation is typically linked to aggressive illness and poor prognosis. Additionally, miRNA expression profiles differ between breast cancer subtypes. For example, miR-221/222 are significantly elevated in triple-negative breast cancer (TNBC), contributing to uncontrolled growth and resistance to endocrine therapy (Adams, Parsons, and Slack 2016). In ovarian cancer, miRNAs have an important role in tumor growth, metastasis, and treatment response. Mutations of the miR-200 lineage has been found to alter epithelial-mesenchymal plasticity, allowing tumor growth and distant metastases. Furthermore, miR-214 and miR-222 lead to resistance to chemotherapy, notably to cisplatin, which is among the most used therapies for ovarian cancer (Choi and Ng 2017). Conversely, multiple miRNAs have tumor-suppressive properties. The miR-34 family regulates pathways like NOTCH along with BCL-2, while miR-199a suppresses revascularization by suppressing HIF-1α activation. Unexpected expressions of miR-130a, miR-214, miR-610, and miR-630 have been directly associated with developing resistance to platinum-based chemotherapy therapy, highlighting their clinical importance. Circulating miRNAs, especially miR-200a/b/c and miR-205, are associated with illness stage, prognosis, and life expectancy, making them useful for diagnosis and prognostic indicators (Fu *et al.* 2023). Recent research also suggests that nanoparticle-mediated distribution of miRNA mimics or antagonists is a promising technique for restoring chemosensitivity and improving the results of therapy in ovarian cancer. Pancreatic cancer constitutes one among the most fatal cancers, and miRNA dysregulation is a major contributor to its aggressiveness (Putri *et al.* 2024).

Table 2. Advantages and Challenges of Using miRNAs as Prognostic Biomarkers in Cancer

Advantages	Challenges
High stability in body fluids (resistant to RNase degradation, freeze–thaw cycles)	Lack of standardized protocols for sample collection, processing, and normalization
Non-invasive detection possible via liquid biopsy (blood, urine, saliva, etc.)	Tumor heterogeneity and inter-patient variability affect reproducibility
Tissue- and disease-specific expression patterns allow precise patient stratification	Small cohort sizes and limited validation in many studies reduce generalizability
Reflect tumor biology, microenvironment interactions, and metastatic potential	Complex regulatory networks and pleiotropic effects complicate interpretation
Potential for multiplex biomarker panels, increasing predictive accuracy	Cross-platform variability (RNA-seq, microarray, qRT-PCR) creates inconsistent results
Can complement existing clinical and pathological prognostic factors	Limited large-scale, multi-center prospective trials available for clinical translation

Cancer-causing miRNAs, including miR-21, miR-231, and miR-155, are persistently elevated and closely linked to increased growth and metastasis, and resistance to the drug gemcitabine, the standard chemotherapy (Kasinski and Slack 2011). Cancer-promoting miRNAs,

like miR-34a, miR-96, and miR-217, have been frequently downregulated. These miRNAs generally suppress essential oncogenic pathways, particularly KRAS communication, and their absence increases tumor aggression. Clinically, high serum levels of miR-21 and miR-155 are connected to an adverse diagnosis, but miR-1290 has been postulated as a potential biomarker for early identification. Restoring tumor-suppressive miRNAs such as miR-34a has been demonstrated to diminish chemoresistance, whilst inhibiting miR-21 increases gemcitabine effectiveness in experimental animals (Singh *et al.* 2024). Furthermore, miRNAs influence the pancreatic tumour environment by regulating relationships between tumour cells with cancer-associated fibroblasts, hence accelerating tumour growth. Collectively, our data highlights miRNAs dual significance as diagnostic indicators and potential therapies in pancreatic cancer. MiRNAs were recently linked to cancer development, progression, and resistance to chemotherapy in liver cancer. Oncogenic miRNAs such as miR-221, miR-222, and miR-21 are often increased, enhancing cell proliferation, angiogenesis, and resistance to sorafenib, the first-line treatment for advanced HCC. In contrast, several miRNAs operate as tumour suppressors (Ji *et al.* 2025). The liver-specific miR-122 is significantly downregulated in HCC, and its absence is related to increased metastasis, poor prognosis, and altered lipid metabolism. Similarly, miR-199a/b suppresses tumors by reducing mTOR and HIF-1α pathways. Viral infections, such as HBV and HCV, further change miRNA expression, with viral proteins like HBx regulating miR-29 and miR-221 expression to induce carcinogenesis. Clinically, circulating miRNAs including miR-122 and miR-192 have emerged as promising biomarkers for early HCC identification and disease monitoring. MiR-122 mimics (such as Miravirsen, which was initially studied in HCV trials) have shown translational ability in recovering suppressive tumour pathways, implying that miRNA-derived therapy may eventually be introduced into HCC treatment methods (Al Ageeli 2024).

3.1. Significance and Clinical potential in Cancer detection

Despite tremendous advances, miRNA translation into everyday clinical practice faces several difficulties. One important shortcoming is the lack of established techniques for sample collection, RNA isolation, and quantification, which contributes to heterogeneity between studies. Furthermore, tumour heterogeneity and patient to patient variability make it difficult to identify universally reliable miRNA biomarkers (Ouyang *et al.* 2019). Another drawback is a lack of understanding of the intricate regulatory frameworks in which miRNAs function, especially their adverse consequences and interconnections with other kinds of non-coding RNAs. Additionally, most clinical investigations are still in the preliminary stages, with only a few large-scale, collaborative validation trials. Addressing these shortcomings is critical for realizing miRNAs full potential as effective diagnostic and therapeutic tools in oncology (Nalbant and Akkaya-Ulum 2024; Ratti *et al.* 2020).

3.2. Therapeutic implications of miRNA Biomarkers

MicroRNA (miRNA) biomarkers play a critical role in precision oncology, with applications including early cancer diagnosis, risk stratification, prognosis, therapeutic monitoring, and minimal residual disease evaluation. Circulating and tissue miRNA profiles reflect pathway activity and tumour-micro-micro-microenvironment dynamics, whereas clinical trials have demonstrated the efficacy of miRNA-targeted treatment methods, such as mimics to restore tumour suppressors and anti-miRs to inhibit oncogenes (Bertoli, Cava, and Castiglioni 2015). For example, miR-34a mimic MRX34 demonstrated target engagement but was limited by immune-related toxicity, whereas miR-16 mimics (TargomiRs) demonstrated tolerance and early action. Similarly, Cobomarsen (MRG-106), a miR-155 inhibitor, and other active programs demonstrate the therapeutic potential of miRNA regulation (Seyhan 2024). Simultaneous improvements in circulating miRNA panels demonstrate their potential as noninvasive diagnostic tools for a variety of cancer types (Winkle *et al.* 2021). **Table 2** highlights the dual nature of miRNAs as prognostic biomarkers: while their stability, non-invasive detection, and disease-specific expression offer strong clinical utility, challenges such as standardization, tumour heterogeneity, and limited large-scale validation currently restrict their widespread application. Overcoming these limitations is essential for translating miRNAs into robust prognostic tools in oncology (Zakari *et al.* 2024).

4. Future Perspectives

The clinical application of miRNA biomarkers and therapies will be dependent on established protocols, large-scale examination, and incorporation into tissue biopsy technologies for precise identification of cancer and monitoring. Improvements in delivery technologies, including nanoparticles, antibody-oligonucleotide conjugates, and exosome carriers, as well as chemically modified oligonucleotides, are expected to increase the safety and efficacy of miRNA therapeutics. Future prospects include multi-omics integration and AI-driven analytics to improve predictive capacity, allowing for adaptive and tailored treatment options. Together, these advancements establish miRNAs as promising tools for the next generation of precision oncology.

5. Summary

MicroRNAs (miRNAs) recently emerging as key regulators of gene expression, playing critical roles in cancer growth, development, and metastasis. Their durability in bodily fluids, tissue- particular expression patterns, and capacity to reveal disease status make them intriguing non-invasive indicators for early cancer characterization, prognosis, and therapeutic monitoring. Regarding clinical care, miRNAs can stratify individuals based on illness subtype, forecast therapeutic responses, and guide personalized treatment options. In breast cancer, miRNAs like let-7, miR-373, miR-520c and miR-155, are the major cause of tumour progression and metastasis. miR-26, miR-20a-5p, miR-25-3p, and others have shown potential as markers used for diagnosis and prognosis in hepatocellular carcinoma (HCC). Research on ovarian cancer has identified that miR-30a-5p, miR-145-5p, and miR-200c can be an effective molecular marker for early detection and prognosis. In pancreatic cancer research, five effective miRNAs such as miR-22, miR-642b, miR-885-5p, miR-16, and miR-196a are being examined for their diagnostic and prognostic value of ductal carcinoma (pancreatic cancer). Furthermore, therapeutic manipulation of dysregulated miRNAs, via miRNA mimics or inhibitors, provides a new path for targeted cancer therapy.

6. Conclusion

MicroRNAs (miRNAs) continue to redefine the landscape of cancer diagnostics and therapeutics, serving as versatile regulators with unique clinical advantages such as stability in biofluids and disease-specific expression profiles. Their emergence as non-invasive biomarkers through liquid biopsies have already improved early detection and prognostic accuracy in multiple cancers, including breast, ovarian, pancreatic, and hepatocellular carcinomas. Distinct miRNA signatures correlate with key clinical outcomes, reinforcing the integration of miRNA profiling into routine cancer care as a complement to traditional approaches. Therapeutically, the field has advanced with miRNA mimics to restore tumour suppressors and anti-miRs to silence oncogenic miRNAs. Preclinical successes, such as those with MRX34, TargomiRs, cobomarsen, and siRNA-derived inclisiran, have been validated in clinical trials with encouraging safety profiles and tangible anti-tumour responses. However, early termination of trials due to immune-related side effects, limited organ specificity, and off-target toxicity highlight the urgent need for safer, more precise delivery systems. Advances such as nanoparticle-based delivery and chemical modifications (e.g., LNA, cholesterol-

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conjugation) are promising, but the complex regulation and tissue targeting of miRNA therapies require ongoing innovation. The rise of single-cell sequencing, CRISPR-based editing, and AI-driven analytics allows for comprehensive mapping of miRNA networks and interactions, deepening understanding of tumour heterogeneity and resistance mechanisms. Multi-omics approaches, integrating genomics, proteomics, and metabolomics, offer new pathways to personalized cancer therapy, tailoring interventions to individual patient profiles and predicted drug responses. AI has shown robust success in prognostic modeling and biomarker identification, although real-world clinical translation demands rigorous validation, reproducibility, and regulatory oversight. Despite remarkable advances, clinical adoption of miRNAs is restricted by lack of standardized detection protocols, biological variability, and the intricate crosstalk of miRNA networks with other regulatory molecules. The withdrawal of key miRNA-based therapies from trials due to unforeseen toxicity and variable efficacy underscores persistent challenges. Addressing these hurdles will require innovative delivery technologies, large-scale clinical validation, and integration of evolving computational methods for predictive risk assessment. Ultimately miRNAs are spearheading a paradigm shift in oncology, acting as diagnostic sentinels, prognostic markers, and therapeutic agents whose impact is amplified by multi-omics strategies and AI-driven personalization. With ongoing technological progress, extensive clinical validation, and development of robust precision delivery systems, miRNAs are poised to revolutionize cancer care, paving the way for adaptive and patient-centric treatments across diverse cancer types.

7. Abbreviation

miRNA	-	Micro RNAs
RISC	-	induces silencing of RNA
ER	-	Estrogen Receptor,
PR	-	Progesterone Receptor
PCR	-	Polymerase Chain Reaction
CLIP	-	Crosslinking immunoprecipitation
RIP-seq	-	RNA immunoprecipitation sequencing
HER2	-	Human Epidermal Growth Factor 2
PDAC	-	Pancreatic Ductal Adenocarcinoma
PITA	-	p53 inhibitor of TIGAR activation
KRAS	-	Kirsten rat sarcoma virus

8. Disclosure Statements

8.1. Author Contribution

NB: Writing – Original Draft Preparation; **JR & BB:** Writing – Review and Editing; **SS:** Validation; Conceptualization; Correction and Supervision. All the authors have read and approved the final manuscript.

8.2. Declaration of Generative AI

The authors declare that no generative AI tools were used in the drafting, writing, or editing of the manuscript. All scientific interpretations and conclusions are the author's own. AI-based tools were used only for language grammar refinement and formatting purposes, and the final content was verified and approved by the authors.

8.3. Ethics approval (for clinical/animal studies)

This study did not involve the participation of human subjects, the use of identifiable human data or tissue, or any experiments on live animals. Consequently, the requirement for ethical approval or informed consent did not apply.

8.4. Informed Consent Statement

Not applicable.

8.5. Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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8.8. Conflicts of Interest

The authors declare that they have no known financial, personal, academic, or other relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript. All authors confirm that there are no competing interests to declare.

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