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Diagnostic and Prognostic Relevance of Circulating microRNAs across Multiple Cancer Types

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Abstract
Cancer is a major global health challenge due to its high morbidity and mortality, underscoring the need for reliable noninvasive biomarkers to support early detection, prognostication, and treatment monitoring. Circulating microRNAs (c-miRNAs), short non-coding RNAs found in body fluids, have attracted considerable attention as potential biomarkers due to their stability, ease of detection, and strong association with tumor biology. This review evaluates the diagnostic and prognostic value of c-miRNAs and their role in precision oncology. A systematic search of PubMed, Scopus, and ScienceDirect identified studies published between 2020 and 2025 that examined c-miRNAs in human fluids in relation to diagnosis, prognosis, or treatment response. Twelve eligible studies included breast, lung, colorectal, and gallbladder cancers. Dysregulated c-miRNAs, particularly miR-21, miR-155, miR-210, and let-7a, were consistently associated with tumor detection, patient survival, and disease progression. Analytical platforms ranged from quantitative RT-PCR to advanced biosensor-based technologies. Collectively, current evidence supports c-miRNAs as promising non-invasive biomarkers that complement conventional clinical tools by enabling earlier and more accurate diagnosis, reducing reliance on invasive biopsies, informing individualized treatment planning, and supporting the wider implementation of precision oncology.

INTRODUCTION

Cancer has become one of the most urgent global health challenges, with both incidence and mortality continuing to rise each year (Sung *et al*., 2021). Projections from the Global Cancer Observatory suggest that cancer is likely to overtake other conditions as the leading cause of death worldwide within the next decade. Since the beginning of the 21st century, this disease has placed a heavy burden not only on public health but also on social and economic systems. Currently, cancer accounts for nearly 17% of all deaths and around 23% of mortality caused by non-communicable diseases. Most cases are diagnosed in adults aged 30-69 years, making it a major contributor to premature deaths globally (Bray *et al*., 2024).

Detecting cancer at an early stage is crucial to extending survival, enhancing treatment success, and lowering disease-related mortality. Reliable prognostic evaluation is essential for guiding individualized therapeutic decisions and driving precision medicine forward (Crosby *et*

al., 2022; Tan *et al*., 2023). Over the past decade, non-invasive biomarkers have emerged as central elements in cancer diagnosis and prognosis, gradually transforming clinical management. These molecular indicators are useful not only for diagnosis, prognosis, monitoring recurrence, and predicting therapeutic response, but also for stratifying patients in drug development and clinical trials. Their integration into oncology provides substantial clinical and economic value by improving treatment outcomes and reducing healthcare expenditures (Das *et al*., 2023; Passaro *et al*., 2024).

Among the non-invasive biomarkers, circulating microRNAs (c-miRNAs) have attracted growing interest. These short non-coding RNAs, approximately 22 nucleotides long, regulate gene expression and can function either as oncogenes or tumor suppressors depending on their molecular targets (Gahlawat *et al*., 2022). Their stability in circulation and detectability in body fluids make them highly promising for clinical applications in diagnosis, prognosis, and treatment monitoring across different cancers.

Several mechanisms maintain the extracellular stability of c-miRNAs. They may be secreted through exosomes, microvesicles, or apoptotic bodies, or be bound to proteins such as argonaute 2 (AGO2), nucleophosmin, and high-density lipoproteins (Geekiyanage *et al*., 2020; Lv & Xiong, 2024; Tito *et al*., 2021). These mechanisms ensure that cmiRNAs remain intact in diverse biological fluids, including plasma, serum, urine, and cerebrospinal fluid (Gahlawat *et al*., 2022; Lim *et al*., 2025). Accumulating evidence further indicates that expression signatures of c-miRNAs can distinguish patients with cancer from healthy individuals, help classify tumor subtypes, predict metastatic potential, and assess responses to therapy. For instance, miR-21 (Rhim *et al*., 2022) and miR-155 (Kalkusova *et al*., 2022) are frequently elevated in lung and breast cancers, whereas miR-92a has been proposed as a biomarker for colorectal cancer (Fathi *et al*., 2025).

Despite their considerable potential, several obstacles remain before c-miRNAs can be translated into clinical practice. These include technical variability in extraction and quantification, inconsistency between studies, and limited validation in large and diverse populations. Therefore, this review aims to synthesize current evidence on the role of c-miRNAs as diagnostic and prognostic biomarkers in multiple cancer types, while also discussing their promise and limitations in advancing precision oncology.

RESEARCH METHODS

A comprehensive literature search was conducted in PubMed, Scopus, and ScienceDirect using the keywords “circulating microRNAs,” “c-miRNAs,” “cancer biomarker,” “diagnosis,” “prognosis,” and specific cancer types, combined with the Boolean operators (“AND” and “OR”).

Original research articles published in English between 2020 and 2025 that investigated c-miRNAs in body fluids for diagnostic, prognostic, or therapeutic monitoring purposes were included. Review articles were used only as supporting references and excluded from the primary analysis. The search results were imported into Mendeley to remove duplicates. The remaining records were first checked for relevance by looking at the title and abstract, and then a full-text review was done based on the inclusion criteria. From each eligible study, key

information was extracted into a standardized table, including author(s) and year, study design, cancer type, sample source, c-miRNA targets, detection methods, clinical endpoints, and main outcomes.

RESULTS AND DISCUSSION

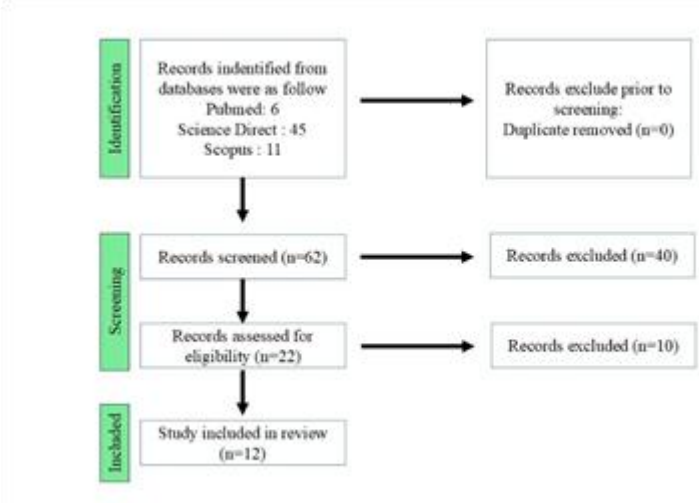

Figure 1. PRISMA Flow Diagram

Table 1. Summary of studies investigating circulating microRNAs as diagnostic and prognostic biomarkers in cancer

Author(s) & Years	Study Design	Cancer Type	Sample Source	c-miRNA Targets	Detection Method	Clinical Endpoints	Main Outcomes
(Canning *et al*., 2023)	Clinical (blood samples from CRC patient)	Colorectal cancer (CRC)	Plasma	miR-21, miR-221	SERS biosensor (iMS probes) (multiplexed, amplification-free), validated with qRT-PCR	Diagnostic performance / discrimination healthy vs cancer	Platform showed ultra-sensitive multiplex detection of circulating miR-21 and miR-221 in patient plasma, results matched qRT-PCR, and distinguished cancer vs control samples
(Liu *et al*., 2020)	Clinical (patient serum sample)	Non-small cell lung cancer (NSCLC)	Serum (exosomal microRNAs)	miR-21, miR-25, miR-155, miR-210, miR-486	tCLN biochip (tethered cationic lipoplex nanoparticle + molecular beacons + TIRF microscopy) validated with qRT-	Diagnostic / Early detection	The tCLN biochip detected exosomal miRNAs with high sensitivity and specificity for NSCLC, outperforming qRT-PCR, including in early-stage detection

Author(s) & Years	Study Design	Cancer Type	Sample Source	c-miRNA Targets	Detection Method	Clinical Endpoints	Main Outcomes
					PCR		
(Wong *et al*., 2021)	Clinical (patient sera)	Breast cancer	Serum	miR-1249	SPR imaging biosensor (label-free, multiplexed), validated with synthetic miRNA and patient samples	Diagnostic performance	The SPR imaging biosensor enabled rapid, label-free detection of circulating miRNA in breast cancer patient sera, distinguishing malignant from benign cases with high sensitivity.
(Qiu *et al*., 2022)	Clinical, Experimental	Breast cancer	Serum	miR-21, miR-155, miR-210	Surface-enhanced Raman scattering (SERS) holography chip	Early detection/biomarker validation	Demonstrated rapid, sensitive, and multiplexed detection of circulating breast cancer-associated miRNAs in patient serum; high potential for non-invasive early diagnosis and clinical screening
(Abbas *et al*., 2022)	Clinical	Breast cancer	Serum	miR-29b, miR-31	Quantitative real-time PCR (qRT-PCR)	Diagnosis and Prognosis	miR-29b and miR-31 were significantly dysregulated in breast cancer patients compared to controls; they showed potential as non-invasive biomarkers for early diagnosis and prognosis of breast cancer.
(Wu *et al*., 2024)	Clinical	Pan-cancer (multiple cancer types)	Plasma	Circulating miRNA pairs signature	qRT-PCR / bioinformatics analysis	Early diagnosis	Identified a unique circulating miRNA pairs signature capable of distinguishing early-stage cancer patients from healthy controls, showing superior diagnostic

Author(s) & Years	Study Design	Cancer Type	Sample Source	c-miRNA Targets	Detection Method	Clinical Endpoints	Main Outcomes
							performance compared to individual miRNAs.
(Blandino *et al*., 2025)	Clinical, Observational	Gallbladder cancer	Serum	miR-4533, miR-671-5p	Small-RNA sequencing	Early diagnosis	Identified miR-4533 and miR-671-5p as overexpressed in GBC serum; miR-4533 correlated with SIPA1L2 in Rap1 signaling pathway; miR-4533 overexpression confirmed in meta-analysis ($p = 4.1\times10^{-4}$); potential for early GBC detection.
(Barone *et al*., 2023)	Clinical	Breast cancer (patients with obesity)	Plasma (derived exosomes)	Let-7a (c-miRNA)	qRT-PCR	Diagnosis and prognosis	Identified Let-7a as significantly downregulated in breast cancer patients with obesity; demonstrated potential as a diagnostic and prognostic biomarker for this subgroup.
(Agahi & Rahaie, 2022)	Analytical	Breast cancer	Plasma-derived exosomes	miR-21, miR-155	DNA tweezers-based nanobiosensor	Early diagnosis	Developed a colorimetric nanobiosensor using DNA tweezers for simultaneous detection of miR-21 and miR-155 in plasma-derived exosomes; achieved high sensitivity with a detection limit of 0.38 nM; demonstrated potential for early breast cancer diagnosis.
(Zhang *et al*., 2020)	Computational/ Bioinfor	Lung cancer	Public plasma/ serum	miR-21, miR-155, miR-210	Bioinformatics analysis	Early diagnosis and	Developed a novel computational approach to

Author(s) & Years	Study Design	Cancer Type	Sample Source	c-miRNA Targets	Detection Method	Clinical Endpoints	Main Outcomes
	matics		datasets			monitoring	identify significant circulating miRNAs for early screening, diagnosis, and monitoring of lung cancer progression; findings suggest potential biomarkers for clinical application.
(Nakamura *et al*., 2022)	Clinical study	Early-onset colorectal cancer	Plasma	miR-193a-5p, miR-210, miR-513a-5p, miR-628–3p	RNA sequencing + qRT-PCR validation	Early diagnosis (distinguish CRC patients from controls)	Circulating miRNA signature accurately identified early-onset CRC patients, supporting non-invasive early detection
(Lasham *et al*., 2020)	Observational study	Breast cancer	Plasma	miR-923	Droplet digital PCR	Early disease recurrence	Plasma levels of miR-923 and CA 15-3 were significantly associated with prognosis; combined with clinicopathological features, they improved the prediction of disease recurrence

1. Summary of Key Findings

This review analyzed multiple studies investigating circulating microRNAs (c-miRNAs) as potential biomarkers across various cancer types, including breast, lung, pancreatic, colorectal, and gallbladder. Several c-miRNAs, such as miR-21, miR-29b, miR-31, miR-193a-5p, miR-210, and let-7a, were consistently reported as dysregulated in patient samples compared to healthy controls (Abbas *et al*., 2022; Barone *et al*., 2023; Blandino *et al*., 2025; Nakamura *et al*., 2022; P. Wu *et al*., 2024). Detection methods ranged from qRT-PCR and small RNA sequencing to advanced biosensors, including surface plasmon resonance imaging, Raman scattering chips, and DNA-based nanomachines (Agahi & Rahaie, 2022; Canning *et al*., 2023; Liu *et al*., 2020; Meng *et al*., 2021; Wang *et al*., 2024). Overall, these studies support the potential clinical utility of c-miRNAs for non-invasive cancer detection and monitoring.

2. Biological Significance of c-miRNAs in Cancer

Circulating microRNAs (c-miRNAs) reflect tumor biology by regulating gene expression in pathways associated with proliferation, apoptosis, metastasis, and angiogenesis (Abbas *et al*., 2022; Wu *et al*., 2024). Dysregulated c-miRNA expression in blood may serve as a surrogate

marker for tumor presence or progression, which could reveal the molecular mechanisms underlying carcinogenesis (Barone *et al*., 2023). Among these, miR-21 is one of the most widely identified oncomiRs, frequently upregulated across various cancer types, and promotes tumorigenesis through suppression of key tumor suppressor genes (Rhim *et al*., 2022).

A major mechanism of miR-21 involves inhibition of PTEN, which activates the PI3K/AKT pathway, leading to increased cell proliferation and decreased apoptosis (Rhim *et al*., 2022). miR-21 also targets PDCD4 and TPM1, critical regulators of cell death, resulting in an anti-apoptotic phenotype that supports tumor survival (Rhim *et al*., 2022). Moreover, miR-21 regulates invasion and metastasis by suppressing RECK and TIMP3, increasing MMP-2 and MMP-9 activity, and promoting epithelial–mesenchymal transition (EMT) (Rhim *et al*., 2022).

Beyond its roles in proliferation and metastasis, miR-21 functions as a pro-angiogenic regulator within the tumor microenvironment. Exosomes derived from tumor-associated macrophages (TAMs) carrying miR-21-5p can be transferred to endothelial cells, where miR-21-5p downregulates LATS1 and VHL, enhancing YAP1 activity and HIF-1α accumulation, which in turn stimulates VEGF expression and promotes angiogenesis in vitro and tumor vascularization in vivo (Yan *et al*., 2024). Similarly, miR-21 from colorectal cancer-derived exosomes increases HIF-1α and VEGF in human endothelial cells (HUVECs), strengthens tube formation, and enhances vascular permeability (He *et al*., 2021). In addition, miR-21 contributes to chemoresistance by activating survival pathways through PTEN and PDCD4 suppression, leading to resistance to chemotherapeutic agents such as cisplatin and doxorubicin (Rhim *et al*., 2022). Collectively, miR-21 is implicated in multiple cancer hallmarks, including proliferation, metastasis, angiogenesis, immunosuppression, metabolic reprogramming, and drug resistance, establishing its importance as a biomarker and therapeutic target (Rhim *et al*., 2022; Zhang *et al*., 2020).

Simultaneously, miR-155 is a multifunctional oncomiR that is often overexpressed in cancers. It plays a role in regulating tumor cells' growth, movement, and spread, as well as changing the tumor microenvironment through processes like angiogenesis and stromal interactions (Hussain *et al*., 2025). Exosomes released by cancer or stromal cells containing miR-155-5p can be internalized by fibroblasts, where miR-155 targets tumor suppressors like SOCS1. Suppression of SOCS1 activates the JAK2/STAT3 pathway, upregulating pro-angiogenic factors, including VEGFA, FGF2, and MMP9, which reprogram fibroblasts into a pro-angiogenic phenotype, enhancing endothelial proliferation, migration, and vascular structure formation (Zhou *et al*., 2018). The effects of miR-155 are context-dependent; overexpression in physiological angiogenesis models can induce endothelial hypersprouting but disrupt proper vascular morphogenesis, resulting in abnormal or “unproductive” angiogenesis (Dong *et al*., 2020). Clinically, miR-155 overexpression correlates with poor prognosis, highlighting its diagnostic and prognostic value (Wu *et al*., 2023).

Similarly, miR-210, known as a “hypoxamiR,” is consistently induced under hypoxic conditions via HIF-1α and plays a key role in cellular adaptation to low oxygen (Hui *et al*., 2020). In tumors, hypoxia-driven miR-210 upregulation promotes angiogenesis, microenvironment remodeling, and cancer cell survival (Lian *et al*., 2023). For example, in pancreatic cancer, tumor-derived exosomal miR-210 suppresses EFNA3, a negative regulator of

angiogenesis, in endothelial cells, thereby enhancing PI3K/AKT/VEGFA signaling and promoting endothelial proliferation, migration, tube formation, and vascular permeability (G. Wu *et al*., 2022). Additionally, exosomal miR-210 can drive normal fibroblasts toward a cancer-associated fibroblast (CAF) phenotype, characterized by upregulation of VEGF, FGF2, and MMP9 via JAK2/STAT3 activation, supporting neovascularization within the tumor microenvironment (Fan *et al*., 2020).

In contrast, let-7a, a member of the let-7 family, generally functions as a tumor-suppressor miRNA. In breast cancer, let-7a overexpression reduces USP32 expression through direct 3'-UTR targeting, thereby inhibiting cell proliferation (Liu *et al*., 2019). In lung adenocarcinoma, let-7a expression is decreased compared with normal tissue, and its re-expression suppresses proliferation, migration, and invasiveness; induces apoptosis; and arrests the cell cycle via Cyclin D1 regulation (Zhao *et al*., 2018). Furthermore, let-7a suppresses CCR7 expression in metastatic breast cancer cells, inhibiting migration and invasiveness, highlighting its capacity to modulate tumor metastatic potential (Kim *et al*., 2012).

Taken together, circulating miRNAs, including oncomiRs such as miR-21, miR-155, and miR-210, as well as tumor-suppressor miRNAs like let-7a, not only reflect tumor biology but also actively regulate key pathways involved in cancer progression, angiogenesis, and tumor microenvironment remodeling. Their multifaceted roles underscore their potential as biomarkers and therapeutic targets in oncology.

3. Technical Considerations and Detection Methods

Detection platforms for circulating miRNAs have varied across studies, ranging from conventional qRT-PCR to amplification-free biosensors capable of multiplexed detection (Agahi & Rahaie, 2022; Canning *et al*., 2023; Meng *et al.*, 2021; X. Wang *et al*., 2024). While qRT-PCR provides high specificity and reproducibility, biosensor-based platforms offer rapid, sensitive, and multiplexed detection with minimal sample preparation; however, variability in sample processing, exosome isolation, and assay standardization remains a challenge, affecting cross-study comparability. Among biosensor-based approaches, surface-enhanced Raman Spectroscopy (SERS) leverages plasmonic resonance in metallic nanostructures to amplify the Raman signal of target molecules, enabling the detection of biomolecules at ultralow concentrations. Canning *et al*., (2023) developed a bimetallic nanostar-based SERS platform for amplification-free, multiplexed detection of circulating miRNAs in colorectal cancer, achieving sensitivity at the zeptomolar scale, while Qiu *et al*., (2022) demonstrated rapid and non-invasive detection of biomarkers in biological fluids using metallic nanostructures that generate "hot spots" to amplify Raman signals. The advantages of SERS include high sensitivity, multiplexing capability, and potential for noninvasive detection, although reproducibility and interference from complex biological matrices remain challenging.

In addition to SERS, nanoparticle-based strategies, such as tethered Cationic Lipoplex Nanoparticles (tCLN), have been employed to capture and detect exosomal miRNAs selectively. tCLN utilizes positively charged nanoparticles to attract negatively charged exosomes from blood samples, allowing sensitive and specific detection of exosomal miRNAs (Qiu *et al*., 2022). This approach enhances specificity toward tumor-derived exosomes and enables multiplexed

biomarker detection by identifying miRNA changes that conventional qRT-PCR may miss. Its advantages include high sensitivity, potential for early detection, and noninvasive application, whereas limitations involve interference from other blood components, the need for pure exosome isolation, specialized detection equipment, and limited clinical validation (Qiu *et al*., 2022).

Meanwhile, DNA-based structures, such as DNA tweezers, provide a simple yet effective alternative for miRNA detection. This method relies on oligonucleotides that undergo conformational changes from an open to a closed state upon binding target miRNAs, triggering the formation of an active G-quadruplex that catalyzes a peroxidation reaction to produce a colorimetric signal via TMB substrate (Agahi & Rahaie, 2022). DNA tweezers allow multiplex detection of up to two miRNAs simultaneously, operate rapidly, and do not require enzymatic amplification. The advantages of this approach include moderate sensitivity with a detection limit of approximately 0.38 nM, the ability to discriminate target from non-target sequences, and cost- and time-efficiency; however, its limitations include potential sensitivity to environmental conditions (e.g., pH, blood composition, inhibitors), lower sensitivity compared to amplification-based methods, and possible interference from non-target molecules in complex biological matrices (Agahi & Rahaie, 2022).

4. Clinical Implications

Accumulating evidence indicates that c-miRNAs could serve as non-invasive biomarkers for early diagnosis, disease monitoring, and prognosis (Blandino et al., 2025; Nakamura et al., 2022; Wu *et al*., 2024). For example, panels of miRNA pairs improved early detection in pan-cancer cohorts (Wu *et al*., 2024), while exosomal miRNA showed promise in detecting early-stage breast and lung cancers (Barone *et al*., 2023; Liu *et al*., 2020). Incorporation of c-miRNAs measurements into clinical practice could reduce dependence on invasive tissue biopsies and enable real-time monitoring of treatment responses.

5. Challenges and Limitations

Several limitations were identified across the studies, including small cohort sizes, heterogeneity in patient populations, and inconsistent miRNA quantification methods (Abbas *et al*., 2022; Blandino *et al*., 2025). Additionally, many studies focused on single miRNAs rather than panels, potentially limiting diagnostic accuracy. Standardization of protocols and multicenter validation studies are crucial to address these issues.

6. Future Directions

Future research should focus on large-scale, prospective studies to validate c-miRNA panels across diverse populations (Nakamura *et al*., 2022; Wu *et al*., 2024). Combining c-miRNA profiling with multi-omics and machine learning approaches could enhance predictive performance. Furthermore, the development of rapid, multiplexed, and sensitive biosensing platforms will facilitate the clinical translation of these biomarkers (Canning *et al*., 2023; Wang *et al*., 2024).

CONCLUSION

Circulating microRNAs (c-miRNAs) hold substantial promise as noninvasive biomarkers for cancer diagnosis, prognosis, and therapeutic monitoring due to their stability and accessibility. While they have the potential to complement conventional diagnostic methods and facilitate precision oncology, challenges related to methodological variability, reproducibility, and limited cohort sizes remain. Standardization and large-scale validation are essential to establish c-miRNAs as reliable clinical tools.

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Author Contributions

G.F.T.P and D.W contributed to designing the study, and preparing the manuscript. Z.N.Z and F.A contributed to proofreading the manuscript.

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Declaration of interest

The authors declare no relevant conflicts of interest related to this study

Data Sharing Statement

The data used in this are available upon reasonable request and in accordance with established procedures

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