Unlocking the potential of microRNA as predictive biomarkers for efficacy and adverse events in immune checkpoint inhibitor therapy (Review)

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Received December 20, 2025; Accepted July 29, 2026

DOI: 10.3892/mmr.2026.13998

Abstract. Immune checkpoint inhibitors (ICIs) have shown promise in cancer therapy by enhancing antitumor immune responses, but patient responses are variable, with some experiencing limited efficacy and others suffering from severe immune-related adverse events (irAEs). Identifying predictive biomarkers for ICI efficacy and toxicity is required for optimizing patient selection and treatment outcomes. MicroRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression, have emerged as potential biomarkers due to their role in immune regulation and tumor biology. Studies have shown that miRNA profiles in tumor tissues and blood can predict ICI responses. Specific miRNAs, such as miR-155, miR-21 and miR-146a, are associated with enhanced antitumor responses, whereas others, such as miR-34a and miR-200c, are linked to resistance by modulating immune evasion. Additionally, altered miRNA expression reflects immune activation or dysregulation, playing a role in irAEs. The present review discussed the potential of miRNAs as predictive biomarkers for ICI therapy, their challenges in clinical integration and their promise for improving ICI treatment precision and safety, although further research is required for clinical application.

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Key words: immune checkpoint inhibitors, microRNAs, cancer therapy, immune-related adverse events, biomarkers

1. Introduction

The development of immune checkpoint inhibitors (ICIs) has enhanced cancer immunotherapy, offering promising treatment options for a variety of malignancies. ICIs, such as anti-programmed cell death protein 1 (PD-1), anti-PD-ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies, enhance the body's immune response against cancer by targeting key regulatory checkpoints within the immune system (1). By blocking inhibitory signals that suppress T cell activity, these therapies help to reactivate the immune system, allowing it to effectively recognize and destroy tumor cells (2). The approval of ICIs has led to notable advances in the treatment of various cancers, including lung cancer, gastric cancer (GC), melanoma, renal cell carcinoma (RCC) and other malignancies (3-7). However, despite their success, patient responses to ICIs are markedly variable, and numerous individuals do not experience durable clinical benefits (8).

A notable challenge in the clinical application of ICIs is heterogeneity in patient response (9). While some patients achieve long-term remission and substantial tumor regression, others exhibit primary resistance, where the tumor does not respond to therapy from the outset. In addition, some patients may experience immune-related adverse events (irAEs), ranging from mild inflammatory responses to life-threatening conditions, including myocarditis, colitis and pneumonitis (10,11). These irAEs are thought to result from an overactivation of the immune system, leading to collateral damage to normal tissues. The incidence and severity of such events vary widely among patients, complicating clinical management and limiting the widespread use of ICIs in certain populations (11,12). Therefore, identifying predictive biomarkers that can help determine which patients are most likely to benefit from ICI therapy and which patients are at risk

for severe irAEs is required for optimizing treatment outcomes and minimizing harm.

Advances have highlighted the potential of microRNAs (miRNAs) as predictive biomarkers for both treatment efficacy and toxicity in ICI therapy (9,13). miRNAs are small, non-coding RNA molecules that play a central role in regulating gene expression at the post-transcriptional level. They modulate various biological processes, including immune cell differentiation, activation and cytokine production, making them key regulators in both tumor biology and immune system function. These molecules are involved in multiple immune pathways, and their expression profiles have been shown to be associated with the immune response in cancer, particularly in the context of immunotherapy (14). miRNAs are also present in various biological fluids, including tumor tissues, serum and plasma, allowing for non-invasive biomarker discovery that could be integrated into clinical practice (15).

Emerging evidence suggests that miRNAs can be used to predict the response of ICIs (16). Several miRNAs have been identified as key players in regulating immune checkpoint pathways and influencing the tumor microenvironment (TME). For example, miR-155, known for its role in promoting T cell activation and regulating inflammatory responses, has been associated with enhanced anti-tumor immunity and favorable ICI outcomes (17). Similarly, miR-21 has been implicated in tumor progression and resistance to therapy, and its expression has been linked to ICI responsiveness in certain cancer types (18). On the other hand, certain miRNAs, such as miR-34a and miR-200c, have been shown to be associated with resistance to ICIs, potentially by regulating immune evasion mechanisms that allow tumors to escape immune surveillance (19,20). These findings suggest that miRNAs could be used as predictive biomarkers to stratify patients, identifying those more likely to benefit from treatment and those at increased risk of resistance.

In addition to their role in predicting efficacy, miRNAs are also implicated in irAEs (21). The development of irAEs following ICI therapy is a complex process that likely involves immune dysregulation and a failure to distinguish self from non-self. Dysregulated miRNA expression may reflect immune system activation or the breakdown of immune tolerance, both of which are key factors in the onset of irAEs (22). Certain miRNAs, such as miR-146a, which regulates inflammation, and miR-34a, which is involved in immune responses, have been shown to be associated with the occurrence of irAEs (23). Alterations in these miRNAs may serve as early indicators of potential irAEs, allowing for timely intervention and monitoring during treatment.

The present review aimed to explore the potential of miRNAs as predictive biomarkers for ICIs therapy, focusing on their role in predicting both treatment efficacy and irAEs. The current state of miRNA research in this field was discussed, the key miRNAs identified in clinical and preclinical studies were examined and the challenges and future directions for incorporating miRNA-based biomarkers into clinical practice were highlighted. Notably, the present review distinguished between predictive biomarkers (identifying patients likely to benefit from a specific therapy) and prognostic biomarkers (informing about disease outcome independent of treatment), and classifies evidence according to its source, clinical cohort, translational/mechanistic or preclinical.

2. Literature search and study selection

To ensure methodological transparency, a structured literature search was conducted following systematic review principles.

Search strategy. A comprehensive literature search was performed using PubMed (https://pubmed.ncbi.nlm.nih.gov/), covering publications from January 2020 to December 2025. Seminal studies published before 2020 were included when they provided essential mechanistic context. The search employed a combination of MeSH terms and free-text keywords, including: (microRNA OR miRNA OR miR OR non-coding RNA) AND (immune checkpoint inhibitor OR anti-PD-1 OR anti-PD-L1 OR anti-CTLA-4 OR immunotherapy) AND (biomarker OR predict OR response OR efficacy OR adverse event OR irAE OR toxicity OR resistance).

Inclusion and exclusion criteria. Studies were included if they met the following criteria: i) Original clinical studies reporting associations between miRNA expression and ICI treatment outcomes (efficacy and/or irAEs) in patients with cancer; ii) mechanistic or preclinical studies providing functional evidence for miRNA involvement in ICI-related immune pathways; and iii) relevant review articles providing contextual framework. Studies were excluded if they were: i) Conference abstracts only; ii) non-English language publications; iii) studies focusing exclusively on miRNA therapeutics without biomarker data; or iv) studies investigating miRNA associations solely with cancer prognosis without reference to immunotherapy.

Study selection and data extraction. Titles and abstracts were independently screened by two authors. Full texts of potentially eligible studies were reviewed, and disagreements were resolved through discussion with other authors. Data extracted from each eligible study included: Cancer type, sample size, sample source, ICI type, miRNA detection method, miRNA(s) identified, direction of expression change, associated clinical endpoint(s) and key findings. Clinical and preclinical/mechanistic studies were recorded separately and are distinguished throughout the present review.

Classification of evidence. The cited evidence was classified into three tiers: i) Clinical biomarker evidence, including results from human patient cohorts where miRNA expression was directly associated with ICI clinical outcomes; ii) translational/mechanistic supporting evidence, such as functional *in vitro* or *ex vivo* studies; and iii) preclinical therapeutic concepts, animal model or therapeutic engineering studies. Furthermore, predictive biomarkers (identifying patients likely to benefit from a specific therapeutic intervention) and prognostic biomarkers (informing about disease outcome independent of treatment type), were explicitly distinguished following the FDA-NIH BEST resource framework (www.ncbi.nlm.nih.gov/books/NBK326791). The present review is a narrative review rather than a systematic review with meta-analysis; however, systematic search and selection

principles were applied to ensure comprehensiveness and transparency.

3. Biological characteristics of miRNAs and their role in immune regulation

miRNA definition and function. miRNAs are small, non-coding RNA molecules, typically 18-25 nucleotides in length, that regulate gene expression at the post-transcriptional level. First discovered in the early 1990s, miRNAs are crucial regulators of biological processes such as development, differentiation, apoptosis and immune responses (24). They exert their effects by binding to the 3' untranslated regions (3' UTRs) of target messenger RNAs (mRNAs), leading to either mRNA degradation or translational repression. This regulation is sequence-specific, allowing each miRNA to target hundreds of different mRNAs and influence complex gene networks (25).

The biogenesis of miRNAs begins with the transcription of primary miRNAs (pri-miRNAs) in the nucleus. These pri-miRNAs are processed by Drosha into precursor miRNAs, which are transported to the cytoplasm and further cleaved by Dicer into mature miRNAs. The mature miRNAs are incorporated into the RNA-induced silencing complex, where they guide the complex to target mRNAs based on complementary sequences. This process enables miRNAs to regulate a wide variety of cellular functions, including immune responses (26,27).

Role of miRNAs in immune regulation. miRNAs play a notable role in regulating the immune system by controlling immune cell differentiation, activation and tolerance (28). They modulate the expression of key cytokines, transcription factors and immune checkpoint molecules, influencing both innate and adaptive immune responses (29). For instance, miR-155 is a notable regulator of T-helper 1 (Th1) cells and cytotoxic T lymphocytes (CTLs), promoting an inflammatory immune response. In $CD4^+$ T cells, miR-155 promotes Th1 polarization by targeting SOCS1 and SHIP1, negative regulators of JAK-STAT and PI3K-AKT signaling, thereby enhancing IFN-γ production, while also suppressing the Th2-driving transcription factor c-Maf. In $CD8^+$ CTLs, miR-155 facilitates effector function through two complementary mechanisms: First, indirectly upregulates T-bet by repressing SHIP1, which directly inhibits T-bet expression, thereby driving effector expansion and IFN-γ secretion; and second, it dampens type I interferon signaling to protect CTLs from anti-proliferative signals. Through these mechanisms, miR-155 facilitates the activation of immune cells, thereby enhancing the ability of the body to combat tumors (30).

By contrast, miR-146a serves as a regulator of immune tolerance by targeting genes involved in the NF-κB signaling pathway, which controls immune activation. By dampening NF-κB activity, miR-146a helps to prevent excessive immune responses and autoimmunity (31,32). miR-21, another key immune-related miRNA, plays a role in balancing immune activation and immune tolerance by modulating immune checkpoints, such as programmed cell death protein 4 (PDCD4) (33,34). These miRNAs ensure that immune responses are appropriately regulated to avoid both autoimmune diseases and insufficient anti-tumor immunity.

miRNAs also regulate the expression of immune checkpoint molecules such as PD-1, PD-L1 and CTLA-4, which are essential for maintaining immune tolerance (35,36). miR-15, for example, has been shown to influence the expression of these checkpoint proteins, affecting CD8+ T cell responses and potentially modulating the efficacy of ICI therapies (37).

miRNA in tumor immunity. In the context of tumor immunity, miRNAs are pivotal in regulating immune evasion mechanisms and the TME. Tumor cells often exploit miRNA regulation to escape immune surveillance and create a microenvironment that suppresses anti-tumor immunity (38,39). miRNAs modulate the expression of various genes involved in immune checkpoint pathways, cytokine production and immune cell infiltration, all of which contribute to immune evasion (35).

For instance, miR-34a is a tumor-suppressive miRNA that is often downregulated in cancers. Its loss is associated with the upregulation of immune checkpoint molecules, such as PD-L1, facilitating immune evasion (40). Similarly, miR-200c and miRNA-21-5p are involved in the regulation of epithelial-to-mesenchymal transition (EMT), a process that enhances cancer cell migration and invasion while reducing immune cell infiltration into tumors (41,42). This helps tumors evade immune detection and promotes resistance to immunotherapy.

Furthermore, miR-155, miR-203 and miR-940 play a role in modulating tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs), which are notable players in maintaining an immunosuppressive TME (43). By affecting the function of these cells, they help tumors evade immune responses, reducing the effectiveness of therapies such as ICIs (44). In addition, miRNAs such as miR-212-3p, miR-203, miR-21 and miR-let-7d have been implicated in shaping the TME by promoting immune cell dysfunction and supporting a pro-tumor environment. These miRNAs contribute to an immunosuppressive microenvironment, which can limit the efficacy of ICI treatments (39). Thus, miRNAs are not only involved in the modulation of immune cell functions but also play a critical role in shaping the immune landscape of tumors.

4. miRNAs in predicting efficacy of ICIs

Predictive biomarkers are critical in enhancing the effectiveness of ICIs by enabling improved patient selection and treatment planning. ICIs, such as anti-PD-1, anti-PD-L1 and anti-CTLA-4 therapies, have demonstrated notable success in treating cancers, but patient responses remain heterogeneous (45). While some patients experience long-term remission, others show limited or no response or develop irAEs (46). Identifying biomarkers that can predict ICI efficacy is essential to maximize therapeutic outcomes and minimize unnecessary treatments (47).

Building on the immune regulatory functions of miRNAs as aforementioned, circulating and tumor tissue-derived miRNAs have been evaluated as predictive biomarkers for ICI efficacy across multiple cancer types. The evidence summarized next is organized by cancer type and, within each, by biospecimen source (circulating vs. tissue), with key findings and associated evidence levels highlighted (48,49). Table I

Table I. List of miRNAs as predictive biomarkers for ICI efficacy.

Cancer	miRNA	Sample	ICI	Endpoint (biomarker type)	Key finding	(Refs.)
Non-small cell lung cancer	miR-1246-5p, miR-1296-5p, miR-4707-3p, miR-1229-3p, miR-874-3p, miR-378c-5p, miR-1468-5p	Plasma EV	Anti-PD-1/PD-L1	PFS (P, T3)	7 EV-miRNAs differentiated responders vs. non-responders (next generation sequencing, n=29)	(51)
	miR-320d, miR-320c, miR-125-5p	Plasma EV	Anti-PD-1/PD-L1	ORR/PFS (P, T3)	Higher in non-responders; longitudinal monitoring value highlighted	(52)
	miR-208a-5p, miR-574-5p, miR-181a-5p	Plasma EV	Anti-PD-1	OS (Prog, T2)	Down in long-term survivors; validated in independent cohort (n=71)	(53)
	miR-625-5p	Plasma EV	Anti-PD-1	ORR/OS (P, T2)	Novel biomarker; effective in PD-L1 ≥50% patients; large cohort (n=174)	(54)
	miR-125a-3p	Serum EV	Anti-PD-1/PD-L1	ORR (P, T3)	Predictive in PD-L1 <50%; regulates PD-L1 via NRG1; functional validation	(55)
	10-miRNA panel (miR-93, miR-138-5p, miR-200, miR-27a, miR-424, miR-34a, miR-28, miR-106b, miR-193a-3p, miR-181a)	Whole plasma	Anti-PD-1	PFS/OS (P, T3)	10-miRNA high-expression pattern -> improved PFS/OS; discovery + validation (n=80)	(56)
	miR-199a-3p, miR-21-5p, miR-28-5p (3-miRNA panel)	Whole plasma	Anti-PD-1/PD-L1	ORR (P, T2)	AUC 0.925, outperformed PD-L1 immunohistochemistry (AUC 0.575); PCR validated	(51)
	miR-126-3p	Whole plasma	Anti-PD-1/chemo	PFS/OS (P, T3)	Higher expression -> longer PFS/OS in 1st-line immunotherapy	(58)
	miR-505-3p	Tumor tissue	NA	OS/TIL (Mech, T3)	Enhances CD8+ T-cell activity via NET1 targeting; improved prognosis	(59)
	MIR155HG	Tumor tissue	Anti-PD-1/PD-L1/CTLA-4	OS/Immune (Prog, T3)	Associated with immune infiltration + checkpoint expression; improved OS in lung adenocarcinoma	(60)
	miR-326	Tumor tissue	NA	CD155/ICI, (Mech T3)	Negatively regulates CD155; lower CD155 -> improved predicted ICI response	(61)
	miR-23a/27a/24-2 cluster	Tumor tissue	Anti-PD-1/PD-L1	PD-L1/MHC-I (Mech, T3)	Cluster -> PD-L1 up + MHC-I down -> immune evasion; eIF3B targeting enhances ICI (preclinical)	(62)
Gastric cancer	miR-451a, miR-142-5p	Plasma EV	Anti-PD-1+chemo	ORR (P, T2)	Up in responders; independently validated by qPCR; PI3K-AKT/MAPK pathways	(64)
	miR-552-5p	Plasma EV	Anti-PD-1/PD-L1	NK function (Mech, T3)	Exosomal miR-552-5p -> PD-1/PD-L1 axis -> NK cell dysfunction	(65)

Table I. Continued.

Cancer	miRNA	Sample	ICI	Endpoint (biomarker type)	Key finding	(Refs.)
	miR-17-5p (LINC01094 ceRNA)	Plasma/tissue	Anti-PD-1/PD-L1	Prog (Prog/Mech, T3)	LINC01094/miR-17-5p -> PD-L1+PD-L2 regulation; TCGA + external validation	(66)
	miR-105-5p	Tumor tissue	Anti-PD-1/PD-L1	PD-L1/CD8 (Mech, T3)	Binds PD-L1 3'UTR; controlled by CT-GABRA3 methylation; overexpression counteracts immune escape	(67)
	miR-BART5-5p (EBV)	Tumor tissue	Anti-PD-1/PD-L1	PD-L1/OS (Prog/Mech, T3)	EBV-encoded; PIAS3/pSTAT3 -> PD- L1 up; adverse outcome in EBV+ gastric cancer	(68)
	miR-744-5p (circSCUBE3)	Tumor tissue	Anti-PD-L1	Resist (Mech, T3)	circSCUBE3/miR-744-5p/ SLC7A5 -> PD-L1 + immune evasion; attenuates anti-PD-L1 *in vivo*	(69)
	miR-141-3p	Tumor tissue	Anti-PD-1	Resist (Mech, T3)	Up in resistant tumors; increases CXCL12 -> immune evasion	(70)
Esophageal squamous-cell carcinoma	miR-199a-5p	Plasma EV	Anti-PD-1+RT	Response (P, T3)	Higher -> increased radiosensitivity + improved anti-PD-1; targets EEPD1	(71)
	miR-1233-5p (pre-Rx); miR-6885-5p, miR-4698, miR-128-2-5p (post-Rx)	Whole plasma	Anti-PD-1 (nivo)	ORR (P, T3)	Pre-Rx AUC 0.895; post-Rx AUC 0.93-0.97 (phase II, n=19)	(72)
	miR-223, miR-1269a, nc886 (RAS)	Tumor tissue	Anti-PD-1	RFS/PD-L1 (Prog/Mech, T3)	Low-RAS=PD-L1-high/ immunogenic (ICI-responsive); High- RAS=TP63amp/immune-resistant	(73)
	miR-34a-5p (LJZD adjuvant)	Tumor tissue	Anti-PD-1	CD8/TIL (Mech, T3)	LJZD restores miR-34a -> disrupts STAT3/IL-6R loop -> enhanced antitumor immunity (mouse)	(75)
CRC	miR-125b-5p (MSC-exo)	Plasma EV	Anti-PD-1	Treg (Mech, T3)	MSC-exosomal miR-125b-5p inhibits FoxP3+ Tregs -> enhances anti-PD-1 (mouse)	(76)
	miR-15b-5p	Tumor tissue	Anti-PD-1	PD-L1/CD8 (P/Mech, T3)	Suppresses PD-L1 via IL-17A/P65/NRF1; low -> PD-L1 up, CD8+ down in MSS CRC	(37)
	miR-497-5p	Tumor tissue	Anti-PD-1/CTLA-4	CTLA-4/PD-L1 (Mech, T3)	Tumor-suppressive; nanoparticle delivery synergizes with anti-PD-1 (preclinical)	(78)
	miR-146b, miR-155, miR-22 cluster	Tumor tissue	Anti-PD-1/CTLA-4	ICI response (Mech, T3)	Enriched in MSI-H/TMB-H; modulate TGF-beta/M1 polarization -> improved ICI response	(79)
	miR-140-3p, miR-148a-3p, miR-200a/c, miR-138-5p, miR-497-5p	Tumor tissue	Anti-PD-1/PD-L1	PD-L1/Viability (Mech, T3)	TS-miRNAs inhibit PD-L1+ oncogenic pathways; nanoparticle delivery overcomes MSS CRC ICI resistance	(80)

Table I. Continued.

Cancer	miRNA	Sample	ICI	Endpoint (biomarker type)	Key finding	(Refs.)
HCC	miR-511-5p, miR-150-3p, miR-342-3p, miR-181a-3p, miR-625-5p, miR-155-5p, miR-142-5p/3p, etc.	Plasma/EV (TCGA)	Anti-PD-1/PD-L1	Immune (Mech, T3)	Multi-omics TCGA; miRNAs linked to antitumor immunity; potential predictive biomarkers	(81)
	miR-105-5p, miR-155-5p, miR-142-5p/3p, miR-30a-5p, miR-486-5p	Plasma/ PBMC	Anti-PD-1/PD-L1	PD-1/TIGIT (Mech, T3)	miR-105-5p strongest enhancer of PBMC-mediated HCC lysis; inhibits PD-1+TIGIT	(82)
	miR-30-5p	Tumor tissue	Anti-PD-1	DPP4/CXCL10 (Mech, T3)	Sponged by circMET -> Snail/ DPP4 -> immunosuppression; high miR-30-5p=improved immune response	(83)
	miR-195-5p, miR-424-5p (NB delivery)	Tumor tissue (NB)	Anti-PD-1/PD-L1	CTL/PD-L1 (Mech, T3)	Nanobubble co-delivery -> PD-1/PD-L1 suppression + sonodynamic ICD (mouse models)	(84,85)
BC	miR-155-5p	Plasma/ serum	Anti-PD-1/PD-L1	ORR/Immune (P, T2)	Enriched in TNBC; CD8+ TILs up, CXCL9/10/11 up -> 'hot' TME -> favorable ICI response	(86)
	miR-20a-5p	Plasma EV	Anti-PD-1	Resist (P/Mech, T3)	Overexpressed in TNBC EV; targets NPAT -> impairs CD8+ cytotoxicity -> anti-PD-1 resistance	(87)
	miR-338-3p, miR-501-3p	Plasma EV	Anti-PD-1/PD-L1	Diagnostic/ immune (Mech, T3)	Combined AUC 0.89; regulate PI3K-Akt/MAPK pathways; potential ICI responsiveness predictor	(88)
	miR-93-5p, miR-149-3p	Tumor tissue	Anti-PD-1/PD-L1	OS/Immune (Prog/Mech, T2)	miR-93-5p suppresses PD-L1/ PD-L2/B7-H6; miR-149-3p downregulates PD-1/TIM-3/ BTLA; improved survival in TCGA/METABRIC	(91)
	miR-138-5p, miR-100-5p, miR-200a, miR-21-5p, miR-5119, miR-195/miR-497	Tumor tissue	Anti-PD-1/PD-L1/ CTLA-4	Multi-immune checkpoints (Mech, T3)	Multi-target immune checkpoint suppression; miRNA-based ICI sensitizers for BC	(91)
	miR-18a-5p	Tumor tissue (ER+)	Anti-PD-1/PD-L1	Wnt/Treg (Prog, T3)	Wnt activation -> Treg up, CD4/ CD8 up, M2 polarization -> poor ICI response in ER+ BC	(90)
	miR-214-3p, miR-34a-5p, miR-200c-3p, miR-424-5p	Tumor tissue (TNBC)	Anti-PD-1/PD-L1	PD-L1/B7H3 (Mech, T3)	Inhibit PD-L1+oncogenic pathways; single-cell-sequencing-guided biomimetic delivery (preclinical)	(92,93)

Table I. Continued.

Cancer	miRNA	Sample	ICI	Endpoint (biomarker type)	Key finding	(Refs.)
Melanoma	miR-615-3p, miR-4649-3p	Whole plasma	Anti-PD-1/CTLA-4	ORR (P, T3)	miR-615-3p decreased in CR; miR-4649-3p increased in non-responders	(94)
	let-7e, miR-99b, miR-125a/b, miR-146b, miR-155, miR-16/17/20a	Plasma/ serum/EV	Anti-PD-1/CTLA-4	ORR/PFS (P, T3)	Multiple circulating miRNAs associated with ipilimumab/ nivolumab/pembrolizumab outcomes	(96)
	miR-100-5p, miR-125b-5p	Tumor tissue	Anti-PD-1	OS (Prog, T3)	Central to MITF-low miRNA-mRNA network; associated with improved OS on anti-PD-1	(100)
	miR-34c, miR-711, miR-641, miR-22 (4-miR signature)	Tumor tissue	Anti-CTLA- 4 (ipilimumab, neoadjuvant therapy)	RFS (Prog, T3)	4-miRNA signature -> improved RFS after neoadjuvant ipilimumab; T-cell activation pathways	(101)
Renal cell carcinoma	miR-146a-5p, miR-126-3p	Plasma EV	Anti-PD-1/PD-L1 (Nivolumab)	irAE/ORR (P, T3)	miR-146a up post-Rx; lower miR-146a -> higher-grade irAE; combined AUC 0.752 (n=35)	(102)
	miR-22, miR-24, miR-99a, miR-194, miR-214, miR-335, miR-339, miR-708 (8- miR lymphocyte signature)	Peripheral lymphocytes	Anti-PD-1 (nivolumab)	PFS >18 months (P, T2)	Induced in long-responders; silenced at baseline -> high at 4 weeks; inverse association with soluble PD-1/PD-L1	(103)
	miR-497-5p	Tumor tissue	Anti-PD-L1	PD-L1/OS (Prog/Mech, T3)	Down -> PD-L1 up; directly targets PD-L1 in ccRCC; shorter OS in TCGA-KIRC	(104)
	MIR155HG	Tumor tissue	Anti-PD-1/PD-L1/ CTLA-4	OS/immune, (Prog T3)	Elevated -> inferior OS in KIRC; associated with immune infiltration + checkpoint expression	(60)

Evidence: T1=validated in ≥2 independent cohorts in ≥2 cancer types; T2=validated in single cancer type with independent cohort; T3=single cohort/exploratory/mechanistic. Endpoint types: P=predictive (ICI-treated), Prog=prognostic (independent of treatment), Mech=mechanistic association. NR=not reported. miRNAs follow standardized miRBase nomenclature. Immune, antitumor immune response; miRNA, micro RNA; DCR, disease control rate; EV, extracellular vesicle; ICI, immune checkpoint inhibitor; TIL, tumor-infiltrating lymphocyte; DB, nanobubble-mediated delivery; ICD, immunogenic cell death; CRC, colorectal cancer; BC, breast cancer; ER, estrogen receptor; TNBC, triple negative BC; HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; RFS, recurrence free survival; ccRCC, clear cell renal cell carcinoma; KIRC, kidney renal clear cell carcinoma; EBV, Epstein-Barr virus; AUC, area under the curve; Treg, regulatory T cell; TCGA, the cancer genome atlas; NK, natural killer; PD-1, programmed cell death protein 1; PDL-1, PD-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ceRNA, competing endogenous RNA.

synthesizes clinical study data highlighting the potential of miRNAs as predictive biomarkers for treatment efficacy in patients with cancer undergoing immune-checkpoint therapies.

Non-small cell lung cancer (NSCLC)

Plasma extracellular vesicle (EV) miRNAs in predicting efficacy of ICIs in NSCLC. Extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as mediators of tumor-immune crosstalk and promising sources of non-invasive biomarkers for predicting ICI efficacy in NSCLC. EV-encapsulated miRNAs exhibit enhanced stability compared with circulating free miRNAs, reflecting dynamic interactions between tumor cells and the immune microenvironment (50).

A landmark study by Shukuya *et al* (51) analyzed plasma EV-derived miRNAs in 29 patients with advanced NSCLC treated with anti-PD-1/PD-L1 monotherapy. Using next-generation sequencing, the researchers identified seven EV-associated miRNAs (miR-1246-5p, miR-1296-5p, miR-4707-3p, miR-1229-3p, miR-874-3p, miR-378c-5p and miR-1468-5p) that showed notable associations differences between responders (patients achieving partial response or stable disease for at least 6 months) and non-responders (patients with progressive disease). Notably, miR-1246-5p and miR-1296-5p were upregulated in non-responders, whereas miR-4707-3p and miR-1229-3p were downregulated.

Huemer *et al* (52) investigated plasma EV miRNAs in EGFR/ALK wild-type advanced NSCLC, identifying 3 miRNAs (miR-320d, miR-320c and miR-125-5p) that were markedly higher in non-responders compared with responders, highlighting the importance of longitudinal monitoring. Genova *et al* (53) conducted a comprehensive analysis in 174 advanced patients with NSCLC treated with anti-PD-1 therapy, identifying miR-208a-5p and miR-574-5p as notably downregulated in long-term survivors. These miRNAs were combined with performance status to create a prognostic model with good prediction of overall survival (OS) in an independent cohort of 71 patients.

Furthermore, Pantano *et al* (54) identified EV-miR-625-5p as a novel biomarker associated with objective response and OS in patients with NSCLC treated with anti-PD-1 therapy, particularly effective in stratifying patients with high PD-L1 expression (≥50%) (54). Another study reported that serum-derived exosomal miR-125a-3p was associated with response to ICI therapy in patients with low PD-L1 expression (<50%) and demonstrated improved prediction compared with tumor PD-L1 status, functioning by targeting neuregulin 1 (NRG1) (55).

Whole plasma miRNAs in predicting efficacy of ICIs in NSCLC. Whole plasma miRNAs have demonstrated marked potential as predictive biomarkers for ICI efficacy in NSCLC. Fan *et al* (56) conducted a comprehensive analysis of serum miRNAs in patients with NSCLC, identifying a 10-miRNA high-expression pattern (including miR-93, miR-138-5p, miR-200, miR-27a, miR-424, miR-34a, miR-28, miR-106b, miR-193a-3p and miR-181a) that was markedly higher in responders and associated with improved progression free survival (PFS) and OS (56).

Shukuya *et al* (51) identified 32 differentially down-regulated miRNAs in pretreatment plasma between responders and non-responders to anti-PD-1/PD-L1 therapy, finding that miR-21-5p, miR-200c-3p, and miR-28-5p were notably down-regulated in responders. A three-miRNA panel (miR-199a-3p, miR-21-5p, miR-28-5p) achieved an area under the curve (AUC) of 0.925 for response prediction, outperforming PD-L1 immunohistochemistry (AUC: 0.575) (51). Another cohort analysis of 51 patients with advanced NSCLC treated with nivolumab demonstrated that elevated serum levels of seven miRNAs (miR-215-5p, miR-411-3p, miR-493-5p, miR-494-3p, miR-495-3p, miR-548j-5p, and miR-93-3p) were associated with prolonged OS (57).

Grenda *et al* (58) demonstrated that higher plasma miR-126 expression was associated with longer PFS and OS in patients with advanced NSCLC receiving first-line immunotherapy or chemoimmunotherapy, suggesting its value as a predictive factor. The potential mechanisms underlying these associations are multifaceted: miRNAs can modulate immune checkpoint pathways, TME remodeling and immune cell activation. For example, miR-126 has been shown to inhibit the PI3K/AKT pathway crucial for regulatory T cell (Treg) function, while miR-200 and miR-34a regulate EMT and PD-L1 expression (58).

miRNAs in tumor tissue for predicting efficacy of ICIs in NSCLC. Studies have identified several tumor tissue miRNAs as potential predictive biomarkers. Zhu *et al* (59) identified the miR-505-3p/NET1 axis as a regulator of CD8+ T-cell infiltration and function, with high miR-505-3p expression associated with improved prognosis and increased CD8+ T-cell infiltration. Peng *et al* (60) showed that MIR155HG expression in tumor tissues is associated with immune cell infiltration and immune checkpoint molecules, with high expression associated with improved OS in lung adenocarcinoma (LUAD). miR-326 has been shown to negatively regulate CD155, a molecule implicated in immune evasion and ICI resistance, with high expression associated with lower CD155 levels and improved response to ICIs in LUAD (61).

The miR-23a/27a/24-2 cluster overexpression in NSCLC tissues upregulated PD-L1 and downregulated MHC-I, contributing to immune evasion and resistance to PD-1/PD-L1 blockade. Targeting the eIF3B pathway significantly enhanced anti-PD-1/PD-L1 efficacy in preclinical models (62). Additionally, miR-3127-5p was found to promote p-STAT3, leading to increased PD-L1 expression and chemoresistance in NSCLC (63).

Summary. Circulating miRNAs (plasma and EV-derived) represent the most extensively studied predictive biomarkers in NSCLC. A three-miRNA panel outperformed PD-L1 IHC (AUC 0.925 vs. 0.575). However, most studies are single-center with modest sample sizes (n=29-174), there is limited overlap in identified miRNAs across studies, no miRNA panel has been prospectively validated for patient stratification and the predictivity vs. prognosticity distinction has not been rigorously addressed. Evidence level: predominantly Tier 3 (single-cohort), with select candidates approaching Tier 2.

GC

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in GC. GC remains a notable global health challenge and predicting which patients will benefit from ICIs remains critical. Hua *et al* (64) identified plasma exosomal miR-451a and miR-142-5p as markedly upregulated in responders to PD-1 blockade combined with chemotherapy. These miRNAs were validated in an independent cohort by quantitative

(q)PCR and are involved in PI3K-AKT, MAPK and RAS signaling pathways (64).

Tang *et al* (65) demonstrated that exosomal miR-552-5p targets the PD-1/PD-L1 axis, leading to natural killer (NK) cell dysfunction. Increased plasma exosomal miR-552-5p levels were associated with downregulation of NK cell-activating receptors. Zhang *et al* (66) identified LINC01094 as a ceRNA sponging miR-17-5p, regulating PD-L1 and PD-L2 expression, contributing to an immunosuppressive TME in GC.

miRNAs in tumor tissue for predicting efficacy of ICIs in GC. In GC, miR-105-5p was identified as a key regulator of PD-L1 expression. This miRNA binds directly to the 3'UTR of PD-L1, leading to its downregulation and enhanced CD8+ T cell activation. The expression of miR-105-5p in GC tissues was controlled by DNA methylation of the CT-GABRA3 promoter (67). miR-BART5-5p, an Epstein-Barr virus (EBV)-encoded miRNA, was shown to target PIAS3, leading to PD-L1 upregulation through the PIAS3/pSTAT3 axis. High expression of miR-BART5-5p was associated with adverse clinical outcomes in patients with EBV-positive GC (68).

Shan *et al* (69) investigated the circSCUBE3/miR-744-5p/SLC7A5 axis regulating PD-L1 expression and immune evasion in GC. *In vivo* assays showed that circSCUBE3 attenuates the anti-tumor effect of PD-L1 inhibitors. Furthermore, miR-141-3p was found to be dysregulated in GC tissues resistant to anti-PD-1 therapy, promoting tumor progression and immune evasion by increasing CXCL12 expression (70).

Summary. Current GC evidence is largely derived from preclinical mechanistic studies and small clinical cohorts. miR-451a and miR-142-5p represent the most clinically advanced candidates with independent qPCR validation. Several identified miRNAs (miR-105-5p, miR-141-3p, miR-BART5-5p) have been characterized primarily through functional studies rather than clinical cohort validation. The EBV-encoded miR-BART5-5p is a unique virus-specific biomarker for EBV-positive GC. Evidence level: Predominantly Tier 3, with limited Tier 2 candidates.

Esophageal squamous cell carcinoma (ESCC)

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in ESCC. In ESCC, miR-199a-5p has been shown to be differentially expressed in plasma EVs derived from patients with varying responses to radiotherapy and immunotherapy combinations. Higher levels of miR-199a-5p were associated with increased radiosensitivity and improved response to anti-PD-1 therapy, potentially by targeting endonuclease/exonuclease/phosphatase family domain-containing protein 1, which is required for homologous recombination repair (71). Sudo *et al* (72) identified serum miRNA predictive markers for nivolumab response in a phase II trial (n=19). miR-1233-5p before treatment (AUC=0.895) and miR-6885-5p, miR-4698, and miR-128-2-5p after treatment (AUC=0.93-0.97) were associated with response.

miRNAs in tumor tissue for predicting efficacy of ICIs in ESCC. Jang *et al* (73) identified a risk assessment score (RAS) for recurrence-associated small non-coding RNA signature including miR-223, miR-1269a and nc886 that stratifies patients with ESCC into low- and high-risk groups. Low-RAS tumors exhibit elevated PD-L1 expression and immunogenic activity, associating with potential ICI responsiveness. Wang *et al* (74) identified tRF-3024b as a key factor in CTL resistance, functioning by sequestering miR-192-5p to increase BCL-2-mediated resistance to cytotoxic T lymphocytes. Han *et al* (75) investigated Liujunzi Decoction (a traditional Chinese medicine formula), finding it disrupted the IL-6-induced miR-34a/STAT3/IL-6R feedback loop and enhanced antitumor immunity by increasing IFN-γ and CD8+ TILs (75).

Summary. ESCC has the most limited clinical miRNA biomarker data among reviewed cancer types. The phase II trial (n=19) identified candidate serum miRNAs, but sample size is critically small without independent validation. Evidence level: Predominantly Tier 3 (exploratory).

Colorectal cancer (CRC)

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in CRC. In CRC, miR-125b-5p delivered via mesenchymal stem cell-derived exosomes can notably enhance anti-PD-1 therapy efficacy in mouse models by inhibiting FoxP3+ Treg expansion, thereby modulating the TME to favor antitumor immunity (76). Another preclinical study revealed that engineered tumor-derived EVs with modified miRNA profiles (such as miR-424 depletion) enhanced CRC immunogenicity and synergize with anti-PD-1 therapy in murine models (77).

miRNAs in tumor tissue for predicting efficacy of ICIs in CRC. miR-15b-5p, frequently downregulated in MSS CRC, directly suppresses PD-L1 via the IL-17A/P65/NRF1 axis. Low expression is associated with elevated PD-L1, reduced CD8+ T-cell infiltration, and poor prognosis (37). miR-497-5p targets CTLA-4 and PD-L1; miR-497-loaded nanoparticles downregulate CTLA-4 and synergize with anti-PD-1 therapy in preclinical models (78). miRNA clusters including miR-146b, miR-155 and miR-22 are enriched in high microsatellite instability (MSI-H) or tumor mutational burden tumors, associating with pro-inflammatory immune infiltration and improved ICIs response (79). Tumor-suppressive miRNAs (miR-140-3p, miR-148a-3p, miR-200 family) inhibit PD-L1 expression and oncogenic pathways. Targeted nanoparticle delivery systems offer potential strategies to overcome ICIs resistance in microsatellite stable (MSS) CRC (80).

Summary. CRC presents unique challenges due to biological differences between MSI-H and MSS subtypes. The critical gap lies in identifying miRNA biomarkers for MSS CRC where ICIs response rates are low. miR-15b-5p and miR-497-5p represent promising candidates, but clinical validation in ICI-treated MSS CRC cohorts is lacking. Evidence level: Predominantly Tier 3, with select Tier 2 candidates in MSI-H CRC.

Hepatocellular carcinoma (HCC)

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in HCC. Shen *et al* (81) used The Cancer Genome Atlas (TCGA) HCC cohort multi-omics analysis to identify miRNAs (miR-511-5p, miR-150-3p, miR-342-3p, miR-181a-3p, miR-625-5p, miR-155-5p and miR-142-5p/3p) linked to antitumor immunity as potential predictive biomarkers. Assal *et al* (82) found that miR-105-5p, miR-155-5p, miR-142-5p/3p, miR-30a-5p and miR-486-5p modulate PD-1/PD-L1 and CD155/TIGIT axes in HCC. miR-105-5p

demonstrated the strongest enhancement of PBMC-mediated HCC cell lysis.

miRNAs in tumor tissue for predicting efficacy of ICIs in HCC. miR-30-5p modulates the TME by targeting Snail, influencing DPP4 and CXCL10 expression. High levels were associated with favorable immune response and improved ICI outcomes (83). Ma *et al* (84) developed nanobubbles co-delivering miR-195 and Ce6 to enhance HCC immunotherapy, suppressing PD-1/PD-L1 interactions and augmenting cytotoxic T lymphocyte activity. Liu *et al* (85) engineered ultrasound-responsive nanobubbles co-loaded with PD-L1 antibody and miR-424 for dual PD-L1 blockade and gene regulation in HCC.

Summary. HCC has extensive mechanistic characterization of miRNA-mediated immune checkpoint modulation, but direct clinical cohort evidence remains sparse. TCGA-based multi-omics analyses require validation in ICI-treated cohorts. Nanobubble delivery systems remain preclinical. Evidence level: Predominantly Tier 3.

Breast cancer (BC)

Whole plasma and plasma EV miRNAs in predicting efficacy ICIs in BC. Plasma-derived miR-155, enriched in triple-negative breast cancer (TNBC), is associated with enhanced antitumor immunity and favorable prognosis, associated with increased CD8+ T-cell infiltration and chemokine production (CXCL9/10/11) (86). EV-packaged miR-20a-5p, overexpressed in TNBC plasma, suppresses CD8+ T-cell function by targeting nuclear protein ataxia-telangiectasia, impairing cytotoxicity and conferring resistance to anti-PD-1 therapy (87). Combined miR-338-3p/miR-501-3p profiles exhibit superior diagnostic accuracy (AUC: 0.89), suggesting predictive utility for ICI responsiveness (88). Selem *et al* (89) identified a let-7a/c-Myc/CCAT1/miR-17-5p axis modulating PD-L1 expression; silencing CCAT1 and restoring let-7a/miR-17-5p sensitized TNBC cells to atezolizumab (89).

miRNAs in tumor tissue for predicting efficacy of ICIs in BC. In estrogen receptor (ER)-positive BC, miR-18a overexpression activates Wnt signaling, promoting an immunosuppressive TME characterized by elevated Treg infiltration, higher CD4+/CD8+ ratio and M2 macrophage polarization (90). Conversely, miR-93-5p, miR-149-3p, miR-195/miR-497, miR-5119, miR-138-5p, miR-100-5p, miR-200a, miR-21-5p and miR-4443 enhance anti-tumor immunity. In which, miR-93-5p suppresses PD-L1, PD-L2 and B7-H6 expression, reducing immune evasion in TNBC, while miR-149-3p downregulates PD-1, TIM-3 and BTLA, augmenting CD8+ T-cell cytotoxicity. Tumor tissue analyses in TCGA and METABRIC cohorts reveal that high miR-93-5p and miR-149-3p levels is associated with improved survival and favorable immune infiltrates, including increased cytotoxic T lymphocytes and reduced Tregs. Furthermore, miR-138-5p and miR-5119 modulate PD-L1 and IDO2, respectively, synergizing with ICIs to enhance tumor immunogenicity (91). miR-214-3p inhibits BC cell proliferation and enhances the tumor immune microenvironment by downregulating B7H3 (92). miR-424-5p, miR-138-5p, miR-570-3p, miR-200c-3p, miR-383-5p, miR-34a-5p, miR-3609, miR-195-5p, and miR-497-5p inhibit PD-L1 expression and regulate oncogenic pathways in TNBC, with single-cell sequencing-guided biomimetic delivery offering personalized therapy approaches (93).

Summary. The strongest evidence is concentrated in TNBC. Plasma-derived miR-155 and EV-packaged miR-20a-5p are the most clinically advanced circulating candidates. Evidence in ER-positive BC is considerably weaker. miRNA biomarker development must account for substantial inter-subtype heterogeneity. Evidence level: Predominantly Tier 3, with select candidates approaching Tier 2 in TNBC.

Melanoma

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in melanoma. Bustos *et al* (94) identified miR-615-3p and miR-4649-3p in plasma as potential biomarkers for monitoring ICI response in metastatic melanoma. miR-615-3p levels decreased in patients achieving a complete response, while miR-4649-3p levels increased in non-responders. Ruggiero *et al* (95) found that the ratio of circulating miR-4488 to miR-579-3p was a notable predictor of PFS in BRAF-mutant melanoma.

Nguyen *et al* (96) reviewed certain miRNAs predicting immunotherapy outcomes in melanoma, including let-7e, miR-99b, miR-125a, miR-125b and miR-146b, which have shown potential as predictive biomarkers for the response of patients with melanoma to MAPK inhibitors. In melanoma, several circulating and tissue miRNAs have been specifically associated with ICI response. In pretreatment serum from patients with melanoma receiving anti-PD-1 therapy, miR-16-5p, miR-17-5p and miR-20a-5p were approximately two-fold higher in responders than in non-responders (97). Serum exosomal miR-532-5p and miR-106b were associated with reduced pembrolizumab response (98). In the context of anti-CTLA-4 therapy, miR-222 was the only miRNA differentially expressed between ipilimumab responders and non-responders; its overexpression downregulates ICAM1 via the ADAR1 axis, impairing T-cell-mediated tumor killing (96). A circulating cell-free miRNA panel, including miR-615-3p, miR-1234-3p and miR-4649-3p, outperformed lactate dehydrogenase in monitoring checkpoint inhibitor response in stage IV melanoma (94). By contrast, miR-155 is not melanoma-specific but was included in an eight-miRNA tumor-derived panel that predicted resistance to both ipilimumab and nivolumab by inducing myeloid-derived suppressor cells (99). With the exception of miR-155, the aforementioned miRNAs have been validated primarily in melanoma cohorts; whether their predictive value extends to other cancers remains to be determined (95).

miRNAs in tumor tissue for predicting efficacy of ICIs in melanoma. Sloane *et al* (100) identified miR-100-5p and miR-125b-5p as central to miRNA-mRNA networks in the microphthalmia-associated transcription factor (MITF)-low melanoma subset, associated with improved OS on anti-PD-1 therapy (100). Another study by Kobeissi *et al* (101) discovered a 4-miRNA signature (miR-34c, miR-711, miR-641 and miR-22) that was notably associated with improved relapse-free survival after neoadjuvant ipilimumab in patients with melanoma. Functional annotation analysis revealed that these miRNAs were involved in various cancer-related pathways, including cell proliferation regulation, apoptosis and T cell activation.

Summary. Despite melanoma being the first cancer type to establish ICI efficacy, miRNA biomarker research is less advanced than expected. The 4-miRNA and MITF-low signatures require external validation. The miRNA ratio approach represents a methodological innovation. Evidence level: Predominantly Tier 3.

RCC

Whole plasma and plasma EV miRNAs in predicting efficacy of ICIs in RCC. Ivanova *et al* (102) evaluated exosomal miRNAs (miR-144, -146a, -149, -126, and -155) in 35 patients with clear cell RCC (ccRCC) before and after ICI therapy. miR-146a levels increased after therapy, whereas miR-126 decreased. The combined AUC for miR-146a and miR-126 was 0.752, with a sensitivity of 64.3% and specificity of 78.9%. Incorvaia *et al* (103) identified a lymphocyte miRNA signature (miR-22, miR-24, miR-99a, miR-194, miR-214, miR-335, miR-339 and miR-708) that was markedly induced in long-responder patients (PFS >18 months). miR-22 and miR-24 levels were inversely associated with plasma soluble PD-1 and PD-L1 levels.

miRNAs in tumor tissue for predicting efficacy of ICIs in RCC. Qu *et al* (104) confirmed that miR-497-5p downregulation is associated with PD-L1 upregulation in ccRCC tissues. Analysis of TCGA- kidney renal clear cell carcinoma (KIRC) dataset linked miR-497-5p downregulation to shorter patient survival. *In vitro* experiments validated PD-L1 as a direct target of miR-497-5p. In addition, research by Peng *et al* (60) showed that elevated MIR155HG is linked to inferior OS in KIRC and is associated with immune cell infiltration and checkpoint molecule expression (60).

Summary. The lymphocyte miRNA signature represents one of the few studies examining miRNAs specifically in immune cells. miR-146a has dual associations with ICI efficacy and irAE severity. Tissue-based miR-497-5p requires clinical correlation in ICI-treated cohorts. Evidence level: Predominantly Tier 3, with lymphocyte signature at Tier 2.

Cross-cancer analysis of miRNA biomarker patterns

miRNAs with reproducible cross-cancer predictive signals. A key strength of the present review is identifying miRNA candidates with consistent associations across multiple cancer types. miR-155-5p is associated with favorable ICI response across NSCLC, CRC, HCC, BC, melanoma and RCC (60), consistently linked to enhanced CD8+ T-cell infiltration and pro-inflammatory cytokine production. Its host gene *MIR155HG* was independently identified as a prognostic indicator across LUAD and KIRC. Tier 1 candidate (validated in ≥3 cancer types). miR-21-5p shows context-dependent associations- upregulated in tumor tissues and associated with ICI resistance in BC and NSCLC (51); however, it is differentially associated with response in some plasma-based studies, underscoring the importance of sample source and cellular origin. Tier 1 candidate with context-dependent directionality. miR-146a-5p demonstrates consistent cross-cancer patterns through negative regulation of NF-κB signaling (23,31,32), by targeting TRAF6 and IRAK1, a mechanism reported in melanoma, NSCLC, GC and HCC, where it dampens innate immune activation and influences ICI response, with the rs2910164 single-nucleotide polymorphism (SNP) providing clinical evidence linking lower expression to both increased severe irAE risk and diminished PFS [hazard ratio (HR)=1.8]. Tier 1 candidate for irAE prediction; Tier 2 for efficacy. miR-200 family members (miR-200a-3p, miR-200b-3p, miR-200c-3p) are consistently associated with ICI response across NSCLC, CRC and BC through EMT regulation and PD-L1 modulation (19,40,41). By contrast, most identified miRNAs are cancer-type-specific and reported in only a single study (for example miR-BART5-5p in EBV-positive GC, miR-552-5p in GC, miR-6885-5p in ESCC), classified as Tier 3.

Common regulatory mechanisms and comparative utility. Several common regulatory themes emerge: i) PD-L1/PD-1 axis modulation is the most frequently reported mechanism across all eight cancer types; ii) CD8+ T-cell infiltration and function-miRNAs enhancing cytotoxic T lymphocyte recruitment consistently associate with favorable outcomes; iii) EMT pathway regulation-miR-200 family and miR-34a link EMT status to ICI sensitivity; and iv) epigenetic-immune crosstalk. Comparing circulating vs. tissue-derived miRNAs, circulating miRNAs offer non-invasive accessibility enabling longitudinal monitoring and have demonstrated superiority over PD-L1 IHC in one study, but are limited by unknown cellular origin and lack of standardized pre-analytical protocols. Tissue miRNAs offer tumor-intrinsic mechanistic resolution but require invasive biopsy and are susceptible to spatial heterogeneity. An integrated approach combining both sources with ctDNA and protein biomarkers may provide the most comprehensive framework.

Evidence tier summary. Based on cross-cancer analysis: Tier 1 (≥2 independent cohorts in ≥2 cancer types): miR-155-5p, miR-21-5p, miR-146a-5p, miR-200 family; Tier 2 (validated in single cancer type with independent cohort): miR-320d/c, miR-625-5p in NSCLC; miR-451a, miR-142-5p in GC; miR-93-5p, miR-149-3p in BC; lymphocyte miRNA signature in RCC; Tier 3 (single cohort, exploratory or purely mechanistic): the majority of remaining candidates. This classification highlights both the progress made and the substantial validation gap that must be addressed before clinical deployment.

5. miRNAs in predicting irAEs

ICIs have revolutionized cancer therapy by enhancing the immune system's ability to target cancer cells. However, this heightened immune activation can also lead to irAEs affecting various organ systems. The ability to predict which patients are at higher risk of developing severe irAEs is crucial for optimizing treatment strategies. Studies have highlighted the potential role of miRNAs as predictive biomarkers for irAEs. Table II synthesizes miRNA data related to irAEs.

Organization of irAEs by organ system. ICI-induced irAEs can affect virtually any organ system. The spectrum includes dermatologic (30-50%), gastrointestinal (diarrhea/colitis; 10-30%), hepatic (5-20%), endocrine (5-15%), pulmonary (3-10%), and less commonly, cardiac (myocarditis; <1% but high mortality), renal (1-5%), neurologic and musculoskeletal events. The present section reviewed miRNA evidence organized by organ system (10-12).

Multisystem irAEs. To the best of our knowledge, miR-146a-5p is the most extensively validated miRNA for

irAE risk. Marschner *et al* (105) demonstrated in miR-146a-deficient mice and a clinical cohort of 167 patients (mainly including those with melanoma and lung cancer) who were ICI-treated that the MIR146A rs2910164 SNP, associated with reduced miR-146a expression, was associated with increased incidence of severe irAEs affecting lungs, liver, colon and skin and diminished PFS (HR=1.8). Therapeutic delivery of miR-146a mimics attenuated autoimmune manifestations without compromising antitumor efficacy. Evidence level: Tier 2 (clinical cohort + mechanistic validation). In patients with RCC, Ivanova *et al* (102) performed longitudinal reverse transcription-qPCR of five immunomodulatory miRNAs in 35 patients with ccRCC receiving nivolumab. miR-146a increased post-therapy while lower miR-146a was associated with higher-grade irAEs across skin events, pneumonitis, colitis, endocrine events, pancreatitis, hepatitis, nephritis, myalgia and joint pain. The combined miR-146a/miR-126 panel achieved AUC 0.752. Evidence level: Tier 3.

Cardiac irAEs. ICI-related myocarditis has a fatality rate approaching 50%. Xia *et al* (106,107) elucidated a miR-34a-5p-driven mechanism in a murine model: PD-1 blockade triggered macrophage miR-34a overexpression, which suppressed KLF4, driving M1 macrophage polarization and cardiac dysfunction. Consistently, PD-1 inhibitor-treated macrophages released miR-34a-5p-enriched exosomes taken up by cardiomyocytes, suppressing PNUTS and accelerating cellular senescence. These findings position miR-34a-5p as a mechanistic driver and candidate risk marker for ICI cardiotoxicity. Notably, the Phase I trial of MRX34, a miR-34a nanoliposomal formulation, was terminated after five immune-mediated serious adverse events, including four fatalities among 85 patients; however, these events were cytokine release syndrome with respiratory failure and neurological manifestations, not cardiac toxicity (49). Whether this broader immune-activation liability is relevant to endogenous miR-34a blockade in the ICI setting remains unknown. The evidence supporting miR-34a-5p as a predictive biomarker for ICI myocarditis therefore remains at the preclinical level (tier 3), pending clinical cohort validation.

Temporal considerations in miRNA-Based irAE prediction. We propose a three-timepoint framework: i) Baseline (pre-treatment), miRNAs for irAE risk stratification the rs2910164 SNP exemplifies this approach; ii) early on-treatment (within 4-6 weeks), dynamic miRNA changes (ΔmiRNA) during the critical irAE manifestation window. The longitudinal study by Ivanova *et al* (102) suggest ΔmiRNA may carry superior predictive information compared with static measurements; and iii) at irAE onset, miRNAs to distinguish immune-related toxicity from other causes of clinical deterioration (infection, tumor progression). No miRNA panel has been validated for this diagnostic application, representing a high-priority knowledge gap.

Dual regulatory roles of key miRNAs in ICI efficacy and toxicity. Several core miRNAs, notably miR-146a, miR-34a and miR-21, are implicated in both antitumor efficacy and immune-related toxicity. In the TME, moderate miR-146a expression facilitates balanced antitumor immunity by preventing NF-κB-driven T-cell exhaustion. In normal tissues, reduced activity unleashes unchecked inflammatory responses manifesting as multi-organ irAEs. The rs2910164 SNP creates a miR-146a 'therapeutic window' concept, levels sufficient to prevent autoimmunity but not so high as to suppress antitumor immunity. miR-34a displays the most notable tissue-dependent duality. In tumor cells, it suppresses PD-L1 through p53-dependent pathways, whereas in cardiac and pulmonary tissue, ICI-induced macrophage overexpression drives M1 polarization and tissue destruction. Systemic supplementation carries inherent toxicity risk, as demonstrated by the MRX34 trial. Future strategies require tumor-targeted delivery. In tumor cells, miR-21-5p promotes EMT and immune evasion through PDCD4 downregulation, associated with ICI resistance. In Tregs and MDSCs, it contributes to immune homeostasis. The net effect depends on dominant cellular source, tumor type, and ICI regimen, highlighting the need for cell-type-specific profiling. These dual roles imply: i) Single miRNA measurements may simultaneously convey efficacy and toxicity information; ii) miRNA ratios (miR-146a/miR-34a) may be more informative than individual levels; iii) cell-type-specific profiling could deconvolve efficacy and toxicity signals; and iv) the miRNA-defined therapeutic window should be incorporated into prospective studies.

Comparison with other emerging irAE biomarkers. Peripheral blood immune cell subsets provide direct cellular resolution but require fresh blood processing and flow cytometry expertise; miRNAs offer superior stability in archived biospecimens. Serum cytokines (IL-6, IL-17, TNF-α) are measurable in stored samples but exhibit diurnal variation and short half-lives (13,75). Autoantibodies are associated with organ-specific irAEs but have modest positive predictive value for individual patients. Gut microbiome composition provides a modifiable biomarker but requires specialized metagenomic sequencing. miRNAs offer a unique combination of advantages, biofluid stability, multi-target regulatory information, compatibility with existing PCR platforms and measurability in baseline and longitudinal samples. However, no miRNA has demonstrated sufficient standalone predictive accuracy for clinical irAE risk stratification, and combinatorial approaches with other biomarker classes warrant active investigation (14).

6. Challenges in translating miRNA biomarkers into clinical practice

The translation of miRNA biomarkers from preclinical research to routine clinical practice faces several notable challenges. A primary obstacle is the heterogeneity of miRNA expression across different tumor types and even within the same cancer type. miRNAs such as miR-21 and miR-155 have both tumor-suppressive and oncogenic roles depending on cellular context, complicating universal biomarker development. Additionally, the dynamic nature of miRNA expression, influenced by TME, genetic mutations and epigenetic modifications, further complicates their use as stable biomarkers (23). Another challenge is the lack of standardized methodologies for miRNA detection and quantification. Variability in sample collection, processing and analysis can lead to inconsistent results across studies (108).

Table II. miRNAs associated with irAEs in ICI therapy.

Organ system	irAE type	miRNA(s)	Expression	Sample	ICI	Key association	(Refs.)
Multisystem	Lung, liver, colon, skin multi-organ injury	miR-146a-5p	Down (rs2910164 SNP)	Blood (genotype)	anti-PD-1/CTLA-4	rs2910164 C allele -> reduced miR-146a -> increased severe irAE; decreased PFS; miR-146a mimic attenuated autoimmunity in mice. C+M, T2	(105)
Multisystem	9 irAE categories (skin, lung, gastrointestinal, endocrine, pancreas, liver, renal, muscle, joint)	miR-146a-5p, miR-126-3p	miR-146a up post-treatment; miR-126 down post-treatment	Plasma EV	anti-PD-1/PD-L1 (nivolumab)	Lower miR-146a -> higher-grade irAE; combined AUC 0.752 (sensitivity 64.3%, specificity 78.9%, n=35 ccRCC). C, T3	(102)
Cardiac	Myocarditis (reduced LVEF, impaired contractility)	miR-34a-5p	Up (PD-1 blockade-induced in macrophages)	Cardiac tissue/EV	anti-PD-1	Macrophage miR-34a -> KLF4 down -> M1 polarization -> cardiac dysfunction; exosomal miR-34a -> cardiomyocyte PNUTS down -> senescence. M, T3	(106,107)
Cardiac	MRX34 trial: systemic miR-34a toxicity	miR-34a-5p	Up (exogenous nanoliposomal)	Systemic	N/A (miR-34a drug)	Phase I terminated: 3/85 fatalities from immune toxicity; indirect clinical evidence of miR-34a systemic toxicity. T, T3	(49)
Pulmonary	Pneumonitis, ARDS, fatal pneumonitis	miR-34a-5p	Up	Clinical associative/ mouse lung	anti-PD-1	Pathological association with severe/fatal pneumonitis; shared macrophage polarization mechanism with cardiac toxicity. C+M, T3	(49,106)
Dermatologic	Rash, pruritus (most common irAE, 30-50%)	None specifically validated	N/A	N/A	N/A	Most common irAE but least studied; miR-146a/miR-126 multisystem studies include skin events within	(102,105)

Table II. Continued.

Organ system	irAE type	miRNA(s)	Expression	Sample	ICI	Key association	(Refs.)
						broader irAE categories. Knowledge gap.	
Gastrointestinal	Colitis, diarrhea	miR-146a-5p	Included in multisystem panels	Blood (genotype)	anti-PD-1/ CTLA-4	Colitis included within multi-organ irAEs in Marschner *et al* (n=167); no GI-specific miRNA validated. C, T3	(105)
Hepatic	Hepatitis	miR-146a-5p, miR-126-3p	Included in multisystem panels	Plasma EV	anti-PD-1/PD-L1	Hepatitis included within 9-category irAE assessment (n=35); organ-specific miRNA data not separately reported. C, T3	(102)
Endocrine	Thyroiditis, hypophysitis, adrenalitis	miR-146a-5p, miR-126-3p	Included in multisystem panels	Plasma EV	anti-PD-1/PD-L1	Endocrine events within irAE spectrum; no organ-specific miRNA validation. C, T3	(102)
Renal	Nephritis	miR-146a-5p, miR-126-3p	Included in multisystem panels	Plasma EV	anti-PD-1/PD-L1	Nephritis within irAE assessment; no renal-specific miRNA validation. C, T3	(102)
Musculoskeletal	Myalgia, joint pain	miR-146a-5p, miR-126-3p	Included in multisystem panels	Plasma EV	anti-PD-1/PD-L1	Myalgia/joint pain within irAE spectrum; no musculoskeletal-specific miRNA validation. C, T3	(102)

Organized by organ system. Notation: up arrow=higher, down arrow=lower miRNA expression. Evidence source: C=Clinical cohort, M=Mouse model, T=Clinical trial. Tiers: T1=reproducible ≥2 cohorts; T2=single cohort + mechanistic validation; T3=exploratory/preclinical. Key observations: i) The irAE miRNA literature is dominated by miR-146a-5p and miR-34a-5p; ii) strongest clinical evidence exists for miR-146a (T2); iii) miR-34a cardiac toxicity data derive from murine models; iv) organ-specific miRNAs for individual irAE types are essentially nonexistent; v) No miRNA has been validated for distinguishing irAEs from other causes of deterioration; and vi) compared with efficacy biomarkers (Table I), the irAE literature is substantially smaller, representing a knowledge gap warranting prioritized investigation. miRNA, micro RNA; NR, not reported; EV, extracellular vesicle; irAEs, immune-related adverse events; PD-1, programmed cell death protein 1; PDL-1, PD-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ARDS, acute respiratory distress syndrome; SNP, single nucleotide polymorphism; PFS, progression free survival; ccRCC, clear cell renal cell carcinoma; AUC, area under the curve; LVEF, left ventricular ejection fraction.

Differences in the extraction methods for miRNAs from plasma or tissue samples can markedly affect measured levels, potentially leading to erroneous conclusions about their predictive value (109). Moreover, the limited availability of large-scale, well-annotated cohorts for validation studies hampers robust biomarker assessment. The majority of current studies are limited by small sample sizes and lack of independent validation sets, raising concerns about generalizability.

Pre-analytical variability. Key pre-analytical factors include: i) Biospecimen type such as plasma vs. serum. serum

contains platelet-derived miRNAs released during coagulation (current consensus favors platelet-depleted plasma); ii) anticoagulant selection, heparin inhibits PCR-based assays and should be avoided; iii) processing time, standardization to within 2 h of venipuncture is recommended; iv) freeze-thaw cycles degrade miRNA integrity; v) hemolysis releases erythrocyte-enriched miRNAs (miR-451a, miR-16-5p), confounding circulating measurements; and iv) normalization strategy, the lack of consensus reference miRNAs is a major barrier to cross-study comparability, commonly used endogenous controls (U6, miR-16-5p, miR-451a) are themselves regulated in cancer and immune activation. Adoption of MIQE guidelines adapted for circulating miRNAs is recommended but not widely practiced in ICI biomarker literature (110).

Detection platform inconsistency. Reverse transcription-qPCR offers highest sensitivity and widest clinical availability but is limited to pre-selected candidates. Small RNA-sequencing provides the broadest dynamic range and novel miRNA discovery but is more expensive with non-standardized bioinformatics pipelines. Microarrays offer intermediate throughput but suffer from cross-hybridization and limited dynamic range. Inter-platform concordance is often poor. Emerging digital PCR platforms offer absolute quantification without standard curves, potentially addressing a key standardization barrier (111,112).

Patient stratification confounders. Patient-level variables that may confound miRNA associations include: i) Tumor stage and disease burden; ii) treatment regimen, ICI monotherapy vs. combination with chemotherapy, radiotherapy or targeted therapy; iii) prior lines of therapy having durably altered circulating miRNA landscapes; iv) comorbidities, including autoimmune diseases, chronic viral infections, metabolic syndrome and renal impairment; and v) concomitant medications such as corticosteroids, antibiotics and proton pump inhibitors. Most published ICI miRNA biomarker studies have not systematically accounted for these confounders, and multivariable analyses incorporating clinical covariates are critically needed.

Biological heterogeneity. Biological sources of variability include: i) Inter-individual genetic variation such as SNPs within miRNA genes, promoters or miRNA-binding sites (the rs2910164 SNP being the most clinically advanced example); ii) epigenetic regulation, DNA methylation and histone modifications at miRNA promoters (such as CT-GABRA3 promoter controlling miR-105-5p in GC); iii) microbiome influence, gut microbiota modulates host miRNA expression; and iv) intra-tumor heterogeneity, single-biopsy miRNA profiling may not capture the full spectrum of miRNA dysregulation. These biological factors must be systematically accounted for to advance miRNA biomarkers toward clinical utility.

The clinical utility of miRNA biomarkers is also impacted by the complexity of their biological roles. miRNAs often regulate multiple pathways, making it challenging to isolate their specific impact on ICI efficacy or irAEs. For example, miR-146a has been implicated in both enhancing ICI efficacy and causing irAEs (105). This dual role highlights the need for a nuanced understanding of miRNA biology. Finally, the integration of miRNA biomarkers into clinical decision-making requires overcoming regulatory and logistical hurdles, including development of standardized protocols, validation in diverse patient populations, establishment of clear clinical guidelines, and ensuring cost-effectiveness and accessibility (113).

7. Conclusion and future directions

The advent of ICIs has markedly altered cancer therapy. However, heterogeneous patient responses and unpredictable irAEs remain the principal clinical challenges. The present review comprehensively examined miRNA evidence across eight major cancer types, synthesizing both circulating and tissue-based data.

miRNAs hold considerable promise as predictive biomarkers. miR-155-5p, miR-21-5p, miR-146a-5p and miR-200 family members have been reproducibly associated with ICI outcomes across multiple cancer types (Tier 1). Circulating miRNAs have demonstrated capacity to outperform PD-L1 IHC in NSCLC; however, a candid assessment reveals a substantial gap between exploratory studies and clinically deployable biomarkers. Prospective validation is almost entirely absent; no miRNA has been prospectively validated in a randomized ICI trial. Assay standardization from collection through normalization is lacking. Cross-tumor-type reproducibility is the exception. The predictive vs. prognostic distinction remains insufficiently addressed, as most studies lack ICI-untreated control arms (114,115).

We propose a pragmatic translational roadmap: Stage 1 (immediate), retrospective validation of Tier 1/2 candidates in existing clinical trial cohorts with standardized assays. Stage 2 (3-5 years), prospective observational studies with pre-specified miRNA panels. Stage 3 (5-10 years), randomized trials incorporating miRNA status as stratification factor. Stage 4 (>10 years), regulatory approval and routine deployment. The field currently resides at Stage 1.

Several cutting-edge directions merit prioritized investigation. Multi-omics integration, combining miRNAs with PD-L1, TMB, MSI, ctDNA and immune infiltration profiles, is likely to yield superior predictive accuracy. Machine learning on multi-dimensional datasets offers a path toward clinically actionable composite scores. Longitudinal dynamic monitoring capturing miRNA kinetics (ΔmiRNA) may provide richer pharmacodynamic information than static baseline measurements. Cell-type-specific miRNA profiling through surface-marker-based EV capture could resolve cellular origin ambiguity. Tumor-targeted miRNA delivery systems that achieve therapeutic intratumoral concentrations while avoiding systemic toxicity could open the door to miRNA-based therapeutic strategies synergizing with ICIs.

In conclusion, miRNAs represent a scientifically compelling and clinically promising class of predictive biomarkers for ICI therapy, with the potential to simultaneously guide efficacy optimization and toxicity mitigation. However, the path from exploratory evidence to routine clinical implementation requires concerted effort across assay standardization, prospective validation, multi-omics integration

and regulatory engagement. The field should neither overstate current evidence maturity nor underestimate the transformative potential of miRNA-based precision immunotherapy tools if remaining translational barriers can be systematically addressed.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Technology Innovation Leading Program of Shaanxi (grant no. 2023KXJ-095), the Basic Research Project of Natural Science of Shaanxi Province (grant no. 2025JC-YBMS-928), the Research Project of Chinese Society of Clinical Oncology-Sai Sheng Fund (grant no. Y-2020Sciclone/qn-0181), Xi'an Association for Science and Technology Young Talent Lifting Program project (grant no. 959202413009), the Shaanxi Provincial People's Hospital Science and Technology Talent Support Program for Leading Talents (grant no. 2022LJ-06) and the Shaanxi Provincial People's Hospital Science and Technology Development Incubation Foundation (grant no. 2023YJY-39).

Availability of data and materials

Not applicable.

Authors' contributions

XW conceived the topic of study. XW, BD, JB and HL reviewed the literature and co-wrote the manuscript. XW wrote and prepared the draft of the manuscript. HL supervised the present review and provided key revisions. All authors contributed to manuscript revision, and read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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