Role of tumor-infiltrating lymphocytes and miR-155 in breast cancer: Insights into carcinogenesis and their potential as prognostic biomarkers (Review)

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Received March 14, 2025; Accepted May 9, 2025

DOI: 10.3892/or.2026.9047

Abstract. Breast cancer is the most common cancer in the female population worldwide. The present review examines the biology of breast cancer, with a focus on the interplay between tumor-infiltrating lymphocytes (TILs) and microRNAs (miRNAs or miRs). TILs, which reflect the immune system activity in combating tumors, are associated with more favorable prognoses and positive response to therapies. Elevated levels of TILs characterize lymphocyte-predominant breast cancers (LPBCs), which are associated with higher therapeutic response rates in triple-negative breast cancer, a type of LPBC. Defining the threshold for LPBCs presents a challenge: TIL levels ≥50% are associated with short-term pathological complete response as well as long-term overall and disease-free survival; however, this percentage is not often achieved in clinical practice. Conversely, a lower threshold of 30% lymphocyte infiltration can predict favorable prognosis for anticancer therapy and allows for the identification of a broader range of patients. The tumor inflammatory landscape is regulated by miRNAs, particularly miR-155. Elevated levels of miR-155 are associated with the presence of TILs and a favorable inflammatory profile, leading to a tumor-inflamed microenvironment. Moreover, miR-155 is associated with various antitumoral immune cells, including $CD8^+$ T cells and M1 macrophages, but negatively associated with pro-tumoral regulatory T cells and M2 macrophages. Overexpression of miR-155 results in an increase in the levels of the C-X-C chemokine ligands, constituted by two conserved cysteines separated by a different amino acid which bind to the same chemokine receptor CXC chemokine receptor 3. These results in activation of T cells a process that involves the inhibition of suppressor of cytokine signaling 1 and an elevated ratio of phosphorylated STAT1/STAT3. Additionally, miR-155 affects key signaling pathways, including the PI3K/AKT and IL-6/STAT3 pathways, and increases sensitivity to immune checkpoint blockade therapy. In clinical samples from patients with BC, serum levels of miR-155 align with both tumor miR-155 levels and the immune status of the tumor. The present review emphasizes the importance of understanding the dynamics between TILs and miRNAs to identify new prognostic and predictive biomarkers, proposing a more integrated and personalized approach in the management of BC.

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Key words: tumor-infiltrating lymphocyte, biomarker, microRNA-155, triple-negative breast cancer

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1. Introduction

It is estimated that one in four people will develop cancer at some point in their lives. Cancer is the first or second leading cause of premature death in many countries, with deaths occurring before the age of 70 years. In the female population, the incidence and mortality from breast cancer are increasing rapidly worldwide, with one in five women being diagnosed with breast

cancer during their lifetime (1). An estimated 43,170 deaths from breast cancer are expected worldwide in 2023 (2).

Understanding tumor biology is essential to elucidate the reasons behind the high incidence of cancer worldwide, especially breast cancer. Detailed analysis of tumor pathophysiology allows us to identify the cellular and molecular processes that contribute to the development and progression of cancer (3-5). Furthermore, this knowledge is crucial for identifying biological markers that may influence cancer progression, enabling the formulation of more effective diagnostic and therapeutic strategies (6-9). microRNA (miRNA or miR), a post-transcriptional gene modulating non-coding small molecule, can target multiple genes, and is key to tumorigenic progression and immune response (10-12).

In patients with breast cancer, altered miRNAs are linked to different tumor hallmark pathways including the presence of Tumor infiltrating lymphocytes (13,14). Among the different types of biomarkers the microRNAs are a strong candidate to be incorporated into the clinical workflow, due to their stability in the body fluids used for diagnostic analysis, making them attractive biological entities (15,16). Moreover, by investigating the miRNAs that trigger and sustain tumor growth, may facilitate development of targeted interventions that aim to improve clinical outcomes and increase patient survival (17). miR-155 has been linked to tumor biology in breast cancer and immune response such as the presence or absence of TILs, demonstrating the strong interplay in tumour biology (18-20).

In the present review, we appraised the current understanding of the miRNAs 155 and TILs in the breast cancer context, more specifically the Triple-Negative subtype. TNBC, presents, gene expression profiling with intrinsic subtypes of female breast cancer, which may correspond to distinct etiological pathways and hold significant therapeutic implications, and impact mortality risk (21).

2. BC biology and classification

Tumor biology and pathological characteristics. The mammary parenchyma comprises ductal epithelium organized in a bilayer arrangement: The luminal epithelial layer comprises cuboidal or columnar cells and the basal layer contains contractile myoepithelial cells. The stromal component is composed of connective tissue, blood vessels and neural elements (22). While tumors of non-epithelial origin, such as sarcomas or skin tumors, can arise in the breast, these cases are rare and not classified as BC despite their anatomical location (23).

On macroscopic pathological examination, lesions manifest as firm, grayish white, gritty masses that randomly invade the surrounding tissue, resulting in an irregular formation, termed stellate configuration. Microscopically, the lesions demonstrate cords and nests of tumor cells with cytological features ranging from indolent to highly malignant. As the malignant cells infiltrate the mammary stroma and adipose tissue, they induce a fibrotic response, frequently producing a clinically palpable mass with radiological density and solid ultrasonographic characteristics typical of invasive carcinoma (24,25).

Invasive ductal carcinoma represents the most common type of BC, accounting for 40-70% of cases. Other histological subtypes include invasive lobular carcinoma (5-15%), apocrine carcinoma (4%), mucinous carcinoma (2%), tubular carcinoma (1.6%), micropapillary carcinoma (0.9-2.0%), metaplastic carcinoma (0.2-1.0%) and cribriform carcinoma (0.4%). Invasive ductal carcinoma is also referred to as invasive carcinoma of no special type or invasive carcinoma not otherwise specified (4).

Certain invasive lobular carcinomas exhibit macroscopic features similar to those of invasive ductal carcinoma. Consequently, immunohistochemical analysis is necessary to evaluate the expression of E-cadherin protein, which mediates epithelial cell adhesion. This protein demonstrates positive expression in ductal tumors while being characteristically absent in lobular neoplasms (26).

Invasive carcinomas are classified into three distinct grades based on a comprehensive evaluation of architectural and cytological features. This classification is performed using a standardized scoring system that reflects the degree of cell differentiation (Fig. 1) (27). Histological analysis at the molecular level is key to grading invasive carcinoma.

Histopathological classification. The histological classification of BC is key for tumor characterization (Table I). Moreover, molecular markers serve a pivotal role in guiding appropriate therapeutic strategies. The molecular classification system developed by Perou *et al* (28) remains widely implemented in contemporary clinical practice.

The diverse spectrum of BC encompasses distinct molecular subtypes, exhibiting specific characteristics that guide therapeutic strategies. Consequently, all newly diagnosed BC must undergo immunohistochemistry (IHC) to identify the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This molecular characterization provides essential information for both prognostic assessment and therapeutic decision-making (Table II) (29).

A tumor is considered positive for ER and PR when these receptors are present in >1% of tumor cells, representing ~80% of BC cases (30). HER2 upregulation occurs in 15-20% of patients and is characterized by intense membrane staining in >10% of invasive tumor cells (IHC 3+) or by HER2 gene amplification, determined through fluorescence in situ hybridization (FISH), with a HER2/chromosome 17 centromeric probe ratio ≥2.0 and ≥4 HER2 copy signals/cell. Tumors that do not express any of these factors are classified as triple-negative (TN)BC, corresponding to 10-15% of cases (31).

Hormone receptor-positive (HR^+) tumors. Tumors that test positive for the hormone receptors estrogen (ER) or progesterone (PR) are classified as hormone receptor-positive (HR+) and are typically categorized as luminal subtypes, according to Perou *et al* (28). The receptors are located in target cells and serve as ligand-dependent transcription factors. When estrogen or an estrogen analog bind ER in the cell nucleus, a conformational change occurs in the binding domain, enabling interactions with coactivators if the ligand is an agonist and blocking these interactions if it is an antagonist, thereby affecting the transcription rates of estrogen-responsive genes (32).

The updated American Society of Clinical Oncology/College of American Pathologists guidelines established that

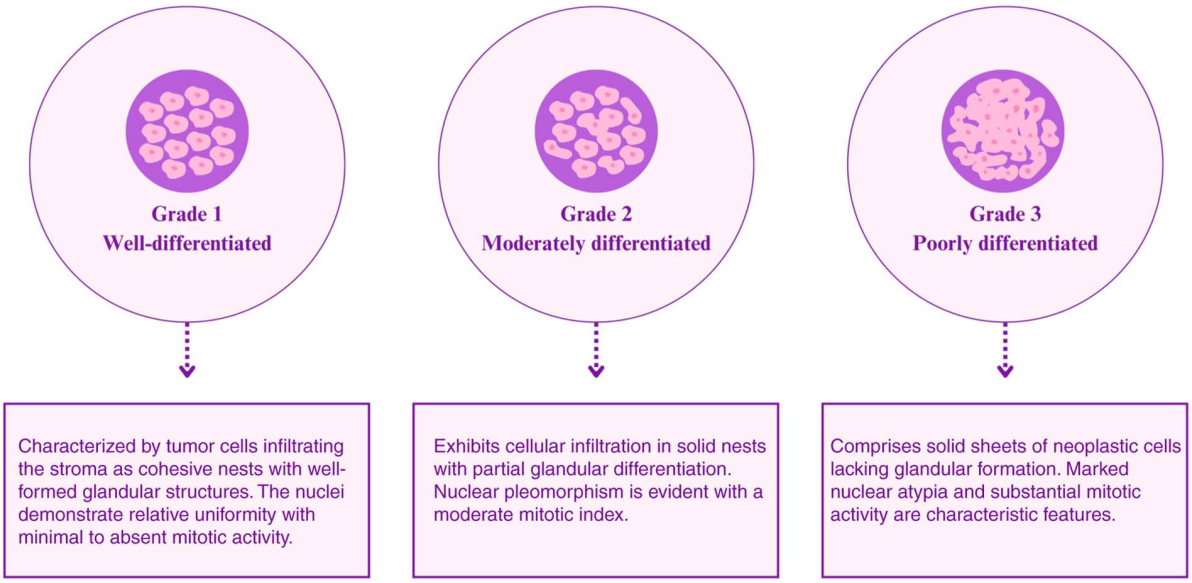

Figure 1. Characterization of breast cancer grading. The grading system remains the international gold standard for prognostic stratification in invasive breast carcinoma.

cancers with ER-positive staining in 1-10% of cells should be classified as ER low positive (33). Limited data currently supports endocrine therapy in this context, as these tumors typically exhibit behavioral patterns more closely resembling TN rather than luminal BC (34).

Superexpressing HER2 tumors. The HER2 oncogene belongs to the epidermal growth factor receptor family. These receptors play a fundamental role in activating signal transduction pathways responsible for epithelial cell proliferation and differentiation, as well as angiogenesis (35). High levels of HER2 expression indicate that patients may benefit from receptor-targeted therapies.

HER2 is primarily identified through western blotting, ELISA or IHC. In cases of indeterminate results, alternative techniques may be employed, including ISH, FISH, chromogenic or silver-enhanced ISH or PCR (36). HER2 expression is classified as negative (IHC 0/1+), indeterminate (IHC 2+), or positive (IHC 3+) based on staining intensity and tumor cell percentage, with indeterminate and positive results requiring confirmatory testing (30).

TNBC. TNBC refers to BC that does not express ER and PR, or with IHC staining levels <1%. Additionally, the HER2 status is 0 or 1+, with negative hybridization (FISH) for $HER2^+$ expression (37).

Triple-negative breast cancer (TNBC) is considered more aggressive than other breast cancer subtypes. It lacks specific targeted therapies, such as hormone therapy used for luminal tumors or anti-HER2 agents indicated for HER2 IHC 3+ cases. TNBC accounts for approximately 15% of breast cancer diagnoses worldwide and is more frequently observed in female patients under the age of 40 years (21).

TNBC is characterized by distinct risk factors supported by epidemiological evidence (38). BRCA mutations, particularly in BRCA1, are found in up to 20% of patients with TNBC, indicating a notable genetic predisposition. Also, African-American patients demonstrate higher susceptibility compared with Caucasian patients, as documented in population-based studies (39,40). Premenopausal status is also a relevant risk factor (21). The absence of targeted therapies for TNBC has driven extensive research to identify predictive biomarkers for treatment response (41-43). Investigations into immune system interactions with TNBC have yielded notable insights into treatment responsiveness (44-46).

3. Tumor-infiltrating lymphocytes (TILs) in BC

Role of TILs in tumor progression and clinical value. Tumor biological behavior is influenced by its intrinsic characteristics and the tumor microenvironment, which interacts with the cancerous cells. This environment is formed by various structures and substances, such as vessels, fibroblasts, myofibroblasts and inflammatory cells (47).

Genetic alterations leading to malignancy are common in somatic cells, and the immune system serves a crucial role in the elimination or inactivation of abnormal cells. Studies in mice have demonstrated an increased incidence of malignant neoplasms in immunodeficient individuals, highlighting the importance of immunity in cancer prevention (48-50).

TIL-mediated immunoediting: Elimination and escape mechanism. TILs are used for tumor classification in the clinical setting. These lymphocytes dynamically engage with other immune system and cancer cells, termed cancer immunoediting cell neoplasia, serving roles that can be either favorable or detrimental to the tumor (51). This process comprises three phases: Elimination, equilibrium and escape (52). The elimination phase occurs when tumor antigens are presented to $CD8^+$ cytotoxic lymphocytes by cells, in combination with human leukocyte antigen molecules for recognition by the T cell receptor (53). Most TILs in cancer are of T cell phenotype, including $CD4^+$ lymphocytes (helper cells) and $CD8^+$ (cytotoxic cells). $CD4^+$ T lymphocytes are

Table I. Histological subtypes of breast cancer.

Characteristic	Invasive breast carcinoma of no special type	Invasive lobular carcinoma	Invasive mucinous carcinoma	Rare entities
Characterization	Heterogeneous group that cannot be categorized into any other group	Tumor cells that are discohesive and typically arranged in a single file or Indian-file pattern, often distributed across a desmoplastic stroma.	Cluster of low- to moderate-grade tumor cells floating in a pool of extracellular mucin.	Tubular carcinoma Cribriform carcinoma Mucinous carcinoma Mucinous cystadenocarcinoma Carcinoma with apocrine differentiation Metaplastic carcinoma
Frequency of cases	80%	5-15%	2%	1%
Biomarkers	ER and HER2	ER^+, $HER2^-$ and aberrant E-cadherin	ER^+, PR^+ and $HER2^-$	Varies according to cancer subtype

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table II. Molecular subtypes of breast cancer based on receptor status (ER, PR, HER2), proliferation index (Ki-67), histological grade and clinical parameters.

		Luminal B			
Characteristic	Luminal A	HER2-	HER2+	HER2+	TN
Biomarkers	ER+ PR+ HER2- Ki-67 low	ER+ PR- HER2- Ki-67 high	ER+ PR-/+ HER2+ Ki-67 low/high	ER- PR- HER2+ Ki-67 high	ER- PR- HER2- Ki-67 high
Frequency of cases	40-50%	20-30%		10-20%	15-20%
Target Therapy	Tamoxifen	Tamoxifen		Herceptin	-
Response to Therapies	Endocrine	Endocrine Chemotherapy		Chemotherapy	Chemotherapy PARP Inhibitors
Prognosis	Good	Intermediate		Poor	Poor
Observations	Controlled cell growth	Fast cancer cell growth		Overexpression of HER2; Faster growth than luminals subtypes	Aggressive subtype; occurs more often in younger women; highest association with BRCA1 mutations

essential for priming tumor-specific $CD8^+$ TILs, in addition to supporting their expansion and memory (54). Tumor elimination also involves the action of natural killer (NK) cells and macrophages in antigen identification. NK cells target tumor cells that have managed to escape from cytotoxic lymphocyte control (55).

During the equilibrium phase, the FOXP3 protein plays a critical role in the generation of $CD4^+$ regulatory T cells (Tregs), which promote immunosuppression, resulting in immunological tolerance for $CD8^+$ cells. Excessive FOXP3 expression is associated with Treg proliferation and severe immunodeficiency, while its absence leads to immune system activation. FOXP3 is also involved in immune escape mechanisms, with impacts on low survival in breast cancer, as it acts by decreasing the immune response in the tumor (56). In the equilibrium phase, the tumor microenvironment presents a high proportion of cytotoxic cells and a low proportion of Tregs due to decreased FOXP3 protein, allowing progression to the next phase (57).

The third stage of the process is immune system evasion, which can occur through decreased immunological recognition due to antigen loss in neoplastic cells, increased cell resistance or survival, reducing apoptosis through STAT3 or BCL-2 activation and development of an immunosuppressive microenvironment. The latter involves the expression of cytokines (VEGF, IL-10, TGF-β) and immunoregulatory molecules, including the B7 family and CD3 expression (52). The B7 family comprise the programmed cell death protein 1 (PD-1), also known as CD279, programmed death-ligand 1 (PD-L1), cytotoxic T-Lymphocyte associated protein 4

CTLA-4, V-domain Ig suppressor of T cell Activation (VISTA), B7 homolog 4 and B and T Lymphocyte Attenuator (BTLA).

Prospective use of TILs in precision oncology. Characterization of immune evasion mechanisms expands prognostic and therapeutic frameworks in oncology. PD-1/PD-L1 checkpoint inhibition has demonstrated substantial efficacy across multiple malignancies, like cutaneous squamous cell carcinoma, with notable response rates in TNBC (58). This approach exemplifies successful translation of immunobiological mechanisms into effective clinical intervention (59). Similarly, CTLA-4 blockade improves survival outcomes in patients with melanoma (60). Recent investigations have identified microRNA (miRNA or miR)-155 as a key immunomodulatory factor influencing effector T cell function and potentially predicting therapeutic response (18,61-63). Integration of multidimensional biomarkers, including PD-L1 expression, tumor mutational burden, microsatellite instability, miR-155 profile and TIL quantification, provides essential stratification parameters, enabling precision in patient selection and treatment optimization protocols (18).

T cell activation requires interaction between complementary costimulatory molecules (B7 on antigen-presenting cells and CD28 on T cells), providing essential secondary signaling. Optimal T cell activation depends on the synchronous delivery of both antigenic peptide recognition and costimulatory signaling (64). In the absence of co-stimulation, antigenic peptide presentation fails to induce complete T cell activation, instead promoting immunological tolerance (65). The degree of T cell activation is determined by the balance between co-stimulation and co-suppression. Clinical trials have demonstrated that PD-1 pathway blockade with anti-PD-1 or anti-PD-L1 therapy enhances T cell-mediated anticancer responses without causing serious adverse events (66,67).

Beyond intrinsic T cell regulation, their activation is influenced by extrinsic factors. Cytokines such as IL-2, released by $CD4^+$ T helper (Th) cells (Th1 and Th17), serve a direct role in promoting the expansion of cancer-specific T cells (68). However, these regulatory cells inhibit specific T cell function, inducing immunosuppression and decreasing immunotherapy efficacy (69).

TILs Working Group consider breast carcinomas rich in inflammatory infiltrates when they exhibit >50% lymphocytic presence in the tumor stroma (70). A previous study showed that, in this context, TNBC is associated with improved progression-free survival (PFS) and overall survival (OS) (42). A meta-analysis including >22,000 patients demonstrated the presence of $CD8^+$ lymphocytes is associated with favorable prognosis, while FOXP3 expression is associated with lower OS and PFS rates (71).

In tumors treated with neoadjuvant chemotherapy, high TIL levels favor the achievement of pathological complete response (pCR) (72,73). A study involving 3,771 patients with different molecular subtypes of BC undergoing neoadjuvant chemotherapy classified TIL expression into three categories (74): Low (0-10%), intermediate (11-59%) and high (60-100%). In patients with luminal cancer, pCR occurred in 45 (6%) of 759 patients with low TILs, 48 (11%) of 435 with intermediate TILs and 49 (28%) of 172 with high TILs. In HER2-positive subtype, pCR was observed in 194 (32%) of 605 patients with low TILs, 198 (39%) of 512 with intermediate TILs and 127 (48%) of 262 with high TIL levels. In patients with TNBC, pCR was achieved in 80 (31%) of 260 patients with low, 117 (31%) of 373 with intermediate and 136 (50%) of 273 with high TIL levels. In univariate analysis, a 10% increase in TILs demonstrated a hazard ratio of 0.93 for disease-free survival (DFS) and 0.92 for OS in TNBC, showing negative results in other tumor subtypes (74).

A study of 1,966 patients with TNBC revealed a 94% recurrence-free survival (RFS) and 95% OS rate in stage I patients with TIL levels ≥50% with TNBC (75). In patients with TIL levels <30%, RFS and OS rates were 78 and 82%, respectively, in patients who did not undergo neoadjuvant therapy. These results confirm TIL abundance in tissue as a notable prognostic factor for patients with TNBC (75).

The clinical evidence regarding the prognostic and predictive value of TILs in BC, particularly in TNBC, affirms their potential use as a clinically actionable biomarker (76). However, the implementation of TILs assessment in routine clinical practice necessitates standardized methodological approaches and clearly defined threshold values for optimal patient stratification. Given the continuous nature of TIL measurements and their varying importance across molecular subtypes, establishing clinically relevant cut-off values is a key step toward integrating this immunological parameter into treatment decision protocols.

4. Clinically relevant cut-off values for TILs in pre-neoadjuvant biopsy samples

Proportion of TILs in BC. Numerous critical aspects must be considered when analyzing TILs. First, the pathologist-reported value refers to the percentage of TILs. The proportion of TILs represents the area of tumor stroma infiltrated total lymphocytes relative to the total area of stroma examined by the pathologist and should be measured using the hematoxylin-eosin method (Fig. 2). Adherence to recommendations by the TILs Working Group is essential for accuracy and reproducibility (70,77).

Higher levels of lymphocytic infiltration serve as predictors of pCR (78). However, a formal recommendation of a clinically relevant cut-off value categorizing breast tumors as having high lymphocytic infiltration is lacking, complicating the establishment of a universal standard for this variable as a therapeutic response biomarker. Meta-analyses reveal cut-off values ranging from 10 to 60% (79,80).

The relevance of high TILs as biomarkers of good therapeutic response has more clinical value for TN tumors compared with other BC subtypes (81). Ochi *et al* (82) categorized tumors into three groups: Low TILs (0-9%), intermediate (10-49%) and high TILs (≥50%), the latter being known as lymphocyte-predominant (LP)BC. The pCR rates in TN tumors with low TILs are 4%, compared with 43.6% in those with intermediate or high TILs. In HER2-positive tumors, pCR rates are 26 vs. 51.9%, respectively, and significant in both cases (82). Loi *et al* (83) observed higher TILs in TNBC (n=134) and $HER2^+$ (n=209) compared with luminal BC subtypes (n=591) (83). The second quartile median of TILs expression was 25.0, 15.0 and 7.5% for these tumor types, respectively. Despite substantial variability in infiltration percentages for TNBC, $HER2^+$ and luminal groups, the upper

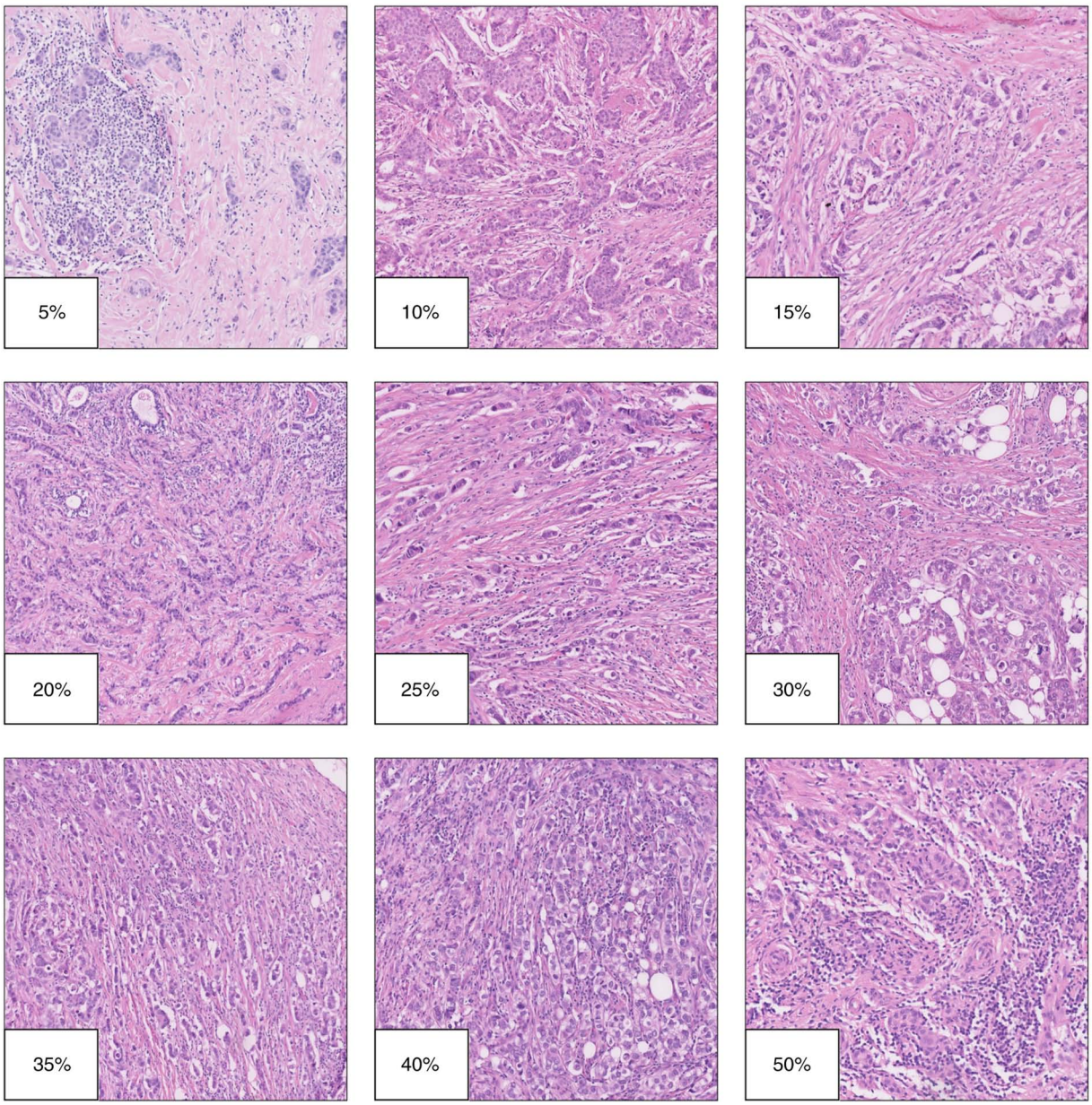

Figure 2. TILs in breast cancer stromal sections. Higher proportions of TILs are associated with improved clinical outcomes. TIL, tumor-infiltrating lymphocyte. Image obtained from International TILS Working Group (70).

quartile showed 40.0, 30.0 and 12.5% infiltration, respectively. This aligns with findings of Stanton *et al* (78,84), which demonstrated TNBC and HER2$^+$ as most frequent subtype of LPBC (78,84) Denkert *et al* (74) reinforced these findings, reporting high TIL percentages (>60%) in 30% of TNBC tumors, 19% in HER2$^+$ and 13% in luminal-HER2-negative tumors (74). Loi *et al* (83) identified TILs (LPBC with a cut-off ≥50%) as predictors of good prognosis for distant disease-free survival in TNBC but not in HER2$^+$ or luminal BC (83). Additionally, Russo *et al* (85) supported these findings by using TILs ≥30% for LPBC classification, a cut-off derived from Liu *et al* (86). In an analysis of 41 TNBC samples, Russo *et al* (85) found that 34% had TILs >30%, with a pCR rate of 78.6% (11/14) compared with 14.8% (4/27) in those with TILs <30%. Furthermore, a significant pCR rate of 71.4% was noted in HER2$^+$ individuals with TILs >30%.

Thresholds for LPBCs: Issues and sensitivity limitations. A fundamental aspect of using TILs for prognosis is determining the appropriate percentage of lymphocytic infiltration that characterizes LPBCs. A widely accepted cut-off value is 50% for high lymphocytic infiltration, as recommended by the TILs Working Group (70). Establishing this threshold is key for accurately identifying LPBCs, which can impact treatment decisions and prognostic evaluation.

Salgado *et al* (70) proposed LPBC classification for tumors with 'more lymphocytes than tumor cells', meaning they exhibit 50-60% lymphocytic infiltration (70). Denkert *et al* (87) reported that 40% of patients with LPBC (>50% TILs) achieved pCR, compared with 7% of patients without lymphocytic infiltration (87). Cut-off values of 50 or 60% predict both short-term pCR responses and long-term OS and DFS (Table III) (82,83,88-91) .

Table III. TIL thresholds and study characteristics.

First author(s), year	Cut-off value, %	Breast subtypes	Lymphocyte type	Number of patients	Duration of follow-up, months	Evaluation indicator	Country	Outcome	(Refs.)
Dieci *et al*, 2014	60	TNBC	All	278	76	OS, DFS	France	High-TIL (n=27): 91% 5-year OS (95% CI, 68-97%). Low-TIL: 55% 5-year OS (95% CI 48-61%)	(88)
Loi *et al*, 2019	50	HER2$^+$, HR$^+$, TNBC	All	1,010	62	OS, DFS	Australia	TNBC (n=134): 10% increase in TILs associated with decreased distant recurrence (HR 0.77, 95% CI 0.61-0.98, P=0.02). HER2$^+$ BC (n=209): 10% increase in lymphocytic infiltration associated with decreased distant recurrence in trastuzumab-treated patients (P= 0.025).	(95)
Ochi *et al*, 2019	50	HER2$^+$, TNBC	All	209	120	DFS, pCR	Japan	Low pre-NAT TILs associated with lower pCR rate: TNBC (4.0 vs. 43.6%); HER2$^+$ BC (26.0 vs. 51.9%). In TNBC with RD: Low pre-NAT TILs associated with shorter RFS (HR 3.844, P=0.024). Low post-NAT TILs demonstrate a non-significant association with shorter RFS (HR 2.836, P=0.061). No association between TIL change and RFS in TNBC or HER2$^+$ BC	(82)
Cerbelli *et al*, 2017	50	TNBC	All	54	-	pCR	Italy	pCR achieved in 35% of cases. Univariate analysis: PD-L1 expression in ≥25% of neoplastic cells associated with pCR (P=0.024). ≥50% sTILs associated with higher pCR frequency (P<0.001). Multivariate analysis: PD-L1 expression on tumor cells significantly associated with pCR (OR 1.13, 95% CI 1.01-1.27).	(91)
Van Bockstal *et al*, 2020	40	HER2$^+$, TNBC	All	35	8	pCR	Belgium	High sTILs (≥40%) significantly associated with increased pCR rate	(92)
Loi *et al*, 2014	30	TNBC	All	2,148[a]	>78	DFS, OS	Australia, France, Italy, Finland, Belgium, Germany and USA	736 iDFS and 548 D-DFS events; 533 deaths. sTILs are a significant prognostic biomarker for: iDFS (HR 0.87, 95% CI 0.83-0.91, P<0.001), D-DFS (HR 0.83, 95% CI 0.79-0.88, P<0.001), OS (HR 0.84, 95% CI 0.79-0.89, P<0.001) Node-negative patients with sTILs ≥30%, showed the following outcomes at 3 years outcomes: iDFS, 92% (95% CI 89-98%), D-DFS, 97% (95% CI 95-99%), OS, 99% (95% CI 97-100%)	(83)
Park *et al*, 2019	30	TNBC	All	476[b]	96	DFS, OS	France, Italy,	A total of 107 deaths, 173 iDFS and 118 D-DFS events. sTILs have independent prognostic value for iDFS	(96)

Table III. Continued.

First author(s), year	Cut-off value, %	Breast subtypes	Lymphocyte type	Number of patients	Duration of follow-up, months	Evaluation indicator	Country	Outcome	(Refs.)
							South Korea	(HR 0.90, 95% CI 0.82-0.97, P<0.01), D-DFS (HR 0.86, 95% CI 0.77-0.95, P<0.01), OS (HR 0.88, 95% CI 0.79-0.98, P=0.015). Patients with stage I tumors and sTILs ≥30% (n=74) had the following 5-year outcomes: iDFS, 91% (95% CI 84-96%), D-DFS, 97% (95% CI 93-100%), OS, 98% (95% CI 95-100%).	
Russo *et al*, 2019	30	HER2$^+$, TNBC	All	187	62.5	OS, pCR	Venezuela	pCR rate: TILs ≥30% = 58.5% (odds ratio, 8.85); TILs <30% = 11% (P<0.001) Association in HER2$^+$ and TN subtypes. No association between TILs and OS (P=0.834) or DFS (P=0.937)	(85)
Floris *et al*, 2021	30	TNBC	All	445	91.56	pCR	Belgium	High sTIL associated with pCR in lean (OR 4.24; 95% CI 2.10-8.56, P<0.001) but not heavier patients (OR 1.48, 95% CI 0.75-2.91, P=0.26) High sTIL associated with increased event-free survival in lean patients (HR 0.22, 95% CI 0.08-0.62, P=0.004) but not heavier patients (HR 0.53, 95% CI 0.26-1.08, P=0.08) Similar results for OS	(93)
Dieci *et al*, 2020	30	TNBC	All	244	81.6	pCR	Italy	TILs confirmed as independent prognostic factor. PD-L1 is a prognostic biomarker: LR χ^2 4.60, P=0.032 (model with classical factors, including age, stage, histological grade and TIL 10% increments). LR χ^2 6.50, P=0.011 (model with classical factors and TIL >30 vs. <30%). In patients treated with neoadjuvant chemotherapy, FOXP3 is a prognostic biomarker in addition to classical factors, including age, stage, histologic grade -, TILs, and pCR (LR χ^2 5.01, P=0.025). In patients without pCR, CD8 and PD-L1 expression significantly increase from baseline to residual disease	(94)
Jimenez *et al*, 2022	20	TNBC	All	80	-	pCR	USA	38/145 extracted MRIRF significantly associated with pCR; 5 non-redundant imaging features. MRIRF model accuracy (P=0.001, 72.7% PPV, 72.0% NPV). TIL model accuracy (P=0.038; 65.5% PPV, 72.6% NPV). Combined MRIRF and TIL model has improved prognostic accuracy (P<0.001, 90.9% PPV; 81.4% NPV)-AUC: 0.632 (TIL); 0.712 (MRIRF); 0.752 (TIL + MRIRF).	(215)

Table III. Continued.

First author(s), year	Cut-off value, %	Breast subtypes	Lymphocyte type	Number of patients	Duration of follow-up, months	Evaluation indicator	Country	Outcome	(Refs.)
Asano *et al*, 2018	10	HER2$^+$, TNBC	All	177	40	OS, DFS, pCR, HR	Japan	High-(n=96) vs. low-TIL (n=81): TNBC and HER2+ BC more frequent (P<0.001 and P=0.040, respectively); higher pCR rate (P=0.003). In TNBC and HER2+ BC, pCR rate is higher in high-TIL group (P=0.013 and P=0.014, respectively). Multivariable analysis: High-TIL status independently predicts favorable prognosis (HR=0.24, P=0.023 and HR=0.13, P=0.036). Biopsy specimens from local recurrence following NAT show decreased TIL.	(216)
Song *et al*, 2017	10	TNBC	All, T, B	180	34.9	DFS, pCR	Korea	Mean number of HEVs in pre-NAT biopsy, 12 (range, 0-72). TILs, TLSs, HEV density and CXCL13 expression are associated with each other Higher CD8$^+$ cell density and CXCL13 expression are significantly associated with better DFS rate	(217)
Khoury *et al*, 2018	46	HER2$^+$, TNBC luminal	All	331	-	pCR	Canadian	pCR rate: TBNC 30.9% (29/95); HER2$^+$ 32.5% (25/77); Luminal 5.6% (9/159) Independent predictors of pCR: Luminal subtype iTIL (OR=1.44, 95% CI 1.08-1.9, P=0.013), TNBC subtype sTIL (OR=1.68, 95% CI 1.29-2.18, P=0.001) and iTIL (OR=1.31, 95% CI 1.05-1.63, P=0.017). HER2$^+$ subtype: sTIL and iTIL do not predict pCR.	(218)
Ruan *et al*, 2018	20 or 10	TNBC	All	166	-	pCR	China	Univariate logistic regression analysis: sTILs (P=0.0001) and iTILs (P=0.001) are associated with pCR. Multivariate logistic regression analysis: sTILs (P=0.006) and iTILs (P=0.04) independent predictors of pCR ROC curve analysis of TNBCs with >20% sTILs (P=0.001) or >10% iTILs (P=0.003) associated with higher pCR rate. Multivariate analysis: 20% sTILs (P=0.005) independently predicts pCR	(219)

pCR, pathological complete response; iDFS, invasive disease-free survival; RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; DDFS, degrees of freedom, F-statistic; NAT, neoadjuvant therapy; PD-L1, programmed cell death protein ligand 1; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; MRIRF, magnetic resonance imaging radiomic feature; HER2BC, human epidermal growth factor receptor 2-enriched breast cancer; CXCL13, C-X-C motif chemokine ligand 13; HEV, high endothelial venule; iTIL, intratumoral TIL; sTIL, stromal TIL; TIL, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer. A total of 2,148 TNBC samples were pooled from nine studies (74). A total of 476 TNBC samples from four centers (75).

Using a >50% TIL cut-off as a significant infiltration marker has limitations regarding sensitivity, as relatively few breast tumors reach this cut-off. Stanton *et al* (78,84) found that ~20% of TN and HER2$^+$ tumors exhibit LPBC with >50% TILs (78,84). Denkert *et al* (47) assessed 3,771 samples, reporting pCR in 50% of high-TIL TNBC tumors and 48% of high-TIL HER2$^+$ tumors (>60% TILs) (74). pCR rates for TNBC and HER2$^+$ with intermediate infiltration (11-59%) were 31 and 39%, respectively. Hence, a cut-off between 11 (low infiltration) and 50% (high infiltration) could enhance sensitivity for identifying individuals with favorable prognosis without compromising the discriminative accuracy.

Comparison of accuracy and sensitivity in LPBCs using lymphocyte infiltration thresholds between 30 and 50%. Studies have used cut-offs between 30 and 50% for defining LPBC (Table III). An analysis from Belgium employed a 40% cut-off (92), while other studies in Venezuela, Belgium and Italy used a 30% cut-off (85,93,94). The prognostic significance of TILs in early-stage TNBC was demonstrated by two pivotal multicenter studies (95) (96). Firstly, a retrospective individual patient data (IPD) meta-analysis was conducted using data from 2,148 early-stage TNBC patients across 9 international studies from Australia, Europe (France, Italy, Finland, Belgium, Germany), and the United States. The analysis demonstrated that a stromal TIL cut-off of ≥30% was associated with significantly better prognosis in early-stage TNBC patients (95). The second study was a retrospective pooled analysis of 476 early-stage TNBC patients from 4 centers who did not receive adjuvant chemotherapy, showing that Stage I patients with sTILs ≥30% had excellent 5-year survival (91-98%) without any systemic treatment (96). The former study evaluated invasive (i)DFS (primary endpoint), distant (D-)DFS and OS, treating TILs as a continuous variable. Treatments included either an anthracycline or a combination of anthracycline and taxane. Patients with node-negative TILs ≥30% showed three-year iDFS of 92% (95% CI, 89-98%), D-DFS of 97% (95% CI, 95-99%) and OS of 99% (95% CI, 97-100%; Fig. 3). The aforementioned study recommend integrating TILs into clinical-pathological diagnostic models (97). In 2,148 individuals, TIL exhibited an interquartile range from 10 to 30%, with a median of 15%. Notably, about one-third of patients showed ≥30% TILs, broadening the pool of individuals benefiting from the biomarker compared with studies using 50% TILs, which was present in one-fifth of patients (78,84). The 30% cut-off aligns with Q3 indicating 30% lymphocytic infiltration as the threshold parameter (95).

Park *et al* (96) investigated whether TILs ≥30% identify those who might not require adjuvant chemotherapy (96). Patients with stage I TNBC (n=74) presented a 5-year iDFS of 91% (95% CI 84-96%), D-DFS of 97% (95% CI 93-100%) and OS of 98% (95% CI 95-100%; Fig. 4). The aforementioned study used the Q3-based cut-off of 30%, consistent with Loi *et al* (95). Compared with the aforementioned study, the median was lower (10 vs. 15%), while the third quartile remained at 30%, confirming its consistency. Stromal TILs ≥30% could signify a subgroup of patients with stage I TNBC with excellent prognosis without adjuvant therapy. This suggests vulnerable groups, such as the elderly or those with comorbidities, may be spared from the toxicity and costs of adjuvant chemotherapy without jeopardizing survival rates. Moreover, TIL evaluation at 30% may yield good reproducibility among pathologists, as at this level, visual differences are easier to be detected. Nonetheless, the use of biomarkers necessitates caution concerning established clinical diagnostic criteria, such as tumor size and lymph node status, to refine pathological analysis and therapeutic insights for each clinical case (98).

Russo *et al* (85), Floris *et al* (93) and Dieci *et al* (94) demonstrated good discriminative capacity with a TIL cut-off of 30% (85,93,94). Russo *et al* (85) reported a five-fold greater incidence of pCR for patients with TILs ≥30% compared with those with TILs <30% (58.5 vs. 11.0%) (85).

TIL thresholds of 30 or 50% not only serve as promising biomarkers for guiding chemotherapy de-escalation in early-stage TNBC, but also inform therapeutic decisions regarding immune checkpoint inhibitors. Measuring TIL and PD-L1 expression aids in identifying immune-enriched tumors, thereby enhancing selection of patients with advanced TNBC or HER2$^+$ BC who are likely to respond to PD-1/PD-L1 inhibitors (99).

Comparative analyses between 30 and 50% thresholds for LPBCs. The recommendation to adopt 30 or 50% as clinical cut-off values for LPBCs is based on their predictive value for pCR and favorable prognostic outcomes in BC. TILs ≥50% are associated with both short-term pCR responses and long-term OS as well as DFS (82,83,88-91). This threshold was initially proposed by the TILs Working Group (70).

Further studies have indicated that cut-off values <50% can also predict favorable prognosis, with the majority using 30% as the cut-off value (85,93,94). Specifically, two studies employed TILs ≥30%: The first identified patients who would benefit from adjuvant therapy, while the second identified individuals with a favorable prognosis who may not require adjuvant chemotherapy (95,96).

In conclusion, both cut-off values for LPBCs are effective in identifying patients who are likely to benefit from therapeutic intervention. The 30% threshold is particularly inclusive, enabling the identification of a broader patient population compared with the stricter 50%, which is less frequently achieved in clinical practice (78,84).

4. miR-155 and TIL activity

The prognostic value of TILs in TNBC is mediated through complex molecular regulatory networks. Post-transcriptional gene regulation via miRNAs is a critical mechanism in the modulation of the tumor inflammatory landscape, with miR-155 emerging as a key mediator. miRNAs are a class of small, non-coding, single-stranded RNAs, typically 18-25 nucleotides in length, that play a crucial role in the post-transcriptional regulation of gene expression. By directly binding to the 3' untranslated regions (UTRs) of target messenger RNAs (mRNAs), miRNAs promote mRNA degradation or inhibit translation (100,101). This control of protein synthesis allows miRNAs to function as modulators of gene expression rather than as complete silencers (100,101).

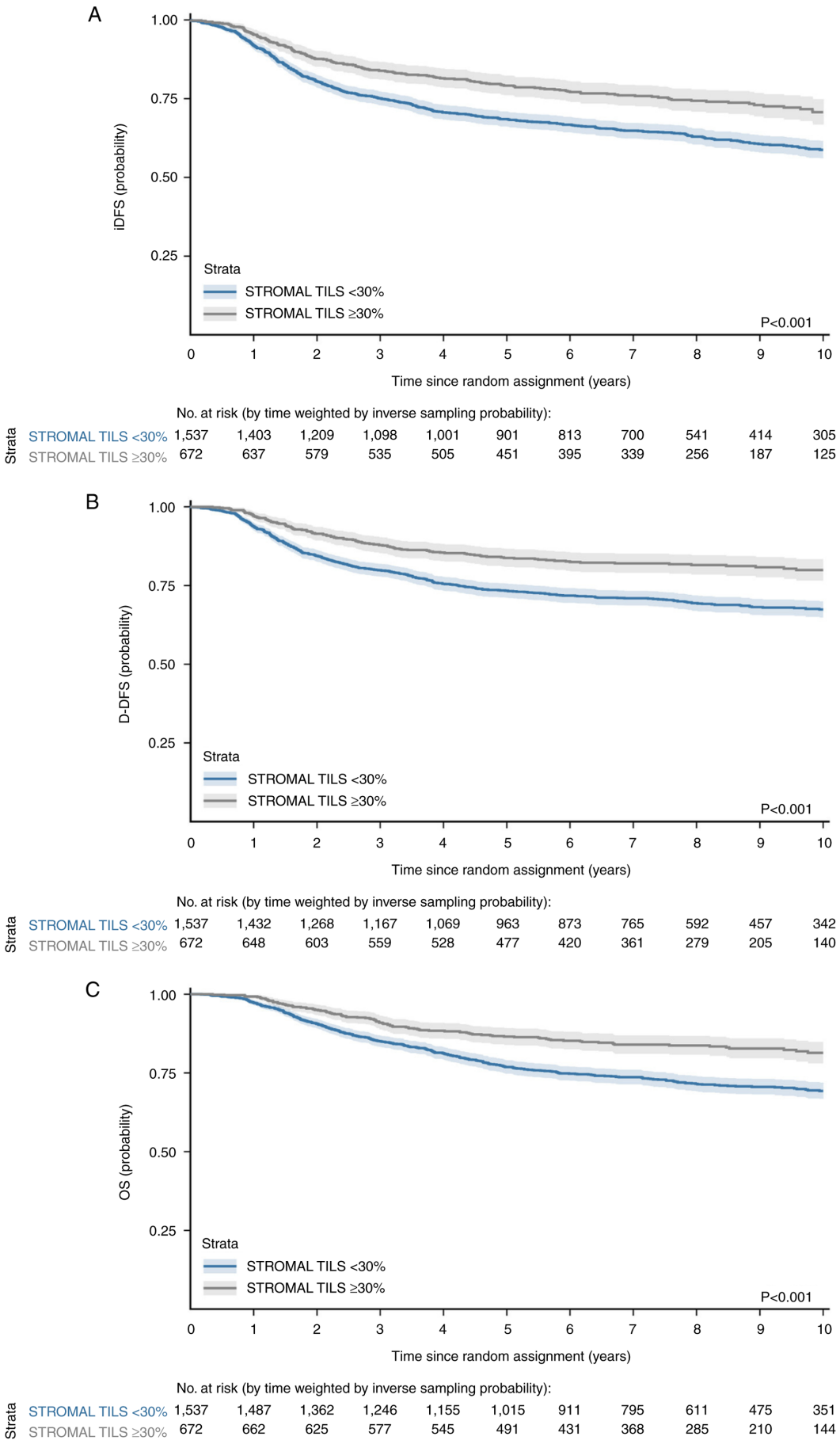

Figure 3. Kaplan-Meier curves for survival based on sTILs. Kaplan-Meier curves of (A) iDFS, (B) D-DFS and (C) OS according to TILs using a 30% cut-off. Shaded areas correspond to 95% CI. P-values correspond to log-rank tests. Figure reproduced with permission from Loi et al, and modified by the author (99). iDFS, invasive disease-free survival; D-DFS, distant disease free survival; OS, overall survival; sTIL, stromal tumor-infiltrating lymphocyte.

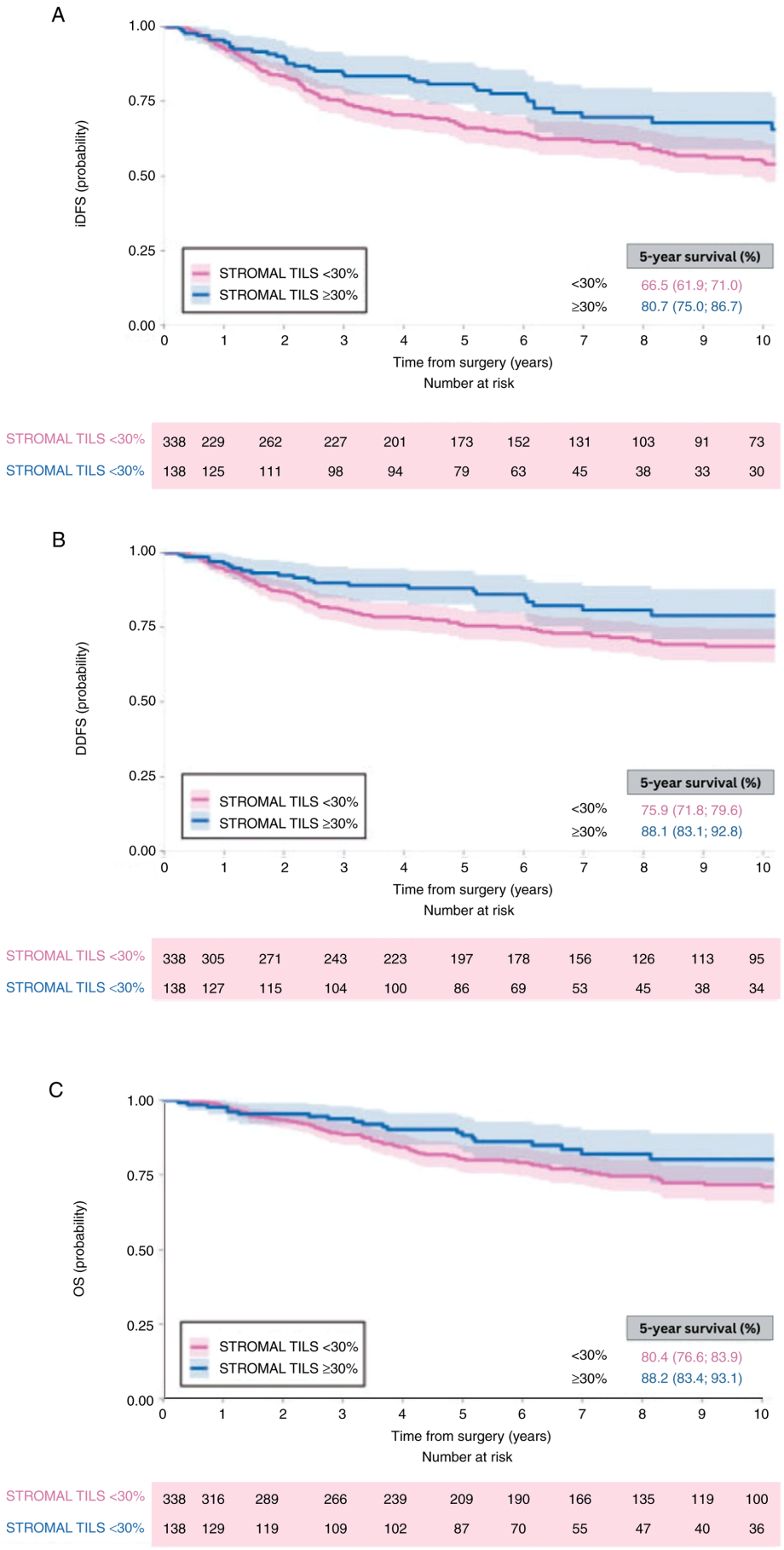

Figure 4. Kaplan-Meier survival curves with a 30% TILs cut-off Kaplan-Meier curves of (A) iDFS, (B) D-DFS and (C) OS in stage I subpopulation according to stromal tumor-infiltrating lymphocytes using a cut-off of 30%. Figure reproduced with permission from Park *et al*, and modified by the author (100). iDFS, invasive disease free survival; D-, distant; OS, overall survival; sTIL, stromal tumor-infiltrating lymphocyte.

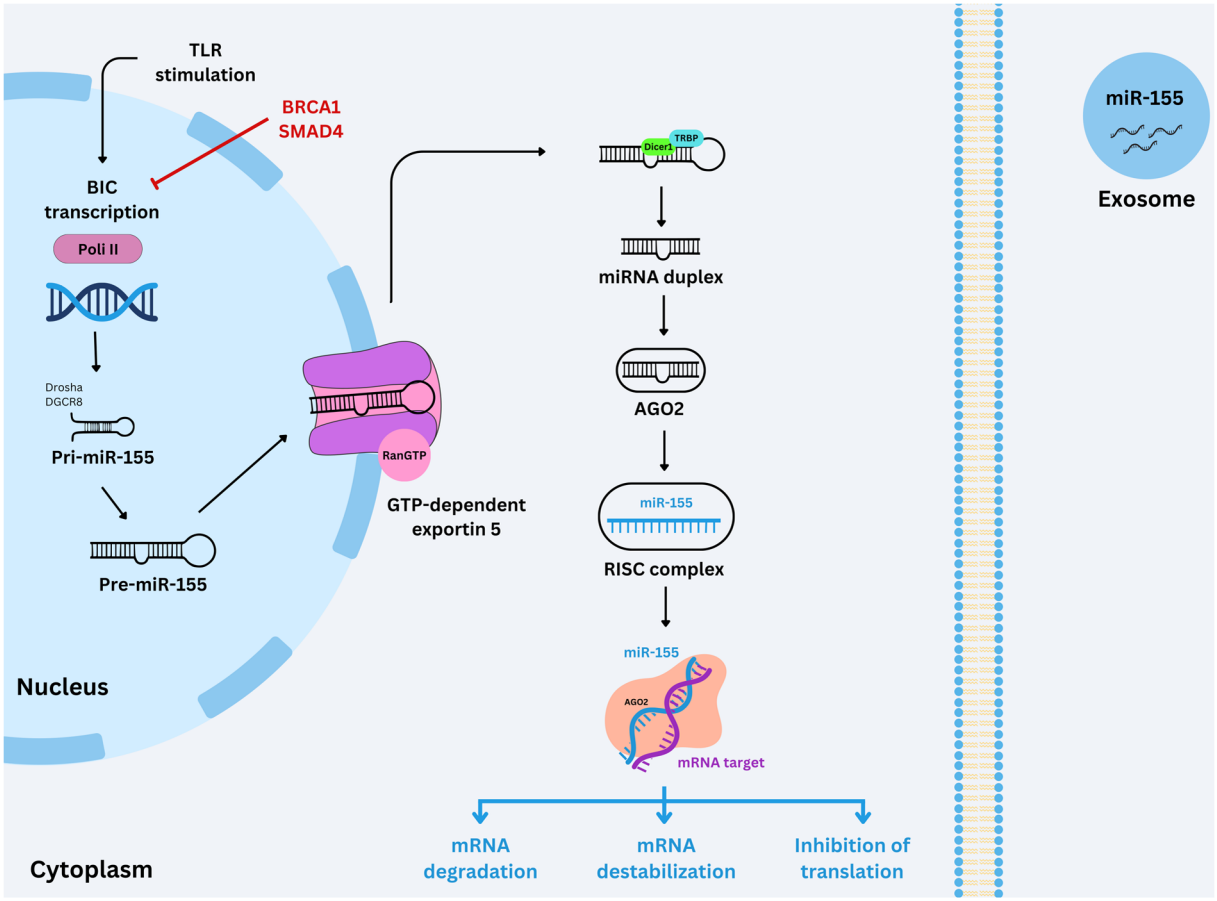

Figure 5. Biogenesis and function of miR-155. TLR stimulation initiates BIC transcription by Pol II in the nucleus, producing pri-miR-155 (negatively regulated by BRCA1/SMAD4). Drosha/DGCR8 processing generates pre-miR-155, which is exported to the cytoplasm via exportin 5. Cytoplasmic Dicer1/TRBP cleaves pre-miR-155 into a duplex that incorporates into AGO2, forming the RISC complex. Mature miR-155 mediates mRNA degradation, destabilization or translational inhibition. miR-155 can be packaged into exosomes for intercellular signaling. miR, microRNA; TLR, toll-like receptor; pri-miR, primary microRNA; DGCR8, DiGeorge syndrome critical region 8 protein; TRBP, transactivation response RNA binding protein; AGO, argonaut proteins; RISC, RNA-induced silencing; BIC, B cell integration cluster; Pol, polymerase.

Biogenesis and function. In animals, miRNAs are transcribed by RNA polymerase II (Pol II) as primary transcripts known as primary miRNAs (pri-miRNAs), which adopt a characteristic hairpin structure (Fig. 5). These pri-miRNAs are processed in the nucleus by the enzymes Drosha and DiGeorge syndrome critical region 8 DGCR8 (DGCR8) is a protein that serves a crucial role in the maturation of microRNAs to generate precursor miRNAs (pre-miRNAs), which are transported to the cytoplasm by the protein exportin-5. In the cytoplasm, a second processing step is performed by the enzyme Dicer, in association with the double-stranded RNA-binding proteins trans-activation response RNA-binding protein. It's a cellular protein that primarily binds to the trans-activation response RNA-binding protein (TRBP) or protein activator of PKR (Protein Kinase R), that are double-stranded RNA-binding proteins resulting in a miRNA duplex 18-25 nucleotides in length. Subsequently, the passenger (sense) strand is degraded, while the guide (antisense) strand, representing the mature miRNA, is incorporated into the RNA-induced silencing complex (RISC). Within RISC, argonaute proteins serve a central role in directing the complex to target mRNAs containing partially complementary sequences within their 3' UTRs. This interaction leads to gene silencing through either translational suppression or mRNA destabilization (102-105).

Evolutionarily conserved across a range of organisms, miRNAs comprise ~1% of the human genome. Despite their small size, these regulatory RNAs exert post-transcriptional control over more than one-third of all protein-coding genes, underscoring their key role in numerous cellular processes and disease pathogenesis (106,107) . miRNA dysregulation is implicated in various pathological conditions, most notably cancer, where altered expression patterns contribute to tumor initiation, progression, and metastasis (20,105,108). Therefore, understanding the role of miRNAs in oncogenesis is key for the development of novel diagnostic and therapeutic strategies (20,105,108)

The first miRNA sequence database, established in 2002, contained 506 entries across six organisms (109,110). By 2010, the number of annotated human miRNAs had grown to 1,424 (111). However, miRNAs may be reclassified over time due to initial misannotations, often stemming from high sequence similarity between precursor miRNAs and minor sequence variants (112).

miRNAs in BC. The search for predictive biomarkers to improve early cancer diagnosis and therapeutic outcomes increasingly emphasizes the analysis of molecular signatures in normal tissue prior to the clinical manifestation of disease (112-114).

In BC, miRNAs have been consistently identified as dysregulated in both tissue and serum/plasma samples (115-117). These alterations contribute to early disease development and progression by modulating the post-transcriptional expression of proto-oncogenes and tumor suppressor genes. Such findings underscore the potential of miRNAs as valuable biomarkers for early detection and targeted intervention in BC (118,119).

The prognostic value of miRNAs in BC connects directly to critical genomic alterations. Genomic instability, a key hallmark of malignancy, affects and is influenced by miRNA expression patterns. This enables tumor cells to acquire multiple growth advantages such as autonomous growth signaling, resistance to inhibitory stimuli, apoptosis evasion, sustained angiogenesis and enhanced metastatic capacity (120). This instability also affects miRNA expression, disrupting key regulatory pathways involved in tumor initiation and progression. miRNAs have emerged as key regulators in the interplay between cancer cells and the immune microenvironment (121). Moreover, miRNAs promote genomic instability by influencing DNA double-strand break repair, mismatch repair mechanisms and DNA methylation patterns (100)

miRNAs are key regulators of the interplay between cancer cells and the immune system, functioning as either oncogenes or tumor suppressors depending on the cellular context. They influence key biological processes including tumorigenesis, cell proliferation, apoptosis and metastasis. Notably, miR-21 and miR-155 are frequently upregulated across numerous types of cancer, like lung cancer or prostate and hematologic tumor, highlighting their prominent roles in tumor initiation and progression (122).

miRNAs exhibit context-dependent functions. For example, miR-10b, miR-103/107 and miR-30d have been characterized as oncogenic, whereas miR-31, miR-29 and members of the miR-200 family act as tumor suppressors (123). Additionally, miR-7 is a negative regulator of epidermal growth factor receptor expression in BC cells, further illustrating the diverse mechanisms by which miRNAs modulate oncogenic signaling pathways (124).

In BC, miRNAs serve influential roles across all molecular subtypes, with specific subsets contributing to key regulatory pathways. For example, miR-21, miR-18a/b, miR-193, miR-302, miR-92, let-7, miR-22, miR-221/222, miR-449a/b and the miR-17-92 cluster modulate ER signaling, a pathway central to HR-positive BC. Furthermore, HER2 protein, a major oncogenic driver in $HER2^+$ BC, is regulated by miR-125a/b, highlighting the diverse roles of miRNAs in shaping the molecular landscape of BC (125).

Beyond their regulatory functions, miRNAs serve as promising diagnostic and prognostic biomarkers in BC research (116). Their dysregulation in tumor development and progression supports their potential use in detection, diagnosis, subtype classification and targeted therapy (117). Distinct miRNA expression profiles reliably differentiate BC tissue from normal counterparts (121). For example, upregulation of miR-21, miR-106a and miR-155, along with reduced expression of miR-126, miR-199a and miR-335, is observed in BC compared with normal tissues (126).

The first comprehensive study evaluating miRNA expression in BC tissue analyzed 76 tumor samples and identified 29 miRNAs with differential expression compared with normal breast tissue; among these, miR-10b, miR-125b, miR-145, miR-21 and miR-155 were key candidates, with miR-155 demonstrating the most pronounced dysregulation (127).

miR-21 is one of the most extensively studied miRNAs in BC and is associated with aggressive tumor characteristics, including advanced clinical stage, high histological grade and HR-negative status (128-130). Its expression is positively regulated by TGF-β, and its upregulation is observed in BC tissue (131).

Further research has revealed subtype-specific miRNA expression patterns (132,133). For example, miR-342 expression is elevated in ER^+ and $HER2^+$ tumors but decreased in TNBC (134). Conversely, miR-520 is upregulated in HR^- tumors, suggesting distinct functional roles across BC subtypes (135). Analysis examining 309 miRNAs in 93 breast tumor samples identified 31 miRNAs associated with favorable prognostic features, including low histological grade and ER^+ status (136). Notably, miR-155 is upregulated in BC tissues compared with normal controls and elevated in ER^- compared with ER^+ tumors (136).

Disruption of miRNA expression patterns can lead to widespread cell dysfunction, including aberrant cell cycle regulation and uncontrolled tumor proliferation (16).

miR-155. miR-155 is an evolutionarily conserved molecule encoded by the host gene MIR155HG, located on chromosome 21 at the 21q21.3 locus (137). This gene spans ~13 kilobases and comprises three exons, with the third exon containing a 1,500-base-pair primary transcript, pri-miR-155, which undergoes sequential processing to produce the mature miR-155 (138). Initially identified as the B cell integration cluster, MIR155HG was first recognized for its role as a retroviral integration site in B cell lymphoma in both human and animal models, marking its role in oncogenesis (139). Mature miR-155 exists in two isoforms: miR-155-5p and miR-155-3p, each exerting distinct regulatory effects. miR-155-3p enhances the production of IFN-α/β by promoting degradation of interleukin-1 receptor-associated kinase 3, whereas miR-155-5p suppresses IFN-α/β production by targeting Transforming growth factor-β (TGF-β)-activated kinase 1, also known as MAP3K7 binding protein 2 (138,140,141). miR-155-5p also modulates immune responses and contributes to drug resistance, while miR-155-3p is implicated in multiple types of cancer, like lung cancer and glioblastoma (141). These diverse functions underscore the multifaceted role of miR-155 in cancer progression and immune regulation (20,138,140-143).

miR-155 has emerged as a promising therapeutic target due to its involvement in immunosuppressive mechanisms and its potential to enhance antitumor immune responses. This miRNA serves a key role in augmenting T cell-mediated immunity by improving T cell functionality, memory formation, cytotoxic activity and IFN-γ production (12). However, while enhancing miRNA expression can potentiate T cell responses against tumors, IFN-γ signaling induces the expression of PD-L1, which may paradoxically promote a pro-tumorigenic environment (12).

miR-155 is one of the most extensively characterized miRNAs in BC (19,20,142,144-148). Initially classified as an oncomiR, it has been implicated in promoting tumorigenesis and disease progression. Elevated expression of miR-155

is associated with tumor development, poor prognosis and resistance to therapy in both solid tumors and hematological malignancies (138,141). Functioning as an oncogene, miR-155 targets genes involved in immune regulation, DNA repair, hypoxia responses and inflammation, thereby influencing both tumor cell behavior and the tumor microenvironment (149). Studies have reported that high miR-155 expression is associated with improved OS in various cancers, including BC (19). This may be attributed to its dual role in both the innate and adaptive immune systems, as it is expressed in immune as well as in tumor cells (150). Consequently, the functional impact of miR-155 in BC remains context-dependent, and whether its expression is pro- or antitumorigenic is under investigation (12,18).

In patients with BC, circulating levels of miR-155 are significantly elevated compared with healthy individuals. Moreover, miR-155 levels tend to decrease following adjuvant cancer treatment, such as surgery and chemotherapy and are highest in tumor with diameter >5 cm, suggesting its potential utility as a biomarker for therapeutic monitoring. Elevated circulating miR-155 is also linked to early-stage tumor recurrence, further supporting its relevance in disease surveillance (151,152).

Upregulation of miR-155 is associated with treatment resistance, notably in trastuzumab-resistant BC. In early-stage patients receiving trastuzumab-based therapy, elevated levels of circulating exosomal miR-155 are an independent predictor of poor event-free survival. Similarly, in metastatic patients undergoing trastuzumab-containing regimens, high circulating miR-155 levels are associated with decreased PFS. These findings underscore the prognostic value of miR-155 in predicting adverse clinical outcomes in both early-stage and metastatic BC (153).

In another study (154), patients with early-stage and metastatic BC were stratified into high and low miR-155 expression groups. Among early-stage patients, decreased miR-155 expression was associated with shorter DFS compared with those with higher expression. Furthermore, miR-155 expression was significantly lower in patients who experienced relapse than in those who remained relapse-free, further supporting its potential prognostic value in BC (154).

A systematic review (147) of 28 studies found that miR-155 overexpression is associated with higher tumor grade and advanced staging. However, inconsistencies were noted across studies regarding the association between miR-155 levels and HR status, and no definitive association was observed between miR-155 expression and other key patient prognostic factors (147).

The diagnostic utility of circulating miR-155 also varies across studies (148,151). Notably, serum-derived miR-155 has greater diagnostic accuracy compared with plasma-derived miR-155 (155). This discrepancy may stem from the coagulation process, which influences the extracellular miRNA profile in blood. Despite these findings, the limited number of studies examining plasma miR-155 underscores the need for further investigation to establish its diagnostic potential in BC (148).

In metastasis, exosomes (nanometer-sized vesicles capable of transporting various biomolecules, including miRNAs) are hypothesized to mediate the transfer of malignant traits to distant cells. miR-155 is enriched in exosomes derived from metastatic BC, suggesting a role in promoting metastatic behavior (156). This is consistent with studies linking miR-155 to chemoresistance, as it has also been detected in exosomes isolated from cancer stem and drug-resistant tumor cells (157,158). Furthermore, a panel of circulating miRNAs, including miR-155, is elevated in the plasma of patients with non-metastatic BC prior to treatment, with levels declining following therapy, supporting its potential use as a biomarker for therapeutic monitoring (159).

miR-155 is a promising therapeutic target due to its involvement in immunoregulatory pathways and its capacity to enhance antitumor immune responses. It serves a critical role in augmenting T cell-mediated immunity by enhancing T cell functionality, memory formation, cytotoxic activity and IFN-γ production. However, while modulation of miR-155 expression strengthens antitumor T cell responses, the resulting increase in IFN-γ signaling may induce upregulation of PD-L1, thereby contributing to an immunosuppressive tumor microenvironment (160).

The search for biomarkers in TNBC has prompted extensive investigation into miRNAs as potential therapeutic targets, providing deeper insight into tumor biology (161,162). miR-155 has emerged as a key regulator of cell proliferation, in part due to its role in maintaining thiamine metabolism in TNBC, as well as its involvement in promoting TGF-β-induced epithelial-mesenchymal transition (12). Although miR-155 is typically characterized as an oncogenic miRNA that promotes tumor growth, angiogenesis and aggressiveness, emerging evidence suggests a context-dependent, protective role in TNBC (163). In this subtype, miR-155 upregulation is associated with improved survival outcomes. A systematic review and meta-analysis demonstrated that low miR-155 expression is predictive of poor OS in patients with TNBC, potentially due to its influence on molecular pathways involved in DNA damage response and repair (163).

miR-155 modulates cell pathways involved in TIL activity. Although BC has not traditionally been considered an immunogenic tumor, the presence of TILs has been consistently documented and is associated with favorable clinical outcomes, particularly in patients with TNBC subtype (75,83,164). In TNBC, an evaluation of plasma miR-155 expression revealed that lower levels are significantly associated with shorter median DFS and OS. Notably, in multivariate analysis, miR-155 emerged as the only independent predictor of decreased DFS (154). Given the key immunoregulatory functions of miR-155, including its roles in B lymphocyte and $CD4^+$ T cell differentiation, as well as Treg activation, these findings suggest that elevated plasma miR-155 levels may reflect a more robust antitumor immune response (154).

miR-155 upregulation enhances TIL activity in tumor immunoediting. Studies using T cell-specific Dicer knockout mice have demonstrated impaired T cell development, aberrant Th cell differentiation and altered cytokine production, underscoring the key role of miRNAs in T cell maturation and function (165, 166).

miR-155 has been identified as a key regulator of Treg and Th17 cell differentiation through its direct targeting of suppressor of cytokine signaling 1 (SOCS1), a negative regulator of the JAK/STAT signaling pathway. By suppressing

SOCS1, miR-155 enhances phosphorylation of STAT5 and STAT3, potentially by alleviating SOCS1-mediated inhibition. Furthermore, miR-155 promotes Th17 cell differentiation and effector function via distinct mechanisms. It facilitates activation of the IL-6/STAT3 signaling pathway, which is key for Th17 lineage commitment and IL-17A production (167). Additionally, miR-155 counteracts the inhibitory effects of IL-10 and TGF-β1 on IL-17A expression, thereby augmenting the pro-inflammatory potential of Th17 cells (167).

Wang *et al* (18) identified a positive association between the expression levels of miR-155 in breast tumors and the presence of antitumoral immune cells, such as $CD8^+$ T cells and M1 macrophages. Conversely, they noted a negative association with protumoral cell types, including Tregs and M2 macrophages. The forced overexpression of miR-155 enhances the production of chemokines CXCL9, CXCL10 and CXCL11, which is driven by SOCS1 inhibition and an increased ratio of phosphorylated STAT1/STAT3. Furthermore, a convolutional neural network analysis confirmed that elevated levels of miR-155 are associated with an increased proportion of TILs, emphasizing its role in enhancing both innate and adaptive immunity (18).

In a mouse model with miR-155-overexpressing tumors, there was an increase in immune checkpoint molecules such as PD-L1 and CTLA4, which are known to inhibit antitumor activity (18). This upregulation was also observed in human BC tissue miR-155 overexpression results in increased PD-L1 expression in both human and murine BC cell lines, suggesting a potential sensitivity to immune checkpoint blockade therapy (18,168).

miR-155 inhibits SOCS1, which affects the activity of tumor-infiltrating lymphocytes (TILs). The downregulation of SOCS1 by direct miR-155 targeting serving a pivotal role in enhancing TILs activity in TNBC. SOCS1, a member of the STAT-induced STAT inhibitor family, negatively modulates pro-inflammatory cytokines via two mechanisms. Firstly, SOCS1 catalyzes the ubiquitination of signaling intermediates recruited by SOCS1. Secondly, it directly inhibits the JAK/STAT pathway (169), thereby preventing excessive levels of pro-inflammatory cytokines, such as IFN (170) and ILs (171).

Increased IFN-γ is associated with more effective anti-tumor response and with an enhancement of T cell response (138,141). Therefore, by targeting SOCS1, miR-155 indirectly promotes IFN-γ production, resulting in more active TILs, which, in TNBC, is associated with a positive prognosis. However, in other types of cancer, such as colorectal cancer (172) and pancreatic cancer (173), SOCS1 is considered a tumor suppressor, and downregulation of SOCS1 can be associated with tumor progression (174).

PI3K/AKT is modulated by miR-155/SOCS1, leading to enhanced TIL activity in the tumor microenvironment. SOCS1 suppresses the PI3K/AKT pathway, which is involved in cell proliferation, meaning miR-155 also promotes cell proliferation. SH-2 containing inositol 5' polyphosphatase 1 (SHIP1), an inositol phosphatase, together with PTEN is a key negative regulator of PI3K/AKT and miR-155 directly targets its expression; when miR-155 is upregulated, SHIP1 expression is reduced, and cell proliferation is promoted together with increased pro-inflammatory cytokine levels. AKT promotes the production of ILs such as IL-6 and IL-12. High TIL levels influence the migration and infiltration of TILs into the tumor site. By increasing chemokine production and cell motility, this pathway may promote the recruitment of TILs into the tumor microenvironment, improving the immune response (175). miR-155 can also enhance the cytotoxic activity of $CD8^+$ T cells, promoting tumor cell death (175).

miR-155 triggers a suppressive cascade that reduces Treg function. SOCS1 maintains FOXP3 expression and Treg cell stability under inflammatory conditions. Treg cells serve an immunosuppressive role in the tumor microenvironment. The transcription factor FOXP3 is key for the normal development of Tregs; decreased FOXP3 is associated with higher proportions of cytotoxic cells, which can lead to a better prognosis. High expression of FOXP3 is associated with immune tolerance of cancer cells. During the equilibrium phase of the immune response in the tumor microenvironment, there is a low proportion of Tregs due to decreased FOXP3 expression, and a high proportion of cytotoxic cells (56,57,176,177).

miR-155 suppresses expression of PD-L1, enhancing TIL activity in TNBC. PD-L1 is a cell surface protein that serves a critical role in suppressing the immune response; its expression on tumor cells is a mechanism for evading immunosurveillance. The interplay between miR-155 and PD-L1 has notable implications for TIL activity in TNBC. When miR-155 downregulates PD-L1, T cell inhibition is reduced, thus enhancing the anti-tumor immune response mediated by TILs (178). Studies have confirmed that miR-155 regulates TILs by targeting specific regions of PD-L1 mRNA (179,180).

However, the increase in pro-inflammatory cytokines such as TNF-α and IFN-γ can indirectly increase PD-L1 expression; the net result of this interaction will dictate the immune evasion in TNBC (181).miR-155 inhibits the IL-6/STAT3 pathway. IL-6 and miR-155 form a positive feedback loop: IL-6 stimulates the expression of miR-155, which inhibits SOCS. By inhibiting SOCS, miR-155 allows increased signaling of cytokines, such as IL-6, further promoting the activation of the IL-6/STAT3 pathway. When SOCS1 is inhibited by miR-155, the IL-6/STAT3 pathway becomes more active, leading to increased production of IL-6 and other pro-inflammatory cytokines.

IL-6 is a pleiotropic cytokine that serves an important role in physiological processes, including cell proliferation, immune surveillance, acute inflammation, metabolism and bone remodeling. IL-6 binds to the IL-6 receptor, which subsequently binds to the glycoprotein 130 receptor creating a signal transducing hexameric receptor complex. JAKs are recruited and activated; activated JAK phosphorylates STAT3 for activation, leading to gene regulation. Constitutively active IL-6/JAK/STAT3 signaling promotes cancer cell proliferation and invasiveness while suppressing apoptosis, and STAT3 enhances IL-6 signaling to promote an inflammatory feedback loop (182).

The IL-6/STAT3 pathway is a key signaling pathway in cancer. IL-6 activates STAT3, which regulates the expression of genes involved in cell proliferation, survival, and inflammation. Targeting this IL-6 has a dual effect on BC which may either be tumorigenic or antitumorigenic. The tumorigenic effect is caused by inhibiting apoptosis, triggering the survival of tumor cells, and allowing metastasis. IL-6 stimulates

miR-155 expression, which targets SOCS, hence promoting the progression of BC (183). Blocking IL-6 pathway can prevent this progression via the inhibition of tumor migration and invasion (184).

Upregulation of miR-155 in dendritic cells (DCs) induces T cell proliferation and IFN-γ and IL-2 secretion. miR-155 promotes DC maturation and increases the expression of MHC Class II (MHCII), CD86, CD40 and CD83, which are key for T cell activation and the generation of effective TILs (185). This enhances the ability of DCs to present antigens to $CD4^+$ T cells, a key step in activating the adaptive immune response and generating effective TILs (55). By increasing CD86 expression, miR-155 enhances the costimulatory signal needed for T cell activation, promoting a more robust immune response and enhancing TIL function. CD40 signaling is vital for effective antigen-presenting cells (APC) activation, which is a key step in generating potent TIL responses. As a marker of mature DCs, the presence of $CD83^+$ DCs in the tumor microenvironment indicates a more active T cell response, enhancing anti-tumor immunity through TILs. miR-155 promotes the production of IL12p70, a cytokine that promotes the differentiation of $CD4^+$ T into Th1 cells, enhances $CD8^+$ cytotoxic T cell activity and stimulates IFN-γ production. These factors that contribute to an enhanced anti-tumor immune response and are necessary for effective TIL function (53,184,185).

miR-155 exerts an inhibitory effect on ecto-5'-nucleotidase (NT5E) expression. NT5E is an enzyme that produces immunosuppressive adenosine in the tumor microenvironment by hydrolyzing AMP. This adenosine helps cancer cells evade destruction by cytotoxic T lymphocytes. Inhibition of NT5E could enhance the ability of the immune system to target and kill tumor cells. NT5E exists in two isoforms, with the shorter isoform able to bind to the longer one and cause its degradation. Several studies have shown that miR-155-5p can directly inhibit NT5E expression by binding its 3' UTR (186,187).

Dual functionality of miR-155 in BC. miR-155 exemplifies the complex, context-dependent functionality characteristic of miRNAs in BC pathophysiology (138,141). miRNA expression profiles vary across the five molecular subtypes of BC, creating unique molecular environments that modulate miRNA function (136). Alteration of the level of expression and activity of the enzymes involved in the biogenesis of the miRNA may drive the unique profiles observed in BC subtypes (138,141). Robust inverse associations have been established between miR-155 expression and ER positivity, demonstrating a direct association with TNBC phenotypes (136).

Interaction with other non-coding RNA regulatory mechanisms and target availability determined by competing endogenous RNAs (ceRNAs) may explain the positive prognostic association observed with miR-155 expression in TNBC (188). Genomic alterations characteristic of TNBC, including mutations and copy number variations, may modify the expression of transcripts and UTRs, thereby altering the abundance of miRNA response elements. These molecular perturbations disrupt ceRNA network homeostasis, potentially influencing miRNA sequestration dynamics, and target transcript regulation, including the positive prognostic association of miR-155 expression in TNBC genomic contexts-which is characterized by high mutational burden, genomic instability and heterogeneity (189).

The unique TNBC microenvironment affects miR-155 functionality through cell-type specific regulatory networks and signaling cascades (138,190). Furthermore, miR-155 demonstrates notable stage-specific effects; elevated expression may promote recurrence in early-stage disease but is associated with improved outcomes in established TNBC. This temporal heterogeneity is complemented by spatial expression gradients within the tumor architecture, emphasizing the contextual nature of miR-155 function in BC progression (190).

The complex regulatory mechanisms of miR-155 within the TNBC microenvironment illustrate the key intersection between basic molecular oncology and translational medicine. The context-dependent functions of miR-155 presents both challenges and opportunities for clinical application, and barriers remain in translating these molecular insights into practical clinical tools.

5. Translating scientific findings into clinical practice and limitations

Strategies for modifying miRNA content in tumor cells. Wang *et al* (18) demonstrated that miRNAs notably enhance the inflammatory state of breast tumors (18) . This finding is important because tumors characterized by a high percentage of TILs, specifically those classified as LPBC (TILs ≥30 or 50%), are associated with improved outcomes for anticancer therapy (70,95,96). The relationship between TILs and tumor response offers a compelling rationale for exploring strategies to enhance lymphocyte infiltration into tumors, thereby generating tumors with an enhanced immune response dubbed as 'hot tumors'. This are characterized by proinflammatory cytokines and T cell infiltration.

Approaches to modulate the tumor microenvironment using checkpoint inhibitor have been investigated to convert 'cold' into 'hot' tumors, which are expected to respond more effectively to immune-modulatory agents (191,192). Wang *et al* (18) demonstrated that increased expression of miR-155 enhances the recruitment of antitumor immune cells to the tumor microenvironment, effectively transforming 'cold' into 'hot' tumors (18).

Modifying miRNA levels in cells is accomplished through two primary methods: Increasing their concentration with target mimics known as miRNA mimics or decreasing their levels using antisense sequences that inhibit specific targets, referred to as antimiRs. Both strategies can be implemented using oligonucleotides or viral vectors. Advancements in biotechnology have improved the stability of synthetic RNA nucleotides, facilitating their use alongside nanoparticles that exhibit high transfection efficiency (193). This progress in nanotechnology, in conjunction with enhancements in oligonucleotide chemistry, has accelerated the development of RNA interference therapeutics (194,195). Challenges in optimizing the use of short RNA nucleotides include improving targeted delivery, enhancing exosomal delivery, using both viral and non-viral vectors and minimizing toxicity and costs (196,197).

The biotechnological development of a miRNA-based strategy aimed at producing an approved drug necessitates an

organized workflow. This process begins with a preclinical stage focused on establishing the proof-of-concept, which involves demonstrating that the alteration of specific miRNAs yields a notable anticancer effect. This is followed by preclinical studies using animal models, ultimately leading to clinical trials designed to secure approval for the treatment as an anticancer therapy (198-200).

miRNAs as blood-based biomarkers for BC. Wang *et al* (18) demonstrated that miR-155 levels in blood samples from patients are an indicator of the tumor inflammatory state (18). Specifically, higher levels of miR-155 in serum are associated with increased expression of this miRNA in tumor samples, as well as an enhanced immune status.

The biotechnological development of blood-based biomarkers necessitates a carefully designed strategy to ensure safe translation to clinical practice. Standardized protocols and testing targets through multicenter studies are crucial for effectively translating miRNA-based signatures to the clinic. One of the challenges of standardization is identifying suitable reference genes to normalize quantitative PCR results. Additionally, following analytical guidelines for accurate data quantification is key. Multicenter studies involving large, independent cohorts of patients from various countries, representing diverse ethnic groups, are required to validate the proposed miRNA-based biomarkers (201,202).

A typical study involves at least two phases, each with distinct patient cohorts, as illustrated by Zou *et al* (203), which developed a panel of serum miRNAs for BC screening. In the initial phase, known as the discovery cohort, researchers assessed a broad range of targets (324 miRNAs) to identify the most promising candidates whose expression levels significantly differ between patients and healthy controls. The targets selected from this phase, often referred to as the 'miRNA signature', are then evaluated in a validation cohort (203). This systematic approach ensures that the identified miRNA signatures possess clinical relevance across different populations, enhancing their potential application in clinical settings. The next step involves conducting clinical trials to evaluate the accuracy of the selected miRNAs in diagnosing the intended disease. These trials are key for establishing the clinical use of biomarkers. Previous reviews have highlighted ongoing trials focused on validating miRNA-based biomarkers (147,148,151,155). In cancer such lymphoma, leukemia and most solid cancers it is consider an oncogenic miRNA. Differently, in TNBC it is linked with a better prognosis due to the regulation of TILs (204-207).

Limitations. Mounting evidence supports the consensus that the proportion of TILs is one of the most reliable biomarkers for prognosticating outcomes in TNBC (78,79). However, determining this proportion can be subjective, heavily relying on the pathologist microscopic evaluation. Previous studies have identified reproducibility issues among different pathologists (77,208). To address this limitation, multicenter initiatives have been launched, particularly by the TILs Working Group, to provide standardized guidelines and training (70,78). While TILs are valuable biomarkers, standardization is crucial for developing laboratory assessments that effectively guide treatment decisions and prognosis in clinical settings (209,210).

The analysis of miRNAs in tumor biology has been advanced by large datasets, such as The Cancer Genome Atlas (211), which provide clinical information alongside mRNA and miRNA expression patterns. This highlights the complexity of the BC transcriptome, characterized by clusters of expressed genes (212). Each miRNA can regulate hundreds of genes, and the miRNome of tumor cells often exhibits multiple dysregulated miRNAs. Thus, it is key to investigate the role of specific miRNAs to ascertain their involvement in cancer biology and the inflammatory status of tumors (213,214).

Research has elucidated the roles of specific miRNAs in TNBC and their potential as biomarkers for TIL infiltration and tumor outcomes, particularly miR-155. Wang *et al* (18) revealed a significant association between miR-155 levels in blood and tumor samples, as well as with cytokines CCL5 and CXCL9/10/11. The sample size for biomarker validation is key, highlighting the need for multicenter studies. Developing multi-target signatures can enhance the accuracy of miRNA biomarkers, making it essential to evaluate metrics such as area under the curve, accuracy, sensitivity and specificity, typically defined using receiver operating characteristic curves (201-203).

An important consideration in using miRNAs to assess the inflammatory status of breast tumors is whether the miRNA is expressed by cancer cells or lymphocytes. This distinction is key, as tumors exhibit varying levels of lymphocyte infiltration (18). In tumors with a higher proportion of TILs, miR-155 content primarily reflects lymphocyte-derived miRNAs. Conversely, in tumors with minimal lymphocyte infiltration, miR-155 expression is predominantly derived from cancer cells. This limitation warrants caution in interpreting miRNAs as biomarkers, despite the potential of miRNAs as targets for developing prognostic assays in BC.

6. Conclusion

Considering the complexity and diversity of BC subtypes, as well as the impact of this variation on diagnosis, prognosis and therapeutic planning, the use of tumor biomarkers has relevance in the field of breast oncology. miR-155 is a promising biomarker for patient stratification in TNBC due to its multifaceted enhancement of TIL activity, operating via key molecular pathways including SOCS1 suppression, PI3K/AKT modulation and IL-6/STAT3 signaling. The detection of miR-155 in both tumor tissue and circulation, coupled with its role in augmenting DC maturation and T cell responses, suggests its potential use as a predictive marker for immunotherapy efficacy.

As elevated TIL presence is associated with improved survival outcomes in TNBC, miR-155 expression profiling may facilitate more precise therapeutic stratification, advancing personalized treatment approaches in this aggressive BC subtype. Properly designed preclinical studies assessing efficacy, toxicity and pharmacokinetic parameters, followed by clinical trials, are key in the development of miRNA-based therapies aimed at improving treatment outcomes in TNBC.

Acknowledgements

Not applicable.

Funding

The present study was supported by The Ministry of Education (grant no. 9249 TED/MEC), the National Council for Scientific and Technological Development, the Coordination for the Improvement of Higher Education Personnel, the Federal District Research Support Foundation (00193-00001738/2022-51) and Foundation for Scientific and Technological Enterprises-Brasília (01/2024).

Availability of data and materials

Not applicable.

Authors' contributions

MMAV conceived the study and wrote and edited the manuscript. FS performed the literature review and wrote and edited the manuscript. SSARF constructed figures and edited the manuscript. MEX and RTA performed the literature review and editing the manuscript. All authors have read and approved the final 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.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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