RESEARCH ARTICLE

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MicroRNAs as Biomarkers of Breast Cancer Recurrence and Disease Progression: A Comprehensive Scoping Review across Molecular Subtypes

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Abstract

Objective: Breast cancer is a heterogeneous disease consisting of molecular subtypes with varying aggressiveness, growth rates, and therapeutic responses. MicroRNAs (miRNAs) hold potential as biomarkers owing to their role in gene expression regulation in cancer, as well as their specificity and stability in clinical samples. The mapping of miRNAs associated with disease recurrence and progression in each breast cancer subtype remains limited. This scoping review aimed to map the scientific literature on miRNAs related to recurrence and disease progression in TNBC, luminal, and HER2+ breast cancer subtypes. **Methods:** Literature searches were conducted in the Scopus and PubMed electronic databases using predefined keywords. Retrieved records were screened, and duplicates were removed. Selection based on title, abstract, and full text was performed according to the established inclusion criteria. Data extracted from eligible studies included cancer subtype, stage, type and timing of sample collection, treatment, miRNA identification technique, miRNA expression patterns, target genes and molecular pathways, clinical outcomes, and biomarker types. This scoping review was developed using the PRISMA-ScR checklist. **Result:** A total of 28 studies were included and reviewed. miRNAs associated with the TNBC subtype were the most investigated in both profiling and non-profiling studies. The patterns of miRNA expression varied among the TNBC, luminal, and HER2+ subtypes. Of the 74 miRNAs identified across all breast cancer subtypes, only two miRNAs (miR-30c-5p and miR-195-5p) were found in different subtypes. The miRNAs in each breast cancer subtype were demonstrated to be prognostic, predictive, or both. **Conclusion:** This scoping review provides an overview of the unique miRNA expression patterns associated with recurrence and disease progression in TNBC, luminal, and HER2+ breast cancer subtypes. The differences in miRNA expression between breast cancer subtypes emphasize the importance of investigating miRNA biomarkers specific to breast cancer subtypes.

Keywords: MicroRNA- Recurrence- Breast cancer subtypes- biomarkers

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Introduction

The incidence of breast cancer reached 2.3 million cases in 2022, with the mortality rate ranking first among cancer-related deaths in women [1]. Hormonal status and physiological conditions in women contribute to the development of breast cancer [2]. Additionally, early age at menarche, older age at first childbirth, and late age at menopause are risk factors for breast cancer [1].

Breast cancer is a highly heterogeneous disease. It is classified into subtypes such as triple-negative breast cancer (TNBC), luminal, and Human Epidermal Growth Factor Receptor type 2-enriched (HER2+). Each subtype varies in terms of aggressiveness, growth rate, and response to treatment [3]. Poor prognosis, therapy resistance, and recurrence can occur and have been reported in the various subtypes of breast cancer [2, 4, 5].

Surgical intervention and therapeutic agents remain the mainstays of breast cancer management. The choice of therapeutic agent is adjusted according to the breast cancer subtype and is usually combined with chemotherapy [4]. Ineffective therapy may lead to metastasis and recurrence, including distant recurrence, which frequently occurs in the bones, lungs, liver, and brain. Early detection of recurrence enables more optimal cancer management, providing patients with a better chance of survival [6–8]. Identifying biomarkers associated with recurrence is crucial for developing better breast cancer management strategies [3]. Several molecules, such as proteins, DNA, lncRNA, and microRNA, have been studied as recurrence

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biomarkers for breast cancer [6–8].

MicroRNAs (miRNAs) are short, single-stranded RNA of approximately 22 nucleotides that act as regulators of gene expression, including oncogenes and tumor suppressor genes in cancer [9]. MiRNAs are highly specific to certain tissues and even particular cells, are resistant to extreme conditions during sample handling, and are especially stable in plasma [3]. This demonstrates that miRNAs hold great potential as biomarkers. The potential of miRNAs as biomarkers has been demonstrated in various studies on diseases, including several types of cancer [5, 10, 11].

The heterogeneity of breast cancer underscores the importance of specific research on cancer subtypes in investigating miRNAs as biomarkers related to recurrence. This scoping review aimed to map scientific research findings on miRNAs associated with recurrence and disease progression in TNBC, luminal, and HER2+ breast cancer subtypes. This scoping review provides an overview of previous studies, patterns of miRNA expression across breast cancer subtypes, and prospects for future research.

Materials and Methods

Source and literature search strategies

The scoping review was prepared based on the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist [12]. A systematic literature search was conducted in two electronic databases, Scopus and PubMed. The literature was searched in each electronic database in October 2025 using the following keywords: ("microRNA" OR "miRNA") AND ("biomarker" OR "biomarkers") AND ("breast cancer" OR "breast neoplasm" OR "mammary carcinoma" OR "breast tumor") AND ("recurrence" OR "relapse" OR "endocrine resistant" OR "antiestrogen resistant" OR "tamoxifen resistant" OR "aromatase inhibitor resistant" OR "fulvestrant resistant"). The parameters used for searching literature in the Scopus database were document type in the form of articles, finalized publication status, article source type as journals, articles in English, and articles published within the range of 2015-2025. A literature search was conducted using predetermined keywords and electronic databases. No hand searching was performed on the reference lists. The initial search strategy was refined in the supplementary search by adding the keywords "trastuzumab resistant" OR "herceptin resistance" OR "pertuzumab resistant" OR "lapatinib resistance" to the initial keywords to reduce the likelihood of artifacts in the HER2+ subtype analysis. The supplementary search used the same databases, parameters, and inclusion criteria as the initial search, with a greater focus on HER2+.

Inclusion and exclusion criteria

The articles included in this scoping review were original research. The samples analyzed were from patients with breast cancer whose subtypes had been identified. The included articles investigated the association between miRNA expression patterns and recurrence, including disease progression, such as disease-free survival (DFS), distant metastasis-free survival (DMFS), relapse-free survival (RFS), event-free survival (EFS), and resistance to therapy. Disease-free survival was defined as the time from the first surgery to the first recurrence event or death from any cause. Event-free survival was defined as the recurrence of breast cancer after surgery, occurrence of a second primary cancer, death, or failure of neoadjuvant therapy due to disease progression.

In this scoping review, prognostic biomarkers are defined as miRNAs that can be used to predict cancer progression, such as recurrence. Predictive biomarkers are defined as miRNAs that can identify cancer patients who benefit or have less benefit from the administration of certain therapeutic agents.

Studies which did not specifically mention breast cancer subtypes and did not investigate the relationship between miRNAs and disease recurrence or progression were excluded. Articles that were not available in full text or could not be downloaded were excluded from this scoping review.

Selection and data extraction

Articles were selected based on predetermined inclusion and exclusion criteria. Duplicate articles were removed, and title and abstract screening were performed. Articles that met the criteria were screened in full text to identify those eligible for inclusion in the scoping review. The data extracted and recorded consisted of first author's name, cancer subtype, sample size, stage, type of recurrence, type and timing of sample collection, treatment, miRNA identification technique, miRNA expression patterns, target genes and molecular pathways regulated by miRNA, clinical outcomes, and biomarker type.

Results

Article search

The initial search of the literature in the electronic databases Scopus and PubMed yielded 463 records. After removing 129 duplicate records, 334 records remained for title and abstract screening. The initial screening yielded 56 reports, which were then subjected to full-text screening; 25 were deemed eligible for inclusion in this scoping review. Additional searches yielded three new studies related to HER2+ subtype. Figure 1 shows the PRISMA-ScR flow diagram from the initial and additional literature search stages to the identification of eligible studies, showing the number of records identified through electronic databases, the number of records excluded, and the number of eligible studies included in this scoping review.

Characteristics of the included studies

Cancer subtypes, sample types, number of samples, miRNA expression, and biomarker function

The TNBC subtype was investigated in 13 studies [13–25], the luminal subtype was investigated in eight studies [26–33], and the HER2+ subtype was investigated in seven studies [34–40]. The types of samples used in miRNA expression studies included tumor tissue (FFPE

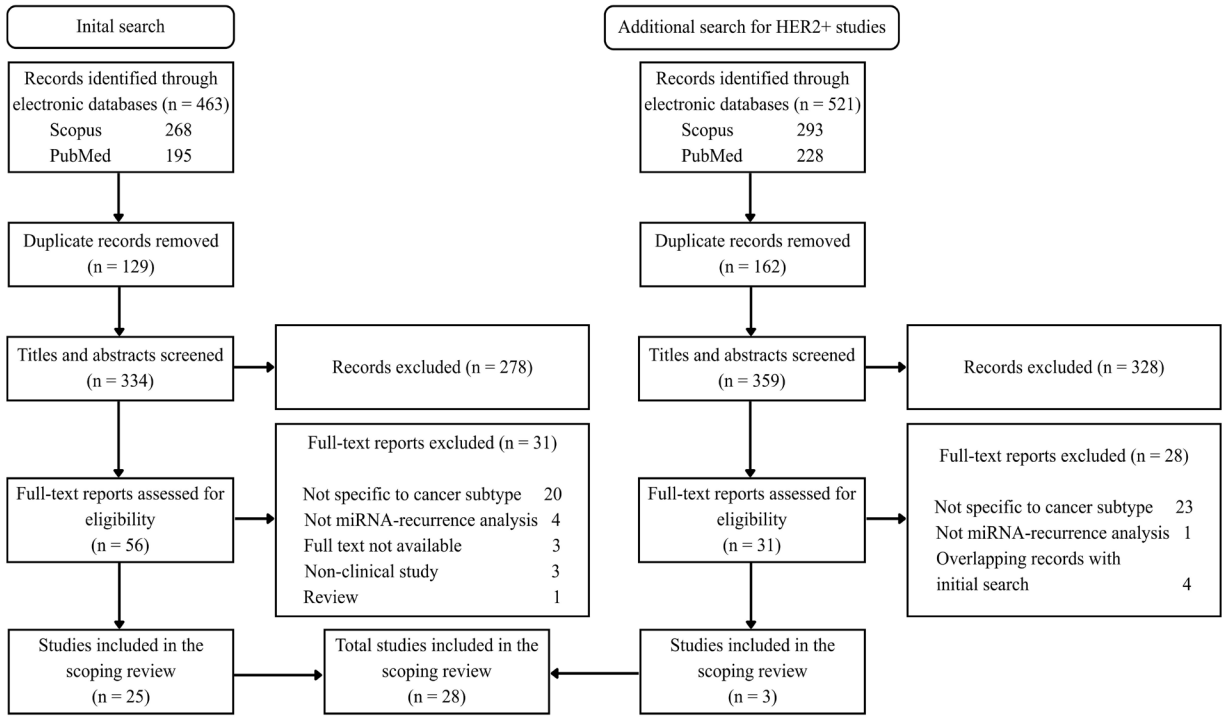

Figure 1. PRISMA-ScR flow diagram of the initial literature search and additional literature search. This flow diagram illustrates the process of literature in the initial and additional searches. A literature search was conducted using the Scopus and PubMed databases. In the initial search, 463 records were identified. Of these, 129 duplicate records were removed, leaving 334 records remaining. A total of 278 records were excluded based on title and abstract screening, and the remaining 56 were subjected to full-text assessment. Thirty-one reports were excluded during the full-text assessment because they were not specific to cancer subtypes, did not involve miRNA analysis related to recurrence, the full text was not available, were not clinical studies, or were review articles. The initial search resulted in the inclusion of 25 studies for review. An additional search was conducted to find literature specifically on HER2+ using the same search method as the initial search but with additional keywords. A total of 521 records were identified in the additional search. Of these, 162 duplicate records were removed, leaving 359 unique records. A total of 328 records were excluded based on title and abstract screening, and the remaining 31 were subjected to full-text assessment. Twenty-eight reports were excluded during the full-text assessment because they were not specific to cancer subtypes, did not involve miRNA analysis related to recurrence, and contained four articles already included in the initial search. The additional search yielded three studies that were included in the review. In total, 28 studies were included in this scoping review.

and fresh frozen tissue), serum, and plasma. Tumor tissue [14, 18–22, 24, 25] and serum [13, 15, 16, 20, 23] have been used in studies investigating the TNBC subtype. Tumor tissue [26–28, 32, 33] and plasma [29–31] have been used in studies investigating the luminal subtype. Tumor tissue [35, 36, 40], serum [37, 39], and plasma [34, 38] have been used in studies investigating the HER2+ subtype.

The number of samples investigated ranged from 25 to 669 for the TNBC subtype, 12 to 139 for the luminal subtype, and 12 to 211 for the HER2+ subtype. The samples investigated by Sueta et al. [23] Group I comprised 24 samples, whereas 16 samples used in group II were partly from group I. Cancer stage was reported in 13 of the 28 studies.

A total of 74 miRNAs were found in the TNBC, luminal, and HER2+ subtypes, with 39 miRNAs found in the TNBC subtype, 16 miRNAs in the luminal subtype, and 19 miRNAs in the HER2+ subtype. Some miRNAs have specific designations for the 5p or 3p strand, but others do not have specific designations for the 5p or 3p strand.

This scoping review found that each miRNA functions as a prognostic or predictive biomarker, or both. Of the 28 studies, two reported that the potential of miRNAs as biomarkers was not statistically significant. Aziz et al. [18] used an adequate sample size (41 samples), but the miRNAs analyzed (miR-21, miR-27b, miR-34a, miR-182, miR-200c, and miR-451a) failed to demonstrate their potential as predictive biomarkers. Zhang et al. [27] used an adequate sample size (62 samples), but one of the miRNAs analyzed (miR-1295a) failed to demonstrate its potential as a prognostic biomarker.

The characteristics of the studies included in this scoping review in terms of cancer subtypes, sample types, miRNA expression, and biomarker function are shown in Table 1. Information regarding the timing of sample collection, cancer stadium, treatment, miRNA analysis technique, miRNA expression (upregulated or downregulated), and the association of miRNA expression with recurrence and cancer progression is provided in Table S1 in the Supplementary File.

Table 1. Characteristics of Included Studies

No.	Author	Subtype	Sample Type	Sample (N)	miRNA	5p/3p Designation	Biomarker Function
1	Borikun et al. 2025 [13]	TNBC	Serum	94	miR-373 and miR-200b miR-125b and miR-205	Not specified Not specified	Prognosis Predictive and prognostic
2	Liu et al. 2023 [14]	TNBC	Frozen tumor tissue	146	miR-27a, miR-206, and miR-214	Not specified	Prognostic
3	Sahlberg et al. 2015 [15]	TNBC	Serum	193 (63 control)	miR-18b, miR-103, miR-107, and miR-652	Not specified	Prognostic
4	Abbas et al. 2022 [16]	TNBC	Serum	200 (100 healthy)	miR-31 and miR-29b	Not specified	Prognostic
5	Panoutsopoulou et al. 2023 [17]	TNBC	Frozen tumor tissue	122	miR-146a	Not specified	Predictive and prognostic
6	Aziz et al. 2022 [18]	TNBC	FFPE tissue	41	miR-21, miR-27b, miR-34a, miR-182, miR-200c, and miR-451a	Not specified	Predictive ($p > 0.05$)
7	Turashvili et al. 2018 [19]	TNBC	FFPE tissue	51	miR-95-3p (Predictive), let-7d-3p, miR-30a- 3p, miR-30a-5p, miR-30c-5p, and miR-128-3p (Prognostic).	Specified	Predictive
8	Kujala et al. 2024 [20]	TNBC	Serum and biopsy tumor tissue	33	miR-21-5p, miR-16-5p, miR-26b-5p, let-7b-5p, and let-7c-5p	Specified	Prognostic
9	Cao et al. 2016 [21]	TNBC	FFPE tissue	466	miR-454	Not specified	Predictive and prognostic
10	Yao et al. 2018 [22]	TNBC	Tissue	382	miR-493	Not specified	Prognostic
11	Sueta et al. 2021 [23]	TNBC	Serum	24 and 16 (study I and II)	miR-195-5p	Specified	Prognostic
12	Wang et al. 2017 [24]	TNBC	FFPE tissue	669 (8 discovery set)	miR-629-3p	Specified	Predictive
13	Turkistani et al. 2021 [25]	TNBC	FFPE tissue	25	miR-1249-3p, miR-1271-3p, and miR-1200	miR-1200 not specified	Prognostic
14	Amorim et al. 2019 [26]	Luminal	Frozen tumor tissue	165 (26 healthy)	miR-30b-5p, miR-30c-5p, miR-182-5p, and miR-200b-3p	Specified	Predictive and prognostic
15	Zhang et al. 2020 [27]	Luminal	FFPE tissue	62	miR-891a-5p and miR-383-5p miR-1295a	Specified Not specified	Prognostic Prognostic ($p > 0.05$)
16	Sevinc et al. 2015 [28]	Luminal	FFPE tissue	40	miR-1266	Not specified	Prognostic
17	Amiruddin et al. 2022 [29]	Luminal	Plasma	34	miR-221	Not specified	Predictive
18	Patellongi et al. 2023 [30]	Luminal	Plasma	34	miR-221 and miR-222	Not specified	Predictive
19	Beilankouhi et al. 2025 [31]	Luminal	Plasma	80	miR-93, miR-382-3p, and miR-182-3p	miR-93 not specified	Predictive
20	Zhong et al. 2016 [32]	Luminal	FFPE tissue	88 (6 discovery set)	miR-4653-3p	Specified	Prognostic and predictive
21	Kim et al. 2025 [33]	Luminal	FFPE tissue	12	miR-483-3p	Specified	Prognostic and predictive
22	Di et al. 2023 [34]	HER2+	Plasma	126	miR-185-5p, miR-146a-5p, and miR-22	miR-22 not specified	Prognostic
23	Du et al. 2016 [35]	HER2+	FFPE tissue	211	miR-150-5p and miR-4734	miR-4734 not specified	Prognostic
24	Fuso et al. 2021 [36]	HER2+	Biopsy tumor tissue and FFPE tissue	200	let-7a-5p, miR-100-5p, miR-101-3p, and miR-199a-3p	Specified	Predictive and prognostic
25	Zhang et al. 2020 [37]	HER2+	Serum	175	miR-1246 and miR-155	Not specified	Predictive and prognostic
26	Rezaei et al. 2023 [38]	HER2+	Plasma	40	miR-195-5p, miR-34c-3p, and miR-1246	miR-1246 not specified	Predictive
27	Yang et al. 2019 [39]	HER2+	Serum	64	miR-200b, miR-135b, miR-29a, and miR-224	Not specified	Predictive
28	Qiao et al. 2020 [40]	HER2+	Frozen tumor tissue	12	miR-455	Not specified	Prognostic

Timing of sample collection, treatment, and cancer stage

The timing of sample collection in studies on the TNBC subtype was as follows: before neoadjuvant therapy (NAT) [13], before adjuvant therapy (AT) [14, 15, 18, 19, 21, 22, 24, 40], before and after NAT [23], after NAT and before AT [17], and before and after AT [20]. For the luminal subtype, sample collection was conducted before AT [26–28, 33], during AT [29–31], and before and during or after AT (recurrence samples) [32]. For the HER2+ subtype, samples were collected before and after NAT [36], after NAT and before AT [34], and before AT [35]. Two TNBC subtype studies [16, 25] and three HER2+ study [37–39] did not report the timing of sample collection.

The therapies administered to patients included NAT alone, AT alone, or both NAT and AT. In the TNBC subtype, NAT alone was reported in one study [13, 23] and AT alone was reported in eight studies [14, 15, 18–22, 24], and both NAT and AT were reported in two studies [17]. AT was reported in all studies on the luminal subtype. For the HER2+ subtype, AT alone was reported in four study [35,38–40], and both NAT and AT were reported in three studies [34, 36, 37].

Thirteen studies reported the cancer stage, with six studies reporting stages I-III [15, 18, 23, 24, 32, 35], three studies reporting stages II-III [13, 29, 30], and four studies reporting stages I-IV. Fifteen studies did not report the patient's stage [14, 17, 20–22, 25–28, 33, 34, 37–40].

miRNA analysis techniques and expression

The analysis techniques used in miRNA investigations are divided into two categories: profiling (NGS, microarray, and NanoString) and non-profiling (qRT-PCR). The qRT-PCR technique [13–18], NGS [19, 20], microarray [21–24], and NanoString [25] have been used in studies investigating the TNBC subtype. The qRT-PCR technique [26–31], microarray [32], and NanoString [33] have been used in studies investigating the luminal subtype. qRT-PCR [34, 38–40], NGS [36], and microarray [35] have been used in studies investigating the HER2+ subtype. Figure 2 shows the network linking miRNAs and miRNA identification techniques, showing the names of miRNAs in each breast cancer subtype identified using profiling (Figure 2-a) and non-profiling (Figure 2-b) techniques.

Twenty-four highly expressed miRNAs in the TNBC subtype include eleven miRNAs (miR-629-3p, miR-1271-3p, miR-548ab, miR-195-5p, miR-18b, miR-103, miR-107, miR-652, let-7b-5p, let-7c-5p, and miR-29b) associated with recurrence, three miRNAs (miR-27a, miR-206, and miR-214) associated with worse DFS, and five miRNAs (miR-125b, miR-21-5p, miR-205, miR-95-3p, and let-7d-3p) associated with worse RFS. One miRNA (miR-493) was associated with better DFS, and two miRNAs (miR-16-5p and miR-26b-5p) were associated with better RFS. Seventeen miRNAs with low expression in the TNBC subtype consist of nine miRNAs (miR-1200, miR-1249-3p, miR-31, miR-21, miR-27b, miR-34a, miR-182, miR-200c, and miR-451a) related to recurrence, one miRNA (miR-146a) related to recurrence and worse DFS, four miRNAs (miR-30a-3p, miR-30a-5p, miR-30c-5p, and miR-128-3p) related to worse RFS, two miRNAs (miR-373 and miR-200b) related to better RFS, and one miRNA (miR-454) related to better DFS. Low expression of miR-21, miR-27b, miR-34a, miR-182, miR-200c, and miR-451a was related to recurrence, but not statistically significant [18].

Six highly expressed miRNAs (miR-1266, miR-221, miR-222, miR-93, miR-382-3p, and miR-483-3p) in the luminal subtype and three miRNAs (miR-1295a, miR-4653-3p, and miR-182-3p) with low expression in the luminal subtype were associated with recurrence. Low expression of two miRNAs (miR-30b-5p and miR-30c-5p) was associated with recurrence and worse DFS. Two miRNAs (miR-891a-5p and miR-383-5p) with low expression levels were associated with worse DMFS.

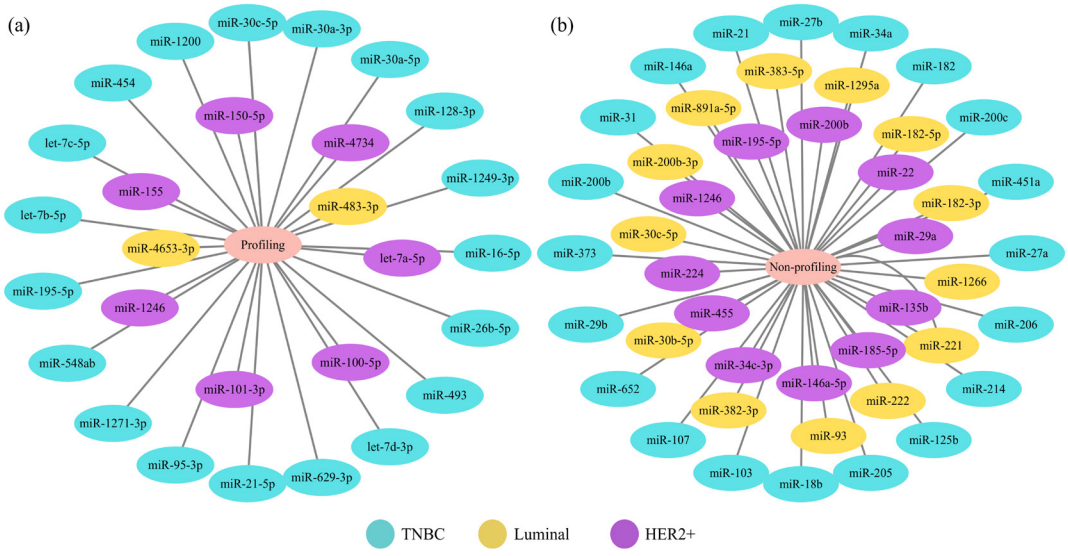

Figure 2. The Network Linking miRNAs and miRNA Identification Techniques. Figure 2-a shows a list of miRNAs identified using profiling techniques (NGS, microarray, and NanoString). Figure 2-b shows a list of miRNAs identified using a non-profiling technique (qRT-PCR). The color of each miRNA node indicates the subtypes of breast cancer. The TNBC, luminal, and HER2+ subtypes are colored blue, yellow, and purple, respectively.

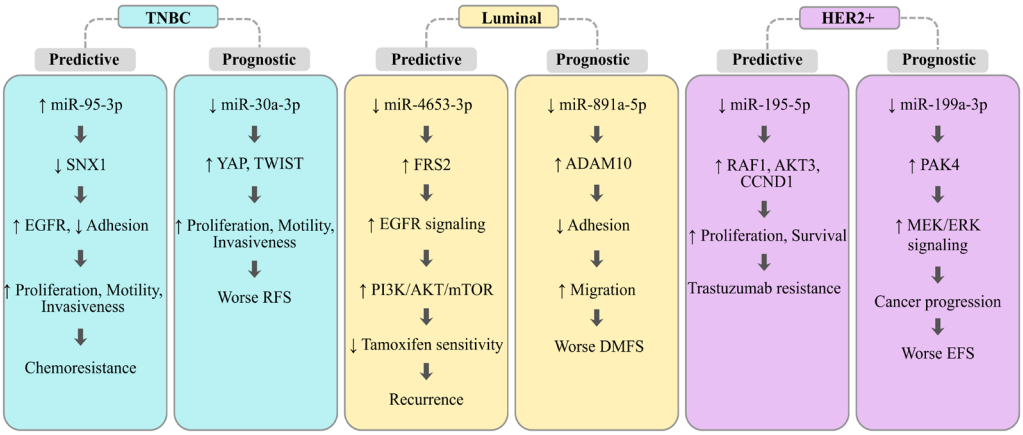

Figure 3. The schematic network shows that miRNAs with 5p or 3p designations affect recurrence in each subtype of breast cancer. The schematic network shows the miRNAs that influence the recurrence of TNBC, luminal, and HER2+ subtypes. In the TNBC subtype, increased expression of miR-95-3p suppresses SNX1 expression, resulting in elevated EGFR levels on the cell membrane and decreased cell adhesion. These triggers increased proliferation, motility, and invasiveness of cancer cells, which may lead to chemoresistance in cancer cells. Decreased expression of miR-30a-3p induced increased expression of YAP and TWIST genes (targets of miR-30a-3p). This leads to increased proliferation, motility, and invasiveness of cancer cells, resulting in worse RFS. In the luminal subtype, decreased expression of miR-4653-3p leads to increased expression of FRS2, resulting in heightened EGFR signaling activity. This enhances the PI3K/AKT/mTOR pathway, thereby reducing tamoxifen sensitivity and potentially triggering cancer recurrence in patients. Decreased expression of miR-891a-5p increases the expression of ADAM10, which can reduce cancer cell adhesion and promote cancer cell migration, leading to worse DMFS. In the HER2+ subtype, decreased expression of miR-195-5p led to increased expression of RAF1, AKT3, and CCND1. These triggers enhanced proliferation and survival of cancer cells, resulting in resistance to trastuzumab. Decreased expression of miR-199a-3p increases the expression of PAK4. This causes heightened MEK/ERK signaling activity, which promotes cancer progression and leads to a worse EFS. The miRNAs displayed for each breast cancer subtype were selected based on the presence of the 5p or 3p designation, their target genes investigated in cell lines, and their potential as predictive or prognostic biomarkers.

Low expression of two miRNAs (miR-200b-3p and miR-182-5p) was associated with recurrence, worse DFS, and worse DMFS. Low expression of miR-1295a was associated with poorer DMFS, but this was not statistically significant [27].

Fourteen highly expressed miRNAs in the HER2+ subtype include six miRNAs (miR-185-5p, miR-146a-5p, let-7a-5p, miR-100-5p, miR-101-3p, and miR-199a-3p) associated with better EFS, three miRNAs (miR-22, miR-1246, and miR-155) associated with worse EFS, one miRNA associated with better RFS (miR-455), and four miRNAs (miR-150-5p, miR-200b, miR-135b, and miR-29a) associated with recurrence. Five miRNAs (miR-4734, miR-224, miR-195-5p, miR-34c-3p, and miR-1246) with low expression were associated with recurrence. The relationship between miRNA expression patterns and cancer recurrence and progression is reported in the respective studies (Table S1).

Two miRNAs were found in different subtypes. miR-30c-5p was found in both the TNBC and luminal subtypes, whereas miR-195-5p was found in the TNBC and HER2+ subtypes. In addition, miRNAs found in the HER2+ subtype (miR-146a-5p) and luminal subtype (miR-200b-3p, miR-182-5p, and miR-182-3p) are similar to miRNAs found in TNBC (miR-146a, miR-200b, and miR-182) and HER2+ (miR-200b) subtypes, but they do not have the 5p or 3p designation in the TNBC and HER2+ subtypes. The Venn diagram shows the number of miRNAs in each breast cancer subtype, miR-30c-5p and miR-195-5p found in different subtypes, and names of miRNAs without 5p or 3p annotations that are like miRNAs with 5p or 3p annotations (Supplementary Figure S1).

Types of recurrence, target genes, and molecular pathways

The types of recurrence reported in studies on the TNBC subtype include local recurrence in one study [13], distant recurrence in three studies [15, 21, 24], and both local and distant recurrence in four studies [18–20, 25]. The types of recurrence reported in studies on the luminal subtype included distant recurrence in three studies [27, 28, 31] and both local and distant recurrences in four studies [26, 29, 30, 33]. The types of recurrence reported in studies on the HER2+ subtype included local recurrence in one study [40] and both local and distant recurrences were reported in two studies [36, 37]. Some studies analyzed miRNA target genes and their molecular pathways, while others obtained this information from the literature. The types of recurrence for each breast cancer subtype and the target genes and pathways regulated by miRNAs in each cancer subtype are listed in Table S2. The miRNAs analyzed by Fuso et al. [36] have dozens of target genes, and only a portion of them is listed in Table S2.

Several studies have investigated miRNAs as biomarkers for breast cancer, as well as the target genes and molecular pathways regulated by miRNAs. Target gene investigations were conducted either in silico or in vitro using cell lines (data not shown in the table). Some miRNAs labeled with 5p or 3p have their target genes

investigated in cell lines, including miR-95-3p, miR-30a-3p, miR-4653-3p, miR-891a-5p, and miR-195-5p [19, 27, 32, 38]. Meanwhile, the target gene of miR-199a-3p [36] was identified from references whose studies used cell lines. Figure 3 shows the recurrence affected by miRNAs with 5p or 3p designations in each subtype of breast cancer.

Discussion

This scoping review successfully mapped studies on miRNA biomarkers in each breast cancer subtype associated with recurrence and cancer progression. The patterns of miRNA expression across the subtypes showed almost no overlap. Of the 74 miRNAs reported in all studies, only miR-30c-5p and miR-195-5p were reported in more than one subtype. These findings support the hypothesis that miRNA expression patterns differ between breast cancer subtypes, indicating that the investigation of miRNA candidates as biomarkers needs to be carried out specifically for each breast cancer subtype. In contrast, the finding of miR-30c-5p and miR-195-5p in more than one subtype shows that not every miRNA found in each subtype can immediately be considered specific to that subtype. Further investigation is needed to determine whether the identified miRNAs are specific to subtypes or are present across multiple breast cancer subtypes.

Some miRNAs in specific subtypes are challenging to interpret, whether they are the same as or different from those in other subtypes. miR-200b, miR-182, and miR-146a in the TNBC subtype have been reported without specifying whether they are 5p or 3p strands. These miRNAs have both 5p and 3p strands listed in the miRBase database, each with different sequences and accession codes. miRNAs without a 5p or 3p strand designation make it difficult to determine whether miR-200b, miR-182, and miR-146a in the TNBC subtype is the same as or different from miR-200b-3p, miR-182-3p or miR-182-5p in the luminal subtype, and miR-146a-5p in the HER2+ subtype. Information on the 5p and 3p strands is crucial, especially for determining target genes. One study revealed that miRNAs with different strands in cancer have different target genes and effects [41]. Further investigation is needed to determine whether the miRNA identified is the 5p or 3p strand, enabling more accurate interpretation.

This review highlights the differences in miRNA expression among breast cancer subtypes, which can be attributed to the multi-target nature of miRNAs. A single miRNA can target more than one gene, and conversely, a single gene can also be targeted by multiple miRNAs. Several studies have reported these findings. For example, miR-221 and miR-222 target PTEN and TIMP3 in the luminal subtype [30], while miR-21-5p and miR-454 target PTEN in the TNBC subtype [20, 21]. This suggests that differences in miRNA expression between breast cancer subtypes may arise because multiple miRNAs can regulate the same gene. Currently, it is unknown whether each breast cancer subtype has a specific miRNA that targets a particular gene. Further investigation is needed to determine whether each cancer subtype expresses unique miRNAs that specifically target certain genes.

Several miRNAs have the potential to serve as predictive biomarkers of adjuvant therapy effectiveness in TNBC and luminal subtypes. Differences in miRNA expression patterns have been reported in several studies investigating miRNAs in cancer subtype, sample type, and at the same sampling time point (before adjuvant therapy), but using different therapeutic agents [19, 21, 24]. Each type of therapeutic agent may have varying effectiveness. miRNAs have the potential to be used as predictive biomarkers for specific therapeutic agents. miR-454, investigated by Cao et al. [21] in the TNBC subtype, shows potential as a predictive biomarker for the diminished efficacy of anthracycline-based agents. This opens opportunities for further investigation into the potential of miRNAs as predictive biomarkers for several types of adjuvant therapy. In addition, several studies have reported the potential of miRNAs as predictive biomarkers for tamoxifen effectiveness [29–31]. Further research should be conducted to investigate whether patients at high risk of resistance would benefit from alternative therapeutic agents to minimize recurrence due to ineffective therapy. miRNAs obtained from cancer tissues, such as miR-454, require cross-specimen validation using liquid biopsy samples to confirm that miR-454 is used in monitor patients. In addition, randomized controlled trials may be considered to determine whether selecting therapeutic agents based on miRNA biomarkers is better than selection without considering miRNA biomarkers. The potential clinical benefits of using miRNAs as predictive biomarkers include patient stratification for the selection of the most appropriate therapeutic agents, allowing patients to gain maximum benefit from therapy. Other clinical benefits include the use of miRNAs to monitor the effectiveness of therapeutic agents while patients are undergoing treatment.

miRNAs also have multiple functions, serving as both predictive and prognostic biomarkers in breast cancer. Some miRNAs, such as miR-125b and miR-205, can predict both the effectiveness of anthracyclines and taxanes, as well as recurrence prognosis in the TNBC subtype [13]. Information about the dual role of miRNAs is valuable, as they can be used to predict both therapeutic response and risk of recurrence. Further investigation and validation are required to identify miRNAs with dual roles. Sevinc et al. [28] reported that miR-1266 shows potential as a prognostic biomarker for recurrence in the luminal subtype, but its potential as a predictive biomarker for tamoxifen efficacy requires further validation in larger populations.

Several studies have conducted internal or external validation to strengthen the findings of miRNAs as biomarkers for breast cancer. External validation on independent cohorts was performed by Sahlberg et al. [15] for the TNBC subtype and by Du et al. [35] for the HER2+ subtype. Successful validation in independent cohorts demonstrates a low risk of overfitting and the potential applicability of miRNA biomarkers to larger populations. Internal validation was carried out by Cao et al. [21] for the TNBC subtype, Zhong et al. [32] for the luminal subtype, and Zhang et al. [37] for the HER2+ subtype. Internal validation is useful for ensuring the reliability

and accuracy of the miRNAs investigated in the same population. The results of internal validation can be used as a consideration for external validation. The smallest sample sizes were 25 samples for the TNBC subtype [25], 12 samples for the luminal subtype [33], and 12 samples for the HER2+ subtype [40]. The miRNAs investigated in these three studies were statistically significant. These three studies need to be confirmed in independent populations with adequate sample sizes to obtain more robust and clinically reliable results.

One study investigated the role of miR-27b and miR-451a as predictive biomarkers for therapy effectiveness in the TNBC subtype, but the results were not statistically significant; thus, the conclusions were weak [18]. Nevertheless, this finding supports the role of miR-27b and miR-451a as diagnostic biomarkers, as low expression of these miRNAs is associated with TNBC breast cancer. In addition, miR-1295a was found to have low expression in patients with luminal breast cancer who experienced metastasis. However miR-1295a is not a strong prognostic biomarker in the luminal subtype as the study failed to find a significant association with DMFS [27].

Selecting different biological materials can complement the investigation of miRNAs as candidate biomarkers for recurrence. Kujala et al. [20] identified miRNAs from tumor tissue biopsy samples and serum taken at the time of cancer diagnosis. Two miRNAs (let-7c-5p and miR-128-3p) from biopsy samples could distinguish between the recurrence and non-recurrence groups, while ten miRNAs from serum samples, including let-7c-5p and miR-128-3p, could distinguish between these groups. Some miRNAs were found in both sample types, whereas others were found only in serum. This leads to the hypothesis that serum miRNAs are not always derived from tumors or that tumor tissue biopsies do not fully represent the entire tumor. The use of different samples provides more comprehensive identification of miRNAs associated with clinical outcomes.

miRNAs have the potential to serve as biomarkers and therapeutic targets. Increased expression of miR-205 in the TNBC subtype was associated with worse RFS. On the other hand, Kumar et al. [42] reported in a cohort study that the expression of miR-205 showed a significant increase at all stages of the TNBC subtype compared to healthy controls, with excellent sensitivity and specificity values. This indicates that the elevated expression of miR-205 plays a crucial role in the poor prognosis of TNBC. In addition to their potential as biomarkers, these two miRNAs can be further investigated as therapeutic targets for TNBC. Future studies should be conducted to prove the impact of suppressing the expression of miR-205 on the prognosis of patients with the TNBC subtype.

Technical harmonization is necessary for the clinical translation of miRNA biomarkers to ensure cross-center comparisons and validation of study results. The sample types used, sample collection times, extraction methods, and data normalization in qRT-PCR must be harmonized to develop clinically applicable assays.

The literature search results indicated an imbalance in the number of research publications among TNBC subtypes (n = 13), luminal (n = 8), and HER2+ (n = 7). Most miRNA research related to recurrence has been conducted on the TNBC subtype because TNBC is the most aggressive subtype, has a poor prognosis, and has limited treatment options, leading to a high rate of early recurrence and metastasis. In addition, the role of miRNAs in TNBC development remains unclear. Apart from the TNBC subtype, many studies have also been conducted on the luminal subtype because of its higher frequency compared to other subtypes, the presence of endocrine therapy resistance, and the fact that recurrence can occur decades after therapy, necessitating efforts to predict the likelihood of future recurrence. These factors contribute to the high proportion of research on TNBC and luminal subtypes compared to the HER2+ subtype.

This review has several limitations, such as incomplete data on crucial variables, such as therapy type and sampling time [25, 37]. This limits the interpretation of the potential of miRNAs as predictive or prognostic biomarkers. Incomplete miRNA nomenclature also limits the interpretation of miRNA expression mapping across cancer subtypes.

In conclusion, this scoping review provides an overview of the unique miRNA expression patterns associated with recurrence and disease progression in TNBC, luminal, and HER2+ breast cancer subtypes, emphasizing the importance of investigating subtype-specific biomarkers. Future miRNA biomarker studies should report the mature strand (5p or 3p) and miRBase accession numbers to enable accurate comparisons between studies and bioinformatics analyses. Based on the mapping results of this scoping review, several concrete and high-priority research directions have emerged. First, prospective multicenter validation is needed for miRNA candidates with clear strand identification for each breast cancer subtype in plasma samples. Second, integrated multi-omic studies are needed to link miRNAs to the molecular pathways regulated by subtype-specific miRNAs in breast cancer. Third, the investigation of single miRNAs compared to miRNA panels to improve the predictive power for recurrence or therapy resistance.

Author Contribution Statement

Muhamad Firmanda conceptualized and wrote this review; Irianiwati Widodo reviewed the manuscript and contributed to the grant acquisition; Teguh Aryandono reviewed the manuscript and contributed to the grant acquisition; Dyah L. Dewi designed, conceptualized, wrote this review and contributed to the grant acquisition. All authors read and approved of the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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