

Clinicopathological and Prognostic Significance of Melatonin Receptor MT1 (MTNR1A) Expression in Breast Cancer Patients: A Systematic Review

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ABSTRACT

Background: Breast cancer caused 0.67 million deaths in 2022, and clinicians need tissue markers that refine risk beyond stage, hormone receptors, and HER2. Melatonin inhibits breast cancer growth through the MT1 receptor (MTNR1A), yet tissue studies disagree on its prognostic value. **Objective:** To evaluate the clinicopathological and prognostic significance of MT1 expression in breast cancer. **Material and Method:** Following PRISMA 2020, we searched PubMed, ScienceDirect, and Europe PMC for observational studies reporting MT1 expression in breast carcinoma tissue with clinicopathological or survival data. We assessed quality with the Newcastle-Ottawa Scale (NOS) and synthesized findings narratively. Eight studies (n = 657) met the criteria; three scored 9/9 and four scored 2/9. MT1-positive tumors ranged from 48.4% to 93.9%, and three studies found lower expression in triple-negative breast cancer (TNBC). High MT1 predicted longer overall survival (OS) in ER-positive patients (HR 0.42; 95% CI 0.21–0.87; p = 0.019) and tamoxifen-treated patients (HR 0.43; 95% CI 0.21–0.90; p = 0.025). In TNBC, MT1 negativity predicted shorter OS (adjusted HR 2.02; p = 0.026) and progression-free survival (adjusted HR 1.91; p = 0.034). A luminal cohort (n = 118) found no survival association (OS: HR 1.001; p = 0.624). We did not pool the data because antibodies, cut-offs, and outcome definitions differed across studies. **Conclusion:** Most breast carcinomas express MT1, with lower levels in TNBC. MT1 is a candidate prognostic marker, but its survival evidence rests on two retrospective cohorts with different methods. Clinical use requires validated MT1-specific antibodies and standardized cut-offs.

Keywords: breast cancer; MTNR1A; melatonin receptor; prognosis

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide, with 2.30 million new cases and 0.67 million deaths in 2022 [1], [2]. Kim et al. [3] projected increases of 38% in cases and 68% in deaths by 2050, concentrated in low-HDI countries. Asia carried the largest burden in 2022, with 985,817 cases and 315,309 deaths [4]. Indonesia ranked eighth worldwide for cases (66,271) and fourth for deaths (22,598) [5]. The national SADANIS program reached only 25.55% of its target population between 2022 and 2024, and almost 70% of cancer patients were still present at an

advanced stage [6]. At Dr. Soetomo General Hospital, the referral center for East Java, breast cancer led all cancer cases in 2019 [7], and three-year survival dropped from 100% in stage IIA to 30% in stage IV [8]. Screening and stage-based treatment leave many patients with poor outcomes, and clinicians need tissue biomarkers that refine risk beyond TNM stage, hormone receptors, and HER2.

Melatonin inhibits breast cancer growth through the MT1 receptor [9]. In ER α -positive cells, MT1 activation lowers cAMP, suppresses ER α expression and transcriptional activity, and blocks linoleic acid conversion to the mitogen 13-HODE [10].

Tissue studies disagree on whether this biology predicts outcome. Jablonska et al. [11] linked higher MT1 to longer overall survival in ER-positive, tamoxifen-treated patients, and Oprea-Ilie et al. [12] linked MT1-negative triple-negative tumors to higher stage and shorter survival. Pistiolis et al. [13] found no association with clinicopathological features or survival in 118 luminal tumors. These studies differ in antibodies, scoring cut-offs, subtypes, and populations, and to our knowledge no systematic review has synthesized them.

The purpose of this systematic review is to evaluate the prognostic and clinicopathological significance of MT1 melatonin receptor expression in breast cancer by synthesizing the available evidence from human tissue studies. Specifically, we ask whether MT1 expression associates with clinicopathological characteristics (age, menopausal status, tumor size, grade, nodal status, stage, ER, PR, HER2, Ki-67, and molecular subtype) and whether it predicts overall, disease-free, progression-free, or breast cancer-specific survival. We hypothesize that higher MT1 expression associates with favorable features and longer survival, with molecular subtype modifying the effect. The findings will help pathologists decide whether MT1 immunohistochemistry belongs in prognostic panels and guide researchers toward standardized scoring and the subtypes most suited to trials of melatonin or MT1 agonists. In Indonesia, where most patients present late, an inexpensive marker that sharpens prognosis would add value to routine pathology practice.

MATERIAL AND METHODS

Study design

This study is a systematic review of observational studies, reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page, et al., 2021). We framed the review question with the PECO approach. The population was patients with histologically confirmed breast carcinoma. The exposure was high or positive MT1 (MTNR1A) expression in tumor tissue, and the comparator was low or negative MT1 expression. The outcomes were clinicopathological characteristics and survival outcomes. We registered the protocol in [PROSPERO, registration number CRD420261531911].

Data collection

We searched three electronic databases: PubMed, ScienceDirect, and Europe PMC. We built the search terms with the PICOS framework (Population, Intervention/Exposure, Comparator, Outcome, Study design) and combined Medical Subject Headings (MeSH) with free-text terms using the Boolean operators AND, OR, and NOT. In PubMed and Europe PMC, we excluded studies indexed only in animals. In Europe PMC, we also limited results to full-text articles and excluded records indexed as reviews. Table 1 reports the full search strategy for each database.

TABLE 1: Search Strategy in PubMed, ScienceDirect, And Europe PMC.

Database	Search strategy
PubMed	("Breast Neoplasms"[Mesh] OR "Carcinoma, Ductal, Breast"[Mesh] OR "Carcinoma, Lobular"[Mesh] OR "breast cancer*" [tiab] OR "breast carcinoma*" [tiab] OR "breast neoplasm*" [tiab] OR "breast tumor*" [tiab] OR "breast tumour*" [tiab] OR "breast malignan*" [tiab] OR "mammary carcinoma*" [tiab] OR "mammary cancer*" [tiab] OR "triple negative breast" [tiab] OR TNBC [tiab]) AND ("Receptor, Melatonin, MT1" [Mesh] OR "Receptors, Melatonin" [Mesh] OR MTNR1A [tiab] OR "melatonin receptor*" [tiab] OR "melatonin membrane receptor*" [tiab] OR Mel1a [tiab] OR "Mel-1a" [tiab] OR MT1R [tiab] OR "MT1 receptor*" [tiab] OR "MT1 melatonin" [tiab] OR "melatonin MT1" [tiab] OR (MT1 [tiab] AND melatonin [tiab])) AND ("Immunohistochemistry" [Mesh] OR "Tissue Array Analysis" [Mesh] OR "Blotting, Western" [Mesh] OR "Prognosis" [Mesh] OR "Survival Analysis" [Mesh] OR "Disease-Free Survival" [Mesh] OR "Neoplasm Staging" [Mesh] OR "Neoplasm Grading" [Mesh] OR "Lymphatic Metastasis" [Mesh] OR "Biomarkers, Tumor" [Mesh] OR immunohistochem* [tiab] OR IHC [tiab] OR immunostain* [tiab] OR immunoreactiv* [tiab] OR "tissue microarray*" [tiab] OR expression [tiab] OR prognos* [tiab] OR surviv* [tiab] OR clinicopatholog* [tiab] OR recurrence [tiab] OR "hazard ratio*" [tiab] OR outcome* [tiab] OR grade [tiab] OR stage [tiab] OR "lymph node*" [tiab]) NOT ("Animals" [Mesh] NOT "Humans" [Mesh])
ScienceDirect	("breast cancer" OR "breast carcinoma" OR "breast neoplasm" OR "mammary carcinoma") AND ("MTNR1A" OR "melatonin receptor" OR "MT1 receptor" OR "melatonin MT1")

Database	Search strategy
Europe PMC	(MESH: "Breast Neoplasms" OR MESH: "Carcinoma, Ductal, Breast" OR MESH: "Carcinoma, Lobular" OR TITLE_ABS: "breast cancer" OR TITLE_ABS: "breast carcinoma" OR TITLE_ABS: "breast neoplasm" OR TITLE_ABS: "breast tumor" OR TITLE_ABS: "breast tumour" OR TITLE_ABS: "mammary carcinoma" OR TITLE_ABS: "triple negative breast" OR TITLE_ABS:TNBC) AND (MESH: "Receptor, Melatonin, MT1" OR MESH: "Receptors, Melatonin" OR TITLE_ABS:MTNR1A OR TITLE_ABS: "melatonin receptor" OR TITLE_ABS: "melatonin receptors" OR TITLE_ABS: "melatonin membrane receptor" OR TITLE_ABS:"MT1 receptor" OR TITLE_ABS:"MT1 melatonin" OR TITLE_ABS: "melatonin MT1" OR TITLE_ABS:Mel1a OR TITLE_ABS:MT1R OR (TITLE_ABS:MT1 AND TITLE_ABS: melatonin)) AND (MESH: "Immunohistochemistry" OR MESH: "Prognosis" OR MESH: "Survival Analysis" OR MESH: "Neoplasm Staging" OR MESH: "Biomarkers, Tumor" OR TITLE_ABS: immunohistochem* OR TITLE_ABS:IHC OR TITLE_ABS: immunostain* OR TITLE_ABS: "tissue microarray" OR TITLE_ABS: expression OR TITLE_ABS: prognos* OR TITLE_ABS: surviv* OR TITLE_ABS: clinicopatholog* OR TITLE_ABS: "hazard ratio" OR TITLE_ABS: recurrence) NOT (MESH: "Animals" NOT MESH: "Humans") AND ((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE: "Review")) AND (HAS_FT:Y)

We included studies that met the following criteria: original observational studies (cohort, case-control, or cross-sectional) in patients with histologically confirmed breast carcinoma; MT1 or MTNR1A expression measured in primary tumor tissue by immunohistochemistry, immunofluorescence, or reverse transcription PCR; patients grouped by MT1 expression level or status; and reported data on at least one clinicopathological characteristic or survival outcome. We excluded in vitro and animal studies, reviews, case reports, editorials, conference abstracts without full text, studies of MT2 or other receptors only, studies without extractable outcome data, retracted articles, and articles not published in English. When several publications reported the same cohort, we kept the most complete one.

We imported all records into Rayyan and removed duplicates. Two reviewers screened titles and abstracts independently, then assessed the full texts of potentially eligible studies against the criteria. A third reviewer resolved disagreements. Figure 1 presents the selection process in a PRISMA 2020 flow diagram, showing records identified per database, duplicates removed, records screened and excluded, full texts assessed, full texts excluded with reasons, and studies included. The same two reviewers extracted data independently into a standardized form in Microsoft Excel. The extracted items were first author, year, country, study design, study period, sample size, patient age and menopausal status, histological type, molecular subtype, specimen type, detection method, antibody and dilution, scoring system and cut-off for high or positive MT1, treatment, follow-up duration, clinicopathological data by MT1 group, and survival estimates. For survival, we extracted hazard ratios (HR) with 95% confidence intervals (CI) from multivariable analyses when available, otherwise from univariable analyses. When a study reported only Kaplan-Meier curves, we estimated the HR using the method of Tierney et al. [14].

We assessed the methodological quality of each study with the Newcastle-Ottawa Scale (NOS), which scores selection, comparability, and outcome domains up to nine stars [15]. We classified studies

scoring 7 to 9 as high quality, 4 to 6 as moderate quality, and below 4 as low quality. Two reviewers performed this assessment independently and resolved disagreements by discussion.

Data analysis

We synthesized the findings narratively, following the Synthesis Without Meta-analysis (SWiM) guideline [16]. We grouped studies by outcome and, within each outcome, by molecular subtype and detection method. For each clinicopathological characteristic, we tabulated the distribution of patients by MT1 group and calculated the odds ratio (OR) with 95% CI per study when the data allowed. For each survival outcome (overall, disease-free, progression-free, and breast cancer-specific survival), we tabulated the HR, 95% CI, and p-value, and recorded whether the analysis adjusted for other prognostic factors. We summarized the direction of effect across studies by vote counting based on the direction of effect, and we considered a result statistically significant at $p < 0.05$ as reported by each study. We presented study characteristics, quality scores, and outcome data in tables and explored differences in antibody, scoring cut-off, subtype, and population as possible explanations for inconsistent findings.

Ethical consideration

This review used only data from previously published studies and involved no direct contact with patients or access to identifiable personal data. Ethical clearance was therefore not required.

RESULTS

Study selection

The database search identified 150,002 records: 147,089 from PubMed, 13 from ScienceDirect, and 2,900 from Europe PMC. After removing 87 duplicates, we screened 149,915 titles and abstracts and excluded 149,892 records: 147,550 did not involve the population of interest, 557 did not assess MT1, and 1,785 had an ineligible study design. We retrieved all 23 remaining reports in full text and excluded 15 because they did not report the outcomes of interest. Eight studies met all criteria. Figure 1 shows the PRISMA 2020 flow diagram.

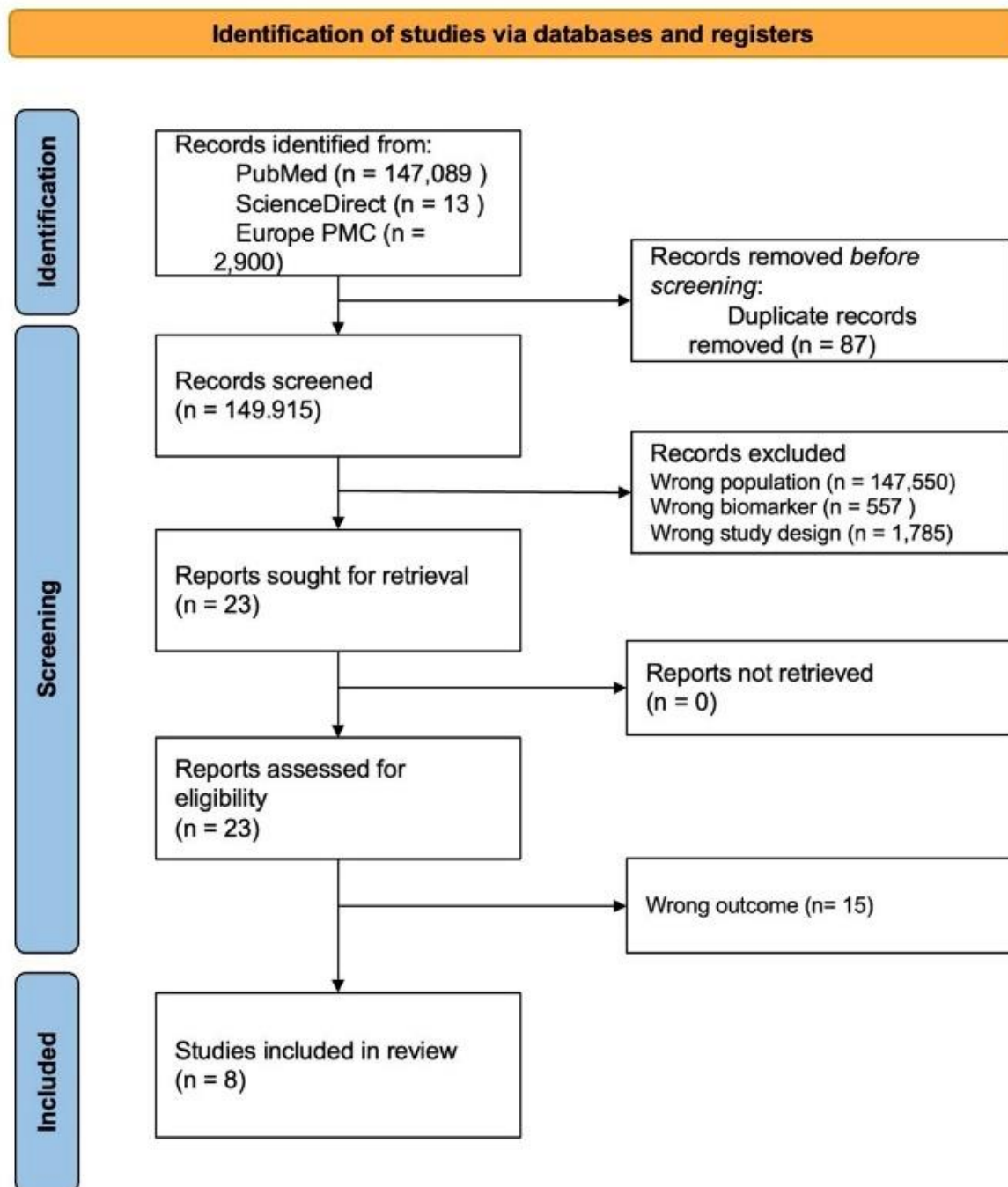


FIGURE 1: PRISMA 2020 Flow Diagram.

Risk of bias

We assessed the risk of bias in all eight studies using the Newcastle-Ottawa Scale (NOS), which awards a maximum of 9 stars across three domains: selection, comparability, and outcome. Total scores ranged from 2 to 9. Three studies had a low risk of bias, one had a moderate risk, and four had a high risk.

Jablonska et al. [11], Oprea-Ilieș et al. [12], and Pistiolis et al. [13] used a retrospective cohort design and achieved the full score of 9/9. All three met every selection criterion, controlled for confounders in the comparability domain, and satisfied all outcome criteria. Rögelsperger et al.

[17], an observational cohort, scored 6/9. This study met all four selection criteria but received no stars for comparability and lost one star in the outcome domain.

The four cross-sectional studies, Lai et al. [18], de Castro et al. [19], Goyal et al. [20], and Rögelsperger et al. [21], each scored 2/9. They earned two stars in the selection domain and none in the comparability or outcome domains. The cross-sectional design involves no follow-up period, and none of these studies have adjusted for confounding variables. We therefore interpreted their findings with caution in the synthesis.

TABLE 2: Risk Of Bias Assessment of Included Studies Using the Newcastle-Ottawa Scale.

No.	Study (Year)	Study Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score	Risk of Bias
1	Jablonska (2013)	Retrospective cohort	★★★★	★★	★★★	9	Low
2	Oprea-Ilies (2013)	Retrospective cohort	★★★★	★★	★★★	9	Low
3	Pistiolis (2025)	Retrospective cohort	★★★★	★★	★★★	9	Low
4	Rögelsperger (2009)	Observational cohort	★★★★	–	★★	6	Moderate
5	Lai (2009)	Cross-sectional	★★	–	–	2	High
6	Castro (2018)	Cross-sectional	★★	–	–	2	High
7	Goyal (2020)	Cross-sectional	★★	–	–	2	High
8	Rögelsperger (2011)	Cross-sectional	★★	–	–	2	High

Characteristics of included studies

Eight studies met the inclusion criteria and entered the narrative synthesis (Table 3). The studies were published between 2009 and 2025 and came from six countries. Four originated in Europe: Poland [11], Sweden [13], and Austria [17], [21]. The United States contributed two studies [12], [18], while Brazil [19] and India [20] contributed one each.

Three studies used a retrospective cohort design [11], [12], [13], and two used a cross-sectional design [19], [20]. The remaining three were observational studies with distinct designs. Lai et al. [18] combined preclinical analysis with retrospective observation, Rögelsperger et al. [17] compared paired tumor and non-cancerous tissue, and Rögelsperger et al. [21] reported a pilot study. Sample collection spanned 1983 to 2017. Lai et al. [18] used the oldest samples (1983–1993), and Pistiolis et al. [13], despite being the most recent publication, analyzed archival samples from 2003–2004. Goyal et al. [20] and Rögelsperger et al. [21] did not report their sampling period.

Population criteria differed across studies. Three studies restricted their samples to invasive ductal carcinoma [11], [13], [18]. Pistiolis et al. [13] applied the narrowest criteria, enrolling postmenopausal patients with ER-positive, HER2-negative (luminal

A/B) tumors who had not received neoadjuvant therapy. Oprea-Ilies et al. [12] included only patients with triple-negative breast cancer (TNBC) and compared African American (n = 84) and Caucasian (n = 53) patients. Goyal et al. [20] compared 15 receptor-positive carcinomas with 15 TNBC cases. de Castro et al. [19] and both Rögelsperger studies enrolled patients with primary breast carcinoma without subtype restriction. Three studies included non-cancerous comparison tissue: Lai et al. [18] used normal breast tissue, Goyal et al. [20] included 12 normal controls, and Rögelsperger et al. [17] used paired non-cancerous tissue.

The eight studies enrolled 657 breast cancer patients in total, with sample sizes ranging from 25 [18] to 190 [11]. Only three studies enrolled more than 100 patients [11], [12], [13]; the other five enrolled 43 patients or fewer. Several studies divided their samples by detection method. Jablonska et al. [11] examined 190 samples by IHC and 29 by qRT-PCR, Lai et al. [18] examined 25 samples by IHC and 25 by RFLP/RT-PCR, and Rögelsperger et al. [21] assigned patients to a PCR group (n = 10) and an IHC group (n = 33). Rögelsperger et al. [17] evaluated 17 of 42 samples quantitatively, and Pistiolis et al. [13] analyzed 25 axillary lymph node samples in addition to 118 primary tumors.

TABLE 3: Characteristics of Studies.

No.	First author	Year	Study design	Country	Sampling period	Sample criteria	Sample size (N)
1	Jablonska	2013	Retrospective cohort	Poland	2000–2006	Patients with IDC	190 (IHC) + 29 (qRT-PCR)
2	Lai	2009	Preclinical/retrospective observational	USA	1983–1993	Patients with IDC and normal breast tissue	25 (IHC) + 25 (RFLP/RT-PCR)
3	Oprea-Ilies	2013	Retrospective cohort	USA	2003–2008	Patients with TNBC	167 (84 AA, 53 C)
4	Pistiolis	2025	Retrospective cohort	Sweden	2003–2004	Postmenopausal patients with ER+/HER2– (luminal A/B) IDC, without neoadjuvant therapy	118 primary tumors + 25 axillary LNs

No.	First author	Year	Study design	Country	Sampling period	Sample criteria	Sample size (N)
5	Rögelsperger	2009	Observational, paired tumor and non-cancerous tissue	Austria	1998–2003	Patients with primary invasive breast carcinoma	42 (17 evaluated quantitatively)
6	Castro	2018	Cross-sectional	Brazil	2014–2017	Patients with primary breast cancer	42
7	Goyal	2020	Cross-sectional	India	NR	Breast carcinoma cases (receptor-positive vs. TNBC) and normal controls	30 tumors (15 receptor-positive, 15 TNBC) + 12 controls
8	Rögelsperger	2011	Observational pilot study	Austria	NR	Patients with primary invasive breast carcinoma	43 (PCR group, n = 10; IHC group, n = 33)

AA, African American; C, Caucasian; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IHC, immunohistochemistry; LN, lymph node; NR, not reported; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RFLP, restriction fragment length polymorphism; TNBC, triple-negative breast cancer.

Patient and tumor characteristics

Table 4 summarizes the clinicopathological characteristics of the included cohorts. Mean patient age ranged from 51.4 years (African American patients in Oprea-Ilieș et al. [12]) to 59.1 years (Caucasian patients in the same study). Pistiolis et al. [13] enrolled only postmenopausal women and reported the highest median age, 66 years (IQR 61–79). Rögelsperger et al. [21] did not report patient age. Only two studies reported menopausal status: 66.8% of the patients in Jablonska et al. [11] were postmenopausal, and Pistiolis et al. [13] included postmenopausal patients exclusively.

Invasive ductal carcinoma (IDC) was the predominant histological type. Four studies included IDC only [11], [13], [18], [20], and Oprea-Ilieș et al. [12] included triple-negative IDC. Rögelsperger et al. [17] and de Castro et al. [19] also

enrolled lobular and other histological types, and de Castro et al. [19] included ductal (7.1%) and lobular (2.4%) carcinoma in situ. Grade 2 tumors formed the largest group in Jablonska et al. [11], Pistiolis et al. [13], de Castro et al. [19], and Rögelsperger et al. [17], whereas most tumors in Oprea-Ilieș et al. [12] were high grade.

Receptor status varied with the selection criteria. ER positivity ranged from 64.3% [17] to 100% [13], and HER2 positivity ranged from 12.6% [11] to 45.2% [17]. TNBC accounted for all cases in Oprea-Ilieș et al. [12], half of the tumors in Goyal et al. [20], and 11.9–17.9% of the tumors in Castro et al. [19] and Jablonska et al. [11]. Three studies obtained specimens before any systemic therapy [13], [17], [19]. In Jablonska et al. [11], 87.4% of patients received adjuvant chemotherapy, 65.2% received tamoxifen, and 48.9% received radiotherapy.

TABLE 4: Clinicopathological Characteristics of Patients in the Included Studies.

Study (Year)	Age (years)	Menopausal status	Histological type	Grade and stage	Molecular subtype	Treatment
Jablonska, 2013	Mean 56.95 (30–84); ≤50: 30%, >50: 70%	Pre: 33.2%; post: 66.8%	IDC (100%)	G1 11.1%, G2 51.1%, G3 37.9%; stage I 25.8%, II 53.2%, III 18.9%, IV 1.6%	ER+ 74.7%, PR+ 67.4%, HER2+ 12.6%, TNBC 17.9%	Mastectomy or quadrantectomy with ALND; adjuvant CT 87.4%, neoadjuvant CT 6.3%; tamoxifen 65.2%; RT 48.9%
Lai, 2009	<50: n = 8; ≥50: n = 17	NR	IDC	G1 n = 9, G2 n = 10, G3 n = 6; TNM stage recorded	ERα+ 76%, PR+ 72%, HER2+ 40%	NR
Oprea-Ilieș, 2013	AA: 51.4 ± 13.7; C: 59.1 ± 12.1	NR (age groups <50 vs. >50)	TNBC (IDC)	Stage I/II n = 94, III/IV n = 41; predominantly high grade	TNBC (100%)	Neoadjuvant CT evaluated
Pistiolis, 2025	Median 66 (IQR 61–79)	Post: 100%	IDC (100%)	NHG I 33.9%, II 46.6%, III 19.5%; N0 56.8%, N1 17.8%, N2 4.2%, N3 5.9%	Luminal A/B (ER+ 100%, HER2– 100%, median PR 70%)	Mastectomy 38.1%, BCS 61.9%; SLNB 29.7%, ALND 55.1%; no neoadjuvant CT

Study (Year)	Age (years)	Menopausal status	Histological type	Grade and stage	Molecular subtype	Treatment
Rögelsperger, 2009	Mean 56 ± 10 (29–76)	NR	IDC n = 29, ILC n = 6, other n = 7	G1 n = 4, G2 n = 21, G3 n = 17; stage I–III	ER+ 64.3%, PR+ 38.1%, HER2+ 45.2%	Specimens obtained at primary surgery before CT
Castro, 2018	Mean 56.6 (24–88); ≤50: 28.5%, >50: 71.5%	NR (age groups ≤50 vs. >50)	IDC 85.7%, DCIS 7.1%, ILC 2.4%, LCIS 2.4%, papillary 2.4%	Grade I 28.6%, II 59.5%, III 11.9%; T1 33.3%, ≥T2 66.7%	Luminal A 64.3%, luminal B 16.7%, HER2+ 7.1%, TNBC 11.9%	No preoperative CT or RT
Goyal, 2020	31–80 (4th–8th decade)	NR	IDC	Classified by grade and nodal status	Receptor-positive (ER+/PR+/HER2+) 50%, TNBC 50%	Core biopsy, lumpectomy, or lumpectomy with axillary clearance
Rögelsperger, 2011	NR	NR	Primary invasive breast carcinoma	NR	ERα+ 81.8% (27/33), ERα– 18.2% (6/33)	Primary surgery

AA, African American; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; C, Caucasian; CT, chemotherapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IQR, interquartile range; LCIS, lobular carcinoma in situ; NHG, Nottingham histological grade; NR, not reported; PR, progesterone receptor; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TNBC, triple-negative breast cancer.

MT1 detection and scoring

All eight studies assessed MT1 protein by immunohistochemistry (Table 5). Seven studies used formalin-fixed, paraffin-embedded whole sections, and Oprea-Ilieș et al. [12] used tissue microarrays with two 1.0-mm cores per tumor. Three studies also measured MT1 mRNA in frozen tissue: Jablonska et al. [11] by real-time qRT-PCR, Lai et al. [18] by semi-quantitative RT-PCR, and Rögelsperger et al. [21] by TaqMan RT-PCR. Rögelsperger et al. [17] combined IHC with automated immunofluorescence quantification.

The studies used antibodies from at least four manufacturers, at dilutions between 1:40 [12] and 1:3200 [11]. Most were rabbit polyclonal antibodies. Rögelsperger et al. [17], [21] did not report the antibody source or dilution. Every study described cytoplasmic staining. Six studies also reported membranous staining, and Goyal et al. [20] reported

nuclear staining as well, while Lai et al. [18] observed no nuclear signal.

Scoring systems and cut-offs differed across all eight studies. Three studies applied the Remmele and Stegner immunoreactive score (IRS), with ranges of 0–12 [21] or 0–15 in a modified form [11], [20]. Oprea-Ilieș et al. [12] and Pistiolis et al. [13] calculated a weighted index, with maximum values of 300 and 400. Lai et al. [18] used a 0–3+ semi-quantitative scale, and two studies relied on digital quantification: TissueQuest [17] and ImageJ optical density [19]. Cut-off derivation followed four approaches: the score distribution (IRS ≥9; [11]), a maximal log-rank statistic (weighted index ≥60; [12]), an IgG isotype control (>10% positive cells; [17]), and staining intensity (3+; [18]). Pistiolis et al. [13], de Castro et al. [19], Goyal et al. [20], and Rögelsperger et al. [21] analyzed MT1 as a continuous variable or as group means.

TABLE 5: MT1 Detection Methods, Scoring Systems, And Expression.

Study	Specimen	Detection method	Antibody (manufacturer, dilution)	Staining localization	Scoring system	Cut-off (derivation)	MT1 expression
Jablonska, 2013	FFPE whole sections (n = 190); frozen tissue (n = 29)	IHC, qRT-PCR, WB, IF	Rabbit polyclonal anti-MT1 (Invitrogen, 1:3200)	Membrane and cytoplasm	Modified IRS (0–15)	Low 0–8, high 9–15 (score distribution)	High: 92 (48.4%); low: 98 (51.6%)
Lai, 2009	Frozen tissue (n = 25); FFPE (n = 25)	IHC, semi-quantitative RT-PCR, Southern blot, RFLP	Anti-MT1 (Abcam, 1:450)	Cytoplasm and membrane, no nuclear staining	Semi-quantitative 0–3+	High 3+, low 0–2+	3+: 15 (60%); 2+: 5 (20%); 1+: 3 (12%); 0: 2 (8%)

Study	Specimen	Detection method	Antibody (manufacturer, dilution)	Staining localization	Scoring system	Cut-off (derivation)	MT1 expression
Oprea-Illies, 2013	FFPE TMA (two 1.0-mm cores per tumor)	IHC	Polyclonal anti-MT1 (Bioscience Research Reagents, OPA1-15641, 1:40)	Cytoplasm	WI = intensity (0–3) × % stained cells (0–300)	Positive WI ≥60 (maximal log-rank statistic)	Positive: 92 (65.7%); negative: 48 (34.3%); AA 51.2% vs. C 88.2% positive
Pistolis, 2025	FFPE whole sections (4 µm)	IHC with digital scanning	Anti-MTNR1B (Abcam, ab203346, 1:200)	Cytoplasm, or cytoplasm and membrane	WI = % stained cells × intensity (1–4) (0–400)	Continuous (median 90% stained cells; median WI 190); positive if >0%	Positive: 100/118 (84.7%); negative: 18/118 (15.3%)
Rögelsperger, 2009	FFPE whole sections (1 µm)	IHC, quantitative IF (TissueQuest)	Rabbit anti-MT1 (NR)	Cytoplasm (n = 21) or membrane (n = 10)	Automated % positive cells	>10% positive cells (IgG isotype control)	Ca > NCa: 8; Ca < NCa: 6; equal: 2 (n = 16)
Castro, 2018	FFPE whole sections (4 µm)	IHC with ImageJ quantification	Anti-MT1 (Sigma, clone 4543, 1:100)	Cytoplasm and membrane	MOD (a.u.)	Continuous (mean per subtype)	Mean: luminal A 154, luminal B 135, HER2+ 144, TNBC 118 a.u.
Goyal, 2020	FFPE whole sections (4 µm)	IHC (streptavidin-biotin, DAB)	Anti-MT1A (Abcam, ab87639, NR)	Membrane, cytoplasm, and nucleus	Modified IRS (0–15)	Mean IRS per age group and subtype	Receptor-positive: 85% moderate to intense; TNBC: 70% moderate, 22% low, 8% intense
Rögelsperger, 2011	Frozen tissue (group 1, n = 10); FFPE whole sections (group 2, n = 33)	qRT-PCR (TaqMan, group 1); IHC (group 2)	Anti-MT1 (NR)	Cytoplasm	IRS (0–12)	Continuous (median IRS 8)	Positive: 31/33 (93.9%)

MT1 expression

The proportion of tumors classified as MT1-high or MT1-positive ranged from 48.4% [11] to 93.9% [21]. Lai et al. [18] found strong (3+) staining in 60% of IDC cases, Oprea-Illies et al. [12] found MT1 positivity in 65.7% of TNBC cases, and Pistolis et al. [13] detected MT1 in 84.7% of luminal tumors. These figures reflect different cut-offs and cannot be compared directly.

Three studies suggested lower MT1 expression in receptor-negative or TNBC tumors. de Castro et al.

[19] recorded the lowest mean optical density in TNBC (118 a.u.) and the highest in luminal A tumors (154 a.u.). Goyal et al. [20] found moderate-to-intense staining in 85% of receptor-positive tumors, compared with moderate staining in 70% and intense staining in 8% of TNBC cases. Within TNBC, Oprea-Illies et al. [12] reported MT1 positivity in 51.2% of African American patients and 88.2% of Caucasian patients. In the paired-tissue comparison by Rögelsperger et al. [17], tumor tissue expressed more MT1 than matched non-cancerous tissue in 8 of 16 cases, less in 6, and an equal amount in 2.

TABLE 6: Association Between Mt1 Expression and Survival Outcomes.

Study	Outcome	Comparison (reference)	HR (95% CI), p-value	Covariates	Events	Follow-up (months)	Outcome definition
Jablonska, 2013	OS, EFS	MT1 low vs. high (ref: high)	OS, all patients: 0.55 (0.30–1.03), p = 0.061; OS, ER+: 0.42 (0.21–0.87), p = 0.019; OS, tamoxifen-treated: 0.43 (0.21–0.90), p = 0.025; OS, ER+ (MV): HR NR, p = 0.041; EFS, ER+ (MV): HR NR, p = 0.045	Tumor size (pT1 vs. pT2–4), nodal status (pN– vs. pN+), grade (G1/G2 vs. G3), stage (I–IIB vs. IIIA–IV)	40 deaths (21.0%); 63 progressions (33.2%)	Mean 59.3 ± 38.5	OS: diagnosis to disease-related death; EFS: time to recurrence or progression

Study	Outcome	Comparison (reference)	HR (95% CI), p-value	Covariates	Events	Follow-up (months)	Outcome definition
Oprea-Ilies, 2013	OS, PFS	MT1 negative vs. positive (ref: positive, WI ≥ 60)	OS (UV): 2.46, $p = 0.003$; OS (MV): 2.02, $p = 0.026$; PFS (UV): 2.22, $p = 0.006$; PFS (MV): 1.91, $p = 0.034$; OS, AA: 2.46, $p = 0.012$; OS, C: 2.01, $p = 0.386$; 95% CI NR	NPI, stage (I/II vs. III/IV)	NR per group (92 positive, 48 negatives analyzed)	Up to 120 (median ~ 60)	OS: diagnosis to death or last follow-up; PFS: diagnosis to first recurrence or metastasis
Pistolis, 2025	OS, BCSS, RFI	Continuous (per 1-unit increase in % MT1 or WI)	OS (UV): 1.001 (0.996–1.008), $p = 0.624$; BCSS (UV): 1.001 (0.988–1.014), $p = 0.877$; RFI (UV): 1.002 (0.991–1.013), $p = 0.728$; BCSS (MV): 0.999, $p = 0.844$; RFI (MV): 1.001, $p = 0.929$	Age, NPI	73 deaths (61.9%); 15 breast cancer deaths; 9 local recurrences (7.7%); 17 distant metastases (14.4%)	Median 182	OS: surgery to death from any cause; BCSS: surgery to breast cancer death; RFI: surgery to recurrence or breast cancer death
Rögelsperger, 2009	Metastatic death, recurrence	MT1 and nestin co-expression, Ca vs. NCa	Not calculated	NA	7 metastatic deaths; 2 local recurrences	Mean 67 ± 19 (11–96)	Death from metastatic disease or recurrence

Lai et al. [18], Castro et al. [19], Goyal et al. [20], and Rögelsperger et al. [21] did not report survival data.

Association with survival

Four studies collected follow-up data, and three of them reported hazard ratios (Table 6). Follow-up ranged from a mean of 59.3 months [11] to a median of 182 months [13]. The studies measured overall survival (OS) in all three cases, alongside event-free survival (EFS), progression-free survival (PFS), breast cancer-specific survival (BCSS), or recurrence-free interval (RFI). Their definitions differed, including the starting point for OS (diagnosis or surgery).

Jablonska et al. [11] recorded 40 deaths and 63 progression events among 190 patients. In the whole cohort, MT1 expression did not reach significance for OS (HR 0.55; 95% CI 0.30–1.03; $p = 0.061$). In ER-positive patients, high MT1 expression predicted longer OS (HR 0.42; 95% CI 0.21–0.87; $p = 0.019$), and the same held for tamoxifen-treated patients (HR 0.43; 95% CI 0.21–0.90; $p = 0.025$). The association remained significant for OS ($p = 0.041$) and EFS ($p = 0.045$) in the ER-positive subgroup after adjustment for tumor size, nodal status, grade, and stage, although the authors did not report the adjusted HRs.

Oprea-Ilies et al. [12] found that MT1-negative TNBC carried a higher risk of death (HR 2.46; $p = 0.003$) and progression (HR 2.22; $p = 0.006$) on log-rank analysis. Both associations persisted after adjustment for the Nottingham Prognostic Index (NPI) and stage, with HRs of 2.02 for OS ($p = 0.026$) and 1.91 for PFS ($p = 0.034$). By race, MT1 negativity predicted shorter OS in African American patients (HR 2.46; $p = 0.012$) but not in Caucasian patients (HR 2.01; $p = 0.386$). The study reported no confidence intervals.

Pistolis et al. [13] analyzed MT1 as a continuous variable in 118 postmenopausal patients with

luminal tumors, among whom 15 died of breast cancer, 9 developed local recurrence, and 17 developed distant metastases. MT1 showed no association with OS (HR 1.001; 95% CI 0.996–1.008; $p = 0.624$), BCSS (HR 1.001; 95% CI 0.988–1.014; $p = 0.877$), or RFI (HR 1.002; 95% CI 0.991–1.013; $p = 0.728$). Adjustment for age and NPI did not change these results.

Rögelsperger et al. [17] followed patients for a mean of 67 ± 19 months and observed 7 deaths from metastatic disease and 2 local recurrences in the analyzed subset. The authors reported descriptive and non-parametric comparisons only and did not calculate hazard ratios. Differences in MT1 cut-offs, analytic approaches, outcome definitions, and reported effect measures precluded pooling, so we synthesized the survival findings narratively.

DISCUSSION

This systematic review examined whether expression of the melatonin receptor MT1 (MTNR1A) in breast carcinoma relates to clinicopathological features and patient outcome. Breast cancer remains a priority problem: in 2022 there were an estimated 2,308,897 new cases of female breast cancer worldwide, 11.6% of all cancers, and 665,684 deaths, 6.9% of all cancer deaths [1]. The pineal gland secretes melatonin, an indoleamine, during darkness. Melatonin acts through two G-protein-coupled receptors, MT1 (encoded by MTNR1A) and MT2 (encoded by MTNR1B), and its anti-proliferative effects in human breast cancer cell lines and xenografts depend largely on MT1 [9], [10].

Eight studies from six countries, with 657 patients in total, met our criteria. MT1 was present in most tumours, with 48.4% to 93.9% classified as high or positive. Three studies found lower expression in

triple-negative and receptor-negative tumours [11], [19], [20]. In ER-positive and tamoxifen-treated patients, high MT1 predicted longer overall survival [11]. In triple-negative breast cancer (TNBC), MT1 negativity independently predicted shorter overall and progression-free survival [12]. A cohort of 118 postmenopausal women with luminal tumours, followed for a median of 182 months, found no prognostic effect [13]. The studies used different cut-offs, analytic approaches, outcome definitions and effect measures, so we could not pool the data and synthesised the survival findings narratively.

Comparison with Previous Evidence

Our results fit several established lines of evidence. The melatonin hypothesis holds that reduced melatonin causes relative hyperestrogenism and favours hormone-dependent breast cancer. Melatonin acts as a selective estrogen receptor modulator, damping ER signalling, and as a selective estrogen enzyme modulator, inhibiting the enzymes that synthesise estrogen [22]. Experimental work on light exposure supports this model. In rats, light at night suppressed nocturnal melatonin and stimulated the growth of human breast cancer xenografts, and melatonin-depleted blood collected from women after light exposure at night had the same effect [23]. Dim light at night also induced tamoxifen resistance in MCF-7 xenografts, and nocturnal melatonin replacement restored sensitivity [24].

Human data on systemic melatonin is less consistent. The International Agency for Research on Cancer classified night shift work as probably carcinogenic to humans [25]. A meta-analysis of ten prospective studies, however, found a combined relative risk of 0.99 (95% CI 0.95–1.03) for any night shift work, and Travis and colleagues concluded that night shift work “has little or no effect on breast cancer incidence” [26]. In the Nurses’ Health Study, higher urinary 6-sulfatoxymelatonin was associated with lower postmenopausal breast cancer risk (odds ratio 0.62, 95% CI 0.41–0.95; [27]), but a meta-analysis of six studies did not confirm this association (pooled RR 0.97, 95% CI 0.88–1.08; [28]). In 216,702 UK Biobank participants, the MTNR1B rs10830963 variant showed no overall association with breast cancer risk [29].

With population-level evidence this mixed, the receptor in the tumour may measure melatonin responsiveness more directly than systemic exposure does. MT1 has practical strengths as a biomarker. Pathologists can measure it by immunohistochemistry on routine paraffin sections, and its ligand is cheap and has low toxicity. Dillon et al. [30] found higher MT1 levels in malignant than in non-neoplastic breast epithelium: 75% of tumour samples showed moderate-to-strong staining, while 68% of non-neoplastic samples were negative or weak. The marker also has clear weaknesses. Estradiol and melatonin themselves regulate MT1 expression, and MTNR1A gene alterations do not map simply onto protein levels [18]. Most of the evidence comes from small retrospective series.

Mechanism of Action

The mechanistic data point to a protective role for MT1 that is strongest in ER-positive disease. MT1 couples to Gαi2, Gαi3, Gαq and Gα11. Through Gαi2, it suppresses forskolin-induced cAMP and estrogen-induced ERα transcriptional activity, and growth inhibition requires both Gαi2 and Gαq [31]. The fall in cAMP blocks linoleic acid uptake and its conversion to the mitogen 13-hydroxyoctadecadienoic acid (13-HODE), which reduces growth-factor signalling [32]. Further downstream, melatonin suppresses aerobic glycolysis (the Warburg effect), inhibits p38 MAPK, represses epithelial-mesenchymal transition and limits LINE-1-driven genomic instability [9]. MT1 also controls local estrogen synthesis. Transfecting MT1 into MCF-7 cells halved aromatase activity and reduced aromatase mRNA by 55%, and in these cells’ melatonin at 1 nM inhibited aromatase activity by 20% [33].

Overexpression experiments link these pathways to tumour growth. MT1 overexpression in MCF-7 cells enhanced melatonin’s suppression of growth and of ERα mRNA, but it did not make ER-negative MDA-MB-231 cells sensitive to melatonin [34]. In nude mice, MT1-overexpressing MCF-7 cells formed 60% fewer palpable tumours, and with melatonin treatment tumour incidence fell by 80% compared with vector-transfected cells [35]. The melatonin agonist S23478-1 increased Bax and decreased Bcl-2 and ERα in rat mammary tumours [36].

These data explain why Jablonska et al. [11] observed benefit in ER-positive and tamoxifen-treated patients: MT1 signalling suppresses the same estrogen axis that tamoxifen targets. The TNBC result of Oprea-Ilie et al. [12] points to effects that do not require the estrogen receptor. ER-negative cell lines express MT1, yet melatonin suppressed proliferation of SK-BR-3 cells and not MDA-MB-231 or BT-20 cells. In MDA-MB-231 cells, Mao et al. [37] traced the defect to signalling downstream of Gαi proteins and to ERK1/2 regulation. The presence of the receptor alone therefore does not guarantee a response.

Melatonin as Adjuvant Therapy and Its Safety

Clinical data on melatonin as treatment are limited. In 14 women with metastatic breast cancer that had progressed on tamoxifen alone, adding melatonin 20 mg each evening produced partial responses in 4, without added toxicity [38]. A meta-analysis of 21 randomised trials in solid tumours found a pooled relative risk for 1-year mortality of 0.63 (95% CI 0.53–0.74). Melatonin also reduced asthenia, leucopenia, nausea, vomiting, hypotension and thrombocytopenia during chemotherapy [39]. One research group conducted most of these trials, which limit their external validity. In early breast cancer, a Swedish registry study of 37,075 patients, 926 of whom used melatonin, found no survival benefit after adjustment (HR for breast-cancer-specific survival 1.037, 95% CI 0.648–1.659 [40]). The supportive-care trials are more encouraging.

Melatonin 3 mg for 4 months improved sleep quality in 95 breast cancer survivors without significant adverse effects [41]. Melatonin 20 mg during the first chemotherapy cycle improved cognitive performance, sleep and depressive symptoms in 36 women [42].

The safety profile is favourable. Across 37 randomised trials in sleep disorders, the most frequent adverse events were daytime sleepiness (1.66%), headache (0.74%), dizziness (0.74%) and hypothermia (0.62%), and no trial reported a life-threatening event [43]. A review of 50 controlled studies found mostly minor, short-lived effects on fatigue, mood and psychomotor performance. A few studies reported endocrine and cardiovascular effects that depended on dose and timing [44]. Two cautions apply to MT1 agonism. Long-term safety data remain scarce [43], and in mice given vector-only MCF-7 cells, daily melatonin increased overall tumour formation [35]. Any benefit may depend on adequate receptor expression in the tumour.

Additional Findings

Lower MT1 in TNBC appeared in studies with three different designs. De Castro et al. [19] reported a mean optical density of 118 a.u. in TNBC, against 154 in luminal A, 135 in luminal B and 144 in HER2-positive tumours. In Goyal et al. [20], 85% of receptor-positive tumours showed moderate-to-intense staining. Among the TNBC cases, 70% showed moderate, 22% low and 8% intense staining. Goyal et al. interpreted the higher MT1 in receptor-positive tumours as a possible reactive response to melatonin deficiency, a hypothesis no study has yet tested.

Oprea-Ilie et al. [12] found MT1 positivity in 51.2% of TNBC from African American women and 88.2% from Caucasian women. MT1 negativity predicted overall survival in African American patients (HR 2.46, $p = 0.012$) but not in Caucasian patients (HR 2.01, $p = 0.386$). With only 53 Caucasian patients, the null result is more likely to reflect low power than a true absence of effect. Data on population differences in melatonin are sparse. In 150 young adults, African Americans excreted less overnight urinary melatonin than European Americans (0.26 ± 0.20 vs 0.34 ± 0.33 , $p = 0.002$; Jeong et al., 2019). That study included both sexes and did not address cancer, and we found no study comparing endogenous melatonin between Black and White women. Any link between the racial difference in tumour MT1 and circadian disruption remains speculative.

Comparisons with non-cancerous tissue were inconsistent. In paired samples, invasive carcinoma expressed more MT1 than matched non-cancerous tissue in 8 of 16 cases and less in 6. MT1/nestin co-staining in more than 10% of tumour cells was associated with higher stage [17]. Dillon et al. [30], by contrast, reported higher expression in tumour tissue across the board. Differences in quantification (image-based analysis) and sampling (paired tissue) may account for part of the discrepancy.

The null result of Pistiolis et al. [13] needs careful reading. The authors' methods describe the antibody they used (Abcam ab203346, 1:200) as intended for "melatonin receptor 1B/MTNR1B staining" [13]. Unless the authors demonstrated cross-reactivity with MT1, the study may have measured MT2 rather than MT1, and its null result cannot count as evidence against the prognostic value of MT1.

Clinical Implications

The clinical implications remain provisional. MT1 immunohistochemistry could add prognostic information for ER-positive patients receiving tamoxifen and for patients with TNBC, particularly African American women. It could also identify candidates for trials of adjuvant melatonin. Neither application is ready for practice. Antibodies, scoring systems and cut-offs first need standardisation and validation in independent cohorts.

Limitations

The included studies share several methodological weaknesses. On the Newcastle-Ottawa Scale, three retrospective cohorts scored 9/9 [11], [12], [13], Rögelsperger et al. [17] scored 6/9, and four cross-sectional studies scored 2/9 [18], [19], [20], [21]. Only three studies enrolled more than 100 patients, and the other five enrolled 43 or fewer. The four cross-sectional studies had no follow-up and did not adjust for confounders, so they cannot inform prognosis.

The assays varied widely between studies. The authors used antibodies from at least four manufacturers at dilutions from 1:40 to 1:3200, and they applied five scoring systems: immunoreactive score, weighted index, intensity grading, digital immunofluorescence and optical density. Cut-offs ranged from score-distribution thresholds to continuous measures. Oprea-Ilie et al. [12] chose their weighted-index cut-off of 60 by maximal log-rank selection, a data-driven approach that may overstate the strength of the association.

Reporting was often incomplete. Oprea-Ilie et al. [12] gave no confidence intervals. Jablonska et al. [11] reported multivariate p -values without adjusted hazard ratios, and their unadjusted HR for the whole cohort (0.55, 95% CI 0.30–1.03) did not reach significance. Rögelsperger et al. [17] recorded only 7 metastatic deaths and 2 local recurrences and calculated no hazard ratios. Some archival material dated back to 1983, and antigen degradation in old paraffin blocks may have lowered staining intensity. Generalisability is limited as well. No study came from East Asia or Africa, the single Indian study analysed 30 tumours, and several cohorts included only invasive ductal carcinoma, luminal tumours or triple-negative tumours.

This review has its own limitations. We searched three databases (PubMed, ScienceDirect and Europe PMC) and could not pool the data. Language and publication bias are possible, since small studies with negative results reach publication less often.

The review followed the PRISMA 2020 process, assessed risk of bias formally and gave a structured synthesis of the assay methods used across studies.

CONCLUSION

Most breast carcinomas express MT1, and expression runs lower in triple-negative and receptor-negative tumours than in luminal tumours. High MT1 predicted longer survival in ER-positive and tamoxifen-treated patients, and MT1 negativity predicted shorter survival in TNBC, but these findings rest on two retrospective cohorts that used different antibodies, scoring systems and cut-offs. The available evidence supports MT1 as a candidate prognostic marker, not as a tool for clinical use. Future studies should validate MT1-specific antibodies against knockdown or overexpression controls, agree on a single scoring system with pre-specified cut-offs, and report results according to the REMARK recommendations [45]. Larger prospective cohorts should include patients from Asia and Africa, cover all molecular subtypes, and measure systemic melatonin alongside tumour MT1. Randomised trials of melatonin added to endocrine therapy or chemotherapy could then stratify patients by MT1 status to test whether receptor expression predicts treatment benefit.

ACKNOWLEDGMENT

Authors would like to express their gratitude to the Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, for its academic support during the preparation of this systematic review.

CONFLICT OF INTEREST

The author declares no conflict of interest.

FUNDING

None.

ETHICAL CLEARANCE

Not applicable. This systematic review analyzed only data from previously published studies and did not involve human participants, identifiable personal data, or animals. Therefore, ethical clearance and informed consent were not required.

AUTHOR CONTRIBUTION

Tan Deasy Tandika Wijaya: writing manuscript data collection; Aditya Sita Sari: editor; Fishella Aprista Rahmanti: translator, data collection.

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