

Prognostic Factors in Hormone Receptor-Positive/ Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Advanced Breast Cancer: A Systematic Literature Review

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Purpose: Advanced breast cancer is a heterogeneous disease with several well-defined subtypes, among which, hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) is most prevalent. Determination of HR and HER2 status influences prognosis and, thus, disease management. Although literature on these prognostic factors exist, especially in the early breast cancer setting, it remains unclear to what extent these factors can guide clinical decision-making in the advanced disease setting. Therefore, we sought to identify the strength and consistency of evidence for prognostic factors in patients with HR+/HER2- advanced breast cancer.

Methods: A systematic literature review (SLR) of the major electronic databases was conducted in November 2018 for primary research studies published since 2010. Endpoints of interest were tumor response, progression-free survival (PFS), overall survival (OS), and breast cancer-specific survival (BCSS).

Results: Seventy-nine studies were included wherein all patients were diagnosed with advanced breast cancer and $\geq 50\%$ of the population were HR+/HER2-. OS was the most commonly assessed endpoint (n=67) followed by PFS (n=33), BCSS (n=5) and tumor response (n=3). The prognostic factors with strongest evidence of association with worse OS were negative progesterone receptor status, higher tumor grade, higher circulating tumor cell (CTC) count and higher Ki67 level, number of metastatic sites (eg multiple vs single) and sites of metastases (eg presence of liver metastases vs absence), shorter time to recurrence or progression to advanced breast cancer, poor performance status, prior therapy attributes in the early or metastatic setting (type of therapy, treatment line, response of prior therapy), and race (black vs white). The prognostic factors that had strongest evidence of association with PFS included CTC count, number and sites of metastases, and absence of prior therapy or higher lines of therapy in the early or metastatic setting. The directionality of association was consistent for all prognostic factors except between lymph node and OS, and *de novo* metastatic breast cancer and PFS.

Conclusion: Multiple disease, treatment, and patient-related prognostic factors impact survival, particularly OS, in patients with HR+/HER2- advanced breast cancer. Treatment outcomes can vary considerably due to these factors. Understanding poorer prognostic factors for patients can result in improved clinical decision-making.

Keywords: advanced breast cancer, prognostic factors, survival

Introduction

Advances in screening and treatment paradigms for breast cancer has led to an overall decline in mortality rate in the past decade.¹ The survival rate depends on stage of breast cancer at diagnosis, among other factors.² The five-year survival rate for patients diagnosed with Stage IV breast cancer is 22%, for Stage III is 72% and Stage II is >90%.³ Clinical decision-making in breast cancer management relies on determination of receptor status, as therapies have been developed that specifically benefit patients depending on hormone receptor (HR) and human epidermal growth factor (HER2) receptor status.^{4–6} HR+/HER2– status is the most common molecular subtype, accounting for two-thirds of US female breast cancer cases.^{7–9}

In addition to advancements in treatment options over time, prognosis of breast cancer is influenced by factors that indicate growth, invasion, and metastatic potential of disease, thereby informing disease course and clinical outcome.⁴ The HR+/HER2– subtype has been associated with improved survival compared with other subtypes in the metastatic setting, also indicating some prognostic relationship between survival and receptor status.^{4,10} Amongst HR+/HER2– subtype, survival is influenced by other disease-related factors such as tumor grade, site of the metastasis (eg bone, liver, lung, or brain), prior therapy, as well as patient-related factors (eg age, race).^{11,12}

Although several studies have identified prognostic factors associated with survival, especially in the early breast cancer setting,^{13–15} it remains unclear to what extent these factors impact prognosis in advanced breast cancer. Currently, there is no comprehensive summary assessing the collective available evidence and the strength of evidence for these prognostic factors among patients with HR+/HER2– advanced breast cancer that can aid clinical decision-making. Therefore, we conducted a systematic literature review (SLR) based on a pre-specified protocol to identify the prognostic factors associated with survival endpoints in patients with HR+/HER2– advanced breast cancer and qualitatively assess the evidence and its strength and consistency.

Method

Data Sources and Search Strategies

A SLR was conducted and reported in accordance with guidelines established by the Centre for Reviews and Dissemination (CRD),¹⁶ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,¹⁷ and Cochrane guidebook.¹⁸ Comprehensive searches were conducted in

major electronic databases (MEDLINE, EMBASE, and Cochrane Controlled Register of Trials) to identify primary research studies published between January 1, 2010 and November 15, 2018. These were supplemented by searches of relevant conference proceedings (American Society of Clinical Oncology, European Society for Medical Oncology, European Cancer Organization, European Cancer Summit, Improving Care and Knowledge through Translational Research Breast Cancer Conference, The International Consensus Conference for Advanced Breast Cancer, San Antonio Breast Cancer Symposium, and American Association for Cancer Research) held in the two prior years to identify abstracts of interest. The primary publications related to the conference abstracts were searched. Relevant SLRs published recently were cross-checked to find additional studies. The search strategy was designed to include an extensive list of search terms (including MeSH/Emtree terms and natural language terms) which were broadly grouped into: 1) HR+/HER2– breast cancer, 2) advanced disease stage, 3) prognostic factors, 4) outcomes—including tumor response, also referred to as objective response or clinical benefit, progression-free survival (PFS), overall survival (OS), and breast cancer-specific survival (BCSS). Disease terms included a combination of terms to identify “advanced stage” breast cancer in combination with terms specific to “HR+/HER2–” status.

Study Selection and Data Extraction

Patients with HR+/HER2– advanced breast cancer were the population of interest for this SLR. However, there were limited studies that included this patient population exclusively. Besides, the proportion of patients with HR+/HER2– subtype widely varied across studies. Hence we decided to exclude studies where <50% of patients were either HR+ or HER2–. Since the proportion of patients with advanced/metastatic breast cancer also varied across studies, we included studies where ≥80% of patients were diagnosed with advanced breast cancer. These eligibility criteria allowed for inclusion of studies with the population of interest, thus striking a balance between validity and generalizability of the review. Observational studies with sample size of ≥300 patients and RCTs with sample size of ≥300 patients were eligible for inclusion. Editorials, letters, commentaries, reviews, invitro-studies, and non-English publications were excluded. Since “prognostic” and “predictive” terms are used, sometimes incorrectly as interchangeable in literature,¹⁹ we excluded studies that reported the interaction p-value between a factor and treatment – indicative of predictive association.

After removing duplicates, two reviewers independently screened abstracts and full-texts for eligibility. Disagreements were resolved by consensus or by a third reviewer. A single reviewer extracted all data, and a separate reviewer independently validated extracted data.

Evidence Assessment

Strength of evidence was determined in terms of consistency of evidence, directionality of association, use of multivariable analyses, and strength of association based on effect size. If >50% of studies that assessed an association found it to be significant, then evidence was considered consistent. Similarly, if the direction of association was the same in >50% of studies that demonstrated a significant association, then directionality of association was deemed consistent. For example, negative progesterone receptor status was associated with worse survival in 100% of studies that reported a significant relationship. Based on hazard ratios (HR) calculated in univariate and multivariate analyses, the strength of associations was categorized as strong ($HR \geq 3$), moderate ($HR = 1.5-2.9$), or weak ($HR < 1.5$).²⁰

Prognostic factors satisfying all the following criteria were deemed to have the strongest evidence of association with OS or PFS: i) consistency of evidence; ii) consistency in the direction of association; iii) at least >5 studies demonstrating a significant association. For example, circulating tumor cell (CTC) count showed the strongest evidence of association with OS in nine out of 10 studies (ie, achieved consistency based on >50% studies with a significant association) and showed consistency in direction of association as well as strength of association based on effect size. The Quality In Prognosis Studies (QUIPS) risk of bias assessment tool was used to assess study quality.²¹ Based on our understanding of the literature base and variability expected in the patient population and study design, we did not plan to conduct a meta-analysis of the relationship between prognostic factors and survival endpoints.

Results

The PRISMA flow diagram summarizes the review (Figure 1). Overall, the SLR included 72 full-text articles and seven conference abstracts (Table 1).^{10,22-98} The studies identified included retrospective data analyses (71%), prospective cohort studies (16.5%), studies with both retrospective and prospective data collections (2.5%), randomized controlled trials (RCTs) or clinical trials (7.5%), and post-hoc analyses of RCTs (2.5%). OS was the most commonly assessed endpoint ($n=67$), followed by PFS

($n=33$), while BCSS ($n=5$) and tumor response ($n=3$) were assessed less frequently. The majority of studies were conducted in Europe ($n=38$), followed by North America ($n=15$), Asia ($n=18$), Northern Africa ($n=1$), the Middle East ($n=1$), and five studies were multinational. One study did not report study location.

Baseline Characteristics

The median age of patients in the included studies ranged between 44–68 years; age was not reported in 12 studies.^{28,31,55,66,84-87,93,97} In 22 studies, the entire study population was HR+ and HER2-, while in eight studies the proportion of patients with HR+ and/or HER2- status was between 80–99%, and the remaining 49 studies included patients with HR+ and/or HER2- status ranging between 50–79%.

Prognostic Factors

Disease-Related Factors

Progesterone Receptor (PR) Expression

Patients with breast cancer positive for progesterone, estrogen, or both receptors were deemed HR positive. The relationship between PR status and OS ($n=10$), PFS ($n=2$), and tumor response ($n=1$) was evaluated, with a significant association reported in 80% ($n=8$), 50% ($n=1$), and 100% ($n=1$) of studies, respectively.^{26,38,45,56,66,72,73,92,98} The association of PR status with BCSS was assessed in one study, and it did not report any significant relationship.⁴⁰ Patients with negative PR status compared with positive were moderately associated with worse OS. The evidence was insufficient to assess the strength of association between PFS/tumor response and PR status.

Tumor Grade

The type of tumor grading system used was reported in only four studies that assessed OS. Two studies used the Scarff Bloom Richardson grading,^{52,88} one utilized the modified Bloom-Richardson grading,⁹⁶ and the other study employed the Elston-Ellis modification of Scarff-Bloom-Richardson grading system.⁸²

The relationship between tumor grade and OS ($n=21$), PFS ($n=4$), BCSS ($n=3$), and tumor response ($n=1$) was evaluated, with a significant association reported in 62% ($n=13$), 75% ($n=3$), 100% ($n=1$), and 100% ($n=1$) of studies, respectively.^{26,28,29,38,42,55,66,73,78,81,82,85,88,90} Survival was worse in patients with poorly to moderately differentiated tumors compared with well-differentiated tumors. Consistency in evidence and directionality of

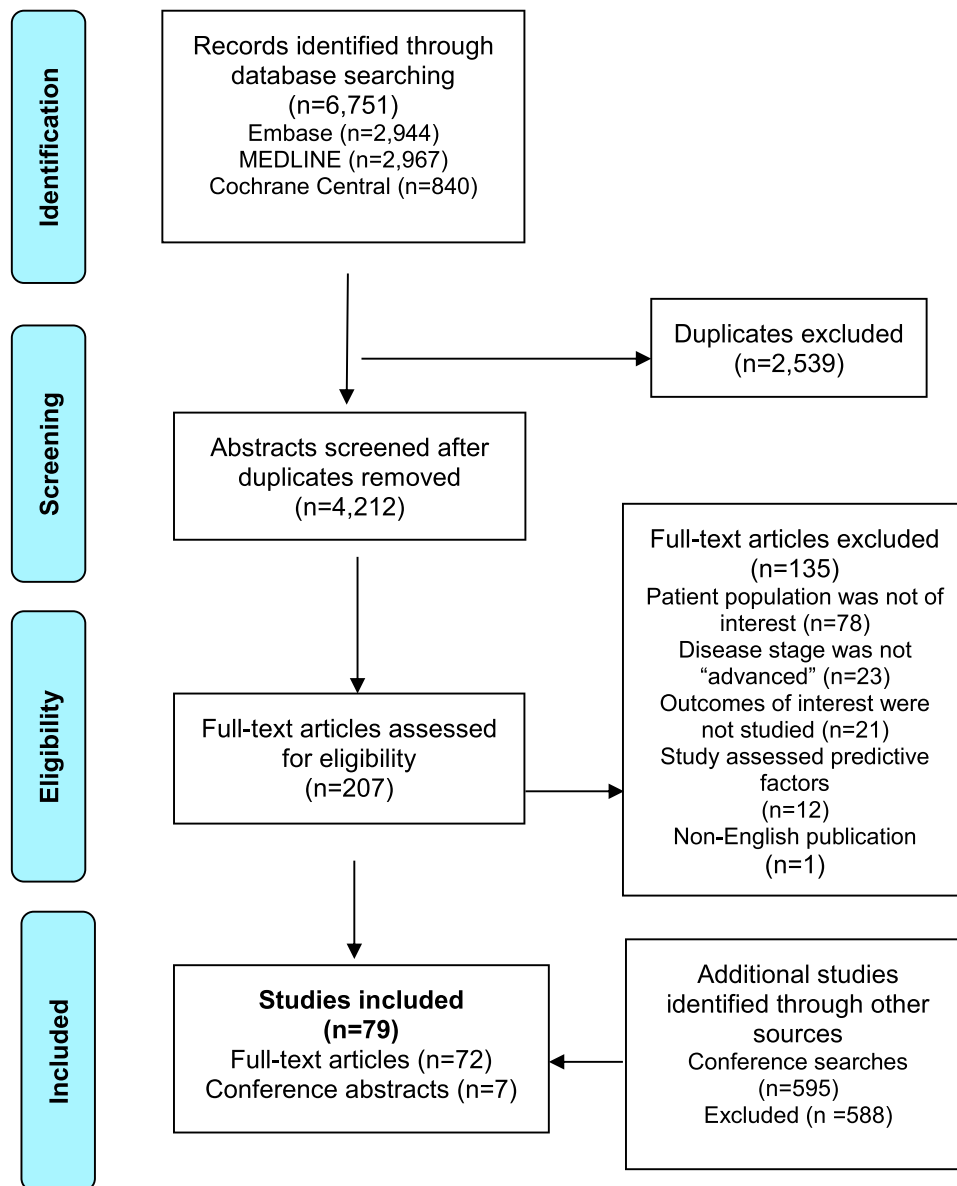


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection.

association was observed for all survival endpoints. Overall, the effect size of the association between tumor grade and survival endpoints was moderate.

Tumor Size

Relationship between tumor size and OS (n=12) and BCSS (n=2) was evaluated, with a significant association reported in 42% (n=5) and 50% (n=1) of studies, respectively.^{28,38,81,90,92} No included study assessed the association between tumor size and PFS or tumor response. In four studies, large tumors (>5 cm diameter) were associated with worse survival,^{28,38,90,92} while one study showed improved OS in patients with T2 tumors

(>2 cm and <5 cm) compared with T1 tumors (≤ 2 cm).⁸¹

Less than 50% of studies that assessed the association between tumor size and OS reported a significant association, although among those, directionality of evidence was consistent in the five studies. Overall, the effect size of the association between tumor size and survival endpoints ranged from weak-to-moderate.

Lymph Node Involvement

The relationship between lymph node involvement and OS (n=11), PFS (n=1), and BCSS (n=2) was evaluated, with a significant association reported in 36% (n=4), 100% (n=1), and 100% (n=2) of studies, respectively.^{28,38,40,66,70,90}

Table 1 Studies Included in the Systematic Literature Review

Study [Ref]	Population in Prognostic Analysis	Sample Size (N)	Age (in Years)	HR + (%)	ER + (%)	PR + (%)	HER2- (%)	Category by HR +/HER2- Status (%)	Description of BC
Arciero et al (2017) ²²	HR+/HER2- subgroup	106,036	Age at diagnosis, Mean (SD), White: 62.4 (13.6); and African American: 58.9 (13.5)	100	NR	NR	100	≥80	Stage III and IV
Aversa et al (2014) ⁶¹	Overall sample=488 Analysis conducted in subgroup of patients with CNS metastases (n=115)	488	Age at first BC diagnosis, Median (range): 51 (22–83) Age at first metastatic recurrence, median (range): 55 (24–85)	67.8	66.2	49.7	68	50–79	mBC with patients starting first-line chemotherapy
Ayala de la Pena et al (2017) (CA) ⁶²	Overall study population	265	Median (range): 59 (19–95)	76	NR	NR	73	50–79	mBC
Beije et al (2016) ⁷⁷	Overall study population	154	Age at inclusion, Median (range) ET: 67 (37–88); and CT: 61 (33–85)	NR	83.7	NR	100	≥80	mBC
Bertaut et al (2015) ⁸⁸	Overall study population	232	Age at diagnosis, Mean (SD): 64.7 (14.7)	84	NR	NR	81	≥80	Stage IV mBC
Bonechi et al (2018) ⁶⁴	Overall study population	31	Median (range): 64 (37–83)	100	93.7	81.2	100	≥80	mBC
Bonotto et al (2017) ³⁰	Overall study population	446	Age of women treated with first-line, Median (range) ET: 68 (39–92); and CT: 58 (30–81)	100	NR	NR	100	≥80	mBC
Boudin et al (2016) ⁵²	Overall study population	235	Median (range): 46 (21–62)	62.1	NR	NR	82.5	50–79	mBC following treatment with high-dose chemotherapy (HDC) and autologous hematopoietic progenitor cell transplantation (AH SCT)
Carbognin et al. (2016) ⁸⁰	Overall study population	335	Age at diagnosis of metastasis, Median (range): 61 (30–91)	100	92.8	78.8	100	≥80	advanced BC
Chandraratna et al. (2016) ⁶⁸	Overall study population	541	Median (range), Everolimus and exemestane: 62 (34–93); Placebo and exemestane: 61 (28–90)	100	100	NR	100	≥80	mBC

(Continued)

Table 1 (Continued).

Study [Ref]	Population in Prognostic Analysis	Sample Size (N)	Age (in Years)	HR + (%)	ER + (%)	PR + (%)	HER2- (%)	Category by HR +/HER2- Status (%)	Description of BC
Chen et al (2018) ⁴¹	Overall sample= 390 analyses conducted in late recurrence group (n=109)	390	Age at diagnosis: Early recurrence: Age group ≤35: 39 (13.9%); Age group >35: 242 (86.1%). Late recurrence: Age group ≤35: 19 (17.4%); Age group >35: 90 (82.6%)	100	NR	NR	100	≥80	Patients with BC who relapsed after surgery
Cinausero et al (2018) ³⁷	Overall study population	410	Age at last line treatment, Median (range): 67.2 (31–92)	71.0	75.9	60.7	82.2	50–79	mBC
Delpach et al (2012) ⁵⁷	Overall study population	241	Median (range): 55 (29–93)	NR	100	75	71	50–79	mBC
Demian et al (2011) ⁸⁶	Metastatic subgroup=20	20	NR	NR	80	80	65	50–79	mBC
den Brok et al (2017) ⁹¹	Subgroup (HR +/HER2-)	Relapse=1,174 De novo: n=406	Relapsed: Age group ≤50 years: 278 (23.7%) Age group >50 years: 896 (76.3%) De novo: Age group ≤50 years: 99 (24.4%) Age group >50 years: 307 (75.6%)	100	100	NR	100	≥80	mBC
Desille-Gbaguidi et al (2018) ⁹⁴	Overall study population	139	Mean (SD, range): 62.7 (15.4, 25–94)	80	77.7	65.5	79.9	50–79	mBC
Dominici et al (2011) ⁸⁹	Overall study population	290	Mean (SD): Non-surgery: 52.2 (13.6); Surgery: 53.4 (14.0)	NR	74.1	NR	67.2	50–79	Stage IV mBC
Elsamany et al (2014) ⁸⁴	Overall study population	60	NR	63.3	NR	NR	63.3	50–79	mBC
Ercolani et al (2018) ⁹²	Overall study population	51	Mean (SD, range): 56 (11.4, 37–76)	NR	69	47	61	50–79	mBC
Fountzilas et al (2013) ⁵⁶	Overall study population	64	Median (range), Group A: 53.4 (32–75) and Group B: 60.65 (31–74)	NR	85.4	68.3	88.5	≥80	mBC

Gampriender et al (2018) ⁴²	Overall study population	116	Median (range), Optimization set: 60 (29–86), Learning set: 61 (34–81)	69	NR	NR	100	50–79	mBC
Gamucci et al (2017) ³⁸	Overall study population	314	Median (range): 55 (27–82)	80.9	NR	NR	100	≥80	mBC
Gerrata et al (2015) ⁶³	Overall study population	544	Median (range): 63 (53–73)	NR	79.4	63.7	78.9	50–79	mBC
Gilbert et al (2011) ²⁹	Overall study population	75	Age before starting capecitabine, Median (range): 53 (36–78)	79	NR	NR	100	50–79	mBC
Giordano et al (2011) ²⁴	Overall study population	517	Median (range): 49.3 (23.3–82)	NR	64.2	43.9	80.5	50–79	mBC
Goetz et al (2017) (CA) ²⁶	MONARCH 2, overall study population	669	Mean (SD): 59.9 (11.4)	100	NR	NR	100	≥80	mBC
Goetz et al (2017) (CA) ²⁶	MONARCH 3, overall study population	493	Mean (SD): 63.1 (9.92)	100	NR	NR	100	≥80	mBC
Gong et al (2018) ⁵⁵	Overall study population	7,482	NR	74.4	NR	NR	67.7	50–79	mBC
Grigolo et al (2017) (CA) ³⁴	Overall study population	104	Median (range): 56 (26–75)	67.3	NR	NR	69.2	50–79	BC patients with leptomeningeal metastasis
Guo et al (2017) ³⁵	Overall study population	176	Median (range): 49.5 (28–80)	NR	56.3	47.7	63.6	50–79	mBC
Inari et al (2017) ⁴⁵	Overall study population	96	Mean (SD): 51 (7.5)	60.4	42.7	40.6	85.4	50–79	mBC (metastatic lesions)
Jacot et al (2018) (CA) ⁴⁷	Overall study population	72	Median (range): 65 (35–87)	NR	69.4	NR	81.9	50–79	mBC
Jansson et al (2016) ⁷⁴	Overall study population	52	Age at mBC diagnosis, Median (range): 60 (40–83)	75	88.4	88.4	82.7	50–79	mBC
Jung et al (2011) ⁴³	Overall study population	553	Median (range): 55 (26–88)	73.1	NR	NR	65.5	50–79	mBC

(Continued)

Table 1 (Continued).

Study [Ref]	Population in Prognostic Analysis	Sample Size (N)	Age (in Years)	HR + (%)	ER + (%)	PR + (%)	HER2- (%)	Category by HR +/HER2- Status (%)	Description of BC
Jung et al (2012) ⁴⁸	Overall study population	557	Median (range): 55 (26–88)	73.2	NR	NR	65.5	50–79	mBC
Kawano et al (2013) ⁷²	Overall study population	69	Median (range): 53 (27–86)	100	92	81	87	≥80	Stage IV, mBC
King et al (2016) ⁹⁵	ER-positive/HER2-negative subgroup	92	Median (range): 52 (21–79)	100	100	NR	100	≥80	Stage IV BC
Kobayashi et al (2016) ⁵³	Overall study population	527	Age starting treatment for mBC, Mean: 55	65.3	NR	NR	71.2	50–79	mBC
Kono et al (2018) ⁸⁷	Overall study population	389	NR	68.8	NR	NR	91	50–79	Untreated primary BC and distant metastasis at diagnosis
Kontani et al (2014) ⁴⁹	Overall study population	70	Median (range): 60 (32–81)	60	NR	NR	81.8	50–79	mBC
Korantzis et al (2012) ⁴⁴	Overall study population	159	Median (range): 60.7 (27.3–86.7)	70	NR	NR	62	50–79	mBC
Lau et al (2017) (CA) ⁹⁷	Overall study population	82	NR	100	NR	NR	100	≥80	mBC
Lawrie et al (2018) ⁹⁶	Overall study population	103	Median (range): 58 (27–86)	100	100	91	HER2- (Score 0 +1) =86.4	≥80	mBC
Leone et al (2017) ⁷⁸	Overall study population	9,143	Median (range): 61 (19–102)	65.9	NR	NR	51.3	50–79	Stage IV BC at initial diagnosis
Li 2017 ³⁸	Overall study population Overall study population	7,199	Median: 58 (IQR 49–67)	NR	73.4	60.6	74	50–79	Stage IV BC

Llombart-Cussac et al. (2014) ⁷¹	Overall study population	2,203	Median (range): 53 (22–93)	69	65	54	100	50–79	Advanced locally recurrent or mBC
Lobbezoo et al (2013) ¹⁰	Overall study population	798	Median (range): 59 (25–93)	76.5	NR	NR	81.4	50–79	mBC
Lobbezoo et al (2015) ⁶⁹	Overall study population	815	Median (range), De novo: 61 (25–89); Recurrent: 64 (25–93)	75	NR	NR	78	50–79	mBC
Lobbezoo et al (2016) ^{54,59}	Overall study population	482	Median (range), Initial CT: 52 (25–80), Initial ET: 61 (30–91)	100	NR	NR	100	≥80	mBC
Manuel et al (2012) ⁵⁹	Overall study population and subgroups	133	Median (range), Cohort A: 59.9 (36.5–84.1), Cohort B: 56.9 (34.7–79.9)	NR	72.1	58.6	73.7	50–79	mBC
Miyoshi, 2016 ³⁸	Overall study population	318	NR	100	100	100	100	≥80	Early and late recurrent BC
Motomura et al (2010) ⁴⁶	Overall study population	41	Median (range): 57 (42–79)	100	97.6	97.5	92.7	≥80	mBC
Muller et al (2012) ⁷⁵	Overall study population	245	Median: 57	NR	69.4	59.2	56.7	50–79	mBC
Munzone et al (2012) ⁸³	Overall study population	203	Median (range): 57 (31–78)	79.3	NR	NR	73.8	50–79	mBC
Nieder et al (2017) ⁷⁹	Overall study population	118	Median (range): 61 (33–87)	NR	77	NR	82	50–79	mBC
Ogiya et al (2017) ^{66,67}	Overall study population	339	NR	NR	100	NR	100	≥80	BC patients with the early and late distant recurrence
Okazaki et al (2018) ⁶⁷	Overall study population	18	Median (range): 51 (34–81)	100	NR	83	100	≥80	Locally advanced or mBC
Paoletti et al (2017) (CA) ³¹	Overall study population	121	NR	NR	100	NR	100	≥80	mBC

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Table 1 (Continued).

Study [Ref]	Population in Prognostic Analysis	Sample Size (N)	Age (in Years)	HR + (%)	ER + (%)	PR + (%)	HER2- (%)	Category by HR +/HER2- Status (%)	Description of BC
Papadaki et al (2018) ³²	Overall sample = 130 Analysis conducted in HER2- subgroup	130	Median (range): 59 (23–82)	NR	68.5	63.8	78.5	50–79	mBC
Park et al (2017) ⁸⁵	Overall study population	100	Mean (range): 48.1 (48–75)	65	NR	NR	75	50–79	Invasive ductal BC with bone-only metastasis
Pascual et al (2017) ⁶⁵	Overall study population	90	Median (range): 62 (37–84)	NR	100	NR	100	≥80	mBC
Peeters et al (2014) ³⁶	Overall study population	154	Median (range): 62.1 (32.9–90.8)	55.2	NR	NR	69.9	50–79	mBC
Pierga et al (2012) ⁵¹	Overall study population	267	Median: 57	62	NR	NR	83	50–79	mBC
Pistilli et al (2017) (CA) ⁵⁰	Overall study population	6,265	Median (range), Age group <45 years: 40.0 (23–44) Age group >45 years: 63 (45–95)	100	NR	NR	100	≥80	mBC
Redondo et al (2018) ⁵⁸	Overall study population	148	Median (range): 50 (29–81)	NR	74.3	61.5	100	50–79	mBC
Ren et al (2016) ⁷³	Overall study population	323	Median: 49	NR	58	45	50	50–79	advanced BC
Schiavon et al (2015) ²³	Subgroup of ESRI wild and mutant type	128	Median, ESRI wild type: 58, ESRI mutant: 64	100	100	NR	84	≥80	advanced BC
Staudigl et al (2015) ⁸¹	Overall study population	114	Age at first diagnosis, Mean: 61.0	76.3	NR	NR	82.5	50–79	mBC
Suh et al (2017) ²⁷	Overall study population	66	Age at the time of treatment, Median: 44	100	NR	NR	100	≥80	mBC and recurrent BC (Luminal A, Luminal B (HER2-), Unknown)
Turker et al (2014) ⁹⁸	Overall study population	302	Median (range): 50 (21–83)	NR	72.2	60.6	59.6	50–79	Stage IIIC with > 10 positive axillary

Uyeturk et al (2014) ²⁵	Overall study population	466	Median (range): 50 (18–90)	73.2	68.5	60.5	65.5	50–79	mBC
Vaz-Luis et al (2015) ⁸⁵	HR+ HER2– subgroup	3,151	NR	100	NR	NR	100	≥80	Stage IV, mBC
Wallwiener et al (2013) ⁷⁶	Overall study population	486	Median (range): 55 (23–91)	NR	67.3	58.7	69.8	50–79	mBC
Wu et al (2017) ⁹⁰	Overall study population	9,256	NR	76.6	NR	NR	74.2	50–79	Stage IV BC
Xie et al (2015) ³³	Overall study population	699	Age at BC diagnosis, Median (range), patients with multiple metastases: 61.0 (35.0–83.0); patients with a single metastasis: 61.0 (33.0–90.0)	100	NR	NR	100	≥80	mBC
Xiong et al (2018) ²⁸	Overall study population	8,901	NR	70.5	NR	NR	65.6	50–79	BC with initial bone metastasis
Yamamura et al (2018) ³⁹	Overall study population	172	For stage IV: Age group <50 years: 12 (18%) Age group 50–70 years: 16 (25%) Age group ≥70 years: 37 (57%) For recurrent mBC: Age group <50 years: 20 (19%) Age group 50–70 years: 25 (23%) Age group ≥70 years: 62 (58%)	100	NR	NR	100	≥80	Stage IV and recurrent and mBC
Yerushalmi et al (2012) ⁹³	Subgroup Luminal A and Luminal B	566	NR	100	NR	NR	100	≥80	mBC
Zhang et al (2013) ⁶⁰	Overall study population	134	Median (range): 52 (28–74)	100	NR	NR	56	50–79	mBC
Zhao et al (2011) ⁷⁰	Overall study population	60	Median (range), Metoncemic Arm: 46 (35–73); Conventional Arm: 51 (33–73)	NR	66.6	NR	76.6	50–79	Stage IV BC with bone metastases

Abbreviations: BC, breast cancer; CT, chemotherapy; ET, endocrine therapy; IQR, interquartile range; mBC, metastatic breast cancer; NR, not reported; SD, standard deviation.

In two of four studies demonstrating a relationship with OS, N1, N2, and N3 categories were associated with better OS than patients with no lymph node involvement (N0),^{28,90} these studies involved stage IV *de novo* metastatic patients from the Surveillance, Epidemiology, and End Results (SEER) registry. The trend, however, was converse in the other two studies, among patients with metastatic disease with no prior diagnosis and another with recurrent disease after breast surgery or neoadjuvant chemotherapy, in which greater lymph node involvement was associated with greater risk of death.^{38,66} The two studies focusing on BCSS and the one study⁷⁰ focusing on PFS also reported higher lymph node involvement was associated with greater risk of death.^{28,90} In summary, the directionality of association was inconsistent across studies assessing OS and lymph node involvement. Overall, the effect size of the association between lymph node involvement and survival endpoints was moderate.

Histological Type

In Gampenrieder et al,⁴² patients with lobular carcinoma (HR=3.44; 95% CI=1.07–11.11; $P=0.039$) or other type of carcinoma (HR=3.19; 95% CI=1.05–9.70; $P=0.041$) were associated with 3-fold greater risk of death compared with ductal carcinoma; similar results were observed for PFS. The effect size of the association between histological type (lobular vs ductal) and survival endpoints was strong. The evidence of association was insufficient as a significant association was reported in only one of five studies with OS and two studies with PFS.

Biomarkers

Relationship between CTC count and OS (n=10), PFS (n=10), and BCSS (n=1) was evaluated, with a significant association reported in 90% (n=9), 80% (n=8), and 0% (n=0) of studies, respectively.^{24,31,32,36,47,51,74–76,83} The presence of a higher CTC count ($\geq 5/7.5$ mL whole blood) was consistently associated with poor OS and PFS.

The relationship between Ki67 expression and OS (n=7), PFS (n=4), and tumor response (n=1) was evaluated, with a significant association reported in 86% (n=6), 100% (n=4), and 100% (n=1) of studies, respectively.^{27,30,45,57,60,66,67,80} Studies did not consistently report the source of the Ki67 (primary or metastatic tumor site). High Ki67 expression was associated with worse OS, PFS, and tumor response. The

thresholds for the Ki67 was inconsistent across studies, with a Ki67 index of $\leq 14\%$ vs $>14\%$ being the most common.

The association of both CTCs and Ki67 with OS and PFS was harmonious with respect to consistency of evidence and directionality of association. Overall, the effect size of the association between these biomarkers and survival endpoints were moderate.

De Novo Metastatic Breast Cancer (mBC)

The relationship between *de novo* mBC and OS (n=5), PFS (n=3), and BCSS (n=1) was evaluated, with a significant association reported in 100% (n=5), 67% (n=2), and 0% (n=0) of studies, respectively.^{30,33,39,57,62,91} Four studies demonstrated longer OS in patients with mBC at diagnosis compared with recurrent breast cancer,^{30,39,57,91} while one study reported shorter OS in patients with *de novo* mBC.⁶² Similarly, one study showed longer PFS associated with patients with *de novo* mBC,³⁰ while another study showed a reverse relationship.³³

The association of *de novo* mBC with OS and PFS was consistent with respect to evidence. The directionality of association was consistent with OS but not with PFS. The effect size of the association between *de novo* mBC and survival endpoints ranged between weak to moderate.

Number of Metastatic Sites

The relationship between number of metastatic sites and OS (n=27), PFS (n=11), and BCSS (n=1) was evaluated, with a significant association reported in 89% (n=24), 55% (n=6), and 100% (n=1) of studies, respectively.^{10,28–30,33,38,39,41,43,44,48,51–55,57,59,60,66,69,71,75,79,80,89} Multiple metastases were associated with significantly worse OS and PFS. There were variations in the way comparisons between the number of metastatic sites were made across studies (eg, ≤ 1 vs >1 ; ≤ 3 vs >3); however, the multiple vs single site of metastases (ie, >1 vs 1) comparison was the most common. Most studies compared either the number of metastatic sites (eg, >1 vs 1) or types of sites/location of metastasis (eg, lungs vs brain, visceral vs non-visceral) However, three studies^{10,28,54} compared multiple metastatic sites (visceral, brain, skin, lymph nodes) to bone metastasis and found significantly greater risk of death associated with the former. Consistency in evidence and directionality of association was observed for OS and PFS. The effect size of the association between number of

metastatic sites and survival endpoints ranged from moderate to strong, depending on the comparison groups.

Sites of Metastasis

Twenty-two of the 34 studies found a significant association between sites of metastasis and OS.^{10,29,30,32,36,38,39,42–44,48,52,54,59,63,69,71,75,78–80,89} Sites of metastasis were compared heterogeneously (eg, visceral vs non-visceral, visceral vs bone, hepatic vs no hepatic, brain vs no brain). Liver involvement was the most widely studied (n=12^{30,32,38,39,43,48,59,63,71,78,79,89}), followed by brain/CNS (n=14^{10,29,30,38,43,48,54,61,63,69,78–80,89}), visceral (n=13^{10,30,36,42–44,52,54,63,69,75,78,99}), bone (n=9–10,^{38,48,54,59,63,69,75,78}), and lung (n=7^{30,38,63,71,78,79,89}). All these studies reported shorter OS associated with the presence of metastasis at these specific sites compared to lack of it (eg, visceral vs non-visceral). Bone metastasis was also often used as the reference category when comparing the effect of other metastatic sites on survival, and was associated with improved prognosis compared to these other sites.^{10,44,54,69,75,78}

Ten of 13 studies reported a significant association with PFS.^{26,29,30,32,33,36,60,63,76,84} Bone was the most assessed site (n=5^{33,36,63,76,84}), followed by liver (n=4^{26,30,32,63}), and visceral (n=4^{30,60,63,76}). As with OS, the presence of metastasis compared with absence in bone, liver, and visceral sites was associated with worse PFS; visceral sites reported worse PFS when compared with bone.^{10,78} Only one study reported poor tumor response associated with liver metastases.²⁶

The definition of visceral sites varied across studies, most commonly defined as lung, liver, pericardial/pleural/peritoneal, and brain. Consistency in evidence and directionality of association was observed for OS and PFS. The overall effect size of association with survival was: moderate for liver, brain, and visceral sites; weak for lung; and ranged from weak to moderate for bone.

Time to Recurrence or Progression to Advanced Breast Cancer

Time to recurrence or progression to advanced breast cancer was most often defined as the time between date of diagnosis of primary breast cancer, and date of diagnosis of first distant metastasis or recurrence. Disease-free interval (DFI), metastasis-free interval (MFI), and recurrence-free interval (RFI) are other terminology used to

describe this. In Zhao et al,⁷⁰ it was defined as the date from surgery to first recurrence. Eight studies did not report the definition.^{36,45,49,52–54,66,71}

The relationship between time to recurrence or progression to advanced breast cancer and OS (n=18) and PFS (n=5) was evaluated, with a significant association reported in 78% (n=14) and 80% (n=4) of studies, respectively.^{10,29,36,39,45,48,49,52–54,60,66,70,71,91} In 13 studies, shorter time to recurrence or progression to advanced breast cancer was associated with worse survival relative to longer time, except in Jung et al,⁴⁸ where the 1–5 years vs <1 year MFI was associated with worse OS (HR=1.30; 95% CI=1.02–1.65; P=0.032). The 2-year time interval was the most commonly studied cut-off point. Four studies showed a shorter time to recurrence or progression to advanced breast cancer (eg, <2 years) was associated with worse PFS.^{29,54,60,70} Consistency in evidence and directionality of association was observed for OS and PFS. The overall effect size of the association between time to recurrence or progression to advanced breast cancer and survival endpoints was moderate.

Prior Therapy

Given the patient population had advanced breast cancer, patients were likely to have received prior therapy (except those with *de novo* mBC) – such as surgery, chemotherapy, radiation therapy, hormone therapy – to treat early breast cancer. Type of prior therapy, line of prior therapy received in the metastatic setting, or clinical benefit to prior therapy were all grouped under the “prior therapy” category in this review.

Twenty-seven of 35 studies found a significant relationship between OS and prior therapy.^{10,25,28,30,33,34,38,44,49,52,54,55,57,58,60,66,71,72,76,79,80,88–91,94} Prior therapy was either adjuvant or neoadjuvant chemotherapy or hormonal therapy in 19 studies that assessed OS.^{10,29,30,32,33,38,41,42,44,45,54,57,58,60,66,71,80,91,92} Lack of 1st-line hormonal therapy in patients with advanced breast cancer was also associated with worse survival compared with receiving hormonal therapy.⁸⁰ Furthermore, the absence of hormonal maintenance therapy in the advanced setting was associated with worse OS in three studies.^{38,58,80} Two studies reported that adjuvant hormonal therapy use was associated with shorter survival compared with lack of use.^{33,54} Lobbezoo et al⁵⁴ reported shorter survival was associated with receipt of initial chemotherapy compared with initial hormonal therapy in the metastatic setting.

Surgery was the prior therapy in ten studies that assessed OS.^{25,28,38,41,55,58,88–90,94} Seven studies showed that receipt of surgery, compared with lack of surgery or best supportive care, resulted in significantly longer survival; five of these studies included *de novo* mBC patients^{28,55,89,90,94} and in the remaining two studies, surgery was conducted in early stage breast cancer.^{38,88}

Prior radiotherapy was received in six studies that evaluated OS.^{38,41,66,79,82,89} First-line radiotherapy (yes vs no) was significantly associated with longer survival for mBC,³⁸ however, the association was not uniform for 1st-line chemotherapy (multiagent vs none/single-agent); Li 2017³⁸ reported improved OS, while Xie et al³³ reported worse OS.

Longer treatment durations in the advanced setting were associated with improved OS, while greater lines of treatment were associated with worse OS.^{66,76} Four studies demonstrated that the presence of clinical benefit or response to a specific treatment was associated with better OS.^{38,52,57,72}

Fifteen studies assessed the association of PFS with line/type of prior therapy; 13 showed a significant relationship.^{23,27,29,30,32,33,38,47,54,58,60,70,76,84} Eleven of the 15 studies reported adjuvant or neoadjuvant chemotherapy or hormonal therapy,^{23,27,29,30,32,33,38,42,54,58,60} while four studies reported chemotherapy as prior treatment.^{47,70,76,84}

Four studies compared multiple vs single lines of treatment and found that increasing treatment line in the metastatic setting correlated with worse prognosis.^{27,32,33,76} In two studies that included *de novo* patients, prognostic relevance was shown for surgery vs no surgery as prior therapy and found improved BCSS in patients undergoing breast-conserving surgery/mastectomy.^{55,90}

There was substantial heterogeneity in reporting of type/class of therapy received. In general, patients receiving interventions (surgery/radiotherapy/systemic therapy), responding to treatments, or receiving fewer lines of treatment in the metastatic setting were likely to have better prognosis. Consistency in evidence and directionality of association was observed for OS, PFS, and BCSS. The effect size of the association between prior therapy attributes and survival endpoints was moderate.

Patient-Related Factors

Age

Relationship between age and OS (n=37), PFS (n=7), and BCSS (n=3) was evaluated, with significant association

reported in 46% (n=17), 29% (n=2), and 67% (n=2) of studies, respectively.^{10,28,30,33,36,38,43,48,55,57,58,62,69,78,84,85,90–92} Among studies that found a significant association, increasing age was associated with worse OS, PFS, or BCSS. The time-point at which age data was collected in the study (whether age at diagnosis or at treatment initiation) was not reported in the majority of included studies. Among studies that did report, age at diagnosis was the most common. In three studies, increasing age was associated with worse OS.^{57,62,69} Age groups compared across studies varied widely (eg, >50 vs ≤50 years, >65, or 50–64 vs 18–49 years). Among the different age group comparisons, age ≥50 years was the most common cut-off point, reported in six studies.^{10,54,55,78,90,91} Less than 50% of studies found a significant association between age and OS as well as PFS, however, the directionality of association was consistent (ie, increasing age was associated with shorter survival). The effect size of the association between age and survival endpoints varied widely across studies, ranging from weak to strong.

Race

Relationship between race and OS (n=13) and BCSS (n=3) was evaluated, with a significant association reported in 54% (n=7) and 100% (n=3) of studies, respectively.^{22,28,38,55,73,78,90} Poorer OS or BCSS was observed in blacks compared with whites. One study reported that better OS was observed for patients of other races vs whites (HR=0.59; 95% CI=0.44–0.78; $P<0.001$).³⁸ One study evaluated but did not report a significant association between race and PFS.³³ Consistency in evidence and directionality of association was observed between race and OS as well as BCSS. The effect size of the association between race and survival endpoints was weak.

Performance Status

Relationship between performance status and OS (n=14) and PFS (n=8) was evaluated, with a significant association reported in 79% (n=11) and 50% (n=4) of studies, respectively. ECOG scale was used in all but two studies; one study employed the World Health Organization (WHO) performance status scale,⁵¹ and one did not define the performance status scale.⁵⁹ Comparison of different ECOG statuses varied across studies; most studies compared ECOG levels ≥2 vs 0–1, three studies compared ≥1 vs 0, while one study compared ≥3 vs 0–2.^{33,34,37,42,51,63,71,80} All studies found poor performance status or limitations in daily activity to be significantly

associated with worse OS or PFS. Consistency in evidence and directionality of association was observed between performance status and OS. Less than 50% of studies found a significant association between PFS and performance status, however, the directionality of association was consistent. The effect size of the association between performance status and survival endpoints was moderate.

Strength of Evidence

Table 2 summarizes the strength of evidence between prognostic factors and survival endpoints. Figure 2 shows the number of studies that reported better, worse, or no association between the prognostic factors and OS (Figure 2A) and PFS (Figure 2B).

Associations between OS and PR status, tumor grade, CTC count, Ki67 level, *de novo* mBC, number and sites of metastases, time to recurrence or progression to advanced breast cancer, race, and prior therapy attributes were consistent (>50% of studies found a significant association). However, the evidence was limited (<50% of studies reported a significant association) for tumor size, histological type, lymph node involvement, and age. The direction of association was consistent for all the prognostic factors summarized in this study except for lymph node involvement. Based on effect size, strength of association with OS was moderate (HR=1.5–2.9) for PR status, tumor grade, Ki67 level, number and sites of metastases, time to recurrence or progression to advanced breast cancer, performance status, and prior therapy attributes, and weak (HR<1.5) for *de novo* metastatic breast cancer and race.

After applying the strongest evidence criteria, disease-related factors – such as PR status, tumor grade, CTC count, Ki67 level, number and sites of metastases, and time to recurrence or progression to advanced breast cancer, performance status, prior therapy attributes, and race – were found to have the strongest evidence of an association with OS.

Associations between PFS and tumor grade, CTC count, Ki67 level, number and sites of metastases, time to disease recurrence or progression to advanced breast cancer, and prior therapy attributes were consistent. However, the evidence was limited for PR status, lymph node involvement, histological type, performance status, age, and race; no data were reported for association between PFS and tumor size or marital status. The direction of association was consistent for all the prognostic factors, except for *de novo* metastatic breast cancer.

Since fewer studies assessed PFS than OS, evidence on prognostic factors related to PFS was limited. Thus, high CTC count, number and sites of metastases, and prior therapy attributes in the early or metastatic setting were the only four prognostic factors with the strongest evidence of an association with worse PFS. Similarly, there was limited information for the other endpoints.

Other Variables

There were many other variables assessed in the included studies. However, these were reported sparsely and we could not assess strength of evidence for them. They consisted of many genetic/biomarkers factors, for example, estrogen receptor gene (ESR1) mutation status,⁶⁸ ligand binding domain (LBD) status,⁹⁷ CA 15–3 level,^{51,70} alkaline phosphatase level,⁷⁹ serum C-reactive protein level (CRP),⁷⁹ lactic acid dehydrogenase (LDH) level,^{51,59,79} along with other demographic-related factors like marital status,⁵⁵ income level,⁵⁵ menopausal status,⁵⁹ and education status.⁵⁵ A high level summary can be found in Table 3.

Quality of Evidence

The overall risk of bias was considered high for three studies, moderate for 22 studies, and low for the remaining 47 studies (Figure 3). Studies that failed to report exclusion criteria, definition of survival endpoints, or did not perform multivariate analysis to account for confounding were deemed “high” risk of bias.

Discussion

This comprehensive SLR was conducted to evaluate the strength and consistency of evidence of prognostic factors associated with survival in patients with HR+/HER2– advanced breast cancer. As commonly observed in oncology literature, OS was the most widely assessed survival endpoint, followed by PFS. The evidence was limited for tumor response (n=3) and BCSS (n=5). Hence, this review focused on prognostic factors associated with OS and PFS.

Higher CTC count, Ki67 level, number of metastases (multiple vs single), and sites of metastases (presence of liver metastases vs absence), prior therapy attributes, negative PR status, higher tumor grade, shorter time to recurrence or progression to advanced breast cancer, poor performance status and race (black vs white) were the prognostic factors with strongest evidence of association with OS and PFS. Previously published studies^{11–12,24–100–104} have also demonstrated the prognostic relationship between survival endpoints and disease-related factors – such as PR status, CTC

Table 2 Strength of Evidence Assessment

Prognostic Factor	Type of Outcome	No. of Studies That Assessed Association	No. of Studies Reporting Significant Association	No. of Studies with Univariate Analysis	No. of Studies with Significant Univariate Analysis	No. of Studies with Multivariate Analysis	No. of Studies with Significant Multivariate Analysis	Consistency Based on >50% Studies with Significant Association	Directionality of Relationship	Strength of Association Based on Effect Size	Studies with Low Sample Size (<100)
PR status	OS	10	8	10	8	7	5	Consistent	Consistent	Moderate	4
	PFS	2	1	1	0	0	0	Inconsistent	NA (single study)	NA	1
Tumor grade	OS	21	13	15	7	15	11	Consistent	Consistent	Moderate	4
	PFS	4	3	2	1	2	1	Consistent	Consistent	Strong	2
Tumor size	OS	12	5	10	4	8	5	Inconsistent	Consistent	Weak-moderate	4
	OS	11	4	10	4	5	1	Inconsistent	Inconsistent	Moderate	5
Lymph node	PFS	1	1	1	1	0	0	NA (single study)	NA (single study)	NA	1
	OS	5	1	4	0	1	1	Inconsistent	NA	Strong	3
Histological type	PFS	2	1	1	0	2	1	Inconsistent	NA (single study)	Strong	2
	OS	10	9	9	8	7	7	Consistent	Consistent	Strong	3
CTC count	PFS	10	8	8	5	6	6	Consistent	Consistent	Moderate	3
	OS	7	6	6	5	4	3	Consistent	Consistent	Moderate	2
Ki67	PFS	4	4	3	3	3	3	Consistent	Consistent	Moderate	2
	OS	5	5	4	4	5	2	Consistent	Consistent	Weak	0
De novo metastatic BC	PFS	3	2	2	1	2	1	Consistent	Inconsistent	Moderate	1
	OS	27	24	21	19	20	14	Consistent	Consistent	Moderate	3
No. of Metastatic sites	PFS	11	6	7	4	9	5	Consistent	Consistent	Moderate	2

Site of metastasis	OS	34	22	21	14	25	19	Consistent	Consistent	Moderate	7
	PFS	13	10	7	6	10	6	Consistent	Consistent	Moderate	4
Time to recurrence or progression to ABC	OS	18	14	12	10	12	9	Consistent	Consistent	Moderate	4
	PFS	5	4	3	3	4	3	Consistent	Consistent	Moderate	3
Prior therapy	OS	35	27	24	18	25	22	Consistent	Consistent	Moderate	6
	PFS	15	13	10	8	12	10	Consistent	Consistent	Moderate	6
Performance	OS	14	11	7	6	11	8	Consistent	Consistent	Moderate	2
	PFS	8	4	3	1	6	4	Inconsistent	Consistent	Moderate	1
Age	OS	37	17	25	10	24	13	Inconsistent	Consistent	Weak–Moderate	5
	PFS	7	2	5	0	3	2	Inconsistent	Consistent	Moderate–Strong	2
Race	OS	13	7	10	6	10	6	Consistent	Consistent	Weak	1
	PFS	1	0	0	0	1	0	NA	NA	NA	0

Abbreviations: BC, breast cancer; BCSS, breast cancer-specific survival; CTC, circulating tumor cell; NA, not applicable; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor.

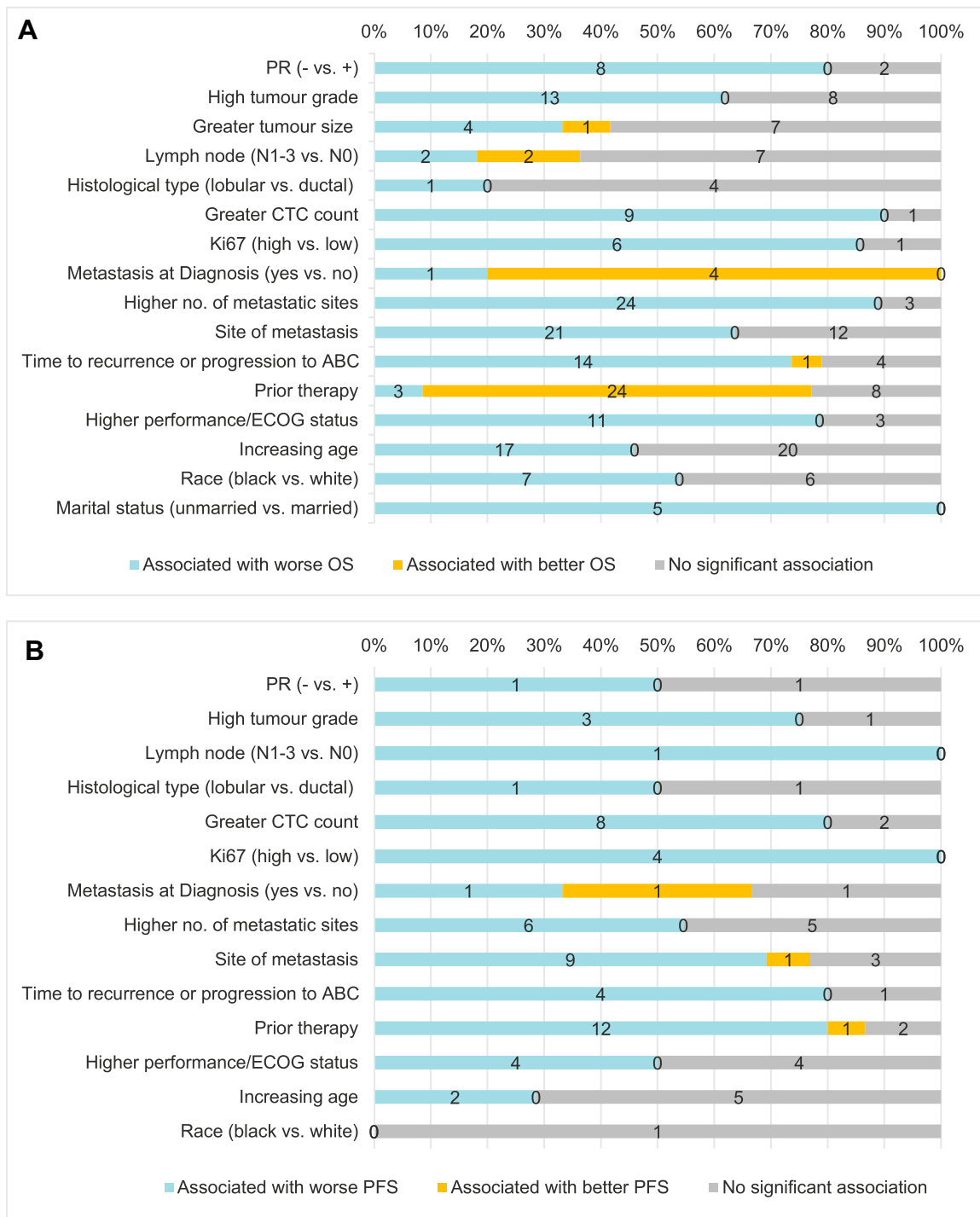


Figure 2 Association between selected prognostic factors and OS (A), and PFS (B).

Abbreviations: BCSS, breast cancer-specific survival; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor.

count, Ki67 level, number and sites of metastasis – and treatment-related factors and performance status. Other studies in the literature^{103,105–107} have also reported older age, black race, and unmarried status to be associated with shorter survival rates. Future cohort studies exclusively in HR+/HER2-

advanced breast cancer will be beneficial to further validate the collective set of prognostic factors with the strongest evidence.

In the advance disease setting, breast cancer is incurable and the treatment goal is mainly palliative, improving

Table 3 Additional Variables Assessed in the Included Studies

Prognostic Factor	Type of Outcome	No. of Studies That Assessed Association	No. of Studies Reporting Significant Association	No. of Studies Reporting Worse Outcome	No. of Studies Reporting Better Outcomes	Summary of Direction of Association
Biomarkers or genetic markers						
ALDH1 (1 vs >1%)	OS	1	1 ⁴⁰	1	–	ALDH1 1% was associated with worse OS than ALDH1 >1%
ALP (high vs normal)	OS	2	1 ⁷⁹	1	–	High ALP was associated with worse OS than normal ALP
ALP > upper limit of normal	PFS	1	1 ⁵¹	1	–	High ALP was associated with worse PFS than normal ALP
Baseline SUVmax (intermediate and highest tertile vs lowest tertile)	OS	1	1 ⁶⁰	–	–	Baseline SUVmax intermediate and highest tertiles were associated with worse OS than the lowest tertile
	PFS	1	1 ⁶⁰	1	–	Baseline SUVmax intermediate and highest tertiles were associated with worse PFS than the lowest tertile
CA 15–3 (high vs normal)	OS	2	1 ⁷⁹	1	–	Higher levels of CA 15–3 was associated with worse OS compared to normal levels
CA 15–3 > upper limit of normal	PFS	1	1 ⁵¹	1	–	CA 15–3 > upper limit of normal was associated with worse PFS
CEA > upper limit of normal	PFS	1	1 ⁵¹	1	–	CEA > upper limit of normal was associated with worse PFS
Serum CRP levels (high, >60 vs normal)	OS	1	1 ⁷⁹	1	–	Higher serum CRP levels compared to normal was associated with worse OS
ESR1 mutations (mutated vs wild type)	OS	1	1 ⁶⁸	1	–	Mutated ESR1 (D538G, Y537S) was associated with worse OS than wild type
	PFS	1	1 ⁶⁸	1	–	Mutated ESR1 (D538G) was associated with worse PFS than wild type
Gamma- glutamyltransferase (GGT) (high vs low risk groups)	OS	1	1 ⁸¹	1	–	High risk groups C and D (elevated and highly elevated GGT) was associated with significantly decreased OS time compared to the low risk groups A and B (normal and normal high GGT)
GIT1 expression (no vs yes)	OS	1	1 ⁹⁶	1	–	Loss of GIT1 expression in lymph nodes (± pattern) was associated with worse OS
Hemoglobin (<11.5 vs ≥11.5 g/dL)	OS	2	2 ^{59,79}	2	–	Lower hemoglobin levels (<11.5 g/dL) was associated with worse OS compared to high levels (≥11.5 g/dL)
HER2 blood mRNA levels (high vs low)	OS	1	1 ⁴⁴	–	1	High blood HER2 mRNA levels were found to be associated with significantly improved OS compared to low levels

(Continued)

Table 3 (Continued).

Prognostic Factor	Type of Outcome	No. of Studies That Assessed Association	No. of Studies Reporting Significant Association	No. of Studies Reporting Worse Outcome	No. of Studies Reporting Better Outcomes	Summary of Direction of Association
IHC, Tau protein (+ vs-)	PFS	1	1 ⁵⁶	-	1	Presence of Tau protein expression was associated with better PFS
IHC, Topo IIa (+ vs-)	PFS	1	1 ⁵⁶	1	-	Topo IIa protein positivity was associated with unfavorable PFS
IL-18 levels (high, ≥8 ng/mL vs low)	OS	1	1 ⁸⁶	-	1	High IL-18 levels (≥8 ng/mL) at the time of diagnosis was associated with better OS than low IL-18 levels
IL-8 (high vs low)	OS	1	1 ⁴⁴	1	-	Higher IL-8 levels compared to lower levels was associated with worse OS
LBD mutations (yes vs no)	OS	1	1 ⁹⁷	1	-	Presence of LBD mutations were associated with worse OS
	PFS	1	1 ⁹⁷	1	-	Presence of LBD mutations were associated with worse PFS
LDH levels (high, ≥600 vs low <600 U/l/mL)	OS	3	3 ^{51,59,79}	3	-	Higher LDH levels was associated with worse OS than lower LDH levels
LDH levels (high vs low)	PFS	1	1 ⁵¹	1	-	LDH levels > upper limit of normal was associated with worse PFS
Lymphocytes (<1 vs ≥1 Giga/L)	OS	1	1 ⁵⁹	1	-	Lower lymphocyte count was associated with worse OS
MAPT RQ values, 50% cut-off (high vs low)	OS	1	1 ⁵⁶	-	1	High MAPT RQ values was associated with better OS
Metastatic EZH2 expression (high vs low)	OS	1	1 ⁴⁵	1	-	High metastatic EZH2 expression was associated with worse OS than low EZH2 expression
NDL (>1 vs ≤1 Giga/L)	OS	1	1 ⁵⁹	1	-	NDL >1 Giga/L was associated with worse OS than NDL ≤1 Giga/L
N-telopeptide of type I collagen (NTx) (<18 nM BCE vs > 18 nM BCE)	PFS	1	1 ⁷⁰	-	1	Baseline serum NTx of less than 18 nM was associated with significantly better PFS than baseline serum NTx of greater than 18 nM
PNIN (<7.5 vs ≥7.5 Giga/L)	OS	1	1 ⁵⁹	-	1	PNIN <7.5 Giga/L was associated with better OS than PNIN ≥7.5 Giga/L
21-gene recurrence score (low vs high risk group)	OS	1	1 ⁹⁵	-	1	Low risk group (<18 score) was associated with better OS than high risk group (≥18 score)

Serum albumin (low vs normal)	OS	I	I ⁷⁹	I	-	-	Low serum albumin compared to normal levels was associated with worse OS
Serum VEGF after 3 months (normal vs abnormal)	PFS	I	I ⁷⁰	-	I	-	Serum VEGF of less than 500 pg/mL (normal) after 3 months of intervention was associated with better PFS compared to VEGF >500 pg/mL (abnormal)
SET _(ER/PR) Index (high vs low)	OS	I	I ⁹⁷	-	I	-	Higher SET _(ER/PR) Index was associated with better OS
SET _(ER/PR) Index (high vs low)	PFS	I	I ⁹⁷	-	I	-	Higher SET _(ER/PR) Index was associated with better PFS
SNP, ABCBI 1236C/T rs1128503 (C vs T or T/C)	PFS	I	I ⁵⁶	I	-	-	SNP, ABCBI 1236C/T rs1128503 (C) was associated with worse PFS than ABCBI 1236C/T rs1128503 (T or T/C)
SNP, ABCBI 2677G/A/T rs2032582 (G or G/A vs T or T/G)	OS	I	I ⁵⁶	I	-	-	SNP, ABCBI 2677G/A/T rs2032582 (G or G/A) was associated with worse OS than ABCBI 2677G/A/T rs2032582 (T or T/G)
SNP, ABCBI 3435C/T rs1045642 (C vs T or T/C)	OS	I	I ⁵⁶	I	-	-	SNP, ABCBI 3435C/T rs1045642 (C) was associated with worse OS than SNP, ABCBI 3435C/T rs1045642 (T or T/C)
Surgical margin (negative, R0 vs positive, R1)	OS	I	I ⁹²	-	I	-	Negative surgical margin was associated with better OS than positive surgical margin
T-cell receptor diversity (≤33 vs >33%)	OS	I	I ⁵⁹	I	-	-	T-cell receptor diversity of ≤33% compared with >33% was associated with worse OS
Demographic or Patient characteristics							
BMI (<20 vs 20-24.9)	OS	I	I ⁴⁸	-	I	-	Low BMI was associated with better OS than higher BMI
Surgical margin (negative, R0 vs positive, R1)	OS	I	I ⁹²	-	I	-	Negative surgical margin was associated with better OS than positive surgical margin
T-cell receptor diversity (≤33 vs >33%)	OS	I	I ⁵⁹	I	-	-	T-cell receptor diversity of ≤33% compared with >33% was associated with worse OS
Demographic or Patient characteristics							
BMI (<20 vs 20-24.9)	OS	I	I ⁴⁸	-	I	-	Low BMI was associated with better OS than higher BMI
Education level (high vs low)	OS	2	2 ^{43,55}	I	I	-	Mixed result (worse and better OS)
BCSS	BCSS	I	I ⁵⁵	I	-	-	Higher education level was associated with worse BCSS

(Continued)

Table 3 (Continued).

Prognostic Factor	Type of Outcome	No. of Studies That Assessed Association	No. of Studies Reporting Significant Association	No. of Studies Reporting Worse Outcome	No. of Studies Reporting Better Outcomes	Summary of Direction of Association
Household income (per \$10,000 annual increase)	OS	1	1 ⁵⁵	–	1	Higher median household income was associated with better OS
	BCSS	1	1 ⁵⁵	–	1	Higher median household income was associated with better BCSS
Insurance status (uninsured vs insured)	OS	1	1 ⁵⁵	1	–	Patients who were uninsured had worse OS than those who were insured
	BCSS	1	1 ⁵⁵	1	–	Patients who were uninsured had worse BCSS than those who were insured
Marital status (unmarried vs married)	OS	5	5 ^{28,55,78,85,90}	5	–	Unmarried status was associated with worse OS than married
	BCSS	2	2 ^{55,90}	2	–	Unmarried status was associated with worse BCSS than married
Menopausal status (yes vs no; post vs pre)	OS	4	2 ^{59,98}	2	–	Presence of menopause was associated with worse OS than absence of menopause; Similarly, postmenopausal status was associated with worse OS compared to postmenopausal status
	PFS	3	1 ⁸⁴	1	–	Postmenopausal status was associated with worse PFS compared to postmenopausal status
Received blood transfusion before RT (yes vs no)	OS	1	1 ⁷⁹	–	1	Receiving blood transfusion before RT was associated with better OS as compared to not receiving
Residence type (rural vs urban)	OS	1	1 ⁵⁵	1	–	Patients from rural residence was associated with worse OS than urban residence
	BCSS	1	1 ⁵⁵	1	–	Patients from rural residence was associated with worse BCSS than urban residence
Comorbidities						
History of hypertension (yes vs no)	OS	2	2 ^{43,48}	2	–	History of hypertension was associated with worse OS
	OS	1	1 ³⁷	1	–	Presence of jaundice was associated with worse OS
Liver function impairment (yes vs no)	OS	1	1 ³⁷	1	–	Impaired liver function was associated with worse OS
	OS	4	4 ^{33,36,48,85}	4	–	Higher Charlson/Deyo scores compared to lower scores were associated with worse OS

Anorexia/weight loss/cachexia (yes vs no)	OS	1		³⁷				—	Presence of anorexia/weight loss/cachexia was associated with worse OS
Risk factors (≥2 vs 0/1)	OS	1		⁷¹				—	Presence of multiple risk factors was associated with worse OS than having a single, or no risk factor
Chronic Pulmonary disease (yes vs no)	OS	2		⁴⁸				—	Presence of chronic pulmonary disease was associated with worse OS compared to absence of the condition
Miscellaneous									
CNS-M (Isolated CNS progression vs CNS-M plus systemic progression)	OS	1		⁶¹				—	Having isolated CNS compared with CNS-M plus systemic progression was associated with reduced risk of OS
Density (high vs low)	PFS	1		⁸⁴				—	High density compared to low was associated with worse PFS
Detection of PD-L1 (+)-CTCs (yes vs no)	PFS	1		⁴⁷				—	Detection of PD-L1 (+)-CTCs was associated with worse PFS
Follow-up interval after diagnosis (2–5 years vs 1 year)	OS	1		⁸⁸				—	Longer follow-up interval after diagnosis compared to shorter was associated with worse OS
Laterality (unknown vs right)	OS	1		²⁸		—			Unknown laterality was associated with better OS than right laterality
Lymph node ratio (>0.75 vs 0.75)	OS	1		⁹⁸				—	Higher lymph node ratio was associated with worse OS
Neutrophil-lymphocyte ratio (NLR)	OS	1		⁶²				—	A higher NLR at diagnosis was associated with worse OS than lower NLR
Prescribing physician (BC specialist vs others)	OS	1		³⁷		—			Evaluation of a BC specialist compared with others was associated with lower risk of death within 30 days
Response status based on PET (responder vs non-responder)	OS	1		⁸²		—			Responders were associated with better OS than non-responders based on PET imaging
SEER region (Detroit, Kentucky vs California)	OS	1		⁸⁵				—	Patients from SEER regions including Detroit and Kentucky were associated with worse OS as compared to patients from California

Abbreviations: ALDH1, aldehyde dehydrogenase 1; ALP, alkaline phosphatase; BC, breast cancer; BCE, bone collagen equivalents per liter; BMI, body mass index; CA 15–3, cancer antigen 15–3; CEA, carcinoembryonic antigen; CRP, C-reactive protein; ESR 1, estrogen receptor 1; EZH2, enhancer of zeste homolog 2; GJT 1, G-protein-coupled receptor kinase interacting protein 1; IHC, immunohistochemistry; IL-18, interleukin-18; LBD, ligand-binding domain; LDH, lactate dehydrogenase; MAPT RQ, microtubule-associated protein tau; NDL, numeration and diversity of lymphocytes or lympho-dipenic status; NLR, neutrophil-lymphocyte ratio; PET, positron emission tomography; PNN, poly nuclear neutrophils; SET_(TP53), cumulative measure of gene expression for transcripts associated with estrogen and progesterone receptors; SNP, single nucleotide polymorphism; SUVmax, maximum standard unit value; VEGF, vascular endothelial growth factor.

quality-of-life and prolonging survival. Many factors are generally considered in developing treatment plans including patient-related factors like patient preferences, age, menopausal status, co-morbidities, performance status, socioeconomic status, psychological factors, treatment availabilities, and disease-related factors like DFI, previous therapies, tumor burden (number and sites), and any need for rapid disease control.¹⁰⁸

This comprehensive review substantiates the importance of these factors in clinical decision-making for HR+/HER2- advanced breast cancer. The directionality of relationship between the prognostic factors and OS and PFS was largely consistent, except for lymph node involvement with OS and *de novo* metastatic breast cancer with PFS. Another published study¹⁰⁹ also reported the divergent association between lymph node involvement and OS. A retrospective cohort study¹⁰⁹ reported patients with N1 Stage IV BC had better OS than did those without lymph node metastasis (HR=0.902, 95% CI=0.825–0.986, *p*-value=0.023). One potential explanation could be that the invasion of tumor cell into lymph nodes may have activated an antitumor immune response, which renders beneficial effect on patients with lymph node metastasis.¹¹⁰ Other studies^{106,111,112} have observed better OS in patients without lymph node metastasis compared to those with lymph node involvement. Similarly, the prognosis of *de novo* stage IV breast cancer was found to be better than those with recurrent tumors in several studies.^{4,113,114}

Definitions of survival endpoints used across studies varied. The most common definition of OS was the time from diagnosis to death from any cause or last follow-up; many studies calculated the time interval from date of treatment initiation or patient selection. There was overlap in definitions of OS and BCSS. Gong et al⁵⁵ defined BCSS as time from date of diagnosis to date of death attributed to breast cancer or date of last follow-up, while Yerushalmi et al⁹³ defined BCSS as time from diagnosis of distant metastasis to death or censor date; two other studies did not define BCSS.^{22,90} It was observed that BCSS was not commonly assessed across included studies.

We observed heterogeneity in the comparison groups for certain prognostic factors – for example, different age groups being compared (eg, >50 vs ≤50, >65, 50–64 vs 18–49); different cut-off points for Ki67 levels (10%, 14%, 25%, 30%); different prior therapies were compared (initial chemotherapy vs initial endocrine therapy, adjuvant endocrine therapy vs absence of prior therapy); site of metastasis (eg, presence vs absence of liver metastasis,

visceral sites vs bone). Due to the differences in categorizations of prognostic factors as well as other factors – such as differences in study design and patient population – it was not possible to perform meta-analysis or derive a single hazard ratio estimate representing the relationship between the prognostic factors and survival endpoints. Despite inconsistencies in comparators groups, we observed an overall trend in directionality of association for some prognostic factors. For example, tumor size >5 cm diameter, CTC count ≥5/7.5 mL whole blood, time to recurrence or progression to advanced breast cancer of <2 years, and multiple vs single site of metastases were associated with worse survival.

This review focused on patients with HR+/HER2- advanced breast cancer; however, in 62% of 79 included studies, the proportion of patients with HR+/HER2- breast cancer ranged between 50–79%. The results of such studies may not be reflective entirely of patients with HR+/HER2- advanced breast cancer. We observed a dearth of studies investigating the prognostic factors in exclusively patients with HR+/HER2- advanced breast cancer. For studies that included *de novo* metastatic patients, including in subgroups, baseline characteristics were captured in the metastatic setting. However, for the remaining studies, it was difficult to distinguish whether baseline characteristics were collected at initial diagnosis or when patients progressed to metastatic stage (as this information was not reported).

This review was subject to some limitations. An overall rating for risk of bias (low/moderate/high) was estimated for each study by taking into account the risk levels for the six domains of the QUIPS tool. The cut-off points chosen to derive the overall rating, though based on previously published SLRs, were essentially arbitrary.^{115–117} Other limitations may be the exclusion of non-English studies, though English language studies from across the globe were included, and that studies published before 2010 and after 2018 were not included. Since the studies included in this SLR were published between 2010–2018, there were no studies that assessed the association between the newer targeted therapies such as CDK4/6 inhibitors, mTOR inhibitor, PI3K inhibitor, or kinase inhibitors, and survival endpoints. The conference abstracts included in this SLR contained limited relevant data and full-text publications related to these abstracts were not available. We found limited evidence on the prognostic value of genetic or tumor biomarkers in patients specifically with HR+/HER2- advanced BC. Some of these studies showed the relationship between tumor markers such as LDH,^{51,59,79} ALP,⁷⁹ CEA,^{51,70} CA,^{51,70} to be associated with survival. This review did not

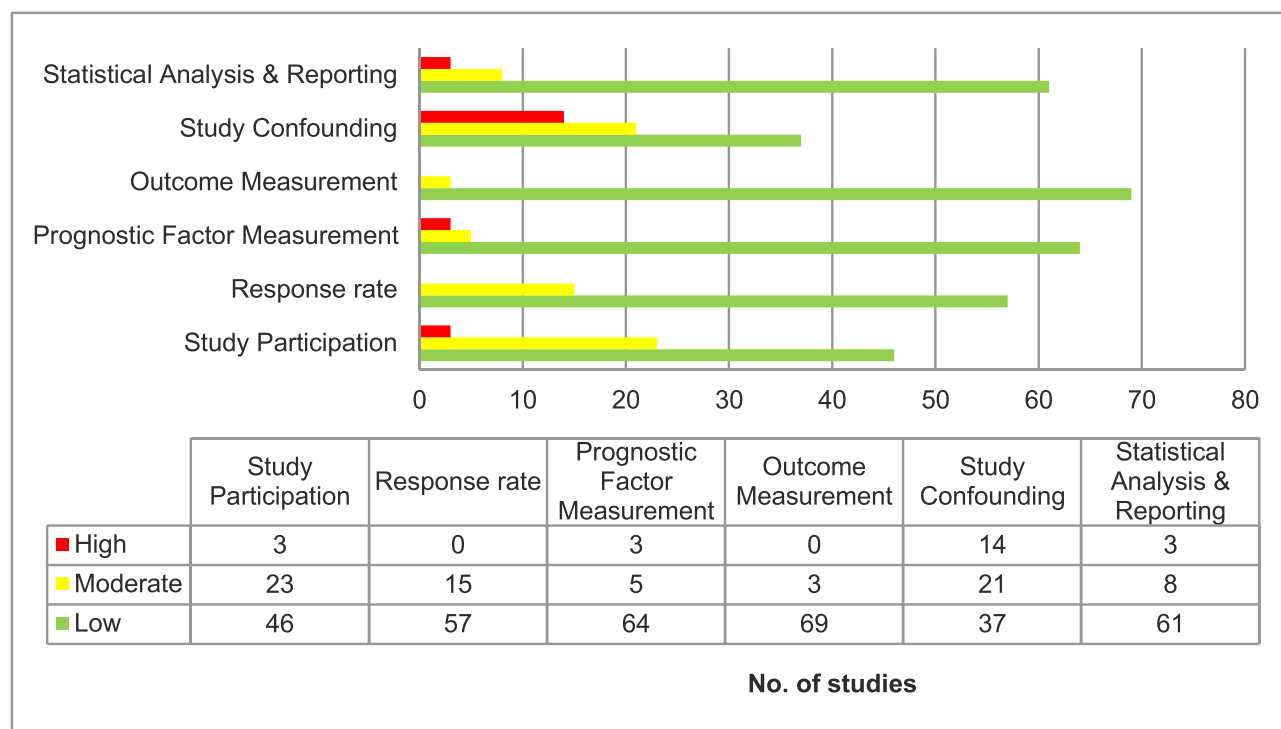


Figure 3 Risk of bias assessment for each domain of QUIPS tool.

distinguish the nature of the outcomes assessed (ie, primary or secondary) and therefore findings must be interpreted cautiously. Additionally, there was uncertainty around the power of subgroup analyses data reported in both observational studies and trials.

Strengths of this review include that this is the first SLR, to our knowledge, to comprehensively assess prognostic factors associated with survival in patients with HR+/HER2– advanced breast cancer. This review presents a complete overview of a large number of studies published recently with multivariate robust results that would help account for confounding of other key variables in understanding the association. This review was performed based on best practice guidelines, included supplementary searches of key conference proceedings and cross-referencing of other SLRs, and incorporated a double-blind study selection process, all of which lend to the robustness of this review’s methodology.

Conclusion

The strongest evidence for prognostic factors associated with worse OS included negative PR status, higher tumor grade, higher CTC count (≥ 5 vs < 5), higher Ki67 levels ($> 14\%$), number of metastatic sites (multiple vs single), specific sites of metastases (presence of liver metastases vs absence), shorter time to recurrence or progression to

advanced breast cancer, absence of prior therapy-related attributes (type of therapy, treatment line, response of prior therapy) in early or metastatic setting, poor performance status, and race (black vs white). The strongest evidence for prognostic factors associated with worse PFS included higher CTC count, number and sites of metastases, and prior therapy-related attributes in early or metastatic settings.

Apart from the commonly used markers recommended for routine use (eg, ER, PR, HER2), evaluation of the aforementioned factors shed light on the history and pathophysiology of the breast cancer in a patient, thereby providing a comprehensive clinical picture that may enable clinicians to enhance personalized treatment approaches and supportive care to improve patient outcomes. Identification of these prognostic factors will also guide future research in the HR+/HER2– advanced breast cancer setting.

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