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 ≥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. The survival rate depends on stage of breast cancer at diagnosis, among other factors. 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%. 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. HR+/HER2– status is the most common molecular subtype, accounting for two-thirds of US female breast cancer cases.

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. 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. 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).

Although several studies have identified prognostic factors associated with survival, especially in the early breast cancer setting, 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 prespecified 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). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and Cochrane guidebook. 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, 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≥3), moderate (HR=1.5–2.9), or weak (HR<1.5).

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. 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). The studies included identified 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. 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 62% (n=8), 50% (n=1), and 100% (n=1) of studies, respectively. 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, one utilized the modified Bloom–Richardson grading, and the other study employed the Elston-Ellis modification of Scarff-Bloom-Richardson grading system.

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. Survival was worse in patients with poorly to moderately differentiated tumors compared with well-differentiated tumors. Consistency in evidence and directionality of
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. 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, while one study showed improved OS in patients with T2 tumors (>2 cm and <5 cm) compared with T1 tumors (≤2 cm). 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.
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)                  | 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)                   | 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)    | Overall study population           | 265             | Median (range): 59 (19–95) | 76       | NR       | NR       | 73       | 50–79                            | mBC                                                                              |
| Beije et al (2016)                    | 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)                  | 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)                  | Overall study population           | 31              | Median (range): 64 (37–83) | 100      | 93.7     | 81.2     | 100      | ≥80                              | mBC                                                                              |
| Bonotto et al (2017)                  | 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)                   | 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 (AHSCT) |
| Chandarlapaty et al. (2016)           | Overall study population           | 335             | Age at diagnosis of metastasis, Median (range): 61 (30–91) | 100      | 92.8     | 78.8     | 100      | ≥80                              | advanced BC                                                                      |

(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) | 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) | 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 |
| Delpech et al (2012) | Overall study population | 241 | Median (range): 55 (29–93) | NR | 100 | 75 | 71 | 50–79 | mBC |
| Demian et al (2011) | Metastatic subgroup=20 | 20 | NR | NR | 80 | 80 | 65 | 50–79 | mBC |
| den Brok et al (2017) | 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) | 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) | 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) | Overall study population | 60 | NR | NR | 63.3 | NR | NR | 63.3 | 50–79 | mBC |
| Ercolani et al (2018) | Overall study population | 51 | Mean (SD, range): 56 (11.4, 37–76) | NR | 69 | 47 | 61 | 50–79 | mBC |
| Fountzilas et al (2013) | 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 |
| Study Authors (Year) | Overall Study Population | Median (Range) | Optimization Set | Learning Set | Age Before Starting Capecitabine | Age at mBC Diagnosis | BC Patients with Leptomeningeal Metastasis |
|----------------------|--------------------------|----------------|------------------|--------------|---------------------------------|----------------------|------------------------------------------|
| Gampenrieder et al (2018) | 116 | Median (range): 60 (29–86), Learning set: 61 (34–81) | 69 | NR | NR | 100 | 50–79 | mBC |
| Gamucci et al (2017) | 314 | Median (range): 55 (27–82) | 80.9 | NR | NR | 100 | ≥80 | mBC |
| Gerratana et al (2015) | 544 | Median (range): 63 (53–73) | NR | 79.4 | 63.7 | 78.9 | 50–79 | mBC |
| Gilbert et al (2011) | 75 | Age before starting capecitabine, Median (range): 53 (36–78) | 79 | NR | NR | 100 | 50–79 | mBC |
| Giordano et al (2011) | 517 | Median (range): 49.3 (23.3–82) | NR | 64.2 | 43.9 | 80.5 | 50–79 | mBC |
| Goetz et al (2017) (CA) | 669 | MONARCH 2, overall study population | Mean (SD): 59.9 (11.4) | 100 | NR | NR | 100 | ≥80 | mBC |
| Goetz et al (2017) (CA) | 493 | MONARCH 3, overall study population | Mean (SD): 63.1 (9.92) | 100 | NR | NR | 100 | ≥80 | mBC |
| Gong et al (2018) | 7,482 | NR | 74.4 | NR | NR | 67.7 | 50–79 | mBC |
| Grigolo et al (2017) (CA) | 104 | Median (range): 56 (26–75) | 67.3 | NR | NR | 69.2 | 50–79 | BC patients with leptomeningeal metastasis |
| Guo et al (2017) | 176 | Median (range): 49.5 (28–80) | NR | 56.3 | 47.7 | 63.6 | 50–79 | mBC |
| Inari et al (2017) | 96 | Mean (SD): 51 (7.5) | 60.4 | 42.7 | 40.6 | 85.4 | 50–79 | mBC (metastatic lesions) |
| Jacot et al (2018) (CA) | 72 | Median (range): 65 (35–87) | NR | 69.4 | NR | 81.9 | 50–79 | mBC |
| Jansson et al (2016) | 52 | Age at mBC diagnosis, Median (range): 60 (40–83) | 75 | 88.4 | 88.4 | 82.7 | 50–79 | mBC |
| Jung et al (2011) | 553 | Median (range): 55 (26–88) | 73.1 | NR | NR | 65.5 | 50–79 | mBC |
| 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) [8] | Overall study population | 557 | Median (range): 55 (26–88) | 73.2 | NR | NR | 65.5 | 50–79 | mBC |
| Kawano et al (2013) [2] | Overall study population | 69 | Median (range): 53 (27–86) | 100 | 92 | 81 | 87 | ≥80 | Stage IV, mBC |
| King et al (2016) [65] | 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) [9] | Overall study population | 70 | Median (range): 60 (32–81) | 60 | NR | NR | 81.8 | 50–79 | mBC |
| Korantzis et al (2012) [64] | 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 | 7,199 | Median: 58 (IQR 49–67) | NR | 73.4 | 60.6 | 74 | 50–79 | Stage IV BC |
| Study Reference                  | Overall study population | Median (range) | 50–79 | 54 | 65 | 69 | Population Type                        |
|--------------------------------|--------------------------|----------------|-------|----|----|----|----------------------------------------|
| Llombart-Cussac et al. (2014)   | 2,203                    | 53 (22–93)     |       | 100|     |    | Advanced locally recurrent or mBC      |
| Lobbezoo et al. (2013)          | 798                      | 59 (25–93)     |       |    |    | 81.4| mBC                                    |
| Lobbezoo et al. (2015)          | 815                      | 61 (25–89); Recurrent: 64 (25–93) | 75 | NR | NR | 78 | mBC                                    |
| Lobbezoo et al. (2016)          | 482                      | 52 (25–80), Initial ET: 61 (30–91) | 100 | NR | NR | 100| ≥80| mBC                                    |
| Manuel et al. (2012)            | 133                      | 59.9 (36.5–84.1), Cohort B: 56.9 (34.7–79.9) | NR | 72.1 | 58.6 | 73.7 | mBC                                    |
| Miyoshi, 2016                  | 318                      | NR             | 100   | 100| 100| 100| ≥80 Early and late recurrent BC        |
| Motomura et al. (2010)          | 41                       | 57 (42–79)     | 100   | 97.6| 97.5| 92.7| ≥80 mBC                                |
| Muller et al. (2012)            | 245                      | 57             | NR    | 69.4| 59.2| 56.7| 50–79 mBC                              |
| Munzone et al. (2012)           | 203                      | 57 (31–78)     | 79.3  | NR | NR | 73.8 | mBC                                    |
| Nieder et al. (2017)            | 118                      | 61 (33–87)     | NR    | 77 | NR | 82 | 50–79 mBC                              |
| Ogiya et al. (2017)             | 339                      | NR             | NR    | 100| 100| 100| ≥80 BC patients with the early and late distant recurrence |
| Okazaki et al. (2018)           | 18                       | 51 (34–81)     | 100   | NR | 83 | 100| ≥80 Locally advanced or mBC            |
| Paoletti et al. (2017) (CA)     | 121                      | NR             | NR    | 100| 100| 100| ≥80 mBC                                |

(Continued)
| Study [Ref] | Sample Size (N) | Population in Prognostic Analysis | Description of BC | Age (in Years) | ER + (%) | PR + (%) | HER2– (%) | Category by HR +/HER2– Status (%) |
|------------|-----------------|----------------------------------|-----------------|---------------|----------|----------|-----------|----------------------------------|
| Papadaki et al (2018) | 130 | Overall sample = 130 | Analysis conducted in HER2− subgroup | Median (range): 59 (23–82) | NR | 68.5 | 63.8 | 78.5 | 50–79 mBC |
| Park et al (2017) | 100 | Overall study population | Median (range): 48.1 (48–75) | 65 NR | 65 NR | 100 | NR | 75 | 50–79 mBC |
| Pascual et al (2017) | 154 | Overall study population | Median (range): 62 (32.9–90.8) | 55.2 NR | 50 NR | 83 | NR | 69.9 | 100 |
| Peeters et al (2014) | 627 | Overall study population | Median: 57 | NR | 100 | NR | 83 | 100 | 50–79 mBC |
| Pierga et al (2012) | 267 | Overall study population | Median (range), Age group <45 years: 40 (23–44) | 62 NR | 50 NR | 45 | NR | 100 | 50–79 mBC |
| Peisters et al (2018) | 333 | Overall study population | Median (range): 50 (29–81) | 58 NR | 50 NR | 45 | NR | 100 | 50–79 advanced BC |
| Schiavon et al (2015) | 128 | Overall study population | Median (range): 59 (24–90) | 100 | NR | 84 | 100 | 82.5 | 50–79 mBC and recurrent BC (Luminal A, Luminal B (HER2−), Unknown) |
| Staudigl et al (2015) | 66 | Overall study population | Median, ESR1 wild type: 50 (29–81), ESR1 mutant: 64 | 76.3 NR | 75.6 NR | 50–79 | NR | 72.2 | Stage IIIC with >10 positive axillary |
| Suh et al (2016) | 302 | Overall study population | Median (range): 50 (21–83) | 76.3 NR | 75.6 NR | 50–79 | NR | 72.2 | 60.6 | 50–79 mBC |
| Turker et al (2014) | 98 | Overall study population | Median (range): 50 (21–83) | 76.3 NR | 75.6 NR | 50–79 | NR | 72.2 | 60.6 | 50–79 mBC |

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| Reference                  | Population Details | Median (range) | Age |50–79 |80–89 |90+ |
|----------------------------|--------------------|----------------|-----|------|------|-----|
| Uyeturk et al (2014)       | Overall study      | 466            | 73.2| 68.5 | 60.5 | 65.5|
|                           | population        |                | 50 (18–90) |      |      |      |
| Vaz-Luis et al (2015)      | HR+ HER2− subgroup | 3,151          | 100 | NR   | NR   | 100 |
|                           |                   |                | ≥80 |      |      |      |
| Wallwiener et al (2013)    | Overall study      | 486            | NR  | 67.3 | 58.7 | 69.8|
|                           | population        |                | 55 (23–91) |      |      |      |
| Wu et al (2017)            | Overall study      | 9,256          | 76.6| NR   | NR   | 74.2|
|                           | population        |                | 50–79|      |      |      |
| Xie et al (2015)           | Overall study      | 699            | 100 | NR   | NR   | 100 |
|                           | population        |                | ≥80 |      |      |      |
| Xiong et al (2018)         | Overall study      | 8,901          | 70.5| NR   | 65.6 | 50–79|
|                           | population        |                | BC with initial bone metastasis |      |      |      |
| Yamamura et al (2018)      | Overall study      | 172            | 100 | NR   | NR   | 100 |
|                           | population        |                | ≥80 |      |      |      |
| Yerushalmi et al (2012)    | Subgroup Luminal A | 566            | 100 | NR   | NR   | 100 |
|                           | and Luminal B      |                | ≥80 |      |      |      |
| Zhang et al (2013)         | Overall study      | 134            | 100 | NR   | NR   | 56  |
|                           | population        |                | 50–79|      |      |      |
| Zhao et al (2011)          | Overall study      | 60             | NR  | 66.6 | 76.6 | 50–79|
|                           | population        |                | Median (range), Metonomic Arm: 46 (35–73); Conventional Arm: 51 (33–73) |      |      |      |

**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 (NO); 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. The two studies focusing on BCSS and the one study focusing on PFS also reported higher lymph node involvement was associated with greater risk of death. 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, 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. The presence of a higher CTC count (≥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. 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 ≤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. Four studies demonstrated longer OS in patients with mBC at diagnosis compared with recurrent breast cancer, while one study reported shorter OS in patients with de novo mBC. Similarly, one study showed longer PFS associated with patients with de novo mBC, while another study showed a reverse relationship.

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 from 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. 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 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. 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=26,30,32,33,36,60,63,76,78), followed by brain/CNS (n=14,30,36,44,48,52,54,59,63,69,71,75,78–80,89). 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. Ten of 13 studies reported a significant association with PFS.

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.

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, it was defined as the date from surgery to first recurrence. Eight studies did not report the definition.46–49,52–54,66,71

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.46–49,52–54,66,67,71 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.
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 2017 38 reported improved OS, while Xie et al 33 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. 73 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, ligand binding domain (LBD) status, CA 15–3 level, alkaline phosphatase level, serum C-reactive protein level (CRP), lactate dehydrogenase (LDH) level, income level, menopausal status, and education status. 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 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 | OS No. of Studies Reporting Significant Association | OS No. of Studies with Univariate Analysis | OS No. of Studies with Significant Univariate Analysis | OS No. of Studies with Multivariate Analysis | OS No. of Studies with Significant Multivariate Analysis | Consistency Based on >50% Studies with Significant Association | Consistency of Relationship | Directionality of Relationship | Strength of Association Based on Effect Size | Studies with Low Sample Size (<100) |
|-------------------------|----------------|---------------------------------------------------|-------------------------------------------|------------------------------------------------------|---------------------------------------------|-------------------------------------------------|---------------------------------------------------------------|-----------------------------|-----------------------------------|-----------------------------------------|----------------------------------|
| PR status               | OS             | 10                                                | 8                                         | 10                                                   | 7                                           | 5                                               | Consistent                                                    | Consistent                   | Consistent                        | Moderate                               | 4                                |
|                         | PFS            | 2                                                 | 1                                         | 1                                                    | 0                                           | 0                                               | Inconsistent                                                  | NA (single study)            | NA                                | 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                                |
| Lymph node              | OS             | 11                                                | 4                                         | 10                                                   | 4                                           | 5                                               | 1                                                            | Inconsistent                 | Inconsistent                      | Moderate                               | 5                                |
|                         | PFS            | 1                                                 | 1                                         | 1                                                    | 1                                           | 0                                               | 0                                                            | NA (single study)            | NA                                | NA                                      | 1                                |
| Histological type       | OS             | 5                                                 | 1                                         | 4                                                    | 0                                           | 1                                               | 1                                                            | Inconsistent                 | NA                                | Strong                                 | 3                                |
|                         | PFS            | 2                                                 | 1                                         | 1                                                    | 0                                           | 2                                               | 1                                                            | Inconsistent                 | NA (single study)            | Strong                                 | 2                                |
| CTC count               | OS             | 10                                                | 9                                         | 9                                                    | 8                                           | 7                                               | 7                                                            | Consistent                   | Consistent                        | Strong                                 | 3                                |
|                         | PFS            | 10                                                | 8                                         | 8                                                    | 5                                           | 6                                               | 6                                                            | Consistent                   | Consistent                        | Moderate                               | 3                                |
| Ki67                    | OS             | 7                                                 | 6                                         | 6                                                    | 5                                           | 4                                               | 3                                                            | Consistent                   | Consistent                        | Moderate                               | 2                                |
|                         | PFS            | 4                                                 | 4                                         | 3                                                    | 3                                           | 3                                               | 3                                                            | Consistent                   | Consistent                        | Moderate                               | 2                                |
| De novo metastatic BC   | OS             | 5                                                 | 5                                         | 4                                                    | 4                                           | 5                                               | 2                                                            | Consistent                   | Consistent                        | Weak                                   | 0                                |
|                         | PFS            | 3                                                 | 2                                         | 2                                                    | 1                                           | 2                                               | 1                                                            | Consistent                   | Inconsistent                      | Moderate                               | 1                                |
| No. of Metastatic sites | OS             | 27                                                | 24                                        | 21                                                   | 19                                          | 20                                              | 14                                                            | Consistent                   | Consistent                        | Moderate                               | 3                                |
|                         | PFS            | 11                                                | 6                                         | 7                                                    | 4                                           | 9                                               | 5                                                            | Consistent                   | Consistent                        | Moderate                               | 2                                |
| Site of metastasis          | OS  | 22 | 21 | 14 | 25 | 19 | Consistent | Consistent | Moderate | 7 |
|----------------------------|-----|----|----|----|----|----|------------|------------|----------|-----|
| PFS                        | 13  | 10 | 7  | 6  | 10 | 6  | Consistent | Consistent | Moderate | 4 |
| Time to recurrence or      | OS  | 18 | 14 | 12 | 10 | 12 | 9          | Consistent | Moderate | 4 |
| progression to ABC         | PFS | 5  | 4  | 3  | 3  | 4  | 3          | Consistent | Moderate | 3 |
| Prior therapy              | OS  | 35 | 27 | 24 | 18 | 25 | 22         | Consistent | Moderate | 6 |
| PFS                        | 15  | 13 | 10 | 8  | 12 | 10 | Consistent | Consistent | Moderate | 6 |
| Performance                | OS  | 14 | 11 | 7  | 6  | 11 | 8          | Consistent | Moderate | 2 |
| PFS                        | 8   | 4  | 3  | 1  | 6  | 4  | Inconsistent| Consistent | Moderate | 1 |
| Age                        | OS  | 37 | 17 | 25 | 10 | 24 | 13         | Inconsistent| Weak–   | Moderate | 5 |
|                            | PFS | 7  | 2  | 5  | 0  | 3  | 2          | Inconsistent| 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.
count, Ki67 level, number and sites of metastasis – and treatment-related factors and performance status. Other studies in the literature 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                                             | 1                                     | –                                        | ALDH1 1% was associated with worse OS than ALDH1 >1%                           |
| ALP (high vs normal)                                   | OS              | 2                                       | 1                                             | 1                                     | –                                        | High ALP was associated with worse OS than normal ALP                           |
| ALP > upper limit of normal                            | PFS             | 1                                       | 1                                             | 1                                     | –                                        | High ALP was associated with worse PFS than normal ALP                           |
| Baseline SUVmax (intermediate and highest tertile vs lowest tertile) | OS  | 1                                       | 1                                             | –                                     | –                                        | Baseline SUVmax intermediate and highest tertiles were associated with worse OS than the lowest tertile |
| CA 15–3 (high vs normal)                               | OS              | 2                                       | 1                                             | 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                                             | 1                                     | –                                        | CA 15–3 > upper limit of normal was associated with worse PFS                  |
| CEA > upper limit of normal                            | PFS             | 1                                       | 1                                             | 1                                     | –                                        | CEA > upper limit of normal was associated with worse PFS                     |
| Serum CRP levels (high, >60 vs normal)                 | OS              | 1                                       | 1                                             | 1                                     | –                                        | Higher serum CRP levels compared to normal was associated with worse OS        |
| ESR1 mutations (mutated vs wild type)                  | OS              | 1                                       | 1                                             | 1                                     | –                                        | Mutated ESR1 (D538G, Y537S) was associated with worse OS than wild type        |
| CEA > upper limit of normal                            | PFS             | 1                                       | 1                                             | 1                                     | –                                        | Mutated ESR1 (D538G) was associated with worse PFS than wild type              |
| Gamma- glutamyltransferase (GGT) (high vs low risk groups) | OS  | 1                                       | 1                                             | 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                                             | 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                                             | 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                                             | 1                                     | –                                        | High blood HER2 mRNA levels were found to be associated with significantly improved OS compared to low levels |

(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                                             | 1                                     | Presence of Tau protein expression was associated with better PFS                |
| IHC, Topo IIa (+ vs –)            | PFS             | 1                                       | 1                                             | 1                                     | Topo IIa protein positivity was associated with unfavorable PFS                  |
| IL-18 levels (high, ≥8 ng/mL vs low) | OS              | 1                                       | 1                                             | 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                                             | 1                                     | Higher IL-8 levels compared to lower levels was associated with worse OS         |
| LBD mutations (yes vs no)         | OS              | 1                                       | 1                                             | 1                                     | Presence of LBD mutations were associated with worse OS                          |
|                                   | PFS             | 1                                       | 1                                             | 1                                     | Presence of LBD mutations were associated with worse PFS                          |
| LDH levels (high, ≥600 vs low <600 UI/mL) | OS              | 3                                       | 3                                             | 3                                     | Higher LDH levels was associated with worse OS than lower LDH levels             |
| LDH levels (high vs low)          | PFS             | 1                                       | 1                                             | 1                                     | LDH levels > upper limit of normal was associated with worse PFS                |
| Lymphocytes (<1 vs ≥1 Giga/L)     | OS              | 1                                       | 1                                             | 1                                     | Lower lymphocyte count was associated with worse OS                              |
| Mapt RQ values, 50% cut-off (high vs low) | OS              | 1                                       | 1                                             | 1                                     | High Mapt RQ values was associated with better OS                                |
| Metastatic EZH2 expression (high vs low) | OS              | 1                                       | 1                                             | 1                                     | High metastatic EZH2 expression was associated with worse OS than low EZH2 expression |
| NDL (>1 vs ≤1 Giga/L)             | OS              | 1                                       | 1                                             | 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                                             | 1                                     | Baseline serum NTx of less than 18 nM was associated with significantly better PFS than baseline serum NTx of greater than 18 nM |
| PNN (<7.5 vs ≥7.5 Giga/L)         | OS              | 1                                       | 1                                             | 1                                     | PNN <7.5 Giga/L was associated with better OS than PNN ≥7.5 Giga/L              |
| 21-gene recurrence score (low vs high risk group) | OS              | 1                                       | 1                                             | 1                                     | Low risk group (<18 score) was associated with better OS than high risk group (≥31 score) |
| **Serum albumin (low vs normal)** | OS | 1 | 1.79 | I | – | Low serum albumin compared to normal levels was associated with worse OS |
| **Serum VEGF after 3 months (normal vs abnormal)** | PFS | 1 | 1.70 | – | 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 | 1 | 1.97 | – | I | Higher SET(ER/PR) Index was associated with better OS |
| **SET(ER/PR) Index (high vs low)** | PFS | 1 | 1.97 | – | I | Higher SET(ER/PR) Index was associated with better PFS |
| **SNP, ABCB1 1236C/T rs1128503 (C vs T or T/C)** | PFS | 1 | 1.56 | I | – | SNP, ABCB1 1236C/T rs1128503 (C) was associated with worse PFS than ABCB1 1236C/T rs1128503 (T or T/C) |
| **SNP, ABCB1 2677G/A/T rs2032582 (G or G/A vs T or T/G)** | OS | 1 | 1.56 | I | – | SNP, ABCB1 2677G/A/T rs2032582 (G or G/A) was associated with worse OS than ABCB1 2677G/A/T rs2032582 (T or T/G) |
| **SNP, ABCB1 3435C/T rs1045642 (C vs T or T/C)** | OS | 1 | 1.56 | I | – | SNP, ABCB1 3435C/T rs1045642 (C) was associated with worse OS than SNP, ABCB1 3435C/T rs1045642 (T or T/C) |
| **Surgical margin (negative, R0 vs positive, R1)** | OS | 1 | 1.92 | – | I | Negative surgical margin was associated with better OS than positive surgical margin |
| **T-cell receptor diversity (≤33 vs >33%)** | OS | 1 | 1.59 | 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 | 1 | 1.48 | – | I | Low BMI was associated with better OS than higher BMI |
| **Surgical margin (negative, R0 vs positive, R1)** | OS | 1 | 1.92 | – | I | Negative surgical margin was associated with better OS than positive surgical margin |
| **T-cell receptor diversity (≤33 vs >33%)** | OS | 1 | 1.59 | 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 | 1 | 1.48 | – | I | Low BMI was associated with better OS than higher BMI |
| **Education level (high vs low)** | OS | 2 | 2.40.55 | I | I | Mixed result (worse and better OS) |
| **BCSS** | 1 | 1.55 | 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                                             |                                     | 1                                      | Higher median household income was associated with better OS |
|                                                       | BCSS            | 1                                       | 1                                             |                                     | 1                                      | Higher median household income was associated with better BCSS |
| Insurance status (uninsured vs insured)               | OS              | 1                                       | 1                                             |                                     | 1                                      | Patients who were uninsured had worse OS than those who were insured |
|                                                       | BCSS            | 1                                       | 1                                             |                                     | 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                                       | 5, 55, 90                                     |                                     | 2                                      | Unmarried status was associated with worse BCSS than married |
| Menopausal status (yes vs no; post vs pre)            | OS              | 4                                       | 2, 5, 98                                      |                                     | 2                                      | Presence of menopause was associated with worse OS than absence of menopause; Similarly, postmenopausal status was associated with worse OS compared to premenopausal status |
|                                                       | PFS             | 3                                       | 1                                             |                                     | 1                                      | Postmenopausal status was associated with worse PFS compared to premenopausal status |
| Received blood transfusion before RT (yes vs no)      | OS              | 1                                       | 1                                             |                                     | 1                                      | Receiving blood transfusion before RT was associated with better OS as compared to not receiving |
| Residence type (rural vs urban)                       | OS              | 1                                       | 1                                             |                                     | 1                                      | Patients from rural residence was associated with worse OS than urban residence |
|                                                       | BCSS            | 1                                       | 1                                             |                                     | 1                                      | Patients from rural residence was associated with worse BCSS than urban residence |

Comorbidities

| 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 |
|-------------------------------------------------------|-----------------|-----------------------------------------|-----------------------------------------------|-------------------------------------|----------------------------------------|--------------------------------------|
| History of hypertension (yes vs no)                   | OS              | 2                                       | 2                                             |                                     | 2                                      | History of hypertension was associated with worse OS |
| Jaundice (yes vs no)                                  | OS              | 1                                       | 1                                             |                                     | 1                                      | Presence of jaundice was associated with worse OS |
| Liver function impairment (yes vs no)                 | OS              | 1                                       | 1                                             |                                     | 1                                      | Impaired liver function was associated with worse OS |
| Charlson/Deyo score (1 vs 0, ≥2 vs 0)                 | OS              | 4                                       | 4                                             |                                     | 4                                      | Higher Charlson/Deyo scores compared to lower scores were associated with worse OS |
### Presence of anorexia/weight loss/cachexia was associated with worse OS

### Presence of multiple risk factors was associated with worse OS than having a single, or no risk factor

### Presence of chronic pulmonary disease was associated with worse OS compared to absence of the condition

### Having isolated CNS compared with CNS-M plus systemic progression was associated with reduced risk of OS

### Detection of PD-L1 (+)-CTCs was associated with worse PFS

### Longer follow-up interval after diagnosis compared to shorter was associated with worse OS

### Unknown laterality was associated with better OS than right laterality

### Higher lymph node ratio was associated with worse OS

### A higher NLR at diagnosis was associated with worse OS than lower NLR

### Evaluation of a BC specialist compared with others was associated with lower risk of death within 30 days

### Responders were associated with better OS than non-responders based on PET imaging

### 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
- ESR1, estrogen receptor 1
- EZH2, enhancer of zeste homolog 2
- GIT1, G-protein-coupled receptor kinase interacting protein 1
- IHC, immunohistochemistry
- IL-18, interleukin-18
- IHB, ligand-binding domain
- LDH, lactate dehydrogenase
- MAPT RQ, microtubule-associated protein tau
- NDL, numeration and diversity of lymphocytes or lympho-divapenic status
- NLR, neutrophil-lymphocyte ratio
- PET, positron emission tomography
- PNN, poly nuclear neutrophils
- SET(ER/PR), 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 studies106,111,112 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 al43 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,51,59,76 ALP,79 CEA,51,70 CA,51,70 to be associated with survival. This review did not
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.

**Acknowledgments**

We thank Michael Friedman for his editorial inputs.

**Funding**

ICON PLC. received funding from Eli Lilly and Company to conduct this review.
Disclosure
Keri Stenger, and Claudia Morato Guimarães are employees and shareholders of Eli Lilly and Company. Gebra Cuyún Carter was an employee of Eli Lilly and Company when the review was being conducted. She is a shareholder of Eli Lilly and Company. She reports personal fees from Exact Sciences. Maitreyee Mohanty, Shivaprasad Singuru, Vanita Tongbram were employees of ICON PLC. Pradeep Basa and Sheena Singh were employees of ICON PLC. When the review was being conducted. Dr. Kuemmel reports personal fees from Eli Lilly and Company, Roche, Genomic Health, Novartis, Amgen, Celgene, Daiichi Sankyo, Sonoscope, AstraZeneca, Somatex, MSD, Pfizer, Puma Biotechnology, PFM medical, non-financial support from Roche, Daiichi Sankyo outside the submitted work. Dr. Guarnieri reports personal fees from Eli Lilly and Company, Novartis, Roche, MSD, outside the submitted work. Dr. Tolanej reports grants and personal fees Eli Lilly and Company, AstraZeneca, Merck, Nektar, Novartis, Pfizer, Genentech/Roche, Immunomedics, Exelixis, Bristol-Myers Squibb, Eisai, Nanostring, Puma, Cyclacel, sanofi, Celldex, Odonate, Seattle Genetics, Silverback Therapeutics, G1 Therapeutics, AbbVie, Anthenex, OncoPep, Kyowa Kirin Pharmaceuticals, Daiichi-Sankyo, Mersana Therapeutics, Certara, CytomX, Samsung Bioepis Inc., Gilead, outside the submitted work.

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