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Review Article

Use of Comorbidity Scores to Predict Treatment Outcomes by Race/Ethnicity in Patients with Breast Cancer: A Systematic Review

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Abstract

Background: There is evidence that race/ethnicity and comorbidities are negatively associated with outcomes in female patients with Breast Cancer (BC). However, this interaction is not well understood. The objective of this review is to identify whether Comorbidity Indices (CIs) can be used to predict outcomes by race/ethnicity in patients with BC.

Methods: A systematic literature review on the use of CIs to predict outcomes by race in patients with BC was performed on English-language articles published 1987-2020 using Ovid. Two independent researchers performed two levels of article selection following PRISMA, and risk of bias (using the Newcastle-Ottawa Scale) was assessed.

Results: Ten studies were identified, all of which used the Charlson CI (CCI) or CCI derivative. All studies were conducted in North America. Most evaluated White/non-Hispanic White (n = 9) or Black/African American (AA) (n = 8) patients; fewer evaluated Asian/Pacific Islander, Hispanic, American Indian/Alaska Native, or First Nations patients. Overall, the results were mixed. Some studies that stratified outcomes by race found that only certain disease stages, outcomes, racial/ethnic subgroups, or higher CCI scores were associated with higher risk of mortality, while others did not. One study found that CCI scores were not associated with survival when added to models using race to predict outcomes, while others found a significant association.

Conclusion: There is limited research on the interaction between race, comorbidities, and outcomes in BC. The studies in this review showed mixed results for the predictive capability of the CCI in racial/ethnic minorities.

ABBREVIATIONS

AA: African American; **BC:** breast cancer; **CCI:** Charlson Comorbidity Index; **CDCI:** Charlson-Deyo Comorbidity Index; **CI:** confidence interval; **ER-:** estrogen receptor-negative; **hCCI:** hypertension-augmented Charlson Comorbidity Index; **HER2+:** human epidermal growth factor receptor-2-positive; **HER2-:** human epidermal growth factor receptor-2-negative; **HR:** hazard ratio; **HR+:** hormone receptor-positive; **HR-:** hormone receptor-negative; **NH:** non-Hispanic; **ns:** not significant; **PR-:** progesterone receptor-negative; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; **SEER:** Surveillance, Epidemiology, and End Results; **SES:** socioeconomic status.

INTRODUCTION

The presence of comorbidities in female patients with Breast Cancer (BC) may negatively affect physician-mediated treatment decisions, thus impacting treatment outcomes [1]. For example, female patients with severe comorbidity are less likely to receive breast-conserving surgery with/without radiotherapy, and are less likely to receive chemotherapy compared with patients without comorbidity [1]. In patients with human epidermal growth factor receptor-2-positive (HER2+) BC specifically,

there is evidence that comorbidities are associated with HER2-targeted treatment completion and treatment decisions [2]. However, the basis for this apparent suboptimal treatment of BC, including HER2+ BC, in patients with comorbidities is unclear. In a literature review that aimed to understand the mechanisms by which comorbidities contribute to poorer observed cancer survival, Søgaard et al. [3] found that several factors may be at play, including physician and patient preferences for treatments, increased risk of toxicity with standard treatments due to comorbid illnesses, lower quality of clinical care, adherence, and the effect of comorbidities themselves [3]. However, there is still a lack of clarity surrounding which of these factors are the most important. Of the factors identified by Søgaard et al. [3] that may impact treatment outcomes, our review focuses on the comorbidities themselves.

Measuring comorbidities in patients with BC using a validated comorbidity index is a method that has been extensively utilized in past research and has the potential to predict treatment outcomes and help inform treatment decisions in these patients [4]. Furthermore, understanding the extent of comorbidities in a population feeds into the estimated global disease burden, which is used for health policy planning and decision making [5]. Historically, the extent of disease burden was based on expert opinion and this person would rate the level of disease burden but the effect of all comorbidities was not adequately addressed [6]. The inclusion of a validated comorbidity index may help to estimate the extent of disease-specific severity weights in a consistent manner, which is important for epidemiology studies of chronic diseases.

Comorbidity indices are often used in research to assign patients a comorbidity score that can be used to estimate their overall comorbidity burden, and potentially their risk of mortality due to comorbidities [7]. Due to their standardization and extensive history of use and validation, the use of comorbidity indices instead of measuring all imaginable individual comorbidities in patients has feasibility benefits, and comorbidity indices have been shown to be effective tools for research [7]. One such validated and commonly used comorbidity index is the Charlson Comorbidity Index (CCI) [8,9]. The CCI was developed in 1987 by Charlson and colleagues [8] as a means of classifying, for research purposes, comorbidities that may be associated with mortality. The CCI was originally developed in a cohort of hospitalized patients and applied to female patients with breast cancer, but has since been applied to many different patient populations [8,10,11]. The current CCI includes comorbidities from several categories, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia/paraplegia, renal disease, malignancies, and acquired immunodeficiency syndrome [10,11]. Based on the presence or absence of specific comorbidities, patients are given a weighted comorbidity score [3,8]. The CCI is reportedly the most widely used comorbidity index, and CCI score is often included as a covariate in research [3,12]. Furthermore, a recent systematic literature review found that the CCI was the most commonly used and validated comorbidity index in research of patients with BC specifically [4].

Although comorbidity as a covariate is associated with treatment options and ultimately survival in BC, it is not the only factor that must be considered. Studies have found that race and/or ethnicity can also impact BC treatment options and outcomes. For example, Black women have a higher lifetime probability of dying from BC compared with non-Hispanic White women (3.1% [1 in 32] vs. 2.6% [1 in 39], respectively; United States [US]) [13]. Furthermore, focusing on BC mortality across different racial groups, the results from a retrospective analysis using data from the Surveillance, Epidemiology, and End Results (SEER) found that compared with non-Hispanic White patients, Black, American Indian, and Hispanic White patients had a 1.3–2.0-fold greater risk of mortality, whereas Asian and Pacific Islander patients had the same mortality risk (adjusting for age and SEER registry) [14]. Reasons for these differences are complex and may include factors such as the number and severity of comorbidities, differences in cancer stage at diagnosis, tumor characteristics, and access to screening, diagnostic, and treatment services [15]. In addition, there is a large body of evidence indicating differences in the types of comorbidity among different racial groups [16-18]. For example, there is evidence that Black/African American women are more likely to have diabetes and hypertension than White women [18,19]. However, the role of comorbidities in BC outcomes among patients of different races/ethnicities still needs to be fully elucidated. Indeed, understanding the severity and type of comorbidities that contribute to BC outcome differences in racial minorities may help physicians to understand and prevent the comparatively worse outcomes seen in racial/ethnic subgroups [20,21].

The three main objectives of this systematic review were:

1. To evaluate from the published literature whether comorbidity index scores are predictive of outcomes in racial/ethnic subgroups of patients with BC, including HER2+ BC specifically.
2. To evaluate whether there are differences in the strength and/or direction of the association between comorbidity index scores and treatment outcomes in different racial/ethnic subgroups of patients with BC, including HER2+ BC specifically.
3. To report (to the extent available in the literature) detailed, quantitative descriptions of these associations.

The methodology and risk of bias of the studies was evaluated as a secondary objective of this systematic review.

METHODS

Study design

This is a systematic review of articles published between January 1, 1987 and May 21, 2020 that aimed to evaluate the use of comorbidity indices in patients with BC and to determine if any racial disparities in outcomes exist. The searches were limited to English language research involving human subjects. No geographical restrictions were used in the search strategy. The original search strategy included only the most recent 10 years (1 January 2010 to 21 May 2020). However, due to a relative lack of literature, the protocol was amended to include all time after 1987, when the CCI was first developed (1 January 1987 to 21

May 2020). Searches were conducted in Ovid (Medline, Embase, Biosis) using pe-defined search terms such as: "comorbidity index", "scores", "outcomes", "prediction", "breast cancer", and "minorities", including synonyms and related terms. A full list of the search terms used and the numbers of identified studies are shown in Supplemental Table 1.

Eligibility criteria

Eligible studies included interventional (e.g., clinical trials) and non-interventional (e.g., cohort studies, case-control studies) analytic research studies. Only studies that used a comorbidity index were included.

The population of interest included female patients with a diagnosis of any type of BC, including: all tumor stages (1-4), metastatic BC, and subtypes (HER2+ and HER2-negative [HER2-], hormone receptor-positive [HR+]), estrogen receptor-positive/progesterone receptor-positive HR+ and hormone receptor-negative [HR-]; estrogen receptor-negative/progesterone receptor-negative HR- [ER-/PR-], triple negative [ER-/PR-/HER2-]; inflammatory BC, ductal carcinoma *in situ*, invasive ductal carcinoma, locally advanced BC, and others. If multiple cancers were evaluated in the study (e.g., breast, lung, colorectal), the BC subgroup must have had independent results reported by racial/ethnic subgroups.

Screening articles

Two levels of article selection were completed. In level 1 screening, titles and abstracts of articles were reviewed. Full texts of articles chosen in level 1 screening were reviewed in level 2 screening. Two researchers completed article selection independently; any uncertainty over inclusion of an article was resolved by agreement between the two researchers, or by a third researcher if an agreement was not reached by the first two. Relevant references in reviews and meta-analyses found in the literature search were to be reviewed for inclusion. The results of the article screening process were documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. In addition, the methods and results sections of included articles were evaluated by one researcher (and quality control was performed by a second researcher) to assess methodology and risk of bias according to the Newcastle-Ottawa Scale for cohort and case-control research designs and the Cochrane criteria for assessing bias in interventional research designs [23,24].

Table 1: Description of articles included in the analysis.
[a]Health and Functioning in Women (HFW) Study uses data from the Metropolitan Detroit Cancer Surveillance System (MDCSS) at the Michigan Cancer Foundation, now called the Barbara Ann Karmanos Cancer Institute; [b]A discrepancy exists within this article regarding whether enrollment ended in 2013 as reported in the abstract and table headings or in 2014 as reported in the methods section.

Reference	Patients Evaluated	Comorbidity index	Racial/ethnic groups evaluated	Design	Data Source and Country	Number of patients per racial/ethnic subgroup
Emerson (2017)[25]	Patients with any primary invasive breast cancer (excluding those with prior other cancer site)	CCI	• American Indian/ Alaska Native	Cohort	Kaiser Permanente Northern California (United States)	• 179 American Indian/Alaska Native
			• Non-Hispanic White			• 25,548 non-Hispanic White
Izano (2014)[26]	Patients aged 40-84 years with newly diagnosed, histologically confirmed primary invasive breast cancer between 1984-1985 or 1987-1988	CCI	• African American	Cohort	Health and Functioning in Women (HFW) Study (United States)	• 170 African American
			• White			• 829 White
Swede (2016)[27]	Patients diagnosed with any primary breast cancer in Connecticut between 1/1/2000 – 12/31/2007	CCI	• Black/African American	Cohort (medical chart review)	Connecticut Tumor Registry (CTR) (an NCI-SEER registry) (United States)	• 202 Black/African American
			• White			• 214 White
Keegan (2015)[28]	Female residents of the San Francisco Bay Area with newly diagnosed invasive breast cancer between 2004-2007	CCI	• Asian/Pacific Islander	Cohort	Kaiser Permanente Northern California (KPNC) (United States)	• 837 Asian/Pacific Islander
			• Non-Hispanic African American			• 479 non-Hispanic African American
			• Hispanic			• 658 Hispanic
			• Non-Hispanic White			• 4237 non-Hispanic White
Sheppard (2011)[29]	Women aged ≥15 years with pathologically confirmed invasive breast cancer between 1995-2004	CCI	• First Nations people	Cohort	Ontario Cancer Registry (OCR), files of Indian and Northern Affairs Canada, and Ontario mortality database (linked) (Canada)	• 287 First Nations people
			• Non-First Nations people			• 671 non-First Nations people
Jemal (2018)[30]	Women aged 18-64 years with a first, primary stage I–III invasive breast cancer between 2004-2013b	CDCI	• Black	Cohort	National Cancer Database (United States)	• 78,737 NH Black
			• White			• 484,760 NH White

Tammemagi (2005)[31]	Patients in the Metropolitan Detroit area with any incident breast cancer between 1985-1990	CCI	• Black • White	Cohort	Henry Ford Health System Tumor Registry (United States)	• 264 Black • 642 White
West (1996) [32]	Female residents of the San Francisco Bay Area of any age with histologically confirmed invasive breast cancer diagnosed between 1/1/1973-12/31/1986	CCI	• Black • White	Cohort	Kaiser Permanente Medical Care Program (United States)	• 418 Black (total) • 850 White (total)
Curtis (2008)[33]	All female patients (aged ≥68) with any subtype of breast cancer diagnosed between 1/1/1994 – 12/31/1999	CCI	• African American • Asian/Pacific Islander • Hispanic • White	Cohort	SEER-Medicare (United States)	• 2479 African American • 1086 Asian/Pacific Islander • 1172 Hispanic • 35,878 White
Braithwaite (2009)[19]	Patients in the San Francisco Bay Area with histologically confirmed invasive breast cancer between 1973-1986	CCI and hCCI	• African American • White	Historical Cohort	Kaiser Permanente Northern California Medical Care Program Comorbidity Study (United States)	• 416 African American • 838 White

Abbreviations: CCI: Charlson Comorbidity Index; **CDCI:** Charlson-Deyo Comorbidity Index; **hCCI:** hypertension-augmented Charlson Comorbidity Index; **NH:** Non-Hispanic; **NCI:** National Cancer Institute; **SEER:** Surveillance, Epidemiology, and End Results Program.

Data extraction

Key data from each selected article were manually extracted by one researcher; they included the specific cancer(s) evaluated in the study and other patient characteristics, name of the comorbidity index used, racial/ethnic subgroups of patients evaluated, data source, study design, country/region in which the research was conducted, sample size, predicted outcome, and results of outcome prediction (e.g., hazard ratio, objective response) by each racial/ethnic subgroup. A second researcher completed quality control on the extracted data.

Outcomes

The outcomes of interest were the clinical endpoints reported for cancer and/or its treatment including survival and mortality outcomes (e.g., overall survival, progression-free survival, non-relapse mortality). If sufficient information was available on other endpoints such as relapse/recurrence of disease, or treatment course decision prediction, they were also included.

Statistical methods

Descriptive statistics were used to provide a summary of the included articles, such as cancers evaluated, comorbidity index used, racial/ethnic subgroups evaluated, sample sizes, regions of conduct, and outcomes/findings where applicable. A meta-analysis was to be completed only if there was low variability across studies. Outcome prediction results were consolidated and presented in a manner consistent with the data available. Inferential statistical analyses were not performed.

RESULTS

We identified 172 articles through database searching and an additional 41 articles through other sources, including a review of reference lists in meta-analyses and review articles identified in the literature search (Figure 1). After duplicates were removed, 151 articles were reviewed in level 1 (title/abstract) screening. Fifty-seven articles were excluded after level 1 screening. Of the remaining 94 articles, 84 were excluded after level 2 screening. The reasons for exclusion were as follows: 61 did not evaluate or report the specific associations between the three variables of interest (comorbidity score, race/ethnicity, outcomes) even if all three variables were included in the study, 14 did not use a comorbidity index to evaluate comorbidities, six were excluded because of their study design, one was excluded because of the patient population evaluated, one was excluded because only an abstract was identified, and one was excluded because it did not evaluate outcomes. The final dataset included 10 studies (Figure 1).

All 10 included studies [19,25-33] used the CCI (or a derivative of the CCI), were cohort studies, and were conducted in North America (Table 1). Most articles included White/non-Hispanic White patients (n = 9) and Black/African American patients (n = 8). Other studies included American Indian/Alaska Native patients (n = 1), First Nations (an indigenous Canadian population) patients (n = 1), Asian/Pacific Islander patients (n = 2), and Hispanic patients (n = 2). None of the included studies evaluated patients with HER2+ BC specifically.

Relationship between comorbidity scores and outcomes in different racial groups

Four of the included articles evaluated the relationship between comorbidities and outcomes, stratified by race/ethnic subgroups (Table 2). Overall, the results were mixed across the studies, and all studies found significant associations in certain subgroups but not others. A study reported by West et al. found that only higher CCI scores (2, 3+) were associated with 10-year mortality in both White and Black patients, whereas a lower score (1) was not associated with 10-year mortality in White or Black patients [32]. Similarly, Swede et al. reported that only a high CCI score (3+) was significantly predictive of death from any cause in African American patients, but that lower CCI

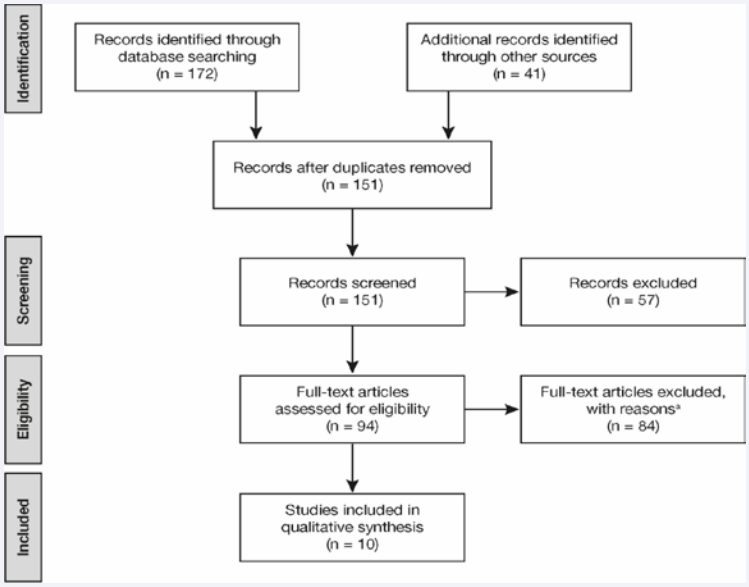

Figure 1 PRISMA flow diagram.

Reasons for full-text article exclusion (total 84): 61-associations between race/ethnicity and outcomes by CCI score or between CCI score and outcomes by race/ethnicity not evaluated (i.e., relationship between all three variables – comorbidities, race/ethnicity, and outcomes – was not reported)

- 14-comorbidity index not used
- 6-incorrect study design (cross-sectional study or review article)
- 1-abstract terminal document
- 1-incorrect patient population evaluated
- 1-outcomes not evaluated

Abbreviations: CCI: Charlson Comorbidity Index; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Table 2: Results of articles that evaluated the relationship between comorbidities and outcomes, stratified by race.
[a]Bolded HRs and 95% CIs indicate statistically significant findings. [b]Adjusted for age, stage, tumor size, and treatment. [c]Adjusted for age at diagnosis and period of diagnosis. [d]Adjusted for age, triple-negative BC status, and SEER summary stage.

Reference	Outcome	Outcome prediction results	Specifications	HR (95% CI)a
West (1996)[32]	• 10-year mortality	• For Black patients, adjusting for other variables,[b] CCI score was significantly associated with 10-year mortality for CCI score 2 and 3+ vs. 0, but was non-significant for CCI score 1 vs. 0	CCI 1 vs. 0	ns
			CCI 2 vs. 0	**2.99 (p<0.001)**
			CCI 3+ vs. 0	**4.29 (p<0.001)**
		• For White patients, adjusting for other variables,[b] CCI score was significantly associated with 10-year mortality for CCI score 2 and 3+ vs. 0, but was non-significant for CCI score 1 vs. 0	CCI 1 vs. 0	ns
			CCI 2 vs. 0	**2.57 (p<0.001)**
			CCI 3+ vs. 0	**3.39 (p<0.001)**
Sheppard (2011)[29]	• Death	• In First Nations patients, adjusted[c] HRs for death for patients with comorbidities (compared to no comorbidities) was significant for patients with Stage I BC. No other significant differences were found	Stage I (n = 95)	**4.65 (1.39–15.53)**
			Stage II (n = 130)	ns
			Stage III–IV (n = 58)	ns
Izano (2014)[26]	• 20-year breast cancer mortality	• CCI score was not significantly associated with 20-year BC mortality in African American or White patients	African American	ns
			White	ns
	• 20-year other-cause mortality	• CCI score was significantly associated with 20-year other-cause mortality with a time-varying effect in White patients and a time-invariant effect in African American patients	African American	**1.57 (1.30–1.90)**
			White	**p<0.001**
Swede (2016)[27]	• Death from any cause	• In a multivariate adjusted model,d CCI score was significantly predictive of death from any cause for Black/African American patients with CCI score ≥3 vs. CCI score = 0. No other significant effects were found for Black/African American patients	CCI 1–2 n = 25) vs. 0 (n = 118)	ns
			CCI 3+ (n = 32) vs. 0 (n = 118)	**5.65 (2.90–11.02)**
		• There were no significant associations between CCI score and death from any cause for White patients	CCI 1–2 (n = 28) vs. 0 (n = 173)	ns
			CCI 3+ (n = 13) vs. 0 (n = 173)	ns

Abbreviations: BC: breast cancer; **CCI:** Charlson Comorbidity Index; **CI:** confidence interval; **HR:** Hazard Ratio; ns, not significant; **SEER:** Surveillance, Epidemiology, and End Results.

scores (1-2) in African American patients were not, and that CCI score was not predictive of death in White patients at all [27]. Sheppard et al. evaluated patients by stage of disease and found that the risk of death in First Nations patients with Stage I BC at diagnosis was higher if they had comorbidities (compared with no comorbidities) – no such association was found for First Nations patients with Stage II or III–IV BC at diagnosis [29]. Izano et al. found that CCI score was significantly associated with 20-year other-cause mortality with time-invariant effect in African American patients and a time-varying effect in White patients [26]. In this study, African American patients had, approximately, a 60% increase in risk of other-cause mortality with each unit increase in CCI score. In contrast, CCI score was not significantly associated with long-term (20-year) BC mortality in African American or White patients [26].

Relationship between race and outcomes, adjusted for comorbidities

Six of the included articles evaluated the relationship between race and outcomes, adjusting for comorbidities (Table 3). Overall, these studies used multivariable analysis with race/ethnicity as a predictor for outcomes with comorbidity score included as a covariate (perhaps as a potential confounder or an intermediate on the causal pathway between race/ethnicity and outcomes) to determine the association between race/ethnicity and survival/mortality when adjusted for comorbidity score (with/without other covariates). Overall, these results were also mixed-while some found that comorbidity score accounted for some of the association of interest, others did not.

Two studies found that comorbidity score accounted for at least some of the association between race/ethnicity and outcomes. Tammemagi et al. reported that race (Black vs. White) was significantly associated with all-cause survival and, after adjustment for CCI, comorbidities accounted for some of this association [31]. The same authors found no association between competing-causes (i.e., non-BC) survival and race either when adjusting or not adjusting for CCI [31]. However, the authors reported that CCI score may account for 29.1% of the difference in risk (all-cause) and 54.2% of the increased risk (competing causes) of the racial disparity in survival outcomes [31].

Braithwaite et al. found that, compared to White patients, African American patients were significantly more likely to die from any cause and that comorbidity (as measured by the CCI

Table 3: Results of included articles that evaluated the relationship between race and outcomes, adjusting for comorbidities.

Reference	Outcome studied	Outcome prediction results	Specifications	HR (95% CI)[a]
Tammemagi (2005) [31]	• All-cause survival	• Race (Black vs. White) was significantly associated with all-cause survival when unadjusted by covariates. When adjusted for CCI score, this association was still significant	Unadjusted	**1.34 (1.11-1.62)**
			Adjusted for CCI	**1.24 (1.02-1.51)**
	• Competing-causes survival	• Race (Black vs. White) was non-significantly associated with competing-causes survival when unadjusted by covariates. When adjusted for CCI score, this association was still non-significant	Unadjusted	1.28 (1.00-1.63)
			Adjusted for CCI	ns
Curtis(2008) [33]	• Overall mortality • Cancer-specific mortality	• In a predictive model[b] for cancer-specific mortality, African American patients had a significantly higher mortality, and Asian/Pacific Islander patients had a significantly lower mortality, compared to White patients. When adding comorbidities to this model, HRs did not change appreciably for any racial/ethnic subgroup	African American	
			Without CCI	**1.12 (1.01-1.23)**
			With CCI	**1.10 (0.10-1.22)**[c]
			Hispanic	
			Without CCI	ns
			With CCI	ns
			Asian/Pacific Islander	
			Without CCI	**0.63 (0.48-0.82)**
			With CCI	**0.62 (0.47-0.80)**
Braithwaite (2009) [19]	• All-cause survival	• In a multivariate analysis, [d] African Americans were significantly more likely to die from any cause compared to White patients. This effect lost significance when both the CCI and the hCCI were added to the model	Without CCI	**1.40 (1.13-1.73)**
			Adjusted for CCI	1.24 (1.00-1.54)[e]
			Adjusted for hCCI	ns
	• Breast cancer-specific survival	• In a multivariate analysis,[d] African Americans were significantly more likely to die from breast cancer compared to White patients. This effect was reduced but still significant when CCI and hCCI were added to the model	Without CCI	**1.48 (1.15-1.90)**
			Adjusted for CCI	**1.38 (1.06-1.79)**
			Adjusted for hCCI	**1.33 (1.07-1.75)**
	• Competing-causes survival	• Competing-causes survival: No significant findings were reported		ns

Keegan (2015)[28]	• Overall survival	• In a multivariate adjusted model,[f] all-cause (overall) mortality was significantly higher in NH White low SES patients, NH African American high SES patients, and NH African American low SES patients compared to NH White high SES patients. No other significant differences were found. When CCI scores were added to this model, HRs were not appreciably changed for any racial subgroup	NH White	
			Low SES (without CCI)	**1.26 (1.06-1.50)**
			Low SES (with CCI)	**28 (1.07-1.52)**
			NH African American	
			High SES (without CCI)	**1.50 (1.05-2.15)**
			High SES (with CCI)	**1.44 (1.01–2.07)**
			Low SES (without CCI)	**1.91 (1.44–2.52)**
			Low SES (with CCI)	**1.88 (1.42–2.50)**
			Hispanic and Asian/ Pacific Islander	
			High/low SES (without CCI)	ns
			High/low SES (with CCI)	ns
	• Breast cancer specific survival	• In a multivariate adjusted model,[f] BC-specific mortality was significantly higher in NH African American low SES patients compared to White high SES patients. No other significant differences were found. When CCI scores were added to this model, HRs were not appreciably changed for any racial subgroup	NH White	
			Low SES (without CCI)	ns
			Low SES (with CCI)	ns
			NH African American	
			High SES (without CCI)	ns
			High SES (with CCI)	ns
			Low SES (without CCI)	**2.07 (1.43-2.98)**
			Low SES (with CCI)	**2.13 (1.47-3.09)**
			Hispanic and Asian/ Pacific Islander	
			High/low SES (without CCI)	ns
			High/low SES (with CCI)	ns
Emerson (2017 [25]	•All-cause mortality	• All-cause mortality was significantly higher in American Indian/Alaska Native patients compared to non-Hispanic White patients when adjusting for patient and disease characteristics. When CCI scores were added to this model, the HR did not appreciably change	Adjusted[g] (without CCI)	**1.52 (1.17–1.99)**
			Adjusted[g] (with CCI)	**1.47 (1.13–1.92)**
	• Cancer-specific mortality	• BC-specific mortality was not significantly higher in American Indian/Alaska Native patients compared to non-Hispanic White patients when adjusting for patient and disease characteristics. When CCI scores were added to this model, the HR did not appreciably change	Adjusted[g] (without CCI)	ns
			Adjusted[g] (with CCI)	ns
Jemal (2018) [30]	•Overall survival	• Among patients with HR+ BC (n = 102,012), Black patients (n = 51,006) had a significantly higher risk of death compared to demographic-matched White patients (n = 51,006). When additionally matched by comorbidities, this was reduced but still significant	Demographic matched[h]	**2.05 (1.94-2.17)**
			Demographic/ comorbidity matched[h]	**1.93 (1.83-2.04)**
		• Among patients with HR- BC (n = 55,462), Black patients (n = 27,731) had a significantly higher risk of death compared to demographic-matched White patients (n = 27,731). When additionally matched by comorbidities, this was reduced but still significant	Demographic-matched[h]	**1.50 (1.43-1.56)**
			Demographic/comorbidity-matched[h]	**1.48 (1.41-1.54)**

and the hypertension-augmented CCI [hCCI]) is an important determinant of this racial disparity [19]. In addition, African American patients were significantly more likely to die from BC, and the CCI and hCCI accounted for some, but not all, of this racial disparity [19].

One additional study found that comorbidities accounted for a low to moderate amount of the association between race/ethnicity and outcomes. Jemal et al. reported that Black patients (with HR+ or HR- BC) had significantly higher risk of death compared to White patients, and CCI accounted for some of this disparity [30]. The authors reported that comorbidities accounted for 11.3% (HR+) and 3.8% (HR-) of the excess risk of death in Black patients [30].

In contrast, three studies found that comorbidity score did not account for the association between race/ethnicity and outcomes, or could only account for a very small amount of the association. Keegan et al. found that all-cause mortality was significantly higher in non-Hispanic White patients of low socioeconomic status (SES) and non-Hispanic African American patients of low/high SES (compared to non-Hispanic White patients of high SES). In this analysis, CCI score did not account for much of the survival disparity by race/SES [28]. BC-specific mortality was significantly higher in non-Hispanic African American patients of low SES (compared to non-Hispanic White of high SES); again, CCI score did not account for much of this disparity [28].

Emerson et al. found that all-cause mortality was significantly higher in American Indian/Alaska Native patients (compared to non-Hispanic White patients), and CCI score did not account for much of this disparity [25]. There were no significant associations between race and BC-specific mortality when adjusting or not adjusting for CCI score [25].

Curtis et al. found that, in a predictive model for cancer-specific mortality, compared to White race, African American race was associated with significantly higher mortality and Asian/Pacific Islander race was associated with significantly lower mortality [33]. In the analysis, the authors considered that comorbidities accounted for only 2% of overall mortality reduction from baseline to full adjustment between African American and White women [33].

Risk of bias analysis

The Newcastle-Ottawa Scale was used to assess the risk of bias in the 10 selected cohort studies (Table 4). This scale awards a possible total of nine stars to a non-interventional study based on its methodology. On the scale, a higher number of stars indicates less risk of bias. Seven of the studies were rated seven stars, two were rated eight stars, and one was rated six stars. Although there is no consensus on the appropriate interpretation of these scores, most studies scored at least seven out of nine stars, indicating that the overall risk of bias was relatively low in the included studies.

Because the included studies only ranged from six to eight stars on the scale, it was difficult to weight the results based on the quality of the studies, especially considering the variation in statistical analysis methods and racial/ethnic subgroups evaluated. All six studies that evaluated the relationship between race and outcomes adjusted for comorbidities were rated seven stars. Of the four studies that evaluated the relationship between comorbidity scores and outcomes stratified by racial/ethnic group, one was rated six stars, one was rated seven stars, and two were rated eight stars. The two studies of lower quality (rated six and seven stars) [27,32] both evaluated Black/African American and White patients and found mixed results: one found a significant association in both African American/Black and White patients for higher CCI scores only, and one found a significant association in only African American/Black, but not White, patients for higher CCI scores. The study of higher quality by Izano et al. [26] that evaluated the same racial/ethnic groups found significant associations between comorbidities and other-cause mortality, but not BC mortality, in both African American and White patients.

DISCUSSION & CONCLUSION

Many risk factors contribute to outcomes in patients with BC [36]. There are several well-established prognostic factors related to survival/mortality in BC, including tumor severity, tumor subtype, and use of new targeted therapies, that appear to be strongly associated with BC outcomes [40]. This review focused on another risk factor whose role appears to be potentially more complex and is lesser understood, such as race/ethnicity [14]. The underlying reasons for racial/ethnic disparities have not been fully elucidated; the extent to which race/ethnicity itself is associated with worse outcomes compared to the extent to which racial health disparities are associated with worse access to health care resources and treatment, and thus worse disease outcomes, requires more research [15,37,38].

Another important determinant of treatment outcomes is the presence of comorbidities before or shortly after BC diagnosis [34]. Current estimates indicate that comorbidities are common, with around 20-35% of patients with BC having at least one comorbidity [3]. Furthermore, the higher the number of comorbid conditions, the greater is the negative impact on overall survival and disease-free survival [35]. For example, a CCI score of 3+ (indicating a higher number of comorbid disease states present) represents the highest risk of 10-year mortality compared with scores of 0 (no comorbidity), or 1 or 2 [27,32].

The CCI is a commonly used general comorbidity index, overall and in BC specifically, and is used as a research tool in retrospective analyses of patient data from administrative databases or medical chart reviews [4,7]. The CCI has also been validated for use clinically not only in breast cancer, where it has been shown to be significantly associated with various survival outcomes [4], but in several other cancer types as well, including head and neck cancer and non-small cell lung cancer [10,11]. However, there is limited evidence of its utility in different racial/ethnic groups, supporting the need for further research on the utility of CCI (and its derivatives) in patients of minority groups.

The main aim of our study was to evaluate whether comorbidity index (specifically CCI) scores are predictive of treatment outcomes in patients with BC by race/ethnicity. We identified 10 studies categorized as having relatively low risk of selection bias that were included in this review. All of these studies were conducted in the US or Canada, which may

Table 4: Evaluation of risk of bias in included articles.

Reference	Representativeness of exposed cohort	Selection of unexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at study start	Comparability of cohorts on basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcome to occur?	Adequacy of follow-up cohorts	Total * (out of 9)
Emerson (2017)[25]	*		*	*	**	*	*		7
Izano (2014) [26]	*		*	*	**	*	*	*	8
Swede (2016) [27]	*		*	*	**	*	*		7
Keegan (2015) [28]	*		*	*	**	*	*		7
Sheppard (2011)[29]	*	*	*	*	**	*	*		8
Jemal (2018) [30]	*		*	*	**	*	*		7
Tammemagi (2005)[31]	*		*	*	**	*	*		7
West (1996) [32]	*		*	*	*	*	*		6
Curtis (2008) [33]	*		*	*	**	*	*		7
Braithwaite (2009)[19]	*		*	*	**	*	*		7

Note: a higher score out of 9 indicates less risk of bias with respect to the Newcastle-Ottawa scale. *Indicates that the study controlled/assessed for only the most important factor; **indicates that the study controlled/assessed for multiple important factors when evaluating the comparability of cohorts.

be reflective of how the CCI is used in the US/Canada versus elsewhere. The results from the included studies showed mixed results overall, indicating that there is a large gap in knowledge regarding the relationship between comorbidity scores, race/ethnicity, and outcomes in patients with BC.

In our analysis, four out of the 10 studies assessed the effect of CCI score on mortality risk with the results stratified by race. Three out of these four studies looked at the impact of CCI score on mortality risk in Black and White patients with BC; two studies found that a higher CCI score was associated with greater mortality risk in both Black and White patients [26,32] but one of these studies found a significant association only for higher CCI scores, not lower CCI scores, and another study found a significant association only for other-cause mortality, not BC mortality. The third study found that a higher CCI score was associated with mortality in Black patients only, but not White patients [27]. The variability in the reported impact of a higher CCI on mortality risk for Black and White patients may reflect the different study designs, patient size, and analysis. However, it is impossible to come to a definitive conclusion regarding the association between comorbidity scores and outcomes in Black/African American and White patients from the limited available evidence. The fourth study looked specifically at First Nations patients subgrouped by stage of disease. First Nations patients with Stage I cancer (but not more advanced stages) and comorbidities were at significantly higher risk of death compared with those with no comorbidities [29]. Because this was the only study identified that evaluated First Nations people, further research is required to understand the true association between comorbidities and outcomes in these patients. Finally, out of these four articles that evaluated the association between comorbidity score and outcomes stratified by race, only Black/African American, White, and First Nations groups were evaluated. No other racial/ethnic groups were evaluated, leaving a very large gap in knowledge for other groups, such as Hispanic, Latino, Asian or Pacific Islanders, and Native American or Alaska Natives.

We also evaluated whether the presence or absence of comorbidities may help to explain the disparities in survival outcomes by race. Six studies evaluated the relationship between race and outcomes with adjustments for comorbidities. The results varied. Two out of the six studies reported that comorbidities were importantly associated with the racial disparities in survival seen between Black and White patients with BC [19,31]. For example, in one study, CCI score was associated with 29.1% of the all-cause survival disparity by race and 52.4% of the competing-cause survival disparity by race [31]. In contrast, three studies found that CCI score had no or only limited associations with the racial disparity in survival [25,28,33]. Finally, one study found that CCI score had low-to-moderate association with racial disparity [30]. The inconsistencies of association of comorbidity and survival among the above-mentioned six studies may be due to factors such as variables included in the model and sample size. Further variability between the studies, in terms of patient populations included and specific racial/ethnic groups evaluated, limits our ability to synthesize these results and draw overall conclusions. However, despite this variability, the CCI score was able to detect some racial disparities in survival between racial subgroups, which is important for the future use of CCI in modeling of

comorbidities in the BC population. Further research is required to determine the extent of the utility of the CCI across racial/ethnic subgroups.

Finally, it is worth noting that the CCI contains a finite number of comorbidities in its index, meaning certain comorbidities that may have significant associations with mortality will not be considered. Although there is evidence that CCI score is a good surrogate marker of overall comorbidity burden and individual comorbidities may not be important, there is also some evidence that individual comorbidities may be important in some instances [7]. Specifically, comorbid diseases that are not included in the CCI may be important considerations in this population. One example of this is hypertension, which is not included in the CCI, but has been observed to be one of the most common comorbidities in patients with breast cancer [39] and has been found to be more common in Black/African American women compared to White women [18,19,40]. Furthermore, there is evidence that hypertension may put patients with BC at increased risk for certain medication side effects, which may affect their treatment decisions and disease outcomes [20]. Thus, hypertension may play an important role in the relationship of interest but is unaccounted for in the CCI. One potential explanation for the exclusion of certain important comorbidities may be the fact that some early developments and adaptations of the CCI were performed in patient samples that consisted of mostly White patients [42]. If there are significant comorbidities missing in the CCI, evidence of the clinical or research utility of comorbidity indices such as the CCI may not accurately reflect the utility or relevance of specific comorbidities in patients with BC. However, several comorbidities that have been shown to be associated with poorer survival in patients with BC, such as diabetes, and comorbidities that are known to be common in patients with breast cancer, such as chronic obstructive pulmonary disease, are accounted for in the CCI, so it is unclear how large of an issue this is in the present context [39,43].

This review has several limitations. First, it is limited by the amount of available literature on the topic of interest, particularly with respect to HER2+ BC. Only 10 articles were eligible and included in the qualitative synthesis, and none of the included articles reported findings by race according to HER2 status. Because of the specific focus on articles that evaluated both race/ethnicity and comorbidity index scores, we excluded many articles that may be relevant to the overall topic of interest. The focus of this review led to the exclusion of the following: articles that evaluated race/ethnicity and comorbidities but did not use a comorbidity index, articles that used a comorbidity index but did not evaluate race/ethnicity or did not explicitly state results by race/ethnicity, and some articles that evaluated both race/ethnicity and comorbidity index scores if they did not present any specific results for these variables. These factors may have contributed to the limited number of articles included in this review.

Furthermore, there was a lack of consistency in the methodology and manner of reporting results, making meta-analysis of the included articles unfeasible. Another limitation may be the CCI itself- the original CCI protocol was published in 1987 and is based on medical records from 685 women who received their first treatment for BC between 1962-1969; therefore, the CCI may be more reflective of comorbidities at the time the original CCI was developed. Although many studies have subsequently validated the CCI across different patient populations [4,10,11], and in doing so have provided a more current picture of comorbidities in the US, the CCI has not been fully validated across different racial/ethnic subgroups. This lack of validation may additionally help to explain why we only found 10 relevant studies. Clearly, more research is needed in this area. Only one study [28] looked at the impact of socio-economic status on BC survival by race, despite the relevance of this variable on treatment outcomes in cancer. Because this review includes only English-language articles, the results may not be generalizable to comorbidity indices and research performed in different languages, as indices translated into other languages need to undergo an independent validation process.

This review did not evaluate specific subtypes of disease, cancer treatments, age of patients, or other factors known to be associated with breast cancer prognosis and outcomes. These additional important prognostic factors may contribute to the heterogeneity in tumor biology and disease outcomes across all patients with BC, and to the variability of importance of comorbidity scores reported from 2% to 29.1% in articles included in this review. The importance of comorbidity scores in predicting BC outcomes relative to other factors was not the focus of this review, and might be important to assess in future research.

Finally, the impact of race/ethnicity on BC outcomes relative to other well-established prognostic factors is still not well understood. As previously mentioned, the role that racial disparities in healthcare access play, compared to the role of race/ethnicity itself was not evaluated here. Future research that incorporates a multidisciplinary approach to evaluate the role of tumor biology, demographics, disparities in care, and other factors is required.

Overall, our literature review identified very few studies that evaluated the relationship between race, comorbidity score, and outcomes in BC. Furthermore, the studies included in this review showed mixed evidence for this relationship. The presence of comorbidities was generally associated with higher mortality and reflected some of the racial disparities between African American and White patients with BC. No studies reported on the use of the CCI in patients with BC from racial minorities by HER2 status, despite HER2 status being an important prognostic factor used to guide BC management. Overall, this review revealed that the current state of the literature evaluating the relationship between comorbidity scores, race/ethnicity, and outcomes in BC is largely lacking. Future research focused on the interaction between race and comorbidity on breast cancer outcomes is needed to understand the extent of the associations between these factors, as well as the causal pathways between the predictors and outcomes to gain a clearer understanding of their importance.

CONFLICT OF INTEREST

Daiichi Sankyo, Inc. funded the design, data collection, and conduct of this research. The decision to submit the article for

publication was made by the authors. M Salas and M Sundararajan are employees of Daiichi Sankyo, Inc. MDH was an employee of Daiichi Sankyo, Inc. at the time of manuscript production. LH was hired as a consultant to Daiichi Sankyo, Inc. At the time of the manuscript production, MH was contracted to work at Daiichi Sankyo, Inc. M Salas is also affiliated with the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

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