Predicting disease-related and patient-reported outcomes in older patients with breast cancer-a systematic review

Plas-Krijgsman, W.G. van der; Boer, A.Z. de; Jong, P. de; Bastiaannet, E.; Bos, F. van den; Mooijaart, S.P.; ... ; Glas, N.A. de

Journal of Geriatric Oncology 12 (2021) 696–704

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Predicting disease-related and patient-reported outcomes in older patients with breast cancer - a systematic review

Willeke G van der Plas-Krijgsman [a,*], Anna Z. de Boer [b], Pauline de Jong [c], Esther Bastiaannet [a,b], Frederiek van den Bos [d], Simon P. Mooijaart [d], Gerrit Jan Liefers [b], Johanneke E.A. Portielje [a], Nienke A. de Glas [a]

[a] Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
[c] Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands
[d] Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands

ARTICLE INFO

Article history:
Received 15 July 2020
Received in revised form 11 November 2020
Accepted 21 January 2021

Available online 30 January 2021

Keywords:
Breast cancer
Geriatric oncology
Geriatric assessment
Prediction

ABSTRACT

The number of older patients with breast cancer has increased due to the aging of the general population. The use of a geriatric assessment in this population has been advocated in many studies and guidelines as it can be used to identify high risk populations for early mortality and toxicity. Additionally, geriatric parameters could predict relevant outcome measures. This systematic review summarizes all available evidence on predictive factors for various outcomes (disease-related and survival, toxicity, and patient-reported outcomes), with a special focus on geriatric parameters and patient-reported outcomes, in older patients with breast cancer.

Studies were identified through systematic review of the literature published up to September 1st 2019 in the PubMed database and EMBASe. A total of 173 studies were included. Most studies investigated disease-related and survival outcomes ($n = 123$, 71%). Toxicity was investigated in 40 studies (23%) and a mere 15% ($n = 26$) investigated patient-reported outcomes. Various measures that can be derived from a geriatric assessment were predictive for survival endpoints. Furthermore, geriatric parameters were among the most frequently found predictors for toxicity and patient-reported outcomes.

In conclusion, this study shows that geriatric parameters can predict survival, toxicity, and patient-reported outcomes in older patients with breast cancer. These findings can be used in daily clinical practice to identify patients at risk of early mortality, high risk of treatment toxicity or poor functional outcome after treatment. A minority of studies used relevant outcome measures for older patients, showing the need for studies that are tailored to the older population.

1. Introduction

The number of older patients with breast cancer has increased due to the aging of the general population [1]. Approximately a third of all newly diagnosed patients are over 70 years of age [2]. Compared to younger patients, older patients experience less benefit from treatment due to a reduced life expectancy, whereas the risk of treatment toxicity is generally higher [3]. Individual weighing of expected treatment benefits and possible risks could potentially aid in achieving better outcomes in terms of survival and quality of life [4]. This is especially relevant in older patients with breast cancer, many of whom die from other causes than breast cancer [5,6]. Prediction models can provide an individualized risk estimation, yet the existing tools are not tailored to the older population, since they do not take the heterogeneous character of this specific population into account, with wide variability in general health status, functionality, and the presence of comorbid conditions.

Furthermore, in addition to expected treatment benefits and risk of toxicity, patient-reported outcomes should be taken into account in the decision-making process. Over the last decade, it has been emphasized that patient-reported outcomes such as functional status, dependency, and quality of life are equally or even more relevant for older patients than disease-specific outcomes such as recurrence and survival [7]. Although patient-reported outcomes are increasingly included in randomized clinical trials and (prospective) cohort studies, their integration in guidelines or prediction tools for clinical practice is still limited.

Performing a geriatric assessment (GA) could potentially provide important predictors for patient-reported toxicity and survival outcomes. Previous studies demonstrated that findings from a GA can predict residual life expectancy and toxicity from chemotherapy [8]. Another study by Hurria et al. showed that GA variables independently predicted the risk of toxicity in older adults with cancer [9]. Moreover,

* Corresponding author at: Department of Medical Oncology, Leiden University Medical Center, Postzone C7-Q, P.O. Box 9600 RC, Leiden, the Netherlands.
E-mail address: W.G.van_der_Plas-Krijgsman@lumc.nl (W.G. van der Plas-Krijgsman).

https://doi.org/10.1016/j.jgo.2021.01.008

available generic life expectancy prediction tools [10–12] and chemotoxicity prediction tools, such as the Cancer and Aging Research Group (CARG) tool, include geriatric parameters [13,14]. A recent systematic review showed that GA affects treatment decision [15]. Therefore, implementation of a GA is strongly advocated [3].

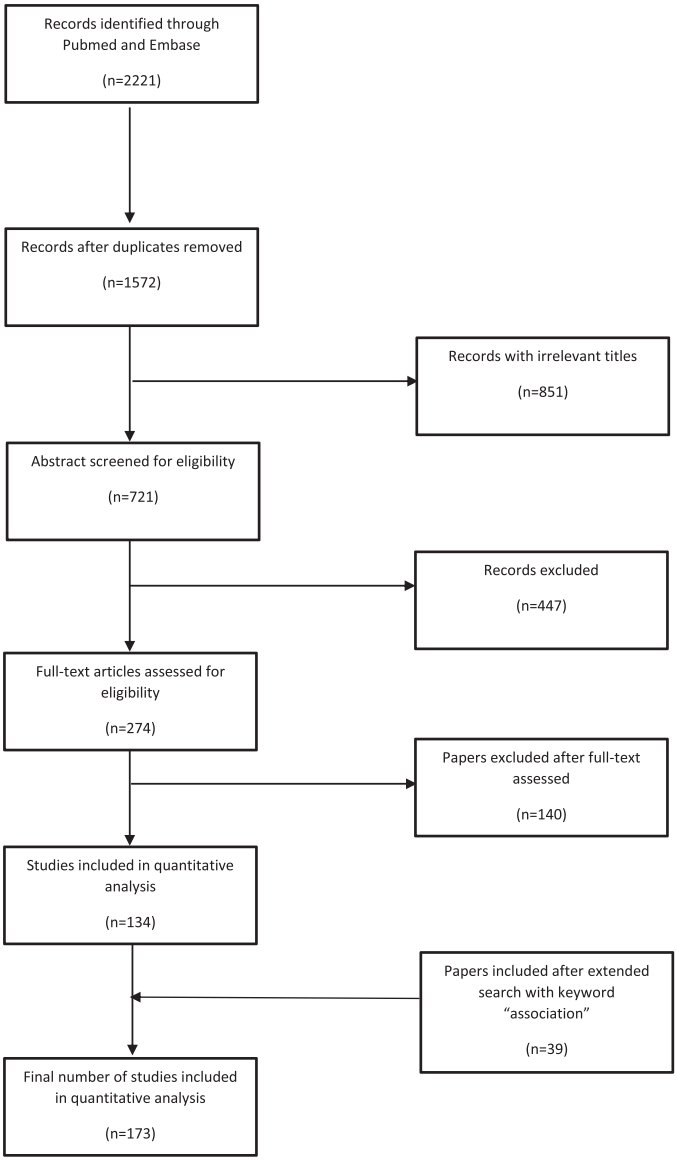
In order to improve prediction of outcome for older patients with breast cancer, the aim of this systematic review was to summarize all available evidence on predictive factors for various outcomes (disease-related and survival, toxicity, and patient-reported outcomes), with a special focus on geriatric parameters and patient-reported outcomes, in older patients with both early-stage and advanced breast cancer.

2. Methods

2.1. Search strategy and article selection

Eligible studies were selected by a systematic review of the available literature in the PubMed database and Embase that was published up to September 1st, 2019. The search strategy was based on the keywords "breast cancer", "older patients" and "prediction". After reviewing the first selection of papers, we performed an extended search, replacing "prediction" with the keyword "association", to obtain more relevant papers. Details of the search and a flowchart of the selection of papers are presented in Fig. 1.

The eligibility of the studies that were identified by the search was assessed independently by two authors (WK and ADB) and any discrepancies were discussed with a third author (NDG). Based on title and abstract screening we retrieved and screened the full text of all potentially relevant studies. We included all longitudinal cohort studies (both retrospective and prospective) that investigated the association between potential predictors and disease-related-, toxicity- and/or patient-reported outcomes in patients with breast cancer (both early-stage and advanced disease), aged 65 years or older. Studies without age specification in the inclusion criteria were included if a subgroup analysis in older patients was performed. Studies that included patients with cancer types other than breast cancer were also included if a subgroup



Pubmed search:

("Breast Neoplasms"[majr] OR (("Breast"[majr] OR "Breast"[ti] OR "breasts"[ti] OR "mammary"[ti] OR "mamma"[ti]) AND ("Neoplasms"[Mesh:NoExp] OR "Neoplasm"[ti] OR "neoplasms"[ti] OR "tumor"[ti] OR "tumors"[ti] OR "tumour"[ti] OR "tumours"[ti] OR "Carcinoma"[Mesh:NoExp] OR "carcinoma"[ti] OR "carcinomas"[ti] OR "cancer"[ti] OR "cancers"[ti] OR "malignancy"[ti] OR "malignancies"[ti] OR "malignant"[ti])))) AND ("predictive"[tw] OR "predictable"[tw] OR "predictability"[tw] OR "predict"[tw] OR "predicting"[tw] OR "predictor"[tw] OR "predictors"[tw] OR "prediction"[tw] OR "predictions"[tw] OR "prognosis"[tw] OR "prognostic"[tw] OR "prognoses"[tw] OR "Prognosis"[Mesh]) AND ("Aged"[majr] OR "Aged, 80 and over"[majr] OR "elderly"[ti] OR "elder"[ti] OR "aged"[ti] OR "old"[ti] OR "older"[ti] OR "oldest"[ti] OR septuagenarian*[ti] OR octagenarian*[ti] OR octogenarian*[ti] OR nonagenarian*[ti] OR centenarian*[ti] OR senescen*[ti] OR "frail elderly"[Majr] OR "geriatric"[ti] OR "geriatrics"[ti] OR "geriatrics"[Majr])

Embase search:

(exp *breast tumor/ OR ((exp *breast/ OR "Breast".ti. OR "breasts".ti. OR "mammary".ti. OR "mamma".ti.) AND (*neoplasm/ OR "Neoplasm".ti. OR "neoplasms".ti. OR "tumor".ti. OR "tumors".ti. OR "tumour".ti. OR "tumours".ti. OR *carcinoma/ OR "carcinoma".ti. OR "carcinomas".ti. OR "cancer".ti. OR "cancers".ti. OR "malignancy".ti. OR "malignancies".ti. OR "malignant".ti.))) AND ("predictive".ti,ab. OR "predictable".ti,ab. OR "predictability".ti,ab. OR "predict".ti,ab. OR "predicting".ti,ab. OR "predictor".ti,ab. OR "predictors".ti,ab. OR "prediction".ti,ab. OR "predictions".ti,ab. OR "prognosis".ti,ab. OR "prognostic".ti,ab. OR "prognoses".ti,ab. OR exp prognosis/) AND (exp *aged/ OR "elderly".ti. OR "elder".ti. OR "aged".ti. OR "old".ti. OR "older".ti. OR "oldest".ti. OR septuagenarian*.ti. OR octagenarian*.ti. OR octogenarian*.ti. OR nonagenarian*.ti. OR centenarian*.ti. OR senescen*.ti. OR exp *frail elderly/ OR "geriatric".ti. OR "geriatrics".ti. OR exp *geriatrics/)

Extended search in Pubmed:

("Breast Neoplasms"[majr] OR (("Breast"[majr] OR "Breast"[ti] OR "breasts"[ti] OR "mammary"[ti] OR "mamma"[ti]) AND ("Neoplasms"[Mesh:NoExp] OR "Neoplasm"[ti] OR "neoplasms"[ti] OR "tumor"[ti] OR "tumors"[ti] OR "tumour"[ti] OR "tumours"[ti] OR "Carcinoma"[Mesh:NoExp] OR "carcinoma"[ti] OR "carcinomas"[ti] OR "cancer"[ti] OR "cancers"[ti] OR "malignancy"[ti] OR "malignancies"[ti] OR "malignant"[ti])))) AND ("Aged"[majr] OR "Aged, 80 and over"[majr] OR "elderly"[ti] OR "elder"[ti] OR "aged"[ti] OR "old"[ti] OR "older"[ti] OR "oldest"[ti] OR septuagenarian*[ti] OR octagenarian*[ti] OR octogenarian*[ti] OR nonagenarian*[ti] OR centenarian*[ti] OR senescen*[ti] OR "frail elderly"[Majr] OR "geriatric"[ti] OR "geriatrics"[ti] OR "geriatrics"[Majr]) AND (”association”[tw] OR ”associated”[tw] OR ”association”[Mesh])

Fig. 1. Flowchart and search details.

analysis in patients with breast cancer was available. Only papers written in English were included. Duplicate studies were excluded.

2.2. Data extraction

The following data were extracted from each selected article: year of publication, study design, study population and total number of patients with breast cancer included in the analysis, investigated outcome(s), significant predictors, type of statistical analysis (univariable or multivariable). For this review we focused on positive findings, meaning that we selected only the statistically significant predictors that were presented in the results and supplementary tables. Predictors were considered statistically significant if the 95% confidence interval of the univariable hazard or odds ratio did not include unity or, in case a hazard or odds ratio was not reported, if the *p*-value was smaller than 0.05. Since we were only interested in prediction and not looking for causality, we chose to primarily include significant predictors identified through univariable analysis, to avoid missing predictors when adjusting for other factors. Results of the multivariable analysis were used if results of a univariable model were not presented. Treatments were not considered as predictive factors because we were interested in predictors that can guide treatment decisions. A meta-analysis was considered unfeasible due to the heterogeneity of the included studies in terms of study population and definitions of predictors and outcomes.

2.3. Data synthesis and analysis

Results of the included studies were summarized by outcome: disease-related-, toxicity- and patient-reported outcomes. Disease-related outcomes comprise survival endpoints, including overall survival, breast cancer-specific survival, and disease recurrence. Composite endpoints, such as disease-free survival, were also included in the analysis. Toxicity-related outcomes included adverse events described for all treatment modalities (surgery, radiotherapy and systemic treatment). Patient-reported outcomes were defined as quality of life outcomes or any outcome concerning a decline in physical, cognitive, or emotional/psychological functioning.

The predictors were categorized in the following categories: disease-related factors, age, sociodemographic factors, comorbidity, performance status, geriatric parameters, and laboratory measures. Sociodemographic factors comprised for example race, partner status, educational and financial status, home situation, and smoking. Geriatric parameters comprised measures of physical function, cognitive function, frailty, emotional and psychological function (such as mood and depression), and nutritional status (such as BMI and assessment of malnutrition). Physical function comprised both objective physical measures such as gait speed and functional status measures related to activities of daily living (ADL) and instrumental activities of daily living (IADL) and falls. Performance score was categorized separately. Cognitive function comprised pre-existing dementia diagnosis, MMSE scores, and QoL measures in relation to the cognitive domain. Frailty measures included primarily well-defined screening tools such as the Vulnerable Elderly Survey-13 (VES-13) and the Cancer-Specific Geriatric Assessment (C-SGA). Living in a nursing home was also considered a measure of frailty.

3. Results

A total of 1572 unique titles were first identified for evaluation. Of these, 721 abstracts were selected for screening and eventually 274 full texts were reviewed. With the initial and extended search strategy combined, a total of 173 articles were included in this review (Fig. 1). Characteristics of the included studies are presented by outcome in Table 1 and Supplementary Tables 1–2.

The first publication dated to 1991, but most of the included studies were published in the last ten years (75%), highlighting that there has been an increase of interest in this topic.

3.1. Disease-related- and survival outcomes

Most papers ($n = 123$, 71%) investigated disease-related and survival outcomes such as overall survival, breast cancer-specific survival, or recurrence. Forty-one studies (33%) investigated composite endpoints consisting of a combination of two outcomes, such as disease-free survival or progression-free survival. Most studies were performed in retrospective cohorts (67%), often with the use of large, population-based registries (31%). Eighteen studies (15%) were performed in a clinical trial-based population, of which eleven trials were composed of patients with advanced or metastatic breast cancer. The median sample size of all 123 studies investigating disease-related and survival outcomes was 950, and 87 papers (71%) specifically included patients aged ≥65 years. Details on all studies investigating disease-related and survival outcomes are presented in Supplementary Table 1.

The top-3 predictor categories for disease-related and survival outcomes were disease-related factors, age, and comorbidity (Fig. 2). In 86 out of the 123 papers investigating disease-related outcomes (70%), tumor characteristics such as tumor stage, grade, hormonal status and tumor markers (e.g., HER2-status) were indicated as predictors. Age was found to be predictive in 60 studies (49%). Besides age and disease-related factors, comorbidity measures such as the Charlson Comorbidity Index (CCI), number of comorbidities, and specific conditions such as cardiovascular disease and diabetes were also predictive in 34 studies (28%), specifically for overall or relative survival and non-cancer mortality. For example, in a large retrospective population-based registry study with 64,034 patients included, the CCI score was found to be predictive for all-cause mortality, with a reported unadjusted hazard ratio of HR 3.69 (95% CI 3.54–3.84) for patients with a CCI score of three or higher compared to patients with a CCI score of zero [16].

In addition, survival endpoints were also predicted by geriatric parameters in a total of 24 studies (20%).

In eleven studies, physical function measures such as gait speed, impaired mobility, and ADL and IADL scores were predictive for survival.

Furthermore, frailty measures such as the Groningen Frailty Indicator and the G8 questionnaire and cognitive status measures such as MMSE scores or pre-existing dementia, were reported as predictive for overall survival in respectively five and four studies. For example, in a prospective multicenter cohort study including 660 patients aged 65 and older with stage I-III breast cancer, three or more deficits in the cancer-specific geriatric assessment (C-SGA) were found to be predictive for both 10-year all-cause mortality and breast-cancer specific mortality, with reported unadjusted hazard ratios of respectively 1.81 (95% CI 1.45–2.26) and 2.19 (95% CI 1.34–3.57) [17].

3.2. Toxicity outcomes

Forty studies (23%) investigated toxicity outcomes, such as dose reduction or early treatment discontinuation and in nineteen studies (48%) the outcome was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). One study used a composite endpoint with a combined toxicity and survival outcome [18]. Most studies investigated toxicity due to treatment with chemotherapy ($n = 26$, 65%), whilst the remaining studies addressed adverse events due to surgical treatment, radiotherapy, endocrine therapy, targeted therapy, or a combination of treatment modalities. Thirteen studies were performed in clinical (randomized controlled) trial populations (33%), of which nine studies were composed of patients with advanced or metastatic breast cancer. The median sample size of all 40 studies investigating toxicity outcomes was 507 and 35 papers (88%) specifically included patients aged ≥65 years. Details on all studies investigating toxicity outcomes are presented in Supplementary Table 2.

Table 1
Characteristics of the 26 included studies investigating patient-reported outcomes.

Sorted by investigated outcome								
Publication		Study setting and population					Results	
Author	Year	Setting	Stage of disease	Age criteria	No of patients[a]	Treatment	Outcome	Predictors
Bellury	2013	Retrospective cohort, registry	All stages	≥70	184	All treatments[a]	Physical function	Comorbidity, symptom bother, marital status
Derks	2016	Prospective cohort, multicenter	All stages	<60, 60–69, and ≥ 70	431	Endocrine treatment	Functional decline	Age
Girones	2010	Prospective cohort, single center	Stage I-III	≥70	91	All treatments	Decline in performance status and decline in function (ADL/IADL)	Age
Huang	2018	Retrospective cohort, registry	All stages	≥65	2489	All treatments	Falls or balance and walking difficulty	Stage, age, comorbidity, ADL, physical activity, fatigue, pain interfering with work, depression, urinary incontinence, vision problem, hearing problem, sensory impairment, race, marital status
Huang	2019	Retrospective cohort, registry	All stages	≥65	437	All treatments	Report of falls in past 12 months	ADL, comorbidity, history of falls, self-reported balance of walking difficulty, sensory impairment in feet
Hurria	2019	Substudy from randomized clinical trial (prospective)	Stage I-III	≥65	256	Chemotherapy	Decline in physical function and resilience (recovery of physical function)	Pretreatment fatige, number of comorbid conditions, nodal status, marital status, appetite, dyspnea, age
Klepin	2010	Retrospective cohort, multicentre	All stages	70–79	49	All treatments	2-year progression to disability or death	20 m usual gait speed and 400 m long-distance corridor walk
Owusu	2016	Prospective cohort, multicentre	Stage I-III	≥65	184	All treatments	Functional decline or death within 12 months of BC treatment	Stage, age, Charlson comorbidity index, Vulnerable Elders Survey (VES-13) score at baseline, race, education, marital status, income
Owusu	2017	Prospective cohort, multicentre	Stage I-III	≥65	123	All treatments	Functional decline *(defined as a decrease in at least one point on the ADL and/or IADL scales from baseline to 12 months)*	Charlson comorbidity index, short physical perfomance battery (sppb), gait speed, grip strength, physical activity, functional disability, geriatric syndromes, Vulnerable Elders Survey (VES-13) score, race, educational status, median household income
Sehl	2013	Prospective cohort, multicenter	Stage I-III	≥65	689	All treatments	Functional decline	Educational status, initial physical function score, charlson comorbidity index, BMI
Singh	2018	Retrospective cohort, single centre	Stage 0-III	≥65	314	All treatments	Functional decline *(defined as an increase of at least one point in ECOG scores within one year of diagnosis)*	Stage, complaints of weakness at diagnosis
Van Abbema	2017	Prospective cohort, multicentre	Stage I-IV	50–69 and ≥ 70	398	All treatments	Functional decline *(defined as ADL decline, IADL decline or functional decline)*	Age, polypharmacy, fatigue
Westrup	2006	Prospective cohort, multicentre	Stage I-IIIa	≥65	644	All treatments	Upper body function and symptoms	Age, BMI, mental health
Baxter	2009	Retrospective cohort, registry	Stage I-III	66–80	21,362	Chemotherapy	Development of dementia	Stage, ER, age, Charlson comorbidity index, marital status
Du	2010	Retrospective cohort, registry	Stage I-IV	≥65	62,565	Chemotherapy vs not	Time to cognitive impairment	Age, number of comorbidities
Lange	2016	Prospective cohort, multicenter	Stage I-III	≥65	119	Chemotherapy vs not	Decline in cognitive function	Age
Mandelblatt	2016	Prospective cohort, multicenter	Stage I-III	≥65	1280	All treatments	Accelerated cognitive decline (EORTC QLQ-C30 scale)	Number of comorbidities, mental health prediagnosis, physical health prediagnosis, frailty score at baseline (based on Searle index)
Raji	2009	Retrospective cohort, registry	Stage I-III	≥68	6932	Chemotherapy	Incident dementia after chemotherapy	Age, number comorbidities, race
Clough	2007	Prospective cohort, multicenter	Stage I-IIIa	≥65	660	All treatments	Changes in emotional health	Comorbidity, physical function at baseline, emotional support, education, income, perception of never being cured
Perkins	2007	Retrospective cohort, registry	All stages	≥70	127	All treatments	Life satisfaction, depression and general health perceptions	Life satisfaction: fatigue, physical functioning, optimism, mastery, spirituality, satisfaction with support Depression: Age, fatigue, physical functioning, optimism, mastery, spirituality, satisfaction with support General health perceptions:

(continued on next page)

Table 1 (*continued*)

Sorted by investigated outcome								
Publication		Study setting and population					Results	
Author	Year	Setting	Stage of disease	Age criteria	No of patients[a]	Treatment	Outcome	Predictors
								fatigue, comorbidity, physical functioning, optimism, mastery, spirituality, social support
Dura-Ferrandis	2017	Prospective cohort, multicentre	Stage I-III	≥65	1280	All treatments	Accelerated decline in physical, emotional and cognitive functioning	Physical decline: age, comorbidity, SF-12 phyical and mental scores, tangible support Cognitive decline: comorbidity, SF-12 physical and mental scores, disengagement, tangible support, education Emotional decline: comorbidity, SF-12 physical and mental scores, optimism, disengagement, selfdistraction, tangible support, education
Magnuson	2019	Prospective cohort, multicenter	Stage I-III	≥50 (subanalysis)	133	Chemotherapy	Change in frailty score (based on Fried frailty phenotype)	Cognitive function at baseline (patient-reported and objective function tests), frailty score at baseline
Mandelblatt	2003	Retrospective cohort, registry	Stage I-II	≥67	1812	Surgical treatment	Several domains of patient-reported symptoms and QoL	Changes in physical functioning domains: age, stage, education, Charlson comorbidity index, arthritis, arm problems at baseline Changes in mental health domains: Age, race, education, Charlson comorbidity index, arthritis, arm problems at baseline Changes in satisfaction domains: perceived ageism, perception of having a choice of therapy, arm problems at baseline
Mogal	2017	Retrospective cohort, registry	Stage I-IV	>65	373	Surgical treatment	Low physical and mental component summary score (PCS-12 and MCS-12)	Low physical component score: Age, number of comorbidities, ADL, stage Low mental component score: number of comorbidities, ADL
Neuner	2014	Retrospective cohort, registry	Stage I-IV	≥65	3083	All treatments	General HR-QoL and breast cancer-specific HR-QoL	General HR-QoL, physical domain (PSC-12): age, race, educational status, income, stage, number of comorbidities General HR-QoL, mental domain (MSC-12): number of comorbidities Breast cancer-specific HR-QoL: income, stage, number of comorbidities
Williams	2019	Retrospective cohort, single center	Stage I-IV	≥65	63	All treatments	HR-QoL domains: fatigue, physical function, pain interference, social roles, anxiety, depression and sleep disturbance	Pre-frail or frail at baseline (Carolina Frailty Index)

[a] All treatments: surgery with/without radiotherapy, chemotherapy, endocrine therapy.

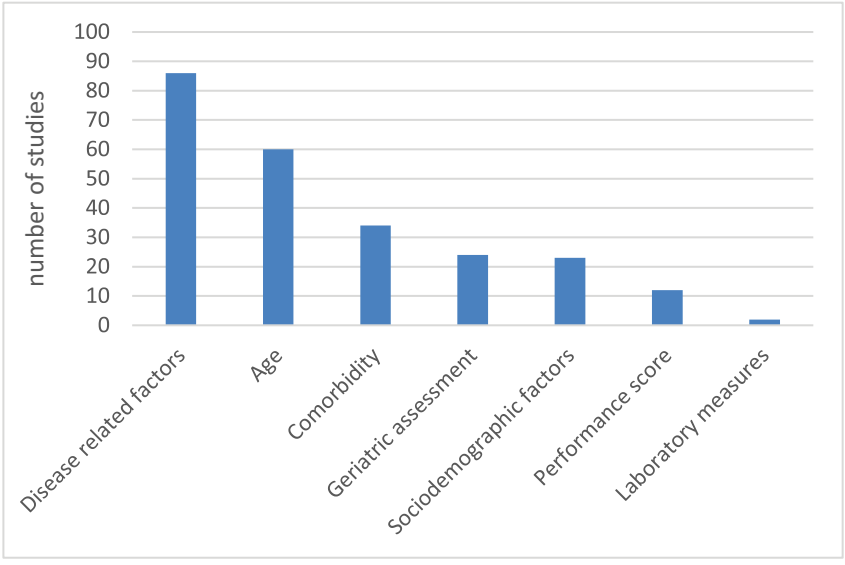


Fig. 2. Predictors found for disease-related and survival outcomes.

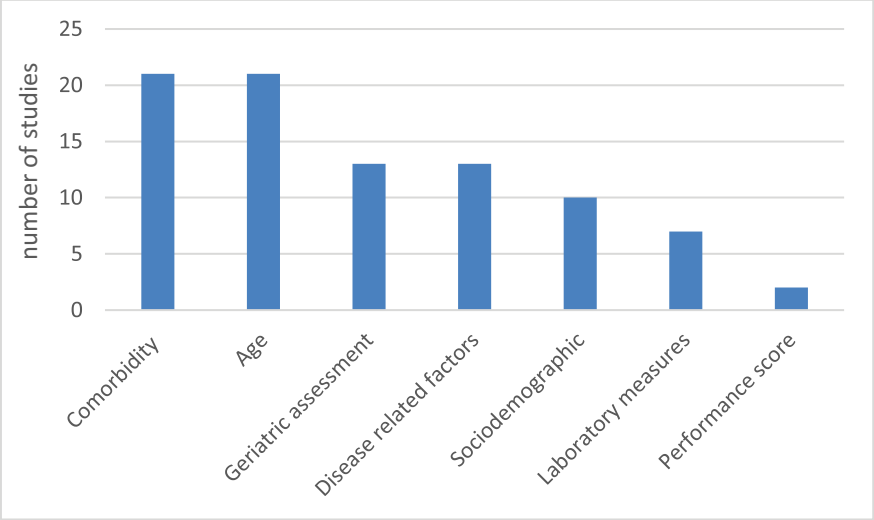


Fig. 3. Predictors found for toxicity outcomes.

The top-3 predictor categories for toxicity outcomes were comorbidity, age, and geriatric parameters together with disease-related factors (Fig. 3). Comorbidity measures were the most frequently found predictors for toxicity outcomes ($n = 21$, 53%). These comorbidity measures comprised CCI score, number of comorbidities, polypharmacy, diabetes, and cardiovascular comorbidity. Age was also frequently indicated as a predictor for toxicity in twenty-one studies (53%). In one-third of the included studies ($n = 13$), geriatric parameters were indicated as predictors for toxicity outcomes, mostly measures of frailty (either defined as living in a nursing home or with use of a prespecified frailty index). For example, in a prospective multicenter cohort study, including 990 patients aged 65 and older with stage I-III breast cancer and receiving endocrine therapy, discontinuation of therapy was predicted by lower cognitive function (HR 1.22, 95% CI 1.08–1.37) and frailty (based on Searle's Frailty Index [19]) with an unadjusted HR of 1.82 (95% CI 1.09–3.06) [20].

Furthermore, laboratory measures such as baseline creatinine clearance and baseline white blood cell count were reported to be predictive for treatment toxicity in seven studies.

3.3. Patient-reported outcomes

Patient-reported outcomes were investigated in twenty-six studies (15%). Physical function was assessed in thirteen studies, cognitive function in five studies and eight studies investigated other health-related quality of life outcomes, such as life satisfaction or mental health, or a combination of domains. The median sample size of the 26 studies investigating patient-reported outcomes was 414. All studies investigated patients with non-advanced breast cancer and 23 studies (88%) specifically included patients aged 65 years or older. Four out of the five studies investigating cognitive function outcomes included older patients specifically treated with chemotherapy. One study was performed in a randomized controlled trial population [21]. Details on all studies investigating patient-reported outcomes are presented in Table 1.

The top-3 predictor categories for patient-reported outcomes were geriatric parameters, comorbidity and age (Fig. 4). In nineteen out of the 26 papers (73%) investigating patient-reported outcomes, geriatric measures were found to be predictors. For physical function outcomes,

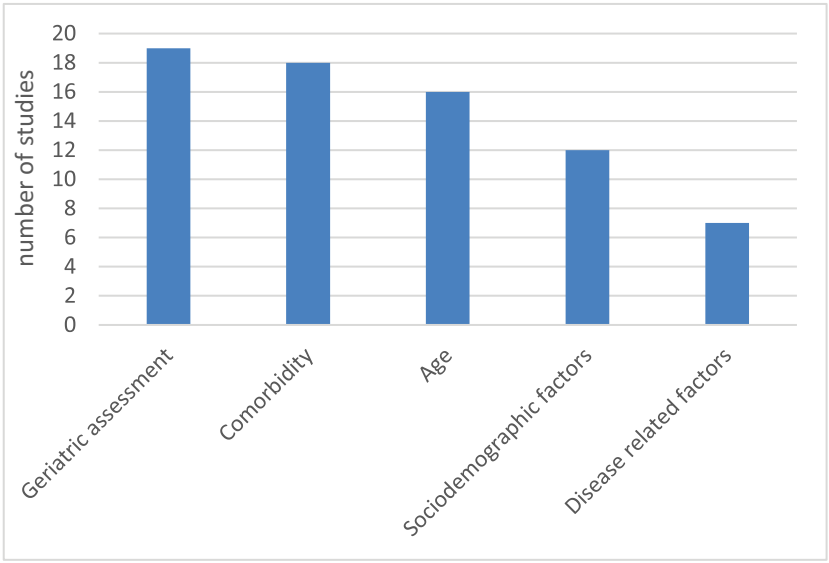


Fig. 4. Predictors found for patient-reported outcomes.

such as functional decline or report of falls, the most frequently found predictors were objective physical measures such as gait speed, self-reported balance or walking difficulties, previous falls, and ADL dependency.

Sociodemographic factors and comorbidity scores were also predictive for physical function outcomes.

For example, in a large retrospective registry-based cohort study, consisting of nearly 2500 patients with breast cancer aged 65 years and older, falls or balance and walking difficulty was predicted by age, comorbidity and various geriatric parameters such as ADL and physical activity, urinary incontinence, sensory impairments, and the presence of depression [22].

For cognitive decline ($n = 5$), age and the number of comorbidities were most frequently found as predictors for the development of cognitive impairments after treatment. For example, in a large prospective, multicenter cohort study, including 1280 older patients with nonmetastatic, invasive breast cancer, self-reported cognitive decline was predicted by comorbidity, together with geriatric parameters such as physical health and frailty scores at baseline [23].

4. Discussion

This systematic review provides an overview of all available evidence on predictors of several outcomes in older patients with breast cancer. This paper shows that most studies in older patients with breast cancer investigate disease-related and survival outcomes, and only a mere 15% assess patient-reported outcomes (Fig. 5). Furthermore, in addition to age and comorbidity, geriatric parameters were among the top-3 most frequently found predictors for toxicity and patient-reported outcomes.

We showed that various measures that can be derived from GA were predictive for survival endpoints. For example, a prospective cohort study by DuMontier et al. showed that, besides age, tumor stage and comorbidity, better mental health and physical function were associated with lower 10-year mortality [24]. However, these findings should be interpreted with caution. Overall survival, and composite endpoints including survival such as disease-free survival, make no distinction between mortality from breast cancer and from other causes. Therefore, our finding that comorbidity, age, and geriatric parameters predict survival outcomes could be (partially) explained by the effect on non-cancer mortality.

Non-cancer mortality is an important endpoint to study in older adults with breast cancer, as the risk of dying due to other causes strongly increases with age. When the factor of competing risk is considered, older patients might experience less benefit of treatment than is demonstrated in clinical trials. Moreover, these patients are more likely to experience toxicity of treatment and decline in quality of life or function due to treatment. In this review, we found only four studies that investigated predictors for other cause mortality, which shows that this subject is still understudied despite the clinical relevance [25–28].

Approximately a quarter of the included studies investigated toxicity outcomes, often combined with disease related endpoints and conducted in a clinical trial setting. Besides well-known predictive factors such as comorbidity, disease-related measures, and baseline laboratory measures, we found that geriatric measures such as physical function and functional independence prior to diagnosis, mental health status (such as mood changes or anxiety), and nutritional status were predictive for toxicity.

For example, Hurria et al. conducted a phase II trial in which the efficacy and tolerability of nab-paclitaxel was assessed in older patients with metastatic breast cancer. The validated Cancer and Aging Research Group (CARG) chemotherapy toxicity risk score was calculated prior to treatment. The results showed that this risk score based on GA and other clinical parameters was a significant predictor for treatment tolerability, with a higher mean risk score associated with a higher likelihood of dose reductions and hospitalizations [29]. Another well-established tool for predicting the risk of chemotoxicity in older patients is the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), which includes GA domains, along with clinical and laboratory parameters, to predict the risk of hematological and non-hematological toxicity on chemotherapy [30].

Unfortunately, only 15% of all studies addressed patient-reported outcomes. Although there is an increasing support and awareness for patient-reported outcome measures, the incorporation of such outcomes is still limited in clinical research and treatment guidelines. The International Society for Geriatric Oncology (SIOG) has previously stated that patient-reported outcomes such as quality of life and preservation of functional and cognitive capacity are just as relevant in the older population with cancer than disease-specific outcomes, emphasizing that such endpoints should be integrated in clinical studies for the older patient [7]. Given explanations for the lack of patient-reported outcomes incorporated in studies is that they are time consuming, requiring the assessment of questionnaires or geriatric screening tools. In contrast, disease specific factors, demographics, age and comorbidity measures are often available in medical registries, thus far less time consuming to investigate as possible predictors.

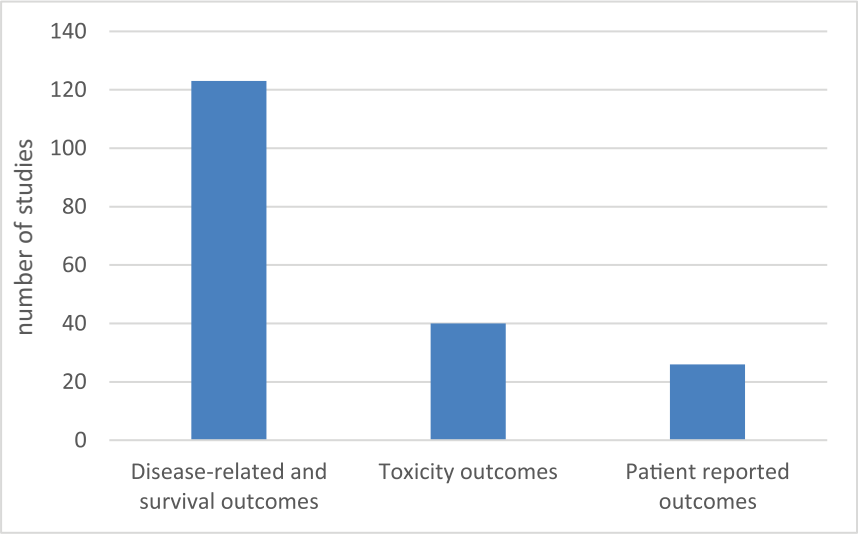


Fig. 5. Number of included studies per outcome.

Nevertheless, a GA can be performed by a nurse in a limited amount of time and requires significantly lower costs compared to many routine diagnostic procedures used in oncologic workup [31], and therefore we would advocate to include PROMs in registry databases. Furthermore, it remains a challenge how to quantify and correctly interpret PROMs such as health-related quality of life or functional decline, as part of these changes might be due to aging itself and not to the cancer or cancer treatments [7].

Our findings emphasize the need for studies investigating patient-reported outcomes. Two examples of included studies can demonstrate how patient-reported outcomes can be incorporated. First, Owusu et al. conducted a multicenter prospective cohort study including 123 patients with breast cancer aged 65 years and older, in which they found that three different performance-based measures, namely the Short Physical Performance Battery (SPPB), gait speed and grip strength, were highly predictive for functional decline among older patients with breast cancer. Besides these functional measures, the use of the Vulnerable Elders Survey (VES-13), a short self-report measure used to identity vulnerable older adults, also appeared to be a useful instrument to predict functional decline [32]. Second, in a prospective, quality of life study in older breast cancer survivors, Dura-Ferrandis et al. found that, besides comorbidity, physical and mental summary scores and socio-emotional factors such as disengagement and tangible support were significantly predictive for accelerated decline in cognitive functioning [33].

Predicting outcomes in older patients with breast cancer can enhance individual treatment decision making and provide better estimates on the risk of toxicity and other unwanted effects of treatment such as decline in function and quality of life. For this specific target population, it is key that the right set of outcomes are incorporated in breast cancer prediction tools, including competing risk, toxicity and patient-reported outcomes. Currently available prediction tools for breast cancer are not tailored to the older population, and solely predict disease related outcomes with the use of primarily tumor-related characteristics. Besides that, studies have shown that these tools are not able to accurately predict survival in older patients [34]. A first key attempt has recently been made with the Age Gap decision tool, a prognostic model for older patients with estrogen-positive, early breast cancer, that predicts survival outcomes, with incorporation of tumor characteristics, comorbidity, and ADL [35].

In this systematic review we found that, besides age and well-known disease-related characteristics, multiple variables that can be derived from a GA were predictive for all investigated outcomes. Even more, patient-reported outcomes were predicted by geriatric measures in over 80% of the included studies. Unfortunately, the assessment of geriatric parameters such as measures for physical function or cognitive decline and frailty screening are often left out in the work-up of older patients with cancer, whilst they are predictive of poor outcome in general oncology [36]. Our review supports the recommendation, as given in a recent consensus paper by SIOG, to perform GA in older patients with breast cancer [37]. Furthermore, as stated before, previous studies have shown that geriatric evaluation affects treatment decisions and can possibly lead to better treatment outcomes [15]. The examples previously given reinforce the additional benefits and usefulness of implementing a GA in the routine clinical care for older patients with breast cancer, providing clinicians with relevant information on geriatric domains that can help identifying those patients at risk of treatment toxicity or poor cognitive and functional outcome. Consequently, with an accurate prediction of all relevant outcomes, clinicians should be able to compose a more individualized treatment plan, with better understanding of the patient's wishes and goals of care.

Currently, our research group is working on the development of the PORTRET tool (Prediction of Outcome, Risk of toxicity and quality of life in older patients TREaTed for breast cancer), specified for older patients with early-stage breast cancer to predict the effect of adjuvant treatment on relevant outcomes. To achieve this, we will estimate survival and recurrence risks while considering the competing risk and present the risk of dying from other causes as a separate outcome. Predicting the risk of toxicity will be integrated in the tool, as well as relevant patient-reported outcomes concerning quality of life such as functional and cognitive decline. This systematic review supports our hypothesis that geriatric parameters can improve prediction of these outcomes.

4.1. Strengths and limitations

This systematic review is to our knowledge the first overview on prediction of outcomes specifically in older patients with breast cancer. We were able to identify a large number of studies and provide a summary of all available evidence. However, by specifying our search as such, we unintentionally may have lost information on predictive variables in studies that did not solely focus on breast cancer.

For this systematic review, we chose to include studies on patients with both curable and non-curable disease, although we understand that goals of care and the impact on the investigated outcomes may certainly differ for patients with early-stage versus advanced-stage breast cancer. However, stage of disease and curability of the cancer is a continuum, in which goals of care and the relevance of certain outcomes may change. We also believe that the relevance of patient-reported outcomes is not only affected by disease related factors, but also by comorbidity and other geriatric parameters, which are similarly present in both curable and non-curable older patients with breast cancer. Furthermore, we chose to only report predictors of outcomes that were statistically significant, and we did not report negative studies as this would result in an overload of information. The heterogeneity of studies made it impossible to perform formal meta-analyses of the data.

For this review, we did not intend to analyze the significant predictors in terms of importance or ranking. Nevertheless, it is relevant to state that the number of times certain variables are found to be predictive is highly dependable on the frequency with which they are investigated. For instance, age was one of the most found significant predictors, yet it is also one of the most included variables in prognostic analyses. Finally, it is possible that we may have missed some relevant articles but given the large number of included studies we believe that we were able to provide a comprehensive overview.

5. Conclusion

This study shows that various geriatric parameters that are derived from a GA can predict survival, toxicity, and patient-reported outcomes in older patients with breast cancer. This can be used in daily clinical practice to identify patients at risk of early mortality, high risk of treatment toxicity or poor functional outcome after treatment. Only a minority of studies in this population used these specific relevant outcome measures for older patients, showing the need for studies that are tailored to the older population. The findings of this systematic review serve as a background study to develop a unique prediction tool specifically designed for older patients with early breast cancer in which both disease-related outcomes and competing risk of death, risk of toxicity and patient-reported outcomes will be incorporated.

Funding

This work was supported by KWF Kankerbestrijding (grant number 11387).

Author contributions

Conceptualization: N.A. de Glas, J.E.A. Portielje, G.J. Liefers, E. Bastiaannet, W.G. van der Plas-Krijgsman.
Data curation: P. de Jong, A.Z. de Boer, W.G. van der Plas-Krijgsman, N.A. de Glas.
Formal analysis: W.G. van der Plas-Krijgsman, A.Z. de Boer, N.A. de Glas.
Funding acquisition: N.A. de Glas, G.J. Liefers, J.E.A. Portielje.

Methodology: N.A. de Glas, P. de Jong, W.G. van der Plas-Krijgsman.
Supervision: G.J. Liefers, J.E.A. Portielje, N.A. de Glas.
Writing - original draft: W.G. van der Plas-Krijgsman, A.Z. de Boer, N.A. de Glas.
Writing - review and editing: All authors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2021.01.008.

References

[1] DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. CA Cancer J Clin 2017;67(6):439–48. https://doi.org/10.3322/caac.21412.
[2] (IKNL) NCCO. Netherlands Cancer Registry (NKR) statistics; 2020.
[3] Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol 2018;19:e305–16.
[4] Battisti NML, McCartney A, Biganzoli L. The conundrum of the association of chemotherapy with survival outcomes among elderly patients with Curable Luminal breast cancer. JAMA Oncol 2020;6:1535–7.
[5] Derks MGM, Bastiaannet E, van de Water W, de Glas NA, Seynaeve C, Putter H, et al. Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial. Eur J Cancer (Oxford, England: 1990) 2018;99:1–8.
[6] de Boer AZ, van der Hulst HC, de Glas NA, Marang-van de Mheen PJ, Siesling S, de Munck L, et al. Impact of older age and comorbidity on locoregional and distant breast cancer recurrence: A large population-based study. Oncol 2020;25(1):e24–30. https://doi.org/10.1634/theoncologist.2019-0412.
[7] Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer–Alliance for clinical trials in oncology–international society of geriatric oncology position article. J Clin Oncol 2013;31:3711–8.
[8] Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. Oncologist 2012;17:1439–49.
[9] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–65.
[10] University of California San Francisco. ePrognosis; 2020.
[11] Schonberg MA, Li V, Marcantonio ER, Davis RB, McCarthy EP. Predicting mortality up to 14 years among community-dwelling adults aged 65 and older. J Am Geriatr Soc 2017;65:1310–5.
[12] Suemoto CK, Ueda P, Beltran-Sanchez H, Lebrao ML, Duarte YA, Wong R, et al. Development and validation of a 10-year mortality prediction model: meta-analysis of individual participant data from five cohorts of older adults in developed and developing countries. J Gerontol A Biol Sci Med Sci 2017;72:410–6.
[13] Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with Cancer. J Clin Oncol 2016;34:2366–71.
[14] Cancer & Aging Research Group (CARG). Chemo-Toxicity Calculator; 2020.
[15] Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - a systematic review. J Geriat Oncol 2018;9:430–40.
[16] Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011;103:1101–11.
[17] Clough-Gorr KM, Thwin SS, Stuck AE, Silliman RA. Examining five- and ten-year survival in older women with breast cancer using cancer-specific geriatric assessment. Eur J Cancer (Oxford, England: 1990) 2012;48:805–12.
[18] Kehl KL, Niu J, Chavez-MacGregor M, Giordano SH. Hospitalization by cytotoxic chemotherapy regimen among older women with stage IV breast cancer. Cancer 2018;124:4685–91.
[19] Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
[20] Bluethmann SM, Alfano CM, Clapp JD, Luta G, Small BJ, Hurria A, et al. Cognitive function and discontinuation of adjuvant hormonal therapy in older breast cancer survivors: CALGB 369901 (Alliance). Breast Cancer Res Treat 2017;165:677–86.
[21] Hurria A, Soto-Perez-de-Celis E, Allred JB, Cohen HJ, Arsenyan A, Ballman K, et al. Functional decline and resilience in older women receiving adjuvant chemotherapy for breast cancer. J Am Geriatr Soc 2019;67:920–7.
[22] Huang MH, Blackwood J, Godoshian M, Pfalzer L. Factors associated with self-reported falls, balance or walking difficulty in older survivors of breast, colorectal, lung, or prostate cancer: results from surveillance, epidemiology, and end results-medicare health outcomes survey linkage. PLoS One 2018;13:e0208573.
[23] Mandelblatt JS, Clapp JD, Luta G, Faul LA, Tallarico MD, McClendon TD, et al. Long-term trajectories of self-reported cognitive function in a cohort of older survivors of breast cancer: CALGB 369901 (Alliance). Cancer 2016;122:3555–63.
[24] DuMontier C, Clough-Gorr KM, Silliman RA, Stuck AE, Moser A. Health-related quality of life in a predictive model for mortality in older breast cancer survivors. J Am Geriatr Soc 2018;66:1115–22.
[25] Griffiths RI, Danese MD, Gleeson ML, Valderas JM. Epidemiology and outcomes of previously undiagnosed diabetes in older women with breast cancer: An observational cohort study based on SEER-Medicare. BMC Cancer 2012;12 (no pagination).
[26] Dasgupta P, Aitken JF, Pyke C, Baade PD. Competing mortality risks among women aged 50–79 years when diagnosed with invasive breast cancer, Queensland, 1997–2012. Breast (Edinburgh, Scotland) 2018;41:113–9.
[27] Traa MJ, Meijs CM, de Jongh MA, van der Borst EC, Roukema JA. Elderly women with breast cancer often die due to other causes regardless of primary endocrine therapy or primary surgical therapy. Breast 2011;20:365–9.
[28] Chapman JA, Pritchard KI, Goss PE, Ingle JN, Muss HB, Dent SF, et al. Competing risks of death in younger and older postmenopausal breast cancer patients. World J Clin Oncol 2014;5:1088–96.
[29] Hurria A, Soto-Perez-de-Celis E, Blanchard S, Burhenn P, Yeon CH, Yuan Y, et al. A phase II trial of older adults with metastatic breast cancer receiving nab-paclitaxel: melding the fields of geriatrics and oncology. Clin Breast Cancer 2019;19:89–96.
[30] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 2012;118:3377–86.
[31] Hamaker ME, Wildes TM, Rostoft S. Time to stop saying geriatric assessment is too time consuming. J Clin Oncol 2017;35:2871–4.
[32] Owusu C, Margevicius S, Schluchter M, Koroukian SM, Berger NA. Short physical performance battery, usual gait speed, grip strength and vulnerable elders survey each predict functional decline among older women with breast cancer. J Geriat Oncol 2017;8:356–62.
[33] Dura-Ferrandis E, Mandelblatt JS, Clapp J, Luta G, Faul L, Kimmick G, et al. Personality, coping, and social support as predictors of long-term quality-of-life trajectories in older breast cancer survivors: CALGB protocol 369901 (Alliance). Psycho-Oncol 2017;26(11):1914–21. https://doi.org/10.1002/pon.4404.
[34] de Glas NA, van de Water W, Engelhardt EG, Bastiaannet E, de Craen AJ, Kroep JR, et al. Validity of adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol 2014;15:722–9.
[35] Ward SE, Holmes GR, Morgan JL, Broggio JW, Collins K, Richards PD, et al. Bridging the age gap: a prognostic model that predicts survival and aids in primary treatment decisions for older women with oestrogen receptor-positive early breast cancer. BJS (Br J Surg) 2020;107:1625–32.
[36] van Deudekom FJ, Schimberg AS, Kallenberg MH, Slingerland M, van der Velden LA, Mooijaart SP. Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review. Oral Oncol 2017;64:27–36.
[37] Scotte F, Bossi P, Carola E, Cudennec T, Dielenseger P, Gomes F, et al. Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. Ann Oncol: Off J Eur Soc Med Oncol 2018;29:1718–26.