Development and validation of the PORTRET tool to predict recurrence, overall survival, and other-cause mortality in older patients with breast cancer in the Netherlands: a population-based study

Willeke G van der Plas-Krijgsman, Daniele Giardiello*, Hein Putter, Ewout W Steyerberg, Esther Bastiaannet, Anne M Stiggelbout, Simon P Mooijaart, Judith R Kroep, Johanneke E A Portielje, Gerrit-Jan Liefers, Nienke A de Glas*

Summary

Background Current prediction tools for breast cancer outcomes are not tailored to the older patient, in whom competing risk strongly influences treatment effects. We aimed to develop and validate a prediction tool for 5-year recurrence, overall mortality, and other-cause mortality for older patients (aged ≥65 years) with early invasive breast cancer and to estimate individualised expected benefits of adjuvant systemic treatment.

Methods We selected surgically treated patients with early invasive breast cancer (stage I–III) aged 65 years or older from the population-based FOCUS cohort in the Netherlands. We developed prediction models for 5-year recurrence, overall mortality, and other-cause mortality using cause-specific Cox proportional hazard models. External validation was performed in a Dutch Cancer registry cohort. Performance was evaluated with discrimination accuracy and calibration plots.

Findings We included 2744 female patients in the development cohort and 13631 female patients in the validation cohort. Median age was 74·8 years (range 65–98) in the development cohort and 76·0 years (70–101) in the validation cohort. 5-year follow-up was complete for more than 99% of all patients. We observed 343 and 1462 recurrences, and 831 and 3594 deaths, of which 586 and 2565 were without recurrence, in the development and validation cohort, respectively. The area under the receiver-operating-characteristic curve at 5 years in the external dataset was 0·76 (95% CI 0·75–0·76) for overall mortality, 0·76 (0·76–0·77) for recurrence, and 0·75 (0·74–0·75) for other-cause mortality.

Interpretation The PORTRET tool can accurately predict 5-year recurrence, overall mortality, and other-cause mortality in older patients with breast cancer. The tool can support shared decision making, especially since it provides individualised estimated benefits of adjuvant treatment.

Funding Dutch Cancer Foundation and ZonMw.

Lancet Healthy Longev 2021; 2: e704–11

See **Comment** page e679

For the Dutch translation of the abstract see **Online** for appendix 1

*Contributed equally

Department of Medical Oncology (W G van der Plas-Krijgsman MD, E Bastiaannet PhD, J R Kroep PhD, Prof J E A Portielje PhD, N A de Glas PhD), **Department of Biomedical Data Sciences** (D Giardiello MS, Prof H Putter PhD, Prof E W Steyerberg PhD, Prof A M Stiggelbout PhD), **Department of Surgery** (E Bastiaannet, G-J Liefers PhD), **and Department of Gerontology and Geriatrics** (S P Mooijaart PhD), **Leiden University Medical Center, Leiden, Netherlands; Division of Molecular Pathology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands** (D Giardiello); **Eurac Research, Institute for Biomedicine, Bolzano, Italy** (D Giardiello); **Department of Public Health, Erasmus MC, Rotterdam, Netherlands** (Prof E W Steyerberg)

Correspondence to: Dr Gerrit-Jan Liefers, Department of Surgery, Leiden University Medical Center, 2300 RC Leiden, Netherlands **g.j.liefers@lumc.nl**

Introduction

The number of older patients with breast cancer has strongly increased in recent years in high-income countries.[1] Despite improved treatment in the past decades, the survival of older patients has only marginally improved,[2] and previous studies showed that both breast cancer-specific and other-cause mortality increase with age.[3] Unfortunately, the evidence base for treatment strategies in older patients with breast cancer is still poor, as clinical trials often exclude older patients because of age restrictions or the presence of comorbid conditions.[4,5]

Among older patients, a large variation in general health status, concomitant diseases, and fitness exists, all of which can influence outcomes of breast cancer treatment. Compared with their younger counterparts, older patients have an increased risk of treatment toxic effects,[6,7] and experience less treatment benefit because of an increasing risk of dying from other causes than breast cancer, especially in patients with comorbidities.[8] Even more, other key endpoints such as quality of life might also be affected by choice of treatment.[9] Therefore, making an individualised decision for adjuvant treatment for older patients that weighs the potential treatment benefits and possible risks is essential, but it remains a recognised challenge for physicians.[10]

Prediction tools can aid in individualising treatment decision making. Yet the tools that are currently available do not accurately predict survival in the older age groups. For example, we have previously shown that the widely used Adjuvant! Online tool does not accurately predict all-cause survival and recurrence in older adults with breast cancer, and, moreover, the tool is no longer available online.[11] The PREDICT tool has been widely

For more on the **PREDICT tool** see https://breast.predict.nhs.uk/tool

Research in context

Evidence before this study

Two validation studies were performed by de Glas and colleagues, to evaluate the validity of Adjuvant! Online and the PREDICT tool in older patients with breast cancer, and they showed that both prediction tools were not able to accurately predict survival and recurrence, especially in the oldest patients (aged ≥85 years) and in patients with many comorbidities. Furthermore, our research group recently conducted a systematic review, in which we searched PubMed and Embase for all relevant articles on predictors for disease-related, toxicity, and patient-reported outcomes that were published up to Sept 1, 2019, using the keywords "breast cancer", "older patients", and "prediction". We concluded that gaeriatric parameters can predict all investigated outcomes in older patients with breast cancer.

Added value of this study

To our knowledge, this is the first prediction tool specifically designed for older patients with breast cancer that incorporates comorbidity, measures of physical functioning, and cognitive functioning as relevant predictors. The tool was internally and externally validated and showed good discriminative performance.

Implications of all the available evidence

With existing tools not being able to accurately predict survival and recurrence in older patients with breast cancer, the PORTRET tool does provide accurate predictions for 5-year overall survival, recurrence, and competing risk of death. The tool can support shared decision making, especially since it provides individualised estimated benefits of adjuvant treatment.

used in clinical practice to predict breast cancer outcomes. A previous validation study showed that the tool performed relatively well in older adults with regard to overall survival and recurrence, with a C-statistic of 0·73 (95% CI 0·70–0·75) for predicted 5-year overall survival, yet failed to make an accurate prediction for the oldest patients (aged ≥85 years) and subgroups of patients with many comorbidities.[12]

Previous studies have also shown that various geriatric parameters or measures of frailty, such as functional capacity, fall risk, cognitive impairment, and nutritional status, are strongly associated with mortality in older patients with cancer.[8] Thus, by adding comorbidity and other geriatric predictors, the prognostic accuracy for this target population could be enhanced, which might result in better individualised decision making and reducing both undertreatment and overtreatment.

The objective of this study was to develop and validate a new prediction tool for older patients with operable breast cancer who received locoregional treatment, that can predict recurrence (local and distant), overall mortality, and other-cause mortality. We also aim to estimate the individually expected benefits of adjuvant systemic treatment, with incorporation of comorbidity and various geriatric predictors.

Methods

Study design and participants

The PORTRET tool (from the prediction of outcome, risk of toxicity and quality of life in older patients treated for breast cancer [the PORTRET] study) was developed using data from the retrospective observational FOCUS cohort.[4,11–16] In this cohort, all consecutive patients aged 65 years or older with breast cancer who were diagnosed in the southwest region of the Netherlands between Jan 1, 1997, and Dec 31, 2004, were included. Trained personnel registered information from the medical charts on tumour characteristics, treatment, disease recurrence, comorbidity, and geriatric characteristics. Follow-up for recurrence was complete for all patients. Follow-up survival data were obtained by linkage of cancer registry data with municipal population registries and was complete up to Jan 1, 2013. Patients with primary breast cancer (stage I–III) who received surgery as primary treatment were included in the development cohort.

We validated the model in an external validation cohort from the Netherlands Cancer Registry, including all consecutive patients aged 70 years or older who were diagnosed with breast cancer in 2005–09, nationwide. The inclusion criteria for the validation cohort were also patients with primary breast cancer (stage I-III) who received surgery as primary treatment. Detailed information of both cohorts has been published elsewhere.[4,11–17] HER2 status was not yet systematically registered in the development cohort, but it was in the validation cohort.

Outcomes, follow-up, and predictors

Outcomes included breast cancer recurrence, overall mortality, and other-cause mortality, defined as mortality without recurrence. Breast cancer recurrence was defined as the first occurring recurrence (invasive, either locoregional or distant). For breast cancer recurrence and other-cause mortality, follow-up started at the diagnosis of the first primary breast cancer and ended at breast cancer recurrence or last date of follow-up (due to death, being lost to follow-up, or end of study), whichever occurred first. This implies that if a (local) recurrence occurred, this was an end of follow-up. For overall mortality, the follow-up ended at death for any cause. Follow-up was administratively censored at 5 years. Breast cancer survival was not available in this database as the Netherlands Cancer Registry does not include causes of death.

Since the PREDICT tool had relatively good performance in older adults, the predictors used in the

PREDICT tool were used as a basis for the PORTRET tool, and they included: age (as a continuous variable), tumour size (as a continuous variable), tumour grade (defined as 1, 2, or 3), nodal status (positive or negative), hormone-receptor status (retrieved from the pathology report, and recorded as positive if positive for either oestrogen or progesterone receptors; positivity was defined as immunohistochemically present in ≥10% of tumour cells), HER2 status (with 2+ or 3+ by immunohistochemistry defined as HER2 positive, and 0–1 defined as HER2 negative), Ki67 (defined as positive if Ki67 was immunohistochemically present in ≥10% of tumour cells, and negative if less than 10% of tumour cells had visible staining), and mode of detection (defined as symptomatic or screen-detected). Additionally, we included the absolute number of comorbidities according to the ICD-10 classification as a predictor. The full list of comorbidities that was counted in our database has been previously published elsewhere (appendix 2, p 6).[16] To further improve prediction, we collected geriatric predictors retrospectively from medical charts. These predictors included walking difficulties (defined as positive when walking difficulties or use of a walking stick was reported in the medical charts), dementia or cognitive impairment (defined as positive if a diagnosis of dementia or cognitive impairment was reported in the medical charts), polypharmacy (defined as positive if taking five or more types of drugs per day), and sensory deficits (defined as positive either if using a hearing aid or if poor vision was reported in the medical charts). Geriatric predictors were not recorded in the validation cohort.

Missing data were imputed ten times using a substantive model-compatible version of fully conditional specification.[18] This approach ensures that the predictors used in the imputation model are compatible with the cause-specific hazards models used for the analyses, assuming the missing data mechanism are missing at random. All predictors used in the analysis models were used for the imputation.

Model development and validation

Cause-specific Cox proportional hazard models were used to predict all outcomes. The resulting cause-specific hazard ratios (HRs) with the corresponding 95% CIs were pooled from the ten imputed data sets using the Rubin's rules.[18] The assumption of the proportional cause-specific hazard was graphically checked using Schoenfield residuals.

The full model comprised all 13 predictors and was only internally validated because of the presence of systematic missing values in the validation cohort. Therefore, a reduced model was developed for both internal and external validations,[19] and included the following predictors: age, tumour size, grade, nodal status, hormone-receptor status, HER2 status, and number of comorbidities. Subsequently, a submodel was developed, excluding comorbidity and geriatric predictors, to assess differences in discriminative performance compared with the full model in the development cohort.

Estimates of expected benefits of adjuvant treatment were calculated by combining risk functions for all outcomes with estimates of treatment effects from the Early Breast Cancer Trialists' Collaborative Group that provide specific subanalyses from randomised clinical trials in older patients.[20] The relative risk was assumed to be 0·70 for chemotherapy, 0·49 for endocrine therapy, and 0·84 for combined chemotherapy and endocrine therapy.

The performance of the models was evaluated for discrimination, to differentiate between patients who experienced the endpoint of interest and those who did not, and calibration, which measures the agreement between observed and predicted absolute risks. Discrimination was quantified by time-dependent area under the receiver operating characteristic curves (AUCs) based on inverse censoring probability weighting at 5 years. Values of AUCs close to 1 indicate good discriminative ability, while values close to 0·5 indicate poor discriminative ability. Calibration was assessed using calibration plots and the expected and observed ratio with the corresponding 95% CI. Discrimination and calibration were estimated in the development cohort and externally validated in the validation cohort.

To assess the validity of the tool in the oldest age groups, a post-hoc sensitivity analysis was performed by calculating the AUCs for patients aged 70–80 years and for patients aged 80 years and older.

See Online for appendix 2

Clinical utility

A decision curve analysis was performed to evaluate the clinical utility of the PORTRET tool, by calculating the net benefit for using the model at various risk threshold probabilities for 5-year recurrence, compared with the strategies of treat all or treat none. The strategy or model with the highest net benefit has a higher clinical utility.[21,22] Moreover, the distribution of the estimated individual benefit of treatment was summarised according to commonly accepted thresholds as defined in the Dutch guidelines, specifically whether the benefit of adjuvant treatment was less than 3% in absolute 10-year risk of mortality.

For more on the **thresholds from the Netherlands Breast Cancer guidelines** see https://richtlijnendatabase.nl/richtlijn/borstkanker/algemeen.html

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We included 2744 female patients in the development cohort and 13 631 female patients in the validation cohort. The number of events were more than sufficient to reliably develop and validate this new prediction model.[23,24] Median age was 74·8 years (range 65–98) in the development cohort and 76·0 years (70–101) in the

	Development cohort (n=2744)	Validation cohort (n=13 631)
Median age, years (range)	74·8 (65–98)	76·0 (70–101)
Tumour size		
Median size, cm (IQR)	2·0 (1·4–3·0)	1·9 (1·3–2·6)
Not known	208 (8%)	270 (2%)
TNM stage		
I	1001 (36%)	6043 (44%)
II	1346 (49%)	5947 (44%)
III	281 (10%)	1615 (12%)
Not known	116 (4%)	26 (<1%)
Grade		
I	383 (14%)	3263 (24%)
II	1067 (39%)	6479 (48%)
III	641 (23%)	3438 (25%)
Not known	653 (24%)	451 (3%)
Nodal status		
Negative	1685 (61%)	9215 (68%)
Positive	956 (35%)	4345 (32%)
Not known	103 (4%)	71 (1%)
ER/PR status		
ER/PR negative	444 (16%)	1886 (14%)
ER and/or PR positive	1905 (69%)	11552 (85%)
Not known	395 (14%)	193 (1%)
HER2-status		
Negative	1243 (45%)	11109 (81%)
Positive	342 (12%)	1201 (9%)
Not known	1159 (42%)	1321 (10%)
Ki-67 status		
Negative	1359 (50%)	NA
Positive	127 (5%)	NA
Not known	1258 (46%)	NA
Mode of detection		
Symptomatic	1461 (53%)	NA
Screen-detected	704 (26%)	NA
Not known	579 (21%)	NA
(Continued from previous column)		
Number of comorbidities		
Median (IQR)	2·0 (0·0–3·0)	1·0 (0·0–2·0)
0–1	1329 (48%)	4027 (30%)
2–4	1143 (42%)	2473 (18%)
5 or more	272 (10%)	112 (1%)
Not known	0	7019 (51%)
Sensory handicap		
No	2222 (81%)	NA
Yes	522 (19%)	NA
Difficulty walking		
No	2464 (90%)	NA
Yes	280 (10%)	NA
Dementia or cognitive impairment		
No	2637 (96%)	NA
Yes	107 (4%)	NA
Polypharmacy (>5 medications per day)		
No	2369 (86%)	NA
Yes	375 (14%)	NA
Adjuvant chemotherapy		
No	2599 (95%)	13402 (98%)
Yes	145 (5%)	229 (2%)
Adjuvant endocrine therapy		
No	1589 (58%)	7168 (53%)
Yes	1155 (42%)	6463 (47%)
Adjuvant radiotherapy		
No	1472 (54%)	6982 (51%)
Yes	1272 (46%)	6649 (49%)

Data are n (%), unless otherwise specified. All differences were significant. ER=oestrogen receptor. NA=not available. TNM=Tumour-Node-Metastases classification of malignant tumours. PR=progesterone receptor.

Table 1: **Baseline characteristics of the development cohort and validation cohort**

validation cohort (table 1). In the development cohort, 1415 (52%) patients had multiple comorbidities, sensory deficits were present in 522 (19%) patients, and 280 (10%) patients experienced walking difficulties. In the validation cohort, data on comorbidity was missing for 7019 (52%) patients. When excluding patients with missing values, 2585 (37%) patients had multiple comorbidities.

5-year follow-up was complete for nearly all patients (>99%) in the development and validation cohorts. The total number of events comprised 343 recurrences in the development cohort and 1462 recurrences in the validation cohort, 831 deaths in the development cohort and 3594 deaths in the validation cohort. 586 deaths in the development cohort and 2565 deaths in the validation cohort were without recurrence.

Of the 343 recurrences in the development cohort, 72 (21%) were locoregional and 260 (76%) were distant, with ten (3%) recurrences of unknown type. In the validation cohort, we observed a similar mix of type of recurrence, with 290 (20%) of 1462 recurrences being locoregional and 1172 (80%) being documented as distant recurrences.

The predictors with the largest effect size for recurrence were tumour size, grade, and nodal status (appendix 2, pp 7–8). Age was the strongest predictor for other-cause mortality (HR 3·5, 95% CI 3·3–3·6 for reduced model, appendix 2, p 8). The geriatric variables dementia or cognitive impairment, walking difficulties, and polypharmacy proved to be highly prognostic for other-cause mortality and overall mortality (appendix 2, p 7).

The estimates of treatment benefits at 5 years for chemotherapy, endocrine therapy, and combined systemic therapy are shown in the appendix 2 (p 2).

Internal validation of the full model showed that the AUCs were 0·77 (95% CI 0·75–0·79) for overall mortality, 0·74 (0·72–0·77) for recurrence, and 0·79 (0·77–0·81) for other-cause mortality (table 2). Internal validation of the reduced model showed AUCs of 0·76 (0·74–0·78) for overall mortality, 0·73 (0·70–0·76) for recurrence, and 0·78 (0·76–0·80) for other-cause mortality. External validation of the reduced model showed AUCs of 0·76 (0·75–0·76) for overall mortality, 0·76 (0·76–0·77) for recurrence, and 0·75 (0·74–0·75) for other-cause mortality (table 2). To assess differences in discriminative performance when excluding comorbidity and the geriatric predictors, a submodel was internally validated, which resulted in a 0·02 decrease in AUC for overall mortality (0·75 [0·73–0·77]) and other-cause mortality (0·77 [0·75–0·80]) compared with the full model (table 2).

Calibration plots are depicted in the figure. The expected–observed events ratio was 0·96 (95% CI 0·93–0·99) for overall mortality, 1·03 (0·98–1·09) for recurrence, and 1·13 (1·09–1·18) for other-cause mortality (table 2).

The PORTRET tool had clinical utility for a range of risk thresholds from 12·5% to 30% risk of 5-year breast cancer recurrence. Use of the PORTRET tool would result in additional clinical benefit and was superior to reference strategies of treat none or treat all (appendix 2, pp 3–5). The full model, including comorbidity and geriatric predictors, showed the highest net benefit compared with both the reduced model and the submodel (appendix 2, p 9).

As a sensitivity analysis we calculated the AUCs for the oldest age groups. The AUCs for patients aged 70–80 years were 0·72 (95% CI 0·71–0·72) for overall mortality, 0·77 (0·77–0·78) for recurrence, and 0·68 (0·67–0·68) for other-cause mortality. For patients aged 80 years and older, the AUCs were 0·68 (0·68–0·69) for overall mortality, 0·73 (0·72–0·73) for recurrence, and 0·67 (0·67–0·68) for other-cause mortality.

	Performance	Overall mortality	Recurrence	Other-cause mortality
Internal validation				
Full model*	AUC at 5 years (95% CI)	0·77 (0·75–0·79)	0·74 (0·72–0·77)	0·79 (0·77–0·81)
Reduced model†	AUC at 5 years (95% CI)	0·76 (0·74–0·78)	0·73 (0·70–0·76)	0·78 (0·76–0·80)
Submodel‡	AUC at 5 years (95% CI)	0·75 (0·73–0·77)	NA	0·77 (0·75–0·80)
External validation				
Reduced model	AUC at 5 years (95% CI)	0·76 (0·75–0·76)	0·76 (0·76–0·77)	0·75 (0·74–0·75)
Reduced model	Expected/observed ratio ratio (95% CI)	0·96 (0·93–0·99)	1·03 (0·98–1·09)	1·13 (1·09–1·18)

AUC=area under the curve. NA=not available. *The full model comprised all 13 predictors: age, tumour size, nodal status, grade, hormone-receptor status, HER2 status, Ki67, mode of detection, comorbidity, polypharmacy, difficulty walking, sensory handicap, and dementia. †The reduced model comprised seven predictors: age, tumour size, nodal status, grade, hormone receptor status, HER2 status, comorbidity. ‡The submodel was the full model excluding comorbidity and the geriatric predictors: polypharmacy, difficulty walking, sensory handicap, and dementia.

Table 2: **Discriminative performance of the PORTRET tool in the development and validation cohorts**

Discussion

In this study, we developed and validated the PORTRET tool to predict recurrence, overall mortality, and other-cause mortality in older patients with breast cancer, including individualised estimations of adjuvant treatment benefits. The tool showed good internal and external validation performance,[23] with improved accuracy in older patients compared with existing breast cancer prediction models, by incorporating comorbidity and geriatric predictors.

Several prediction tools have been developed for patients with early breast cancer. As previously stated, the widely used PREDICT tool was relatively accurate in predicting survival in older patients,[12] and it was therefore chosen as a starting point for the development of our tool. However, PREDICT could not accurately predict outcome for the oldest patients and patients with comorbidities; for example, it overestimated overall survival in patients over 75 years of age by 10–15%,[12] which might be due to the under-representation of the oldest patients in the development cohort. Moreover, comorbidity and other determinants of frailty were not incorporated as predictors in previous models. This means that the general risk prediction was based on chronological age and tumour characteristics, which is sufficient in a younger patient population that is more homogeneous than the older population in terms of general health and functioning. Yet, within the older population and its wide diversity in health status and concomitant diseases, a more individual risk estimation is needed to accurately weigh the expected benefits and potential harms of treatment, also considering the individual competing risk of death. The need to take geriatric factors and comorbidity into consideration was confirmed by our findings in the submodel analysis, in which the exclusion of comorbidity and geriatric predictors led to lower AUCs and lower clinical net benefit than did the full model (table 2, appendix 2, p 9). By including comorbidity and geriatric predictors, the PORTRET tool can further individualise risk estimation compared with PREDICT, and it can add benefit especially for predicting outcomes in the oldest patients and patients with multiple comorbidities.

The accurate prediction of the competing risk of death is a substantial aspect of the PORTRET tool. Although there are existing tools that estimate remaining life expectancy in older adults available such as Lee-index/ePrognosis, the major advantage of the PORTRET tool is that it combines this outcome with breast cancer-specific outcomes.[25] Competing risk increases with age[3] and is therefore an important factor to consider in the decision making for adjuvant treatment in older patients with breast cancer,[26] especially in patients with higher comorbidity count or with pre-stated vulnerability in terms of physical or cognitive functioning. Previous studies showed that both age and comorbidity are strong predictors of other-cause mortality,[27] which was also

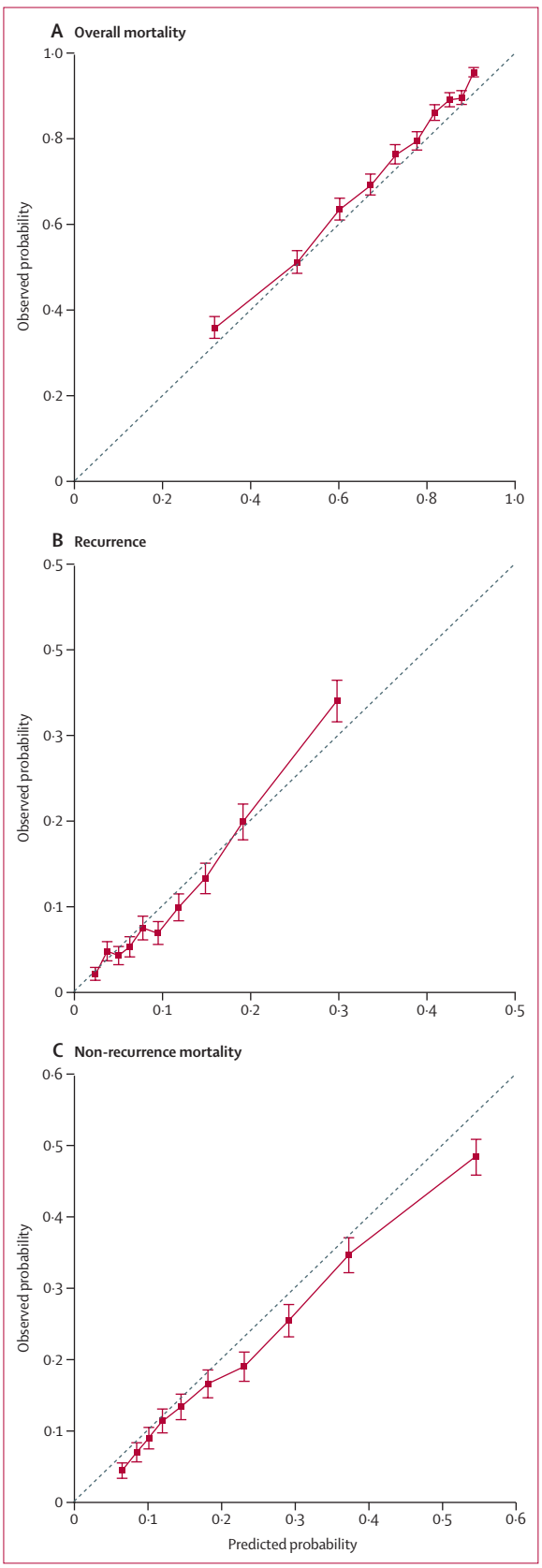

Figure: Observed versus predicted 5-year overall mortality (A), recurrence (B), and non-recurrence mortality (C)

confirmed in this study and in a recent systematic review that we conducted before the development of the tool.[28] By not considering competing risks, physicians might tend to overtreat a proportion of older patients, especially patients with lower risk tumours and a higher burden of comorbidity, who will not experience the desired treatment benefit because of a high probability of early death due to other causes. On the contrary, older patients with a lower burden of comorbidity and low competing risk currently might face undertreatment, when using models that provide predictions averaged for age alone and adjuvant systemic treatment is omitted despite longer life expectancy.

A major strength of this study was that we were able to develop the tool within a large, population-based cohort, with a high mean age of 76 years and a sample size of over 2700 patients. A large percentage of patients had multiple comorbidities (51%) and a fair proportion of patients had functional problems. The geriatric variables that are incorporated in the model were not collected through a formal comprehensive geriatric assessment, but they are easy to assess in daily clinical practice. We deliberately decided to use absolute numbers of comorbidities to enhance the feasibility of the tool. This is consistent with recent studies that confirm that the number of comorbidities is highly predictive of mortality in an older population with breast cancer.[16,29]

This study has some limitations. First, some details were more frequently missing in the development cohort, such as HER2 status. This is explained by changes in the Dutch Cancer Registry. This systematic pattern supported the missing at random assumption as needed for multiple imputation. Also, breast cancer mortality was not available as the Dutch Cancer registry does not include causes of death. We note that establishing causes of death is notoriously unreliable in older adults, which makes recurrence a more suitable endpoint for effects of breast cancer treatment.[30] Our definition of other-cause mortality might have underestimated the risk of dying from other causes, as all patients with recurrence could not die of other causes per definition. Yet, we have recently investigated mortality rates in patients with recurrences, and we showed that older patients with breast cancer recurrence almost always die of breast cancer, even if this was only a local recurrence (unpublished material; Anna Z de Boer). Further evaluation of the occurrence of other cause mortality after recurrence is necessary. In addition, the geriatric predictors were not available in the validation set, which might explain the slightly lower AUC.

The development and validation cohorts have structural differences, in terms of timeframe and region. However, treatment strategies in the Netherlands are nationally applied, with strong adherence to guidelines. There are no major differences in treatment strategy in the country, as was shown in a previous publication.[31] There was no possibility of duplicate entry between the two cohorts, as

only the first diagnosis of breast cancer allowed patients to enter the dataset. Furthermore, shifts in diagnostic methods (such as the determination of hormone-receptor status, HER2, and Ki67), and changes in clinical practice and prognosis might have occurred since the inclusion years of both cohorts, which would limit generalisability to current patients. However, previous studies have shown that both treatment strategies and prognosis improved only marginally in older patients.[32] Model implementation and further validation of the tool should be encouraged to evaluate its prognostic value in current clinical practice. We aim to keep updating the model with more recent data and longer follow-up of existing cohorts, and with additional geriatric predictors, especially when new data with regard to treatment effects and markers for older adults with breast cancer will become available. Our predictions can probably be more individualised if more such markers are included. The current version of the PORTET tool contains a relatively small set of key prognostic factors, and it is well interpretable.

The estimates of adjuvant treatment effects were derived from pooled randomised clinical trial data, for which additional modelling was needed. Randomised clinical trial data might lack external validity for older adults, as the included older patients are usually highly selected.[4] Furthermore, there are no data for different chemotherapy regimens, extended endocrine therapy, or trastuzumab in the older population available.[1] Nevertheless, with very limited data on systemic treatment effects in older patients,[1] this is currently the best available data. Our approach is similar to that used for Adjuvant! Online and PREDICT.[33,34] Ideally, a prediction model is developed within a large randomised controlled trial, including predictive analyses of heterogeneity of treatment effects within the same trial to obtain an individualised prediction.[35] We deliberately chose not to use available data from the development cohort because of the small sample size, and the substantial risk of bias by indication when estimating treatment effects in observational data.[36]

The available follow-up data on survival and recurrence enabled us to predict 5-year outcomes, but they were not sufficient to provide additional 10-year outcome predictions. Nevertheless, the predictive value for the given length of time is particularly relevant for the older patient with breast cancer, and we aim to update the model with longer follow-up in the future. We were unable to predict breast cancer-specific mortality because causes of death were unregistered in the development cohort, yet previous studies show that determining cancer-specific mortality is complex in older patients, with often a high frequency of competing events in relation to the cancer-specific events, especially when studying indolent cancer types such as hormone-receptor-positive breast cancer.[37]

Finally, while the percentage of patients who received adjuvant chemotherapy is low in both cohorts, it is similar to known percentages from Dutch clinical practice, where the administration of chemotherapy is substantially lower than in other European countries.[38]

The PORTRET tool accurately predicts 5-year overall survival and recurrence in older patients with breast cancer, and it can aid in shared decision making. Individualised estimates of expected benefits from adjuvant systemic treatments are now readily available, also regarding the impact of comorbidity and measures of frailty on the competing risk of other-cause mortality.

Contributors

NAdG, JEAP, and G-JL contributed to the study concept and design. DG, EWS, and HP contributed to the statistical analyses. DG, WGvdP-K, and NAdG contributed to the data analysis and interpretation. WGvdP-K and NAdG contributed to the manuscript preparation. All authors reviewed and approved the final manuscript. DG, NAdG, and WGvdP-K verified the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data will not be made available as these data belong to a third party (National Cancer Registry).

For the **current version of the PORTET tool** see https://bit.ly/3pd2BKn

Acknowledgments

This study was funded by the Dutch Cancer Foundation (KWF 2018–11387, Prediction of Outcome, Risk of Toxicity and quality of life in older patients TREaTed for breast cancer, the PORTRET study), and supported by ZonMw (grant number 843002623).

References

1 Biganzoli L, Battisti NML, Wildiers H, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). *Lancet Oncol* 2021; **22:** e327–40.

2 de Glas NA, Jonker JM, Bastiaannet E, et al. Impact of omission of surgery on survival of older patients with breast cancer. *Br J Surg* 2014; **101:** 1397–404.

3 van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA* 2012; **307:** 590–97.

4 van de Water W, Kiderlen M, Bastiaannet E, et al. External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer. *J Natl Cancer Inst* 2014; **106:** dju051.

5 Hurria A, Levit LA, Dale W, et al. Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology statement. *J Clin Oncol* 2015; **33:** 3826–33.

6 Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol* 2007; **25:** 3699–704.

7 Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011; **29:** 3457–65.

8 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.

9 Battisti NML, Reed MWR, Herbert E, et al. Bridging the age gap in breast cancer: impact of chemotherapy on quality of life in older women with early breast cancer. *Eur J Cancer* 2021; **144:** 269–80.

10 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:** 1535–37.

11 de Glas NA, van de Water W, Engelhardt EG, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. *Lancet Oncol* 2014; **15:** 722–29.

12 de Glas NA, Bastiaannet E, Engels CC, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. *Br J Cancer* 2016; **114:** 395–400.

13 de Glas NA, Kiderlen M, Bastiaannet E, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast Cancer Res Treat* 2013; **138:** 561–69.

14 Engels CC, Kiderlen M, Bastiaannet E, et al. The clinical value of HER-2 overexpression and PIK3CA mutations in the older breast cancer population: a FOCUS study analysis. *Breast Cancer Res Treat* 2016; **156:** 361–70.

15 Kiderlen M, de Glas NA, Bastiaannet E, et al. Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis. *Ann Oncol* 2013; **24:** 3011–16.

16 Kiderlen M, de Glas NA, Bastiaannet E, et al. Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study. *Breast Cancer Res Treat* 2014; **145:** 185–92.

17 de Boer AZ, van der Hulst HC, de Glas NA, et al. Impact of older age and comorbidity on locoregional and distant breast cancer recurrence: a large population-based study. *Oncologist* 2019; **25:** e24–30.

18 Bartlett JW, Taylor JM. Missing covariates in competing risks analysis. *Biostatistics* 2016; **17:** 751–63.

19 Fletcher Mercaldo S, Blume JD. Missing data and prediction: the pattern submodel. *Biostatistics* 2020; **21:** 236–52.

20 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365:** 1687–717.

21 Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; **26:** 565–74.

22 Vickers AJ, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* 2008; **8:** 53.

23 Steyerberg EW. Clinical prediction models: A practical approach to development, validation, and updating, 2nd edn. New York (USA): Springer, 2019.

24 Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020; **368:** m441.

25 Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006; **295:** 801–08.

26 Wildiers H, Mauer M, Pallis 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:** 3711–18.

27 Derks MGM, van de Velde CJH, Giardiello D, et al. Impact of comorbidities and age on cause-specific mortality in postmenopausal patients with breast cancer. *Oncologist* 2019; **24:** e467–74.

28 van der Plas-Krijgsman WG, de Boer AZ, de Jong P, et al. Predicting disease-related and patient-reported outcomes in older patients with breast cancer—a systematic review. *J Geriatr Oncol* 2021; **2:** 696-704.

29 de Boer AZ, Bastiaannet E, Putter H, et al. Prediction of other-cause mortality in older patients with breast cancer using comorbidity. *Cancers (Basel)* 2021; **13:** 1627.

30 Schaffar R, Rapiti E, Rachet B, Woods L. Accuracy of cause of death data routinely recorded in a population-based cancer registry: impact on cause-specific survival and validation using the Geneva Cancer Registry. *BMC Cancer* 2013; **13:** 609.

31 van de Water W, Bastiaannet E, Dekkers OM, et al. Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. *Br J Surg* 2012; **99:** 813–20.

32 de Glas N, Bastiaannet E, de Boer A, Siesling S, Liefers GJ, Portielje J. Improved survival of older patients with advanced breast cancer due to an increase in systemic treatments: a population-based study. *Breast Cancer Res Treat* 2019; **178:** 141–49.

33 Candido Dos Reis FJ, Wishart GC, Dicks EM, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. *Breast Cancer Res* 2017; **19:** 58.

34 Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001; **19:** 980–91.

35 Kent DM, van Klaveren D, Paulus JK, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement: explanation and elaboration. *Ann Intern Med* 2020; **172:** W1-25.

36 Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. *BMJ* 2016; **352:** i493.

37 de Glas NA, Kiderlen M, Vandenbroucke JP, et al. Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients. *J Natl Cancer Inst* 2015; **108:** djv366.

38 Derks MGM, Bastiaannet E, Kiderlen M, et al. Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. *Br J Cancer* 2018; **119:** 121–29.