BRÖSTCANCER FÖRBUNDET

Forskningsrapport

Huvudsökande:
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Frågeställning:
Kartläggning av kortsiktiga, allvarliga konsekvenser av cytostatika hos äldre samt hur man kan riskstratifiera bröstcancerpatienter inför val om cytostatika ska ges eller inte i botande situation.

Tre frågor till Christine:

Hur kan resultatet av er forskning hjälpa patienterna, rent konkret?
De ingående projekten syftar till att förbättra omhändertagandet av framför allt äldre patienter med bröstcancer, med fokus på riskstratifiering och avvägningen mellan behandlingens nytta och risken för allvarliga biverkningar. Vår publicerade studie visade att dödligheten under det första året efter bröstcancerdiagnos hos patienter ≥70 år var relativt låg. Resultaten talar för att cytostatikabehandling kan vara säker även för äldre patienter. Samtidigt krävs en individuell risk–nyttoanalys. En viktig del av forskningen är därför att utvärdera verktyg för riskbedömning. Vi har i en stor svensk kohort utvärderat prediktionsverktyget PREDICT för yngre patienter och visat att den senaste versionen har bättre träffsäkerhet än den tidigare. Vi validerar nu PREDICT specifikt för äldre patienter. Vi ska även utvärdera PORTRET, ett nytt lanserat prediktionsverktyg utvecklat för äldre patienter. Om verktyget visar god träffsäkerhet i en svensk population kan det implementeras i klinisk praxis och ge läkare och patienter ett bättre underlag för individualiserade behandlingsbeslut. Vi undersöker även om AI-baserad patologisk bedömning som förutsäger låg respektive hög risk för återfall, påverkar behandlingsval i klinisk praxis jämfört med dagens genexpressionsanalyser för patienter med intermediär risk.

Hur viktigt har stödet från Bröstcancerförbundet varit för er forskning?
Stödet har varit väldigt viktigt för att kunna samla in data och presentera data gällande patientnära forskning och som kan komma bröstcancerpatienter till nytta i klinisk praxis. Bidraget från Bröstcancerförbundet har möjliggjort för sökande att finansiera fortsatta forskningsprojekt efter disputation, där några projekt är fortsatt pågående och där resultat är att vänta framöver och andra slutförda och resultat presenterade.

Vad vill du hälsa alla Bröstcancerförbundets givare?
Sökande är väldigt tacksam för bidrag från Bröstcancerförbundets givare. Detta gör det möjligt att bedriva klinisk forskning med projekt som förväntas ge resultat som kan vara till nytta för bröstcancerpatienter, med hopp om att förbättra vården för dessa.

Christines publikationer finns att läsa på efterföljande sidor för dig som vill läsa mer.

Slutrapport för beviljade forskarmånader från Bröstcancerförbundet

Sökande beviljades forskningsmånader för att ges möjlighet att fortsätta bedriva olika forskningsprojekt inom bröstcancer. Anslaget beviljades 2023, men sökande har parallellt med pågående projekt haft lagstadgad frånvaro i form av föräldraledighet under september 2023-augusti 2024, varför progressen varit något fördröjd i de pågående projekten. Sökande blev beviljad förlängd rekvisitionstid till juni 2026. Nedan följer en slutrapport.

Titeln på de ingående projekten som sökande fick anslag för var ***Riskstratifiering inför behandlingsval med cytostatika samt allvarliga, kortsiktiga konsekvenser av cytostatika med fokus på äldre patienter med primär bröstcancer.***

Delprojekt 1 syftar till att undersöka den potentiella effekten av riskstratifiering av AI-verktyget Stratipath Breast gällande rekommendation om adjuvant cytostatika. Vidare vill vi bland annat studera jämförelsen av risk baserat på genexpressionsanalys Prosigna och Stratipath Breast. Projektet har fortskridit och studieorterna Västerås och Örebro inkluderar patienter i kliniken. Intensiv dialog har förts kontinuerligt mellan involverade parter i Region Jönköping för att kunna initiera metoden lokalt i Jönköping, i dagsläget pågår fortfarande diskussioner och därför har studiestart i vår region försenats påtagligt och processen pågår än. Under 2026 pågår planering för att även Linköping ska delta som studieort, när de implementerat metoden. Sökande är huvudansvarig och drivande i projektet och skrivit protokoll och etikansökningar samt haft kontakt med studieorter för studiestart. Sökande har genomfört ytterligare tilläggsansökan till etikprövingsmyndigheten för att få möjlighet att använda den senaste versionen av AI-metoden till studien, vilket godkänts. Under våren 2026 har ytterligare dialog förts i styrgruppen om att ändra flödet ytterligare så det anpassas efter den rapport från TLV som inkommit, vilket pågår. Ny tilläggsansökan kommer skrivas. Bidraget från Bröstcancerförbundet har använts för att finansiera sökandes forskningstid (lön inkl. sociala avgifter) för projektet, vilket innefattar att skriva protokoll, göra etikansökningar, ändringsansökningar, hålla i startmöten och uppföljningsmöten med berörd personal och utforma dokument som krävs inom ramen för studien, samt att föra intensiva dialoger på ledningsnivå för att implementera metoden regionalt. Projektet fortskrider och på lång sikt planeras insamling av data efter 5 och 10 år.

Delprojekt 2 syftar till att validera instrument PORTRET för riskstratifiering för äldre kvinnor med bröstcancer genom att jämföra predikterat med faktiskt utfall för patienter i en svensk databas (BCBaSe). Projektet syftar också till att validera det sedan längre tillbaka tillgängliga verktyget PREDICT som används i klinisk praxis i olika typer av bröstcancergrupper, varav äldre (≥70 år) är en subgrupp. PORTRET som studien ämnar validera lanserades först online slutet av 2025, vilket var senare än beräknat. Sökande har tillsammans med övriga medarbetare vidgat projektet till flera delprojekt som syftar att validera det för flera undergrupper av patienter. Sökande har först en lång dialog med utvecklare av PORTRET och har fått algoritmen tillgänglig och nu ska statistiker genomföra analyserna. Manus har förberetts så långt det går i väntan på resultaten. Vi har parallellt publicerat ett vetenskaplig artikel på det arbete som berör yngre patienter (≤40 år) för att undersöka hur PREDICT skattar deras utfall. Vi kommer också undersöka PREDICT och dess styrka att prediktera utfall i de med HER2+ samt ER-låg bröstcancer. Således kommer en stor valideringsstudie för äldre patienter gällande riskstratifieringsinstrument att genomföras för både PORTRET och PREDICT där projektet är under dataanalys och manusförfattning. Bidraget från Bröstcancerförbundet har använts för att finansiera sökandes forskningstid (lön inkl. sociala avgifter) för valideringsprojekten av PORTRET/PREDICT.

Delprojekt 3 syftar till att undersöka risken för allvarliga biverkningar, definierade som kortvarig dödlighet, hos äldre bröstcancerpatienter som behandlas med olika cytostatika samt den potentiella effekten av behandling relaterat till neoadjuvant eller adjuvant intention. Vi har arbetat intensivt med projektet och skrivet en vetenskaplig artikel som publicerats i tidskriften *Journal of Geriatric Oncology* 2025. Arbetet genererade en studiekohort på 4072 äldre bröstcancerpatienter som behandlats med neoadjuvant eller adjuvant kemoterapi. Intressant var att 1-årsmortaliteten var 1,5 % (63 av 4072 patienter), vilket är att betrakta som lågt. Riskfaktorer som var oberoende associerade med 1-årsmortalitet var högre ålder, större tumörstorlek, positivt körtelstatus, förekomst av trippelnegativ bröstcancer och användning av neoadjuvant jämfört med adjuvant kemoterapi. Inget samband hittades avseende typ av kemoterapi-regim och 1-årsmortalitet. Mediantiden till död var 7 månader. Dödsorsaken klassificerades huvudsakligen som bröstcancerrelaterad (neoadjuvant: 78 %, n=14; adjuvant: 49 %, n=22), följt av potentiella behandlingsrelaterade dödsfall (neoadjuvant: 11 %, n=2; adjuvant: 27 %, n=12).

Slutsatsen av studien var att korttidsmortaliteten under det första året efter bröstcancerdiagnos bland äldre (≥70 år) bröstcancerpatienter var relativt låg. Den högre risken bland patienter som behandlades med neoadjuvant kemoterapi kan tillskrivas ”störfaktorer” och behöver studeras vidare. Den låga risken för potentiell behandlingsrelaterad död tyder på att kemoterapi i denna aspekt anses vara säker och äldre patienter bör inte diskvalificeras för denna behandling. Vi hade som mål att inkludera även antalet sjukhusinläggningar i studien, men den variabeln har inte varit möjlig att få ut från databasen som vi använde. Eventuellt kommer föröka titta på detta i ett senare arbete. Bidraget från Bröstcancerförbundet har använts för att finansiera sökandes forskningstid (lön inkl. sociala avgifter) för att arbeta med projektet; tolka data, skriva manuskript, göra tabletter och figurer till arbetet, submittera och korrigera det slutliga arbetet till färdig publikation.

Sammanfattningsvis har bidraget från Bröstcancerförbundet möjliggjort för sökande att finansiera fortsatta forskningsprojekt efter disputation, där några projekt är fortsatt pågående och andra slutförda och accepterats i vetenskaplig tidskrift.

Bifogar publicerade artiklar:
-*Short-term mortality in older (≥70 years) patients with early breast cancer treated with neo-/adjuvant chemotherapy: A Swedish nationwide retrospective population-based study.*

-*PREDICT v3.0 outperforms v2.2 in young (25–40 years) breast cancer patients according to real-world data from a large Swedish population-based registry*

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Research Paper

Short-term mortality in older (≥70 years) patients with early breast cancer treated with neo-/adjuvant chemotherapy: A Swedish nationwide retrospective population-based study

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ABSTRACT

Introduction: There are substantial differences in the utilization of chemotherapy between younger and older patients, mainly due to the higher risk for adverse events among older patients. Short-term mortality after chemotherapy could reveal fatal side effects of treatment. The aim of this study was to explore the impact of treatment setting (neoadjuvant vs. adjuvant) and different chemotherapeutic agents on short-term mortality among older patients with early breast cancer.

Material and Methods: The population-based, national, research database BCBaSe 3.0 was used as a data source to identify older (≥70 years old) patients with stage I–III breast cancer, diagnosed between 2008 and 2019, who received neoadjuvant or adjuvant chemotherapy. Primary outcome was short-term mortality defined as death due to any cause within one year after breast cancer diagnosis. Multivariable logistic regression analysis was applied to investigate the impact of treatment setting and different chemotherapeutic agents (anthracycline-based vs. taxane-based vs. sequential anthracyclines and taxanes) on outcome, adjusted for potential confounders.

Results: In total, 4072 older patients were treated with neoadjuvant or adjuvant chemotherapy and median age was 73 years (quartile [Q]1–Q3; 71–75). The one-year mortality rate was 1.5 % (95 % confidence interval [CI]: 1.2–1.9 % [63 of 4072 patients]). Risk factors independently associated with one-year mortality were older age, larger tumor size, positive nodal status, presence of triple negative breast cancer, and use of neoadjuvant as compared to adjuvant chemotherapy (odds ratio [OR]: 2.00, 95 % CI: 1.04–3.84). No association was found between type of chemotherapeutic regimen and one-year mortality. Median time to death was 7 months (interquartile range: 5–9). The reason for death was mainly classified as breast cancer-related (neoadjuvant: 78 %, $n = 14$; adjuvant: 49 %, $n = 22$), followed by potential treatment-related deaths (neoadjuvant: 11 %, $n = 2$; adjuvant: 27 %, $n = 12$).

Discussion: The short-term mortality rate at first year after diagnosis among older (≥70 years) patients with breast cancer was relatively low. The higher risk among patients treated with neoadjuvant chemotherapy could be attributed to residual confounding and deserves further evaluation. The low risk of potential treatment-associated death suggests that chemotherapy in this respect is safe, and older patients should not be disqualified for this treatment.

1. Introduction

Older patients with early breast cancer have a comparable benefit from adjuvant chemotherapy as their younger counterparts [1–6] and do experience substantial clinical benefit from neoadjuvant chemotherapy as well [7,8]. However, underutilization of adjuvant systemic therapy in older patients has been observed [9–12], and these patients have a higher risk of treatment side effects that must be taken into

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consideration [4,13–15].

There are limited treatment guidelines for older patients, and age itself should not be used as the primary determinant [16]. Current therapeutic approaches regarding chemotherapy regimens for older patients with early breast cancer are mostly based on extrapolation of evidence from younger patients, since older patients are underrepresented in randomized trials [17–21]. According to international guidelines, adjuvant taxane-based chemotherapy regimens are the preferred option followed by anthracycline-based regimens, whereas sequential treatment is recommended only in fit, older patients with high-risk disease [22]. Additionally, although adjuvant therapy is the preferred option for most older patients, fit older patients could be considered for neoadjuvant strategies [22]. This highlights the complexity of treatment decision-making for chemotherapy use among older patients with breast cancer due to the limited evidence, the higher risk for side effects, and the competing risk of dying due to causes other than breast cancer. In addition, the guidelines recognize the paucity of evidence from randomized trials that lies behind recommendations on specific treatment regimens and settings [22].

In Sweden, sequential regimens containing anthracycline and taxanes have traditionally been the standard treatment approach for older patients, and the Swedish National Treatment Guidelines for breast cancer encourage similar treatment approaches between younger and older patients regarding neoadjuvant therapy [23]. As a result, Swedish real-world data on sequential chemotherapy regimens and treatment in neoadjuvant setting are available and can be used to expand the knowledge on chemotherapy use in older patients with breast cancer.

We, therefore, performed a nationwide, population-based cohort study to explore the risk of short-term mortality (defined as death due to any cause within one year) in older (≥70 years) patients with breast cancer treated with different chemotherapeutic regimens and in different settings (neoadjuvant vs. adjuvant). Short-term mortality was chosen as a proxy that could reflect fatal toxicity to chemotherapy.

2. Materials and Methods

2.1. Data Source and Study Population

The research database Breast Cancer Data Base Sweden (BCBaSe) 3.0 was used as data source in this nationwide, register-based, retrospective cohort study [24]. As described previously [25], BCBaSe 3.0 contains linked data from several Swedish national databases of interest such as the National Quality Registry for Breast Cancer (NKBC) and the Cause of Death Registry [26,27].

Patient-, tumor-, and treatment-related characteristics including information on chemotherapy regimens and setting were obtained from NKBC. The completeness of the NKBC is high, (>99 %), with a low proportion of missing data for most variables (<5 %) and high validity [28]. Type of chemotherapy was grouped as anthracycline-based, taxane-based, and sequential anthracycline- and taxane-based treatment. Patients who received both neoadjuvant and adjuvant chemotherapy were classified as patients in the neoadjuvant setting only. The Cause of Death Registry was used for the variables cause and date of death, whereas The International Statistical Classification of Diseases and Related Health Problems (ICD) coding system was used to define and to characterize the cause of death [27,29].

A flow chart of the present study cohort is illustrated in Fig. 1, showing inclusion and exclusion criteria. We included patients (men/women) who were ≥70 years old, diagnosed with primary (stage I–III) breast cancer, treated with neoadjuvant or adjuvant chemotherapy between 2008 and 2019 (n = 4074). Two patients had missing survival data, generating a final study population of 4072 patients for further analysis.

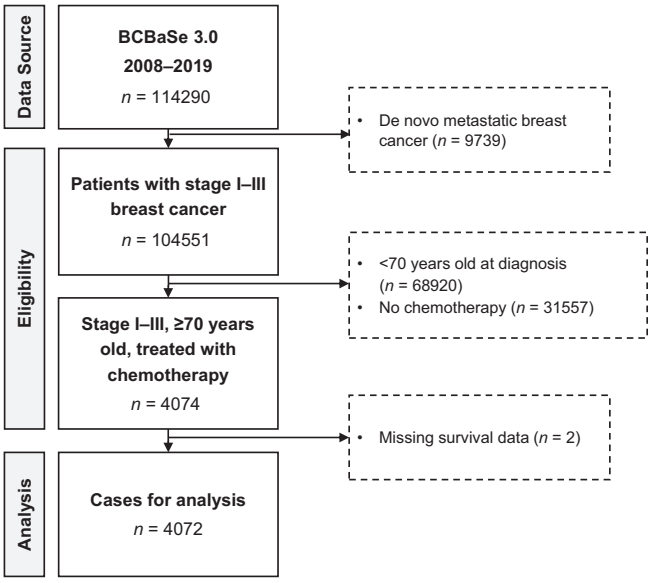

Fig. 1. Flow chart of study population.
Abbreviations: BCBaSe, Breast Cancer Data Base Sweden

2.2. Study Endpoints and Definitions

The primary endpoint was short-term mortality defined as death due to any cause within one year from breast cancer diagnosis. The minimum follow-up required for inclusion was 28 days. Follow-up time of a patient was either the date of an event, or the date of last of follow-up within this study.

Estrogen receptor (ER)- and progesterone receptor (PR) positivity was defined according to Swedish guidelines as ER/PR ≥10 %. Human epidermal growth factor receptor 2 (HER2) positivity was defined as HER2 3+ (as assessed by immunohistochemistry) or HER2 2+ and amplification of *HER2* by in situ hybridization, the rest were considered HER2-negative [30]. Breast cancer subtype was categorized as luminal (ER-positive/HER2-negative), HER2-positive (irrespective of ER status), and triple negative breast cancer (TNBC, defined as ER/PR/HER2-negative). Tumor grade was defined according to the Nottingham histological grade (NHG) system [30,31]. Breast cancer stage (I–III) was applied according to the American Joint Committee on Cancer (AJCC) 8th edition [32].

2.3. Ethics

BCBaSe is a research database approved by the regional ethics board in Stockholm (reference number: 2019-02610). For this study, an additional approval was obtained (reference number: 2024-01947-02). As BCBaSe is a registry-based data source, the Swedish Ethical Review Authority waived the need for informed consent.

2.4. Statistical Analyses

Numbers and percentages, as well as median and interquartile range (IQR), were used as descriptive statistics for categorical and continuous variables, respectively. The outcome short-term mortality was analyzed as dichotomous variables (death due to any cause vs. not). For analysis of association between different characteristics and outcome of interest, Chi2-test was used for categorial and Mann-Whitney *U*-test for continuous variables, respectively.

Multivariable logistic regression model was applied to investigate the impact of different chemotherapy regimens (anthracycline-based vs. taxane-based vs. sequential anthracycline- and taxane-based) as well as the treatment setting (adjuvant vs. neoadjuvant) on outcome adjusted

Table 1
Patient- and tumor-related characteristics between patients with breast cancer that died within one year from diagnosis compared to patients alive at year one.

Characteristics	All patients *n* = 4072 *n* (%)	Death at one year *n* = 63 *n* (%)	Alive at one year *n* = 4009 *n* (%)	*p*-value
Age at diagnosis, median (Q1-Q3)	73 (71–75)	74 (72–78)	73 (71–75)	0.01
Age at diagnosis, in categories				
70–75	3079 (75.6)	34 (1.1)	3045 (98.9)	<0.001
76–80	823 (20.2)	20 (2.4)	803 (97.6)	
>80	170 (4.2)	9 (5.3)	161 (94.7)	
Year of diagnosis				
2008–2011	485 (11.9)	7 (1.4)	478 (98.6)	0.92
2012–2015	1446 (35.5)	22 (1.5)	1424 (98.5)	
2016–2019	2141 (52.6)	34 (1.6)	2017 (98.4)	
Sex				
Male	47 (1.2)	1 (2.1)	46 (97.9)	0.52
Female	4025 (98.8)	62 (1.5)	3963 (98.5)	
Region				
Northern	420 (10.3)	4 (1.0)	416 (99.0)	0.46
Stockholm–Gotland	974 (23.9)	15 (1.5)	959 (98.5)	
Mid-Sweden	703 (17.3)	11 (1.6)	692 (98.4)	
South	620 (15.2)	11 (1.8)	609 (98.2)	
Southeast	588 (14.4)	5 (0.9)	583 (99.1)	
Western	759 (18.6)	16 (2.1)	743 (97.9)	
Stage at diagnosis				0.20
Stage I	1191 (29.2)	17 (1.4)	1174 (98.6)	
Stage II	1470 (36.1)	22 (1.5)	1448 (98.5)	
Stage III	1411 (34.7)	24 (1.7)	1387 (98.3)	
T status*				
T1	2024 (49.7)	19 (0.9)	2005 (99.1)	0.002
T2–3	2048 (50.3)	44 (2.1)	2004 (97.9)	
N status*				
N0	1902 (46.7)	17 (0.9)	1885 (99.1)	0.006
N1–3	2065 (50.7)	40 (1.9)	2025 (98.1)	
Missing	105	6	99	
Grade (NHG)				
I	149 (3.7)	2 (1.3)	147 (98.7)	<0.001
II	1427 (35.0)	6 (0.4)	1421 (99.6)	
III	2057 (50.5)	41 (2.0)	2016 (98.0)	
Missing	439	14	425	
Molecular subtype				
Luminal	1883 (46.2)	17 (0.9)	1866 (99.1)	<0.001
HER2-positive	1246 (30.6)	17 (1.4)	1229 (98.6)	
TNBC	834 (20.5)	29 (3.5)	805 (96.5)	
Missing	109	0	109	
Type of surgery in breast				
Breast conserving	1857 (45.7)	16 (0.9)	1843 (99.1)	<0.001
Mastectomy	2191 (53.8)	46 (2.1)	2145 (97.9)	
Missing	24	1	23	
Type of surgery in axilla				
Sentinel node biopsy	2011 (49.4)	18 (0.9)	1993 (99.1)	<0.001
Axillary clearance	1966 (49.4)	41 (2.1)	1925 (97.9)	
Missing	95	4	91	
Endocrine therapy				
Yes	2674 (65.7)	9 (0.3)	2665 (99.7)	<0.001
No	1398 (34.3)	54 (3.8)	1344 (96.2)	
Radiotherapy				
No	935 (23.0)	41 (4.4)	894 (95.6)	<0.001
Breast only	1365 (33.5)	4 (0.3)	1361 (99.7)	
Breast and regional lymph nodes	1772 (43.5)	18 (1.0)	1754 (99.0)	
Trastuzumab (neoadjuvant/adjuvant)				
No	2804 (68.9)	50 (1.8)	2754 (98.2)	0.006
Yes	1220 (30.0)	8 (0.7)	1212 (99.3)	
Missing	48	5	43	
Chemotherapy, setting				
Neoadjuvant	651 (16.0)	18 (2.8)	633 (97.2)	0.006
Adjuvant	3421 (84.0)	45 (1.3)	3376 (98.7)	
Chemotherapy, type**				
Anthracycline-based	1398 (34.3)	27 (1.9)	1371 (98.1)	0.18
Taxane-based	587 (14.4)	11 (1.9)	576 (98.1)	
Sequential anthracycline- and taxane-based	2087 (51.3)	25 (1.2)	2062 (98.8)	

T1; tumor size ≤20 mm, T2; tumor size >20 mm.
N0; node-negative, N1–3; node-positive.
Abbreviations: HER2, human epidermal growth factor receptor 2; NHG, Nottingham histological grade; Q, quartile; TNBC, triple negative breast cancer.
* clinical (c) and pathological (p) TN status in the neoadjuvant and adjuvant settings, respectively.
** Distribution of treatment regimens; neoadjuvant setting: anthracycline-based 19.5 % (n = 127/651), taxane-based 12.6 % (n = 82/651) and sequential chemotherapy 67.9 % (n = 442/651); adjuvant setting: anthracycline-based 37.2 % (n = 1273/3421), taxane-based 14.8 % (n = 505/3421) and sequential chemotherapy 48.1 % (n = 1645/3421). Difference in treatment distribution according to treatment setting; $p < 0.001$.

for potential confounders. We initially chose covariates in the model based on the statistically significance in bivariate analyses (age, tumor size [T] status, nodal [N] status, histological grade, molecular subtype, type of breast surgery, type of axillary surgery, endocrine therapy, and radiotherapy) as well as target variables of interest (chemotherapy setting and type). We used the clinical (c) and pathological (p) T and N status for the neoadjuvant and adjuvant setting, respectively. Patients with missing data (119 out of 4072) were excluded from the multivariable analysis. To avoid multicollinearity, we excluded the following variables: initial tumor stage (associated with T and N status), type of axillary surgery (associated with N status), endocrine therapy and trastuzumab treatment (associated with molecular subtype), radiotherapy (associated with type of breast surgery), and grade (>10 % missing values). The results were presented with odds ratios (ORs) and corresponding 95 % confidence interval (CI).

Reasons for death were presented according to the ICD coding system and were further categorized as breast cancer-related, potential treatment-related, other malignant diseases, and other causes unrelated to cancer or treatment. Median (IQR) time from diagnosis (months) to death was also calculated. A p-value <0.05 was considered statistically significant in all statistical analyses. All statistical analyses were performed with IBM SPSS Statistics, Version 28.0.0.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study Population

In total, data from 114290 patients were initially retrieved from the BCBaSe 3.0. Of these, 4074 patients had stage I–III disease, were ≥70 years old, and were treated with chemotherapy (Fig. 1). The chemotherapy utilization rate was approximately 11 % (4074 out of 35631 patients). After excluding two patients with missing survival data, 4072 patients were included in the study cohort. Patient- and tumor-related characteristics are presented in Table 1.

Median age at diagnosis was 73 years (Q1–Q3; 71–75) and the median follow-up time was 49 months (IQR: 28–80 months). The proportion of patients in the study cohort (stage I–III disease, ≥70 years old, treated with chemotherapy) increased over time when compared to all patients ≥70 years old in each time period from the database (year of diagnosis 2008–2011; 5.6 % [485 out of 8623], 2012–2015; 11.6 % [1446 out of 12506], and 2016–2019; 14.8 % [2141 out of 14502]). There were similar proportions regarding tumor size and nodal status with approximately 50 % in each category (T1; 50 % [n = 2024], T2–3; 50 % [n = 2048], N0; 47 % [n = 1902], and N1–3; 51 % [n = 2065]). Stage at diagnosis was evenly distributed (stage I [29 %, n = 1191], stage II [36 %, n = 1470] and stage III [35 %, n = 1411]). The molecular subtype proportions were 46 % luminal (n = 1883), 31 % HER2-positive (n = 1246), and 21 % TNBC (n = 834).

3.2. Chemotherapy Regimens and Treatment Setting

As presented in Table 1, 16 % (n = 651) of the patients received neoadjuvant and 84 % (n = 3421) adjuvant chemotherapy. Sequential chemotherapy was prescribed in 51 % (n = 2087), anthracycline-based therapy in 34 % (n = 1398), and taxane-based in 14 % (n = 587) of the study cohort. The distribution of different treatment regimens in the neoadjuvant (n = 651) and adjuvant setting (n = 3421) were as follows; neoadjuvant setting: anthracycline-based 20 % (n = 127), taxane-based 13 % (n = 82) and sequential chemotherapy 68 % (n = 442); adjuvant setting: anthracycline-based 37 % (n = 1273), taxane-based 15 % (n = 505) and sequential chemotherapy 48 % (n = 1645).

3.3. Prognostic Factors for Short-term Mortality

In total, 63 out of 4072 patients died within one year from breast cancer diagnosis resulting in an overall mortality rate at one year of 1.5 % (95 % CI: 1.2–1.9 %). In bivariate analyses, short-term mortality was associated with older age, higher T and N status, higher histological grade, triple-negative subtype, mastectomy, axillary clearance, no use of adjuvant endocrine therapy, radiotherapy or trastuzumab, and use of neoadjuvant chemotherapy (Table 1). In the multivariable logistic regression analysis (Table 2), the following parameters were independently associated with short-term mortality; age at diagnosis (OR: 1.10, 95 % CI: 1.02–1.18), tumor size (T2–3 vs. T1; OR: 1.94 95 % CI: 1.05–3.59), nodal status (N1–3 vs. N0; OR: 1.98, 95 % CI: 1.08–3.66), triple-negative subtype (TNBC vs. luminal; OR: 4.21, 95 % CI: 2.18–8.10), and the use of neoadjuvant chemotherapy (neoadjuvant vs. adjuvant; OR: 2.00, 95 % CI: 1.04–3.84). Type of chemotherapy regimen was not associated with short-term mortality (sequential anthracycline- and taxane-based vs. anthracycline-based [OR: 0.58, 95 % CI: 0.32–1.05], taxane-based vs. anthracycline-based [OR: 0.67, 95 % CI: 0.29–1.52]).

Table 2
Multivariable logistic regression analysis for death within one year after breast cancer diagnosis among patients aged ≥70 years old treated with chemotherapy.

Characteristics*	OR	95 % CI
Age at diagnosis	1.10	1.02–1.18
T status**		
T1	1	
T2–3	1.94	1.05–3.59
N status**		
N0	1	
N1–3	1.98	1.08–3.66
Molecular subtype		
Luminal	1	
HER2-positive	1.50	0.71–3.18
TNBC	4.21	2.18–8.10
Type of surgery in breast		
Breast conserving	1	
Mastectomy	1.39	0.73–2.63
Chemotherapy, setting		
Adjuvant	1	
Neoadjuvant	2.00	1.04–3.84
Chemotherapy, type		
Anthracycline-based	1	
Taxane-based	0.67	0.29–1.52
Sequential anthracycline- and taxane-based	0.58	0.32–1.05

T1; tumor size ≤20 mm, T2; tumor size >20 mm.
N0; node-negative, N1–3; node-positive.
Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; OR, odds ratio; TNBC, triple negative breast cancer.
* According to complete case approach; 199 patients were excluded due to missing values; 3873 patients were included in the multivariable model.
** clinical (c) and pathological (p) TN status in the neoadjuvant and adjuvant settings, respectively.

3.4. Time to and Reasons for Death within One Year from Diagnosis

The time from breast cancer diagnosis to death is illustrated in Fig. 2. Median time until death among those who died within one year was 7 months (IQR: 5–9) in the whole cohort (n = 63), while it was 7 months (IQR: 4–9 months) in the neoadjuvant setting (n = 18) and 8 months (IQR: 6–10 months) in the adjuvant setting (n = 45).

The reasons for death among the 63 patients that died within one year were defined according to the ICD coding system (Appendix A. Supplementary data, Table A1). We categorized the causes into breast cancer-related (57 %, n = 36), potential treatment-related (22 %, n = 14), other malignant diseases (8 %, n = 5), and other causes unrelated to cancer or treatment (13 %, n = 8). Among those who received neoadjuvant chemotherapy, the most common cause of death was breast cancer (78 %; 14 of 18 deaths), followed by potential treatment-related (11 %; 2 of 18 deaths), and other causes unrelated to cancer or treatment (11 %; 2 of 18 deaths) (Table 3). The corresponding numbers among

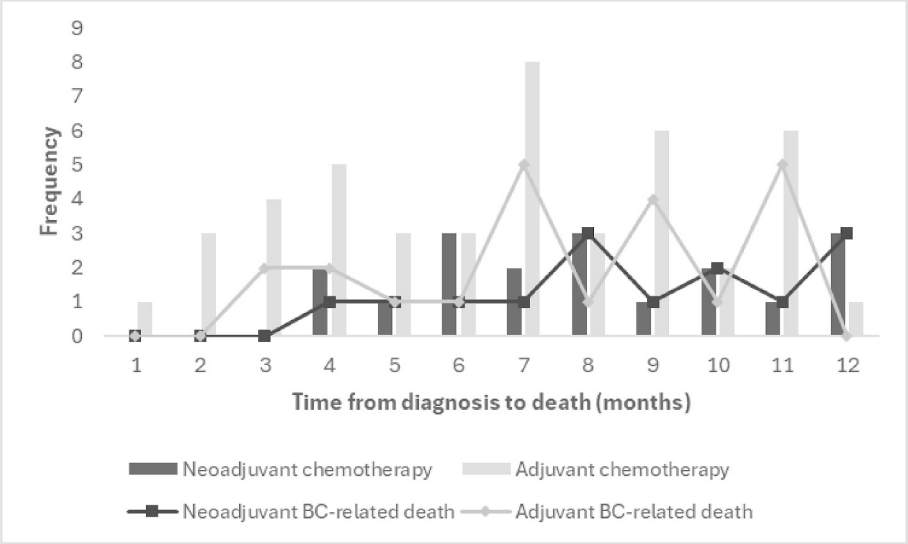

Fig. 2. Schematic distribution of time to death within one year from diagnosis for older patients in the neoadjuvant ($n = 18$) and adjuvant setting ($n = 45$), and proportion of breast cancer-related deaths.
Abbreviations: BC, breast cancer

Table 3
Proportion of causes of death between patients treated with neoadjuvant and adjuvant chemotherapy.

Reason for death within one year from diagnosis	Neoadjuvant $n = 18$ n (%)	Adjuvant $n = 45$ n (%)
Breast cancer-related	14 (77.8)	22 (48.9)
Potential treatment-related	2 (11.1)	12 (26.7)
Other malignant diseases	–	5 (11.1)
Other causes unrelated to cancer or treatment	2 (11.1)	6 (13.3)
In total	18 (28.6)	45 (71.4)

those who received adjuvant chemotherapy were breast cancer-related reasons (49 %; 22 of 45 deaths), potential treatment-related (27 %; 12 of 45 deaths), other causes unrelated to cancer or treatment (13 %; 6 of 45 deaths), and other malignant diseases (11 %; 5 of 45 deaths) (Table 3).

4. Discussion

In this study of patients with breast cancer aged ≥70 years treated with neoadjuvant or adjuvant chemotherapy, the short-term mortality rate within the first year after diagnosis was 1.5 %, mostly attributed to breast cancer-related deaths. Apart from patient age and other well-known prognostic clinicopathological parameters, the use of chemotherapy in the neoadjuvant setting was associated with an increased risk of short-term mortality, whereas type of chemotherapy regimen did not seem to impact the risk. The increasing trend in the use of chemotherapy among older patients over time suggests a progressively positive treatment approach. Despite less selective use the one-year mortality rate remained consistent across each time period.

The overall mortality of 1.5 % during the first year after breast cancer diagnosis in our study seems to be rather low in comparison to a population-based study from the United States where the mortality rate was 2.9 % [33]. According to their results, the risk of death in a matched control group was 1.3 %. The difference in mortality rates between our cohort and theirs cannot be explained by differences in patient and tumor characteristics as our patient cohort was generally older but had similar stage and tumor biology. However, the inclusion period differs by one decade and the differences in mortality rates may reflect improvements in cancer care over time. Both studies identified similar variables as predictors for higher short-term mortality: age, advanced stage, and more aggressive tumor biology. In fact, Rosenstock et al. showed a steady increase in mortality by age and almost a fourfold increase in OR for those >80 years old [33]. These and our results reflect the fact that the older patient population should not be regarded as a homogeneous group. Age alone does not make the population heterogeneous, but there is an assumed association between age in older patients and increased comorbidities, sensitivity to toxicities, and impaired functional status. Therefore, each additional year of age seems to have a more notable impact on outcomes in older patients. In total, we both found similar distribution of breast cancer and non-breast cancer related deaths, with nearly 60 % of deaths attributed to breast cancer, however we report fewer events (49 %) in the adjuvant setting. Although miscoding of the cause of death cannot be entirely ruled out, the frequency of breast cancer-related deaths within one year of diagnosis likely reflects a patient selection where older patients might more often be selected for neoadjuvant or adjuvant chemotherapy only if their disease is highly aggressive. In comparison, younger patients are offered neo/adjuvant chemotherapy for less advanced stages and their risk of breast cancer-related death during the first year is considered low. Notably, even if the chemotherapy utilization rate in our cohort seems rather low (11 %), and undertreatment of older patients is regarded as an issue [9–12], a substantial proportion of patients receiving chemotherapy in our study cohort had less advanced and aggressive disease, thus implying a changing pattern in patient selection for chemotherapy among older patients over time.

The use of neoadjuvant chemotherapy treatment appears to be increasing in older patients, especially among those with HER2-positive or TNBC, as well as in more advanced disease [34]. However, treatment-related toxicities, dose reduction, and early treatment discontinuation in the neoadjuvant setting are more frequently reported in older versus younger patients [35]. Interestingly, we demonstrated a doubled risk of short-term mortality among patients treated in neoadjuvant compared to adjuvant setting. This result could support the recommendation from international guidelines to carefully select only fit older patients for this approach [22]. However, the reason behind our observation is not easily addressed. Despite the adjustments made in our analyses, the retrospective study design precludes any claim of causality, and it cannot be ruled out that the association between neoadjuvant setting and short-term mortality could be attributed to residual confounding. The numerical difference in cause of death between the two treatment settings,

with more patients dying due to breast cancer in the neoadjuvant compared to in the adjuvant setting, partly supports the hypothesis of residual confounding since patients in the neoadjuvant setting might be those with more aggressive disease leading to higher numbers of breast cancer-related deaths. Another plausible explanation could be that patients in the neoadjuvant setting receive more intense chemotherapy regimens (longer duration and dose-dense strategies). Then we would expect a shorter median time to death in neoadjuvant compared to adjuvant setting as deaths related to chemotherapy are expected during or shortly after chemotherapy. This was, however, not the case as similar time periods were observed. The observation should, however, be interpreted carefully due to the small number of events in the analysis. Even though there was a significant difference regarding treatment regimens between those in the neoadjuvant and adjuvant setting, treatment regimen differences did not explain the mortality differences when analyzed by Cox regression. Whether differences in chemotherapy doses could lie behind the imbalance in deaths between patients in different settings cannot be answered by the current study due to lack of data on this variable in our cohort.

Regarding type of treatment, international guidelines recommend sequential chemotherapy treatment only for highly selected, fit older patients with very high-risk disease [22]. The rationale behind this recommendation is the lack of data on sequential treatment among older patients, as these patients were less commonly included in trials of sequential treatment [36]. According to the latest meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, early breast cancer chemotherapy regimens containing both anthracycline and taxane (in sequence or in combination) are more effective than anthracycline-free regimens [36]. The reported benefit was seen regardless of age, but the proportion of older women participating in the included trials was low, with a median participant age of 53 years and with more than half of the primary studies having upper age limits of 70 years. Rosenstock et al. found no association between anthracycline-based therapy and one-year mortality but had no data on taxanes [33]. Interestingly, we found type of chemotherapy regimen not to be associated with short-term mortality. On the contrary, we observed a trend towards a lower mortality for the sequential regimen as compared to the anthracycline-only regimen, supporting the use of sequential regimens for selected older patients. Moreover, the rate of potentially treatment-related mortality was generally low (11 % and 27 % in the neoadjuvant and adjuvant settings, respectively), reflecting a large proportion of patients with high-risk breast cancer disease among those given chemotherapy, especially in the neoadjuvant setting.

Strengths of this study are the population-based nature of the data source, with validated variables, including type of chemotherapy regimen, and a large number of patients [28,37]. Limitations to consider are the lack of information on comorbidity and on the duration and doses of chemotherapy that precludes deeper analyses of factors associated with higher short-term mortality among patients receiving neoadjuvant chemotherapy. Moreover, the risk of miscoding of the cause of death within one year should be kept in mind when interpreting the results [38–40]. Finally, we utilized short-term mortality as a proxy for fatal toxicity due to chemotherapy, thus excluding clinical situations such as prolonged hospitalizations and organ-specific toxicities with long-term sequelae that could impact patients' quality of life and influence the decision-making process regarding chemotherapy in older patients. Using geriatric assessments can predict treatment toxicity and should guide treatment decisions [41], while their effect on short-term mortality yet remains unclear.

5. Conclusions

In conclusion, we demonstrated a relatively low risk of short-term mortality of 1.5 % within the first year among older patients with breast cancer treated with chemotherapy. The risk of potential treatment-associated death was low, suggesting that older patients should not be disqualified for chemotherapy treatment. Choice of sequential treatment with anthracyclines and taxanes did not seem to impact short-term mortality, and this treatment approach could be suitable for selected older patients; the effect of possible confounding by indication should also be considered. Even though short-term mortality was substantially higher among patients treated with neoadjuvant chemotherapy, the risk of residual confounding should be acknowledged. Further clinical studies with longitudinal study design focusing on treatment decision based on geriatric assessment, patients' quality of life, and risk of toxicities in older patients undergoing neoadjuvant and/or adjuvant chemotherapy are needed to provide deeper insights into the optimal therapeutic approach for this challenging patient population.

Author Contributions

Concept and design: CL, AV.
Data acquisition: AV.
Formal analysis: AV.
Data interpretation: CL, AV, IF, KE.
Writing original draft: CL, AV.
Review and editing: All authors.
The final version was approved by all authors.

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Declaration of Competing Interest

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2025.102220.

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Breast Cancer Research

RESEARCH

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PREDICT v3.0 outperforms v2.2 in young (25–40 years) breast cancer patients according to real-world data from a large Swedish population-based registry

Christine Lundgren[1,2*], Irma Fredriksson[3,4], Antonios Valachis[5†] and Daniel Robert Smith[6,7†]

Abstract

Background PREDICT is a widely used prognostic tool supporting treatment decisions in breast cancer care. As v3.0 was recently released, we performed an external validation of PREDICT v2.2 and v3.0 in young (≤ 40 years) breast cancer patients.

Methods We included Swedish non-metastatic breast cancer patients aged ≤ 40 years, diagnosed between 2008–2019, from a registry-based research database. Outcomes were all-cause and breast cancer-specific mortality (BCSM) at 5- and 10-years, in all and in prespecified patient subgroups (by molecular subtype and nodal status). Model calibration and discrimination were evaluated by the integrated calibration index (ICI) and time dependant area under the receiver operator curve (tdAUC), respectively.

Results In total, 3015 patients were included. PREDICT v2.2 consistently overestimated both all-cause mortality and BCSM at 5- ($ICI_{\text{all-cause mortality}}$ = 5.10%, 95% confidence interval (CI) 4.93–5.27; ICI_{BCSM} = 4.91%, 95% CI 4.71–5.13) and 10- years ($ICI_{\text{all-cause mortality}}$ = 9.75%, 95% CI 9.02%–10.5, ICI_{BCSM} = 9.71%, 95% CI 8.88–10.4). In contrast, PREDICT v3.0 showed much better calibration (5 years; $ICI_{\text{all-cause mortality}}$ = 0.69%, 95% CI 0.60–0.78; ICI_{BCSM} = 0.65%, 95% CI 0.57–0.73; 10 years; $ICI_{\text{all-cause mortality}}$ = 5.10%, 95% CI 4.65–5.5%; ICI_{BCSM} = 4.76%, 95% CI 4.31–5.19), although miscalibration remained in high-risk groups. Discrimination was excellent for predicting 5-year outcomes in both models but declined for 10-year predictions.

Conclusions PREDICT showed good discrimination in young patients. Although version 3.0 showed better calibration than v2.2, risk overestimation in high-risk patients may affect treatment decision-making and warrants cautious interpretation.

Keywords PREDICT model, Young patients, Breast cancer, Prognosis

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Background

Young (≤40 years) patients constitute 5% of newly diagnosed invasive early breast cancer in Sweden [1]. Beyond the classical clinicopathologic prognostic factors in early breast cancer, age is independently associated with inferior outcome [2–5]. This association between younger age and worse prognosis is attributed to more aggressive tumor biology, which is also reflected in gene expression and tumor phenotype levels [6, 7].

Current treatment guidelines for young patients with early breast cancer stipulate that age in addition to biological tumor factors, should guide treatment decision making [8, 9]. Gene expression profiling has been explored to aid decision on chemotherapy; however, the benefit of adjuvant chemotherapy in younger patients cannot be dismissed, even in those with low genomic risk [10, 11]. Accordingly, prognostic tools based on easily accessible patient- and tumor-related characteristics are essential for supporting clinical decisions.

Initially developed in 2010, PREDICT is the most widely used prognostic tool for supporting treatment decisions in breast cancer patients [12]. Several updates have been released, including refitted versions designed to better account for the increased risk in younger patients, as only 7% of the patients in the original cohort were younger than 40 years old [12–17]. While PREDICT performs reasonably well in validated cohorts of middle-aged patients, its prognostic estimates are less reliable for the youngest and oldest patients [13, 14, 18]. Notably, PREDICT´s performance in younger women is risk-dependent and tends to overestimate mortality in poor prognosis subgroups [13, 14]. Recently, a new version of PREDICT (v3.0) was launched, incorporating the relative harms of radiotherapy and chemotherapy [19, 20]. However, limited validation data are currently available for this version [21, 22].

The aim of the present study was to externally validate PREDICT v2.2 and v3.0 in a nationwide, population-based cohort of young (≤40 years) breast cancer patients in Sweden, focusing on 5- and 10-year all-cause- and breast cancer-specific mortality (BCSM) outcomes.

Materials and methods

Study design and main objectives

This was an analytical retrospective cohort study utilizing real-world data from a Swedish nationwide, population-based register. The objectives were to externally validate the PREDICT model (v2.2 and v3.0) using observed outcomes.

Data source and patient selection

The National Quality Register for Breast Cancer (NKBC) in Sweden is a nationwide register containing detailed information on tumor- and treatment-related characteristics for patients diagnosed with early breast cancer with > 99% coverage using the Swedish National Cancer Register as gold standard [1]. NKBC has been used as the main data source for the research database BCBaSe 3.0 where data from NKBC (newly diagnosed patients with breast cancer between January 2008 and December 2019) has been linked to other relevant Swedish National Registries. For the scope of the current study, NKBC data has been enriched with the Cause of Death Registry, providing information on cause and date of death [23, 24].

Eligible patients from the current study were patients registered in BCBaSe 3.0 who fulfilled the following inclusion criteria: female patients 25–40 years old inclusive at diagnosis, stage I–III invasive breast cancer (according to the American Joint Committee on Cancer (AJCC) 8th edition [25] and treated with surgery for the primary tumor (Fig. 1). Patients with only in situ cancer were excluded from the analyses.

Mapping of variables

The following baseline variables were included in the v2.2 model; age at diagnosis (25–40 years), postmenopausal (yes/no/unknown), estrogen receptor (ER) status (positive/negative), human epidermal growth factor receptor 2/Erb-B2 Receptor Tyrosine Kinase 2 (HER2/ERRB2) status (positive/negative/unknown), Ki67 (positive/negative/unknown (> 10% of tumor cells staining positive)), invasive tumour size (mm), tumour grade (1/2/3), detection (screening/symptoms/unknown), positive nodes (numbers), and if at least one, micrometastases only (yes/no/unknown). Additional variables in PREDICT v3.0 includes smoker (yes/never or Ex) and progesterone receptor (PR) status (positive/negative/unknown).

All PREDICT variables were available in our study cohort except for smoking habits, which has been newly introduced as a predictor for PREDICT v3.0. Accordingly, we pre-specified all patients as non-smokers (a sensitivity analysis was also performed in which all patients were defined as smokers). According to Swedish statistics, the smoking habits for this young age group should approximately correspond to on average no more than 10% during the inclusion periods, making this assumption reasonable [26]. HER2 status was defined as positive either by HER2 3 + (as assessed by immunohistochemistry) or HER2 2 + and amplification of *HER2* by in situ hybridization. For tumor grade, we used the Nottingham histological grade (NHG) system [27, 28]. ER status was defined according to Swedish national guidelines; a tumor was considered ER-positive if ≥ 10% of tumor cells stained positive and considered ER-negative if < 10% of tumor cells stained positive [27]. Patients with missing ER status and NHG data, were excluded (Fig. 1).

Regarding treatment strategies, the following treatment variables are considered in PREDICT v2.2; endocrine therapy (no/yes), chemotherapy (none, 2nd gen (standard-dose, anthracycline-based such as FEC (fluorouracil, epirubicin and cyclophosphamide))/3rd gen (high-dose,

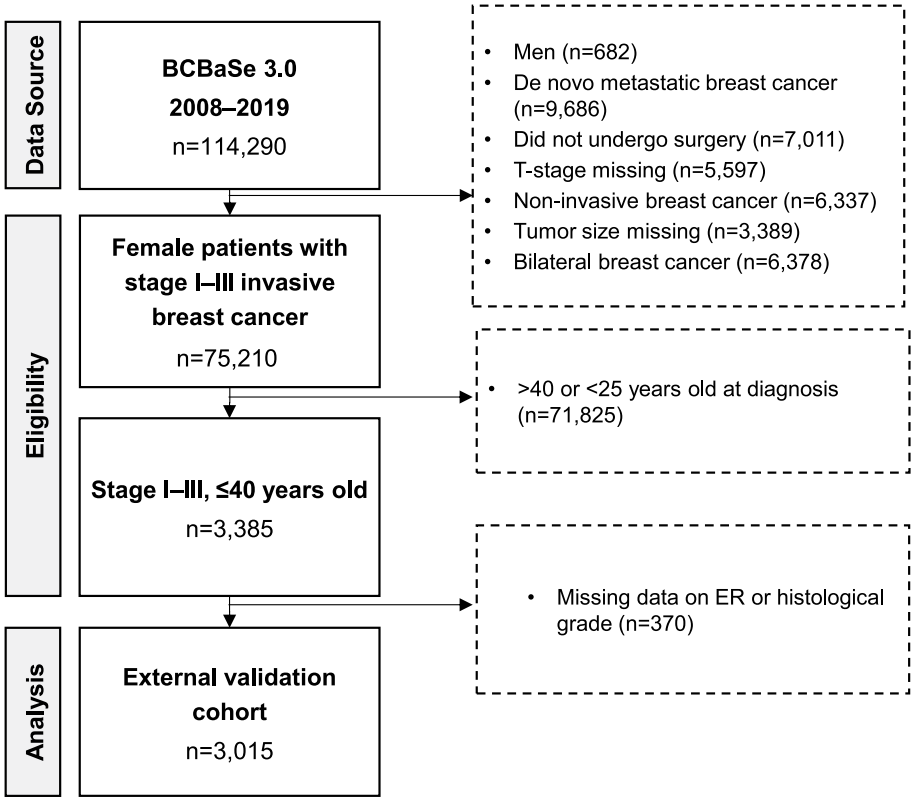

Fig. 1 Study flowchart. *Abbreviations*: BC, breast cancer; ER, estrogen receptor

anthracycline- or taxane- based that contain taxanes such as paclitaxel and docetaxel)), trastuzumab (no/yes), bisphosphonates (no/yes). Additional treatment strategies for PREDICT v3.0 includes radiotherapy (no/yes), and if yes, the mean heart dose in Gray (Gy) is to be reported. Information on endocrine therapy (up to 5 years), radiotherapy, and chemotherapy were retrieved from NKBC. However, no data on heart dose were available and therefore, we coded 0 for right-sided and 2 for left-sided breast cancer as specified in the PREDICT instructions.

The outcomes were 5- and 10-year all-cause mortality and BCSM, defined as death due to any cause and death due to breast cancer diagnosis, respectively. For each time horizon (5 and 10 years), analyses were restricted to patients with sufficient potential follow-up, defined as having a diagnosis date at least 5 or 10 years prior to the end of registry follow-up (9 March 2021). Consequently, the number of patients included decreases for longer follow-up periods.

Statistical analyses

We computed descriptive statistics for all variables required by PREDICT using the median and interquartile range (IQR) range for continuous variables and frequency and percentage for categorical variables. All patients retrieved from the database were entered to the PREDICT algorithms. If any variable was missing, the patient was not excluded if that variable had an "unknown" option in PREDICT. The predicted outcome for overall survival was calculated for each patient and compared with that reported in the database regarding all-cause and BCSM. The follow-up was censored at 5- and 10 years. R code containing the algorithms for PREDICT v.2.1 and 3.0 was obtained from Paul Pharoah who developed the PREDICT model (personal communication). The only difference between v2.1 and v2.2 is that the latter allows for ten years of hormone therapy, thus affecting 15-year survival (Paul Pharoah, personal communication). Since we could not validate 15-years outcomes due to insufficient follow-up, we hereafter refer to validation of v2.2.

In predictive modeling, there are two major aspects of predictive accuracy that need to be quantified: *calibration* measures the ability of the model to make unbiased estimates of the outcome, whereas *discrimination* assesses the model's ability to separate patients' outcomes [29]. Discrimination was assessed using the time dependent AUC (Area Under the Receiver Operating Characteristic Curve, tdAUC), accounting for competing risks (e.g. emigration, death from other causes) as required [30]. Calibration was assessed using smooth calibration curves [31]. For each prediction horizon (5- and 10- year) and outcome (breast cancer death, all-cause death), we used generalized additive models (GAM's) to model the event status (0 = censored, 1 = event) assuming the Poisson distribution with a logarithmic link function (piece-wise exponential model) [32]. Cubic smoothing splines were used to flexibly model

the baseline hazard and the complementary log–log of predicted risk (that computed by PREDICT). We relaxed the proportional hazards assumption by including a tensor product interaction term between the above terms, but with an additional shrinkage penalty allowing the term to shrink towards zero. For the competing risk cases (e.g. emigration, death from other cause), cause was modelled as a categorical parametric term which was allowed to vary (interact) with the baseline hazard and predicted risk. As above, an additional penalty was applied to the interaction terms allowing the term to shrink towards zero. We then plotted the model-based estimate of observed risk against predicted risk with 95% confidence intervals (CIs). From the fitted model, we computed the Integrated Calibration Index (ICI), defined as the mean absolute difference between "observed" (model-based) and predicted risk. Confidence intervals for tdAUC and ICI were computed using the percentile bootstrap with 200 replications.

We assessed calibration and discrimination for the whole cohort, as well as for prognostic subgroups that reflect clinical and anatomical risks, namely, molecular subtype (Luminal (ER + /HER2 negative (HER2–)), HER2 positive (HER2 +), triple-negative breast cancer (TNBC)), as well as according to nodal status (N0; node-negative, and N + ; node-positive). Comparison between the models was performed assuming all patients as both smokers and non-smokers in the v3.0.

Statistical analysis was conducted in R [30, 33], relying heavily on the tidyverse suite, mgcv pammtools and tdROC. For differences in ICI or tdROC, CI not including zero was considered statistically significant. R code to fully reproduce the analyses may be requested from the corresponding author.

Results

Baseline characteristics

Descriptive statistics for baseline variables for 5- and 10-year outcomes are shown in Table 1, illustrating the total number of patients for each follow-up time period as well as in subgroups of interest. Of the 3015 patients included in the cohort, 1883 had potential follow-up for 5-year analysis and 726 for 10-year analysis, based on the registry follow-up cut-off. Between 2008 and 2019, 1883 women, with a median age at diagnosis of 37 years (IQR = 34–39) were eligible for the 5-year follow-up analyses. In total, 107 (5.7%) patients died from breast cancer whilst 8 (0.4%) and 21 (1.1%) died from other causes or emigrated, respectively. Most women (based on 5 years follow-up cohort, n = 1883)) had tumors that were ER-positive (n = 1387; 74%), PR-positive (n = 1235; 66%), HER2-negative (n = 1448; 77%) and histological grade 3 (n = 1031; 55%). More patients were node-negative (N0; n = 1135; 60%). Overall, approximately half of the cohort received endocrine therapy (n = 1059; 56%) and in total 769 (41%) and 345 (18%), received standard anthracycline and taxane/high-dose anthracycline chemotherapy, respectively. The corresponding values for patients (n = 726) in the 10-year follow-up cohort are presented in Table 1.

Performance of PREDICT v2.2 vs v3.0 in all patients at 5- and 10 years follow-up

Calibration curves revealed excellent performance of PREDICT at low risk of death (between approximately 0–20% probability of death), though the calibration curve departed from the line of unity at higher risk (approximately 20–80%) but tended back towards the line of unity at very high risk (Fig. 2). This was true for both model v2.2 and v3.0, and no difference was noted regarding smoking status. PREDICT v2.2 overestimated risk of death at 5 years ($ICI_{\text{all-cause mortality}}$ = 5.10%, 95% CI 4.93–5.27; ICI_{BCSM} (ICI = 4.91%, 95% CI 4.71–5.13), and the magnitude of overestimation increased at 10 years ($ICI_{\text{all-cause mortality}}$ = 9.75%, 95% CI 9.02–10.5; ICI_{BCSM} = 9.71%, 95% CI 8.88–10.4) (Table 2 and Fig. 3). PREDICT v3.0 was better calibrated than v2.2 at both time horizons, though again performed better at 5 years ($ICI_{\text{all-cause mortality}}$ = 0.69%, 95% CI 0.66–0.78; ICI_{BCSM} = 0.65%, 95% CI 0.57–0.73) compared to 10 years ($ICI_{\text{all-cause mortality}}$ = 5.10%, 95% CI 4.65–5.52; ICI_{BCSM} = 4.76%, 95% CI 4.31–5.19) (Table 2 and Figs. 3–4). The difference in performance was significantly better for v3.0 as compared to v2.2 for both outcomes and time horizons (Table 2 and Fig. 4).

Discrimination was excellent for 5-year risks and was similar across outcomes and PREDICT versions (v2.2: $tdAUC_{\text{all-cause mortality}}$ = 80.1%, 95% CI 76.8–84.2; v2.2: $tdAUC_{BCSM}$ = 81.9%, 95% CI 78.4–85.5; v3.0: $tdAUC_{\text{all-cause mortality}}$ = 81.0%, 95% CI 77.4–84.4; v3.0: $tdAUC_{BCSM}$ = 81.8%, 95% CI 77.8–84.8 (Table 2, Figs. 3 and 4). Discriminative ability decreased for 10-year risk, though was again similar between PREDICT versions and outcomes (v2.2: $tdAUC_{\text{all-cause mortality}}$ = 66.8%, 95% CI 61.1–72.3; v2.2: $tdAUC_{BCSM}$ = 70.3%, 95% CI 63.6–75.8; v3.0: $tdAUC_{\text{all-cause mortality}}$ = 67.2%, 95% CI 61.3–72.5; v3.0: $tdAUC_{BCSM}$ = 70.1%, 95% CI 63.7–74.8).

Performance of PREDICT v2.2 vs v3.0 by molecular subtype and nodal status

Subgroup analyses by molecular subtype and nodal status (Tables 2) showed substantial overestimation by PREDICT v2.2 in HER2-positive patients, with ~ 10% miscalibration at 5 years ($ICI_{\text{all-cause mortality}}$ = 10.0%, 95% CI 9.21–10.9, ICI_{BCSM} = 9.9%, 95% CI 9.09–10.8), and ~ 20% at 10 years. In contrast, v3.0 reduced miscalibration to ~ 4.5% at 5 years ($ICI_{\text{all-cause mortality}}$ = 4.42%, 95% CI 4.04–4.88; ICI_{BCSM} = 4.56%, 95% CI 4.04–5.11) and ~ 10% at 10 years (Table 2 and Figs. 3–4). In TNBC, both versions showed similar moderate overestimation, with 2–4% error at

Table 1 Patient- and tumor characteristics for all patients, and for subgroups of interest at 5 and 10 years follow-up, respectively

Variable	All		Node-negative		Node-positive		Triple-negative		Luminal		HER2 +	
	5y n = 1883[1]	10y n = 726[1]	5y n = 1135[1]	10y n = 418[1]	5y n = 748[1]	10y n = 308[1]	5y n = 353[1]	10y n = 145[1]	5y n = 1095[1]	10y n = 395[1]	5y n = 390[1]	10y n = 155[1]
Events												
Censored	1747 (93%)	611 (84%)	1080 (95%)	369 (88%)	667 (89%)	242 (79%)	302 (86%)	120 (83%)	1043 (95%)	334 (85%)	363 (93%)	133 (86%)
Died from breast cancer	107 (5.7%)	94 (13%)	37 (3.3%)	37 (8.9%)	70 (9.4%)	57 (19%)	47 (13%)	25 (17%)	38 (3.5%)	48 (12%)	16 (4.1%)	14 (9.0%)
Died from other causes	8 (0.4%)	12 (1.7%)	6 (0.5%)	6 (1.4%)	2 (0.3%)	6 (1.9%)	3 (0.8%)		3 (0.3%)	9 (2.3%)	2 (0.5%)	3 (1.9%)
Emigrated	21 (1.1%)	9 (1.2%)	12 (1.1%)	6 (1.4%)	9 (1.2%)	3 (1.0%)	1 (0.3%)		11 (1.0%)	4 (1.0%)	9 (2.3%)	5 (3.2%)
Age at diagnosis (years)	37 (34, 39)	37 (34, 39)	37 (34, 39)	37 (34, 39)	37 (34, 39)	37 (34, 39)	36 (32, 38)	35 (32, 38)	38 (35, 40)	38 (35, 40)	37 (33, 39)	37 (34, 39)
ER												
Negative	496 (26%)	203 (28%)	312 (27%)	127 (30%)	184 (25%)	76 (25%)	353 (100%)	145 (100%)	19 (1.7%)	5 (1.3%)	110 (28%)	42 (27%)
Positive	1387 (74%)	523 (72%)	823 (73%)	291 (70%)	564 (75%)	232 (75%)			1076 (98%)	390 (99%)	280 (72%)	113 (73%)
PR												
Negative	644 (34%)	274 (38%)	398 (35%)	167 (40%)	246 (33%)	107 (35%)	353 (100%)	145 (100%)	120 (11%)	52 (13%)	153 (39%)	64 (41%)
Positive	1235 (66%)	450 (62%)	734 (65%)	250 (60%)	501 (67%)	200 (65%)			975 (89%)	343 (87%)	237 (61%)	91 (59%)
Unknown	4 (0.2%)	2 (0.3%)	3 (0.3%)	1 (0.2%)	1 (0.1%)	1 (0.3%)						
HER2												
Negative	1448 (77%)	540 (74%)	898 (79%)	320 (77%)	550 (74%)	220 (71%)	353 (100%)	145 (100%)	1,095 (100%)	395 (100%)		
Positive	392 (21%)	156 (21%)	212 (19%)	82 (20%)	180 (24%)	74 (24%)					390 (100%)	155 (100%)
Unknown	43 (2.3%)	30 (4.1%)	25 (2.2%)	16 (3.8%)	18 (2.4%)	14 (4.5%)						
Ki67[2]												
Negative	96 (5.1%)	20 (2.8%)	76 (6.7%)	14 (3.3%)	20 (2.7%)	6 (1.9%)	1 (0.3%)		91 (8.3%)	20 (5.1%)	3 (0.8%)	
Positive	865 (46%)	81 (11%)	528 (47%)	53 (13%)	337 (45%)	28 (9.1%)	166 (47%)	22 (15%)	496 (45%)	38 (9.6%)	196 (50%)	19 (12%)
Unknown	922 (49%)	625 (86%)	531 (47%)	351 (84%)	391 (52%)	274 (89%)	186 (53%)	123 (85%)	508 (46%)	337 (85%)	191 (49%)	136 (88%)
Tumor size (mm)	20 (13, 28)	20 (14, 30)	17 (12, 24)	18 (12, 25)	23 (17, 35)	25 (18, 35)	22 (16, 31)	22 (16, 30)	18 (12, 27)	19 (13, 28)	20 (14, 29)	22 (15, 29)
Tumour grade												
1	201 (11%)	79 (11%)	160 (14%)	63 (15%)	41 (5.5%)	16 (5.2%)	2 (0.6%)	2 (1.4%)	187 (17%)	72 (18%)	9 (2.3%)	4 (2.6%)
2	651 (35%)	232 (32%)	394 (35%)	128 (31%)	257 (34%)	104 (34%)	13 (3.7%)	6 (4.1%)	513 (47%)	177 (45%)	111 (28%)	42 (27%)
3	1031 (55%)	415 (57%)	581 (51%)	227 (54%)	450 (60%)	188 (61%)	338 (96%)	137 (94%)	395 (36%)	146 (37%)	270 (69%)	109 (70%)
Detection mode												
Clinically detected	1610 (86%)	627 (86%)	962 (85%)	357 (85%)	648 (87%)	270 (88%)	328 (93%)	137 (94%)	895 (82%)	323 (82%)	347 (89%)	138 (89%)
Screen detected	266 (14%)	95 (13%)	169 (15%)	58 (14%)	97 (13%)	37 (12%)	24 (6.8%)	7 (4.8%)	196 (18%)	70 (18%)	41 (11%)	16 (10%)
Unknown	7 (0.4%)	4 (0.6%)	4 (0.4%)	3 (0.7%)	3 (0.4%)	1 (0.3%)	1 (0.3%)	1 (0.7%)	4 (0.4%)	2 (0.5%)	2 (0.5%)	1 (0.6%)
Number positive lymph nodes												
0	1135 (60%)	418 (58%)	1,135 (100%)	418 (100%)			232 (66%)	95 (66%)	666 (61%)	225 (57%)	211 (54%)	82 (53%)
1	317 (17%)	130 (18%)			317 (42%)	130 (42%)	57 (16%)	24 (17%)	175 (16%)	75 (19%)	74 (19%)	24 (15%)

Table 1 (continued)

Variable	All		Node-negative		Node-positive		Triple-negative		Luminal		HER2 +	
	5y n = 1883[1]	10y n = 726[1]	5y n = 1135[1]	10y n = 418[1]	5y n = 748[1]	10y n = 308[1]	5y n = 353[1]	10y n = 145[1]	5y n = 1095[1]	10y n = 395[1]	5y n = 390[1]	10y n = 155[1]
2	152 (8.1%)	57 (7.9%)			152 (20%)	57 (19%)	29 (8.2%)	12 (8.3%)	96 (8.8%)	31 (7.8%)	26 (6.7%)	13 (8.4%)
3	86 (4.6%)	39 (5.4%)			86 (11%)	39 (13%)	12 (3.4%)	6 (4.1%)	53 (4.8%)	25 (6.3%)	20 (5.1%)	7 (4.5%)
4	43 (2.3%)	20 (2.8%)			43 (5.7%)	20 (6.5%)	4 (1.1%)	1 (0.7%)	26 (2.4%)	10 (2.5%)	11 (2.8%)	7 (4.5%)
≥ 5	150 (8.0%)	62 (8.5%)			150 (20%)	62 (20%)	19 (5.4%)	7 (4.8%)	79 (7.2%)	29 (7.3%)	48 (12%)	22 (14%)
Radiotherapy												
No	809 (43%)	466 (64%)	580 (51%)	298 (71%)	229 (31%)	168 (55%)	163 (46%)	103 (71%)	442 (40%)	246 (62%)	178 (46%)	97 (63%)
Yes	1074 (57%)	260 (36%)	555 (49%)	120 (29%)	519 (69%)	140 (45%)	190 (54%)	42 (29%)	653 (60%)	149 (38%)	212 (54%)	58 (37%)
Radiation to heart (grays)												
0	1298 (69%)	589 (81%)	816 (72%)	350 (84%)	482 (64%)	239 (78%)	248 (70%)	121 (83%)	743 (68%)	320 (81%)	277 (71%)	125 (81%)
2	585 (31%)	137 (19%)	319 (28%)	68 (16%)	266 (36%)	69 (22%)	105 (30%)	24 (17%)	352 (32%)	75 (19%)	113 (29%)	30 (19%)
Endocrine therapy												
No	824 (44%)	465 (64%)	517 (46%)	283 (68%)	307 (41%)	182 (59%)	341 (97%)	143 (99%)	293 (27%)	216 (55%)	169 (43%)	89 (57%)
Yes	1059 (56%)	261 (36%)	618 (54%)	135 (32%)	441 (59%)	126 (41%)	12 (3.4%)	2 (1.4%)	802 (73%)	179 (45%)	221 (57%)	66 (43%)
Chemotherapy												
None	769 (41%)	475 (65%)	541 (48%)	295 (71%)	228 (30%)	180 (58%)	114 (32%)	90 (62%)	523 (48%)	281 (71%)	107 (27%)	83 (54%)
Standard anthracycline	769 (41%)	238 (33%)	415 (37%)	116 (28%)	354 (47%)	122 (40%)	165 (47%)	50 (34%)	391 (36%)	110 (28%)	197 (51%)	68 (44%)
Taxanes / high-dose anthracycline	345 (18%)	13 (1.8%)	179 (16%)	7 (1.7%)	166 (22%)	6 (1.9%)	74 (21%)	5 (3.4%)	181 (17%)	4 (1.0%)	86 (22%)	4 (2.6%)
Trastuzumab therapy												
No	1582 (84%)	641 (88%)	975 (86%)	376 (90%)	607 (81%)	265 (86%)	351 (99%)	145 (100%)	1,089 (99%)	393 (99%)	100 (26%)	74 (48%)
Yes	301 (16%)	85 (12%)	160 (14%)	42 (10%)	141 (19%)	43 (14%)	2 (0.6%)		6 (0.5%)	2 (0.5%)	290 (74%)	81 (52%)
Bisphosphonate therapy												
No	1872 (99%)	726 (100%)	1132 (100%)	418 (100%)	740 (99%)	308 (100%)	353 (100%)	145 (100%)	1087 (99%)	395 (100%)	387 (99%)	155 (100%)
Yes	11 (0.6%)		3 (0.3%)		8 (1.1%)				8 (0.7%)		3 (0.8%)	

[1]n (%); [2] positive defined as > 10% according to the PREDICT algorithm; Median (Q1, Q3)

Abbreviations: ER, Estrogen receptor; HER2, Human epidermal growth factor receptor; PR, Progesterone receptor

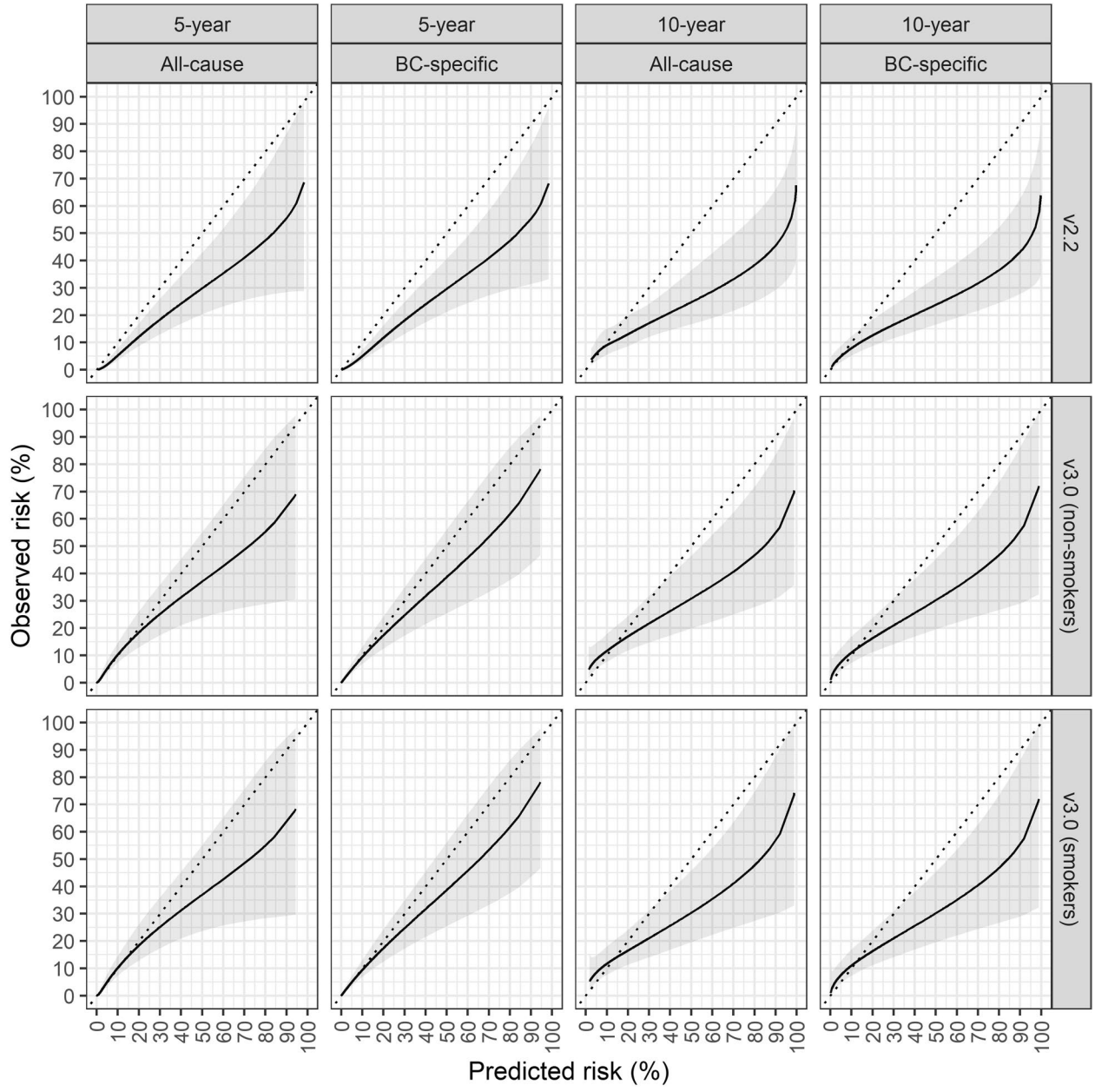

Fig. 2 Calibration plots for PREDICT v2.2 and v3.0. Observed and predicted risks (%) for all patients with respect to both all-cause and breast cancer-specific survival. V3.0 is illustrated assuming all patients to be smokers or non-smokers. *Abbreviations*: BC, breast cancer

5 years and 8–9% at 10 years. In node-negative cases, both models showed good accuracy, with minimal overestimation by PREDICT v3.0 (≤ 0.5%) at 5 years. In node-positive disease, overestimation was substantial, particularly for v2.2. At 10 years, ICIs reached 16.5% (95% CI 15.2–17.9) and 7.7% (95% CI 6.77– 8.66) for PREDICT v2.2 and v3.0, respectively. All data are detailed in Table 2. Statistical differences between the models were seen across all subgroups, except for TNBC at 10 years for both outcomes (Table 2 and Fig. 4). Calibration plots for the different subgroups are available as Supplementary files (Supplementary Figure S1–5).

Discriminatory performance across subgroups is summarized in Table 2 and Figs. 3–4). Notably, reduced discriminatory capacity was observed in patients with TNBC at 10 years, with tdAUCs for all-cause mortality of 59.1% (95% CI 46.3–73.1) for PREDICT v2.2 and 59.2% (95% CI 47.2–70.0) for v3.0. Similar patterns were observed for BCSM, and no significant differences were noted between the two PREDICT models.

Table 2 Calibration and discrimination of PREDICT v2.2 and v3.0 in all patients and in different subgroup across 5- and 10 years horizons

Horizon	Death	Integrated calibration index (%)			Time dependent AUC (%)		
		v.3.0	v.2.2	v.3.0-v2.2[a]	v.3.0	v.2.2	v.3.0-v2.2[a]
All patients							
5-year	All-cause	0.69 [0.60, 0.78]	5.10 [4.93, 5.27]	− 4.42 [− 4.61, − 4.20]	81.01 [77.38, 84.43]	80.95 [76.82, 84.19]	− 0.06 [− 4.91, 4.85]
	BC-specific	0.65 [0.57, 0.73]	4.91 [4.71, 5.13]	− 4.26 [− 4.49, − 4.04]	81.83 [77.81, 84.83]	81.92 [78.44, 85.47]	0.09 [− 5.01, 5.25]
10-year	All-cause	5.10 [4.65, 5.52]	9.75 [9.02, 10.49]	− 4.66 [− 5.53, − 3.88]	67.21 [61.29, 72.46]	66.76 [61.11, 72.33]	− 0.46 [− 8.43, 6.92]
	BC-specific	4.76 [4.31, 5.19]	9.71 [8.88, 10.42]	− 4.95 [− 5.79, − 4.00]	70.09 [63.67, 74.80]	70.33 [63.55, 75.79]	0.25 [− 7.50, 8.68]
HER2 +							
5-year	All-cause	4.42 [4.04, 4.88]	9.98 [9.21, 10.91]	− 5.56 [− 6.60, − 4.58]	87.05 [79.72, 94.57]	88.34 [78.99, 94.58]	1.28 [− 10.55, 12.71]
	BC-specific	4.56 [4.04, 5.11]	9.87 [9.09, 10.84]	− 5.31 [− 6.34, − 4.39]	87.54 [75.12, 95.36]	88.61 [79.07, 95.64]	1.07 [− 11.79, 15.78]
10-year	All-cause	9.81 [8.08, 11.22]	19.78 [17.50, 22.18]	− 9.97 [− 12.86, − 6.99]	73.08 [59.01, 85.53]	73.06 [56.51, 84.75]	− 0.02 [− 17.43, 20.57]
	BC-specific	10.59 [8.82, 12.49]	20.34 [18.24, 22.50]	− 9.74 [− 12.54, − 6.70]	75.28 [61.17, 85.66]	75.58 [61.76, 87.56]	0.30 [− 17.31, 16.49]
Luminal							
5-year	All-cause	0.57 [0.49, 0.67]	4.04 [3.80, 4.24]	− 3.47 [− 3.69, − 3.20]	82.12 [75.40, 88.12]	81.88 [75.18, 87.58]	− 0.23 [− 8.50, 8.35]
	BC-specific	0.54 [0.48, 0.60]	3.67 [3.44, 3.94]	− 3.13 [− 3.39, − 2.90]	82.42 [75.07, 89.29]	81.76 [75.29, 88.80]	− 0.66 [− 9.87, 10.13]
10-year	All-cause	4.07 [3.92, 4.25]	6.63 [5.65, 7.47]	− 2.56 [− 3.40, − 1.57]	68.86 [61.87, 76.39]	67.64 [59.51, 74.18]	− 1.22 [− 12.01, 7.93]
	BC-specific	2.82 [2.71, 2.95]	6.71 [5.83, 7.51]	− 3.89 [− 4.72, − 2.93]	73.11 [65.75, 79.21]	72.18 [65.62, 80.90]	− 0.94 [− 9.97, 10.88]
Triple-negative							
5-year	All-cause	2.79 [2.51, 3.09]	3.94 [3.54, 4.37]	− 1.15 [− 1.71, − 0.66]	64.19 [56.42, 72.16]	63.32 [55.84, 73.36]	− 0.87 [− 11.77, 9.43]
	BC-specific	1.68 [1.45, 1.98]	4.25 [3.81, 4.71]	− 2.57 [− 3.10, − 2.05]	67.09 [58.89, 76.23]	66.89 [58.99, 74.23]	− 0.20 [− 11.74, 11.67]
10-year	All-cause	8.63 [7.42, 9.93]	9.33 [8.39, 10.39]	− 0.70 [− 2.33, 0.95]	59.17 [47.24, 69.95]	59.07 [46.32, 73.05]	− 0.10 [− 18.70, 17.91]
	BC-specific	7.91 [6.76, 9.26]	8.06 [7.11, 9.19]	− 0.16 [− 1.65, 1.64]	59.12 [44.99, 69.69]	58.87 [47.64, 70.73]	− 0.25 [− 15.30, 17.05]
Node-negative							
5-year	All-cause	0.51 [0.49, 0.53]	3.01 [2.95, 3.07]	− 2.50 [− 2.57, − 2.43]	81.96 [76.81, 86.72]	81.87 [76.65, 86.46]	− 0.09 [− 6.47, 7.35]
	BC-specific	0.56 [0.55, 0.58]	2.86 [2.78, 2.96]	− 2.29 [− 2.39, − 2.21]	82.71 [77.09, 87.78]	83.27 [77.05, 88.57]	0.55 [− 6.90, 8.93]
10-year	All-cause	3.59 [3.32, 3.84]	5.42 [5.00, 6.02]	− 1.84 [− 2.40, − 1.30]	61.54 [52.30, 70.09]	62.92 [53.86, 70.90]	1.38 [− 10.78, 14.23]
	BC-specific	3.02 [2.75, 3.28]	4.54 [3.91, 5.13]	− 1.53 [− 2.22, − 0.84]	65.30 [58.24, 73.10]	67.65 [58.50, 75.85]	2.35 [− 9.14, 11.58]
Node-positive							
5-year	All-cause	1.72 [1.56, 1.93]	8.37 [7.96, 8.79]	− 6.65 [− 7.09, − 6.12]	77.29 [70.86, 82.57]	76.59 [70.48, 81.13]	− 0.70 [− 8.07, 6.61]
	BC-specific	1.94 [1.75, 2.19]	8.07 [7.67, 8.53]	− 6.13 [− 6.58, − 5.75]	77.29 [71.44, 82.45]	76.58 [71.13, 81.63]	− 0.71 [− 7.51, 6.77]
10-year	All-cause	7.86 [7.15, 8.78]	15.95 [14.56, 17.37]	− 8.09 [− 9.64, − 6.08]	65.91 [58.43, 73.32]	64.92 [56.50, 71.32]	− 0.99 [− 12.08, 10.66]
	BC-specific	7.71 [6.77, 8.66]	16.50 [15.21, 17.86]	− 8.79 [− 10.43, − 7.27]	68.19 [60.08, 75.47]	67.97 [59.95, 75.59]	− 0.22 [− 10.88, 9.84]

[a]difference between PREDICT versions

Assumed non-smokers for PREDICT v3.0

Abbreviations: AUC, Area under curve; BC, Breast cancer; HER2, Human epidermal growth factor receptor; v., Version of PREDICT

Discussion

This external validation of the prognostic model PREDICT was conducted using real-world data from a large, contemporary Swedish cohort of breast cancer patients aged ≤ 40 years at diagnosis. Our analysis showed that PREDICT tended to overestimate both all-cause mortality and BCSM, and more pronounced at 10-year follow-up. The overestimation was particularly notable among high-risk patients, such as those with HER2-positive and node-positive disease. PREDICT version 3.0 showed improved accuracy over version 2.2 across both outcomes and time horizons.

Prior studies of older PREDICT versions have reported mixed results depending on the prognostic risk groups under study [13, 14, 34]. A Dutch validation study in patients < 50 years old found PREDICT v1.3 underestimated 10-year all-cause mortality in "good" prognosis subgroups but overestimated this endpoint in "poor" prognosis subgroups [13]. Maishman et al. observed that PREDICT v1.1 was more accurate at 8–10 years than at 5 years, but it underestimated 5-year deaths by 56% in ER-positive tumors, while overestimated deaths by 21% in ER-negative tumors [14]. Similarly, Wang et al. found that PREDICT v2.2 underestimated 10-year all-cause mortality by 33% in untreated node-negative patients < 40 years, particularly in ER-positive cases [35]. Limited data exists for PREDICT v3.0, but SEER results suggest similar miscalibration patterns by ER status (− 8% in ER-positive, + 2% in ER-negative patients) for 10-year all-cause mortality [22]. According to our data, PREDICT v3.0 demonstrated a 67–82% ability to distinguish between survivors and non-survivors across prediction horizons, however with a higher performance at 5 compared to 10 years. The results are consistent with findings from Grootes et al. [20] and

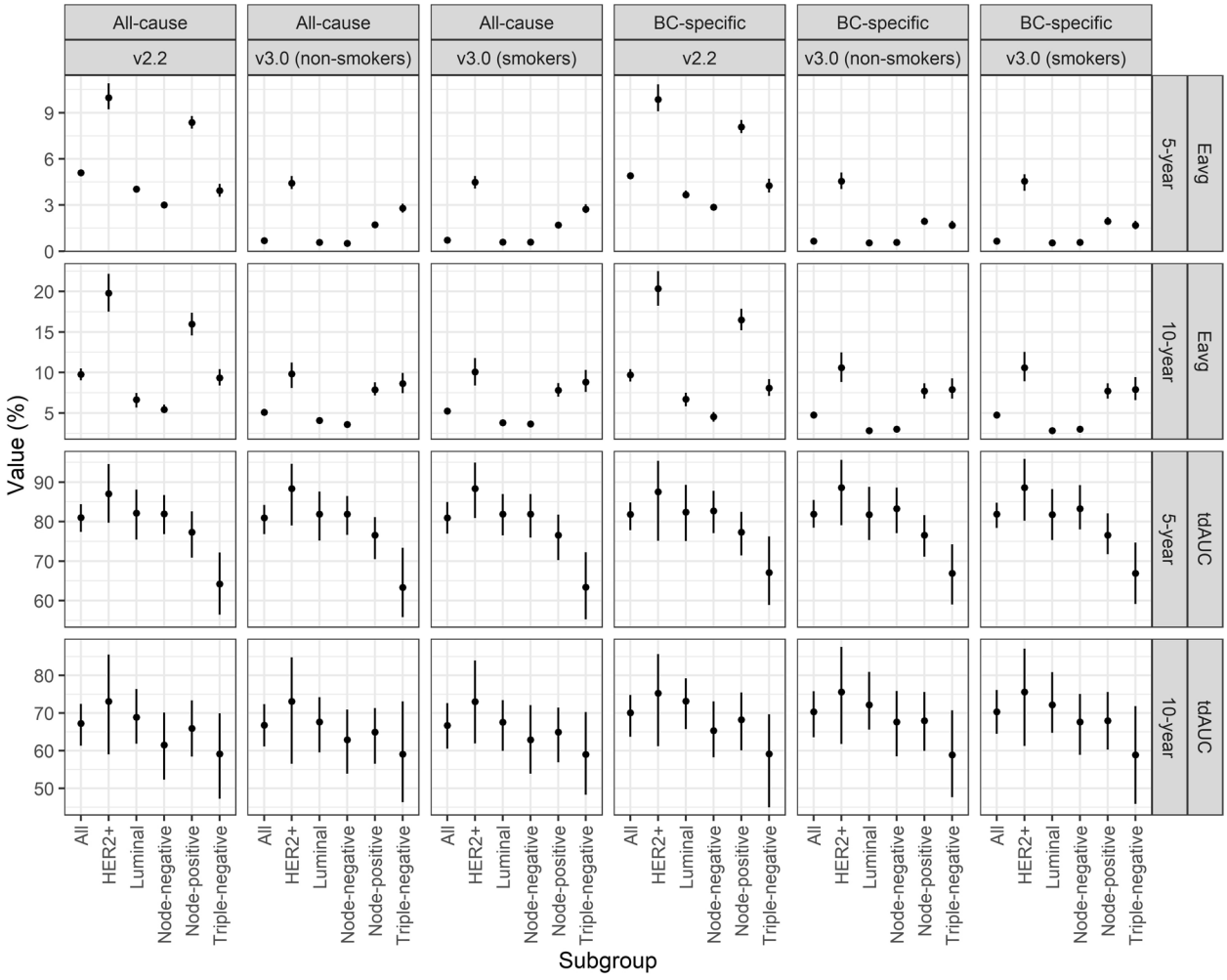

Fig. 3 Calibration and discriminatory values (%) for all patients and specific subgroups. Calibration (Eavg) and discriminatory (tdAUC) values for all patients and in subgroups of interest with respect to both all-cause and breast cancer-specific survival. V3.0 is illustrated assuming all patients to be smokers or non-smokers. *Abbreviations*: BC, breast cancer; HER2, human epidermal growth factor receptor; tdAUC, time dependent area under the receiver operating characteristic curve

a study from United States [22] validating the v3.0 model. We validated both all-cause and BCS mortality, i.e. cause of death was known. The results regarding these outcomes were in general similar, and not surprising since young patients are not expected to have competing risk of deaths other than breast cancer. Our calibration data indicate that PREDICT v3.0 overestimated 5-year all-cause and BCS mortality, but only on average 0.7%. The figures for v2.2 were less accurate, indicating an overestimation of on average 5% and 10% after 5- and 10 years follow-up, respectively. In general, a more pronounced miscalibration was detected in high-risk patients, also apparent in prespecified subgroup analyses. Our findings demonstrated a clear improvement in predictive performance with PREDICT v3.0, compared to v2.2, also reported in the recent publication from the U.S [22]. This suggests better calibration in younger patients and may reflect improved risk–benefit alignment in estimating treatment effects.

The clinical relevance of PREDICT's tendency to overestimate mortality, particularly in version 2.2, is nevertheless substantial, as it may significantly influence adjuvant treatment decisions in young patients with breast cancer, especially those classified as high-risk. Assuming a threshold for clinical benefit from adjuvant systemic therapy of ≥ 3%, even minor degrees of model miscalibration could have a direct impact on therapeutic decision-making. While calibration appeared acceptable for low-risk patients, the extent of miscalibration increased substantially among high-risk individuals. For these patients, especially over a 10-year horizon, PREDICT v2.2 overestimated mortality by as much as 30 to 40 percentage points. Given the longer life expectancy and reduced influence of competing mortality risks in younger patients, precise prognostic stratification in this population is imperative. Overestimation of absolute treatment benefit in poor-prognosis subgroups may lead to overtreatment, as the perceived benefit may be

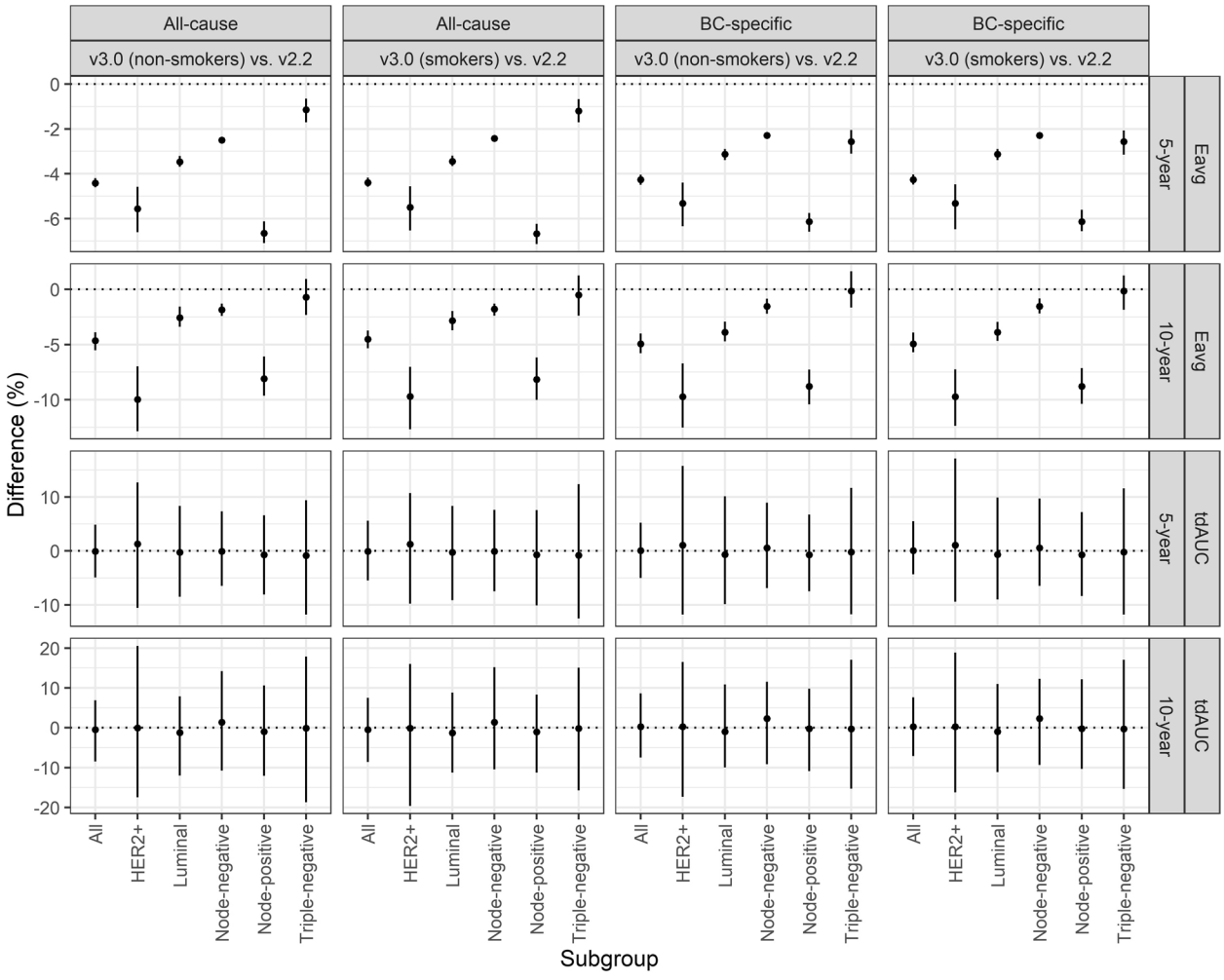

Fig. 4 Calibration and discriminatory differences (%) for all patients and specific subgroups. Calibration (Eavg) and discriminatory (tdAUC) differences for all patients and in subgroups of interest with respect to both all-cause and breast cancer-specific survival. V3.0 is illustrated assuming all patients to be smokers or non-smokers. *Abbreviations*: BC, breast cancer; HER2, human epidermal growth factor receptor; tdAUC, time dependent area under the receiver operating characteristic curve

overrepresented. This was less pronounced in v3.0 by our results. The authors behind this updated version of PREDICT, concluded that the v3.0 re-classified patients, in that 38% of those considered as high risk (by Cambridge Unit) by v2.2 would be low according to v3.0 and spared the harms of treatment [20].

The more pronounced miscalibration, particularly observed in high-risk groups, likely reflects a combination of factors related to both model structure and evolving clinical practice. First, there were few young patients included in the PREDICT development cohort (2% < 35 years old) and second, the inclusion period in that cohort was 1999–2003 [36], and this differs by a decade as compared to our cohort. Third, inaccurate estimation of treatment benefits to newer treatment strategies could explain the miscalibration of contemporary patients, since the relative risk reduction of treatment in PREDICT are derived from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG*)* meta-analyses [37, 38]. Patients classified as high-risk typically have greater exposure to systemic therapies and more aggressive disease biology, and therefore benefit most from advances in treatment that are not fully captured in earlier model versions. As a result, absolute risks may be overestimated when historical treatment effects are applied to contemporary patients. In addition, geographical differences in clinical practice, population characteristics, and subtype distribution between the development cohorts and our Swedish population may also contribute to the observed miscalibration. Finally, biological features of tumors in young patients that cannot be captured with the current clinicopathological factors, makes extrapolation from prediction models developed mainly from older populations uncertain. In addition, small inaccuracies in relative risk estimates or baseline risk can become amplified at higher predicted risk levels, leading to greater absolute

miscalibration in these groups. Notably, this pattern was substantially attenuated in PREDICT v3.0, suggesting that incorporation of more recent treatment effects improves calibration, although some overestimation remains.

PREDICT exhibited very good- to excellent- discriminatory performance across the cohort. As discrimination is determined by the coefficients from the underlying cause-specific Cox proportional hazards models, recalibration using population-specific coefficients is unlikely to yield major gains. Instead, the observed miscalibration likely originates from inaccuracies in the baseline hazard functions, suggesting that recalibrating these baselines could further improve model performance. Given the representativeness of our cohort in terms of patient and tumor characteristics for the broader young breast cancer population, our findings are likely generalizable. However, evolving therapeutic standards and the rapid incorporation of novel agents underscore the need for continuous updates of prognostic tools. Future efforts should aim to enhance model validity by integrating additional prognostic factors including genomic assays and expanding follow-up durations. Moreover, subsequent versions of PREDICT may benefit from continued recalibration to contemporary populations and from incorporating more detailed treatment information, particularly for patients at the highest risk as discussed above. One could also discuss the value of adding more unmeasurable variables such as socioeconomic status and comorbidities, however, one must also keep in mind that the PREDICT model should be user-friendly and the variables easy to categorise.

This study has several strengths, including a large, population-based cohort and high-quality data with accurate cause-of-death classification. It represents an independent validation using robust methodology. Limitations include incomplete data for some PREDICT v3.0 variables, notably smoking status, and cardiac radiotherapy dose. As smoking was a key missing variable, all patients were assumed non-smokers and assumed as reasonable based on national statistics for this age group [26], which was also supported by sensitivity analyses illustrating similar results. As presented in Table 1, there was a certain proportion of patients that did not receive standard treatment (anti-HER2 in the HER2 positive and endocrine therapy in the Luminal subgroup, respectively) and these data should affect both endpoints at both time horizons. Nevertheless, the PREDICT overestimated mortality in these subgroups. Lastly, we were unable to estimate outcomes beyond 10 years, which may limit relevance for younger patients.

Conclusions

Recent and previous PREDICT models are generally accurate for outcome estimation in breast cancer patients ≤ 40 years old but tend to overestimate risk in high-risk subgroups, particularly at 10 years. While the updated version shows improvement, it should be used cautiously in young high-risk patients, as it may overestimate risks and impact treatment decisions.

Abbreviations

AJCC	American joint committee on cancer
BCSM	Breast cancer-specific mortality
CI	Confidence interval
ER	Estrogen receptor
ERRB2	Erb-B2 receptor tyrosine kinase 2
GAM	Generalized additive model
Gy	Gray
ICI	Integrated calibration index
IQR	Interquartile range
HER2	Human epidermal growth factor receptor 2
NHG	Nottingham histological grade
NKBC	The swedish national quality register for breast cancer
PR	Progesterone receptor
tdAUC	Time dependent area under the receiver operating characteristic curve
TNBC	Triple-negative breast cancer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-026-02271-2.

Supplementary Material 1.

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Author contributions

Conception, methodology and design: DS, AV, CL. Data acquisition/curation: DS, AV, IF. Formal analysis/software: DS. Data interpretation/validation: DS, AV, CL, IF. Writing—original draft: CL, DS, AV. Writing—review and editing: All authors. The final version was approved by both authors.

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Data availability

All data are available upon reasonable request.

Declarations

Ethics approval and consent to participate

The research database BCBaSe 3.0 has been approved by the regional ethical review board in Stockholm at 25th June 2019 (reference number: 2019–02610). An amendment for utilizing BCBaSe 3.0 to validate PREDICT was approved by the Swedish Ethical Review Authority at 20th April 2024 (reference number: 2024–01947-02). As BCBaSe is a registry-based data source, the Swedish Ethical Review Authority waived the need for informed consent.

Consent for publication

Not applicable.

Competing interests

CL has received financial scholarship from Pfizer but is not in conflict of this project. IF has received institutional research grants from MSD, unrelated to the current work. AV has received institutional research grant from Roche and MSD, unrelated to the current work. DS declares no competing interests.

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Research Paper

Short-term mortality in older (≥70 years) patients with early breast cancer treated with neo-/adjuvant chemotherapy: A Swedish nationwide retrospective population-based study

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ABSTRACT

Introduction: There are substantial differences in the utilization of chemotherapy between younger and older patients, mainly due to the higher risk for adverse events among older patients. Short-term mortality after chemotherapy could reveal fatal side effects of treatment. The aim of this study was to explore the impact of treatment setting (neoadjuvant vs. adjuvant) and different chemotherapeutic agents on short-term mortality among older patients with early breast cancer.

Material and Methods: The population-based, national, research database BCBaSe 3.0 was used as a data source to identify older (≥70 years old) patients with stage I–III breast cancer, diagnosed between 2008 and 2019, who received neoadjuvant or adjuvant chemotherapy. Primary outcome was short-term mortality defined as death due to any cause within one year after breast cancer diagnosis. Multivariable logistic regression analysis was applied to investigate the impact of treatment setting and different chemotherapeutic agents (anthracycline-based vs. taxane-based vs. sequential anthracyclines and taxanes) on outcome, adjusted for potential confounders.

Results: In total, 4072 older patients were treated with neoadjuvant or adjuvant chemotherapy and median age was 73 years (quartile [Q]1–Q3; 71–75). The one-year mortality rate was 1.5 % (95 % confidence interval [CI]: 1.2–1.9 % [63 of 4072 patients]). Risk factors independently associated with one-year mortality were older age, larger tumor size, positive nodal status, presence of triple negative breast cancer, and use of neoadjuvant as compared to adjuvant chemotherapy (odds ratio [OR]: 2.00, 95 % CI: 1.04–3.84). No association was found between type of chemotherapeutic regimen and one-year mortality. Median time to death was 7 months (interquartile range: 5–9). The reason for death was mainly classified as breast cancer-related (neoadjuvant: 78 %, $n = 14$; adjuvant: 49 %, $n = 22$), followed by potential treatment-related deaths (neoadjuvant: 11 %, $n = 2$; adjuvant: 27 %, $n = 12$).

Discussion: The short-term mortality rate at first year after diagnosis among older (≥70 years) patients with breast cancer was relatively low. The higher risk among patients treated with neoadjuvant chemotherapy could be attributed to residual confounding and deserves further evaluation. The low risk of potential treatment-associated death suggests that chemotherapy in this respect is safe, and older patients should not be disqualified for this treatment.

1. Introduction

Older patients with early breast cancer have a comparable benefit from adjuvant chemotherapy as their younger counterparts [1–6] and do experience substantial clinical benefit from neoadjuvant chemotherapy as well [7,8]. However, underutilization of adjuvant systemic therapy in older patients has been observed [9–12], and these patients have a higher risk of treatment side effects that must be taken into

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consideration [4,13–15].

There are limited treatment guidelines for older patients, and age itself should not be used as the primary determinant [16]. Current therapeutic approaches regarding chemotherapy regimens for older patients with early breast cancer are mostly based on extrapolation of evidence from younger patients, since older patients are underrepresented in randomized trials [17–21]. According to international guidelines, adjuvant taxane-based chemotherapy regimens are the preferred option followed by anthracycline-based regimens, whereas sequential treatment is recommended only in fit, older patients with high-risk disease [22]. Additionally, although adjuvant therapy is the preferred option for most older patients, fit older patients could be considered for neoadjuvant strategies [22]. This highlights the complexity of treatment decision-making for chemotherapy use among older patients with breast cancer due to the limited evidence, the higher risk for side effects, and the competing risk of dying due to causes other than breast cancer. In addition, the guidelines recognize the paucity of evidence from randomized trials that lies behind recommendations on specific treatment regimens and settings [22].

In Sweden, sequential regimens containing anthracycline and taxanes have traditionally been the standard treatment approach for older patients, and the Swedish National Treatment Guidelines for breast cancer encourage similar treatment approaches between younger and older patients regarding neoadjuvant therapy [23]. As a result, Swedish real-world data on sequential chemotherapy regimens and treatment in neoadjuvant setting are available and can be used to expand the knowledge on chemotherapy use in older patients with breast cancer.

We, therefore, performed a nationwide, population-based cohort study to explore the risk of short-term mortality (defined as death due to any cause within one year) in older (≥70 years) patients with breast cancer treated with different chemotherapeutic regimens and in different settings (neoadjuvant vs. adjuvant). Short-term mortality was chosen as a proxy that could reflect fatal toxicity to chemotherapy.

2. Materials and Methods

2.1. Data Source and Study Population

The research database Breast Cancer Data Base Sweden (BCBaSe) 3.0 was used as data source in this nationwide, register-based, retrospective cohort study [24]. As described previously [25], BCBaSe 3.0 contains linked data from several Swedish national databases of interest such as the National Quality Registry for Breast Cancer (NKBC) and the Cause of Death Registry [26,27].

Patient-, tumor-, and treatment-related characteristics including information on chemotherapy regimens and setting were obtained from NKBC. The completeness of the NKBC is high, (>99 %), with a low proportion of missing data for most variables (<5 %) and high validity [28]. Type of chemotherapy was grouped as anthracycline-based, taxane-based, and sequential anthracycline- and taxane-based treatment. Patients who received both neoadjuvant and adjuvant chemotherapy were classified as patients in the neoadjuvant setting only. The Cause of Death Registry was used for the variables cause and date of death, whereas The International Statistical Classification of Diseases and Related Health Problems (ICD) coding system was used to define and to characterize the cause of death [27,29].

A flow chart of the present study cohort is illustrated in Fig. 1, showing inclusion and exclusion criteria. We included patients (men/women) who were ≥70 years old, diagnosed with primary (stage I–III) breast cancer, treated with neoadjuvant or adjuvant chemotherapy between 2008 and 2019 (n = 4074). Two patients had missing survival data, generating a final study population of 4072 patients for further analysis.

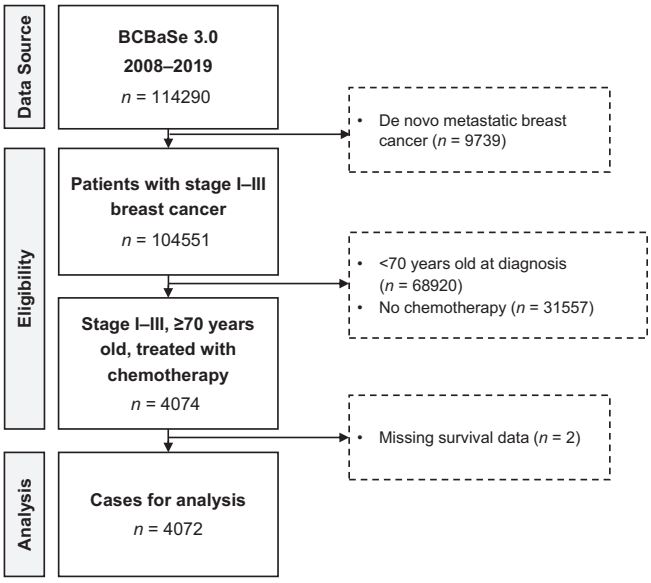

Fig. 1. Flow chart of study population.
Abbreviations: BCBaSe, Breast Cancer Data Base Sweden

2.2. Study Endpoints and Definitions

The primary endpoint was short-term mortality defined as death due to any cause within one year from breast cancer diagnosis. The minimum follow-up required for inclusion was 28 days. Follow-up time of a patient was either the date of an event, or the date of last of follow-up within this study.

Estrogen receptor (ER)- and progesterone receptor (PR) positivity was defined according to Swedish guidelines as ER/PR ≥10 %. Human epidermal growth factor receptor 2 (HER2) positivity was defined as HER2 3+ (as assessed by immunohistochemistry) or HER2 2+ and amplification of *HER2* by in situ hybridization, the rest were considered HER2-negative [30]. Breast cancer subtype was categorized as luminal (ER-positive/HER2-negative), HER2-positive (irrespective of ER status), and triple negative breast cancer (TNBC, defined as ER/PR/HER2-negative). Tumor grade was defined according to the Nottingham histological grade (NHG) system [30,31]. Breast cancer stage (I–III) was applied according to the American Joint Committee on Cancer (AJCC) 8th edition [32].

2.3. Ethics

BCBaSe is a research database approved by the regional ethics board in Stockholm (reference number: 2019-02610). For this study, an additional approval was obtained (reference number: 2024-01947-02). As BCBaSe is a registry-based data source, the Swedish Ethical Review Authority waived the need for informed consent.

2.4. Statistical Analyses

Numbers and percentages, as well as median and interquartile range (IQR), were used as descriptive statistics for categorical and continuous variables, respectively. The outcome short-term mortality was analyzed as dichotomous variables (death due to any cause vs. not). For analysis of association between different characteristics and outcome of interest, Chi2-test was used for categorial and Mann-Whitney U-test for continuous variables, respectively.

Multivariable logistic regression model was applied to investigate the impact of different chemotherapy regimens (anthracycline-based vs. taxane-based vs. sequential anthracycline- and taxane-based) as well as the treatment setting (adjuvant vs. neoadjuvant) on outcome adjusted

Table 1
Patient- and tumor-related characteristics between patients with breast cancer that died within one year from diagnosis compared to patients alive at year one.

Characteristics	All patients *n* = 4072 *n* (%)	Death at one year *n* = 63 *n* (%)	Alive at one year *n* = 4009 *n* (%)	*p*-value
Age at diagnosis, median (Q1-Q3)	73 (71–75)	74 (72–78)	73 (71–75)	0.01
Age at diagnosis, in categories				
70–75	3079 (75.6)	34 (1.1)	3045 (98.9)	<0.001
76–80	823 (20.2)	20 (2.4)	803 (97.6)	
>80	170 (4.2)	9 (5.3)	161 (94.7)	
Year of diagnosis				
2008–2011	485 (11.9)	7 (1.4)	478 (98.6)	0.92
2012–2015	1446 (35.5)	22 (1.5)	1424 (98.5)	
2016–2019	2141 (52.6)	34 (1.6)	2017 (98.4)	
Sex				
Male	47 (1.2)	1 (2.1)	46 (97.9)	0.52
Female	4025 (98.8)	62 (1.5)	3963 (98.5)	
Region				
Northern	420 (10.3)	4 (1.0)	416 (99.0)	0.46
Stockholm–Gotland	974 (23.9)	15 (1.5)	959 (98.5)	
Mid-Sweden	703 (17.3)	11 (1.6)	692 (98.4)	
South	620 (15.2)	11 (1.8)	609 (98.2)	
Southeast	588 (14.4)	5 (0.9)	583 (99.1)	
Western	759 (18.6)	16 (2.1)	743 (97.9)	
Stage at diagnosis				0.20
Stage I	1191 (29.2)	17 (1.4)	1174 (98.6)	
Stage II	1470 (36.1)	22 (1.5)	1448 (98.5)	
Stage III	1411 (34.7)	24 (1.7)	1387 (98.3)	
T status*				
T1	2024 (49.7)	19 (0.9)	2005 (99.1)	0.002
T2–3	2048 (50.3)	44 (2.1)	2004 (97.9)	
N status*				
N0	1902 (46.7)	17 (0.9)	1885 (99.1)	0.006
N1–3	2065 (50.7)	40 (1.9)	2025 (98.1)	
Missing	105	6	99	
Grade (NHG)				
I	149 (3.7)	2 (1.3)	147 (98.7)	<0.001
II	1427 (35.0)	6 (0.4)	1421 (99.6)	
III	2057 (50.5)	41 (2.0)	2016 (98.0)	
Missing	439	14	425	
Molecular subtype				
Luminal	1883 (46.2)	17 (0.9)	1866 (99.1)	<0.001
HER2-positive	1246 (30.6)	17 (1.4)	1229 (98.6)	
TNBC	834 (20.5)	29 (3.5)	805 (96.5)	
Missing	109	0	109	
Type of surgery in breast				
Breast conserving	1857 (45.7)	16 (0.9)	1843 (99.1)	<0.001
Mastectomy	2191 (53.8)	46 (2.1)	2145 (97.9)	
Missing	24	1	23	
Type of surgery in axilla				
Sentinel node biopsy	2011 (49.4)	18 (0.9)	1993 (99.1)	<0.001
Axillary clearance	1966 (49.4)	41 (2.1)	1925 (97.9)	
Missing	95	4	91	
Endocrine therapy				
Yes	2674 (65.7)	9 (0.3)	2665 (99.7)	<0.001
No	1398 (34.3)	54 (3.8)	1344 (96.2)	
Radiotherapy				
No	935 (23.0)	41 (4.4)	894 (95.6)	<0.001
Breast only	1365 (33.5)	4 (0.3)	1361 (99.7)	
Breast and regional lymph nodes	1772 (43.5)	18 (1.0)	1754 (99.0)	
Trastuzumab (neoadjuvant/adjuvant)				
No	2804 (68.9)	50 (1.8)	2754 (98.2)	0.006
Yes	1220 (30.0)	8 (0.7)	1212 (99.3)	
Missing	48	5	43	
Chemotherapy, setting				
Neoadjuvant	651 (16.0)	18 (2.8)	633 (97.2)	0.006
Adjuvant	3421 (84.0)	45 (1.3)	3376 (98.7)	
Chemotherapy, type**				
Anthracycline-based	1398 (34.3)	27 (1.9)	1371 (98.1)	0.18
Taxane-based	587 (14.4)	11 (1.9)	576 (98.1)	
Sequential anthracycline- and taxane-based	2087 (51.3)	25 (1.2)	2062 (98.8)	

T1; tumor size ≤20 mm, T2; tumor size >20 mm.
N0; node-negative, N1–3; node-positive.
Abbreviations: HER2, human epidermal growth factor receptor 2; NHG, Nottingham histological grade; Q, quartile; TNBC, triple negative breast cancer.
* clinical (c) and pathological (p) TN status in the neoadjuvant and adjuvant settings, respectively.
** Distribution of treatment regimens; neoadjuvant setting: anthracycline-based 19.5 % (n = 127/651), taxane-based 12.6 % (n = 82/651) and sequential chemotherapy 67.9 % (n = 442/651); adjuvant setting: anthracycline-based 37.2 % (n = 1273/3421), taxane-based 14.8 % (n = 505/3421) and sequential chemotherapy 48.1 % (n = 1645/3421). Difference in treatment distribution according to treatment setting; $p < 0.001$.

for potential confounders. We initially chose covariates in the model based on the statistically significance in bivariate analyses (age, tumor size [T] status, nodal [N] status, histological grade, molecular subtype, type of breast surgery, type of axillary surgery, endocrine therapy, and radiotherapy) as well as target variables of interest (chemotherapy setting and type). We used the clinical (c) and pathological (p) T and N status for the neoadjuvant and adjuvant setting, respectively. Patients with missing data (119 out of 4072) were excluded from the multivariable analysis. To avoid multicollinearity, we excluded the following variables: initial tumor stage (associated with T and N status), type of axillary surgery (associated with N status), endocrine therapy and trastuzumab treatment (associated with molecular subtype), radiotherapy (associated with type of breast surgery), and grade (>10 % missing values). The results were presented with odds ratios (ORs) and corresponding 95 % confidence interval (CI).

Reasons for death were presented according to the ICD coding system and were further categorized as breast cancer-related, potential treatment-related, other malignant diseases, and other causes unrelated to cancer or treatment. Median (IQR) time from diagnosis (months) to death was also calculated. A p-value <0.05 was considered statistically significant in all statistical analyses. All statistical analyses were performed with IBM SPSS Statistics, Version 28.0.0.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study Population

In total, data from 114290 patients were initially retrieved from the BCBaSe 3.0. Of these, 4074 patients had stage I–III disease, were ≥70 years old, and were treated with chemotherapy (Fig. 1). The chemotherapy utilization rate was approximately 11 % (4074 out of 35631 patients). After excluding two patients with missing survival data, 4072 patients were included in the study cohort. Patient- and tumor-related characteristics are presented in Table 1.

Median age at diagnosis was 73 years (Q1–Q3; 71–75) and the median follow-up time was 49 months (IQR: 28–80 months). The proportion of patients in the study cohort (stage I–III disease, ≥70 years old, treated with chemotherapy) increased over time when compared to all patients ≥70 years old in each time period from the database (year of diagnosis 2008–2011; 5.6 % [485 out of 8623], 2012–2015; 11.6 % [1446 out of 12506], and 2016–2019; 14.8 % [2141 out of 14502]). There were similar proportions regarding tumor size and nodal status with approximately 50 % in each category (T1; 50 % [n = 2024], T2–3; 50 % [n = 2048], N0; 47 % [n = 1902], and N1–3; 51 % [n = 2065]). Stage at diagnosis was evenly distributed (stage I [29 %, n = 1191], stage II [36 %, n = 1470] and stage III [35 %, n = 1411]). The molecular subtype proportions were 46 % luminal (n = 1883), 31 % HER2-positive (n = 1246), and 21 % TNBC (n = 834).

3.2. Chemotherapy Regimens and Treatment Setting

As presented in Table 1, 16 % (n = 651) of the patients received neoadjuvant and 84 % (n = 3421) adjuvant chemotherapy. Sequential chemotherapy was prescribed in 51 % (n = 2087), anthracycline-based therapy in 34 % (n = 1398), and taxane-based in 14 % (n = 587) of the study cohort. The distribution of different treatment regimens in the neoadjuvant (n = 651) and adjuvant setting (n = 3421) were as follows; neoadjuvant setting: anthracycline-based 20 % (n = 127), taxane-based 13 % (n = 82) and sequential chemotherapy 68 % (n = 442); adjuvant setting: anthracycline-based 37 % (n = 1273), taxane-based 15 % (n = 505) and sequential chemotherapy 48 % (n = 1645).

3.3. Prognostic Factors for Short-term Mortality

In total, 63 out of 4072 patients died within one year from breast cancer diagnosis resulting in an overall mortality rate at one year of 1.5 % (95 % CI: 1.2–1.9 %). In bivariate analyses, short-term mortality was associated with older age, higher T and N status, higher histological grade, triple-negative subtype, mastectomy, axillary clearance, no use of adjuvant endocrine therapy, radiotherapy or trastuzumab, and use of neoadjuvant chemotherapy (Table 1). In the multivariable logistic regression analysis (Table 2), the following parameters were independently associated with short-term mortality; age at diagnosis (OR: 1.10, 95 % CI: 1.02–1.18), tumor size (T2–3 vs. T1; OR: 1.94 95 % CI: 1.05–3.59), nodal status (N1–3 vs. N0; OR: 1.98, 95 % CI: 1.08–3.66), triple-negative subtype (TNBC vs. luminal; OR: 4.21, 95 % CI: 2.18–8.10), and the use of neoadjuvant chemotherapy (neoadjuvant vs. adjuvant; OR: 2.00, 95 % CI: 1.04–3.84). Type of chemotherapy regimen was not associated with short-term mortality (sequential anthracycline- and taxane-based vs. anthracycline-based [OR: 0.58, 95 % CI: 0.32–1.05], taxane-based vs. anthracycline-based [OR: 0.67, 95 % CI: 0.29–1.52]).

Table 2
Multivariable logistic regression analysis for death within one year after breast cancer diagnosis among patients aged ≥70 years old treated with chemotherapy.

Characteristics*	OR	95 % CI
Age at diagnosis	1.10	1.02–1.18
T status**		
T1	1	
T2–3	1.94	1.05–3.59
N status**		
N0	1	
N1–3	1.98	1.08–3.66
Molecular subtype		
Luminal	1	
HER2-positive	1.50	0.71–3.18
TNBC	4.21	2.18–8.10
Type of surgery in breast		
Breast conserving	1	
Mastectomy	1.39	0.73–2.63
Chemotherapy, setting		
Adjuvant	1	
Neoadjuvant	2.00	1.04–3.84
Chemotherapy, type		
Anthracycline-based	1	
Taxane-based	0.67	0.29–1.52
Sequential anthracycline- and taxane-based	0.58	0.32–1.05

T1; tumor size ≤20 mm, T2; tumor size >20 mm.
N0; node-negative, N1–3; node-positive.
Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; OR, odds ratio; TNBC, triple negative breast cancer.
* According to complete case approach; 199 patients were excluded due to missing values; 3873 patients were included in the multivariable model.
** clinical (c) and pathological (p) TN status in the neoadjuvant and adjuvant settings, respectively.

3.4. Time to and Reasons for Death within One Year from Diagnosis

The time from breast cancer diagnosis to death is illustrated in Fig. 2. Median time until death among those who died within one year was 7 months (IQR: 5–9) in the whole cohort (n = 63), while it was 7 months (IQR: 4–9 months) in the neoadjuvant setting (n = 18) and 8 months (IQR: 6–10 months) in the adjuvant setting (n = 45).

The reasons for death among the 63 patients that died within one year were defined according to the ICD coding system (Appendix A. Supplementary data, Table A1). We categorized the causes into breast cancer-related (57 %, n = 36), potential treatment-related (22 %, n = 14), other malignant diseases (8 %, n = 5), and other causes unrelated to cancer or treatment (13 %, n = 8). Among those who received neoadjuvant chemotherapy, the most common cause of death was breast cancer (78 %; 14 of 18 deaths), followed by potential treatment-related (11 %; 2 of 18 deaths), and other causes unrelated to cancer or treatment (11 %; 2 of 18 deaths) (Table 3). The corresponding numbers among

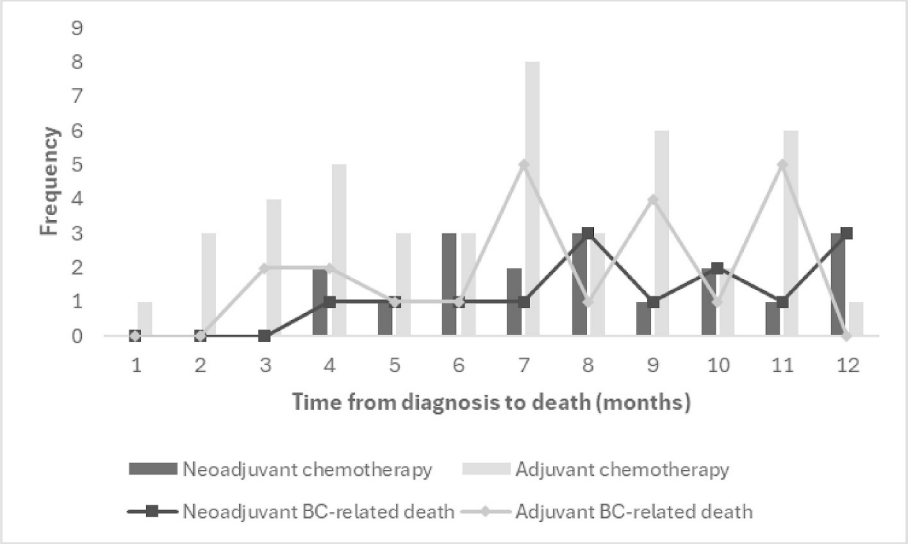

Fig. 2. Schematic distribution of time to death within one year from diagnosis for older patients in the neoadjuvant ($n = 18$) and adjuvant setting ($n = 45$), and proportion of breast cancer-related deaths.
Abbreviations: BC, breast cancer

Table 3
Proportion of causes of death between patients treated with neoadjuvant and adjuvant chemotherapy.

Reason for death within one year from diagnosis	Neoadjuvant $n = 18$ n (%)	Adjuvant $n = 45$ n (%)
Breast cancer-related	14 (77.8)	22 (48.9)
Potential treatment-related	2 (11.1)	12 (26.7)
Other malignant diseases	–	5 (11.1)
Other causes unrelated to cancer or treatment	2 (11.1)	6 (13.3)
In total	18 (28.6)	45 (71.4)

those who received adjuvant chemotherapy were breast cancer-related reasons (49 %; 22 of 45 deaths), potential treatment-related (27 %; 12 of 45 deaths), other causes unrelated to cancer or treatment (13 %; 6 of 45 deaths), and other malignant diseases (11 %; 5 of 45 deaths) (Table 3).

4. Discussion

In this study of patients with breast cancer aged ≥70 years treated with neoadjuvant or adjuvant chemotherapy, the short-term mortality rate within the first year after diagnosis was 1.5 %, mostly attributed to breast cancer-related deaths. Apart from patient age and other well-known prognostic clinicopathological parameters, the use of chemotherapy in the neoadjuvant setting was associated with an increased risk of short-term mortality, whereas type of chemotherapy regimen did not seem to impact the risk. The increasing trend in the use of chemotherapy among older patients over time suggests a progressively positive treatment approach. Despite less selective use the one-year mortality rate remained consistent across each time period.

The overall mortality of 1.5 % during the first year after breast cancer diagnosis in our study seems to be rather low in comparison to a population-based study from the United States where the mortality rate was 2.9 % [33]. According to their results, the risk of death in a matched control group was 1.3 %. The difference in mortality rates between our cohort and theirs cannot be explained by differences in patient and tumor characteristics as our patient cohort was generally older but had similar stage and tumor biology. However, the inclusion period differs by one decade and the differences in mortality rates may reflect improvements in cancer care over time. Both studies identified similar variables as predictors for higher short-term mortality: age, advanced stage, and more aggressive tumor biology. In fact, Rosenstock et al. showed a steady increase in mortality by age and almost a fourfold increase in OR for those >80 years old [33]. These and our results reflect the fact that the older patient population should not be regarded as a homogeneous group. Age alone does not make the population heterogeneous, but there is an assumed association between age in older patients and increased comorbidities, sensitivity to toxicities, and impaired functional status. Therefore, each additional year of age seems to have a more notable impact on outcomes in older patients. In total, we both found similar distribution of breast cancer and non-breast cancer related deaths, with nearly 60 % of deaths attributed to breast cancer, however we report fewer events (49 %) in the adjuvant setting. Although miscoding of the cause of death cannot be entirely ruled out, the frequency of breast cancer-related deaths within one year of diagnosis likely reflects a patient selection where older patients might more often be selected for neoadjuvant or adjuvant chemotherapy only if their disease is highly aggressive. In comparison, younger patients are offered neo/adjuvant chemotherapy for less advanced stages and their risk of breast cancer-related death during the first year is considered low. Notably, even if the chemotherapy utilization rate in our cohort seems rather low (11 %), and undertreatment of older patients is regarded as an issue [9–12], a substantial proportion of patients receiving chemotherapy in our study cohort had less advanced and aggressive disease, thus implying a changing pattern in patient selection for chemotherapy among older patients over time.

The use of neoadjuvant chemotherapy treatment appears to be increasing in older patients, especially among those with HER2-positive or TNBC, as well as in more advanced disease [34]. However, treatment-related toxicities, dose reduction, and early treatment discontinuation in the neoadjuvant setting are more frequently reported in older versus younger patients [35]. Interestingly, we demonstrated a doubled risk of short-term mortality among patients treated in neoadjuvant compared to adjuvant setting. This result could support the recommendation from international guidelines to carefully select only fit older patients for this approach [22]. However, the reason behind our observation is not easily addressed. Despite the adjustments made in our analyses, the retrospective study design precludes any claim of causality, and it cannot be ruled out that the association between neoadjuvant setting and short-term mortality could be attributed to residual confounding. The numerical difference in cause of death between the two treatment settings,

with more patients dying due to breast cancer in the neoadjuvant compared to in the adjuvant setting, partly supports the hypothesis of residual confounding since patients in the neoadjuvant setting might be those with more aggressive disease leading to higher numbers of breast cancer-related deaths. Another plausible explanation could be that patients in the neoadjuvant setting receive more intense chemotherapy regimens (longer duration and dose-dense strategies). Then we would expect a shorter median time to death in neoadjuvant compared to adjuvant setting as deaths related to chemotherapy are expected during or shortly after chemotherapy. This was, however, not the case as similar time periods were observed. The observation should, however, be interpreted carefully due to the small number of events in the analysis. Even though there was a significant difference regarding treatment regimens between those in the neoadjuvant and adjuvant setting, treatment regimen differences did not explain the mortality differences when analyzed by Cox regression. Whether differences in chemotherapy doses could lie behind the imbalance in deaths between patients in different settings cannot be answered by the current study due to lack of data on this variable in our cohort.

Regarding type of treatment, international guidelines recommend sequential chemotherapy treatment only for highly selected, fit older patients with very high-risk disease [22]. The rationale behind this recommendation is the lack of data on sequential treatment among older patients, as these patients were less commonly included in trials of sequential treatment [36]. According to the latest meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, early breast cancer chemotherapy regimens containing both anthracycline and taxane (in sequence or in combination) are more effective than anthracycline-free regimens [36]. The reported benefit was seen regardless of age, but the proportion of older women participating in the included trials was low, with a median participant age of 53 years and with more than half of the primary studies having upper age limits of 70 years. Rosenstock et al. found no association between anthracycline-based therapy and one-year mortality but had no data on taxanes [33]. Interestingly, we found type of chemotherapy regimen not to be associated with short-term mortality. On the contrary, we observed a trend towards a lower mortality for the sequential regimen as compared to the anthracycline-only regimen, supporting the use of sequential regimens for selected older patients. Moreover, the rate of potentially treatment-related mortality was generally low (11 % and 27 % in the neoadjuvant and adjuvant settings, respectively), reflecting a large proportion of patients with high-risk breast cancer disease among those given chemotherapy, especially in the neoadjuvant setting.

Strengths of this study are the population-based nature of the data source, with validated variables, including type of chemotherapy regimen, and a large number of patients [28,37]. Limitations to consider are the lack of information on comorbidity and on the duration and doses of chemotherapy that precludes deeper analyses of factors associated with higher short-term mortality among patients receiving neoadjuvant chemotherapy. Moreover, the risk of miscoding of the cause of death within one year should be kept in mind when interpreting the results [38–40]. Finally, we utilized short-term mortality as a proxy for fatal toxicity due to chemotherapy, thus excluding clinical situations such as prolonged hospitalizations and organ-specific toxicities with long-term sequelae that could impact patients' quality of life and influence the decision-making process regarding chemotherapy in older patients. Using geriatric assessments can predict treatment toxicity and should guide treatment decisions [41], while their effect on short-term mortality yet remains unclear.

5. Conclusions

In conclusion, we demonstrated a relatively low risk of short-term mortality of 1.5 % within the first year among older patients with breast cancer treated with chemotherapy. The risk of potential treatment-associated death was low, suggesting that older patients should not be disqualified for chemotherapy treatment. Choice of sequential treatment with anthracyclines and taxanes did not seem to impact short-term mortality, and this treatment approach could be suitable for selected older patients; the effect of possible confounding by indication should also be considered. Even though short-term mortality was substantially higher among patients treated with neoadjuvant chemotherapy, the risk of residual confounding should be acknowledged. Further clinical studies with longitudinal study design focusing on treatment decision based on geriatric assessment, patients' quality of life, and risk of toxicities in older patients undergoing neoadjuvant and/or adjuvant chemotherapy are needed to provide deeper insights into the optimal therapeutic approach for this challenging patient population.

Author Contributions

Concept and design: CL, AV.
Data acquisition: AV.
Formal analysis: AV.
Data interpretation: CL, AV, IF, KE.
Writing original draft: CL, AV.
Review and editing: All authors.
The final version was approved by all authors.

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Declaration of Competing Interest

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2025.102220.

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