Early Death Incidence and Prediction in Stage IV Breast Cancer

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Statistical Analysis **C**
Data Interpretation **D**
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Background:
The early death of patients is a global cancer issue. We aimed to identify the risk factors for early death in stage IV breast cancer. Predictive nomograms for early death evaluation were generated based on the risk factors.

Material/Methods:
Based on the Surveillance, Epidemiology, and End Results (SEER) database, patients diagnosed with IV breast cancer were selected. The risk factors for early death (survival time ≤1 year) were identified using logistic regression model analysis. Predictive nomograms were constructed and internal validation was performed.

Results:
A total of 5998 (32.6%) breast cancer patients were diagnosed as early death in the construction cohort. Age older than 50 years, unmarried status, black race, uninsured status, triple-negative type, grade (II and III), tumor size >5 cm, and metastasis to lung, liver, and brain were risk factors for total early death, while Luminal B subtype, N1 stage, and surgical interventions were associated with lower risk of early death. As for cancer-specific and non-cancer-specific early death, several factors were not consistent between the 2 groups. Nomograms for all-cause, cancer-specific, and non-cancer-specific early death were constructed. The calibration curve showed satisfactory agreement. The areas under the ROC curve (AUC) were 78.3% (95% CI: 77.7–78.9%), 75.8% (75.1–76.4%), and 72.3% (71.6–72.9%), respectively. In the validation cohort, a total of 689 (19.3%) patients were diagnosed as early death and the calibration curve showed satisfactory agreement. The AUCs of the all-cause, cancer-specific, and non-cancer-specific early death prediction were 74.0% (95% CI: 72.5–75.4%), 73.5% (72.0–74.9%), and 68.6% (67.0–70.1%), respectively.

Conclusions:
Nomograms were generated to predict early death, with good calibration and discrimination. The predictive model can provide a reference for identifying cases with high risk of early death among stage IV breast cancer patients and play an auxiliary role in guiding individual treatment.

MeSH Keywords:
Breast Neoplasms • Nomograms • SEER Program

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Background

Breast cancer is a worldwide problem, and is the leading cause of cancer morbidity and mortality in females [1]. The long-term survival of breast cancer patients has been investigated, and the global 5- and 10-year pooled survival rates were reported to be 73% (95% CI: 71–75%) and 61% (95% CI: 54–67%), respectively [2].

Early death is a crucial issue in the management of cancer. A series of studies have been conducted to investigate early death in cancer, including lung cancer [3], bladder cancer [4], and colorectal cancer [5]. The related factors for early death revealed in these studies provided evidence for cancer treatment. For primary breast cancer, around 10% of the patients died during the first year after initial diagnosis. Age over 80 years and distant metastases at presentation were proved to be the risk factors leading to early death. Meanwhile, surgery was reported to be able to decrease the risk of early death (OR=0.29, 95% CI: 0.24–0.35) [6].

As to the United States, approximately 5% of women with newly diagnosed breast cancer were reported to present with stage IV at diagnosis [7]. The proportion of stage IV breast cancer was even higher in the Asian population [8]. Compared with patients in early stage, patients in advanced stage were reported to have worse survival. The reported unadjusted median overall survival was 3.52 years in patients after surgery and 2.36 years in those without surgery [9].

The identification of factors correlated with early death in stage IV breast cancer is important. Based on a large cohort, we sought to identify the patients who died within 12 months after stage IV breast cancer diagnosis and to investigate the risk factors. Furthermore, predictive nomograms based on the results from the logistic regression model were constructed to predict the early death in stage IV breast cancer and to guide personalized early death risk screening.

Material and Methods

Data source and cohort selection

The National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database (*https://seer.cancer.gov/*) covers approximately 28% of the population in the USA. The data used in the present study were obtained from the latest version by April 2019, which was named as Incidence – SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975–2016 varying).
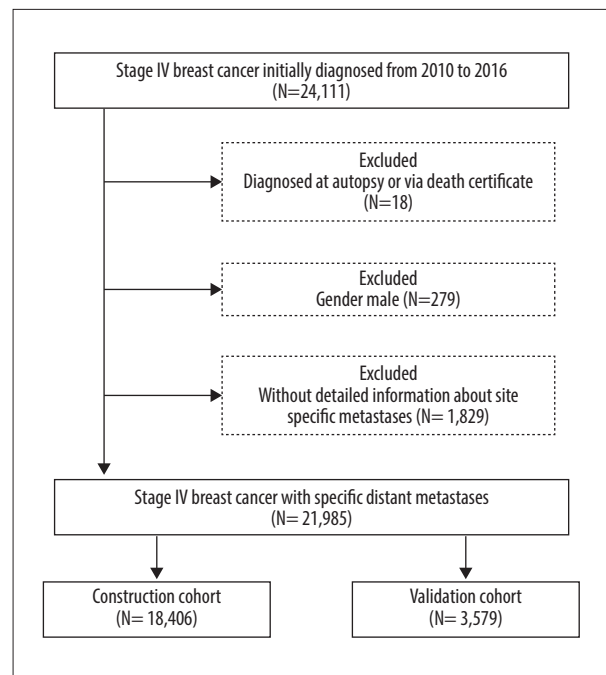
Figure 1. Selection procedure for patients with stage IV breast cancer.

Breast cancer patients at stage IV diagnosed between 2010 and 2015 were included into the construction cohort. In order to validate performance of the prediction model, temporal validation was conducted as internal validation. In the validation cohort, breast cancer patients at stage IV diagnosed in 2016 were used to validate the performance. The exclusion criteria were as follows: patients diagnosed at autopsy or via death certificate, male patients, and those without detailed information about site-specific metastases. The flow-chart of subject selection is listed in Figure 1. As in a previous study, early death in breast cancer patients was defined as death within 1 year after initial diagnosis [6].

Statistical analysis

The variables of the extracted data from the SEER database included age at diagnosis (<50, 50–59, 60–69, 70–79, and ≥80 years), marital status (married and unmarried), race (white, black and others), insurance recode (insured and uninsured), breast cancer subtypes (Luminal A, Luminal B, HER2 enriched, and triple-negative), tumor grade (I to IV: well, moderately, poorly, and undifferentiated, respectively), primary tumor site (C50.4-outer quadrant, UOQ; C50.5-lower outer quadrant, LOQ; C50.3-lower inner quadrant, LIQ; C50.2-upper inner quadrant, UIQ; C50.1-central portion, CEN; others including C50.0-Nipple, C50.6-Axillary tail of breast and C50.8-Overlapping lesion of breast), laterality (left-sided, right-sided, one side, NOS and paired sides), tumor size (0–2, 2–5 and >5 cm), N stage (N0, N1, N2 and N3), bone metastasis (no or yes),

brain metastasis (no or yes), liver metastasis (no or yes), lung metastasis (no or yes), surgery treatment (no surgery; partial mastectomy, PM; total mastectomy, TM; radical mastectomy, RM; and others, including local tumor destruction, subcutaneous mastectomy, and bilateral mastectomy).

All of the variables in our study were categorical data, which are presented as numbers and percentages. A logistics regression model was used to identify the risk factors for early death. Variables with P<0.05 in the univariate analysis were further used in the multivariate analysis to determine the potential risk factors. The cases with missing data were excluded from the logistics analysis. Based on the results from the logistic regression model, the nomograms for all-cause, cancer-specific, and non-cancer-specific early death were formulated using the rms package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The calibration plots produced by bootstrapping with 1000 resamples were used to test the calibration of the nomograms. The discrimination of the nomograms was evaluated by the receiver operating characteristics (ROC). A greater area under the curve (AUC) close to 1.0 indicated better ability of discrimination.

Data extraction was performed using the SEER*Stat Software and statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were two-sided, and P<0.05 was considered significant.

Ethics statement

The SEER dataset is a freely available database, and the data released by SEER do not require informed patient consent because cancer is a reportable disease in every state in the USA. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Clinical characteristics and incidence of early death

After excluding patients diagnosed by autopsy or death certificate, male patients, and those without complete records, a total of 18 406 breast cancer patients at stage IV were enrolled in the construction cohort. Patients' basic characteristics are summarized in Table 1. According to the pre-definition, 5998 (32.6%) patients were categorized as early death, among whom 4416 patients died due to cancer-specific cause. Most patients with early death were diagnosed after age 50 years (89.2%). The most common cancer subtype was Luminal A (38.3%), followed by triple-negative (19.4%), Luminal B, and HER2 enriched type. Except for the unknown grade, grade III (37.0%) and II (23.9%) were the most common types. Distant

metastasis was found in 3842 (64.1%) patients in bone, 2471 (41.2%) patients in lung, 2178 (36.3%) patients in liver, and 820 (13.7%) patients in brain. A total of 5094 (84.9%) patients did not receive any surgical intervention.

Risk factors for early death

In the univariate logistic regression, diagnosis age older than 50 years, unmarried status, black race, uninsured status, HER2-enriched and triple-negative types, grade (II–IV), tumor size >5 cm, paired sides, and distant metastases (lung, liver and brain) were associated with greater risk of total early death. Other race, Luminal B subtype, N1 and N2 stage, and surgical interventions significantly decreased the risk of early death. As for cause of death, uninsured status, Luminal B subtype, tumor size 2–5 cm and >5 cm, and N3 stage showed different trends in the cancer-specific and non-cancer-specific early death. Table 2 provides detailed information.

When adjusting these factors in the multivariate logistic regression, the independent risk factors for total early death included age older than 50 years, unmarried status, black race, uninsured status, triple-negative type, grade (II and III), tumor size >5 cm, and metastasis to lung, liver, and brain. Luminal B subtype, N1 stage, and surgical interventions were significantly associated with lower risk of early death. Unmarried status, uninsured status, Luminal B subtype, grade (II and III), tumor size 2–5 cm and >5 cm, N1 stage, and metastasis to bone and lung were not consistent between the cancer-specific and non-cancer-specific early death groups. Table 3 provides detailed information.

Performance of the nomograms for predicting early death

Nomograms predicting the risk of early death are shown in Figure 2 (Figure 2A–2C for all-cause, cancer-specific, and non-cancer-specific early death, respectively). Excellent ability of calibration was achieved in the 3 predictive models, with all calibration curve close to the 45-degree line (Figure 3A–3C for all-cause, cancer-specific, and non-cancer-specific early death, respectively). All 3 nomograms showed satisfactory strength of discrimination (Figure 3D–3F). The AUC for nomograms of the all-cause, cancer-specific, and non-cancer-specific early death prediction were 78.3% (95% CI: 77.7–78.9%), 75.8% (95% CI: 75.1–76.4%), and 72.3% (95% CI: 71.6–72.9%), respectively.

In the validation cohort, a total of 689 (19.3%) breast cancer patients were diagnosed as early death, among whom 508 patients died due to cancer-specific causes. Patients' basic characteristics are shown in Supplementary Table 1. The calibration curve showed satisfactory agreement (Supplementary Figure 1A–1C). As shown in Supplementary Figure 1D–1F, the AUC for nomograms of the all-cause, cancer-specific, and non-cancer-specific early death prediction were 74.0% (95%

Table 1. Description of the early death for patients with IV breast cancer in the construction cohort.

Subject characteristics	Patients No. (%)			
	No early death	Total early death	Cancer specific early death	Non-cancer specific early death
Age				
<50	2790 (22.5)	645 (10.8)	521 (11.8)	124 (7.8)
50–59	3256 (26.2)	1178 (19.6)	923 (20.9)	255 (16.1)
60–69	3267 (26.3)	1506 (25.1)	1128 (25.5)	378 (23.9)
70–79	1952 (15.7)	1318 (22.0)	940 (21.3)	378 (23.9)
≥80	1143 (9.2)	1351 (22.5)	904 (20.5)	447 (28.3)
Marital status				
Married	5790 (46.7)	1993 (33.2)	1477 (33.4)	516 (32.6)
Unmarried	5922 (47.7)	3674 (61.3)	2697 (61.1)	977 (61.8)
Unknown	696 (5.6)	331 (5.5)	242 (5.5)	89 (5.6)
Race				
White	9466 (76.3)	4409 (73.5)	3252 (73.6)	1157 (73.1)
Black	1906 (15.4)	1208 (20.1)	881 (20)	327 (20.7)
Others	987 (8.0)	369 (6.2)	274 (6.2)	95 (6.0)
Unknown	49 (0.4)	12 (0.2)	9 (0.2)	3 (0.2)
Insurance				
Insured	11727 (94.5)	5527 (92.1)	4033 (91.3)	1494 (94.4)
Uninsured	437 (3.5)	308 (5.1)	265 (6.0)	43 (2.7)
Unknown	244 (2.0)	163 (2.7)	118 (2.7)	45 (2.8)
Subtypes				
Luminal A	7274 (58.6)	2295 (38.3)	1645 (37.3)	650 (41.1)
Luminal B	1961 (15.8)	544 (9.1)	427 (9.7)	117 (7.4)
HER2 enriched	891 (7.2)	424 (7.1)	323 (7.3)	101 (6.4)
Triple negative	908 (7.3)	1164 (19.4)	871 (19.7)	293 (18.5)
Unknown	1374 (11.1)	1571 (26.2)	1150 (26)	421 (26.6)
Grade				
Grade I	979 (7.9)	212 (3.5)	140 (3.2)	72 (4.6)
Grade II	4401 (35.5)	1432 (23.9)	1021 (23.1)	411 (26)
Grade III	4220 (34.0)	2220 (37.0)	1689 (38.2)	531 (33.6)
Grade IV	56 (0.5)	45 (0.8)	37 (0.8)	8 (0.5)
Unknown	2752 (22.2)	2089 (34.8)	1529 (34.6)	560 (35.4)
Tumor site				
UOQ	2930 (23.6)	1141 (19)	832 (18.8)	309 (19.5)
LOQ	684 (5.5)	226 (3.8)	162 (3.7)	64 (4.0)
LIQ	453 (3.7)	154 (2.6)	104 (2.4)	50 (3.2)
UIQ	794 (6.4)	284 (4.7)	204 (4.6)	80 (5.1)
CEN	761 (6.1)	288 (4.8)	212 (4.8)	76 (4.8)
Others	2577 (20.8)	1059 (17.7)	767 (17.4)	292 (18.5)
Unknown	4209 (33.9)	2846 (47.4)	2135 (48.3)	711 (44.9)

Table 1 continued. Description of the early death for patients with IV breast cancer in the construction cohort.

Subject characteristics	Patients No. (%)			
	No early death	Total early death	Cancer specific early death	Non-cancer specific early death
Laterality				
Left-sided	6030 (48.6)	2848 (47.5)	2110 (47.8)	738 (46.6)
Right-sided	5799 (46.7)	2684 (44.7)	1972 (44.7)	712 (45.0)
One side, NOS	51 (0.4)	35 (0.6)	29 (0.7)	6 (0.4)
Paired sides	528 (4.3)	431 (7.2)	305 (6.9)	126 (8.0)
Tumor size				
0–2 cm	1937 (15.6)	705 (11.8)	438 (9.9)	267 (16.9)
2–5 cm	4721 (38.0)	1871 (31.2)	1346 (30.5)	525 (33.2)
>5 cm	3263 (26.3)	1580 (26.3)	1274 (28.8)	306 (19.3)
Unknown	2487 (20.0)	1842 (30.7)	1358 (30.8)	484 (30.6)
N stage				
N0	2860 (23.0)	1490 (24.8)	991 (22.4)	499 (31.5)
N1	4321 (34.8)	1634 (27.2)	1266 (28.7)	368 (23.3)
N2	1131 (9.1)	370 (6.2)	276 (6.3)	94 (5.9)
N3	3092 (24.9)	1613 (26.9)	1237 (28)	376 (23.8)
Unknown	1004 (8.1)	891 (14.9)	646 (14.6)	245 (15.5)
Bone Met				
No	3562 (28.7)	2156 (35.9)	1525 (34.5)	631 (39.9)
Yes	8846 (71.3)	3842 (64.1)	2891 (65.5)	951 (60.1)
Brain Met				
No	11786 (95.0)	5178 (86.3)	3792 (85.9)	1386 (87.6)
Yes	622 (5.0)	820 (13.7)	624 (14.1)	196 (12.4)
Liver Met				
No	9722 (78.4)	3820 (63.7)	2712 (61.4)	1108 (70)
Yes	2686 (21.6)	2178 (36.3)	1704 (38.6)	474 (30)
Lung Met				
No	8861 (71.4)	3527 (58.8)	2521 (57.1)	1006 (63.6)
Yes	3547 (28.6)	2471 (41.2)	1895 (42.9)	576 (36.4)
Surgery				
No surgery	8177 (65.9)	5094 (84.9)	3785 (85.7)	1309 (82.7)
PM	1174 (9.5)	298 (5.0)	195 (4.4)	103 (6.5)
TM	984 (7.9)	201 (3.4)	132 (3)	69 (4.4)
RM	1851 (14.9)	339 (5.7)	251 (5.7)	88 (5.6)
Others	38 (0.3)	9 (0.2)	5 (0.1)	4 (0.3)
Unknown	184 (1.5)	57 (1.0)	48 (1.1)	9 (0.6)

UOQ – upper outer quadrant; LOQ – lower outer quadrant; LIQ – lower inner quadrant; UIQ – upper inner quadrant; CEN – central portion; NOS – not otherwise specified; PM – partial mastectomy; TM – total mastectomy; RM – radical mastectomy.

Table 2. Univariate logistic regression for analyzing the risk factors for early death in patients with IV breast cancer.

Subject characteristics	Total early death		Cancer specific early death		Non-cancer specific early death	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age						
<50	Ref	1.0	Ref	1.0	Ref	1.0
50–59	1.57 (1.40–1.74)	<0.001	1.47 (1.31–1.66)	<0.001	1.63 (1.31–2.03)	<0.001
60–69	1.99 (1.80–2.22)	<0.001	1.73 (1.54–1.94)	<0.001	2.30 (1.87–2.83)	<0.001
70–79	2.92 (2.62–3.26)	<0.001	2.26 (2.00–2.54)	<0.001	3.49 (2.83–4.30)	<0.001
≥80	5.11 (4.55–5.74)	<0.001	3.18 (2.81–3.60)	<0.001	5.83 (4.74–7.17)	<0.001
Marital status						
Married	Ref	1.0	Ref	1.0	Ref	1.0
Unmarried	1.80 (1.69–1.92)	<0.001	1.67 (1.55–1.79)	<0.001	1.60 (1.43–1.78)	<0.001
Race						
White	Ref	1.0	Ref	1.0	Ref	1.0
Black	1.36 (1.26–1.48)	<0.001	1.29 (1.18–1.41)	<0.001	1.29 (1.13–1.47)	<0.001
Others	0.80 (0.71–0.91)	0.001	0.83 (0.72–0.95)	0.007	0.83 (0.67–1.03)	0.089
Insurance						
Insured	Ref	1.0	Ref	1.0	Ref	1.0
Uninsured	1.50 (1.29–1.74)	<0.001	1.81 (1.55–2.11)	<0.001	0.65 (0.47–0.88)	0.006
Subtypes						
Luminal A	Ref	1.0	Ref	1.0	Ref	1.0
Luminal B	0.88 (0.79–0.98)	0.017	0.99 (0.88–1.11)	0.864	0.67 (0.55–0.82)	<0.001
HER2 enriched	1.51 (1.33–1.71)	<0.001	1.57 (1.37–1.80)	<0.001	1.14 (0.92–1.42)	0.234
Triple negative	4.06 (3.68–4.48)	<0.001	3.49 (3.15–3.87)	<0.001	2.26 (1.95–2.62)	<0.001
Grade						
Grade I	Ref	1.0	Ref	1.0	Ref	1.0
Grade II	1.50 (1.28–1.76)	<0.001	1.59 (1.32–1.92)	<0.001	1.18 (0.91–1.53)	0.214
Grade III	2.43 (2.08–2.84)	<0.001	2.67 (2.22–3.21)	<0.001	1.40 (1.08–1.80)	0.010
Grade IV	3.71 (2.44–5.65)	<0.001	4.34 (2.79–6.75)	<0.001	1.34 (0.63–2.86)	0.454
Tumor site						
UOQ	Ref	1.0	Ref	1.0	Ref	1.0
LOQ	0.85 (0.72–1.00)	0.051	0.84 (0.70–1.02)	0.072	0.92 (0.70–1.22)	0.564
LIQ	0.87 (0.72–1.06)	0.173	0.81 (0.64–1.01)	0.058	1.09 (0.80–1.49)	0.577
UIQ	0.92 (0.79–1.07)	0.272	0.91 (0.77–1.08)	0.271	0.98 (0.76–1.26)	0.852
CEN	0.97 (0.84–1.13)	0.712	0.99 (0.83–1.17)	0.870	0.95 (0.73–1.23)	0.705
Others	1.06 (0.96–1.17)	0.287	1.04 (0.93–1.16)	0.477	1.06 (0.90–1.26)	0.472

Table 2 continued. Univariate logistic regression for analyzing the risk factors for early death in patients with IV breast cancer.

Subject characteristics	Total early death		Cancer specific early death		Non-cancer specific early death	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Laterality						
Left-sided	Ref	1.0	Ref	1.0	Ref	1.0
Right-sided	0.98 (0.92–1.05)	0.534	0.97 (0.91–1.04)	0.419	1.01 (0.91–1.13)	0.848
One side, NOS	1.45 (0.94–2.24)	0.090	1.63 (1.04–2.56)	0.033	0.83 (0.36–1.90)	0.655
Paired sides	1.73 (1.51–1.98)	<0.001	1.50 (1.30–1.73)	<0.001	1.67 (1.36–2.04)	<0.001
Tumor size						
0–2 cm	Ref	1.0	Ref	1.0	Ref	1.0
2–5 cm	1.09 (0.98–1.21)	0.100	1.29 (1.15–1.45)	<0.001	0.77 (0.66–0.90)	0.001
>5 cm	1.33 (1.20–1.48)	<0.001	1.80 (1.59–2.03)	<0.001	0.60 (0.51–0.71)	<0.001
N stage						
N0	Ref	1.0	Ref	1.0	Ref	1.0
N1	0.73 (0.67–0.79)	<0.001	0.92 (0.83–1.01)	0.065	0.51 (0.44–0.59)	<0.001
N2	0.63 (0.55–0.72)	<0.001	0.76 (0.66–0.89)	<0.001	0.52 (0.41–0.65)	<0.001
N3	1.00 (0.92–1.09)	0.976	1.21 (1.10–1.33)	<0.001	0.67 (0.58–0.77)	<0.001
Bone Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	0.72 (0.67–0.77)	<0.001	0.81 (0.76–0.87)	<0.001	0.65 (0.59–0.73)	<0.001
Brain Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	3.00 (2.69–3.35)	<0.001	2.65 (2.37–2.96)	<0.001	1.77 (1.51–2.08)	<0.001
Liver Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	2.06 (1.93–2.21)	<0.001	2.15 (2.00–2.32)	<0.001	1.21 (1.08–1.36)	0.001
Lung Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	1.75 (1.64–1.87)	<0.001	1.80 (1.68–1.93)	<0.001	1.20 (1.08–1.33)	0.001
Surgery						
No surgery	Ref	1.0	Ref	1.0	Ref	1.0
PM	0.41 (0.36–0.47)	<0.001	0.38 (0.33–0.45)	<0.001	0.69 (0.56–0.85)	<0.001
TM	0.33 (0.28–0.38)	<0.001	0.31 (0.26–0.38)	<0.001	0.57 (0.44–0.73)	<0.001
RM	0.29 (0.26–0.33)	<0.001	0.32 (0.28–0.37)	<0.001	0.38 (0.31–0.48)	<0.001
Others	0.38 (0.18–0.79)	0.009	0.30 (0.12–0.76)	0.011	0.85 (0.31–2.37)	0.756

SEER – Surveillance, Epidemiology, and End Result; OR – odds ratio; CI – confidence interval; Ref – reference; NA – not applicable; UOQ – upper outer quadrant; LOQ – lower outer quadrant; LIQ – lower inner quadrant; UIQ – upper inner quadrant; CEN – central portion; NOS – not otherwise specified; PM – partial mastectomy; TM – total mastectomy; RM – radical mastectomy.

Table 3. Multivariate logistic regression for analyzing the risk factors for early death in patients with IV breast cancer.

Subject characteristics	Total early death		Cancer specific early death		Non-cancer specific early death	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age						
<50	Ref	1.0	Ref	1.0	Ref	1.0
50–59	1.59 (1.35–1.89)	<0.001	1.51 (1.26–1.80)	<0.001	1.52 (1.09–2.13)	0.014
60–69	2.22 (1.88–2.63)	<0.001	1.84 (1.54–2.20)	<0.001	2.5 (1.83–3.44)	<0.001
70–79	3.48 (2.90–4.17)	<0.001	2.41 (1.98–2.93)	<0.001	4.25 (3.08–5.86)	<0.001
≥80	7.04 (5.78–8.57)	<0.001	3.95 (3.21–4.87)	<0.001	7.37 (5.31–10.22)	<0.001
Marital status						
Married	Ref	1.0	Ref	1.0	Ref	1.0
Unmarried	1.40 (1.26–1.56)	<0.001	1.39 (1.23–1.56)	<0.001	1.19 (1–1.42)	0.052
Race						
White	Ref	1.0	Ref	1.0	Ref	1.0
Black	1.36 (1.19–1.57)	<0.001	1.28 (1.10–1.48)	0.001	1.34 (1.08–1.67)	0.009
Others	0.91 (0.74–1.12)	0.381	0.94 (0.75–1.17)	0.570	0.88 (0.61–1.27)	0.505
Insurance						
Insured	Ref	1.0	Ref	1.0	Ref	1.0
Uninsured	1.31 (1.00–1.72)	0.048	1.52 (1.15–2.00)	0.003	0.61 (0.33–1.11)	0.103
Subtypes						
Luminal A	Ref	1.0	Ref	1.0	Ref	1.0
Luminal B	0.78 (0.67–0.91)	0.002	0.81 (0.68–0.96)	0.014	0.83 (0.63–1.08)	0.164
HER2 enriched	1.17 (0.97–1.42)	0.107	1.11 (0.90–1.36)	0.318	1.23 (0.9–1.69)	0.193
Triple Negative	3.76 (3.23–4.37)	<0.001	3.06 (2.62–3.57)	<0.001	2.09 (1.66–2.62)	<0.001
Grade						
Grade I	Ref	1.0	Ref	1.0	Ref	1.0
Grade II	1.56 (1.25–1.95)	<0.001	1.59 (1.22–2.06)	0.001	1.27 (0.91–1.79)	0.165
Grade III	2.22 (1.76–2.79)	<0.001	2.29 (1.76–2.99)	<0.001	1.42 (1–2.02)	0.053
Grade IV	1.44 (0.70–2.93)	0.321	1.95 (0.94–4.07)	0.075	0.57 (0.13–2.49)	0.454
Laterality						
Left-sided	Ref	1.0	Ref	1.0	Ref	1.0
Right-sided	0.99 (0.90–1.10)	0.888	1.00 (0.89–1.12)	0.998	0.98 (0.83–1.15)	0.768
One side, NOS	–	1.000	–	1.000	–	1.000
Paired sides	2.66 (0.72–9.79)	0.142	2.45 (0.67–8.94)	0.176	1.28 (0.15–10.76)	0.821
Tumor size						
0–2 cm	Ref	1.0	Ref	1.0	Ref	1.0
2–5 cm	1.05 (0.91–1.22)	0.519	1.21 (1.02–1.43)	0.027	0.82 (0.66–1.02)	0.070
>5 cm	1.32 (1.13–1.54)	0.001	1.69 (1.42–2.01)	<0.001	0.67 (0.53–0.86)	0.001

Table 3 continued. Multivariate logistic regression for analyzing the risk factors for early death in patients with IV breast cancer.

Subject characteristics	Total early death		Cancer specific early death		Non-cancer specific early death	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
N stage						
N0	Ref	1.0	Ref	1.0	Ref	1.0
N1	0.77 (0.67–0.89)	<0.001	0.97 (0.84–1.13)	0.731	0.56 (0.45–0.69)	<0.001
N2	0.82 (0.67–1.01)	0.066	0.91 (0.72–1.14)	0.419	0.77 (0.56–1.06)	0.112
N3	0.94 (0.81–1.09)	0.395	1.03 (0.87–1.20)	0.769	0.84 (0.67–1.05)	0.117
Bone Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	1.11 (0.99–1.24)	0.088	1.15 (1.02–1.31)	0.027	0.91 (0.76–1.1)	0.325
Brain Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	3.67 (3.04–4.40)	<0.001	2.94 (2.44–3.54)	<0.001	2.03 (1.55–2.65)	<0.001
Liver Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	2.28 (2.03–2.56)	<0.001	2.2 (1.95–2.48)	<0.001	1.41 (1.17–1.7)	<0.001
Lung Met						
No	Ref	1.0	Ref	1.0	Ref	1.0
Yes	1.30 (1.16–1.45)	<0.001	1.36 (1.21–1.53)	<0.001	0.96 (0.8–1.15)	0.675
Surgery						
No surgery	Ref	1.0	Ref	1.0	Ref	1.0
PM	0.46 (0.38–0.56)	<0.001	0.44 (0.35–0.54)	<0.001	0.76 (0.57–1)	0.049
TM	0.42 (0.34–0.51)	<0.001	0.41 (0.32–0.52)	<0.001	0.71 (0.52–0.98)	0.036
RM	0.39 (0.33–0.46)	<0.001	0.41 (0.34–0.49)	<0.001	0.59 (0.45–0.77)	<0.001
Others	0.75 (0.29–1.94)	0.557	0.65 (0.22–1.93)	0.435	1.23 (0.28–5.34)	0.786

SEER – Surveillance, Epidemiology, and End Result; OR – odds ratio; CI – confidence interval; Ref – reference; NA – not applicable; UOQ – upper outer quadrant; LOQ – lower outer quadrant; LIQ – lower inner quadrant; UIQ – upper inner quadrant; CEN – central portion; NOS – not otherwise specified; PM – partial mastectomy; TM – total mastectomy; RM = radical mastectomy.
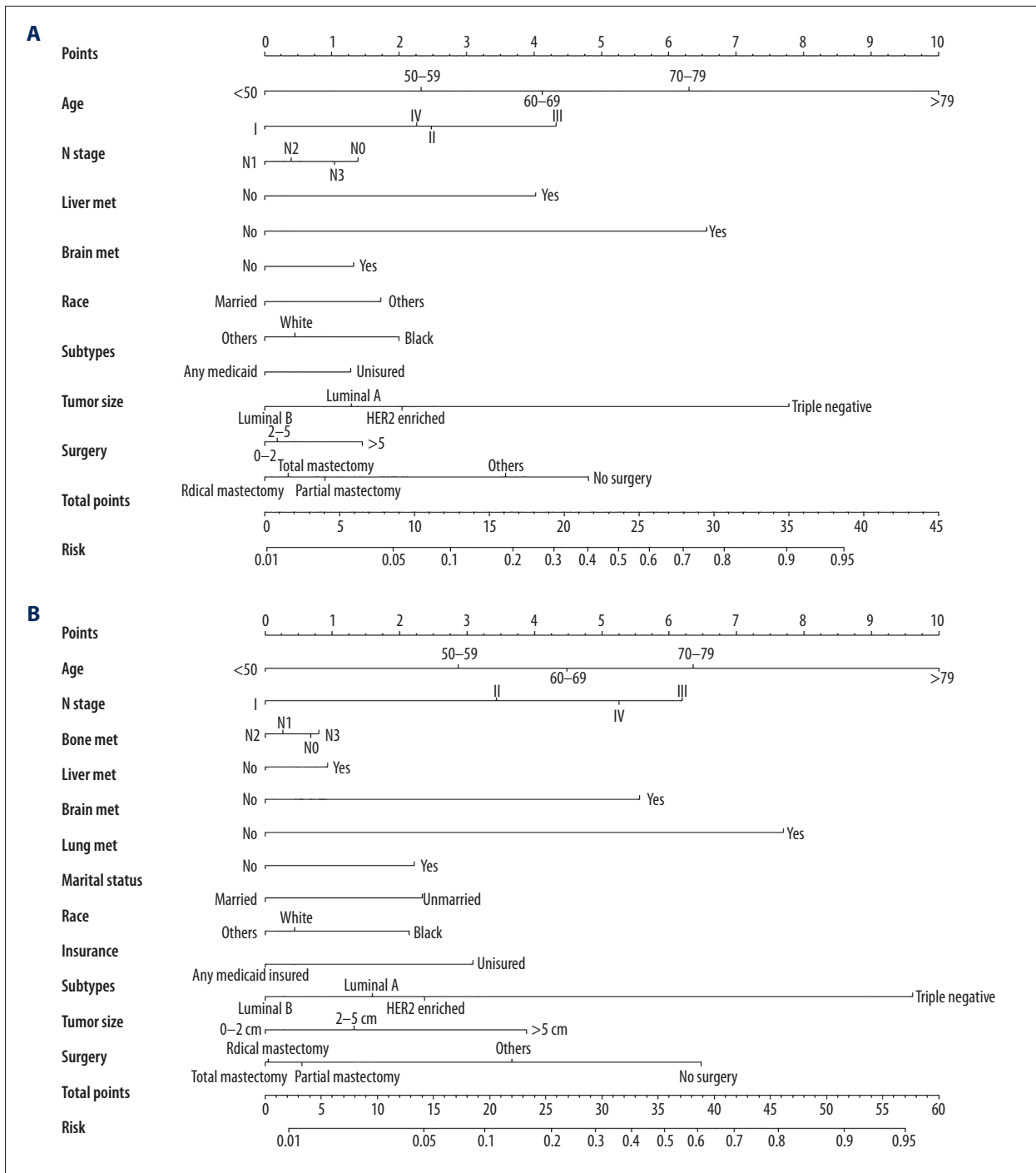
CI: 72.5–75.4%), 73.5% (72.0–74.9%), and 68.6% (67.0–70.1%), respectively.

Discussion

The present study in a large cohort is the first to prove that the survival of one-third of the stage IV breast cancer patients was less than 12 months. Compared with the previously reported proportion of early death by the national cancer database (19.4%), the proportion in the present study is higher [10].

Cardiovascular disease and breast cancer were previously reported to be the primary causes of mortality in breast cancer survivors [11]. In the present study, the cancer-specific cause was proved to be the most important reason, resulting in 73.6% of all the early deaths in the patients with stage IV breast cancer. Efforts to reduce the risk of cancer-specific early death are crucial to improving the total survival.

Several risk factors were identified in the present study for patients with early death. Age was found to be a common risk factor for early death, and most of the early death cases
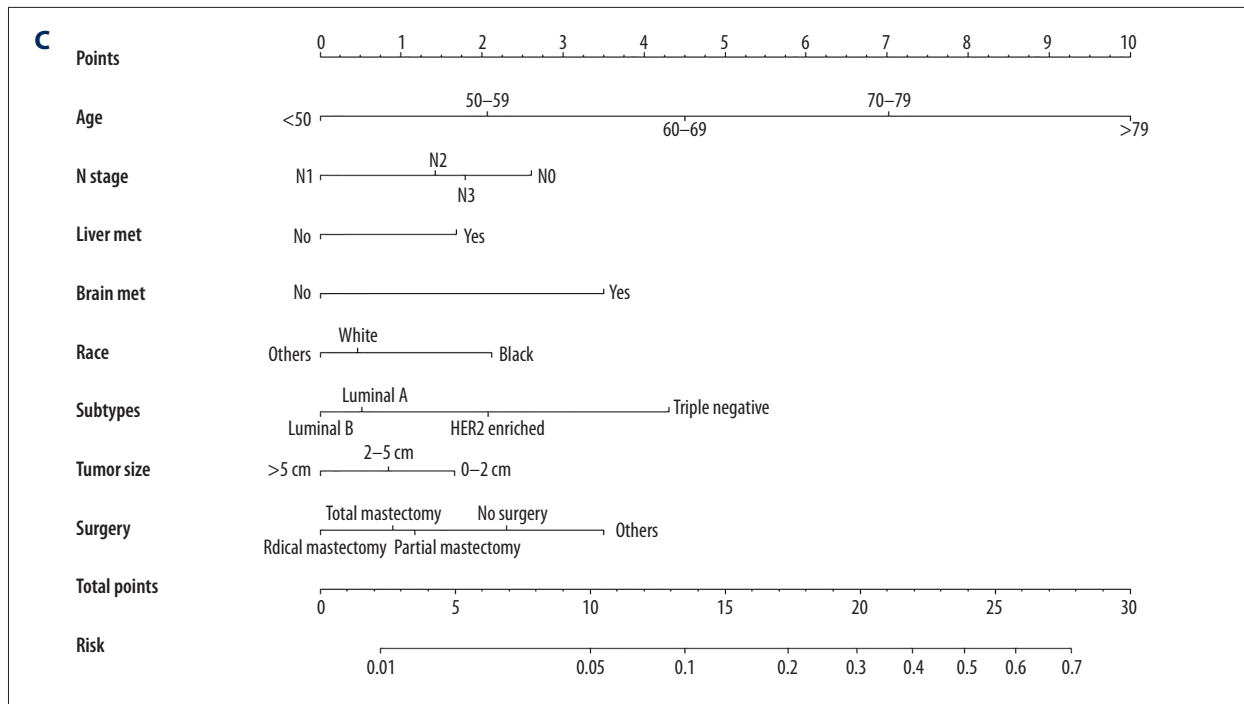
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Figure 2. Nomograms for predicting (**A**) all-cause early death; (**B**) cancer-specific early death and (**C**) non-cancer-specific early death in stage IV breast cancer patients.

were patients older than 50 years. The proportion of early death due to the 2 causes showed disparities in age at diagnosis, with a trend of more non-cancer-specific early death in older patients, which is consistent with a previous study [12]. Therefore, health care should be provided to meet the needs of patients in specific age groups.

Since the pioneering work by Perou et al. [13] and Sorlie et al. [14], breast cancer has been divided into different subtypes, and enormous studies have been conducted to investigate the relationship between survival and each subtype. In the present study, different subtypes were associated with various odds of early death. Compared with the Luminal A breast cancer, the triple-negative type was a risk factor resulting in more cancer-specific and non-cancer-specific early death. Luminal B was a protective factor for cancer-specific early death. The trend was also reported in the latest study [15]. Therefore, clear pathological diagnosis is important to predict early death and more studies should be performed among patients with triple-negative breast cancer.

Distant metastasis was the main characteristic of stage IV breast cancer. Bone was the most common metastatic site in our study, followed by lung, liver, and brain. Multivariate analysis showed that metastasis to liver and brain was a common risk factor for cancer-specific and non-cancer-specific early death, while metastases to bone and lung were associated with higher odds of cancer-specific early death. Due to the fact that

bone and lung accounted for three-quarters of all metastases, more screenings should be scheduled to test these organs.

Socioeconomic variables were significantly associated with cancer management [16]. Because unmarried and uninsured patients are less likely to receive adequate mental and financial support, such patients have limited resources for their cancer treatment. Compared with white patients, black patients also had higher risk for early death. Previous studies have investigated the racial differences in breast cancer molecular features, and indicated black patients were more likely to have basal-like and HER2-enriched breast cancer subtypes [17]. Another study reported that black women were significantly more likely to develop triple-negative breast cancer [18]. In addition to the biological disadvantage, neoadjuvant chemotherapy was less likely to be completed in non-white patients, after controlling other factors [19]. The underlying reasons should be investigated in further studies.

Among the investigated variables in this study, surgery was the most important protective factor for lower odds of early death. Partial, total, and radical mastectomy can significantly decrease the risk of early death. Surgery resulting in improved survival of breast cancer with distant metastasis has been reported in several studies [20,21]. However, only less than 15% of all stage IV patients received surgery in this cohort from the SEER database. As with all retrospective reviews, there was a possible patient selection bias contributing to the better
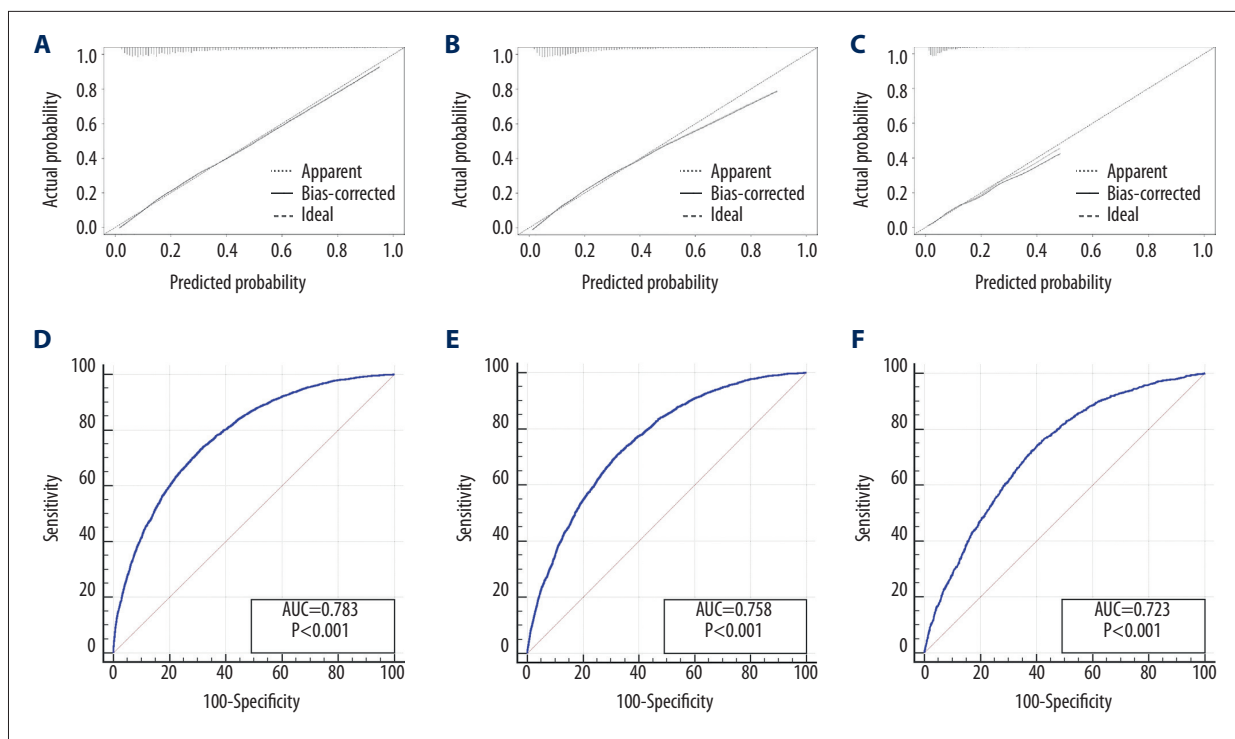
Figure 3. The calibration curve and ROC curve for assessing the calibration and discrimination of the nomograms in predicting all-cause early death (**A, D**), cancer-specific early death (**B, E**) and non-cancer-specific early death (**C, F**) in the construction cohort.

results in the patients after surgery [9]. Patients with better conditions and less risk were reported to be more likely to receive surgical interventions [7]. Therefore, the actual benefit from surgery for stage IV breast cancer should be evaluated.

In the current clinical processing, it was not convenient to predict the possibility of early death for individual patients. Several risk factors for early death were revealed in the present study. Based on the revealed factors, the nomograms were constructed, and this predictive system can be an effective method for use in clinical practice [5].

Our study had several limitations. First, we defined the early death as those who died within 1 year after diagnosis. With larger populations, other intervals such as 3 and 6 months should be further investigated. Second, the SEER database only recorded the synchronous metastasis in breast cancer, and data on patients with metachronous metastasis were not available. Third, breast cancer has distinct heterogeneity, and

patients with different subtypes should receive different individual treatment modalities. However, detailed information on targeted treatment and specific regimens of adjuvant chemotherapy were not available in the SEER database.

Conclusions

Early death occurs in one-third of stage IV breast cancer patients, and the cancer-specific death was the most common cause. A series of risk factors for early death were identified. Based on these factors, nomograms for predicting early death were constructed. This predictive system can guide and schedule targeted treatment regimens for patients with stage IV breast cancer.

Conflicts of interest

None.

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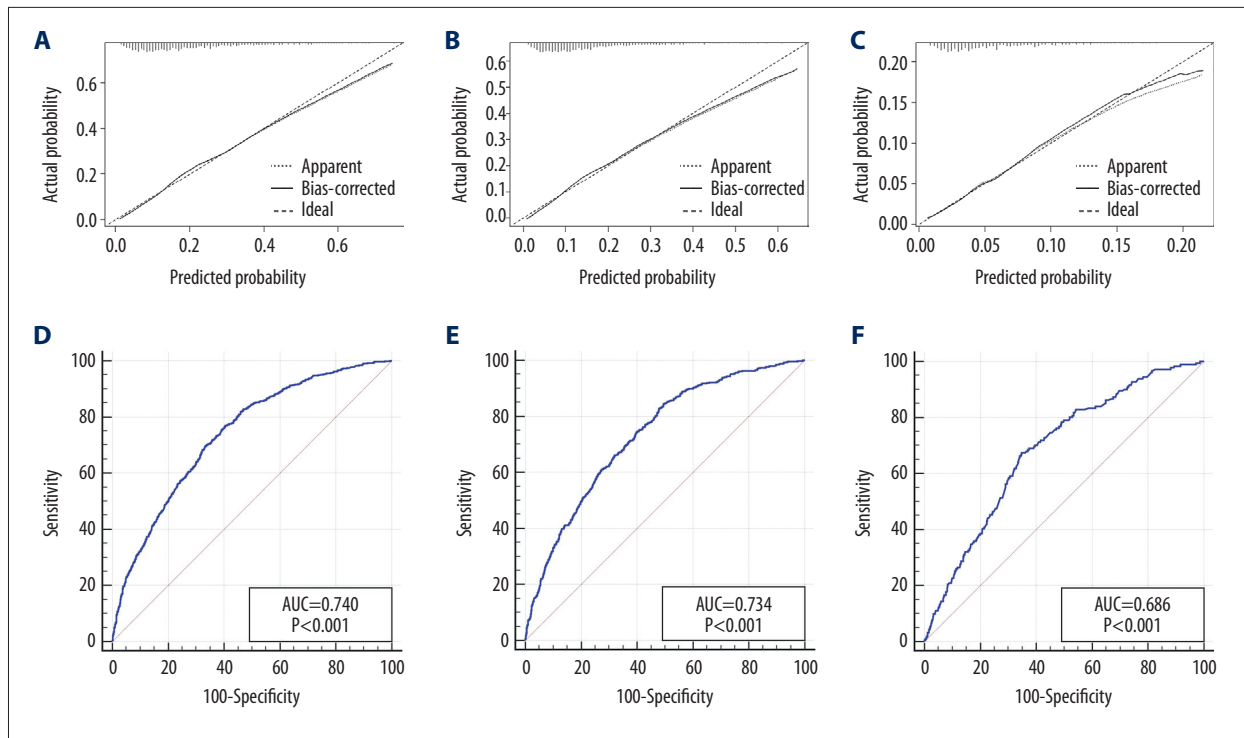
Supplementary Data

Supplementary Table 1. Description of the early death for patients with IV breast cancer in the validation cohort.

Subject characteristics	Patients No. (%)			
	No early death	Total early death	Cancer specific early death	Non-cancer specifi early death
Age				
<50	600 (20.8)	64 (9.3)	51 (10.0)	13 (7.2)
50–59	655 (22.7)	131 (19)	101 (19.9)	30 (16.6)
60–69	771 (26.7)	178 (25.8)	136 (26.8)	42 (23.2)
70–79	527 (18.2)	133 (19.3)	97 (19.1)	36 (19.9)
≥80	337 (11.7)	183 (26.6)	123 (24.2)	60 (33.1)
Marital status				
Married	1341 (46.4)	213 (30.9)	164 (32.3)	49 (27.1)
Unmarried	1390 (48.1)	441 (64)	321 (63.2)	120 (66.3)
Unknown	159 (5.5)	35 (5.1)	23 (4.5)	12 (6.6)
Race				
White	2206 (76.3)	498 (72.3)	369 (72.6)	129 (71.3)
Black	402 (13.9)	147 (21.3)	109 (21.5)	38 (21)
Others	260 (9.0)	41 (6.0)	27 (5.3)	14 (7.7)
Unknown	22 (0.8)	3 (0.4)	3 (0.6)	0 (0)
Insurance				
Insured	2737 (94.7)	640 (92.9)	466 (91.7)	174 (96.1)
Uninsured	75 (2.6)	31 (4.5)	27 (5.3)	4 (2.2)
Unknown	78 (2.7)	18 (2.6)	15 (3.0)	3 (1.7)
Subtypes				
Luminal A	1612 (55.8)	239 (34.7)	174 (34.3)	65 (35.9)
Luminal B	476 (16.5)	76 (11.0)	58 (11.4)	18 (9.9)
HER2 enriched	222 (7.7)	55 (8.0)	42 (8.3)	13 (7.2)
Triple negative	295 (10.2)	110 (16.0)	76 (15.0)	34 (18.8)
Unknown	285 (9.9)	209 (30.3)	158 (31.1)	51 (28.2)
Grade				
Grade I	204 (7.1)	27 (3.9)	22 (4.3)	5 (2.8)
Grade II	1065 (36.9)	139 (20.2)	98 (19.3)	41 (22.7)
Grade III	1006 (34.8)	233 (33.8)	172 (33.9)	61 (33.7)
Grade IV	5 (0.2)	3 (0.4)	2 (0.4)	1 (0.6)
Unknown	610 (21.1)	287 (41.7)	214 (42.1)	73 (40.3)
Tumor site				
UOQ	764 (26.4)	128 (18.6)	93 (18.3)	35 (19.3)
LOQ	162 (5.6)	19 (2.8)	12 (2.4)	7 (3.9)
LIQ	98 (3.4)	20 (2.9)	12 (2.4)	8 (4.4)
UIQ	161 (5.6)	32 (4.6)	24 (4.7)	8 (4.4)
CEN	188 (6.5)	32 (4.6)	26 (5.1)	6 (3.3)
Others	577 (20.0)	116 (16.8)	86 (16.9)	30 (16.6)
Unknown	940 (32.5)	342 (49.6)	255 (50.2)	87 (48.1)

Supplementary Table 1 continued. Description of the early death for patients with IV breast cancer in the validation cohort.

Subject characteristics	Patients No. (%)			
	No early death	Total early death	Cancer specific early death	Non-cancer specifi early death
Laterality				
Left-sided	1371 (47.4)	312 (45.3)	233 (45.9)	79 (43.6)
Right-sided	1387 (48.0)	310 (45.0)	226 (44.5)	84 (46.4)
One side, NOS	10 (0.3)	3 (0.4)	2 (0.4)	1 (0.6)
Paired sides	122 (4.2)	64 (9.3)	47 (9.3)	17 (9.4)
Tumor size				
0–2 cm	414 (14.3)	86 (12.5)	63 (12.4)	23 (12.7)
2–5 cm	1076 (37.2)	196 (28.4)	138 (27.2)	58 (32.0)
>5 cm	794 (27.5)	177 (25.7)	138 (27.2)	39 (21.5)
Unknown	606 (21.0)	230 (33.4)	169 (33.3)	61 (33.7)
N stage				
N0	664 (23)	196 (28.4)	142 (28.0)	54 (29.8)
N1	1200 (41.5)	243 (35.3)	180 (35.4)	63 (34.8)
N2	329 (11.4)	53 (7.7)	40 (7.9)	13 (7.2)
N3	430 (14.9)	74 (10.7)	60 (11.8)	14 (7.7)
Unknown	267 (9.2)	123 (17.9)	86 (16.9)	37 (20.4)
Bone Met				
No	1014 (35.1)	254 (36.9)	166 (32.7)	88 (48.6)
Yes	1876 (64.9)	435 (63.1)	342 (67.3)	93 (51.4)
Brain Met				
No	2747 (95.1)	612 (88.8)	448 (88.2)	164 (90.6)
Yes	143 (4.9)	77 (11.2)	60 (11.8)	17 (9.4)
Liver Met				
No	2289 (79.2)	411 (59.7)	282 (55.5)	129 (71.3)
Yes	601 (20.8)	278 (40.3)	226 (44.5)	52 (28.7)
Lung Met				
No	2055 (71.1)	423 (61.4)	306 (60.2)	117 (64.6)
Yes	835 (28.9)	266 (38.6)	202 (39.8)	64 (35.4)
Surgery				
No Surgery	2127 (73.6)	633 (91.9)	467 (91.9)	166 (91.7)
PM	220 (7.6)	18 (2.6)	13 (2.6)	5 (2.8)
TM	240 (8.3)	17 (2.5)	13 (2.6)	4 (2.2)
RM	263 (9.1)	16 (2.3)	12 (2.4)	4 (2.2)
Others	14 (0.5)	0 (0)	0 (0)	0 (0)
Unknown	26 (0.9)	5 (0.7)	3 (0.6)	2 (1.1)

UOQ – upper outer quadrant; LOQ – lower outer quadrant; LIQ – lower inner quadrant; UIQ – upper inner quadrant; CEN – central portion; NOS – not otherwise specified; PM – partial mastectomy; TM – total mastectomy; RM – radical mastectomy.

Supplementary Figure 1. The calibration curve and ROC curve for assessing the calibration and discrimination of the nomograms in predicting all-cause early death (**A, D**), cancer-specific early death (**B, E**) and non-cancer-specific early death (**C, F**) in the validation cohort.

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