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SUPPLEMENTAL DATA

Development and internal validation of prognostic nomograms for overall and breast cancer-specific survival in de novo stage IV HER2-positive breast cancer

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Table S1. Variable importance ranking and forward iterative selection (OOB C-Index) for OS and BCSS

Variable	OS			BCSS		
	Rank	VIMP	C-Index	Rank	VIMP	C-Index
Chemotherapy	1	0.1992	0.4289	1	0.2054	0.4299
Age	2	0.1076	0.5530	2	0.1214	0.5622
Surgery	3	0.0627	0.6673	3	0.0701	0.6787
Brain	4	0.0444	0.6652	5	0.0311	0.7054
Lung	5	0.0229	0.7125	4	0.0326	0.7047
Liver	6	0.0146	0.7188	10	0.0099	0.7275
PR	7	0.0145	0.7380	11	0.0090	0.7399
Marital status	8	0.0110	0.7449	7	0.0202	**0.7315***
Laterality	9	0.0107	**0.7607***	14	0.0055	0.7439
ICD-O-3	10	0.0095	**0.7654**	16	0.0027	0.7401
Grade	11	0.0092	0.7556	12	0.0090	0.7429
T stage	12	0.0066	0.7564	8	0.0199	0.7296
Bone	13	0.0041	0.7582	13	0.0063	0.7441
Race	14	0.0038	0.7541	6	0.0279	0.7123
ER	15	0.0033	0.7498	15	0.0034	**0.7451**
Radiation	16	-0.0001	0.7472	17	-0.0002	0.7369
N stage	17	-0.0015	0.7369	9	0.0128	0.7366

Bold values with an asterisk (*) denote the optimal parsimonious feature subset chosen by the algorithm. OS selected the top 9 variables with an OOB C-index of 0.7607, while BCSS selected the top 7 variables with an OOB C-index of 0.7315.

Abbreviations: BCSS, breast cancer-specific survival; C-index, concordance index; ER, estrogen receptor; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; OOB, out-of-bag; OS, overall survival; PR, progesterone receptor; VIMP, variable importance.

Table S2. Number of patients at risk and cumulative event counts at 1, 3, and 5 years for OS and BCSS

Outcome	Cohort	Time (months)	Number at risk	Cumulative events
OS	Training	12	894	165
OS	Training	36	389	281
OS	Training	60	110	335
OS	Validation	12	387	63
OS	Validation	36	168	126
OS	Validation	60	40	148
BCSS	Training	12	894	135
BCSS	Training	36	389	235
BCSS	Training	60	110	280
BCSS	Validation	12	387	54
BCSS	Validation	36	168	109
BCSS	Validation	60	40	129

"Number at risk" refers to patients still under follow-up (event-free and uncensored) at each time point. "Cumulative events" represents the total outcome events observed up to and including that time point, such as deaths from any cause for OS or breast cancer-specific deaths for BCSS. **Abbreviations:** BCSS, breast cancer-specific survival; OS, overall survival.

Table S3. Time-specific HRs for chemotherapy

Follow-up time	HR for chemotherapy
6 months	0.240
12 months	0.315
24 months	0.413
36 months	0.485
48 months	0.543
60 months	0.592

Abbreviation: HR, hazard ratio.

Table S4. **Sensitivity analysis of the BCSS model using an extended Cox model with a time-varying chemotherapy effect**

Variable	HR	95% CI	*p*
Age 40–69 years	1.039	0.690–1.563	0.856
Age ≥70 years	1.380	0.868–2.196	0.174
Surgery	0.382	0.267–0.546	<0.001
Lung metastasis	1.587	1.245–2.023	<0.001
Brain metastasis	2.109	1.475–3.016	<0.001
Race, Other	0.702	0.453–1.087	0.113
Race, White	0.728	0.533–0.996	0.047
Unmarried	1.201	0.939–1.538	0.145
Chemotherapy	0.119	0.068–0.207	<0.001
Chemotherapy × log(time)	**1.481**	**1.184–1.853**	**<0.001**

Abbreviations: BCSS, breast cancer-specific survival; CI, confidence interval; HR, hazard ratio.

Table S5. **Fine–Gray competing-risk regression analysis of breast cancer-specific death**

Variable	Training cohort sHR (95% CI)	*p*	Validation cohort sHR (95% CI)	*p*
Chemotherapy				
No/Unknown	Reference	—	Reference	—
Yes	0.336 (0.250–0.450)	<0.001	0.311 (0.202–0.479)	<0.001
Age (years)				
<40	Reference	—	Reference	—
40–69	0.995 (0.676–1.464)	0.979	1.348 (0.726–2.502)	0.344
≥70	1.306 (0.818–2.087)	0.264	1.748 (0.867–3.522)	0.118
Surgery				
No/Unknown	Reference	—	Reference	—
Surgery	0.393 (0.274–0.564)	<0.001	0.486 (0.305–0.775)	0.002
Lung metastasis				
No	Reference	—	Reference	—
Yes	1.496 (1.164–1.922)	0.002	0.950 (0.641–1.407)	0.798
Brain metastasis				
No	Reference	—	Reference	—
Yes	1.863 (1.290–2.692)	<0.001	2.568 (1.649–4.000)	<0.001
Race				
Black	Reference	—	Reference	—
Other	0.737 (0.479–1.132)	0.163	0.558 (0.292–1.065)	0.077
White	0.742 (0.547–1.006)	0.055	0.605 (0.390–0.937)	0.024

Marital status				
Married	Reference	—	Reference	—
Unmarried	1.172 (0.914–1.502)	0.212	1.434 (0.995–2.067)	0.053

Abbreviations: CI, confidence interval; sHR, subdistribution hazard ratio.

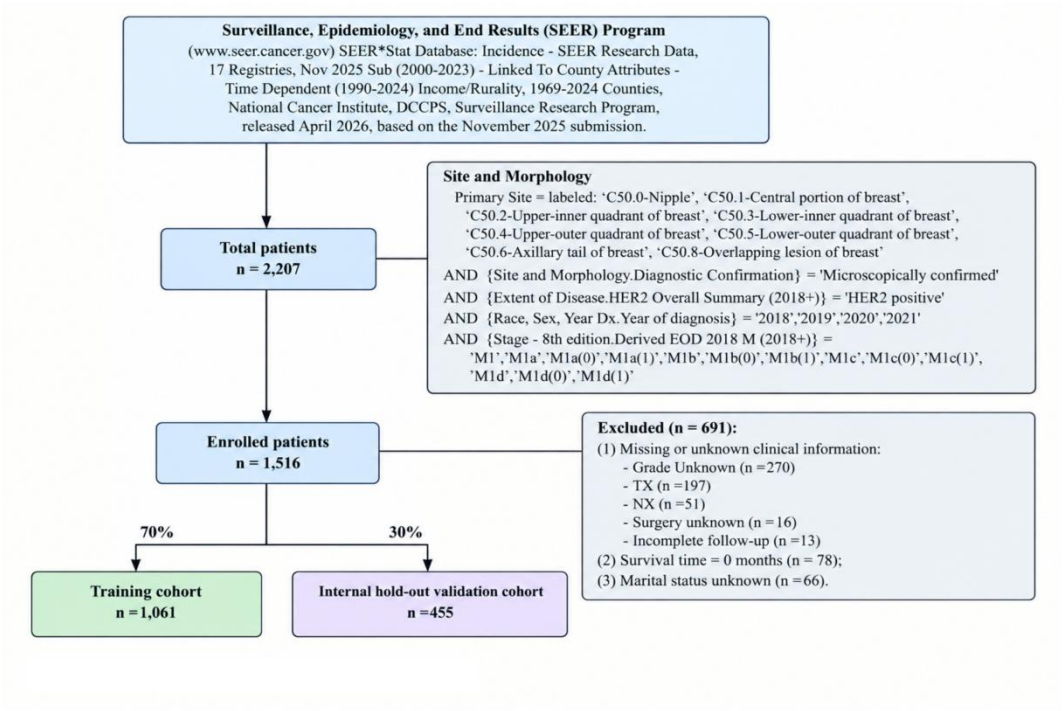


Figure S1. Flow diagram of patient selection and cohort allocation. Patients with de novo stage IV HER2-positive breast cancer diagnosed between 2018 and 2021 were identified from the SEER database using predefined site, morphology, stage, and HER2-status criteria. Of 2,207 initially identified patients, 691 were excluded because of missing or unknown clinical information (including grade, T stage, N stage, surgery status, or incomplete follow-up), survival time of 0 months, or unknown marital status. The final analytic cohort included 1,516 eligible patients, who were randomly assigned to the training cohort (n = 1,061) and the internal hold-out validation cohort (n = 455) in a 70:30 ratio. **Abbreviations**: HER2, human epidermal growth factor receptor 2; SEER, Surveillance, Epidemiology, and End Results.