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ARTICLE

Clinical Characteristics and Prognosis of Breast Signet Ring Cell Carcinoma: A Propensity Score-Matched, Population-Based Study

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Abstract

Aims/Background Breast signet ring cell carcinoma (SRCC) represents an uncommon tumour that has not been extensively studied. This investigation sought to assess the clinical characteristics and prognosis of breast SRCC and compare them with those of invasive ductal carcinoma (IDC).

Methods We obtained clinicopathological data from the Surveillance, Epidemiology, and End Results (SEER) database, including 222 patients with breast SRCC and 492,559 patients with IDC. Clinical features, treatments, and survival outcomes were compared between the two groups. Propensity score matching (PSM) methodology was used to balance baseline characteristics when evaluating overall survival (OS) and cancer-specific survival (CSS). Sensitivity analyses employing E-values quantified the potential impact of unmeasured confounding, and multiple imputation by chained equations (MICE) was used to address missing data for molecular subtype and histological grade. Additionally, predictive models in the form of nomograms were developed to estimate OS and CSS for patients with breast SRCC.

Results Compared with IDC, breast SRCC was significantly associated with older age and more advanced tumour, node, metastasis (TNM) stage ($p < 0.05$ for all). Kaplan-Meier analyses revealed that breast SRCC patients exhibited markedly poorer survival outcomes (OS and CSS, $p < 0.05$) compared to IDC patients before PSM. For breast SRCC, the median OS was 67.0 months and the median CSS was 90.0 months. The OS rates at 3, 5, and 8 years stood at 60.9%, 51.5%, and 39.6%, respectively, while the corresponding CSS rates were 67.7%, 59.7%, and 48.6%. Following PSM analysis, survival outcomes between breast SRCC and IDC patients became comparable ($p > 0.05$). Multivariable assessment identified age, histological grade, T stage, and surgical intervention as independent OS predictors ($p < 0.05$ for all) in breast SRCC, while histological grade, T stage, and surgical approach were independent CSS factors ($p < 0.05$ for all). The nomograms were subsequently validated using the concordance index (C-index), receiver operating characteristic (ROC), calibration curves, and decision curve analysis (DCA), demonstrating robust prognostic capability. Sensitivity analysis revealed E-values of 1.35 (OS) and 1.49 (CSS), which exceeded typical confounder effects. Multiple imputation demonstrated consistent results (OS: hazard ratio [HR] = 1.20, 95% confidence interval [CI] 0.94–1.54; CSS: HR = 1.30, 95% CI 0.86–1.97), supporting the robustness of the findings.

Conclusion Breast SRCC is associated with poorer outcomes primarily due to more advanced stage at presentation rather than histological type alone. Nomograms were developed to estimate OS and CSS for patients with breast SRCC.

Key words: signet ring cell carcinoma; breast cancer; SEER; nomogram

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Introduction

Invasive ductal carcinoma (IDC) represents a predominant form of breast cancer, whereas signet ring cell carcinoma (SRCC) is an uncommon breast malignancy, accounting for approximately 1.0%–4.5% of all cases (Akouh et al, 2023; An et al, 2021). SRCC most commonly occurs in the gastrointestinal tract and is highly invasive (An et al, 2021; Bartosch et al, 2015; Corsini et al, 2021; Curigliano et al, 2019). In 1976, Steinbrecher and Silverberg (1976) were the first to report SRCC as a distinct subtype of breast cancer, characterised by unique morphological and biological characteristics (Dahoud et al, 2024). In particular, the large amount of mucin in SRCC cells displaces the nucleus to one side, resulting in the characteristic signet-ring morphology (Drubay et al, 2022). Pathologically, SRCC is defined by the presence of abundant intracytoplasmic mucin in $\geq$20% of tumour cells, which imparts a discohesive, signet ring cell appearance. This subtype is often associated with prominent lymphovascular invasion and a high Kiel-67 (Ki-67) proliferation index, distinguishing it from conventional IDC (Higami et al, 2024). At the molecular level, SRCC frequently exhibits downregulation of E-cadherin and concurrent upregulation of vimentin, indicative of an epithelial-mesenchymal transition phenotype that correlates with increased invasiveness and metastatic propensity compared to IDC (Hiraki et al, 2017). Immunophenotypically, SRCC most often demonstrates strong estrogen receptor positivity, variable progesterone receptor expression, low human epidermal growth factor receptor 2 (HER2) amplification, and aberrant Mucin 1 (MUC1) glycosylation with cytoplasmic accumulation. These alterations promote anti-apoptotic signalling and enrich cancer stem–like cell populations, further driving aggressive behaviour and therapy resistance (Howlader et al, 2018; Jin et al, 2017).

Breast SRCC diagnosis requires the identification of signet ring cells comprising at least 20% of the tumour tissue, while excluding other parts of SRCC that are transferred to the breast (Kartotaroeno et al, 2024; Kasapoğlu et al, 2024). Breast SRCC can originate from either ductal or lobular epithelial cells (Drubay et al, 2022; Howlader et al, 2018). Studies have shown that SRCC of the breast is often accompanied by lymph nodes and distant metastases, which increase invasiveness and lead to a poor prognosis (Liu et al, 2025; Mehdi et al, 2021). Existing data on breast SRCC are primarily derived from case reports and small-sample studies (Akouh et al, 2023; An et al, 2021; Liu et al, 2025; Mehdi et al, 2021). Due to its rarity, the biological behaviour of breast SRCC has only been investigated in a limited number of studies. Furthermore, the scarcity of long-term follow-up data with prognostic information means that the determinants influencing patient survival in breast SRCC remain unclear. Comprehensive comparative analyses of demographic, clinicopathological features, and prognostic outcomes between breast SRCC and IDC are currently lacking.

To obtain precise data regarding the clinical features of patients diagnosed with breast SRCC and IDC, we conducted a retrospective analysis using patient records from the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2017. The research objectives encompassed: (1) to characterize the clinicopatho-

logical attributes of breast SRCC, (2) to evaluate the clinicopathological differences between breast SRCC and IDC, (3) to assess outcome disparities between breast SRCC and IDC through propensity score matching (PSM) analysis, (4) to identify potential prognostic indicators for breast SRCC, and (5) to develop nomograms to forecast survival outcomes in patients with breast SRCC.

Methods

Data Collection

The National Cancer Institute maintains the SEER repository (https://seer.cancer.gov/), which aggregates cancer statistics from 18 registry centres across 14 states, encompassing 35% of the United States (US) population. This comprehensive dataset enables the analysis of patient information from diverse centres, thereby mitigating potential selection bias associated with single-institution studies. Given that SEER is a publicly accessible database that ensures patient anonymity, institutional review board approval and participant consent were deemed unnecessary for this analysis. Data extraction was conducted using the SEER*Stat platform (version 8.4.4, National Cancer Institute, Bethesda, MD, USA). The inclusion criteria for this study were as follows: patients diagnosed with histologically verified IDC (ICD-O-3 8500/3) and SRCC (ICD-O-3 8490/3) between 1 January 2000 and 31 December 2017. The exclusion criteria were: (1) male patients, (2) diagnoses established through autopsy or death certificate, (3) cases in which SRCC or IDC was not the only primary malignancy, and (4) incomplete survival data or status. The participant selection algorithm is illustrated in Fig. 1.

To evaluate the clinicopathological features of patients with breast SRCC, the following information was extracted: age, race, marital status, laterality, pathological grade, American Joint Committee on Cancer tumour, node, metastasis (AJCC-TNM, 6th/7th edition) stage, T stage, lymph node and distant metastases, molecular subtype, estrogen receptor (ER) status, progesterone receptor (PR) status, surgery, radiotherapy, chemotherapy, and survival outcomes. Overall survival (OS) and cancer-specific survival (CSS) were defined as study endpoints. OS represented the interval from initial diagnosis to death from any cause, while CSS was defined as the interval from initial diagnosis to death specifically attributed to SRCC or IDC.

Statistical Analysis

Clinicopathological characteristics of the breast SRCC and IDC cohorts were compared. Frequencies and rates (%) were used for descriptive statistics. Categorical variables were analysed using the Pearson chi-square (χ^2) or Fisher's exact test. OS and CSS between breast SRCC and IDC patients were compared using the Kaplan-Meier methodology. To minimise bias due to differences in demographics, clinicopathological, and treatment, PSM was performed. Each primary breast SRCC case was matched to an IDC case (1:1 ratio) using nearest neighbour matching with a calliper width of 0.02. Matching variables included age, race, marital status, laterality, grade, tumour stage, T stage, lymph node metastasis status, dis-

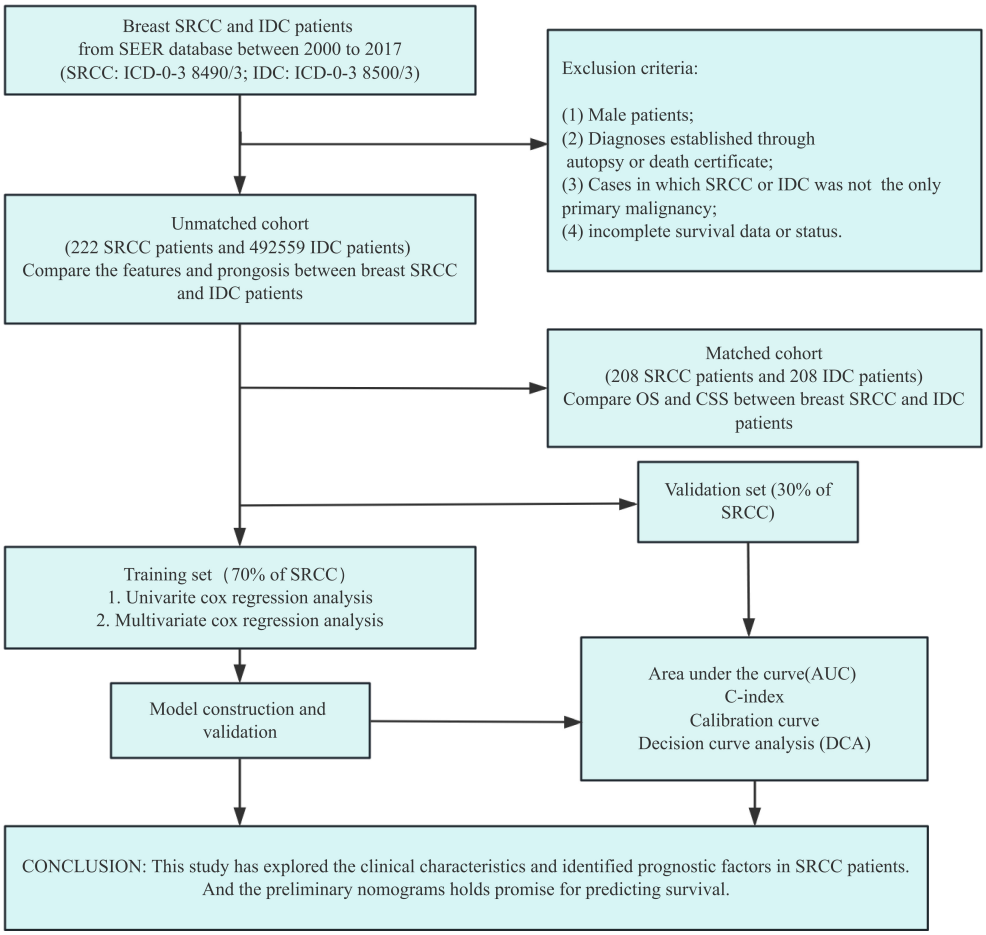

Fig. 1. Study flowchart for patients' inclusion and exclusion. SRCC, signet ring cell carcinoma; IDC, invasive ductal carcinoma; OS, overall survival; CSS, cancer-specific survival.

tant metastasis status, molecular subtype, ER status, PR status, surgery, radiotherapy, and chemotherapy. To address potential unmeasured confounding in the PSM-matched cohort, a sensitivity analysis was conducted using E-values, which quantify the minimum strength of association that an unmeasured confounder would need with both the exposure (SRCC *vs* IDC) and the outcome (OS/CSS) to nullify the observed effect. Additionally, for variables with substantial missing data (e.g., molecular subtype, grade), multiple imputation by chained equations (MICE) was performed, generating 5 imputed datasets. Analyses were conducted on each imputed dataset and pooled to assess the robustness of the results. Comparisons between original and imputed data distributions were conducted to evaluate the impact of missingness. Following this, breast SRCC cases were allocated into training and validation sets at a 7:3 ratio, utilising R software (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria). The training set served to establish independent OS and CSS predictors for female breast SRCC patients and develop prognostic nomograms. The validation set was used to assess the nomogram prediction accuracy. Prognostic elements for SRCC were identified through univariate and multivariate Cox regression analyses. Only variables with statistical significance

($p < 0.05$) in univariate analysis were included in the multivariate model, and those remaining significant ($p < 0.05$) were incorporated into the nomogram. Backwards elimination was applied for variable selection. Nomogram predictive precision and discriminative capacity were evaluated using the area under the curve (AUC), concordance index (C-index), and calibration curves. Decision curve analysis (DCA) was employed to evaluate the clinical utility of the nomograms. Statistical significance was defined as $p < 0.05$ (two-sided) for all analyses. Data processing was performed using R (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 25.0, IBM, Armonk, NY, USA).

Results

Comparison of Clinicopathological Characteristics Between Patients With Breast SRCC and IDC

According to the inclusion and exclusion criteria, this study included 222 cases of breast SRCC and 492,559 cases of IDC. Table 1 depicts the clinicopathological features and treatment modalities of these patients. Compared with those with IDC, patients with breast SRCC were older ($p < 0.05$) and exhibited higher T stage ($p < 0.05$), as well as increased lymph node metastasis ($p < 0.05$) and distant metastasis rates ($p < 0.05$). The majority of breast SRCC cases were hormone receptor (HR)+/HER2– tumours (41/56). Regarding therapeutic interventions, the frequency of chemotherapy administration was similar between the breast SRCC and IDC groups. However, patients with breast SRCC surgical procedures ($p < 0.05$) and radiation therapy ($p < 0.05$) are less frequent than those with IDC.

Comparison of Survival Between Patients With Breast SRCC and IDC

The calculated median OS and CSS for breast SRCC patients were 67.0 months and 90.0 months, respectively (Fig. 2). The 3-, 5-, and 8-year OS rates for breast SRCC patients were 60.9%, 51.5%, and 39.6%, respectively, while the corresponding 3-, 5-, and 8-year CSS rates were 67.7%, 59.7%, and 48.6%. As shown in Fig. 2A,B, both OS and CSS were significantly lower in breast SRCC patients compared to those with IDC ($p < 0.05$). Given that most of the breast SRCC patients exhibited HR+/HER– tumours, additional analyses were conducted to compare OS and CSS between HR+/HER– breast SRCC and HR+/HER– IDC patients. As demonstrated in Fig. 2C,D, OS and CSS were significantly lower in HR+/HER– breast SRCC patients compared to HR+/HER– IDC patients ($p < 0.05$). PSM analysis incorporated 208 IDC patients matched with 208 breast SRCC patients. The baseline characteristics revealed no substantial variations between the two groups ($p > 0.05$ for all; **Supplementary Table 1**). In the matched cohort, Kaplan-Meier analysis indicated no significant differences in OS (all patients: $p > 0.05$; HR+/HER– patients: $p > 0.05$) and CSS (all patients: $p > 0.05$; HR+/HER– patients: $p > 0.05$) between breast SRCC and IDC patients (Fig. 3). Furthermore, univariate and multivariate Cox proportional hazards analyses for OS and CSS in the matched cohort demonstrated that SRCC was not an independent prognostic factor ($p > 0.05$ for all; **Supplementary Table 2**).

Table 1. Baseline characteristics of patients with SRCC and IDC.

Variables	SRCC	IDC	χ^2 value	*p*-value
Number	n = 222	n = 492,559		
Age			33.42	<0.01
<60	72 (32.43%)	255,268 (51.82%)		
≥60	150 (67.57%)	237,291 (48.18%)		
Race			12.22	<0.01
White	192 (86.49%)	389,201 (79.02%)		
Black	18 (8.11%)	52,446 (10.65%)		
Asian or Pacific Islander	9 (4.05%)	47,891 (9.72%)		
Unknown	3 (1.35%)	3021 (0.61%)		
Marital status			7.76	0.02
Married	103 (46.40%)	274,244 (55.68%)		
Not married	107 (48.20%)	195,570 (39.70%)		
Unknown	12 (5.41%)	22,745 (4.62%)		
Laterality			1386.20	<0.01
Left	106 (47.75%)	249,753 (50.71%)		
Right	94 (42.34%)	242,075 (49.15%)		
Other	22 (9.91%)	731 (0.15%)		
Grade			260.26	<0.01
I	12 (5.41%)	88,890 (18.05%)		
II	68 (30.63%)	189,183 (38.41%)		
III	68 (30.63%)	179,987 (36.54%)		
IV	3 (1.35%)	3645 (0.74%)		
Unknown	71 (31.98%)	30,854 (6.26%)		
Stage			349.68	<0.01
I	43 (19.37%)	229,205 (46.53%)		
II	58 (26.13%)	164,046 (33.30%)		
III	37 (16.67%)	56,388 (11.45%)		
IV	67 (30.18%)	23,596 (4.79%)		
Unknown	17 (7.66%)	19,324 (3.92%)		
T stage			-	<0.01
T0	0 (0%)	270 (0.05%)		
T1	60 (27.03%)	282,393 (57.33%)		
T2	64 (28.83%)	143,183 (29.07%)		
T3	16 (7.21%)	23,655 (4.80%)		
T4	20 (9.01%)	19,764 (4.01%)		
Unknown	62 (27.93%)	23,294 (4.73%)		
N stage			159.48	<0.01
N0	101 (45.50%)	310,601 (63.06%)		
N1	44 (19.82%)	118,172 (23.99%)		
N2	20 (9.01%)	30,046 (6.10%)		
N3	18 (8.11%)	16,912 (3.43%)		
Unknown	39 (17.57%)	16,828 (3.42%)		

Table 1. Continued.

Variables	SRCC	IDC	χ^2 value	*p*-value
M stage			339.12	<0.01
M0	145 (65.32%)	463,307 (94.06%)		
M1	67 (30.18%)	23,596 (4.79%)		
Unknown	10 (4.50%)	5656 (1.15%)		
Molecular subtype			48.10	<0.01
HR+/HER2– (Luminal A)	41 (18.47%)	163,027 (33.10%)		
HR+/HER2+ (Luminal B)	4 (1.80%)	30,579 (6.21%)		
HR–/HER2+ (HER2 enriched)	2 (0.90%)	13,515 (2.74%)		
HR–/HER2– (Triple negative)	9 (4.05%)	30,107 (6.11%)		
Unknown	166 (74.77%)	255,331 (51.84%)		
ER			40.42	<0.01
Negative	41 (18.47%)	101,753 (20.66%)		
Positive	145 (65.32%)	361,041 (73.30%)		
Unknown	36 (16.22%)	29,765 (6.04%)		
PR			77.99	<0.01
Negative	76 (34.23%)	149,259 (30.30%)		
Positive	99 (44.59%)	309,242 (62.78%)		
Unknown	47 (21.17%)	34,058 (6.91%)		
Surgery			273.83	<0.01
No surgery	78 (35.14%)	35,684 (7.24%)		
Breast-conserving	71 (31.98%)	267,482 (54.30%)		
Mastectomy	69 (31.08%)	187,616 (38.09%)		
Unknown	4 (1.80%)	1777 (0.36%)		
RT			28.50	<0.01
Not done	147 (66.22%)	237,944 (48.31%)		
Done	75 (33.78%)	254,615 (51.69%)		
CT			2.57	0.11
Not done	135 (60.81%)	273,196 (55.46%)		
Done	87 (39.19%)	219,363 (44.54%)		

Abbreviations: SRCC, signet ring cell carcinoma; IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; RT, radiotherapy; CT, chemotherapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Sensitivity Analysis for Unmeasured Confounding and Missing Data

To evaluate the robustness of our PSM findings, we conducted a sensitivity analysis using E-values. For OS (hazard ratio [HR] = 1.18), the E-value was 1.35, indicating that an unmeasured confounder associated with both histological type and survival by a risk ratio of $\geq$1.35 would be required to fully explain the observed effect. Similarly, for CSS (HR = 1.27), the E-value was 1.49 (Table 2). These values exceed those typically observed for common clinical confounders (e.g., grade, treatment adherence), supporting the robustness of our results.

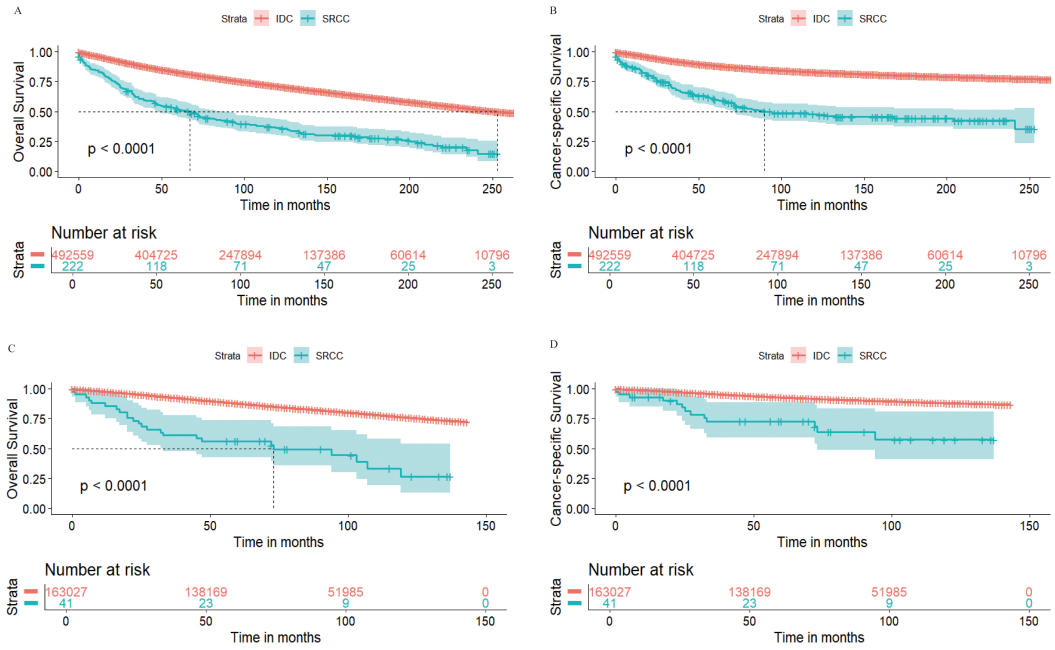

Fig. 2. Kaplan-Meier analysis comparing survival between breast SRCC and IDC. Kaplan-Meier analysis comparing (A) overall survival and (B) cancer-specific survival between patients with SRCC and IDC in the entire cohort and (C) overall survival and (D) cancer-specific survival between patients with SRCC and IDC, including only patients with HR+/HER2– breast cancer.

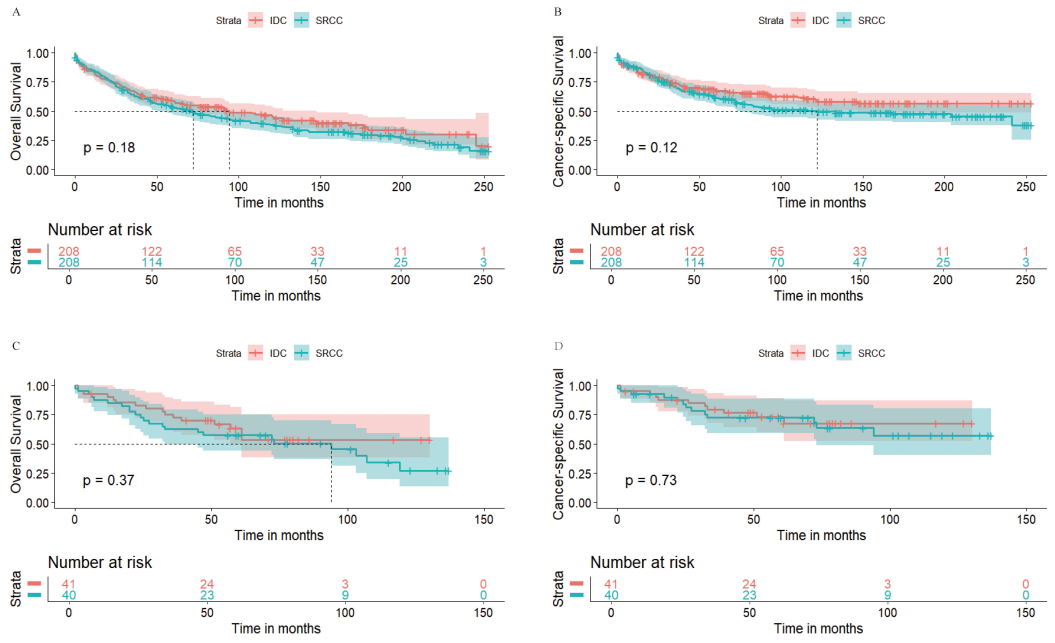

Fig. 3. Kaplan-Meier analysis comparing survival between breast SRCC and IDC after PSM. Kaplan-Meier analysis comparing (A) overall survival and (B) cancer-specific survival between patients with SRCC and IDC in the propensity-score matched cohort, and (C) overall survival and (D) cancer-specific survival between patients with SRCC and IDC in the propensity score-matched cohort, including only patients with HR+/HER2– breast cancer. PSM, propensity score matching.

Regarding missing data, molecular subtype (74.77% missing), grade (31.98% missing), and T stage (27.93% missing) were imputed using MICE. Post-imputation

Table 2. Sensitivity analysis of unmeasured confounding using E-values in the PSM-matched cohort.

Outcome	HR (95% CI)	E-value (point estimate)	E-value (lower CI bound)
OS	1.18 (0.92–1.51)	1.35	1.12
CSS	1.27 (0.84–1.72)	1.49	1.21

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; CSS, cancer-specific survival. Interpretation: E-values >1.0 suggest robustness against unmeasured confounding.

analyses showed consistent results with the primary analysis (OS: HR = 1.20, 95% confidence interval [CI]: 0.94–1.54; CSS: HR = 1.30, 95% CI: 0.86–1.97). Baseline characteristics between the original and imputed datasets were comparable (all $p > 0.05$; **Supplementary Table 3**), indicating minimal bias from missing data.

Effects of Different Treatment Regimens on Prognosis in Patients With Breast SRCC

The investigation examined treatment outcomes and survival rates in a group of 222 patients with breast SRCC. Of these, 140 patients underwent surgical procedures, including breast-conserving surgery in 71 cases and mastectomy in 69 cases. Additionally, 75 patients (33.78%) received radiotherapy, and 87 patients (39.19%) received chemotherapy. To evaluate the impact of different treatment regimens in breast SRCC, PSM analysis was conducted, incorporating variables such as age, grade, and tumour stage. Matched cohorts for each treatment regimen were subsequently analysed. Statistical analysis using the Kaplan-Meier method indicated that surgical intervention markedly improved CSS ($p < 0.05$), while OS was also improved, although not significantly ($p > 0.05$). No significant differences in OS ($p > 0.05$) or CSS ($p > 0.05$) were found between breast-conserving surgery and mastectomy. Furthermore, neither radiotherapy nor chemotherapy demonstrated a significant impact on OS or CSS ($p > 0.05$ for all comparisons; **Supplementary Fig. 1A–H**).

Prognostic Factors for Breast SRCC

Breast SRCC cases were allocated into training and validation sets in a 7:3 ratio, utilising R software. There were no statistically significant differences in baseline characteristics between the training and validation sets ($p > 0.05$ for all, **Supplementary Table 4**). Univariate and multivariate Cox regression analyses were executed to determine potential prognostic factors for OS and CSS among breast SRCC patients in the training set. As illustrated in **Supplementary Tables 5,6**, univariate Cox analysis indicated that OS was significantly associated with age, grade, T stage, M stage, PR status, and surgery ($p < 0.05$ for all), while CSS was significantly associated with grade, T stage, M stage, PR status, and surgery ($p < 0.05$ for all). Following adjustment for confounding variables, multivariate Cox evaluation revealed that grade (OS: HR = 1.80; 95% CI: 1.06–3.07, $p < 0.05$; CSS: HR = 3.67; 95% CI: 1.73–7.77, $p < 0.05$), T stage (OS: HR = 2.31; 95% CI: 1.21–4.39, $p < 0.05$; CSS: HR = 2.64; 95% CI: 1.26–5.57, $p < 0.05$), and surgery (OS:

HR = 0.47; 95% CI: 0.24–0.92, $p < 0.05$; CSS: HR = 0.32; 95% CI: 0.15–0.65, $p < 0.05$) functioned as independent predictors of both OS and CSS. Additionally, age at diagnosis was identified as an independent predictor of OS (OS: HR = 1.87; 95% CI: 1.14–3.09, $p < 0.05$).

Construction and Evaluation of Prognostic Nomograms for Breast SRCC

Nomograms specific for OS- and CSS-specific were constructed using independent prognostic indicators identified through multivariate Cox regression analysis (Fig. 4A,B). In the training set, the C-indices for OS- and CSS-specific nomograms were 0.77 (95% CI: 0.68–0.86, $p < 0.05$) and 0.82 (95% CI: 0.74–0.90, $p < 0.05$), respectively. In the validation set, the corresponding C-indices were 0.75 (95% CI: 0.62–0.89, $p < 0.05$) for OS and 0.80 (95% CI: 0.77–0.93, $p < 0.05$) for CSS. Receiver operating characteristic (ROC) analysis in the training set revealed nomogram AUC values of 0.80 (95% CI: 0.73–0.87, $p < 0.05$), 0.84 (95% CI: 0.78–0.91, $p < 0.05$), and 0.88 (95% CI: 0.82–0.94, $p < 0.05$) for 3-, 5-, and 8-year OS predictions, respectively. For CSS predictions, the AUC values were 0.84 (95% CI: 0.78–0.91, $p < 0.05$), 0.88 (95% CI: 0.82–0.94, $p < 0.05$), and 0.89 (95% CI: 0.84–0.95, $p < 0.05$) (Fig. 4C,D). In the validation set, the AUC values for 3-, 5-, and 8-year OS predictions were 0.71 (95% CI: 0.59–0.84, $p < 0.05$), 0.75 (95% CI: 0.62–0.87, $p < 0.05$), and 0.89 (95% CI: 0.81–0.97, $p < 0.05$), respectively. For CSS patients, the AUC values were 0.80 (95% CI: 0.68–0.91, $p < 0.05$), 0.81 (95% CI: 0.69–0.93, $p < 0.05$), and 0.91 (95% CI: 0.82–1.00, $p < 0.05$) (Fig. 4E,F). Calibration plots revealed alignment between nomogram-predicted survival probabilities and actual survival outcomes in both cohorts (Fig. 5A–L). Additionally, DCA demonstrated that these nomogram models provided substantial positive net benefits (Fig. 6A–L).

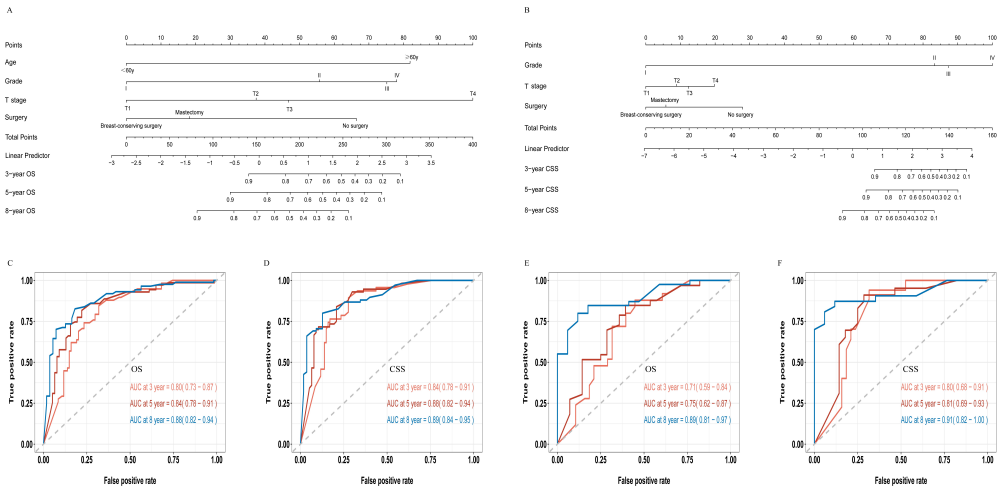

Fig. 4. The nomograms and ROC analysis of the models. Established OS (A) and CSS (B) specific nomogram for predicting survival among SRCC patients. ROC analysis of the nomogram for 3-, 5-, and 8-year OS (C) and CSS (D) in the training set. ROC analysis of the nomogram for 3-, 5-, and 8-year OS (E) and CSS (F) in the validation set. ROC, receiver operating characteristic; OS, overall survival; CSS, cancer-specific survival; AUC, area under the curve.

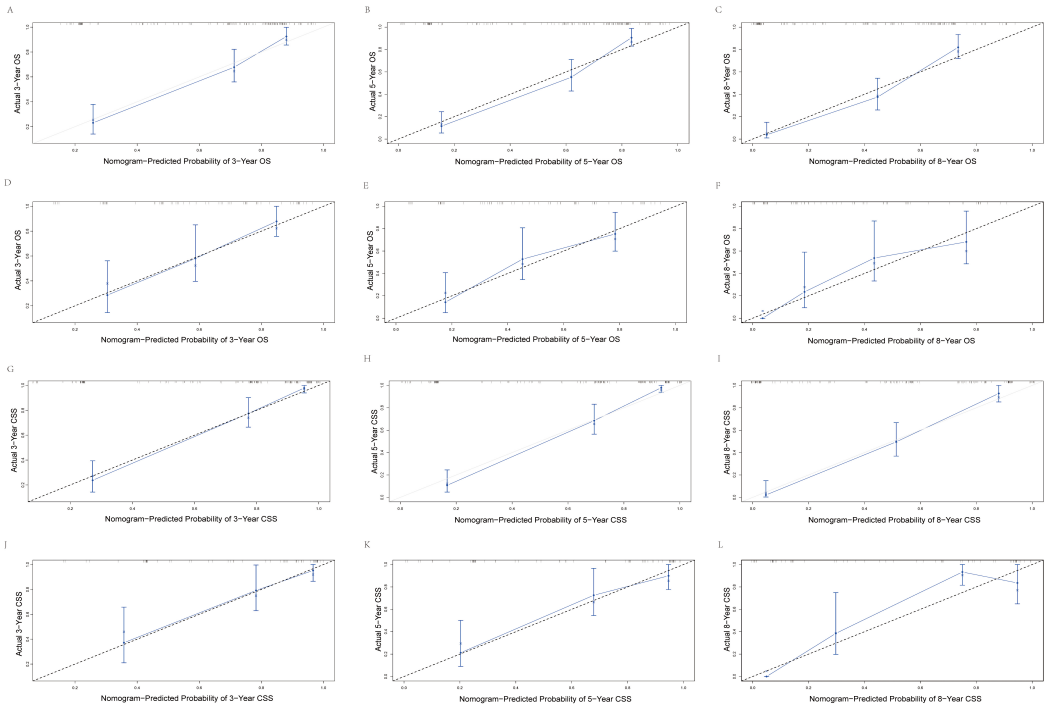

Fig. 5. Calibration curves for each nomogram. Calibration curves of the OS nomogram at 3 years (A), 5 years (B), and 8 years (C) were generated in the training set and 3 years (D), 5 years (E), and 8 years (F) in the validation set. Calibration curves of the CSS nomogram at 3 years (G), 5 years (H), and 8 years (I) were generated in the training set and 3 years (J), 5 years (K), and 8 years (L) in the validation set. OS, overall survival; CSS, cancer-specific survival.

Discussion

Breast SRCC represents an uncommon malignancy with limited documented data. Most studies on breast SRCC exist primarily as individual case descriptions or limited patient cohorts. Consequently, the clinicopathological features and prognosis of breast SRCC remain undefined. Furthermore, it is unclear whether the clinicopathological characteristics of breast SRCC differ from those of IDC.

In this retrospective study, we compared the clinicopathological characteristics and prognosis of 222 individuals with SRCC and 492,559 individuals with IDC from the SEER database to understand breast SRCC more accurately. The breast SRCC cohort exhibited an older age at diagnosis, higher tumour grade, more advanced T stage, elevated rates of lymph node metastasis, and increased distant metastasis compared to the IDC cohort. Previous research indicates that SRCC is typically diagnosed between ages 28 and 90, with a higher prevalence in patients over 60 years of age (Mehdi et al, 2021). The current analysis revealed that approximately 68% of breast SRCC patients were above 60 years old, a proportion notably higher than that observed in the IDC cohort, suggesting that breast SRCC predominantly affects older individuals. SRCC is characterised by high malignancy, poor differentiation, and an advanced stage at diagnosis. In this study, the rates of lymph node metastasis (36.94%) and distant metastasis (30.18%) were higher in patients with breast SRCC than in those with IDC. These findings are consistent with previ-

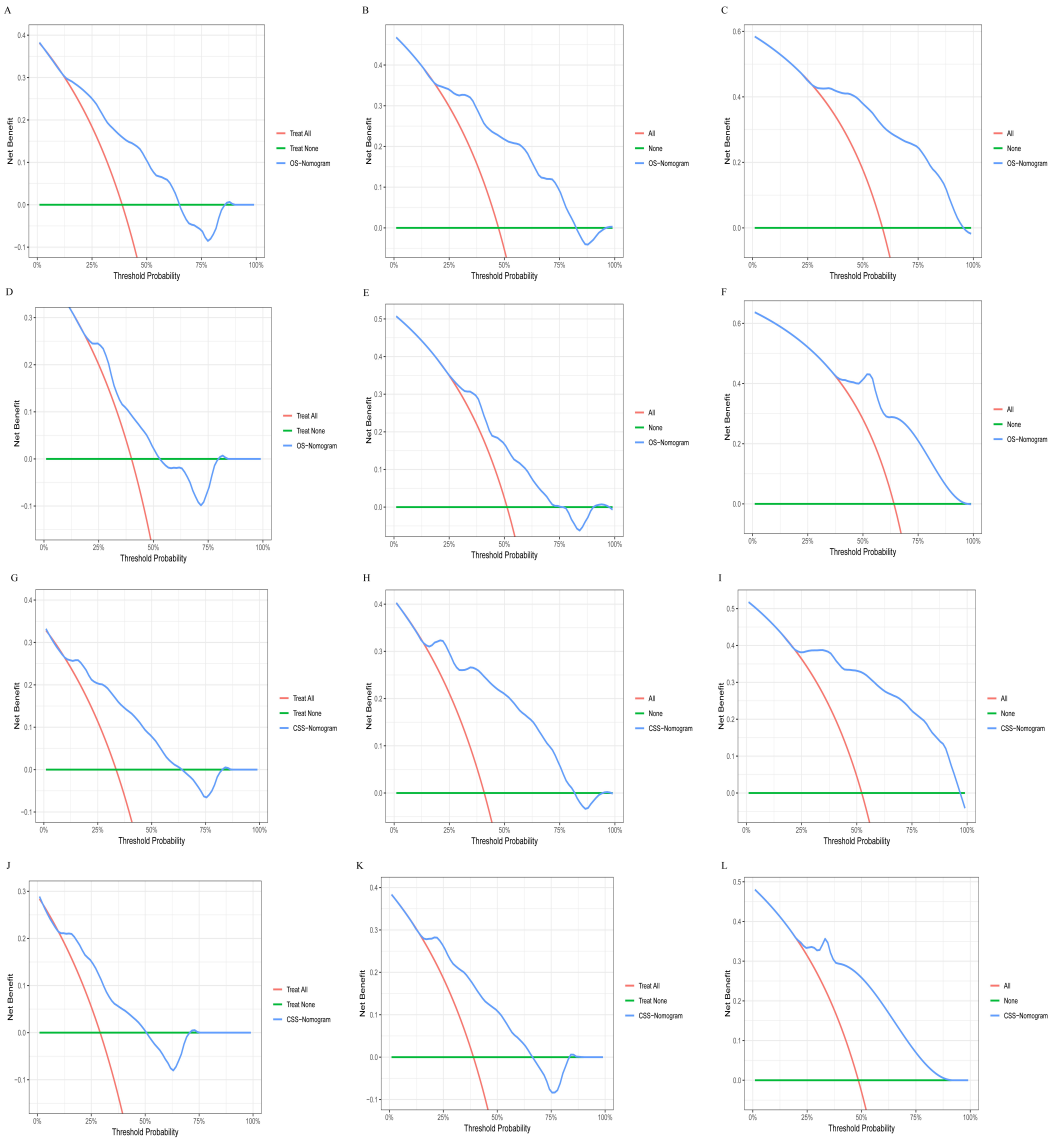

Fig. 6. Decision curve analysis (DCA) for each nomogram. DCA of the prognostic nomogram for estimating OS at 3 years (A), 5 years (B), and 8 years (C) were generated in the training set and 3 years (D), 5 years (E), and 8 years (F) in the validation set. DCA of the prognostic nomogram for estimating CSS at 3 years (G), 5 years (H), and 8 years (I) were generated in the training set and 3 years (J), 5 years (K), and 8 years (L) in the validation set. OS, overall survival; CSS, cancer-specific survival.

ous reports demonstrating the aggressive behaviour of SRCC, including a tendency for lymph node metastasis and vascular infiltration, which has been attributed to the abundance of signet ring cells (Merino and Livolsi, 1981). Similarly, Wu et al (2016) reported that patients with breast SRCC exhibited elevated rates of lymph node metastasis and tumour stage. Collectively, these findings suggest the importance of routine examination of lymph nodes and distant organs to detect metastases in patients with SRCC. In this study, 56 subjects provided sufficient data regarding the hormonal marker expression and HER2 status. Based on this information, patients we categorised as follows: luminal A (41/56), luminal B (4/56), HER2-enriched (2/56), and triple-negative (9/56). The majority of breast SRCC cases

were HR+/HER2–, aligning with previous studies (Merino and Livolsi, 1981; Myers et al, 2024). Regarding treatment, a higher proportion of patients with breast SRCC underwent surgery; nonetheless, the percentage of individuals who did not receive surgical intervention was notably elevated in the SRCC cohort compared to the IDC cohort. Approximately 86.71% of patients with stage I–III breast SRCC received surgery, which was markedly lower than that observed in the IDC cohort (96.02%). Despite the relatively large tumour burden associated with SRCC, our findings indicate that fewer patients with SRCC underwent radiotherapy and chemotherapy.

Studies have shown that the prognosis of breast SRCC is poorer than that of non-SRCC. Zheng et al (2023) reported that breast SRCC exhibits higher rates of lymph node metastasis and mortality compared to other breast cancer subtypes lacking signet ring cells. Similarly, Merino and Livolsi (1981) found that the 7-year CSS rate of 24 patients with breast SRCC was only 60%. In our investigation, patients with breast SRCC exhibited decreased CSS and OS compared to those with IDC. However, our observed survival rates for breast SRCC were lower than those reported in previous studies, such as Mehdi et al (2021), who found that the 5-year OS of 51.5% *vs* 89.7% for stage I and 72.4% *vs* 80.1% for stage II in their cohort. This discrepancy may be attributable to differences in cohort characteristics; Mehdi et al (2021) focused on early-stage SRCC with higher treatment adherence, whereas our cohort included a greater proportion of advanced-stage cases (30.18% stage IV), likely reflecting the commonly observed heterogeneity. To minimise baseline differences between the SRCC and IDC cohorts, we matched patients with breast SRCC and those with IDC in a ratio of 1:1 via PSM. After matching for clinical features and treatment regimens, no significant differences in OS or CSS were observed between the two cohorts. These findings suggest that timely detection and treatment are more critical for prognosis than the SRCC histology itself. The absence of survival differences after PSM challenges the traditional view of SRCC as intrinsically more aggressive, instead highlighting the importance of early diagnosis and adherence to guideline-concordant therapy. Supporting this, a study of colorectal SRCC found that stage-matched patients who underwent complete resection had survival outcomes comparable to those with adenocarcinoma (Nukada et al, 2021). Similarly, our analysis demonstrated that surgical intervention was independently associated with improved CSS in SRCC (HR = 0.32), underscoring the importance of timely and appropriate treatment. PSM also balanced key prognostic variables such as stage, grade, and treatment, which are primary determinants of survival in breast cancer (Nuytens et al, 2024). This suggests that the historically poor prognosis of SRCC may be due to its tendency for advanced-stage presentation rather than inherent biological aggressiveness. Furthermore, standardised therapies—including surgery and systemic treatment—may mitigate histology-specific risks. For instance, studies in gastric SRCC have shown that radical resection and adjuvant chemotherapy can eliminate survival disparities compared to non-SRCC tumours (Liu et al, 2025). In breast cancer, molecular subtyping and targeted therapies often play a more significant role in determining outcomes than histologic classification (Ohashi et al, 2016). Thus, our findings align with emerg-

ing evidence that histology-specific survival differences diminish when patients are matched for stage and treatment (Howlader et al, 2018). Future studies should explore whether SRCC-specific therapies, such as mucin-targeted agents, could further narrow residual outcome gaps.

Furthermore, we analysed prognostic factors for breast SRCC. Compared to individuals who did not undergo surgical intervention, patients receiving breast-conserving surgery or mastectomy demonstrated extended OS and CSS. A previous study demonstrated that patients with early-stage breast cancer who underwent breast-conserving surgery exhibited superior OS compared to those treated with mastectomy (Myers et al, 2024). However, due to the advanced stage at diagnosis in most breast SRCC cases, breast-conserving surgery does not significantly improve prognosis compared to mastectomy. Research has shown morphological heterogeneity among cancers with signet ring cell features at different primary sites, leading us to hypothesise that signet ring cell carcinomas in different locations may exhibit varying sensitivities to chemotherapy and radiotherapy (Oral et al, 2020). For example, patients with esophageal and cervical SRCC have shown resistance to radiotherapy (Patel et al, 2014; Piessen et al, 2009). The impact of radiotherapy on the prognosis of breast SRCC remains unclear. In this study, neither OS nor CSS was significantly improved in breast SRCC patients who underwent radiotherapy. The beneficial effects of chemotherapy have been verified in studies of SRCC arising in other tissues. For instance, Hiraki et al (2017) showed that patients with gallbladder SRCC treated with intensive adjuvant chemotherapy achieved long-term survival, and chemotherapy has also been shown to improve survival in patients with gastrointestinal tract SRCC (Nukada et al, 2021; Piyush et al, 2017). However, in our study, chemotherapy did not significantly improve OS or CSS in patients with breast SRCC. Given the advanced T stage and more invasive lymph node metastasis in these patients, neoadjuvant chemotherapy should be considered. Although chemotherapy has not yet demonstrated significant effects on OS or CSS, neoadjuvant treatment may reduce tumour mass and lymph node involvement, potentially facilitating surgical resection and improving prognosis (Rossi et al, 2024).

The observed fluctuation in AUC values for OS prediction in this study (3-year: 0.71 *vs* 8-year: 0.89) may reflect the evolving influence of prognostic factors over time. Early-stage outcomes (e.g., 3-year survival) are often affected by treatment-related complications or residual micrometastases, whereas long-term survival (e.g., 8-year) is more strongly associated with intrinsic tumour biology and durable treatment responses (Sheng et al, 2022). Similar trends have been reported in nomograms for triple-negative breast cancer, where AUC increased from 0.488 (1-year) to 0.691 (5-year) with extended follow-up (Shrestha et al, 2024). These findings underscore the importance of contextualising model performance within the clinical timeline.

Our sensitivity analysis using E-values suggested that unmeasured confounders (e.g., tumour biology) would need to exert substantial effects (HR $\geq$1.35) to negate the observed null association between SRCC and survival after PSM, which is unlikely given known clinical factors. Furthermore, multiple imputation for missing data demonstrated consistent results, reinforcing the reliability of our conclusions

despite incomplete molecular and grade information. The lack of an association between SRCC and improved survival following chemoradiotherapy is consistent with recent studies suggesting that SRCC is inherently less sensitive to these therapies. Several biological characteristics of SRCC may contribute to its reduced responsiveness. Notably, the accumulation of intracellular mucin creates a physical barrier that prevents effective drug penetration and reduces the cytotoxic effects of chemotherapy and radiotherapy (Wang et al, 2020). Additionally, overexpression and aberrant glycosylation of mucins such as MUC1 in SRCC have been shown to activate survival pathways, thereby protecting tumour cells from apoptosis induced by these treatments. MUC1 is involved in promoting resistance by regulating mitochondrial dynamics and enhancing cancer stem cell properties, both of which are associated with resistance to conventional therapies (Wu et al, 2016). These molecular mechanisms, combined with the clinical evidence showing poor responses to chemotherapy and radiotherapy in SRCC patients, suggest that the low sensitivity of SRCC to these modalities is likely due to its unique histological and molecular features rather than to confounding clinical factors (Zheng et al, 2023).

This study has several limitations. First, the SEER database does not provide detailed information on specific treatment regimens, including chemotherapy agents, endocrine therapy duration, or HER2-targeted therapies. Consequently, we were unable to evaluate molecular subtype-specific treatment responses, such as the efficacy of trastuzumab in HER2-positive tumours or endocrine therapy optimisation in hormone receptor-positive subtypes. Second, critical variables like HER2 status and Ki-67 index had substantial missing rates, limiting stratified analyses by molecular or proliferative profiles. Third, as a retrospective study, residual confounding from unmeasured factors, such as socioeconomic disparities or treatment adherence, cannot be excluded. Finally, although propensity score matching balances observable confounders, unmeasured biological heterogeneity, such as variations in the tumour microenvironment, may persist. Prospective studies integrating detailed treatment metadata, molecular profiling, and socioeconomic variables are warranted to validate these findings.

Conclusion

In conclusion, the poorer outcomes observed in breast SRCC are primarily attributable to advanced stage at diagnosis rather than histological type alone. A predictive nomogram system was developed to estimate OS and CSS in patients with breast SRCC.

Key Points

- Compared with IDC, breast SRCC exhibits more aggressive clinicopathological characteristics.
- The poorer outcomes of breast SRCC are mainly due to advanced stage at presentation, rather than histological type alone.
- Surgical intervention is positively correlated with enhanced OS and CSS in patients with breast SRCC.
- Radiotherapy and chemotherapy do not provide significant survival benefits in breast SRCC patients.
- A predictive nomogram system was established to estimate OS and CSS in patients with breast SRCC.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

YZ: conception and design, administrative support; YL: administrative support, provision of study materials or patients, data analysis and interpretation, manuscript writing; CG: collection and assembly of data; KN: collection and assembly of data, data analysis and interpretation. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0245.

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