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Long-term outcomes of skin-sparing mastectomy and nipple-sparing mastectomy versus traditional mastectomy in breast cancer: a case-control study based on preoperative ultrasound and clinical indicators

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Abstract

Background and objective Nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) are recognized for their aesthetic benefits in breast cancer patients. However, detailed evaluations with large samples of their long-term oncological effectiveness are limited. This study aims to compare the long-term oncologic outcomes of NSM/SSM and traditional mastectomy (TM) in patients with stage I-III breast cancer and to identify influential preoperative factors.

Methods Among the 12,802 breast cancer patients who underwent surgery from 2009 to 2022 in West China Hospital of Sichuan University, 295 NSM/SSM patients and 584 TM patients were selected after propensity score matching adjusted for variables. Survival outcomes were analyzed using Kaplan-Meier estimates, Fisher's exact test, and log-rank tests, with Cox regression identifying survival predictors.

Results The median follow-up period was 97.93 months. Local recurrence (LR) was 5.76 ± 1.36% for NSM/SSM compared to 3.25 ± 0.73% for TM ($p = 0.076$). Overall survival (OS) was comparable ($p = 0.601$), while disease-free survival (DFS) showed a trend toward significance ($p = 0.066$). However, there was a significant difference in distant metastasis-free survival (DMFS) ($p = 0.029$). The 5-year OS rates between the matched groups were similar (98.11% vs. 98.09%, $p = 1.000$), while the TM group exhibited higher 5-year DFS(95.14% vs. 92.03%, $p = 0.335$). Following the univariate analysis, multivariate analysis identified significant DFS predictors: stage (HR = 2.701, $p = 0.031$), radiotherapy (HR = 1.928, $p = 0.018$), and targeted therapy (HR = 5.584, $p < 0.001$). For OS, significant predictors included stage (HR = 8.309, $p = 0.021$) and PR status (HR = 0.35, $p = 0.010$).

Conclusions NSM/SSM demonstrated comparable OS and DFS to TM, though with lower DMFS. Preoperative ultrasound parameters showed no significant impact on long-term outcomes, confirming the oncologic safety of NSM/SSM. Tailored adjuvant therapies and appropriate follow-up may further optimize patient prognoses.

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Keywords Breast cancer, Nipple-sparing mastectomy (NSM), Skin-sparing mastectomy (SSM), Breast-conserving surgery (BCS), Oncologic outcomes

Introduction

Surgical treatment has always been the core of comprehensive breast cancer therapy. In recent years, breast-conserving surgery (BCS) and breast reconstruction surgery have gradually become mainstream surgical methods. At the same time, traditional radical mastectomy (RM) and modified radical mastectomy (MRM) have seen a declining trend [1]. The concept of surgical treatment has shifted from "maximum tolerable treatment" to "minimum effective treatment" [2]. Nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) have evolved as preferred surgical options for breast cancer patients due to their enhanced aesthetic outcomes and potential psychological benefits, especially when NSM combined with breast reconstruction preserves the breast skin and nipple-areola complex (NAC) [3]. Increasing evidence supports their oncologic safety and effectiveness, paralleling traditional mastectomy (TM) methods while significantly improving patient quality of life.

Systematic reviews and cohort studies have further shown the role of NSM and SSM in oncological safety. A study showed long-term outcomes and suggested that NSM could be safely performed even in patients with tumors close to the nipple, with careful preoperative planning and follow-up [4]. Similarly, Cho highlighted comparable oncologic outcomes between patients undergoing immediate reconstruction after NSM and those choosing TM, underscoring the procedure's safety and efficacy [5]. The oncologic safety of SSM is established, showing recurrence rates comparable to TM, and it is recognized as the standard procedure without an increased risk of local recurrence (LR). Conversely, NSM retains a small amount of ductal tissue behind the nipple, raising concerns about a potentially higher risk of LR [6, 7].

Building on the understanding of oncologic safety, other research has emphasized the importance of patient selection and surgical technique in maximizing the benefits of NSM and SSM. Studies have shown that NSM patients had significantly higher Psychosocial Well-Being and Sexual Well-Being scores compared to SSM patients in the 1–5 years follow-up cohort; however, these differences were not significant in the 6–10 follow-up years cohort. A study found that NSM enhances both aesthetic satisfaction and physical comfort post-surgery. Additionally, dissatisfaction with breasts was linked to factors such as receipt of adjuvant chemotherapy, postmastectomy radiation therapy, and higher BMI [8].

LR is a problem that needs to be emphasized after NSM and SSM. Further, rates of locoregional recurrence of NSM and SSM in the literature range are comparable and range from 0–14.3% [9–12]. In a recent retrospective analysis of 387 instances of NSM following prior breast surgery, the study reported five-year overall survival (OS) of 99.1% and disease-free survival (DFS) of 93.8%. Notably, there were no instances of nipple recurrence, thereby affirming the safety of these procedures [13]. Preoperative ultrasound results can be used to assist the surgeon in determining the postoperative outcome of NSM and SSM. By measuring the distance between the tumor and the dermis, ultrasound can assess the feasibility of NSM or SSM and the potential risk of locoregional recurrence. Studies indicate that maintaining a tumor-to-dermis distance of at least 2 millimeters can effectively control the risk of locoregional recurrence. Additionally, this measurement is critical in preventing skin flap necrosis due to inadequate blood supply [14]. Another study developed a nomogram that incorporates tumor-nipple distance (TND) $\leq$ 1.0 cm, and clinical tumor size (CTS) > 4.0 cm among other factors to predict NAC involvement risk, which can be used to differentiate between low, medium, and high risk of NAC involvement before surgery [15]. Molecular typing has also emerged as a potential marker of prognosis, as Danica et. showed that low ER (estrogen receptor) and PR (progesterone receptor) expression were risk factors for LR of breast cancer, and the size of the initial tumor and the size of the implant were not risk factors for LR.

Given the lack of research on the role of preoperative ultrasound, especially in assessing TND and quadrant location, for guiding surgical decisions between TM and NSM/SSM, this case-control study analyzes the OS and distant metastasis-free survival (DMFS) in patients undergoing SSM/NSM compared to TM at our hospital. The strengths of our study are the comparison of the oncologic safety of TM versus NSM/SSM in a large single-center cohort and the fact that the SEER database does not include specific data on preoperative ultrasound measurements of tumor distance and tumor quadrant in breast cancer. Additionally, the study examines the impact of preoperative ultrasound findings and clinicopathological factors on these outcomes.

Methods

Study design and participants

This retrospective case-control study was conducted at West China Hospital of Sichuan University and included a cohort of 12,802 breast cancer patients who underwent surgical intervention from January 2009 to January 2022, approved by the Ethics Committee of West China Hospital of Sichuan University (No.427). The study's primary objective was to compare the local recurrence (LR), disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) between patients undergoing nipple-sparing mastectomy (NSM) or skin-sparing mastectomy (SSM) and those undergoing traditional mastectomy (TM). The secondary objective was to analyze the impact of preoperative ultrasound results and tumor characteristics on prognosis. In this study, NSM and SSM were combined into a single group for comparison with TM due to the relatively small sample sizes in each individual subgroup. This approach was adopted to ensure adequate statistical power while still enabling meaningful comparison. While there may be some heterogeneity between NSM and SSM, we believe that the clinical differences between the two techniques are less significant than the differences between mastectomy types. A series of inclusion criteria were applied to ensure the robustness of our analysis as shown in Fig. 1: (1) meeting the diagnostic criteria for breast cancer, (2) having a unilateral primary tumor, and (3) providing informed consent. Exclusion criteria included: (1) severe comorbidities affecting other organs, (2) other malignancies, (3) distant metastasis, (4) stage IV or T4 disease, (5) age ≤ 18, (6) pregnancy or lactation, and patients with loss to follow-up or missing pathological data were also excluded from the study. After applying these exclusion criteria, 1,527 patients remained eligible for inclusion in the study.

After applying propensity score matching (PSM) to adjust for potential confounders and ensure balanced baseline characteristics between the two groups (Fig. 2), 1,527 patients remained eligible for inclusion. However, due to the strict matching criteria, further reduction in sample size occurred. Some patients were excluded because no suitable match could be found, while others were removed due to imbalances in key variables after matching. Ultimately, 295 patients who underwent NSM/SSM and 584 patients who underwent traditional mastectomy (TM) were included in the final analysis.

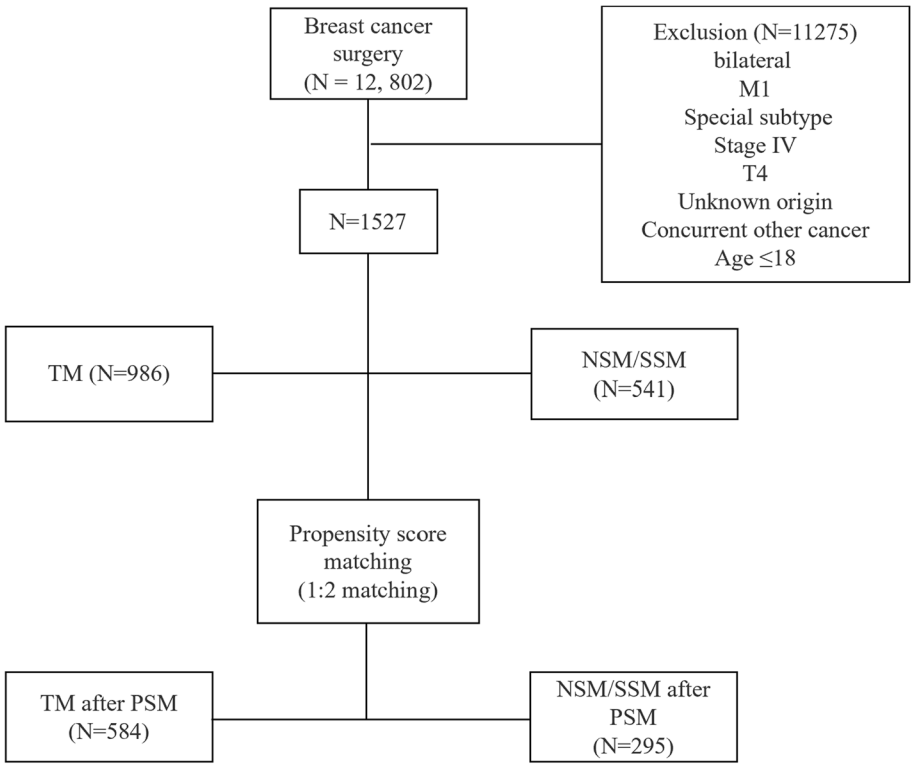

Fig. 1 Patient selection. This figure represents the included and excluded cases in the collected data. *NSM* nipple sparing mastectomy; *SSM* skin-sparing mastectomy; *TM* traditional mastectomy; *PSM* propensity score matching

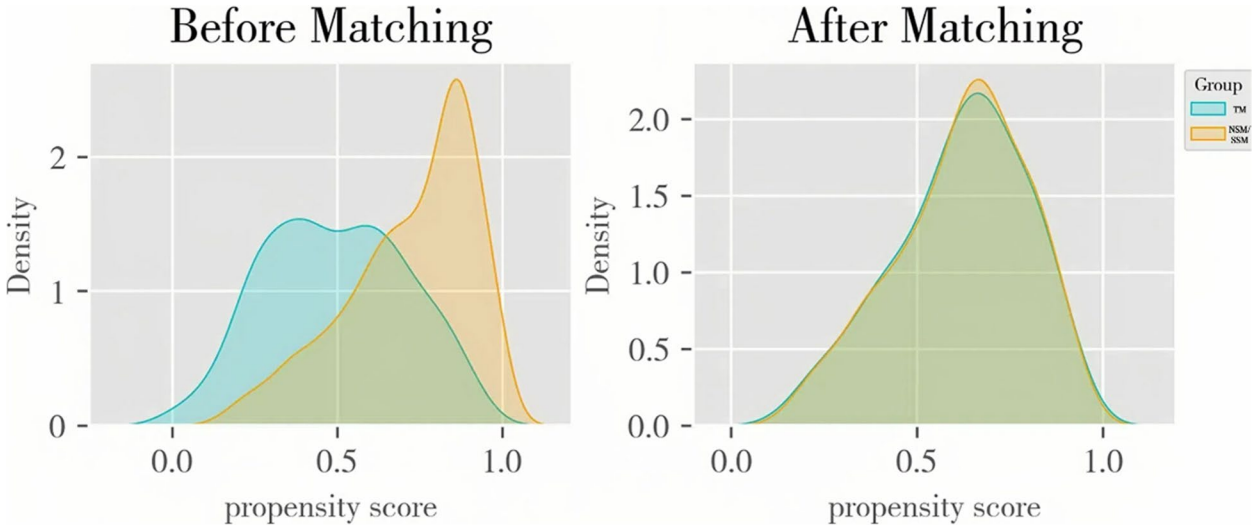

Fig. 2 Probability Density Curves Before and After Matching. *TM* total mastectomy; *NSM* nipple-sparing mastectomy; *SSM* skin-sparing mastectomy

Data collection and variables

Data on clinicopathological factors, treatment modalities, and survival outcomes were collected from medical records. Variables adjusted for in the PSM included axillary lymph node intervention, age, preoperative ultrasound results (tumor size, quadrant location, distance from the nipple, number of nodules, multifocal cancer, presence of calcifications), histological type, pathological tumor (pT) and node (pN) stage, stage, grade, received therapies such as post mastectomy irradiation, post mastectomy chemotherapy, endocrine or targeted therapies, ER status, PR status, HER2 status, and Ki-67%. Preoperative ultrasound was used to measure the distance between the tumor and the dermis, the distance between the tumor and the nipple, tumor size, the presence of calcifications, and whether the cancer was multifocal. Retro-areolar frozen-section biopsy specimens were collected intraoperatively in NSM to assess the nipple-areola complex (NAC). If the retro-areolar tissue was positive for cancer in frozen or permanent biopsy, the NAC was fully removed, converting the procedure to SSM. No cases in the cohort required conversion to TM due to procedural failure. These measurements are crucial in predicting postoperative outcomes for NSM and SSM.

Statistical analysis

All data analyses were performed using R version 4.2.2 (2022-10-31). Propensity scores were calculated using logistic regression, and propensity score matching was applied to balance the baseline characteristics between the groups as shown in Table 1. All statistical tests in the balance analysis were two-sided, with $p < 0.05$ considered statistically significant. Normally distributed continuous variables were expressed as mean ± standard deviation (Mean ± SD) and compared between groups using the independent samples t-test. Non-normally distributed continuous variables were expressed as a median and interquartile range [M (Q1, Q3)] and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages [n (%)] and compared using the Pearson χ^2 test or Fisher's exact test. Standardized mean differences (SMD) were also used to compare group differences.

Survival outcomes, specifically OS, DFS, and DMFS, were analyzed using Kaplan-Meier estimates and compared using log-rank tests. In the analysis of 5-year OS and DFS, Fisher's exact test was applied to compare the differences between the groups. Univariate and multivariate analyses were conducted to identify significant predictors of DFS and OS. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the effects of various factors on survival outcomes.

Results

Patient, clinical, and treatment characteristics

After applying inclusion and exclusion criteria, matched using PSM, we analyzed 295 patients who underwent NSM/SSM and 584 patients who underwent TM for breast cancer, from January 2009 to January 2022. All NSM cases had negative retro-areolar margins confirmed intraoperatively using frozen-section HE staining. Before PSM, a total of 541 patients underwent NSM and SSM. Of these, 146 patients underwent NSM (26.98%) and 395 patients underwent SSM (73.02%). After matching, the number of patients who underwent NSM was 94

(31.86%), while 201 patients underwent SSM (68.14%). Table 1 summarizes the characteristics of patients in the NSM/SSM and TM groups before and after PSM.

For all variables, no significant differences were detected post-matching as shown in Table 1, indicating that the matching process was successful. Before matching, there were significant differences between the TM and NSM/SSM groups for several variables, including age ($p < 0.001$), tumor size ($p < 0.001$), and quadrant location ($p < 0.001$). After matching, these differences were minimized. Typically, an SMD < 0.10 indicates an acceptable balance between groups, while an SMD between 0.10 and 0.34 suggests a small difference. These results are further supported by non-significant p-values and reduced SMDs, with all SMDs below 0.10 indicating minimal imbalance between the groups. Furthermore, variables like age, operation on axillary lymph nodes and distance of the tumor from the nipple exhibited minimal changes in their distributions between the groups, with all p-values remaining non-significant after matching. This ensures that the two groups were well-balanced in terms of these key variables.

In all cases, 163 (18.54%) received targeted therapy, 716 (81.45%) did not receive targeted therapy, 70 (42.94%) were treated with CDK4/6 inhibitors, 59 (36.19%) with VEGF inhibitors, 9 (5.52%) with PI3K/AKT/mTOR inhibitors, 7 (4.29%) with immune checkpoint inhibitors, and 18 (11.04%) underwent other treatments. Out of 295 NSM/SSM patients, 216 (73.22%) underwent axillary lymph node dissection (ALND), and 78 (26.441%) underwent sentinel lymph node biopsy (SLNB). 67 cases (22.71%) were under 35 years old, 224 cases (75.93%) were between 35 and 55 years old, and 4 cases (1.36%) were over 55 years old.

Tumor size distribution showed that 211 patients (36.13%) of TM had tumors smaller than 2 cm, 205 patients (35.01%) had tumors between 2 and 5 cm, and 17 patients (2.91%) had tumors ≥ 5 cm. In the NSM/SSM group, 105 (35.59%) had tumors smaller than 2 cm, 105 (35.59%) between 2 and 5 cm, and 7 (2.37%) with tumors ≥ 5 cm. For quadrant location, the majority of both groups had tumors in the upper outer quadrant: 213 patients (36.47%) in TM and 103 patients (34.91%) in NSM/SSM. A smaller proportion of tumors were located in the central region: 19 patients (3.25%) in TM and 9 patients (3.05%) in NSM/SSM. Regarding the distance of the tumor from the nipple, 117 patients (20.03%) in the TM group had a tumor located 0–1 cm from the nipple, while 61 patients (20.67%) in the NSM/SSM group were in the same range. The distribution of histological types showed that invasive ductal carcinoma (IDC) was the most common in both groups: 465 patients (79.62%) in the TM group and 234 patients (79.32%) in the NSM/SSM group.

For preoperative ultrasound results, in the TM group, 455 patients (77.91%) had one nodule, while 223 patients (75.59%) in the NSM/SSM group had one. A total of 41 TM patients (7.02%) had two nodules, compared to 22 (7.46%) in the NSM/SSM group. In TM group, 83 patients (14.21%) exhibited multiple nodules, whereas in the NSM/SSM group, 49 patients (16.61%) had multiple nodules. Multifocal cancer was present in 10 TM patients (1.71%) and 4 NSM/SSM patients (1.36%). Regarding the presence of calcifications, 143 TM patients (24.49%) had calcifications, while 67 NSM/SSM patients (22.71%) had calcifications. Other characteristics as pT, pN, stage, neoadjuvant chemotherapy, post mastectomy irradiation, post mastectomy chemotherapy, endocrine therapy, targeted therapy, ER, PR, Ki-67, HER2 s are shown in Table 1.

Survival and prognosis

The median follow-up period was 97.93 months, from 2.40 to 187.56 months. Among the 295 patients of NSM/SSM, 13 experienced a recurrence, resulting in a local recurrence (LR) of 4.406%, and there were 26 cases of distant metastasis. In the TM group of 584 patients, 25 experienced a recurrence, with a LR of 4.280%, and 48 developed distant metastasis. For the NSM/SSM group, the average LR is 5.76%±1.36%, compared to 3.25%±0.73% in the TM group. The p-value is 0.076. The metastasis rate is 8.39%±2.25% for the NSM/SSM group and 8.14%±3.12% for the TM group. With a p-value of 0.897, there is no statistically significant difference in LRand metastasis rates between the groups.

We observed the overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS) in two groups of patients by Kaplan-Meier estimates curves as shown in Fig. 3 The results showed the following: for DFS, the hazard ratio (HR) was 0.929 (95% CI, 0.591–1.503; $p = 0.066$), which suggests a trend toward a difference between the two groups, although it does not reach statistical significance. For DMFS, the HR was 0.942 (95% CI, 0.547–1.572; $p = 0.029$), indicating a statistically significant difference favoring the TM group. For OS, the HR was 1.027 (95% CI, 0.519–2.561; $p = 0.601$), showing no significant difference between the groups. These findings indicate no statistically significant differences in DFS and OS between the two groups, with the TM group showing better DMFS.

Furthermore, the 5-year OS rates were similar between the groups, with 98.11% for TM and 98.09% for NSM/SSM. However, the 5-year DFS rates were higher in the TM group (95.14%) compared to the NSM/SSM group

Table 1 Characteristics of baseline of patients in the NSM/SSM and TM groups before and after propensity score matching

Variables	Before Matching				After Matching			
	TM ($n=986$)	NSM/SSM ($n=541$)	*p*-value	SMD	TM ($n=584$)	NSM/SSM ($n=295$)	*p*-value	SMD
Operation on axillary lymph nodes, *n* (%)			0.093	0.090			0.150	0.105
ALND	713 (72.312)	369 (68.207)			400 (68.493)	216 (73.220)		
SLNB	271 (27.485)	171 (31.608)			182 (31.164)	78 (26.441)		
No operation	2 (0.203)	1 (0.185)			2 (0.342)	1 (0.339)		
Age, *n* (%)			< 0.001	0.307			0.685	0.056
<35	189 (19.325)	169 (31.355)			140 (23.972)	67 (22.712)		
≥35, <55	762 (77.914)	365 (67.718)			434 (74.315)	224 (75.932)		
≥55	27 (2.761)	5 (0.928)			10 (1.712)	4 (1.356)		
Size, *n* (%)			< 0.001	0.580			0.824	0.047
0	5 (0.517)	1 (0.186)			3 (0.514)	1 (0.339)		
<2 cm	254 (26.267)	210 (39.033)			211 (36.130)	105 (35.593)		
2–5	290 (29.990)	224 (41.636)			205 (35.103)	105 (35.593)		
≥5	23 (2.378)	17 (3.160)			17 (2.911)	7 (2.373)		
NA	395 (40.848)	86 (15.985)			148 (25.342)	77 (26.102)		
Quadrant, *n* (%)			< 0.001	0.630			0.975	0.065
Upper outer	270 (27.467)	235 (43.519)			213 (36.473)	103 (34.915)		
Lower inner	56 (5.697)	28 (5.185)			35 (5.993)	15 (5.085)		
Lower outer	84 (8.545)	78 (14.444)			69 (11.815)	35 (11.864)		
Upper inner	122 (12.411)	95 (17.593)			99 (16.952)	55 (18.644)		
Central	32 (3.255)	17 (3.148)			19 (3.253)	9 (3.051)		
NA	419 (42.625)	87 (16.111)			149 (25.514)	78 (26.441)		
Distance of the tumor from the nipple, *n* (%)			< 0.001	0.569			0.536	0.118
0–1	164 (16.633)	99 (18.299)			117 (20.034)	61 (20.678)		
>1, ≤2	93 (9.432)	99 (18.299)			67 (11.473)	43 (14.576)		
>2, ≤5	243 (24.645)	191 (35.305)			193 (33.048)	91 (30.847)		
>5, ≤8	40 (4.057)	39 (7.209)			35 (5.993)	13 (4.407)		
NA	446 (45.233)	113 (20.887)			172 (29.452)	87 (29.492)		
Histological type, *n* (%)			0.373	0.092			0.480	0.059
DCIS	134 (13.590)	88 (16.266)			85 (14.555)	40 (13.559)		
IDC	803 (81.440)	422 (78.004)			465 (79.623)	234 (79.322)		
ILC	13 (1.318)	10 (1.848)			12 (2.055)	7 (2.373)		
Mixed	14 (1.420)	9 (1.664)			9 (1.541)	6 (2.034)		
Others	22 (2.231)	12 (2.218)			13 (2.226)	8 (2.712)		
pT, *n* (%)			0.697	0.035			0.448	0.138
0	34 (3.448)	20 (3.697)			22 (3.767)	17 (5.763)		
1	408 (41.379)	229 (42.329)			252 (43.151)	126 (42.712)		
2	482 (48.884)	257 (47.505)			267 (45.719)	133 (45.085)		
3	58 (5.882)	32 (5.915)			40 (6.849)	19 (6.441)		
4	4 (0.406)	3 (0.555)			3 (0.514)	0 (0.000)		
pN, *n* (%)			< 0.001	0.417			0.773	0.041
0	619 (62.779)	379 (70.055)			402 (68.836)	206 (69.831)		
1	161 (16.329)	101 (18.669)			110 (18.836)	54 (18.305)		
2	54 (5.477)	36 (6.654)			36 (6.164)	16 (5.424)		
3	20 (2.028)	12 (2.218)			12 (2.055)	7 (2.373)		
NA	132 (13.387)	13 (2.403)			24 (4.110)	12 (4.068)		
Stage, *n* (%)			0.573	0.032			0.481	0.089
0	20 (2.028)	12 (2.218)			14 (2.397)	11 (3.729)		

Table 1 (continued)

Variables	Before Matching				After Matching			
	TM ($n=986$)	NSM/SSM ($n=541$)	*p*-value	SMD	TM ($n=584$)	NSM/SSM ($n=295$)	*p*-value	SMD
I	273 (27.688)	154 (28.466)			169 (28.938)	85 (28.814)		
II	511 (51.826)	281 (51.941)			295 (50.514)	151 (51.186)		
III	182 (18.458)	94 (17.375)			106 (18.151)	48 (16.271)		
Neoadjuvant chemotherapy, *n* (%)			0.682	0.022			0.842	0.014
No	866 (87.830)	479 (88.540)			514 (88.014)	261 (88.475)		
Yes	120 (12.170)	62 (11.460)			70 (11.986)	34 (11.525)		
Post mastectomy irradiation, *n* (%)			0.414	0.044			1.000	0.000
No	643 (65.213)	364 (67.283)			390 (66.781)	197 (66.780)		
Yes	343 (34.787)	177 (32.717)			194 (33.219)	98 (33.220)		
Post mastectomy chemotherapy, *n* (%)			0.776	0.015			0.861	0.013
No	18 (1.826)	11 (2.033)			15 (2.568)	7 (2.373)		
Yes	968 (98.174)	530 (97.967)			569 (97.432)	288 (97.627)		
Endocrine therapy, *n* (%)			0.458	0.040			0.638	0.034
No	239 (24.239)	122 (22.551)			143 (24.486)	68 (23.051)		
Yes	747 (75.761)	419 (77.449)			441 (75.514)	227 (76.949)		
Targeted therapy, *n* (%)			< 0.001	0.295			0.294	0.076
No	846 (85.801)	401 (74.122)			470 (80.479)	246 (83.390)		
Yes	140 (14.199)	140 (25.878)			114 (19.521)	49 (16.610)		
ER, *n* (%)			0.286	0.057			0.524	0.046
Negative	254 (25.761)	126 (23.290)			144 (24.658)	67 (22.712)		
Positive	732 (74.239)	415 (76.710)			440 (75.342)	228 (77.288)		
PR, *n* (%)			0.219	0.066			0.646	0.033
Negative	303 (30.730)	150 (27.726)			171 (29.281)	82 (27.797)		
Positive	683 (69.270)	391 (72.274)			413 (70.719)	213 (72.203)		
Ki67, *n* (%)			0.145	0.084			0.553	0.049
Negative	448 (45.436)	224 (41.405)			264 (45.205)	140 (47.458)		
Positive	524 (53.144)	310 (57.301)			311 (53.253)	150 (50.847)		
NA	14 (1.420)	7 (1.294)			9 (1.541)	5 (1.695)		
HER2, *n* (%)			0.305	0.055			0.426	0.057
Negative	550 (55.781)	287 (53.050)			334 (57.192)	177 (60.000)		
Positive	436 (44.219)	254 (46.950)			250 (42.808)	118 (40.000)		
Grade, *n* (%)			0.078	0.142			0.905	0.068
0	266 (26.978)	114 (21.072)			141 (24.144)	68 (23.051)		
1	17 (1.724)	12 (2.218)			14 (2.397)	10 (3.390)		
2	322 (32.657)	194 (35.860)			199 (34.075)	104 (35.254)		
3	381 (38.641)	221 (40.850)			230 (39.384)	113 (38.305)		
Number of nodules shown by ultrasound, *n* (%)			< 0.001	0.606			0.413	0.096
1	841 (85.294)	329 (60.813)			455 (77.911)	223 (75.593)		
2	45 (4.564)	60 (11.091)			41 (7.021)	22 (7.458)		
3	5 (0.507)	18 (3.327)			5 (0.856)	1 (0.339)		
4	0 (0.000)	3 (0.555)			0 (0.000)	0 (0.000)		
5	0 (0.000)	1 (0.185)			0 (0.000)	0 (0.000)		
Several	90 (9.128)	130 (24.030)			83 (14.212)	49 (16.610)		
NA	5 (0.507)	0 (0.000)			0 (0.000)	0 (0.000)		
Multifocal cancer, *n* (%)			0.001	0.160			0.910	0.029
No	975 (98.884)	522 (96.488)			574 (98.288)	291 (98.644)		
Yes	11 (1.116)	19 (3.512)			10 (1.712)	4 (1.356)		

Table 1 (continued)

Variables	Before Matching				After Matching			
	TM ($n=986$)	NSM/SSM ($n=541$)	p-value	SMD	TM ($n=584$)	NSM/SSM ($n=295$)	p-value	SMD
The presence of calcifications, *n* (%)			< 0.001	0.338			0.560	0.042
No	802 (81.339)	361 (66.728)			441 (75.514)	228 (77.288)		
Yes	184 (18.661)	180 (33.272)			143 (24.486)	67 (22.712)		

TM total mastectomy, *NSM* nipple-sparing mastectomy, *SSM* skin-sparing mastectomy, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *NA* not available, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *pT* pathological tumor size, *pN* pathological node status, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

(92.03%), indicating that the TM group may have a lower risk of recurrence.

Univariate and multivariate analysis

The univariate analysis of DFS indicated several significant factors (Table 1). The type of surgery (NSM/SSM vs. TM) showed a hazard ratio (HR) of 1.635 (95% CI, 0.962–2.780; $p=0.069$). The axillary procedure (SLNB vs. ALND) had a significant impact with an HR of 3.302 (95% CI, 0.654–2.120; $p=0.011$). Tumor size (< 2 cm vs. ≥ 2 cm) was associated with an HR of 1.552 (95% CI, 0.858–2.806; $p=0.146$). Tumor stage (1 vs. 2–3) was significantly associated with DFS, with an HR of 3873 (95% CI, 1.660–9.035; $p=0.002$). Radiotherapy showed a notable association with an HR of 2.949 (95% CI, 1.742–4.992; $p<0.001$), and targeted therapy had a high HR of 5.892 (95% CI, 3.509–9.893; $p<0.001$). In the multivariate analysis, the axillary procedure (SLNB vs. ALND) had an HR of 2.179 (95% CI, 0.826–5.751; $p=0.116$). The tumor stage (1 vs. 2–3) remained significant with an HR of 2.701 (95% CI, 1.092–6.68; $p=0.031$). Radiotherapy showed significance with an HR of 1.978 (95% CI, 1.123–3.484; $p=0.018$). Targeted therapy maintained a high HR of 5.584 (95% CI, 3.323–9.382; $p<0.001$). These findings showed that stage 2–3, absence of postoperative radiotherapy, and absence of targeted therapy were significantly and independently with lower DFS in the multivariate analysis.

The univariate analysis identified several factors associated with OS (Table 2). The axillary procedure (SLNB vs. ALND) had an HR of 7.029 (95% CI, 0.944–52.317; $p=0.057$). Tumor stage (1 vs. 2–3) was significantly associated with OS, with an HR of 10.32 (95% CI, 1.393–76.435; $p=0.022$). The pT stage (1 vs. 2–3) showed significance with an HR of 2.953 (95% CI, 1.186–7.355; $p=0.02$). The Cox regression analysis indicated that tumor staging as an overall variable was significant in the model (Wald $\chi^2=17.711$, df = 3, $p<0.001$), suggesting that different tumor stages have an overall impact on survival time. However, further analysis revealed that the individual stage categories (stage1, stage2, stage3) did not show significant differences compared to the reference category (p values were 0.899, 0.939, and 0.897, respectively).PR status (positive vs. negative) was significant with an HR of 0.357 (95% CI, 0.16–0.794; $p=0.012$). In the multivariate analysis, tumor stage (1 vs. 2–3) remained significant with an HR of 8.309 (95% CI, 0.927–74.458; $p=0.021$). PR status continued to show significance with an HR of 0.35 (95% CI, 0.155–0.768; $p=0.01$). These findings indicated that stage 2–3 and PR-negative status were significant factors in both univariate and multivariate analyses, with both independently associated with reduced OS in the multivariate analysis.

Discussion

Our study evaluates the long-term oncologic outcomes of NSM and SSM compared to TM in breast cancer patients, with a median follow-up time of 97.93 months. Our results indicate that the local recurrence (LR) of NSM/SSM and TM was 5.76% vs. 3.25% ($p=0.076$), which is comparable and close to the data reported in the existing research, and previous studies focused on the 5-year follow-up results and reported a LR of 3.9–6.2% for NSM and 3.3% for SSM [5, 16]. The higher LR in the NSM/SSM group may be due to residual subclinical tumor foci in the subcutaneous tissue and skin, particularly when thicker skin flaps or subcutaneous fat are retained for better cosmetic outcomes, as evidenced by a systematic review showing that 81.8% of LR after mastectomy are located in these areas [17]. Additionally, the technical complexity of NSM/SSM and surgeon experience may influence outcomes. Although our follow-up period is relatively long (median 97.93 months), longer follow-up is needed to fully evaluate the long-term oncologic safety of these procedures [18]. The results suggest that NSM/SSM are oncologically safe options that supported previous reports [12, 19, 20], providing comparable OS and DFS to TM, though NSM/SSM with lower DMFS, ,as a meta-analysis of patients with invasive breast cancer indicated that OS, DFS, and LR in patients who underwent SSM/NSM did not differ from those of patients who underwent a TM [7]. The 5-year OS for the TM and NSM/SSM groups were 98.11% and 98.09%, showing similar results. However, the 5-year DFS

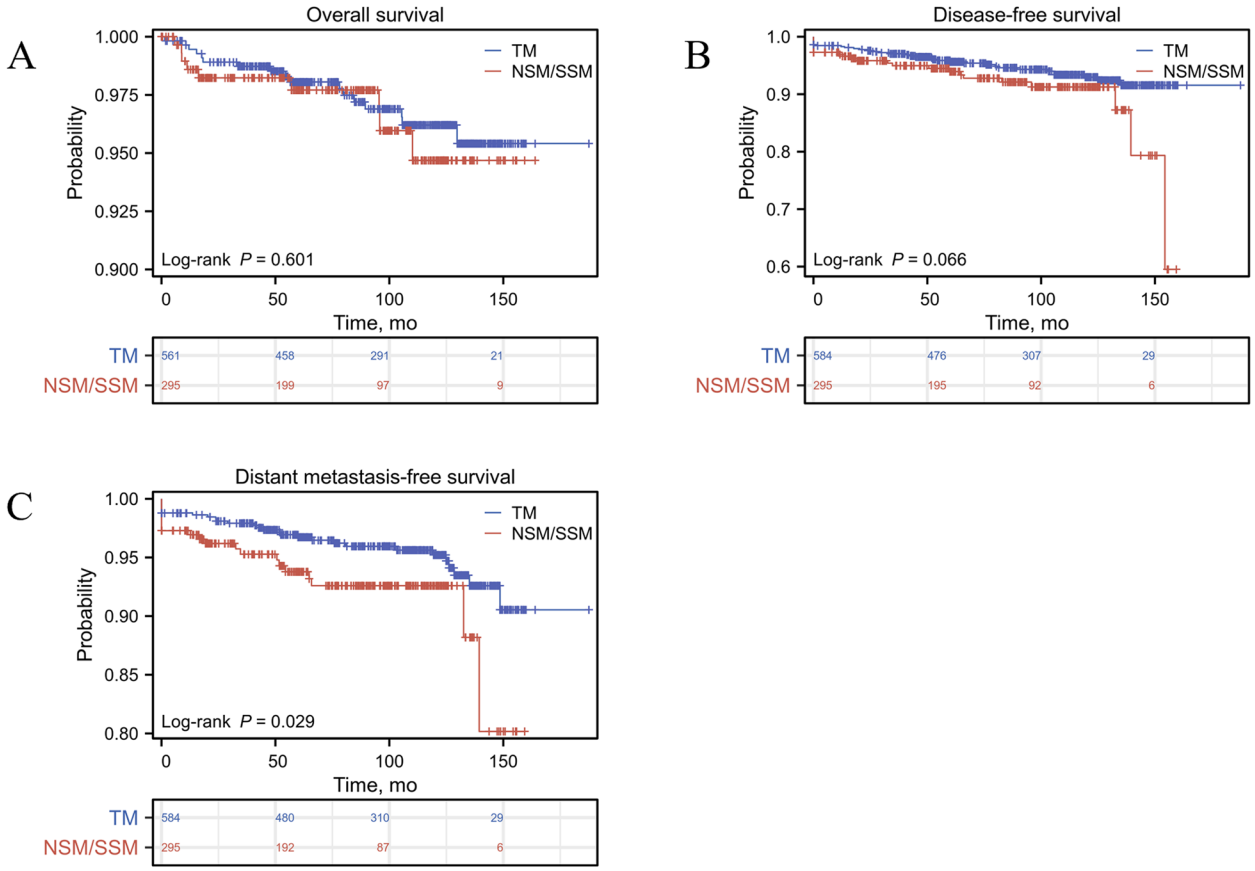

Fig. 3 Survival analysis of OS, DFS, and DMFS. *TM* total mastectomy; *NSM* nipple-sparing mastectomy; *SSM* skin-sparing mastectomy

was higher in the TM group (95.14%) compared to the NSM/SSM group (92.03%), suggesting a slightly higher risk of recurrence with NSM/SSM. The 5-year DFS for NSM has been reported as 83.4% in young women [21], and 92.3% in a retrospective analysis based on SEER database data [22]. This also aligns with previous studies on DFS in NSM, including some with SSM patients, have reported rates ranging from 70.5 to 96.3% with no significant differences compared to TM, with variations based on specific patients such as cancer stage, neoadjuvant chemotherapy, tumor-to-nipple distance thresholds, or specific subtypes like DCIS or invasive carcinoma [23–28], this discrepancy may be due to differences in patient selection, and treatment protocols.

In the results of DFS univariate analysis, there was no statistically significant difference in the results between tumors more than 2 cm and less than 2 cm away from the nipple ($p=0.091$). Traditionally, NSM was recommended for tumors located more than 2 cm from the nipple. However, recent findings suggest that NSM can be safely performed for tumors with a tumor-nipple distance (TND) of less than 2 cm, including those as close as 5 mm, provided that the nipple-areola complex (NAC) is not clinically involved with cancer [29, 30], which supports our results. We believe that NSM is a total subcutaneous glandular excision of the nipple-areola region as long as the tumor is located within the gland and does not involve the subcutaneous fat layer or the nipple. Unlike the previous report of preserving 2–5 mm of subcutaneous glands in the nipple-areola area to ensure the blood supply of the nipple-areola, because whether or not the glands in the areola area are preserved after NSM does not preserve the vertical blood supply of the breast, the nipple-areola can only rely on the dermis and subcutaneous vascular network of the breast for blood supply, and the surgeon can find the right level of excision, and the delicate operation can ensure that all the glands on the deeper side of the areola can be excised without damaging the vascular network in the dermis of the nipple-areola. Therefore, we believe that the simple distance of the tumor from the nipple may not be a contraindication to preserving the nipple-areola, which also proves the oncological safety of NSM. Our study also highlights the importance of integrating preoperative ultrasound parameters, including tumor quadrant location, TND, nodule count, multifocality, and calcifications,

Table 2 Univariate and Multivariate Analysis of Factors Affecting Disease-Free Survival (DFS) and Overall Survival (OS)

Factors	Unitivariate analysis of DFS			Multivariate analysis of DFS		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Surgery (TM vs. NSM/SSM)	1.635	0.962–2.780	0.069			
Axillary procedure (SLNB vs. ALND)	3.302	0.654–2.120	0.011	2.179	0.826–5.751	0.116
Age (< 35 vs. ≥ 35)	1.177	0.654–2.120	0.586			
Size (< 2 vs. ≥ 2)	1.552	0.858–2.806	0.146			
Quadrant (central zone vs. upper inner)	0.779	0.235- 4.710	0.585			
Quadrant (central zone vs. lower inner)	1.523	0.317- 1.911	0.431			
Quadrant (central zone vs. upper outer)	0.968	0.535- 4.338	0.93			
Quadrant (central zone vs. lower outer)	1.47	0.472- 1.989	0.361			
Distance from nipple (< 2 vs. ≥ 2)	1.73	0.917–3.264	0.091			
pT (1 vs.2–3)	1.558	1.336–4.226	0.014	1.256	0.628–2.511	0.520
Node status (positive vs. negative)	1.48	0.863–2.538	0.154			
Stage (1 vs. 2–3)	3,873	1.660–9.035	0.002	2.701	1.092–6.68	0.031
Neoadjuvant chemotherapy	1.037	0.470–2.285	0.929			
Radiotherapy	2.949	1.742–4.992	< 0.001	1.978	1.123–3.484	0.018
Post mastectomy chemotherapy	1.019	0.141- 7.378	0.985			
Endocrine therapy	0.899	0.492- 1.642	0.729			
Targeted therapy	5.892	3.509–9.893	< 0.001	5.584	3.323–9.382	< 0.001
ER	0.846	0.470–1.523	0.577			
PR	0.617	0.363–1.049	0.074			
Ki67	1.385	0.818–2.346	1.385			
HER2	0.756	0.435–1.313	0.32			
Nodules on ultrasound (1 vs. ≥ 2)	0.901	0.477–1.703	0.748			
Multifocal cancer	1.893	0.460–7.781	0.377			
Calcify	1.295	0.742–2.260	0.363			
Factors	Unitivariate analysis of OS			Multivariate analysis of OS		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Surgery (TM vs. NSM/SSM)	1.369	0.606–3.09	0.45			
Axillary procedure (SLNB vs. ALND)	7.029	0.944–52.317	0.057			
Age (< 35 vs. ≥ 35)	0.781	0.328–1.86	0.577			
Size (< 2 vs. ≥ 2)	1.904	0.76–4.774	0.17			
Quadrant (central zone vs. upper inner)	1.086	0.13–9.067	0.94			
Quadrant (central zone vs. lower inner)	0.758	0.085–6.782	0.804			
Quadrant (central zone vs. upper outer)	0.949	0.121–7.417	0.96			
Quadrant (central zone vs. lower outer)	1.26	0.14710.789	0.833			
Distance from nipple (< 2 vs. ≥ 2)	1.355	0.533–3.444	0.523			

Table 2 (continued)

pT (1 vs.2–3)	2.953	1.186–7.355	0.02	0.578	0.461–4.001	0.493
Node status (positive vs. negative)	1.651	0.732–3.727	0.227			
Stage (1 vs. 2–3)	10.32	1.393–76.435	0.022	8.309	0.927–74.458	0.021
Neoadjuvant chemotherapy	0.327	0.044–2.419	0.273			
Radiotherapy	0.528	0.245–1.140	0.055			
Post mastectomy chemotherapy	20.654	0.000–23911	0.669			
Endocrine therapy	0.45	0.197–1.028	0.058			
Targeted therapy	2.084	0.873–4.978	0.098			
ER	0.49	0.214–1.119	0.091			
PR	0.357	0.16–0.794	0.012	0.350	0.155–0.768	0.010
Ki67	1.473	0.727–2.988	0.283			
HER2	0.634	0.262–1.527	0.314			
Nodules on ultrasound (1 vs. ≥ 2)	0.689	0.235–2.016	0.496			
Multifocal cancer	0.048	0.000–12897.0	0.634			
Calcify	1.425	0.609–3.336	0.414			

HR hazard ratio; *CI* confidence interval; *TM* total mastectomy; *NSM* nipple-sparing mastectomy; *SSM* skin-sparing mastectomy; *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *pT* pathological tumor size; *ER* estrogen receptor; *PR* progesterone receptor; *HER2* human epidermal growth factor receptor 2

into the selection of surgical approaches. Although these variables did not demonstrate statistical significance in multivariate analysis, they remain clinically significant, reaffirming that different preoperative ultrasound findings may not compromise the oncologic safety of NSM/SSM compared with TM. Moreover, while central calcifications may indicate residual DCIS, their inclusion in this study underscores the importance of a comprehensive preoperative evaluation.

In our study, univariate and multivariate analyses identified several significant predictors of DFS and OS. Our results showed that stage 2–3, absence of postoperative radiotherapy and targeted therapy were significantly associated with lower DFS. Stage 2–3 and PR-negative status were significantly associated with lower OS, both maintaining their significance in univariate and multivariate analysis. These findings suggest the potential benefits of tailored adjuvant therapies following NSM/SSM, indicating that comprehensive treatment strategies may improve patient outcomes.

Despite these promising results, our study has several limitations. Our study lacks genetic information, such as BRCA gene status. BRCA testing is not routinely performed in our institution as it is a self-funded test, and not all patients undergo genetic testing. The lack of BRCA information may obscure potential differences in outcomes, particularly in triple-negative breast cancer or patients with a family history [31]. Future studies with comprehensive genetic testing could better clarify the impact of BRCA mutations on surgical and treatment outcomes. Another limitation of our study is the lack of long-term cosmetic outcomes and patient satisfaction assessments, which are crucial for evaluating the overall success of breast-conserving surgeries. The retrospective design, challenges in recalling patients dispersed across a wide geographical area restricted the collection of such data. Future studies should incorporate standardized tools for cosmetic evaluation (e.g., photographic assessments) and patient satisfaction (e.g., Breast-Q) to better balance oncologic safety with postoperative quality of life [32]. We did not specifically consider the size of the NAC when selecting patients, as NAC size varies significantly between individuals. This may be considered a limitation, as NAC size could impact complications such as ischemia or necrosis, which would limit our ability to fully evaluate the safety and feasibility of NSM procedures. In our study, all NSM cases had negative retro-areolar margins confirmed intraoperatively using frozen-section HE staining. However, nipple margins following neoadjuvant chemotherapy may show distortion and shrinkage, complicating accurate assessment. Emerging technologies like the Cancer Diagnostic Probe, which demonstrates high sensitivity in margin evaluation [33], could enhance surgical precision and oncologic safety in such cases. Although nearly all preoperative ultrasound assessments were performed at our institution using breast-specialized ultrasonography and conducted exclusively by experienced physicians in the breast imaging specialty group, ensuring high-quality and reliable assessments, variability may still exist due to differences

in individual operator techniques. Additionally, we did not include patients' BMI data, which has been shown to affect surgical outcomes and overall prognosis in breast cancer patients. Financial and insurance-related factors may have influenced the outcomes, as a study have highlighted that insurance policies can impact breast cancer patients' choices for surgical and adjuvant treatments [34]. These limitations suggest the need for more comprehensive data collection in future studies to validate our findings.

The strengths of this study include the evaluation of a relatively large cohort of NSM and SSM patients over an extended period. Our study substantiates the oncologic safety of NSM and SSM compared with TM, demonstrating acceptable LR and comparable outcomes in OS. These findings advocate for the inclusion of NSM and SSM as viable surgical options in the comprehensive treatment regimen for breast cancer, reflecting their integration into personalized oncologic strategies. Further research should continue to refine patient selection criteria and surgical techniques to optimize outcomes for breast cancer patients undergoing NSM and SSM.

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Research involving human participants
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University (No.427).

Authors' contributions
M.S. conceptualized the study, developed the methodology, conducted formal analysis, and wrote the original draft. Y.J. reviewed the manuscript, curated the data, and performed formal analysis. L.X. managed the project administration. R.L. supervised the study. X.Z. also contributed to project administration. Q.L. acquired funding, validated the results, and reviewed the manuscript. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University (No.427).

Consent for publication
All authors have approved the manuscript for publication. Informed consent was obtained from all participants included in the study.

Competing interests
The authors declare no competing interests.

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