



# Association of Axillary Lymph Node Evaluation With Survival in Women Aged 70 Years or Older With Breast Cancer

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# Edited by:

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#### Specialty section:

This article was submitted to Surgical Oncology, a section of the journal Frontiers in Oncology

Received: 19 August 2020 Accepted: 23 October 2020 Published: 28 January 2021

#### Citation:

Luo SP, Zhang J, Wu QS, Lin YX and Song CG (2021) Association of Axillary Lymph Node Evaluation With Survival in Women Aged 70 Years or Older With Breast Cancer. Front. Oncol. 10:596545. doi: 10.3389/fonc.2020.596545 <sup>1</sup> Department of Breast Surgery, Fujian Medical University Union Hospital, Fuzhou, China, <sup>2</sup> Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China, <sup>3</sup> Department of Orthopedics, Fujian Medical University Union Hospital, Fuzhou, China

**Background:** Survival in elderly patients undergoing sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) has not been specifically analyzed. This study aimed to explore the association between different types of axillary lymph node (ALN) evaluations and survival of elderly breast cancer patients.

**Methods:** A retrospective cohort study was conducted of invasive ductal breast cancer patients 70 years and older in the Surveillance, Epidemiology, and End Results database (2004–2016). Analyses were performed to compare the characteristics and survival outcomes of patients who received surgical lymph node dissection and those who did not. Breast cancer specific survival (BCSS) and overall survival were compared by using Cox proportional hazards regression analysis and propensity score matching (PSM) methods to account for selection bias from covariate imbalance.

**Results:** Of the 75,950 patients analyzed, patients without ALN evaluation had a significantly worse prognosis, while there was no significant difference for BCSS between using a sentinel lymph node biopsy (SLNB) and an axillary lymph node dissection (ALND) after adjustment for known covariates [adjusted hazard ratio (HR) = 0.991, 95% confidence interval (CI) = 0.925–1.062, p = 0.800]. In the stratification analyses after PSM, the ALND did not show a significant BCSS advantage compared with SLNB in any subgroups except for the pN1 stage or above. Furthermore, after PSM of the pN1 stage patients, SLNB was associated with a significantly worse BCSS in hormone receptor negative (HR–) patients (HR = 1.536, 95%Cl = 1.213–1.946, p < 0.001), but not in the hormone receptor positive (HR+) group (HR = 1.150, 95%Cl = 0.986–1.340, p = 0.075).

**Conclusion:** In our study, ALND does not yield superior survival compared with SLNB for elderly patients with pN1 stage HR+ breast cancer. Although our findings are limited by the bias associated with retrospective study design, we believe that in the absence of

January 2021 | Volume 10 | Article 596545

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results from randomized clinical trials, our findings should be considered when recommending the omission of ALND for elderly breast cancer patients.

Keywords: sentinel lymph node biopsy, axillary lymph node dissection, elderly breast cancer, propensity score matching, Surveillance Epidemiology and End Results database

# INTRODUCTION

Since the early 2000s surgical techniques for axillary treatment and staging of patients with primary breast cancer have become less extensive and more focused on minimizing the risk related to surgery (1). Sentinel lymph node biopsy (SLNB) could reduce the side effects of axillary lymph node dissection (ALND) within a certain range of adaptation and provide an equivalent outcome. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trial (2) validated that the usage of SLNB for avoiding ALND in patients with clinically node-negative (cN0) breast cancer had no impact on prognosis. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (3) eliminated the demand for ALND for breast cancer patients with one or two positive sentinel lymph nodes who were treated with breast conserving surgery (BCS) and whole breast irradiation.

However, there are no clinical studies specifically for elderly breast cancer patients previously, and the evidence of optimal axillary lymph node evaluation is limited. In 2012, the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) (4) updated their recommendations regarding elderly breast cancer (EBC) patients. It was proposed that elderly patients with cN0 breast cancer could be exempted from axillary lymph node evaluation. Since no survival improvement with ALND was identified in relevant studies (5, 6), the Society of Surgical Oncology Choosing Wisely Guidelines recommended in 2016 that surgeons "do not routinely use sentinel node biopsy in clinically node-negative women ≥70 years of age with hormone receptor-positive (HR+) invasive breast cancer". This recommendation aroused extensive discussion (7-9) about whether cN0 elderly breast cancer patients can be exempted from axillary lymph node evaluation. No clinical studies have yet been conducted to investigate the difference in survival between SLNB and ALND in elderly breast cancer patients.

A sentinel lymph node biopsy is minimally invasive compared with axillary lymph node dissection, with the risk of lymphedema being only 3–7% for SLNB while it is 15–20% for ALND (10). In the era of precision medicine, our study aimed to explore the association between different types of axillary lymph node evaluations with survival and provide new insight into axillary management for elderly breast cancer patients.

# METHODS

### Data Source and Study Population

Women 70 years and older with invasive ductal breast cancer diagnosed between January 2004 and December 2016 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) Program (Nov 2018 Submission). We utilized the SEER\*Stat version 8.3.6 to extract the target population's information. Patients with missing or unknown T-, N-, M-stage, grade, estrogen receptor (ER) status, progesterone receptor (PR) status, number of lymph nodes (LNs) removed, surgery type, or survival data were excluded from this study, so were patients with metastatic disease (Supplemental Figure 1). The data elements included patient characteristics, cancer staging, type and timing of first course of treatment, as well as survival outcome information. The SEER database did not specify the axillary surgery type as ALND or SLNB. Therefore, we use the number of nodes examined as an alternative in this study. According to the definition of ALND, which was set as a standard by the American Joint Commission on Cancer (AJCC), ALND should involve at least six lymph nodes. Hence, we used five examined lymph nodes as the cut-off value for SLNB and ALND. Patients with five or fewer lymph nodes examined were categorized as having received SLNB, while patients with six or more nodes examined were categorized as having undergone ALND (11, 12). Those with 0 to 5 positive regional lymph nodes were included into this study. Patients with more than five positive lymph nodes, who might have a worse prognosis, would be directly assigned into the ALND group within the classification rules.

For the general population, the study groups were defined as those who underwent surgical LN evaluation, including SLNB (fewer than six lymph nodes examined) and ALND (six or more lymph nodes examined) and aim to identify the survival differences among the three groups, then to obtain relevant information on whether axillary assessment could be exempted. For the pathological stage N1 cohort, the survival of SLNB and ALND patients was further evaluated and compared in order to get information on the conditions under which ALND can be avoided when a small number of lymph nodes are positive. The primary endpoint of this study was breast cancer specific survival (BCSS).

### **Statistical Analysis**

Patient characteristics are summarized with N (%) of inclusion categorical variables and *mean* (SD) of the number of examined nodes and survival time. Associations between axillary surgery modality, patient demographics, and clinical pathological characteristics were assessed using the Pearson  $\chi^2$  or Fisher's exact test and the Wilcoxon rank sum test for continuous variables. The Kaplan–Meier method was applied to generate unadjusted survival curves, while the log-rank test was used to assess the differences. Univariable and multivariable Cox proportional hazards regression analysis was conducted to estimate the association between different types of axillary lymph node evaluations and survival after adjusting for exploratory variables that were shown to have a significant effect on survival.

To avoid the impact of the different characteristics between the two study groups (SLNB group *vs.* ALND group), we adopted the 1:1 nearest neighbor propensity score matching (PSM) method to eliminate the imbalance. Within the matched patient groups, we assessed survival outcomes of different axillary surgery effects with stratification analyses and explored the different effects in patient-, tumor-, and treatment-level subgroups. Kaplan–Meier estimators were calculated for each group and were compared by using the log-rank test.

All tests were two-sided, and a p value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS software version 24.0 (IBM Corp., Armonk, USA) and R version 3.6.2 (The R Project for Statistical Computing, Vienna, Austria).

## RESULTS

## Basic Characteristics and Survival Analyses of the Overall Population

A total of 75,950 eligible elderly breast cancer patients (the median follow-up time was 64 months) were included in this retrospective analysis, of whom 46,253 (60.9%) underwent SLNB, 18,346 (24.2%) underwent ALND, and 11,351 (14.9%) did not receive LN evaluation (the No group) with the median follow-up time of 58, 84 and 58 months respectively. Patient characteristics are listed in **Supplemental Table 1**. Elderly patients had more Luminal-type

breast cancer, and among them the ER positive-type made up 84.2% and among the PR positive-type 72.9%. There were fewer human epidermal growth factor receptor-2 (HER2) positive patients (7.1%) than HER2 negative patients (52.1%). Fewer patients received LN evaluation in the older age groups. The proportion of elderly breast cancer patients undergoing SLNB who were diagnosed after 2010 (52.8%) was higher than that in 2004–2009 (34.8%). The patients in the SLNB group received more lumpectomies (75.3%) and more radiotherapy (55.1%), while the ALND group had more mastectomies (58.3%).

The results of univariable and multivariable Cox proportional hazard regression analyses are shown in **Supplemental Table 2**. It was found that age, race, marital status, grade, T stage, N stage, ER, PR, HER2 status, and different types of adjuvant treatments were independent prognostic factors for elderly breast cancer patients. Survival curves stratified by different types of axillary lymph node evaluations before matching are reported in **Figure 1**. In the univariate analysis, the SLNB group had a better BCSS performance than the ALND group (HR = 0.457, 95%CI = 0.430–0.485, p < 0.001). However, after adjusting for the other prognostic factors, there were no significant differences in BCSS between the two groups (SLNB group *vs.* ALND group: adjusted HR = 0.991, 95%CI = 0.925–1.062, p = 0.800), while the cohort without a LN evaluation had the worst prognosis.



FIGURE 1 | Kaplan–Meier curves [(A) breast cancer specific survival; (C) overall survival] and the survival curves of adjusted by other prognostic factors [(B) breast cancer specific survival; (D) overall survival] stratified by different types of axillary lymph node evaluations.

# Stratification Analyses of the Matched SLNB and ALND Groups

We performed a 1:1 PSM with maximum allowed differences of  $\pm 0.5\%$  for propensity scores on the SLNB and ALND groups

(**Supplemental Figure 2**). Relevant results of the matched stratification analyses are displayed in **Table 1**. In the matched groups, the SLNB group and the ALND group did not show significant BCSS differences (HR 0.994, 95%CI = 0.916–1.078,

TABLE 1 | The matched stratification analyses of breast cancer specific survival (BCSS).

Variables         No. of patients         No. of patients         No. of patients         No. of patients         Survival Rates         Full         Prain           Total         13,246         114.1         91.4%         13,246         1,162         91.20%         0.9940.016-1.07%         0.877           2004-2009         6,477         761         88.0%         6,588         804         97.76         0.9940.016-1.07%         0.298           2005-2016         6,597         3303         325         91.7%         3.342         347         91.26%         0.0460.051-1.101         0.467           75-70         3,3303         325         91.7%         3.342         347         91.26%         0.0460.051-9.101         0.329           80-44         2,653         281         88.0%         2.576         282         80.4%         0.0460.051-9.100         0.329           80-44         1.148         2.25         8.46%         1.200         1.42         8.43%         0.0460.064-1.036         0.16%           80-64         1.128         1.129         0.43         9.17%         0.0450.064-1.036         0.16%           80-64         9.11%         1.120         1.42         8.43         0.0460.064-1.036	Variables	SLNB group			ALND group			BCSS	
Total constraint         13,246         1141         91,4%         13,246         1,162         91,20%         0.9940,916-1.07%         0.877           Total adignosis         6,847         761         82,8%         6,858         90,49%         0.0180         0.0180         0.0180         0.028         0.0160         0.0286         0.0490         0.0286         0.0490         0.0286         0.0490         0.0180		No. of patients	No. of events	Survival Rates	No. of patients	No. of events	Survival Rates	HR (95%CI)	P value
Yaor at diagnosis         Link         Link <thlink< th="">         Link         Link<td>Total</td><td>13.246</td><td>1141</td><td>91.4%</td><td>13.246</td><td>1.162</td><td>91.20%</td><td>0.994(0.916-1.078)</td><td>0.877</td></thlink<>	Total	13.246	1141	91.4%	13.246	1.162	91.20%	0.994(0.916-1.078)	0.877
2004-2007         6,847         761         88.6%         6,888         90.4         67.88         90.4         67.88         90.4         67.88         90.4         67.88         90.4         67.88         90.4         67.84         90.4         67.85         90.4 <td>Year at diagnosis</td> <td></td> <td></td> <td></td> <td></td> <td>.,</td> <td></td> <td></td> <td></td>	Year at diagnosis					.,			
2010-2016         6,598         380         94.4%         6,658         358         94.6%         1.115(0.983-1261)         0.145           Apr         77-70         5.270         310         94.1%         6,658         358         94.6%         0.946(08 10-101)         0.477           77-70         5.393         225         91.7%         5.342         341         91.7%         1.115(0.983-1261)         0.145           80-94         2.553         221         80.9%         2.576         222         83.1%         1.012(0.899-1155)         0.273           80-7         1.494         225         94.9%         1.370         10         94.4%         0.84(0594-115.0)         0.276           Race         1.12         90.9%         1.220         1.42         84.8%         0.84(01694-115.0)         0.276           Mariad         1.278         61         9.28%         5.648         4.24         9.25%         0.75(0.477-0.864)         0.026           Mariad         5.58         9.28         0.474         9.24%         0.476(08-0.167)         0.752           Singin         7.130         61         9.9%         6.682         5.45         9.17%         0.98(01670-1.06)         0.755	2004-2009	6 847	781	88.6%	6 588	804	87.8%	0 945(0 856-1 042)	0 258
Note         Oracle         Oracle <thoracle< th=""> <thoracle< th=""></thoracle<></thoracle<>	2010-2016	6,399	360	94.4%	6,658	358	94.6%	1 115(0 963-1 291)	0.145
row         row <td></td> <td>0,000</td> <td>000</td> <td>04.470</td> <td>0,000</td> <td>000</td> <td>04.070</td> <td>1.110(0.000 1.201)</td> <td>0.140</td>		0,000	000	04.470	0,000	000	04.070	1.110(0.000 1.201)	0.140
norm         12.003         12.95         11.7%         12.004         24.77         12.100         0.12.970, 0.12.77, 0.07.30           BB-34         2.953         2.91         80.20%         2.976         2.92         83.1%         1.1010, 0.921, 0.07         0.1376           BC-         1.444         2.25         64.8%         1.370         190         86.1%         1.1110, 0.914, 3.20         0.246           Black         1.125         112         90.0%         1.220         142         84.4%         0.440, 0.864, 0.026           Other         1.273         61         95.2%         5.648         424         92.5%         0.026           Martial         5.926         412         92.6%         0.026, 0.0147, 0.943         0.026           Martial         5.928         4.94         92.5%         1.019(0.890, -1.67)         0.792           Single         7,130         821         90.0%         7.042         604         90.1%         0.2790, 889, -1.121         0.026           Laterality         6,562         545         91.7%         0.381(0.870, -1.06)         0.735           Single         6,184         617         90.890         0.890(0.890, -1.490         0.930	70 74	5.270	210	0/ 1%	5 259	242	02.6%		0.467
Charles         Cases         Cases         Cases         Cases         Cases         Cases         Cases           65-4         2,163         26,116         62,046         2,576         22         89,186         1,110,00,081-1,150         0.273           85+         1,144         223         84,8%         1,370         190         86,115         1,110,00,081-1,150         0.273           Rec           91,4%         1,0240,094-1,153         0.249         0.0440         0.0249         0.0470         0.0249         0.0470         0.0249         0.0490         0.021         0.0419         0.0429         0.0249         0.0249         0.0249         0.0249         0.0249         0.0249         0.0249         0.0249         0.0249         0.0249 <td>75 70</td> <td>3,270</td> <td>325</td> <td>01 7%</td> <td>3,042</td> <td>247</td> <td>01.2%</td> <td>0.943(0.010-1.101) 0.027(0.707 - 1.070)</td> <td>0.407</td>	75 70	3,270	325	01 7%	3,042	247	01.2%	0.943(0.010-1.101) 0.027(0.707 - 1.070)	0.407
Onlyme         2,000         200         81,00         10100038-1180         0.010           Bit         1,114         216         81,00         11140038-1180         0.0270           Race	80.84	0,909	020	91.7 %	0.576	047	91.270	1 012(0 850 1 105)	0.329
C3+         1,140         220         64.5%         1,370         180         10.140,376-1,322         02/20           White         1,064,3         968         91.1%         11,124         96.3         91.4%         1.054(0,964-1,153)         02.46           Black         1,276         61         95.2%         902         67         92.6%         0.073(0,477-0,984)         0.026           Marital         Marital         Varial         94.4%         7.042         69.4         90.1%         0.037(0,282-1,080,017,067,087,087,087,087,087,0167,07,082,017,067,087,087,087,087,017,067,017,067,087,087,087,087,017,067,087,087,087,087,087,087,087,087,017,087,087,087,087,087,087,087,087,087,08	00-04	2,000	201	09.0%	2,370	202	09.170	1.013(0.039-1.193)	0.070
Hane         Hane <th< td=""><td>00+ D</td><td>1,404</td><td>220</td><td>04.0%</td><td>1,370</td><td>190</td><td>80.1%</td><td>1.114(0.916-1.352)</td><td>0.273</td></th<>	00+ D	1,404	220	04.0%	1,370	190	80.1%	1.114(0.916-1.352)	0.273
Winter         L, D84.3         968         91.1%         L1, L24         96.3         91.4%         LD240, D46-1, 15.3         0.240           Cher         1, 278         61         95.2%         90.2         67         92.6%         0.6776, 0.777-0.964         0.028           Marital           Marital           0.675         0.776, 0.777-0.964         0.028           Single         7,130         681         90.4%         7.042         694         90.1%         0.9500, 0.803-1.687, 0.675           Unknown         590         48         91.9%         5.566         44         92.1%         0.9500, 0.807-1.121, 0.959           Cateratify          6.849         623         90.9%         6.862         545         91.7%         0.6810, 0.870-1.162, 0.959         0.950           Cate          71         97.4%         2.965         105         96.1%         0.830, 0.69-9.923         0.013           1         5.951         386         93.5%         5.954         4.04         93.2%         0.9900, 0.890-1.149         0.990           11         5.171         40.67         652         87.4%         4.965         68.8%         0.97	Race	1 00 10	000	01 10/	11 104	050	01 40/		0.040
Black         1,12b         112         90.9%         1,220         142         98.4%         0.04900.058-1.080         0.170           Marital                 Marital                 Marital                  Marital                     Single         7,150         681         90.9%         6.562         545         91.7%         0.9610.870-1401         0.800.830-1431         0.800           Laterality            0.6561         90.9%         6.662         545         91.7%         0.9610.870-1409         0.960           III         5.961         366         93.5%         5.854         404         93.2%         0.9990.0892-1431         0.383           T Stage            0.663         85.8%         0.8770.877-089         0.657           T 12         2.687         7.78         4.2424         78         81.4%	vvnite	1,0843	968	91.1%	11,124	953	91.4%	1.054(0.964-1.153)	0.246
Other         1,278         61         90,2%         90,2         67         92,6%         0.026 bits         0.028           Marital         Marital         Marital         Second         92,6%         0.028 bits         0.028 bits <td>BIACK</td> <td>1,125</td> <td>112</td> <td>90.9%</td> <td>1,220</td> <td>142</td> <td>88.4%</td> <td>0.843(0.658-1.080)</td> <td>0.176</td>	BIACK	1,125	112	90.9%	1,220	142	88.4%	0.843(0.658-1.080)	0.176
Marriad         S26         412         92.5%         5.648         424         92.5%         1.019(0.880-1.167)         0.782           Single         7,130         681         90.4%         7.042         694         92.5%         0.976(0.880-1.087)         0.782           Lukroum         590         48         91.9%         556         44         92.5%         0.90(0.620-1.431)         0.906           Laterality          518         91.9%         6.562         545         91.7%         0.981(0.870-1.106)         0.755           Latt         6,849         623         90.9%         6,684         617         90.8%         1.003(0.897-1.121)         0.959           Grade           71         97.4%         2,685         404         93.2%         0.999(0.89-1.149)         0.990           III         6,967         263         85.8%         1.027(0.92-1.149)         0.683           TStage           714         0.66         6.96         8.108         21         94.8%         0.956(0.834-1.096)         0.517           T2         4,367         552         87.4%         4.642         472         88.5%         0.227(0.870-1.149)<	Other	1,278	61	95.2%	902	67	92.6%	0.675(0.477-0.954)	0.026
Marnad         5,525         412         92,5%         5,643         424         92,5%         1,019(0,890-1,167)         0.785           Single         7,130         681         90,4%         7,042         694         90,1%         0,576(0,880-1,687)         0.675           Laterality         Fight         6,397         518         91,9%         6,562         545         91,7%         0.989(0,820-1,431)         0.0959           Grade           5,651         36,69         6,684         617         90,8%         1.003(0,897-1,121)         0.9599           Grade           2,691         71         97,4%         2,695         105         96,1%         0.683(0,506-0,923)         0.013           III         4,604         684         85,1%         4,597         653         85,8%         1.027(0,922-1,143)         0.033           TStage         T         71         97,4%         4,567         653         85,8%         0.97(0,870-197)         0.690           T3         306         88         77,8%         4,264         79         81,4%         1.206(0,890-1,635)         0.226           T4         312         96         0.677%	Marital								
Single         7,130         681         90.4%         7,042         694         90.1%         0.978(0.880-1.087)         0.075           Laterality                  Bight         6,5849         623         90.9%         6,682         545         91.7%         0.989(0.830-1.131)         0.9959           Grade             90.9%         6,682         545         91.7%         0.991(0.870-1.104)         0.959           Grade           90.8%         1.003(0.897-1.121)         0.959           Grade            90.8%         0.999(0.890-1.149)         0.959           Grade           90.8%         5.564         404         93.2%         0.999(0.890-1.149)         0.633           III         4.604         66.9%         8.108         421         94.8%         0.996(0.834-1.008)         0.633           T2         4.367         556         87.4%         4.244         79         81.4%         1.206(0.890-1.630)         0.201           T3         396         88         77.8%         4.244 <th< td=""><td>Married</td><td>5,526</td><td>412</td><td>92.5%</td><td>5,648</td><td>424</td><td>92.5%</td><td>1.019(0.890–1.167)</td><td>0.782</td></th<>	Married	5,526	412	92.5%	5,648	424	92.5%	1.019(0.890–1.167)	0.782
Unknown 590 48 91.9% 556 44 92.1% 0.550(0.630-1.431) 0.306 Laterality Fight 6.397 518 91.9% 6.562 543 91.7% 0.981(0.870-1.108) 0.755 Later 16,849 623 90.9% 6.682 645 91.7% 0.981(0.870-1.108) 0.755 Grade I 2,691 71 97.4% 2,695 105 96.1% 0.683(0.560-0.923) 0.013 III 4,5051 386 93.5% 5,564 404 93.2% 0.999(0.898-1.149) 0.990 III 4,5051 386 93.5% 5,564 404 93.2% 0.999(0.898-1.149) 0.990 III 4,5051 386 93.5% 4,597 653 85.8% 1.027(0.522-1.143) 0.633 T Stage T 1 4 7 1 40.64 684 86.1% 4,597 659 86.5% 0.957(0.870-1.070) 0.690 T3 396 88 77.8% 424 79 81.4% 1.206(0.803-1.591) 0.517 T2 4,367 552 87.4% 4,386 599 86.5% 0.957(0.870-1.070) 0.690 T3 396 88 77.8% 424 79 81.4% 1.206(0.803-1.633) 0.226 T4 312 95 69.6% 3.708 421 79.8% 1.27(0.1254-2.331) 0.001 N 5tage N 5	Single	7,130	681	90.4%	7,042	694	90.1%	0.978(0.880–1.087)	0.675
Lateraity           Right         6.397         518         91.9%         6.562         545         91.7%         0.881(0.870-1.06)         0.755           Left         6.849         623         90.9%         6.562         545         91.7%         0.881(0.870-1.06)         0.755           Grade           90.9%         1.003(0.897-1.121)         0.959           II         2.5951         386         93.5%         5.954         404         93.2%         0.999(0.889-1.149)         0.990           III         4.04         684         95.5%         4.967         663         85.8%         0.102(0.922-1.143)         0.933           T Stage           91.37%         4.366         589         86.5%         0.037(0.870-1.097)         0.600           T3         396         88         77.8%         4.24         79         81.4%         1.208(0.890-1.633)         0.228           T4         312         95         69.6%         348         73         79.0%         1.11(41.204-2.331)         0.001           N1         4.268         521         87.7%         4.242         422         83.6%         1.248(1.007-1.408)         0.071	Unknown	590	48	91.9%	556	44	92.1%	0.950(0.630-1.431)	0.806
Right         6,397         518         91.9%         6,662         545         91.7%         0.981(0.870-1.106)         0.755           Carde           90.9%         6,664         617         90.8%         1.003(0.897-1.121)         0.359           Grade           90.9%         6,664         617         90.8%         0.039(0.897-1.121)         0.959           II         5,951         386         93.5%         5,954         404         93.2%         0.939(0.689-1.149)         0.990           III         4,064         684         95.5%         4,063         85.8%         1.027(0.822-1.143)         0.990           TStage         7         552         87.4%         4,366         589         86.5%         0.977(0.870-1.097)         0.690           T2         4,367         552         87.4%         4,366         589         86.5%         0.977(0.870-1.097)         0.690           T3         396         88         77.7%         4,436         589         86.5%         0.977(0.870-1.97)         0.690           N3 tage         9         9.7%         8,709         6.44         92.6%         0.819(0.31-0.120)         0.001	Laterality								
Left 6.849 623 90.9% 6.684 617 90.8% 1.039(0.897-1.121) 0.959 Grade	Right	6,397	518	91.9%	6,562	545	91.7%	0.981(0.870-1.106)	0.755
Grade         View         View <t< td=""><td>Left</td><td>6,849</td><td>623</td><td>90.9%</td><td>6,684</td><td>617</td><td>90.8%</td><td>1.003(0.897-1.121)</td><td>0.959</td></t<>	Left	6,849	623	90.9%	6,684	617	90.8%	1.003(0.897-1.121)	0.959
1         2,691         71         97.4%         2,695         106         96.1%         0.683(0.506-0.923)         0.013           III         4,504         684         93.5%         5,954         404         93.2%         0.990(0.869-1.149)         0.990           T Stage                  T1         8,171         406         96.0%         8,108         421         9.4,8%         0.956(0.834-1.066)         0.517           T2         4,367         552         87.4%         4,366         589         86.5%         0.977(0.870-1.037)         0.663           T3         396         88         77.8%         424         79         81.4%         1.206(0.890-1.655)         0.226           T4         312         95         69.6%         348         73         70.0%         0.71         6.65         0.819(0.71-0.916)         0.001           N1         4,268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.406)         0.001           N2         133         61         67.7%         2667         44         83.5%         2.886(1.180-25.307)         0.030	Grade								
II         5,951         386         93.5%         5,954         404         93.2%         0.9990.0809-1.149         0.9390           III         4,604         684         85.1%         4,597         653         85.8%         1.027(0.922-1.143)         0.633           Stage                  T1         8,171         406         9.0%         8,108         421         9.4.8%         0.956(0.834-1.096)         0.517           T2         4,367         552         87.4%         4,366         589         86.5%         0.977(0.870-1.097)         0.690           T3         396         88         77.8%         424         79         81.4%         1.206(0.890-1.655)         0.226           T4         4.268         521         87.8%         4.242         472         88.9%         0.819(0.731-0.918)         0.001           N1         4.268         521         87.8%         4.242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         287         2.366         744         83.5%         2.886(1.180-25.307)         0.030 <t< td=""><td>1</td><td>2,691</td><td>71</td><td>97.4%</td><td>2,695</td><td>105</td><td>96.1%</td><td>0.683(0.506-0.923)</td><td>0.013</td></t<>	1	2,691	71	97.4%	2,695	105	96.1%	0.683(0.506-0.923)	0.013
III         4,604         684         85.1%         4,597         653         85.8%         1.027(0.922-1.13)         0.633           T Stage		5,951	386	93.5%	5,954	404	93.2%	0.999(0.869-1.149)	0.990
T Stage         No.         No.           T1         8,171         406         95.0%         8,186         599         96.6%         0.957(0.870-1.097)         0.690           T2         3.96         88         77.8%         4.24         79         81.4%         1.206(0.894-1.097)         0.090           T3         3.96         88         77.8%         4.24         79         81.4%         1.206(0.890-1.635)         0.226           T4         312         95         9.96%         3.48         73         79.0%         1.716(1.264-2.33)         0.001           NStage         No         8.771         550         93.7%         8,709         644         92.6%         0.819(0.731-0.918)         0.001           N1         4.268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         267         44         83.5%         2.886(1.980-4.271)         <0.001	111	4,604	684	85.1%	4,597	653	85.8%	1.027(0.922-1.143)	0.633
T1         8,171         406         95.0%         8,108         421         94.8%         0.956(0.834-1.096)         0.517           T2         4,367         552         87.4%         4,366         569         86.5%         0.977(0.870-1.097)         0.690           T3         396         88         77.8%         424         79         81.4%         1.206(0.80-1.635)         0.226           T4         312         95         69.6%         348         73         79.0%         1.716(1.264-2.331)         0.001           NStage           71         550         83.7%         8,709         644         92.6%         0.819(0.731-0.918)         0.001           N1         4,268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         267         44         83.5%         2.886(1.180-25.307)         0.030           N2         183         61         66.7%         267         44         83.5%         2.886(1.180-25.307)         0.031           N2         65.65         747         80.662         454         93.2%         0.950(0.832-1.08) <td>T Stage</td> <td>,</td> <td></td> <td></td> <td>,</td> <td></td> <td></td> <td>· · · · · · · · · · · · · · · · · · ·</td> <td></td>	T Stage	,			,			· · · · · · · · · · · · · · · · · · ·	
T2       4,367       552       87.4%       4,366       589       86.5%       0.977(0.870-1.097)       0.690         T3       396       88       77.8%       424       79       81.4%       1.206(0.890-1.635)       0.226         T4       312       95       69.6%       348       73       79.0%       1.716(1.264-2.331)       0.001         NStage            0.890       0.819(0.731-0.918)       0.001         N1       4.268       521       87.7%       4.722       472       88.9%       1.243(1.097-1.408)       0.001         N2       183       61       66.7%       2.67       44       83.5%       2.886(1.950-4.271)       <0.001	T1	8.171	406	95.0%	8.108	421	94.8%	0.956(0.834-1.096)	0.517
T3         396         88         77.8%         424         79         81.4%         1.206(0.890-1.635)         0.226           T4         312         95         69.6%         348         73         79.0%         1.716(1.264-2.331)         0.001           NStage            550         93.7%         8,709         644         92.6%         0.819(0.731-0.918)         0.001           N1         4,268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         267         44         83.5%         2.86(1.950-4.271)         <0.001	T2	4.367	552	87.4%	4.366	589	86.5%	0.977(0.870-1.097)	0.690
T4         312         95         69.6%         348         73         70.0%         1.716(1.264-2.33)         0.001           NS         Stage                 NO         8,771         550         93.7%         8,709         644         92.6%         0.819(0.731-0.918)         0.001           N1         4,268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         267         44         88.5%         2.886(1.950-4.271)         <0.001           N3         24         9         62.5%         28         2         92.9%         5.465(1.180-25.307)         0.030           Type of Surgery                       <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <         <	T3	396	88	77.8%	424	79	81.4%	1.206(0.890-1.635)	0.226
N Stage         No.         8,771         550         93,7%         8,709         644         92,6%         0.819(0.731-0.918)         0.001           N1         4,268         521         87,8%         4,242         472         88,9%         1.243(1.097-1.408)         0.001           N2         183         61         66,7%         267         44         83,5%         2.88(1.950-4.27)         <0.001	T4	312	95	69.6%	348	73	79.0%	1.716(1.264-2.331)	0.001
No         8,771         550         93.7%         8,709         644         92.6%         0.819(0.731-0.918)         0.001           N1         4,268         521         87.8%         4,242         472         88.9%         1.243(1.097-1.408)         0.001           N2         183         61         66.7%         267         44         83.5%         2.886(1.950-4.271)         <0.001	N Stage	0.2	00	001070	0.10		1010/0		
Nn         April         Bod         Brin	NO	8 771	550	93.7%	8 709	644	92.6%	0 819(0 731-0 918)	0 001
N1         1,220         32.1         0.1.5%         1,22         112         0.0.5%         1,2240(1,057-1,140)         0.001           N2         183         61         66.7%         267         44         83.5%         2.888(1,950-4,271)         <0.001	NI1	4 268	521	87.8%	4 242	472	88.0%	1 2/3(1 007_1 /08)	0.001
N2         103         01         00.7%         201         144         00.5%         2.050/(1.305-4.21/1)         COMOT           N3         24         9         62.5%         28         2         92.9%         5.465(1.180-25.307)         0.030           Type of Surgery         . <td< td=""><td>N/2</td><td>183</td><td>61</td><td>66.7%</td><td>267</td><td>112</td><td>83.5%</td><td>2 886(1 950_4 271)</td><td>&lt;0.001</td></td<>	N/2	183	61	66.7%	267	112	83.5%	2 886(1 950_4 271)	<0.001
No         14         6         6.3.%         2.0         2         9.2.3.%         9.4.0(1.100-2.3.3.7)         0.000           Type of Surgery         No         14         4         71.4%         16         4         75.0%         1.019(0.253-4.103)         0.979           BCS         6,579         417         93.7%         6,662         454         93.2%         0.950(0.832-1.085)         0.451           Mastectomy         6,653         720         89.2%         6,568         704         89.3%         1.013(0.913-1.124)         0.812           Radiation	N2	24	0	62.5%	201	-++	02.0%	5 465(1 190 25 207)	0.001
Processingery         No         14         4         71.4%         16         4         75.0%         1.019(0.253-4.103)         0.979           BCS         6,579         417         93.7%         6,662         454         93.2%         0.950(0.832-1.085)         0.451           Mastectomy         6,653         720         89.2%         6,568         704         89.3%         1.013(0.913-1.124)         0.812           Radiation                  Yes         5,567         372         93.3%         5,432         385         92.9%         0.957(0.830-1.104)         0.546           No/Refused         7,679         769         90.0%         7,814         777         90.1%         1.019(0.922-1.126)         0.715           Chemotherapy                    Yes         2,651         277         89.6%         2,746         251         90.9%         1.206(1.017-1.431)         0.031           No/Unknown         10,595         80.6%         2,516         396         84.3%         1.005(0.876-1.154)         0.213      N	Tupo of Surgory	24	9	02.070	20	2	92.970	3.403(1.100=23.307)	0.030
No         14         4         1/1.4%         16         4         75.0%         1.019(0.253-4.103)         0.979           BCS         6,579         417         93.7%         6,662         454         93.2%         0.950(0.832-1.085)         0.451           Mastectomy         6,653         720         89.2%         6,568         704         89.3%         1.013(0.913-1.124)         0.812           Radiation	No.	14	4	71 40/	10	4	75.00/	1 010/0 050 4 100)	0.070
BCS         6,679         417         93.7%         6,662         464         93.2%         0.930(0.832=1.063)         0.431           Mastectomy         6,653         720         89.2%         6,568         704         89.3%         1.013(0.913=1.124)         0.812           Radiation               0.957(0.830=1.104)         0.546           No/Refused         7,679         769         90.0%         7,814         777         90.1%         1.019(0.922=1.126)         0.715           Chemotherapy             0.933         0.943(0.859=1.034)         0.531           No/Unknown         10,595         864         91.8%         10,500         911         91.3%         0.943(0.859=1.034)         0.213           ER Status                    Positive         10,724         729         93.2%         10,730         766         92.9%         0.976(0.882=1.081)         0.645           Negative         2,522         412         83.7%         2,516         396         84.3%         1.005(0.876=1.154)         0.941 <td>NO DCC</td> <td>14</td> <td>4</td> <td>71.4%</td> <td>01</td> <td>4</td> <td>75.0%</td> <td>1.019(0.253-4.103)</td> <td>0.979</td>	NO DCC	14	4	71.4%	01	4	75.0%	1.019(0.253-4.103)	0.979
Maskedotiny         6,653         7.0         89.2%         6,566         7.04         69.3%         1.013(0.913-1.124)         0.812           Radiation         7         9         9         0.957(0.830-1.104)         0.546           No/Refused         7,679         769         90.0%         7,814         777         90.1%         1.019(0.922-1.126)         0.715           Chemotherapy         7         9         9         0.96%         2,746         251         90.9%         1.206(1.017-1.431)         0.031           No/Unknown         10,595         864         91.8%         10,500         911         91.3%         0.943(0.859-1.034)         0.213           ER Status         7         93.2%         10,730         766         92.9%         0.976(0.882-1.081)         0.645           Negative         2,522         412         83.7%         2,516         396         84.3%         1.005(0.876-1.154)         0.941           PR Status         7         9.084         535         94.1%         9.202         604         93.4%         0.920(0.819-1.034)         0.163           Negative         9.084         535         94.1%         9.202         604         93.4%         0.920(0.819	BUS Maataatamu	0,579	417	93.7%	0,002	404	93.2%	0.950(0.632-1.065)	0.451
PadiationYes5,56737293.3%5,43238592.9%0.957(0.830–1.104)0.546No/Refused7,67976990.0%7,81477790.1%1.019(0.922–1.126)0.716ChemotherapyYes2,65127789.6%2,74625190.9%1.206(1.017–1.431)0.031No/Unknown10,59586491.8%10,50091191.3%0.943(0.859–1.034)0.213ER Status </td <td></td> <td>0,003</td> <td>720</td> <td>09.2%</td> <td>0,000</td> <td>704</td> <td>69.3%</td> <td>1.013(0.913-1.124)</td> <td>0.012</td>		0,003	720	09.2%	0,000	704	69.3%	1.013(0.913-1.124)	0.012
Yes         5,567         372         93.3%         5,432         385         92.9%         0.957(0.830-1.104)         0.546           No/Refused         7,679         769         90.0%         7,814         777         90.1%         1.019(0.922-1.126)         0.715           Chemotherapy	Radiation	5 507	070	00.00/	5 400	005	00.00/	0.057/0.000 4.404	0 5 40
No/Herused         7,679         769         90.0%         7,814         777         90.1%         1.019(0.922-1.126)         0.715           Chemotherapy         Yes         2,651         277         89.6%         2,746         251         90.9%         1.206(1.017-1.431)         0.031           No/Unknown         10,595         864         91.8%         10,500         911         91.3%         0.943(0.859-1.034)         0.213           ER Status         Positive         10,724         729         93.2%         10,730         766         92.9%         0.976(0.882-1.081)         0.645           Negative         2,522         412         83.7%         2,516         396         84.3%         1.005(0.876-1.154)         0.941           PR Status         P         Status         9         9,202         604         93.4%         0.920(0.819-1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819-1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819-1.034)         0.163           Negative         9,331         281	Yes	5,567	372	93.3%	5,432	385	92.9%	0.957(0.830-1.104)	0.546
Chemotherapy           Yes         2,651         277         89.6%         2,746         251         90.9%         1.206(1.017–1.431)         0.031           No/Unknown         10,595         864         91.8%         10,500         911         91.3%         0.943(0.859–1.034)         0.213           ER Status                  Positive         10,724         729         93.2%         10,730         766         92.9%         0.976(0.882–1.081)         0.645           Negative         2,522         412         83.7%         2,516         396         84.3%         1.005(0.876–1.154)         0.941           PR Status                  PR Status           9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           HER2 Status                <	No/Refused	7,679	769	90.0%	7,814	777	90.1%	1.019(0.922-1.126)	0.715
Yes       2,651       277       89.6%       2,746       251       90.9%       1.206(1.017–1.431)       0.031         No/Unknown       10,595       864       91.8%       10,500       911       91.3%       0.943(0.859–1.034)       0.213         ER Status       Positive       10,724       729       93.2%       10,730       766       92.9%       0.976(0.882–1.081)       0.645         Negative       2,522       412       83.7%       2,516       396       84.3%       1.005(0.876–1.154)       0.941         PR Status       Positive       9,084       535       94.1%       9,202       604       93.4%       0.920(0.819–1.034)       0.163         Negative       4,162       606       85.4%       4,044       558       86.2%       1.041(0.928–1.167)       0.497         HER2 Status       Positive       916       71       92.2%       964       61       93.7%       1.347(0.956–1.897)       0.088         Negative       5,331       281       94.7%       5,527       285       94.8%       1.088(0.923–1.284)       0.314         Borderline       152       8       94.7%       167       12       92.8%       0.677(0.277–1.657)	Chemotherapy			(					
No/Unknown         10,595         864         91.8%         10,500         911         91.3%         0.943(0.859–1.034)         0.213           ER Status         Positive         10,724         729         93.2%         10,730         766         92.9%         0.976(0.882–1.081)         0.645           Negative         2,522         412         83.7%         2,516         396         84.3%         1.005(0.876–1.154)         0.941           PR Status         Positive         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         9,084         1066         85.4%         4,044         558         86.2%         1.041(0.928–1.167)         0.497           HER2 Status         Positive	Yes	2,651	277	89.6%	2,746	251	90.9%	1.206(1.017-1.431)	0.031
ER Status         Positive       10,724       729       93.2%       10,730       766       92.9%       0.976(0.882–1.081)       0.645         Negative       2,522       412       83.7%       2,516       396       84.3%       1.005(0.876–1.154)       0.941         PR Status       Positive       9,084       535       94.1%       9,202       604       93.4%       0.920(0.819–1.034)       0.163         Negative       9,084       535       94.1%       9,202       604       93.4%       0.920(0.819–1.034)       0.163         Negative       9,084       535       94.1%       9,202       604       93.4%       0.920(0.819–1.034)       0.163         Negative       9,084       535       94.1%       9,202       604       93.4%       0.920(0.819–1.034)       0.163         Negative       9,084       636       85.8%       4,044       558       86.2%       1.041(0.928–1.167)       0.497         HER2 Status       Positive       916       71       92.2%       964       61       93.7%       1.347(0.956–1.897)       0.088         Negative       5,331       281       94.7%       5,527       285       94.8%	No/Unknown	10,595	864	91.8%	10,500	911	91.3%	0.943(0.859–1.034)	0.213
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PR Status           Positive         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         4,162         606         85.4%         4,044         558         86.2%         1.041(0.928–1.167)         0.497           HER2 Status         Positive         916         71         92.2%         964         61         93.7%         1.347(0.956–1.897)         0.088           Negative         5,331         281         94.7%         5,527         285         94.8%         1.088(0.923–1.284)         0.314           Borderline         152         8         94.7%         167         12         92.8%         0.677(0.277–1.657)         0.393           Not 2010+         6,847         781         88.6%         6,588         804         87.8%         0.945(0.856–1.042)         0.258	Negative	2,522	412	83.7%	2,516	396	84.3%	1.005(0.876–1.154)	0.941
Positive         9,084         535         94.1%         9,202         604         93.4%         0.920(0.819–1.034)         0.163           Negative         4,162         606         85.4%         4,044         558         86.2%         1.041(0.928–1.167)         0.497           HER2 Status         916         71         92.2%         964         61         93.7%         1.347(0.956–1.897)         0.088           Negative         5,331         281         94.7%         5,527         285         94.8%         1.088(0.923–1.284)         0.314           Borderline         152         8         94.7%         167         12         92.8%         0.677(0.277–1.657)         0.393           Not 2010+         6,847         781         88.6%         6,588         804         87.8%         0.945(0.856–1.042)         0.258	PR Status								
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HER2 Status           Positive         916         71         92.2%         964         61         93.7%         1.347(0.956-1.897)         0.088           Negative         5,331         281         94.7%         5,527         285         94.8%         1.088(0.923-1.284)         0.314           Borderline         152         8         94.7%         167         12         92.8%         0.677(0.277-1.657)         0.393           Not 2010+         6,847         781         88.6%         6,588         804         87.8%         0.945(0.856-1.042)         0.258	Negative	4,162	606	85.4%	4,044	558	86.2%	1.041(0.928-1.167)	0.497
Positive         916         71         92.2%         964         61         93.7%         1.347(0.956-1.897)         0.088           Negative         5,331         281         94.7%         5,527         285         94.8%         1.088(0.923-1.284)         0.314           Borderline         152         8         94.7%         167         12         92.8%         0.677(0.277-1.657)         0.393           Not 2010+         6,847         781         88.6%         6,588         804         87.8%         0.945(0.856-1.042)         0.258	HER2 Status								
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Borderline         152         8         94.7%         167         12         92.8%         0.677(0.277-1.657)         0.393           Not 2010+         6,847         781         88.6%         6,588         804         87.8%         0.945(0.856-1.042)         0.258	Negative	5,331	281	94.7%	5,527	285	94.8%	1.088(0.923-1.284)	0.314
Not 2010+ 6,847 781 88.6% 6,588 804 87.8% 0.945(0.856-1.042) 0.258	Borderline	152	8	94.7%	167	12	92.8%	0.677(0.277-1.657)	0.393
	Not 2010+	6,847	781	88.6%	6,588	804	87.8%	0.945(0.856-1.042)	0.258

p = 0.877) (**Figure 2A**) and OS differences (HR = 0.965, 95% CI = 0.923–1.009, p = 0.113) (**Figure 2B**). Similar results were observed in the different patient, tumor, and treatment subgroups, except in the Grade 1, T4 stage, and different N stage subgroups. In the pN0 stage subgroup, the SLNB group had a better breast cancer prognosis. On the contrary, the prognosis of the ALND group was better with N1 stage and above.

# Exploratory Analyses of pN1 Stage Matched Groups

For exploratory analyses of the pN1 stage cohort, elderly breast cancer patients treated with SLNB were matched 1:1 to patients from the ALND group (**Supplemental Figure 3**); the baseline characteristics before and after matching are listed in **Supplemental Table 3**. Regardless of matching or not, all the variables were identified to be significantly associated with BCSS except for the marital status and HER2 status (**Table 2**). Kaplan–Meier curves of the whole cohort in the two axillary surgery groups revealed no significant differences (HR = 0.972, 95%CI = 0.878–1.077, p = 0.591) (**Figure 3A**). However, after adjustments using other prognostic factors, the risk of death in the ALND group was significantly lower than in the SLNB group, both before and after matching cohorts (**Table 2**; **Figure 3B**).

We further evaluated whether the BCSS advantage of ALND still existed when considering different numbers of positive lymph nodes or different hormone receptor status (**Figures 3C-E**). It demonstrates that the SLNB group still showed a survival disadvantage in BCSS compared to the ALND group even though there was only one positive lymph node (HR = 1.205, 95%CI = 1.031-1.409, p = 0.019) (**Figure 3C**). Moreover, the survival differences between the two groups was also affected by the hormone receptor status. In the hormone receptor positive (HR+) subgroup the ALND group patients no longer had an absolute BCSS advantage (HR = 1.150, 95%CI = 0.986-1.340, p = 0.075) (**Figure 4A**). Whereas, the hormone receptor negative (HR-) subgroup had similar outcomes (SLNB group *vs.*  ALND group: HR = 1,536, 95%CI = 1.213–1.946, *p* < 0.001) (**Figure 4B**).

### Further Exploratory Analysis in Number of Positive Lymph Nodes and Hormone Receptor Status

We confirmed that the baseline characteristics of the HR+ and HR– subgroups were comparable in the matched SLNB group and ALND group (**Supplemental Table 4**). Figure 5 shows the hazard ratios (HRs) of the SLNB group *versus* the ALND group on the basis of various combinations of hormone receptor status and number of positive lymph nodes. In the HR+ subgroup the SLNB groups were comparable with the ALND groups in BCSS performance regardless of the number of positive lymph node. While for the HR– subgroup, the BCSS of SLNB group was worse than that of the ALND group although only one lymph node was positive, and the SLNB group had worse survival when there were more positive lymph nodes.

# DISCUSSION

More than 30% of breast cancers are diagnosed in patients older than 70 years old (13, 14). By now, the average life expectancy of women over the age of 65 is 86.6 years, with one in four women achieving an age above 90 years old (15). Our study is of particular importance in light of the aging population and serves as a reference since there is a lack of randomized data to guide clinical decision-making. The most common manifestation of breast cancer in elderly patients is a higher grade and HRpositive invasive ductal carcinoma (**Table 1**). Some studies have also indicated that the incidence of ER+ breast cancer increased and that of HER2 decreased with age (14, 16, 17).

Previously published high-quality prospective studies of axillary treatments did not focus on elderly patients exclusively (2, 3, 18, 19). These studies paid more attention to whether



#### TABLE 2 | Multivariate analysis by Cox proportional hazard model in before and after matching pN1 stage cohorts.

Variables		Before Match	ling	After Matching	
		HR (95%CI)	P value	HR (95%CI)	P value
Age	70–74	Ref		Ref	
	75–79	1.225(1.074-1.396)	0.002	1.215(1.014-1.454)	0.034
	80-84	1.450(1.258-1.672)	<0.001	1.422(1.174 <b>-</b> 1.723)	<0.001
	85+	1.716(1.463-2.014)	<0.001	1.729(1.408-2.124)	<0.001
Race	White	Ref		Ref	
	Black	1.139(0.981-1.323)	0.088	1.112(0.898-1.377)	0.331
	Other	0.680(0.534-0.865)	0.002	0.635(0.456-0.885)	0.007
Marital	Married	Ref		Ref	
	Single	1.017(0.914-1.132)	0.759	1.050(0.911-1.211)	0.502
	Unknown	0.870(0.659-1.149)	0.327	0.867(0.598-1.257)	0.451
Grade	I.	Ref		Ref	
	II	1.975(1.560-2.500)	<0.001	1.897(1.426-2.522)	<0.001
	III	3.112(2.450-3.951)	<0.001	3.035(2.269-4.061)	<0.001
T Stage	T1	Ref		Ref	
Ū.	T2	1.900(1.686-2.141)	<0.001	1.900(1.629-2.216)	<0.001
	Т3	3.214(2.639-3.914)	<0.001	2.905(2.204-3.829)	<0.001
	T4	3.413(2.799-4.163)	<0.001	2.922(2.240-3.810)	<0.001
The Number of Positive LN	1	Ref		Ref	
	2	1.273(1.133-1.430)	<0.001	1.224(1.044-1.433)	0.012
	3	1.473(1.281-1.694)	<0.001	1.539(1.234-1.920)	<0.001
Type of Surgery	No	Ref		Ref	
	BCS	0.280(0.203-0.386)	<0.001	0.127(0.047-0.342)	<0.001
	Mastectomy	0.295(0.217-0.403)	<0.001	0.135(0.050-0.364)	<0.001
Type of Axillary Surgery	SLNB	Ref		Ref	
	ALND	0.763(0.682-0.853)	<0.001	0.781(0.686-0.889)	<0.001
Radiation	Yes	Ref		Ref	
	No	1.464(1.299-1.651)	<0.001	1.427(1.220-1.668)	<0.001
Chemotherapy	Yes	Ref		Ref	
	No	1.457(1.292-1.645)	<0.001	1.541(1.302-1.824)	<0.001
EB Status	Positive	Ref		Bef	
	Negative	1 559(1 352-1 798)	<0.001	1 404(1 162–1 698)	<0.001
PB Status	Positive	Bef		Bef	101001
- Trotatio	Negative	1 644(1 437-1 880)	<0.001	1 757(1 477-2 089)	<0.001
HFR2 Status	Positive	Bef	-01001	Bef	-0.001
	Negative	1 090(0 880-1 348)	0.430	0.989(0.763-1.283)	0 935
	Borderline	0.938(0.546-1.612)	0.400	1 085(0 574-2 050)	0.802
	Not 2010+	1 247(1 018-1 528)	0.033	1.061(0.824-1.365)	0.648
	1101 20107	1.247(1.010-1.020)	0.000	1.001(0.024-1.000)	0.040

Bold P values mean that the difference is statistically significant.

axillary evaluation could be omitted (5–8, 20). The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) in 2012 (4) and the Society of Surgical Oncology of the Choosing Wisely campaign in 2016 recommended that elderly breast cancer patients could be exempted from axillary lymph node evaluation when it was clinically determined that axillary lymph nodes were negative (5, 6). A subsequent meta-analysis composed of two randomized controlled trials involving 692 patients found that omission of axillary evaluation would not result in significant difference of overall breast cancer specific mortality (21).

In our study we demonstrated that, after adjustment by other factors, axillary lymph node surgery (both SLNB and ALND) raised the breast cancer-specific survival by more than 40% compared to patients who did not receive lymph node assessment (**Table 2**). Similarly, Chagpar et al. (7) revealed that after controlling for tumor size, grade, patient age, comorbidities, and treatment factors, patients who did not have LN evaluation had a worse survival compared with those who had axillary evaluation. It was also

indicated that axillary surgery was associated with higher rates of adjuvant therapy and improved overall survival for elderly cN0 breast cancer patients in a study from Tamirisa et al. (22). Lymph node evaluation was shown to provide important information for determining their adjuvant therapy options (7).

It is well known that SLNB is minimally invasive, with a 2–7% risk of upper extremity lymphedema, in comparison with the 15–20% risk associated with ALND (10, 23). Therefore, in the social context of population aging and precision medicine, it is necessary and imperative to identify whether elderly patients need ALND or not. To the best of our knowledge, this is the largest cohort that has been evaluated to compare SLNB and ALND in elderly breast cancer patients. We performed PSM analyses to address the limitations of a retrospective study from a large SEER sample of patients who underwent axillary surgery. After reliable Cox regression analyses and matched stratification analyses, SLNB did not imply higher breast cancer specific mortality among the cohort, in both subgroups with or without other kind of treatments and regardless of the ER, PR, and HER2 status.



We were concerned that the survival of SLNB group patients is concentrated in the stage N0 patients; in the stage N1 and above patients ALND still needs to be selected. A metaanalysis based on four trials showed no significant differences in OS and DFS between ALND and regional nodal irradiation (RNI) in short- or long-term outcomes (24). Hence, RNI may be an alternative treatment for adjuvant management of the axilla in selected patients, and an optimal radiation



FIGURE 4 | Breast cancer specific survival of hormone receptor positive (HR+) (A) and hormone receptor negative (HR-) (B) stratified by SLNB and ALND in the matching pN1 stage patients.



strategy approach for elderly patients warrants further study. However, it is undeniable that local control of the axilla isõ still important in the treatment of elderly breast cancer patients.

Our exploratory analyses for the stage N1 cohort detected that with HR+ breast cancer in elderly patients with 1 to 3 positive lymph nodes, you could omit further lymph node dissection: True in both the with and without radiation subgroups. The HR– patients still required ALND even when there was only one positive lymph node. Some studies have concluded that the adjuvant therapy strategies for HR+ elderly breast cancer should only be followed by endocrine therapy, and the axillary lymph node dissection can be avoided (5, 20). At present, the guidelines for breast cancer therapy recommend that the standard adjuvant endocrine therapy for postmenopausal patients is five years of aromatase inhibitor (AI). And for patients at high risk, a prolonged AI treatment can reduce the risk of relapse (25–28). In elderly patients with HR+ breast cancer, endocrine therapy plays an important role in the adjuvant therapy. Therefore, we hypothesize from our observations that the method of performing intensive endocrine therapy is more important than local treatment in the case of sentinel lymph nodes.

Inevitably, there are several limitations related to the design and data source in our study. Firstly, the number of examined recorded in the SEER database is the final total removed number, and unfortunately, we cannot determine the exact procedure of the axilla surgery. Even though the analyses based on PSM could effectively reduce the effects of the observed confounding factors, it cannot address unobserved confounding factors, nor the unavoidably cases lost. Secondly, the data about endocrine therapy in the SEER database is inaccessible despite the importance in adjuvant treatment of HR+ breast cancer, which makes the analyses of adjuvant therapy for elderly breast cancer incomplete. Thirdly, locoregional recurrence or disease-free survival is not included in the SEER database, and this precludes assessment of these end points. Lastly, it is unfortunate that cases receiving neoadjuvant chemotherapy could not be identified in the SEER database, which may lead to changes in axillary management.

To summarize, our findings suggest that ALND can be omitted in elderly patients with pN1 stage HR+ breast cancer. This study is the first to use a large number of cases of elderly patients for evaluation of the relative effectiveness between SLNB and ALND with BCSS as the primary endpoint. Although our findings are limited by the bias associated with retrospective study design, we believe that in the absence of randomized clinical trials, our findings should be considered when recommending the omission of ALND for elderly breast cancer patients. However, we still need further accurate prospective randomized studies to optimize patient selection for the omission of ALND.

# DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

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# **AUTHOR CONTRIBUTIONS**

S-PL and JZ conceptualized and designed the study. S-PL, JZ, and Q-SW developed the methodology. S-PL, JZ, and Y-XL took part in the acquisition, analysis, and interpretation of the data. S-PL, JZ, and C-GS wrote, reviewed, and/or revised the manuscript. C-GS and JZ supervised the study. All authors contributed to the article and approved the submitted version.

# **FUNDING**

This study was funded by National Natural Science Foundation of China (81672817).

# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020. 596545/full#supplementary-material

 $\label{eq:superior} \begin{array}{c} \mbox{Supplementary Figure 1} & | \ \mbox{Flow diagram for identifying eligible elderly patients} \\ (\geq 70 \ \mbox{years old}) \ \mbox{with breast cancer}. \end{array}$ 

Supplementary Figure 2 | The histogram (A) and dot plots (B) of before and after propensity score matching on SLNB group and ALND group of the total cohort.

Supplementary Figure 3 | The histogram (A) and dot plots (B) of before and after propensity score matching on SLNB group and ALND group of the pN1 stage cohort.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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