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Original Research

Research on the Effects of Chemotherapy on Survival Outcomes for Older Patients with Primary Triple-Negative Breast Cancer after Surgery: A Propensity Score Matching and Competing Risk Analysis of the SEER Database

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Abstract

Background: The population of older women (≥70 years old) with triple-negative breast cancer (TNBC) is increasing, but there are few prognostic studies for these patients. In the study, we explored the effects of chemotherapy on breast cancer-specific death (BCSD) and other cause-specific death (OCSD) in older patients with TNBC. **Methods**: In accordance with the inclusion and exclusion criteria, we extracted primary TNBC older patients (≥70 years old) from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2019. We used propensity score matching (PSM), cumulative incidence function (CIF) and multivariate Fine and Gray competitive risk analyses to explore the effects of chemotherapy on survival for older patients with primary TNBC after surgery. **Results**: After one-to-one matched PSM analysis, we identified 2478 primary TNBC patients (≥70 years old) finally. CIF analysis showed that the 3-year, 5-year and 8-year mortalities were 15.34%, 20.30% and 23.73% for BCSD, and 7.36%, 13.20% and 23.02% for OCSD. The survival analysis showed that patients who received chemotherapy had a better overall survival than those who did not received chemotherapy (hazard ratio 0.72, 95% confidence interval 0.63–0.82, $p < 0.001$). There was no difference in BCSD between older patients with chemotherapy and no chemotherapy. The OCSD rate for patients with chemotherapy was lower than that of those with no chemotherapy (Gray's test, $p < 0.001$). Diseases of heart were the most common cause of death in elderly patients with TNBC. After multivariate Fine and Gray competitive risk, age in diagnosis, race black, tumor grade, T status, N status and receiving radiotherapy were proven to be independent predictive factors of BCSD. Meanwhile, age in diagnosis, radiotherapy status, and chemotherapy status were proven to be independent predictive factors of OCSD. **Conclusions**: For older patients (≥70 years old) with TNBC, chemotherapy improved overall patient survival by reducing the rates of OCSD, but not by reducing the rates of BCSD. The impact of non-cancer causes of death on the prognosis of older cancer patients should not be ignored.

Keywords: SEER database; chemotherapy; breast cancer-specific death; older patient; TNBC; competing risk

1. Introduction

Breast cancer is the most prevalent malignancy in women worldwide. The incidence and mortality of breast cancer increases with age [1]. Triple-negative breast cancer (TNBC), makes up 12–18% of breast cancer patients [2], is a type of breast cancer that lacks the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) [3–5]. TNBC is more likely to recur and metastasize than type of luminal or HER2 positive, and it has relatively a lower survival rate [6]. Due to the lack of definitive targets, novel therapeutic interventions were limited, and chemotherapy remains the primary treatment [7]. With the aging of the population, older women with TNBC will also be increasing. However, data on TNBC treatment, including chemotherapy, in older patients (≥70 years old) are still scarce.

Older breast cancer patients frequently had one or more concomitant illnesses at the time of diagnosis because of the patient's own factors (*e.g.*, heart disease, chronic obstructive pulmonary disease, diabetes, hypertension, and arthritis) [8]. The mortality rate of breast cancer in older women was relatively high due to numerous reasons such as inadequate treatment and the presence of multiple comorbidities [9]. In daily clinical practice, the presence of comorbidities often reduces available treatments and increases their likelihood of dying from non-breast cancer causes [8]. Chemotherapy was recommended by many authoritative guidelines for patients with TNBC [10,11]. However, the guidelines did not provide specific treatment recommendations for older patients with TNBC. There haven't been any significant randomized studies on the advantages of chemotherapy for older patients (≥70 years

old) with TNBC, and it's unlikely that there will be any in the near future [12]. One study found TNBC in older women who were at least 70 years old should be treated with chemotherapy [13]. One research reported that the CSS (cancer-specific) and OS (overall survival) results of older patients diagnosed with Stage T1-4N0M0 TNBC who were given any adjuvant chemotherapy improved from 88.9% to 92.2% for CSS and 77.2% to 88.6% for OS after three years [14]. But these studies endpoint was overall survival, and patient-specific causes of death or other cause of death were not further differentiated.

In this study, we collected a large cohort of patients from the Surveillance, Epidemiology, and End Results (SEER) database, and conducted a competing risk analysis in the study for TNBC patients ($\geq$70 years old), receiving chemotherapy or not.

2. Materials and Methods

2.1 Data Sources

The SEER 18 registries' research data from 1975 to 2019 were available in the SEER database's current version (https://seer.cancer.gov). For analysis, we received authorization to use study data from November 2021 (Reference number: 11078-Nov2021). SEER*Stat software (Version 8.4.0.1, National Institutes of Health, Bethesda, Rockville, MA, USA) was used to collect all data on TNBC patients ($\geq$70 years old). No informed consents were required because the patients' identities have been removed from the database. This study required no informed consent from patients because the SEER database was publicly accessible worldwide. Therefore, it was deemed exempt from review by the Ethics Committee of the Jiangxi Cancer Hospital of Nanchang University.

2.2 Patients and Variables Selection

Patients who met the following criteria were included: (1) diagnosed with TNBC between 2010 and 2019 (candidates in this study were included between 2010 and 2019 since HER2 status was only reported in SEER data after 2010); (2) with primary cancer; (3) aged 70 years and over, and (4) diagnosed as M0 stage. Then, patients who met the following requirements were disqualified: (1) unknown or no surgery information; (2) survival time $<$3 months; (3) bilateral breast cancer; (4) Paget's disease; (5) unknown or uncertain clinical data including T status, N status; (6) unknown histologic grade; (7) unknown breast cancer specific death. The sample selection process is shown in Fig. 1.

In this investigation, the following information was gathered for each patient: patient id, age, sex, race recode (white, black, other), marital status at diagnosis, year of diagnosis, laterality, ICD-O-3 Hist/behave, surgery information, radiation recode, chemotherapy recode, AJCC (American Joint Committee on Cancer) T status, AJCC N status, AJCC M status, TNM (tumor node metastasis) status, grade, sequence number, SEER cause-specific death classification, SEER other cause of death classification and survival months. Age was classified as 70–79; 80–89, 90–99 and 100+ years. Race was classified as white, black and others. Marital status was classified as single and married. Tumor laterality was classified as left and right. Histologic grade was classified as grade I, II, III and IV. Histologic type was classified as infiltrating lobular carcinoma, infiltrating duct carcinoma and other type of carcinoma. AJCC T status was classified as T0, T1, T2, T3 and T4. AJCC N status was classified as N0, N1, N2 and N3. AJCC TNM stage was classified as stage I, II and III. Surgical treatment was classified as mastectomy and partial mastectomy. Radiotherapy and chemotherapy were classified as receiving or not. Causes of death were categorized as breast cancer-specific death (BCSD) or other cause-specific death (OCSD).

2.3 Endpoints

Causes of patient death included BCSD and OCSD. The OCSD was considered as a competing event. The survival time was from the date of diagnosis of breast cancer to the date of death or to the date of last follow-up.

2.4 Statistical Analysis

Propensity score matching (PSM) was subsequently done with 1:1 nearest neighbor method without replacement. Balance of propensity-matched groups was assessed and confirmed with mean standardized differences, with absolute values greater than 0.1 being considered unacceptably imbalanced. Survival curves were produced by the Kaplan-Meier method, and the log-rank test was used to compare the overall survival rates between two groups. The "cmprsk" package in R statistical software (Version 4.1.3, the Vienna University of Economics and Business, Vienna, Austria) was used for statistical analysis [15]. The mortality rates between groups were analyzed using the cumulative incidence function, and differences between groups were analyzed using Gray's test. The variables with p value less than 0.1 in the univariate analysis were incorporated into the multivariate analysis. The partial proportional risk regression model was performed using the "crr" function. R statistics software 4.1.3 was used to perform all statistical analyses. All statistical tests were two-sided, and the level of significance was set at $p < 0.05$.

3. Results

3.1 Characteristics between No Chemotherapy and Chemotherapy Patients

Patients were followed up until November 2019, and the median follow-up time was 61 months (ranging from 3 to 119 months). Fig. 1 depicted the process of including participants from the SEER database. We initially acquired 10,110 TNBC patients ($\geq$70 years old). Subsequently, we excluded 1411 patients with no surgery performed, 366 patients with survival time $<$3 months, 2 patients with bi-

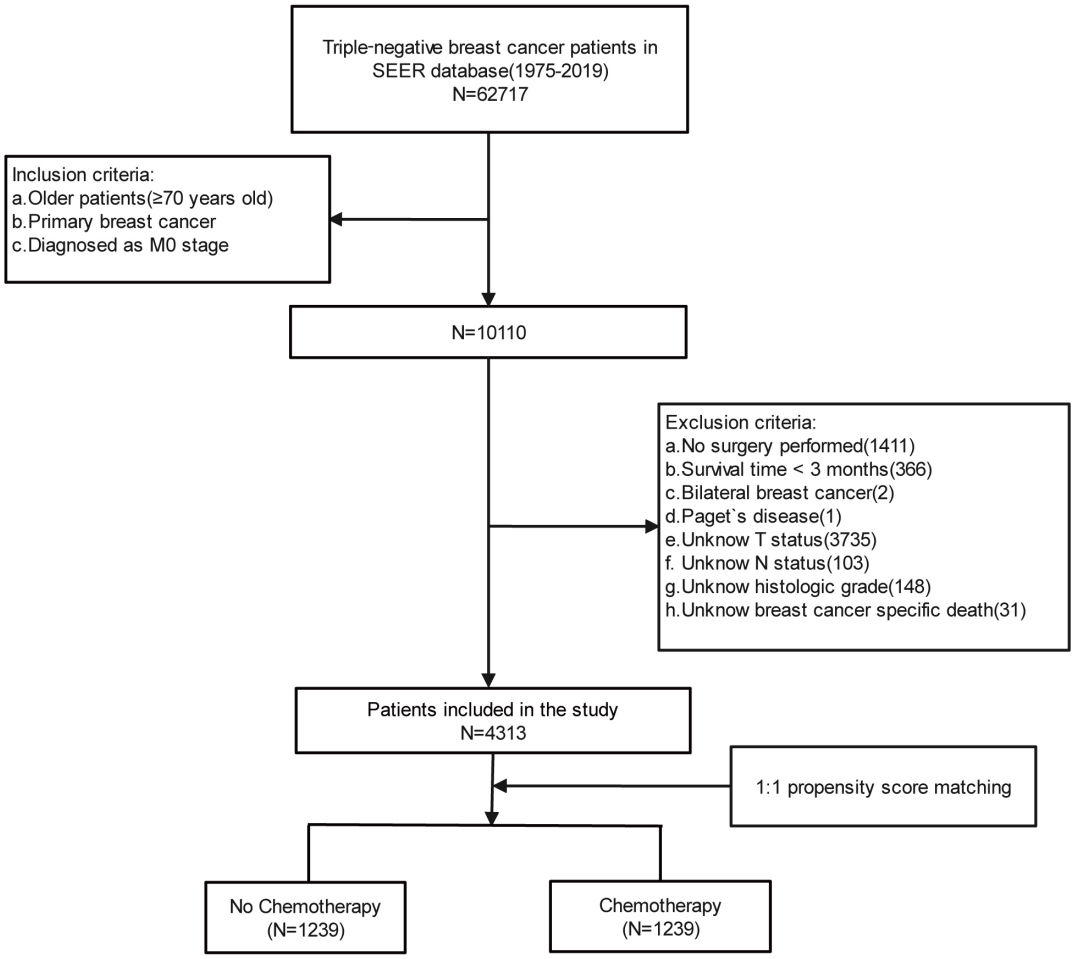

Fig. 1. The flowchart of the included population in this study.

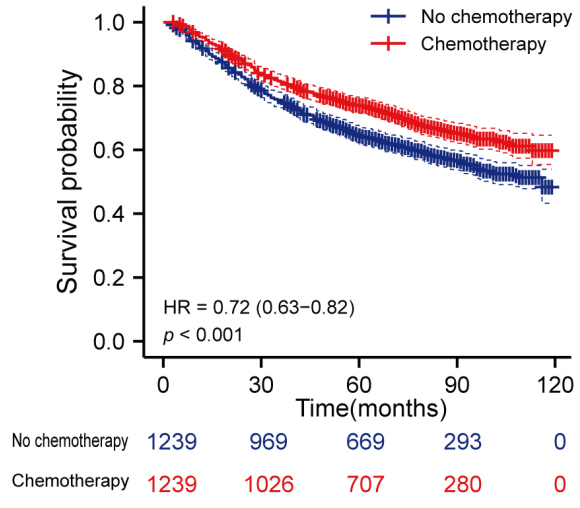

Fig. 2. Kaplan-Meier curves for overall survival in old patients (≥70 years old) with TNBC with chemotherapy and no chemotherapy. TNBC, Triple-negative breast cancer.

lateral breast cancer, and 1 patient with Paget's disease, 4017 patients with unknown clinical information. Finally, a total of 4313 older women (≥70 years old) patients with TNBC were enrolled, of whom 2452 (56.9%) had received chemotherapy after surgery and 1861 (43.1%) had not received chemotherapy after surgery. Prior to PSM analysis, the result revealed that there were more chemotherapy patients in 70–79 years old ($p < 0.001$), married women ($p < 0.001$), and histologic grade III ($p < 0.001$). Furthermore, there were more patients in T1 status (T1: 56.1% *vs.* 42.9%, $p < 0.001$), N0 status (N0: 81.0% *vs.* 60.9%, $p < 0.001$), and grade I (51.5% *vs.* 33.2%, $p < 0.001$) in no chemotherapy group than chemotherapy group (Table 1). After 1:1 matched PSM analysis, there were no statistically significant differences in the distribution of baseline characteristics between the two groups (expect Laterality and TNM status, Table 1).

3.2 Survival Analysis of Older Patients Receiving Chemotherapy and No-Chemotherapy

By propensity score matching, 1239 patients undergoing chemotherapy were matched against 1239 patients who did not receive chemotherapy. The survival analysis

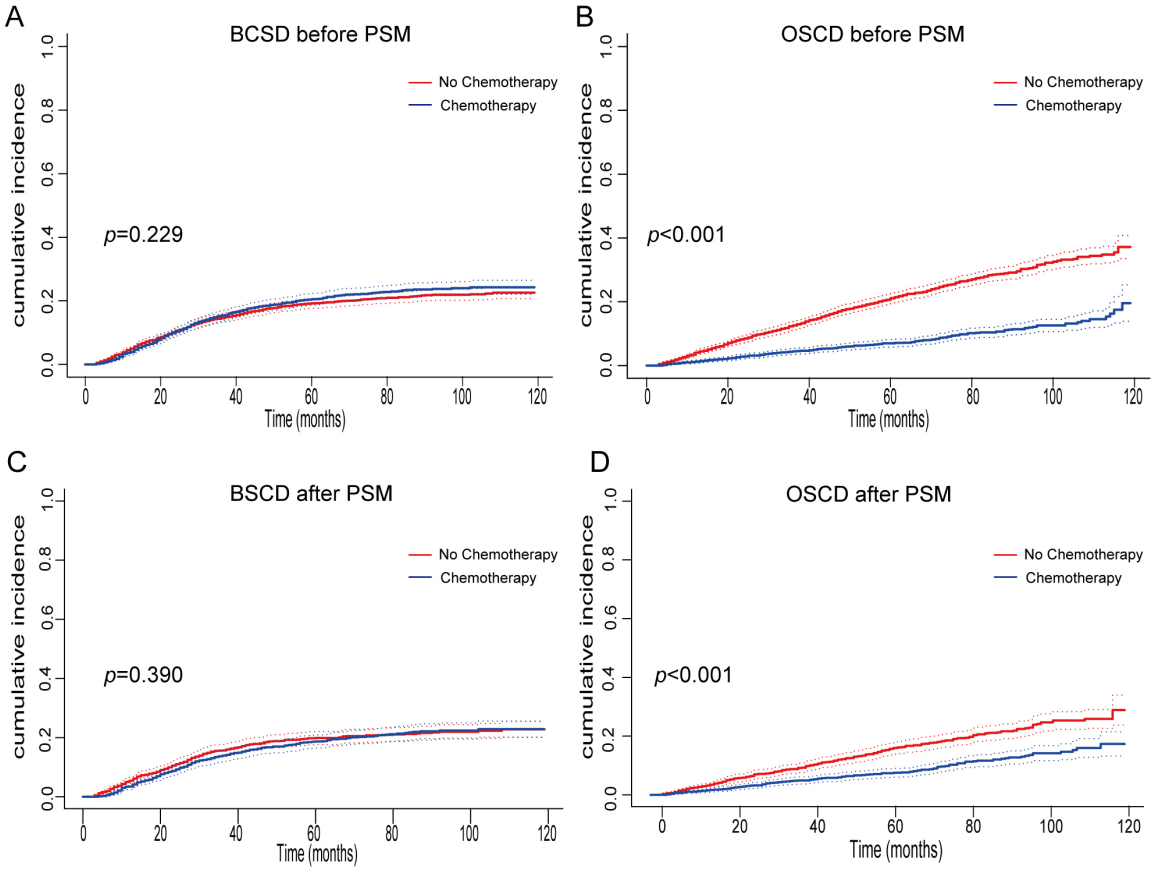

Fig. 3. Cumulative incidence function analysis of old patients (≥70 years old) with TNBC with chemotherapy and no chemotherapy before and after PSM analysis. (A) BCSD before PSM. (B) OCSD before PSM. (C) BCSD after PSM. (D) OCSD before PSM. BCSD, breast cancer-specific death; OCSD, other cause-specific death; PSM, propensity score matching. p value < 0.05 was considered statistically significant.

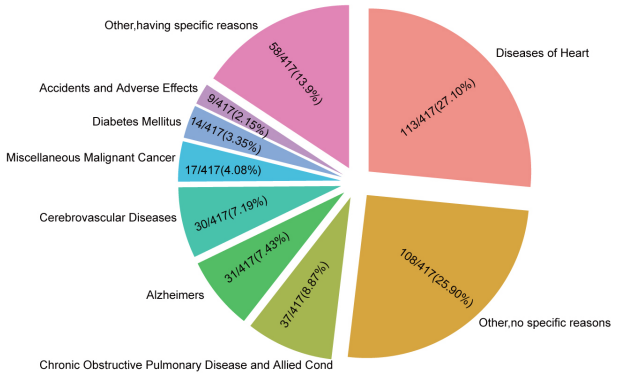

Fig. 4. The OCSD classification in older patients (≥70 years old) with triple negative breast cancer. OCSD, other cause-specific death.

showed that patients who received chemotherapy had a better prognosis than those who did not received chemotherapy (HR (hazard ratio) 0.72; 95% CI (confidence interval) 0.63–0.82; $p < 0.001$) (Fig. 2). Despite the univariate analysis suggested the patients who received chemotherapy had a better prognosis than patients who were not treated with chemotherapy, the study endpoint of the survival analysis was all death events and the death causes of the patient were not specifically distinguished as BCSD or OCSD. Next, as shown in Fig. 3A, there was no difference about BCSD between older patients with chemotherapy and no chemotherapy (Gray's test, $p = 0.229$) before PSM. Meanwhile, after PSM, there was still no difference between two groups (Gray's test, $p = 0.390$, Fig. 3C). Additionally, the OCSD rate for chemotherapy patients was lower than that of no-chemotherapy patients both before and after PSM (Gray's test, both $p < 0.001$, Fig. 3B,D, which suggested that chemotherapy was a positive prognostic factor in OCSD for older patients with TNBC. From these results, it was clear that chemotherapy increased survival in older TNBC patients because chemotherapy reduced OCSD rate, not BCSD rate. In the OCSD classification, diseases of heart were the most leading cause of death in older patients with TNBC, and the detailed ranking of causes of death was shown in Fig. 4.

Table 1. Baseline characteristics of patients (≥70 years old) diagnosed with TNBC in the SEER database before and after propensity score matching.

Characteristics	Before PSM			After PSM		
	No Chemotherapy	Chemotherapy	*p* value	No Chemotherapy	Chemotherapy	*p* value
Total	n = 2452 (56.9)	n = 1861 (43.1)		n = 1239 (50)	n = 1239 (50)	
Age (years)			<0.001			0.751
70–79	1215 (49.6)	1608 (86.4)		982 (79.3)	991 (80.0)	
80–89	1045 (42.6)	245 (13.2)		251 (20.3)	240 (19.4)	
90–99	189 (7.7)	8 (0.4)		6 (0.5)	8 (0.6)	
100+	3 (0.1)	0 (0.0)				
Race			0.689			0.180
Black	336 (13.7)	272 (14.6)		189 (15.3)	187 (15.1)	
Other	177 (7.2)	131 (7.0)		79 (6.4)	103 (8.3)	
White	1939 (79.1)	1458 (78.3)		971 (78.4)	949 (76.6)	
Marital			<0.001			0.223
Married	858 (35.0)	920 (49.4)		546 (44.1)	515 (41.6)	
Single	1594 (65.0)	941 (50.6)		693 (55.9)	724 (58.4)	
Histologic grade			<0.001			0.127
I	113 (4.6)	27 (1.5)		21 (1.7)	27 (2.2)	
II	655 (26.7)	355 (19.1)		258 (20.8)	301 (24.3)	
III	1666 (67.9)	1463 (78.6)		953 (76.9)	902 (72.8)	
IV	18 (0.7)	16 (0.9)		7 (0.6)	9 (0.7)	
Laterality			0.968			0.006
Left	1286 (52.4)	974 (52.3)		634 (51.2)	703 (56.7)	
Right	1166 (47.6)	887 (47.7)		605 (48.8)	536 (43.3)	
Histologic			0.112			0.260
Infiltrating Lobular carcinoma	45 (1.8)	32 (1.7)		16 (1.3)	26 (2.1)	
Infiltrating duct carcinoma	1992 (81.2)	1557 (83.7)		1023 (82.6)	1024 (82.6)	
Other type of carcinoma	415 (16.9)	272 (14.6)		200 (16.1)	189 (15.3)	
T status			<0.001			0.456
T0	0 (0.0)	3 (0.2)				
T1	1376 (56.1)	798 (42.9)		667 (53.8)	649 (52.4)	
T2	837 (34.1)	824 (44.3)		456 (36.8)	450 (36.3)	
T3	159 (6.5)	125 (6.7)		66 (5.3)	82 (6.6)	
T4	80 (3.3)	111 (6.0)		50 (4.0)	58 (4.7)	
N status			<0.001			0.226
N0	1985 (81.0)	1134 (60.9)		948 (76.5)	903 (72.9)	
N1	302 (12.3)	461 (24.8)		187 (15.1)	215 (17.4)	
N2	92 (3.8)	167 (9.0)		60 (4.8)	71 (5.7)	
N3	73 (3.0)	99 (5.3)		44 (3.6)	50 (4.0)	
TNM status			<0.001			0.048
I	1264 (51.5)	618 (33.2)		599 (48.3)	546 (44.1)	
II	936 (38.2)	866 (46.5)		487 (39.3)	507 (40.9)	
III	252 (10.3)	377 (20.3)		153 (12.3)	186 (15.0)	
Surgery			0.061			0.123
Mastectomy	1132 (46.2)	805 (43.3)		514 (41.5)	553 (44.6)	
Partial mastectomy	1320 (53.8)	1056 (56.7)		725 (58.5)	686 (55.4)	
Radiotherapy			<0.001			0.243
No	1499 (61.1)	816 (43.8)		649 (52.4)	679 (54.8)	
Yes	953 (38.9)	1045 (56.2)		590 (47.6)	560 (45.2)	

TNBC, triple-negative breast cancer; SEER, the Surveillance, Epidemiology, and End Results; TNM, tumor node metastasis; PSM, propensity score matching.

3.3 Univariate Analysis by CIF for BCSD or OCSD

During the follow-up period, there were 512 patients died from breast cancer and 386 patients died from other causes. Accordingly, Table 2 showed the cumulative occurrences of BCSD and OCSD during 3-, 5-, and 8-year periods grouped by different clinical factors. Across the three, five, and eight-year periods, the overall mortality rate for breast-related causes was 15.34%, 20.30% and 23.73%, respectively. A higher cumulative incidence was observed in those patients who were 80–89 years of age, married, black, in grade IV, with advanced T and N statuses, underwent mastectomy, and did not receive radiotherapy. Statistics showed that tumor location, histologic type, and receiving chemotherapy had no impact on BCSD outcomes.

Table 2. Cumulative incidence function analysis of death causes in patients (≥70 years old) diagnosed with TNBC.

Characteristics	BCSD						OCSD					
	Event	%	3 years (%)	5 years (%)	8 years (%)	*p* value	Event	%	3 years (%)	5 years (%)	8 years (%)	*p* value
Total	512	100.00	15.34	20.30	23.73		386	100.00	7.36	13.20	23.02	
Age (years)						<0.001					0.00	<0.001
70–79	335	65.43	11.91	16.22	19.45		255	66.06	5.87	10.51	18.39	
80–89	167	32.62	28.41	36.37	40.64		128	33.16	13.72	25.95	45.17	
90–99	10	1.95	69.39	79.59	NA		3	0.78	20.00	20.00	NA	
Race						0.034						0.055
Black	94	18.36	17.10	24.84	29.88		63	16.32	8.39	12.73	24.75	
White	389	75.98	15.12	19.82	23.22		305	79.02	7.48	13.72	23.43	
Other	29	5.66	14.08	16.08	16.97		18	4.66	3.96	8.43	15.31	
Marital						0.001						0.003
Married	190	37.11	12.58	16.91	20.82		145	37.56	6.27	11.21	20.00	
Single	322	62.89	17.42	22.87	25.91		241	62.44	8.21	14.78	25.44	
Grade						<0.001						0.002
I	1	0.20	2.08	2.08	2.08		5	1.30	0.00	4.56	23.71	
II	89	17.38	11.09	15.08	17.73		67	17.36	4.97	9.74	17.32	
III	415	81.05	16.79	22.19	26.01		313	81.09	8.31	14.57	24.96	
IV	7	1.37	40.74	48.15	48.15		1	0.26	10.00	10.00	10.00	
Laterality						0.441						0.999
Left	268	52.34	15.02	19.90	22.99		209	54.15	7.69	13.44	23.27	
Right	244	47.66	15.71	20.77	24.61		177	45.85	6.98	12.93	22.73	
Histologic						0.183						0.148
Infiltrating lobular carcinoma	428	83.59	22.88	28.94	36.89		2	0.52	2.78	6.13	6.13	
Infiltrating duct carcinoma	13	2.54	15.21	20.25	24.18		319	82.64	7.34	13.09	22.68	
Other type of carcinoma	71	13.87	15.25	19.65	19.65		65	16.84	7.95	14.54	26.36	
T status						<0.001						<0.001
T1	138	26.95	6.58	10.01	12.02		160	41.45	4.20	8.78	17.46	
T2	255	49.80	21.03	27.91	33.36		171	44.30	10.05	17.39	28.67	
T3	64	12.50	41.09	46.97	50.56		29	7.51	15.51	23.88	36.58	
T4	55	10.74	44.95	53.56	60.27		26	6.74	18.19	30.68	46.24	
N status						<0.001						<0.001
N0	242	47.27	8.63	12.44	15.29		256	66.32	5.66	10.44	19.84	
N1	142	27.73	28.47	35.18	41.41		82	21.24	12.09	21.62	30.73	
N2	67	13.09	43.78	56.09	60.71		30	7.77	14.26	28.53	47.26	
N3	61	11.91	57.77	71.98	74.32		18	4.66	16.50	28.28	51.32	
Surgery						<0.001						0.001
Mastectomy	304	59.38	21.63	28.58	32.97		186	48.19	9.54	16.15	26.96	
Partial mastectomy	208	40.63	10.68	14.18	16.87		200	51.81	5.81	11.16	20.31	
Radiotherapy						<0.001						0.001
No	309	60.35	17.50	23.12	27.03		230	59.59	8.84	15.33	26.35	
Yes	203	39.65	12.88	17.13	20.02		156	40.41	5.70	10.85	19.40	
Chemotherapy						0.390						<0.001
No	260	50.78	16.41	21.24	23.92		253	65.54	9.57	18.11	28.77	
Yes	252	49.22	14.28	19.38	23.57		133	34.46	5.19	8.33	17.02	

TNBC, triple-negative breast cancer; BCSD, breast cancer-specific death; OCSD, other cause-specific death.

Meanwhile, the 3-year, 5-year and 8-year other cause-specific mortalities were 7.36%, 13.20% and 23.02%. Patients with older ages (80–89), single status, advanced grades, advanced T status, advanced N status, mastectomy and patients did not receive radiotherapy and chemotherapy for OCSD were associated with higher cumulative incidences of OCSD. In the cumulative incidence function (CIF) of OCSD, no statistically significant differences were seen for race, laterality, or histologic type.

3.4 Prognostic Factors for BCSD and OCSD in Older TNBC Patients by the Fine and Gray Model

After the univariate analysis of CIF, the Fine and Gray method was used to perform multivariate analysis of BCSD and OCSD in older TNBC patients. BCSD had been found to be associated with age at diagnosis, race, tumor grade, T status, N status, and having received radiotherapy. The results of our study showed that, for older TNBC patients, subjects of 80–89 years and 90–99 years had worse BCSD (80–89 *vs*. 70–79: SHR (subdistribution hazard ratio) 1.240; 95% CI 1.004–1.532, $p = 0.046$; 90–99 *vs*. 70–79: SHR 2.462; 95% CI 1.290–4.697, $p = 0.006$). Moreover, race black, compared with patients with other race (expect for race white) had worse BCSD (Black *vs*. other: SHR 1.590; 95% CI 1.021–2.476, $p = 0.040$). Compared to patients with grade I, those with higher grades had worse BCSD (IV *vs*. I : SHR 14.832; 95% CI 1.700–129.381, $p = 0.015$). Furthermore, patients with advanced T stages were more likely to develop BCSD compared to those with T1 stages (T2 *vs*. T1: SHR 2.066; 95% CI 1.648–2.589, $p < 0.001$; T3 *vs*. T1: SHR 2.805; 95% CI 1.983–3.969, $p < 0.001$; T4 *vs*. T1: SHR 2.707, 95% CI 1.838–3.985, $p < 0.001$). Patients with advanced N status were also likely to have a higher risk of BCSD in comparison with those with N0 stage (N1 *vs*. N0: SHR 2.184; 95% CI 1.736–2.747, $p < 0.001$; N2 *vs*. N0: SHR 3.319; 95% CI 2.419–4.554, $p < 0.001$; N3 *vs*. N0: SHR 4.761; 95% CI 3.436–6.596, $p < 0.001$). Patients with radiotherapy were more likely to have better OCSD than those without radiotherapy (yes *vs*. no: SHR 0.795; 95% CI 0.649–0.973, $p = 0.026$) (Fig. 5A). When it came to OCSD, age in diagnosis, radiotherapy status, and chemotherapy status were proven to be independent predictive factors of OCSD (Fig. 5B). Based on the results of our research, we found that OCSD was more likely to occur in older TNBC patients, subjects of 80–89 years (80–89 *vs*. 70–79: SHR 1.897; 95% CI 1.497–2.403, $p < 0.001$). A greater proportion of patients who received radiotherapy or chemotherapy had better OCSD than those who did not receive radiotherapy or chemotherapy (yes *vs*. no: SHR 0.750; 95% CI 0.594–0.945, $p = 0.015$; yes *vs*. no: SHR 0.512; 95% CI 0.415–0.632, $p < 0.001$) (Fig. 5B).

4. Discussion

In this study, the main objective was to examine how chemotherapy affected BCSD and OCSD in older TNBC women (≥70 years old) based on SEER data from 2010 to 2019. Firstly, it was found by log-rank test that older TNBC receiving chemotherapy had a better prognosis than those not receiving chemotherapy, and similar findings had been reported in previous studies [13,16]. Next, we found that chemotherapy improved overall survival of patients by reducing OCSD, not BCSD by using competitive risk analysis. To our knowledge, this was the first and largest population-based study to look at this issue in older women (≥70 years old) with TNBC.

Because chemotherapy-induced toxicity was more severe and the advantages were less favorable than younger patients, the benefit-risk balance in clinical practice for elderly patients was difficult [17]. Therefore, the choice of chemotherapy for the elderly needs to be more cautious. Many randomized controlled trials had shown that adjuvant systemic chemotherapy improves overall patient survival in younger patients with TNBC [18–20]. Unfortunately, the number of patients older than 70 was small in these randomized controlled trials [21–23], so the results of these trials were not as convincing in guiding the value of chemotherapy in older women with TNBC. There had been some previous small retrospective analyses of the treatment of older breast cancers, most commonly assessing women aged 60–65 years and older. In a SEER database analysis with a small percentage of older patients, the use of chemotherapy was not linked to better survival in the elderly [24]. However, these studies had tended to examine the effect of chemotherapy on overall survival using ER-negative patients as a subgroup [25,26]. Without exception, none of these studies made a specific distinction between the endpoint death events as BCSD or OCSD. Next, in Table 2 and Fig. 5, the univariate CIF and multivariate Fine and Gray competitive risk analysis method were used to select the independent prognostic factors of BCSD and OCSD in older TNBC patients. Firstly, patients of 80–89 years were found to have a higher risk of OCSD. Advanced age implied a significant decline in physical function [27]. Thus, advanced age was the most significant factor affecting OCSD. Our study, which was consistent with earlier studies [28], discovered that racial disparity played a significant effect in the survival prognosis of BCSD for older TNBC patients. It was an important reason that black people had greater rates of triple-negative breast cancer than white [29]. The result of competitive risk analysis suggested that grade, T status and N status were more correlated with BCSD, which was consistent with another research [30]. Surgery was still the primary treatment for breast cancer. Because the patients who participated in our study had surgery, it was not possible to assess BCSD and OCSD in patients who had surgery versus those who did not. However, our study found that the risk of BCSD or OCSD was not influenced by the type of surgery. In our study, radiotherapy and chemotherapy both had an impact on the OCSD, and radiotherapy also had an impact on the BCSD.

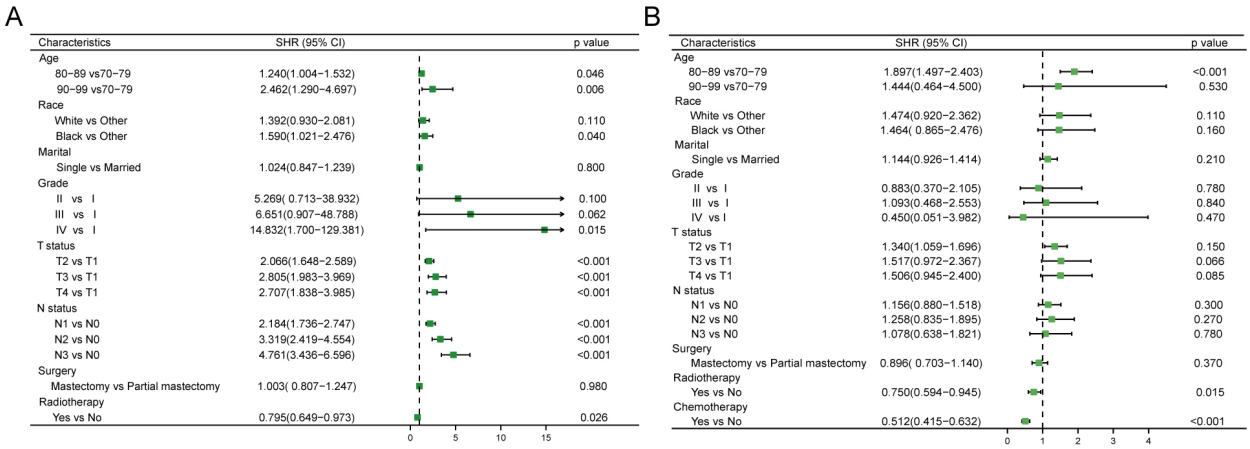

Fig. 5. Forest plot showed prognostic factors for BCSD (A) and OCSD (B) in older TNBC patients by the Fine and Gray model. BCSD, breast cancer-specific death; OCSD, other cause-specific death.

In this study, with a median follow-up time of 61 months follow-up, a total of 898 older breast cancer patients died. Of these, 386 patients (43.0%) died from other causes except breast cancer. Among them, diseases of heart, chronic obstructive pulmonary disease and Alzheimer were three common non-breast cancer causes of death in the elderly TNBC patients (Fig. 4). There was a risk of developing various chronic diseases for older patients, such as heart disease or lung disease, before and after the diagnosis of breast cancer. All of these diseases could be important causes of death in breast cancer patients. Actually, age was no longer the main factor determining the best treatment plan for breast cancer patients, and functional level and comorbidities must also be taken into account [31]. One study showed that 2% to 10% of breast cancer patients died from CVD (cardiovascular disease), especially if the patient had risk factors for CVD themselves, their risk of CVD death would be higher [32]. In addition, the death risk of CVD in breast cancer patients may also be increased by the cardiotoxic effects of treatment, such as receiving radiotherapy and chemotherapy. Therefore, it was very important to know the risk of CVD in breast cancer patients, especially if one treatment might be cardiotoxic.

Due to the special characteristics of elderly patients, another issue to consider was the impact of chemotherapy on quality of life. In clinical work, the choice of chemotherapy for an elderly patient with TNBC who has multiple chronic conditions might be a tricky situation for both the physician and the patient. Chemotherapy had the potential to aggravate pre-existing disease in patients. In older breast cancer patients, chemo-endocrine therapy resulted in net reductions in quality-adjusted life years (QALYs) for all 75 years and older. As treatment effectiveness improve, chemotherapy had greater benefits, but at the same time, the toxicity of chemotherapy reduces patients' QALYs [33]. However, the difference between the two groups largely disappeared at about 12 months. The study also suggested that these transient changes in QoL (quality of life) were a modest contribution to improved survival [34]. Some specialists advised to add chemotherapy for some people with high-risk characteristics and anticipated life expectancies longer than five years [35]. Therefore, when choosing a chemotherapy protocol, in addition to the benefit of chemotherapy, the side effects of chemotherapy and the length of survival of the patient need to be considered.

In this study, chemotherapy induced reduction of OCSD, not BCSD, of patients with TNBC. This result was similar to the study of Schonberg *et al.* [36] that chemotherapy could significantly improve the non-breast cancer survival among all women (adjusted hazard ratio [aHR], 0.6; range, 0.4 to 0.8). We analyzed some reasons for this. Firstly, elderly patients had numerous underlying diseases, and death from underlying diseases often preceded death from breast cancer. The study of Ferrigni *et al.* [37] found the main cause of death was often due to other causes besides breast cancer (20% due to other causes, 14% due to unknown causes), with only 6 patients (5%) dying from causes related to their breast cancer. Studies by Colzani *et al.* [38] and Cyr A *et al.* [39] also showed that older breast cancer patients were unlikely to suffer breast cancer-related mortality. Hence, causes other than breast cancer become more important as causes of death in the oldest old patients [38,39]. Therefore, OSCD was more likely to occur than BSCD. Secondly, due to limitations in access to the SEER database, we did not have access to the underlying disease and severity of the patient at the time of breast cancer diagnosis. This result would be more plausible if patients with underlying disease could be put through PSM between the chemotherapy and no-chemotherapy groups. Thirdly, chemotherapy was the recommended regimen for the adjuvant treatment of TNBC. Many elderly TNBC patients did not receive chemotherapy due to a variety of fac-

tors. Patients who received chemotherapy might have a higher awareness of diseases (including cancer and other underlying diseases) compared to those who did not receive chemotherapy. Although chemotherapy drugs (such as paclitaxel) commonly used for breast cancer had side effects in older patients, the common side effects had little impact on patient survival [40–42]. The difference in awareness may lead to older patients who receive chemotherapy being more receptive to treatment for other underlying diseases. This might be one of the reasons for reduction of OCSD of patients with TNBC who received chemotherapy.

There were still some areas for improvement in this study. Firstly, we used the PSM method to make the baseline information of the two cohorts as balanced as possible. However, in this process, some patients were excluded, which might lead to selection bias or inaccurate results. Secondly, there are various regimens of adjuvant chemotherapy for breast cancer, but due to the limitations of the SEER database, we were unable to obtain the relevant chemotherapy protocols, which prevented us from performing a stratified analysis of these elderly TNBC patients. Thirdly, the presence or absence of patient's previous chronic disease was equally important for the OCSD. Because we were unable to obtain the prevalence of chronic disease in elderly patients prior to the diagnosis of breast cancer, we were unable to judge whether the prevalence of chronic disease was balanced between the chemotherapy and no-chemotherapy groups. Finally, as a retrospective study, the inevitable selection bias in patient selection might affect the conclusions, and we hoped that larger prospective randomized controlled trials with a higher level of evidence would be able to validate the conclusions in the future.

5. Conclusions

For older patients ($\geq$70 years old) with TNBC, chemotherapy improves overall patient survival by reducing the rates of OCSD, but not by reducing the rates of BCSD. Therefore, the impact of non-cancer causes of death on the prognosis of older cancer patients should not be ignored, and the benefit and adverse effects of treating the primary disease should be fully weighed in clinical work. Future treatments for patients with older TNBC may take some cues from this study.

Availability of Data and Materials

The datassets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

CWH, BH, THY designed the research; THY acquired funds; CWH, JC, MJ, RC collected the data, and performed the analysis. CWH, JC wrote the manuscript. CWH, JLL, GXW, THY contributed to the statistical analysis and to the final version of the manuscript. GXW, THY supervised the project. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study required no informed consent from patients because the SEER database was publicly accessible worldwide. Therefore, it was deemed exempt from review by the Ethics Committee of the Jiangxi Cancer Hospital of Nanchang University. The study was performed in accordance with the principles of the Declaration of Helsinki. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

The authors declare no conflict of interest.

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