Effect of Molecular Subtype on Mortality in U.S. Adult Women with Inflammatory Breast Cancer

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Murphy John

Abstract

Background: Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer characterized by rapid progression and poor prognosis. The molecular subtypes of breast cancer, Luminal A, Luminal B, HER2 Positive, and Triple Negative, have been associated with varying survival outcomes. However, the impact of these subtypes specifically on IBC mortality remains underexplored.

Methods: We conducted a retrospective cohort study of patients diagnosed with IBC using the SEER database. The cohort was stratified by molecular subtype, age, race, marital status, nodal stage, distant metastasis, and treatment modalities. Cox proportional hazards regression models were used to assess the association between molecular subtype and IBC-specific survival, adjusting for potential confounders.

Results: Our findings demonstrate significant survival differences across molecular subtypes. The Triple Negative subtype exhibited the poorest prognosis (aHR=2.51, 95%CI: 1.79-2.21, P<0.001), with a median survival of 1.7 years and 1-, 5-, and 10-year survival rates of 67%, 24%, and 21%, respectively. In contrast, the Luminal B subtype had the best outcomes (aHR=0.72, 95%CI: 0.56-0.74, P<0.001), with a median survival of 9.4 years and a 10-year survival rate of 50%.

Conclusions: These findings highlight the importance of subtype classification in prognostication and treatment planning for IBC.

Introduction

Inflammatory breast cancer (IBC) is a rare but aggressive subtype of breast cancer, accounting for 2% to 6% of all breast cancer cases in the United States [1], [2]. IBC presents differently than other types of breast cancer. It often lacks a breast lump and may not appear on a mammogram, making accurate diagnosis challenging and potentially delaying treatment. IBC causes symptoms of breast inflammation, such as swelling and redness, due to cancer cells blocking lymphatic vessels in the skin, giving the breast an "inflamed" appearance [3].

Clinically, IBC is categorized as T4d in the TNM classification for its aggressive biological behavior. In spite of multimodal therapy, IBC has a local recurrence rate of up to 50% and survival rates of only 35% to 40%, significantly lower than those of other types of breast cancer [4]. Despite its rarity, IBC disproportionately accounts for up to 10% of all breast cancer-related deaths [1], [2].

Because IBC is rare, its biological characteristics are not commonly reported and the molecular alterations that result in poor prognosis are not well understood. However, hormone receptors (HR) and human epidermal growth factor receptor-2 (HER2), which define the molecular status of IBC through immunohistochemistry (IHC), are fundamental markers used to demonstrate molecular features, predict prognosis, and optimize therapeutic regimens [5]. IBC tumors are characterized by combinations of hormone receptors and oncogenes, allowing the majority to be characterized as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 Positive (HR-/HER2+), and Triple Negative by IHC.[6]. Studies have shown that these four molecular subtypes reveal the prognostic discrepancies in both common breast cancers and IBC [4], [7], [8], [9]. A previous study examined the association between molecular subtype and survival outcomes in IBC patients using SEER data from 2010 to 2013 [5]. However, no studies utilizing the updated SEER database have investigated this relationship.

Therefore, using the most recent Surveillance, Epidemiology, and End Results (SEER) data, this study aims to assess the effect of molecular subtype on IBC-specific mortality in adult females with IBC.

Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is an authoritative source of information on cancer incidence and survival in the United States (https://seer.cancer.gov/). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48% of the U.S. population. This study utilized SEER incidence data from 2010 to 2021.

Study Population

The study population focuses on adult females diagnosed with IBC. Data was extracted from the SEER 17 Registries (2000-2021) using the SEER*Stat software (version 8.4.4; Surveillance Research Program, NCI, Bethesda, MD). The specific criteria used to identify patients with IBC were as follows: (1) Site and Morphology (TNM 7/CS v0204 Schema recode) was limited to "Breast"; (2) Derived TNM classification, AJCC 7th edition (2010-2015) was limited to "T4d", SEER Combined T (2016-2017) was limited to "c2D" and "p4D", and EOD 8th edition (2018+) was limited to "T4D"; and (3) Histology type (ICD-O-3) ranged from 8500 to 8549. Year of diagnosis was limited to 2010 to 2021 because SEER started collecting breast cancer molecular subtype in 2010. To limit our data to adult females, age at diagnosis was limited to patients 20 years and older and sex was limited to "Female".

Variables

For each case, the following information from SEER was obtained: age at diagnosis (20-49, 50-69, and >=70), race (white, black, other), marital status (unmarried, married), N (node) stage (N0, N1, N2, N3), M (metastasis) stage (M0, M1), grade (I/II, III/IV), radiation (no/unknown, yes), chemotherapy (no/unknown, yes), surgery (no/unknown, yes), and survival months. Breast cancer subtypes were classified as Luminal A (HR+/HER2-), Luminal B (HR+/HER+), HER2 Positive (HR-/HER2+), and Triple Negative. In addition, cases with incomplete information on any of these characteristics and patients who survived less than one month were excluded from the study. To focus on IBC-specific mortality, patients with an unknown cause of death or whose death was attributed to other causes were excluded.

Statistical Analysis

Clinicopathological characteristics were compared between IBC subtype using Pearson's Chi-squared test. Median, 1-, 5-, and 10-year survival for IBC is estimated for each variable using the Kaplain-Meier method and compared using the log-rank test in the subgroups. The proportional hazards assumption was assessed visually with log minus log plots and statistically by calculating the Pearson's product moment correlation coefficient of the Schoenfeld residuals and ranked survival times. After determining the assumption of proportional hazards was not violated, univariate and multivariate Cox proportional hazards regressions were used to model the relationship between potential covariates and IBC-specific survival. We obtained hazard ratios (HR), 95% confidence intervals (CI), and p-values for each covariate. All statistical analyses were performed using version 3.7-0 of the survival package in R version 4.3.3.

Results

Clinicopathological characteristics

A total of 5969 adult female IBC cases were eligible from 2010-2021 in the SEER database for our study population. Of these, 1829 were excluded; 165 had a survival time less than 1 month, 487 had an unknown or competing cause of death, and 1177 had incomplete information. The remaining 4140 were included in our analysis, as shown in Figure 1.

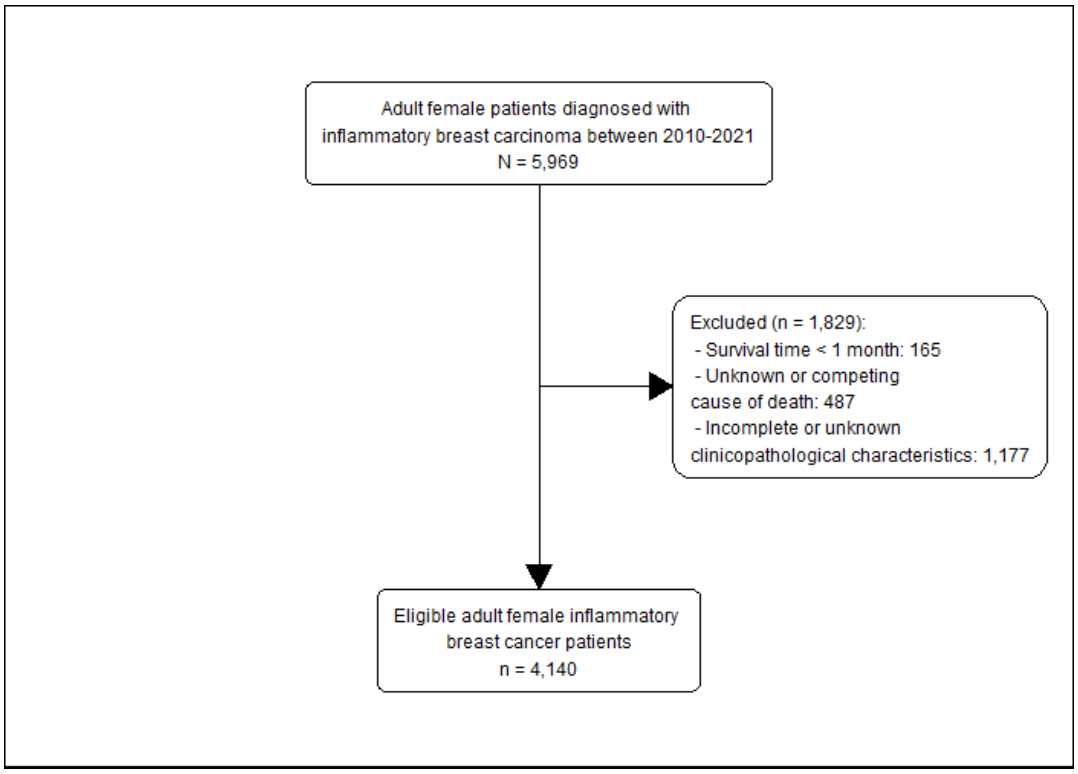

Figure 1: Flowchart of IBC patients screening on SEER database

The clinicopathological characteristics of eligible patients are summarized in Table 1. The age subgroup of 20–49 years accounts for 35.1% of Luminal B cases, a higher proportion compared to other subtypes. Moreover, Luminal B and HER2 Positive subtypes appear to affect younger age groups more frequently than Luminal A, with 85.4% and 84.5% of cases, respectively, occurring in patients under 69 years, compared to 76.5% for Luminal A. A higher proportion of Black patients is observed in the Triple Negative group compared to other subtypes. Comparing marital status reveals that the Triple Negative subtype affects the highest percentage of unmarried women. Triple Negative patients also have the highest proportion of N3 node stage and cancer grade III/IV.

Table 1: Clinicopathological characteristics by cancer subtype

Characteristic	Overall N = 4,140	Luminal A N = 1,735	Luminal B N = 781	HER2 Positive N = 661	Triple Negative N = 963	p-value
Age						<0.001
20-49 years	1,196 (28.9%)	452 (26.1%)	274 (35.1%)	186 (28.1%)	284 (29.5%)	
50-69 years	2,132 (51.5%)	874 (50.4%)	393 (50.3%)	373 (56.4%)	492 (51.1%)	
>=70 years	812 (19.6%)	409 (23.6%)	114 (14.6%)	102 (15.4%)	187 (19.4%)	
Race						<0.001
White	3,081 (74.4%)	1,332 (76.8%)	594 (76.1%)	494 (74.7%)	661 (68.6%)	
Black	705 (17.0%)	262 (15.1%)	112 (14.3%)	106 (16.0%)	225 (23.4%)	
Other	354 (8.6%)	141 (8.1%)	75 (9.6%)	61 (9.2%)	77 (8.0%)	
Marital Status						0.015
Unmarried	2,218 (53.6%)	936 (53.9%)	387 (49.6%)	345 (52.2%)	550 (57.1%)	
Married	1,922 (46.4%)	799 (46.1%)	394 (50.4%)	316 (47.8%)	413 (42.9%)	
N Stage						<0.001
N0	475 (11.5%)	197 (11.4%)	74 (9.5%)	83 (12.6%)	121 (12.6%)	
N1	1,955 (47.2%)	794 (45.8%)	398 (51.0%)	354 (53.6%)	409 (42.5%)	
N2	723 (17.5%)	342 (19.7%)	123 (15.7%)	95 (14.4%)	163 (16.9%)	
N3	987 (23.8%)	402 (23.2%)	186 (23.8%)	129 (19.5%)	270 (28.0%)	
M Stage						0.023
M0	2,615 (63.2%)	1,056 (60.9%)	488 (62.5%)	434 (65.7%)	637 (66.1%)	
M1	1,525 (36.8%)	679 (39.1%)	293 (37.5%)	227 (34.3%)	326 (33.9%)	
Grade						<0.001
I/II	1,452 (35.1%)	835 (48.1%)	280 (35.9%)	167 (25.3%)	170 (17.7%)	
III/IV	2,688 (64.9%)	900 (51.9%)	501 (64.1%)	494 (74.7%)	793 (82.3%)	
Radiation						0.2
No/Unknown	1,993 (48.1%)	842 (48.5%)	355 (45.5%)	311 (47.0%)	485 (50.4%)	
Yes	2,147 (51.9%)	893 (51.5%)	426 (54.5%)	350 (53.0%)	478 (49.6%)	

Characteristic	Overall N = 4,140	Luminal A N = 1,735	Luminal B N = 781	HER2 Positive N = 661	Triple Negative N = 963	p-value
Chemotherapy						<0.001
No/Unknown	576 (13.9%)	340 (19.6%)	87 (11.1%)	47 (7.1%)	102 (10.6%)	
Yes	3,564 (86.1%)	1,395 (80.4%)	694 (88.9%)	614 (92.9%)	861 (89.4%)	
Surgery						0.056
No/Unknown	1,500 (36.2%)	656 (37.8%)	267 (34.2%)	216 (32.7%)	361 (37.5%)	
Yes	2,640 (63.8%)	1,079 (62.2%)	514 (65.8%)	445 (67.3%)	602 (62.5%)	

Proportional Hazards Assumption

The proportional hazards assumption was assessed for each covariate visually using log minus log plots, as shown in Figure 2.

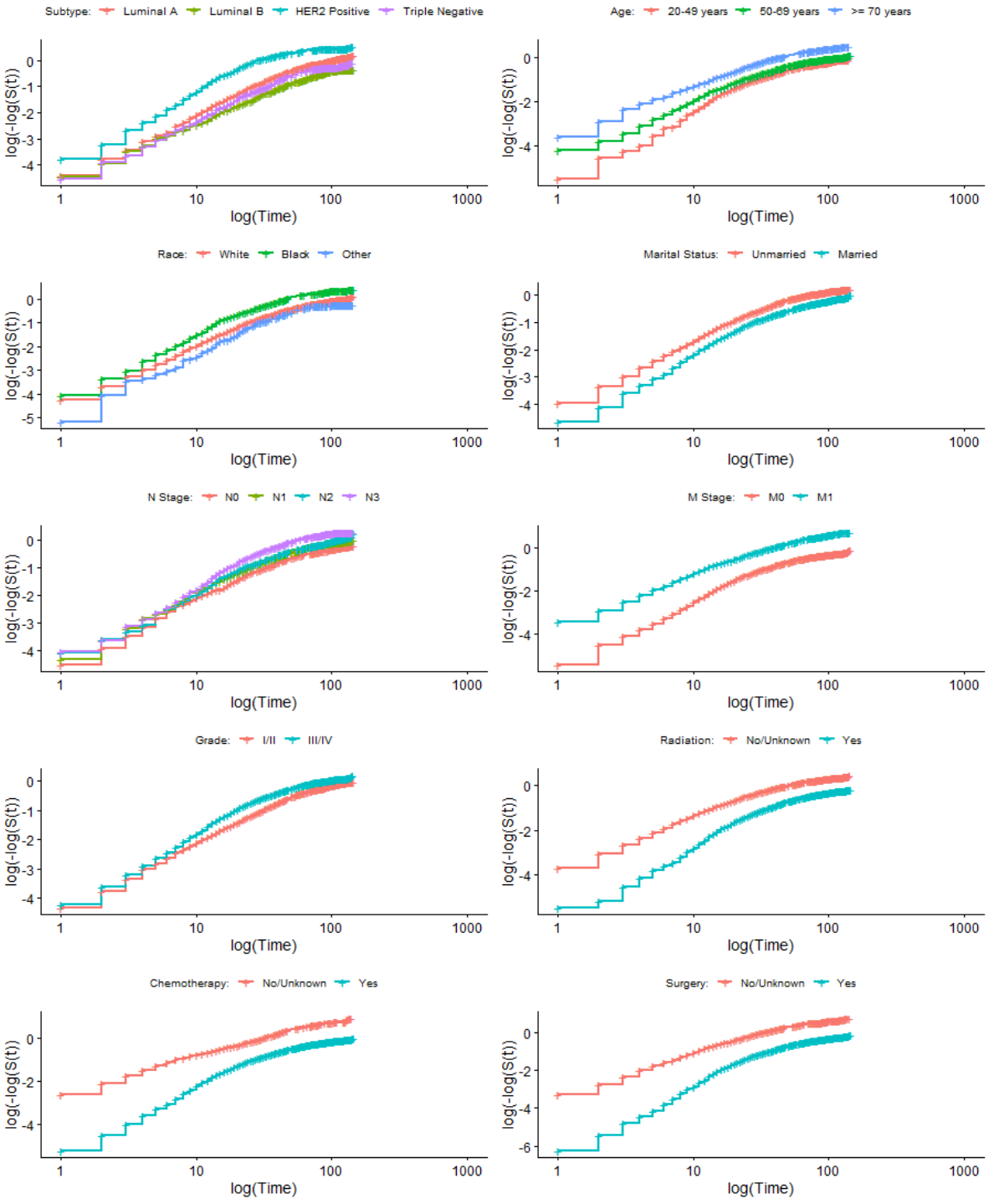

Figure 2: Log minus log plots

Upon inspection, slight deviations from parallelism were observed for the covariates subtype, grade, radiation, chemotherapy, and surgery. Therefore, Schoenfeld residuals were extracted from the full Cox proportional hazards model. The correlation between Schoenfeld residuals and ranked survival times for each covariate is presented in Table 2.

Table 2: Schoenfeld Residual and Ranked Survival Time Correlation

Variable	Correlation	p.value
Luminal B	-0.034	0.128
Triple Negative	-0.128	<0.001
HER2 Positive	-0.043	0.054
50-69 years	-0.033	0.142
>=70 years	-0.031	0.161
Black	0.009	0.692
Other	0.008	0.703
Married	-0.003	0.876
N1	-0.004	0.856
N2	-0.004	0.84
N3	0.016	0.459
M1	-0.006	0.797
Grade: III/IV	-0.042	0.062
Radiation: Yes	0.070	0.002
Chemotherapy: Yes	0.110	<0.001
Surgery: Yes	0.074	0.001

While the p-values for Triple Negative subtype, grade, radiation, chemotherapy, and surgery are statistically significant at the 0.05 level, the observed correlations are not of large magnitude. Respectively, the correlations are -0.128, -0.042, 0.070, 0.110, and 0.074. Given that these values are relatively small in magnitude, we proceed with the Cox proportional hazards regression model.

Survival Analysis

Table 3 presents the median survival in years, along with 1-, 5-, and 10-year survival percentages, stratified by clinicopathological characteristics, all of which show statistically significant differences based on the log-rank test. Survival outcomes differ significantly by subtype, with the Triple Negative subtype showing the poorest prognosis, including a median survival of 1.7 years and 1-, 5-, and 10-year survival rates of 67%, 24%, and 21%, respectively. Conversely, the Luminal B subtype has the best outcomes, with a median survival of 9.4 years and a 10-year survival rate of 50%. Racial disparities are evident in the data, as Black patients have the poorest survival outcomes, with a median survival of 2.4 years compared to 4.6 years for White patients and 5.4 years for patients of other races. Unmarried women experience poorer survival compared to married women. Although 1-year survival is similar across all node stages, nodal involvement significantly affects long-term outcomes, with the N3 stage showing the lowest median survival of 2.7 years and the poorest 5- and 10-year survival rates. Survival differences are also pronounced by distant metastasis, with M1 stage associated with worse outcomes. Additionally, higher cancer grades correlate with poorer survival. In terms of treatment, patients who receive radiation, chemotherapy, or surgery exhibit better survival outcomes across all measurements.

Table 3: Survival for IBC by Clinicopathological Characteristics

Characteristic	Median Survival (years)	1 Year	5 Year	10 Year	p-value
Subtype					<0.001
Luminal A	4.3	86%	47%	33%	
Luminal B	9.4	90%	63%	50%	
Triple Negative	1.7	67%	24%	21%	
HER2 Positive	5.8	88%	53%	44%	
Age					<0.001
20-49 years	5.8	89%	53%	42%	
50-69 years	4.3	83%	47%	37%	
>=70 years	2.2	72%	30%	21%	
Race					<0.001
White	4.6	84%	48%	37%	

Characteristic	Median Survival (years)	1 Year	5 Year	10 Year	p-value
Black	2.4	75%	30%	23%	
Other	5.4	89%	51%	45%	
Marital Status					<0.001
Unmarried	3.2	79%	39%	30%	
Married	5.8	86%	53%	41%	
N Stage					<0.001
N0	7.8	86%	56%	46%	
N1	4.7	83%	48%	38%	
N2	4.1	84%	47%	34%	
N3	2.7	80%	34%	25%	
M Stage					<0.001
M0	7.7	90%	57%	47%	
M1	2.1	70%	26%	14%	
Grade					<0.001
I/II	5.4	86%	52%	39%	
III/IV	3.4	81%	42%	33%	
Radiation					<0.001
No/Unknown	2.4	73%	33%	24%	
Yes	7.4	92%	57%	45%	
Chemotherapy					<0.001
No/Unknown	1.6	60%	18%	11%	
Yes	5.0	86%	50%	39%	
Surgery					<0.001
No/Unknown	1.8	65%	23%	15%	
Yes	7.3	92%	57%	46%	

We conducted univariate and multivariate analyses based on the data in Table 3. The results of the Cox proportional hazards regression models are presented in Table 4.

Table 4: Crude and Adjusted Cox Proportional Hazards Regression Models

Characteristic	HR	95% CI	p-value	aHR	95% CI	p-value
Subtype						
Luminal A	-	-	-	-	-	-
Luminal B	0.65	0.56, 0.74	<0.001	0.72	0.63, 0.83	<0.001
Triple Negative	1.99	1.79, 2.21	<0.001	2.51	2.24, 2.82	<0.001
HER2 Positive	0.80	0.69, 0.91	0.001	0.92	0.80, 1.06	0.3
Age						
20-49 years	-	-	-	-	-	-
50-69 years	1.21	1.09, 1.35	<0.001	1.10	0.99, 1.23	0.074
>=70 years	2.02	1.78, 2.29	<0.001	1.55	1.35, 1.77	<0.001
Race						
White	-	-	-	-	-	-
Black	1.57	1.41, 1.75	<0.001	1.24	1.11, 1.39	<0.001
Other	0.81	0.68, 0.97	0.021	0.81	0.68, 0.97	0.021
Marital Status						
Unmarried	-	-	-	-	-	-
Married	0.70	0.64, 0.76	<0.001	0.88	0.80, 0.96	0.005
N Stage						
N0	-	-	-	-	-	-
N1	1.26	1.08, 1.47	0.004	1.27	1.08, 1.48	0.003
N2	1.34	1.13, 1.59	<0.001	1.51	1.27, 1.80	<0.001
N3	1.78	1.51, 2.10	<0.001	1.75	1.48, 2.06	<0.001
M Stage						

Characteristic	HR	95% CI	p-value	aHR	95% CI	p-value
M0	-	-	-	-	-	-
M1	2.56	2.35, 2.80	<0.001	1.95	1.76, 2.16	<0.001
Grade						
I/II	-	-	-	-	-	-
III/IV	1.32	1.20, 1.45	<0.001	1.20	1.09, 1.32	<0.001
Radiation						
No/Unknown	-	-	-	-	-	-
Yes	0.47	0.43, 0.51	<0.001	0.76	0.69, 0.85	<0.001
Chemotherapy						
No/Unknown	-	-	-	-	-	-
Yes	0.37	0.33, 0.42	<0.001	0.50	0.44, 0.57	<0.001
Surgery						
No/Unknown	-	-	-	-	-	-
Yes	0.34	0.32, 0.38	<0.001	0.59	0.52, 0.66	<0.001

Univariate Analysis

In the univariate analysis, subtype, age, race, marital status, N stage, M stage, grade, radiation, chemotherapy, and surgery were all significantly associated with IBC-specific survival. These variables were therefore included in the multivariate analysis.

Multivariate Analysis

The multivariate analysis revealed that subtype, age, race, marital status, N stage, M stage, grade, radiation, chemotherapy, and surgery were independent predictors of IBC-specific survival. The Luminal B subtype was associated with better survival (aHR=0.72, 95%CI: 0.56-0.74, P<0.001), whereas the Triple Negative subtype showed the poorest survival outcomes (aHR=2.51, 95%CI: 1.79-2.21, P<0.001). In terms of treatment, our results found that the existing therapies are effective in improving survival. That is, radiation (aHR=0.76, 95%CI: 0.69-0.85, P<0.001), chemotherapy (aHR=0.50, 95%CI: 0.44-0.57, P<0.001), and surgery (aHR=0.59, 95%CI: 0.52-0.66, P<0.001).

Discussion

In this large population-based cohort of adult women diagnosed with IBC, we found better survival in Luminal B molecular subtype patients and poorer in Triple Negative. These findings are consistent with previous literature, which similarly identified Triple Negative IBC as a particularly aggressive form of breast cancer with poorer prognoses compared to hormone receptor-positive subtypes [3].

The racial disparities observed in our study, wherein Black participants had the poorest outcomes, align with existing evidence of inequities in IBC survival rates by race [2]. This result might be due to the higher incidence of Triple Negative breast cancer observed in Black American women, a finding observed in this study and in prior works [12]. Furthermore, unmarried women experienced worse outcomes, consistent with studies suggesting that social support and marital status are important predictors of cancer survival [14]. This could be related to the higher incidence of Triple Negative subtype observed in unmarried patients. Additionally, prior studies have found that in the U.S., Black women experience lower marriage rates compared to other racial and ethnic groups and face higher rates of marital instability, with divorce rates exceeding those of White and Hispanic women [15].

Treatment modalities, including radiation, chemotherapy, and surgery, were independently associated with improved survival outcomes in this study. These results are consistent with prior research demonstrating the efficacy of multimodal therapy in managing IBC [16]. However, the significantly poorer outcomes for the Triple Negative subtype highlight a need for improved therapeutic strategies targeting this group.

Limitations

This study has several strengths, including the use of a large, diverse patient population and robust multivariate analyses that accounted for key clinicopathological factors. However, several limitations should be acknowledged. First, this study excluded 1177 individuals diagnosed with IBC due to incomplete data, which may introduce bias if the missing data were not random. Additionally, since this study focused on IBC-specific survival, individuals with unknown causes of death or those who died from causes unrelated to IBC were excluded (n=487), potentially limiting the broader applicability of these findings. Future research could address missing data through techniques like multiple imputation, and consider implementing a competing events analysis to provide a more comprehensive view of survival outcomes. Another limitation of this study is the slight deviations from the proportional hazards assumption in the Cox model for several covariates, including subtype, grade, radiation, chemotherapy, and surgery. Although the correlations between Schoenfeld residuals and ranked survival times were statistically significant, their small magnitudes suggest minimal practical impact. We proceeded with the Cox model, but these deviations should be interpreted with caution. Future

research may consider using time-varying coefficients to address potential non-proportionality in hazard ratios.

Furthermore, this study did not examine the combined effects of treatment modalities, such as how chemotherapy, radiation, and surgery work in synergy. Future research should focus on evaluating specific treatment combinations to optimize multimodal therapy for IBC patients. Lastly, while this study focused exclusively on IBC, comparing molecular subtypes in IBC patients to those in non-IBC patients could yield important insights into how subtype-specific outcomes differ between forms of breast cancer. Such comparisons could inform whether treatment strategies should differ by cancer type.

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