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ORIGINAL RESEARCH

Using Restricted Mean Time Lost to Evaluate the Prognostic Effects on Locally Advanced Breast Cancer Considering Competing Risks

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Background: In the presence of competing risks, when the baseline risk is unclear, if only the sub-distribution hazard ratio (SHR) is reported in the results, which is related to the cumulative incidence function, the survival disparity of events of interest between groups cannot be clarified. In contrast, the difference in restricted mean time lost (RMTLd), which is the difference in the areas under the cumulative incidence between two groups, can well compensate for the deficiencies of SHR and explain the effects on a time scale, facilitating clinical interpretation and communication.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to collect information on female patients with locally advanced breast cancer diagnosed between 2010 and 2015. The prognostic factors of breast cancer death were evaluated considering competing risk. Univariable and multivariable analyses were conducted to get SHR and RMTLd.

Results: SHR can indicate the direction of prognostic factors, while RMTLd can quantify prognostic effects and provide time-scale interpretation. For instance, in adjuvant radiotherapy, the SHR showed a protective effect, which can be quantified as an average increase of 4.15 months in survival time.

Discussion: In the presence of competing risks, the combined use of absolute measure RMTLd can more intuitively explain the prognostic effect, which is convenient for clinical practice and communication.

Keywords: locally advanced breast cancer, competing risks, restricted mean time lost, sub-distribution hazard ratio

Introduction

Breast cancer is the most common malignancy that threatens women's health, with an estimated 290,000 newly diagnosed female breast cancer patients and approximately 43,000 female deaths annually in the United States.[1] Patients with locally advanced breast cancer (LABC) account for 10–20% of all breast cancer patients in the United States.[2] LABC patients are generally more likely to have local recurrence and distant metastasis than patients with early-stage breast cancer, and are more likely to have reduced quality of life and overall survival.[3] Therefore, it is important to identify prognostic factors of LABC and quantify their effects. For instance, adjuvant radiotherapy (ART) after surgery for breast cancer can halve the risk of recurrence within 10 years.[4]

Breast cancer patients without distant metastases generally have longer survival and are likely to die from other causes. Therefore, the overall death in breast cancer patients is usually a composite endpoint. If a study aims to investigate the effect of different postoperative ARTs on the survival prognosis of breast cancer patients and the event of interest is death due to any cause, then the event of interest may include death due to breast cancer and cardiovascular disease. If a study focuses on deaths due to breast cancer, then deaths due to other causes are competing events. Competing events can prevent events of interest from occurring; competing events and events of interest are not independent.[5] Most previous oncology-related studies either directly used the composite endpoint as the primary

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endpoint or treated competing events as censored, ignoring their impact.[6] Several studies have reported that disregarding the influence of competing events, such as by treating them as censored, overestimates the cumulative incidence of events of interest[7–9] (Figure 1A). If the incidence of competing events is high, using the composite outcome as the primary outcome may lead to the opposite conclusion,[10] especially in the case of public health, and potentially mislead decision-making and healthcare resource allocation. Therefore, the analysis should be conducted within this specific context, taking into account the presence of competing events.

Previous breast cancer-related studies used cause-specific hazard models and the Fine-Gray model to analyze the patient survival status in the presence of competing risks.[11–14] However, it is recommended to use the Fine-Gray model related to cumulative incidence to obtain a more accurate effect value—sub-distribution hazard (SHR)—to evaluate the effects of prognosis factors in the event of interest.[15,16] The Fine-Gray model also needs to satisfy the proportional hazards assumption (SHR does not change with time). In observational studies, the sample size is usually large, the follow-up time is long, and the proportional hazards assumption of the model is generally difficult to satisfy,[17] which makes the practical meaning of SHR difficult to interpret. SHR has its own drawbacks: first, it is a relative measure, and

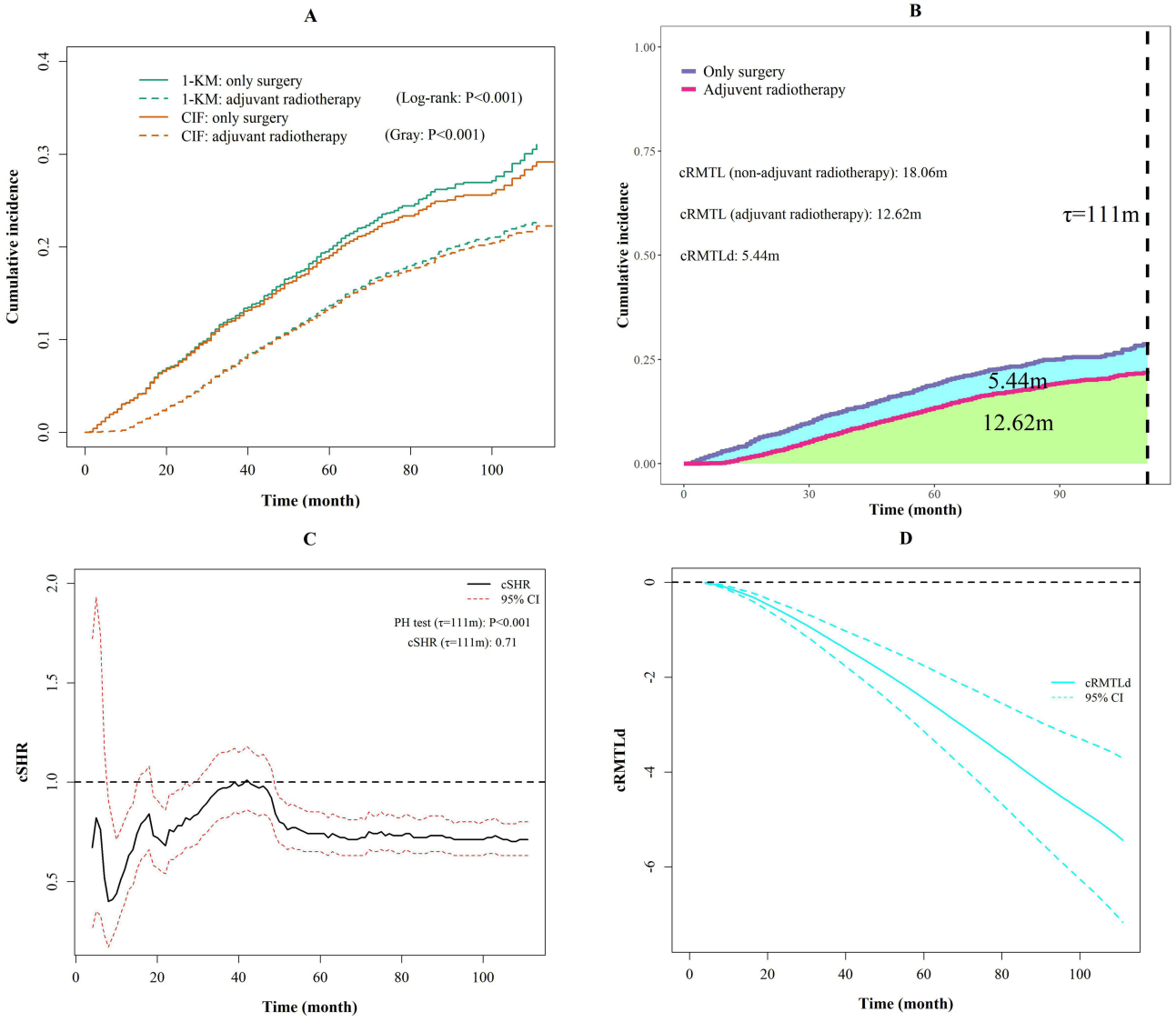

Figure 1 Crude analysis on adjuvant radiotherapy. (**A**) Crude estimation of cumulative incidence by 1−KM and CIF. Kaplan-Meier and CIF estimation of cumulative incidence for death due to breast cancer. (**B**) Area under the CIF curve. The area under the CIF-estimated cumulative incidence curve (RMTL). (**C**) cSHR varying over adjuvant radiotherapy vs only surgery. The crude sub-distribution hazard ratio (cSHR) for death due to breast cancer varies over time. (**D**) cRMTLd varying over time adjuvant radiotherapy vs only surgery. The difference in the area under the CIF estimated cumulative incidence curve (cRMTLd) varies over time.

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second, its precise meaning is relative rate rather than relative risk.[7,18] Therefore, the actual meaning of SHR is the intensity of the event at a given moment, rather than the risk of the event occurring. SHR estimated using the Fine-Gray model can only provide a directional reference to the relative risk (if SHR is >1, then relative risk is >1), and determining SHR alone (without knowing the baseline risk) does not provide an estimate of the magnitude of the relative risk.[18,19] Nevertheless, SHR remains the most commonly used measure to quantify the effect of treatment on outcomes in tumor-related studies that consider competing risks.[20] To better quantify the effect of prognostic factors on outcomes when the Fine-Gray model does not satisfy the proportional hazards assumption, we utilized the alternative time-scale-based restricted mean time lost (RMTL) in the presence of competing risks.[21–26] The geometric meaning of RMTL is the area under the cumulative incidence curve (Figure 1B) within the time window from the start of follow-up ($t = 0$) to a prespecified time horizon (τ), and its between-group effect size is the difference in RMTLs (RMTLd). τ is usually chosen based on the clinical context, usually a specific time point of interest, eg, in LABC, physicians may be interested in how much time patients lose in survival over 3 or 5 years. In observational studies, the maximum observed inter-worldly minima of different groups are usually chosen in order to maximize the use of follow-up information. RMTLd is an absolute measure, and even if the baseline RMTL is ambiguous, reporting RMTLd alone may provide a reasonable quantification of the effects of prognostic factors. For example, in this study, the event of interest was death due to breast cancer. RMTL can be interpreted as the average survival time lost within the time window from 0 to τ for LABC patients who died from breast cancer. Taking the prognostic factor ART as an example, the between-group effect size RMTLd is the additional survival time lost due to breast cancer death in LABC patients who did not receive ART compared with those who received ART from the start of follow-up to τ (Figure 1B, cyan area); this, in turn, can be interpreted as the additional survival time gained in LABC patients who received ART compared with those who did not receive ART.

Furthermore, in the multivariable analysis considering the competing risks, we utilized the RMTL regression model.[22] Similar to a univariable RMTL analysis, the multivariable RMTL regression model requires a prespecified τ. The model yields a between-group effect size of RMTLd, the interpretation of which is similar to that of univariable RMTLd. Neither the univariable nor the multivariable-related RMTL method requires consideration of proportional hazards assumptions and yields absolute measures on a time scale in which the actual meaning of the measures is better interpreted and communicated.

The absolute measure RMTLd obtained using the RMTL regression model can be recommended as a complement to SHR in the prognostic analysis that considers competitive risks, due to its intuitive interpretation and the fact that the model itself is not subject to proportional hazards assumptions. Several studies have recommended the use of different types of measures to evaluate differences and obtain a more comprehensive understanding of survival disparities.[17,27] Therefore, this study aims to use RMTLd combined SHR to assess the prognostic impact of LABC patients after partial mastectomy using data from a real-world observational study, allowing for a more intuitive interpretation of the effect from the perspective of the clinicians and patients.

Methods

Data Source

Data for the study were obtained from the Surveillance, Epidemiology, and End Results (SEER) databases. We extracted female patients aged 30–80 years with histologically diagnosed primary breast cancer from 2010 to 2015 from 17 US registries (approximately 26.5% of the US population) using SEER*Stat 8.4.0.1 statistical software. Patients with LABC (including T3 or T4 tumors and any N2 or N3, clinical stage IIB-T3N0 to stage III)[2] were further screened from the database, and those who had undergone partial mastectomy were selected according to their breast cancer surgical codes (see Figure 2 for additional information on inclusion and exclusion criteria). In addition to information about surgical treatment, the SEER database contains information on other modalities of treatment, including radiotherapy. For illustration, we divided all LABC patients into two groups according to whether they underwent postoperative ART. The event of interest for LABC patients was death due to breast cancer, and all other causes of death were considered competing events. Patients' follow-ups ended in death caused by breast cancer or other causes, the last follow-up, or December 31, 2019, whichever occurred first. The true follow-up time of the patients was the total follow-up time minus the time gap between diagnosis and treatment.

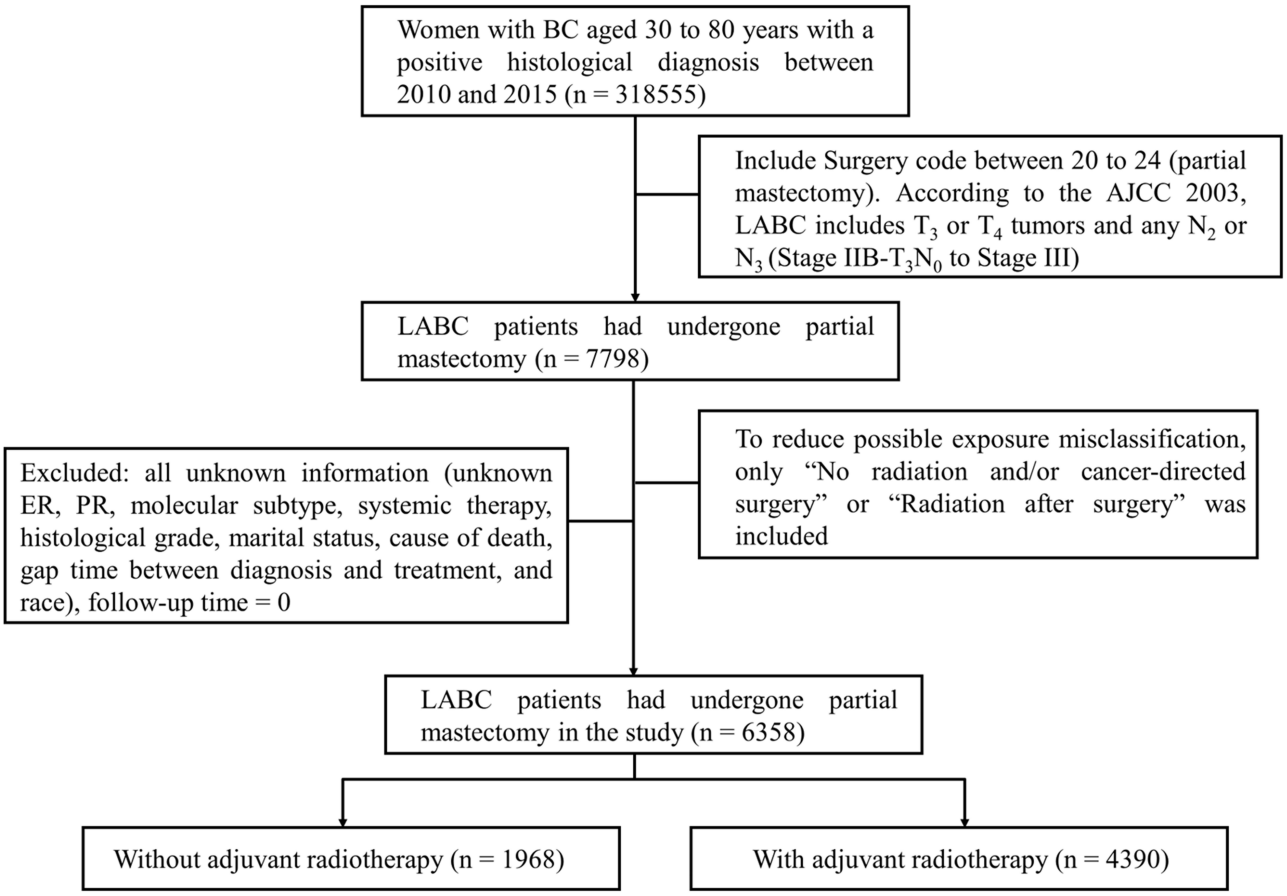

Figure 2 Procedures for inclusion and exclusion of LABC patients with partial mastectomy.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics and compared using χ^2 test for categorical variables and Student's t test for continuous variables. The time window (τ) in this study was taken as the minimum value of the maximum event time of death due to breast cancer for patients in the ART and non-ART (NART) groups ($\tau = 111\,months$).

Crude Analysis

In the crude analysis, only one prognostic factor was included every time. The Kaplan-Meier method and cumulative incidence function (CIF) were used for the analysis. The prognostic factor ART was used to elucidate. First, the cumulative incidence curve of death due to breast cancer was estimated using the Kaplan-Meier method by considering the competitive events as censored (ignoring the effect of competing risks), and the difference between the two groups was tested using the log-rank test. Second, the cumulative incidence curve of death due to breast cancer was estimated using CIF in the presence of competing risks. The difference between the groups was tested using the Gray test, and the crude SHR (cSHR) was estimated using the Fine-Gray model. The final estimated SHR can be regarded as the weighted average of the SHR at each time point before the prespecified time horizon (τ).[28] Therefore, when estimating cSHR, the events of interest or competing events occurring after τ should be regarded as censored so that cSHR at τ can be accurately estimated, and the proportional hazards assumption of the model is also tested.[29] The area under the CIF-estimated cumulative incidence curve is crude RMTL (cRMTL), and the difference in cRMTL (cRMTLd) was calculated for the ART and NART groups, and 95% confidence intervals (CIs) were estimated for both groups.[21] We summarize the distinctions between SHR and RMTLd in Table 1.

Table 1 Differences Between SHR and RMTLd

	SHR	RMTLd
Treatment Effect	Overall effect of a specific event	Overall effect of a specific event
Estimation Period	From study start to the maximum event time across both groups. If a SHR is of interest at a specific time point (τ), events of interest occurring after τ should be set to censoring	From study start to τ
Statistical Inference	The baseline sub-distribution hazard cannot be estimated due to the semi-parametric nature of the Fine-Gray model	The baseline RMTL, interpretable as the mean time lost due to the specific event within the time period in control group in clinical trials.
Hypothesis Test	The Gray test	RMTLd test
Model Assumption	Proportional sub-distribution hazards assumption	None required
Clinical Interpretation	Based on a risk-based perspective, SHR can be interpreted as the ratio of sub-distribution instantaneous event rates for the specific event	Based on a time-based perspective, RMTLd can be interpreted as the extra mean time lost due to the specific event

Multivariable-Adjusted Analysis

The RMTL regression models were used in the adjusted analysis,[22] which is based on the RMTL pseudo-value method, and the same variables were included in both the Fine-Gray and the RMTL regression models. In the Fine-Gray model, a proportional hazards test was performed separately for each variable. The coefficients obtained from the RMTL regression model are similar to linear regression; for categorical variables, the meaning is the average increase or decrease in survival time from the start of follow-up until the moment τ for patients with certain characteristics compared with the control group, and for continuous variables, the meaning is the average increase or decrease in survival time for each unit increase in the independent variable. As the event of interest in this study is death due to breast cancer, a negative coefficient (ART vs NART group) indicates that the average survival time loss of patients with certain characteristic factors is reduced, and this factor is a protective factor.

Statistical tests were two-sided with a significance level α of 0.05. All statistical analyses were performed using R version 4.2.2.

Results

Descriptive Analysis

A total of 6358 women aged 30–80 years who had undergone partial mastectomy for LABC were included (Table 2), among whom 4390 (69.0%) received ART after partial mastectomy. The incidence of competing risks was 6.2%,

Table 2 Baseline Characteristics

Characteristics	Level	No radiotherapy	Radiotherapy	*p-value*
No. of patients		1968	4390	
Age (mean (SD))		59.1 (11.3)	57.8 (11.0)	<0.001
Age group (%)	≤60	1036 (52.6)	2562 (58.4)	<0.001
	>60	932 (47.4)	1828 (41.6)	
Race (%)	Black	295 (15.0)	621 (14.1)	0.665
	White	1508 (76.6)	3403 (77.5)	
	Other	165 (8.4)	366 (8.3)	

(*Continued*)

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Table 2 (Continued).

Characteristics	Level	No radiotherapy	Radiotherapy	*p-value*
N stage (%)	N0	398 (20.2)	878 (20.0)	0.029
	N1	272 (13.8)	624 (14.2)	
	N2	905 (46.0)	2141 (48.8)	
	N3	393 (20.0)	747 (17.0)	
T stage (%)	T1	439 (22.3)	1013 (23.1)	0.147
	T2	713 (36.2)	1594 (36.3)	
	T3	645 (32.8)	1473 (33.6)	
	T4	171 (8.7)	310 (7.1)	
Stage (%)	IIB	323 (16.4)	755 (17.2)	0.002
	IIIA	1093 (55.5)	2599 (59.2)	
	IIIB	159 (8.1)	289 (6.6)	
	IIIC	393 (20.0)	747 (17.0)	
PR (%)	Negative	683 (34.7)	1496 (34.1)	0.646
	Positive	1285 (65.3)	2894 (65.9)	
ER (%)	Negative	424 (21.5)	1002 (22.8)	0.272
	Positive	1544 (78.5)	3388 (77.2)	
Subtype (%)	HR-/HER2-	295 (15.0)	644 (14.7)	0.607
	HR-/HER2+	116 (5.9)	298 (6.8)	
	HR+/HER2-	1310 (66.6)	2896 (66.0)	
	HR+/HER2+	247 (12.6)	552 (12.6)	
Histological type (%)	Other types	304 (15.4)	583 (13.3)	0.005
	Lobular carcinoma	238 (12.1)	457 (10.4)	
	Infiltrating duct carcinoma	1426 (72.5)	3350 (76.3)	
Systemic therapy (%)	No	522 (26.5)	158 (3.6)	<0.001
	STBS	271 (13.8)	643 (14.6)	
	STAS	1057 (53.7)	2893 (65.9)	
	STBAS	118 (6.0)	696 (15.9)	
Marital status (%)	Unmarried	398 (20.2)	849 (19.3)	0.431
	Married	1570 (79.8)	3541 (80.7)	
Time (mean (SD)) month		65.7 (30.9)	71.7 (27.0)	<0.001
Cause of death (%)	Alive	1355 (68.9)	3412 (77.7)	<0.001
	Died of BC	448 (22.8)	748 (17.0)	
	Died of OC	165 (8.4)	230 (5.2)	

Notes: N stage and T stage were according to the 7th edition of the AJCC (American Joint Committee on Cancer). Other races: American Indian/AK Native, Asian/Pacific Islander.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SD, standard deviation; STBS, systemic therapy before surgery; STAS, systemic therapy after surgery; STBAS, systemic therapy both before and after surgery; BC, breast cancer; OC, other cause.

accounting for 25.4% of all-cause deaths. Among LABC patients who received partial mastectomy, the mean follow-up time was visually higher in the ART group than in the NART group (71.7 m vs 65.7 m, *p-value* < 0.001). Survival rates were higher in the ART group than in the NART group (77.7% vs 68.9%), and the proportions of deaths from breast cancer and competing events were lower in the ART group than in the NART group.

Crude Analysis

As shown in Figure 1A, the Kaplan–Meier method estimated that the cumulative incidence curve of the ART group was below that of the NART group, and the *p-value* of the Log-rank test was <0.001, indicating that the survival rate of death from breast cancer in the ART group was lower than that in the NART group. Similarly, the CIF-estimated cumulative incidence curve for the ART group was lower than that for the NART group, and the *p-value* of the Gray test was <0.001, indicating that the survival rate of death from breast cancer in the ART group was lower than that in the NART group

(Figure 1A). Treating competing events as censoring would overstate the cumulative incidence of the events of interest, as evidenced by the fact that all the KM curves were above the CIF curve. At follow-up to $\tau = 111m$, the estimated univariable cSHR using the Fine-Gray model was 0.71 (95% CI 0.63–0.79); however, the *p-value* for the proportional hazards test was <0.001, indicating that the cSHR may have changed over time; the estimated trend of cSHR from 4 m to 111 m is shown in Figure 1C. Within the time window from $t = 0$ to $\tau = 111\,m$, the cRMTL using CIF was estimated to be 12.62 m (95% CI: 11.78 m–13.46 m) for the ART group and 18.06 m (95% CI 16.54 m–19.57 m) for the NART group, and the cRMTLd (ART vs NART group) was −5.44 m (95% CI −7.17 m to −3.71 m). It indicates that within the time window from $t = 0$ to $\tau = 111\,m$, patients in the NART group lost an average of 5.44 m more survival time due to breast cancer death than did patients in the ART group (Figure 1B). The value of cRMTLd decreased from 4 m to 111 m (ie, its absolute value increased) with increasing follow-up time (Figure 1D). The crude analysis results of other prognostic factors are shown in Table 3.

Multivariable-Adjusted Analysis

After controlling for other factors, the covariate-adjusted SHR (aSHR) and covariate-adjusted RMTLd (aRMTLd) in the ART group compared with those in the NART group were 0.75 (95% CI 0.66–0.85) and −4.15 m (95% CI −5.89 m to −2.42 m), respectively (Table 4). The *p-values* of the proportional hazards test for all variables of the Fine-Gray model

Table 3 Results of the Crude Analysis ($\tau = 111\,m$)

TCharacteristics	Fine-Gray Model		RMTL Regression Model	
	cSHR (95% CI)	*p-value*	cRMTLd, Month (95% CI)	*p-value*
Radiotherapy (ref: no)				
Yes	0.71 (0.63, 0.79)	<0.001	−5.44 (−7.17, −3.71)	<0.001
Age (ref: ≤60)				
>60	1.13 (1.01, 1.27)	0.035	1.92 (0.40, 3.44)	0.013
Race (ref: black)				
White	0.59 (0.52, 0.68)	<0.001	−8.24 (−10.68, −5.80)	<0.001
Other	0.46 (0.35, 0.60)	<0.001	−10.90 (−14.19, −7.62)	<0.001
Stage (ref: IIB)				
IIIA	2.02 (1.63, 2.50)	<0.001	6.29 (4.65, 7.94)	<0.001
IIIB	2.62 (1.98, 3.48)	<0.001	10.68 (7.24, 14.12)	<0.001
IIIC	3.74 (2.99, 4.69)	<0.001	15.95 (13.48, 18.42)	<0.001
Subtype (ref: HR-/HER2-)				
HR-/HER2+	0.55 (0.43, 0.70)	<0.001	−11.76 (−15.83, −7.68)	<0.001
HR+/HER2-	0.42 (0.37, 0.48)	<0.001	−15.87 (−18.58, −13.16)	<0.001
HR+/HER2+	0.34 (0.28, 0.42)	<0.001	−18.34 (−21.44, −15.24)	<0.001
ER (ref: negative)				
Positive	0.49 (0.43, 0.55)	<0.001	−12.36 (−14.50, −10.23)	<0.001
PR (ref: negative)				
Positive	0.46 (0.41, 0.52)	<0.001	−11.95 (−13.67, −10.22)	<0.001
Systemic therapy (ref: No)				
STBS	1.07 (0.86, 1.32)	0.531	0.24 (−3.13, 3.60)	0.890
STAS	0.75 (0.63, 0.90)	0.002	−4.86 (−7.58, −2.15)	<0.001
STBAS	0.91 (0.73, 1.14)	0.462	−2.26 (−5.60, 1.09)	0.186
Histological type (ref: other types)				
Lobular carcinoma	0.98 (0.78, 1.25)	0.900	−0.53 (−3.38, 2.32)	0.715
Infiltrating duct carcinoma	1.08 (0.92, 1.28)	0.352	1.35 (−0.77, 3.47)	0.213
Marital status (ref: unmarried)				
Married	0.83 (0.73, 0.95)	0.008	−2.78 (−4.76, −0.80)	0.006

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval; STBS, systemic therapy before surgery; STAS, systemic therapy after surgery; STBAS, systemic therapy both before and after surgery.

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Table 4 Results From the Multivariable-Adjusted Fine-Gray Model and RMTL Regression Model for $\tau = 111\,m$

Characteristics	Multivariable-Adjusted Fine-Gray Model		Multivariable-Adjusted RMTL regression model
	aSHR (95% CI)	*p-value* of PH test	aRMTLd, Month (95% CI)
Intercept	——	——	23.48 (18.78, 28.18)
Radiotherapy (ref: no)			
Yes	0.75 (0.66, 0.85)	<0.001	−4.15 (−5.89, −2.42)
Age (ref: ≤60)			
>60	1.28 (1.13, 1.43)	0.044	3.57 (2.08, 5.06)
Race (ref: black)			
White	0.71 (0.61, 0.83)	0.075	−5.33 (−7.71, −2.94)
Other	0.59 (0.45, 0.77)	0.134	−6.97 (−10.09, −3.86)
Histological grade (ref: grade 1)			
Grade 2	1.45 (1.11, 1.89)	<0.001	2.71 (0.82, 4.61)
Grade 3 and 4	2.07 (1.58, 2.72)	<0.001	7.37 (5.16, 9.58)
Stage (ref: stage IIB)			
Stage IIIA	2.21 (1.77, 2.74)	0.182	7.25 (5.57, 8.93)
Stage IIIB	2.46 (1.83, 3.30)	0.007	9.50 (6.14, 12.86)
Stage IIIC	3.87 (3.05, 4.87)	0.606	15.79 (13.34, 18.25)
PR (ref: negative)			
Positive	0.60 (0.51, 0.71)	<0.001	−7.11 (−9.5, −4.71)
Subtype (ref: HR-/HER2-)			
HR-/HER2+	0.54 (0.42, 0.69)	0.002	−11.62 (−15.6, −7.65)
HR+/HER2-	0.80 (0.66, 0.98)	<0.001	−6.49 (−10.05, −2.94)
HR+/HER2+	0.51 (0.40, 0.66)	0.002	−11.57 (−15.24, −7.90)
Systemic treatment (ref: No)			
STBS	0.95 (0.75, 1.21) [a]	0.120	−1.77 (−5.16, 1.61) [a]
STAS	0.78 (0.64, 0.95)	0.011	−3.78 (−6.54, −1.01)
STBAS	1.11 (0.86, 1.42) [a]	0.161	0.40 (−2.94, 3.74) [a]
Marital status (ref: Unmarried)			
Married	0.85 (0.73, 0.98)	0.219	−2.31 (−4.23, −0.40)

Notes: [a]*p-value* > 0.05.

Abbreviations: PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; PH, proportional hazards; CI, confidence interval; STBS, systemic therapy before surgery; STAS, systemic therapy after surgery; STBAS, systemic therapy both before and after surgery.

are shown in Table 3, indicating that ART (*p-value* < 0.001) did not meet the proportional hazards assumption. With other factors fixed, white Americans and other ethnic groups had a lower risk of death from breast cancer than blacks, with an aSHR of 0.71 (95% CI 0.61–0.83) and 0.59 (95% CI 0.45–0.77), respectively, and an aRMTLd of −5.33 m (95% CI −7.71 m to −2.94 m) and −6.97 m (95% CI −10.09 m to −3.86 m), respectively. The prognosis of patients with higher stages and higher histological grades was worse, and both aSHR and aRMTLd increased with increasing stages and grades. In both models, negative progesterone receptor (PR) and subtype HR−/HER2− (hormone receptor negative and HER2 human epidermal growth factor receptor negative) were risk factors, and only systemic treatment after surgery had a protective effect. In this case, the RMTL regression model can be calculated as follows:

$$\begin{aligned}\mathrm{RMTL} &= 23.48 - 4.15 \times \text{radiotherapy} + 3.57 \times \text{age} - 5.33 \times \text{white}\\ &- 6.97 \times \text{other race} + 2.71 \times \text{grade 2} + 7.37 \times \text{grade 3\&4}\\ &+7.25 \times \text{stage IIIA} + 9.50 \times \text{stage IIIB} + 15.79 \times \text{stage IIIC}\\ &- 7.11 \times \mathrm{PR} - 11.62 \times (\mathrm{HR-/HER2+}) - 6.49 \times (\mathrm{HR+/HER2-})\\ &- 11.57 \times (\mathrm{HR+/HER2+}) - 1.77 \times (\text{systemic therapy before surgery})\\ &- 0.40 \times (\text{systemic therapy both before and before surgery})\end{aligned} \tag{1}$$

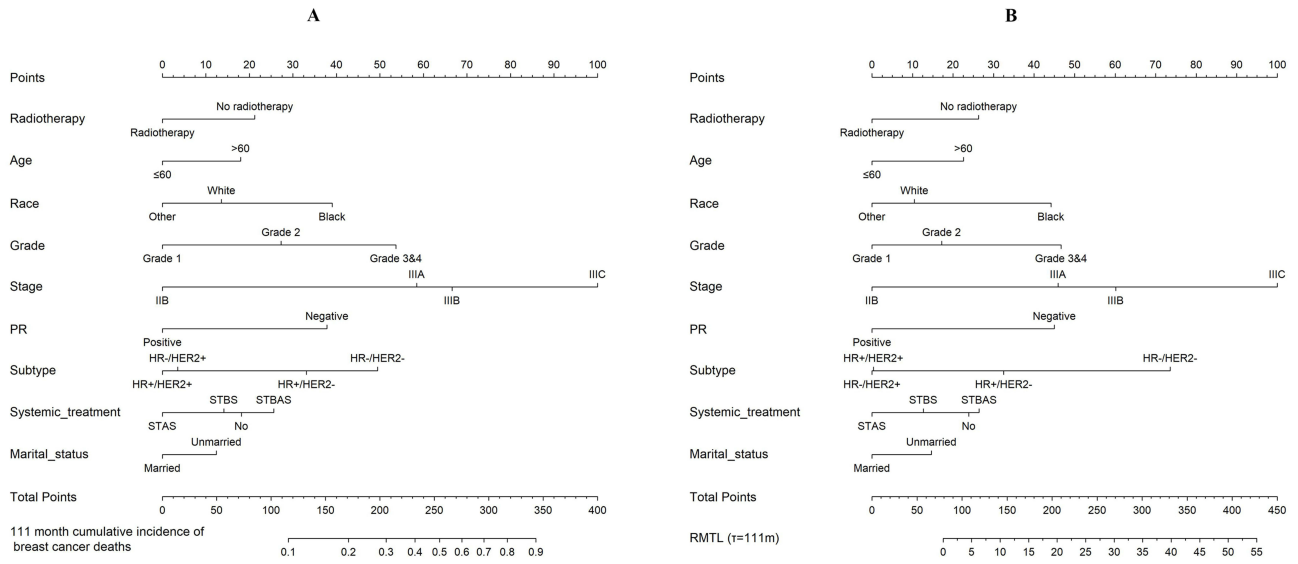

Figure 3 Nomogram for predictive analysis. (**A**) Nomogram for Fine-Gray model. Nomogram for predicting the cumulative incidence of death due to breast cancer (τ=111m) using the Fine-Gray model. Points for characteristics: no radiotherapy 21, age>60 18, race black 39, race white 14, grade 2 27, grade 3and4 54, stage IIIA 58, stage IIIB 67, stage IIIC 100, PR negative 38, subtype HR−/HER+ 4, subtype HR+/HER− 33, subtype HR−/HER− 44, no systemic treatment 18, STBS 14, STBAS 26, unmarried 12. (**B**) Nomogram for RMTL regression model. Nomogram for predicting RMTL due to breast cancer death (τ=111m) using the RMTL regression model. Points for characteristics: no radiotherapy 26, age>60 23, race black 44, race white 10, grade 2 17, grade 3and4 47, stage IIIA 46, stage IIIB 60, stage IIIC 100, PR negative 45, subtype HR−/HER+ 0, subtype HR+/HER− 32, subtype HR−/HER− 74, no systemic treatment 24, STBS 13, STBAS 26, unmarried 15.
Abbreviations: STBS, systemic therapy before surgery; STAS, systemic therapy after surgery; STBAS, systemic therapy both before and after surgery.

Predictive Analysis Under Multivariable Model

The Fine-Gray and RMTL regression models can be used to predict the cumulative incidence and aRMTL, respectively. The aRMTL for a particular patient can be predicted directly by substituting the characteristic factors of that patient into Equation (1). The predicted cumulative incidence and aRMTL of death due to BC for a patient ($\tau = 111\,m$), aged >60 years, with ART, Asian, grade 2, stage IIIB, PR-negative, subtype HR+/HER2−, without systemic treatment, and unmarried, were 32.6% and 21.64 m (95% CI 13.60 m to 29.68 m), respectively. These characteristics of this patient were scored as 0, 18, 0, 27, 67, 38, 33, 18, and 12, respectively, with a total score of 213 (Figure 3A), and 0, 23, 0, 17, 60, 45, 32, 24, and 15, respectively, with a total score of 216 (Figure 3B). The bottom two lines of the nomograms are the total score and the corresponding cumulative incidence of death due to breast cancer or RMTL due to breast cancer death. It can be seen that the values predicted by the nomogram and the values predicted by the model are very close.

Discussion

This study focuses on the application and interpretation of SHR and RMTLd in real studies through prognostic factors ART. The benefit of ART in patients depends mainly on the risk of tumor recurrence, particularly in early-stage breast cancer, which can effectively reduce the risk of recurrence. Meta-analyses have shown that ART after partial mastectomy improves the prognosis of breast cancer patients.[4,30] However, in the presence of competing risks, ART effect assessments are mostly based on SHR, which is a relative measure that cannot determine the actual risk magnitude of patients in the absence of a definite baseline risk and is often misunderstood by physicians and patients in clinical practice.[19,31] When estimating SHR using the Fine-Gray model, the variables must satisfy the proportional hazards assumption; the interpretation of SHR becomes more difficult when the proportional hazards assumption is not satisfied. For example, in this study, the *p-value* of the proportional hazards test of ART in either the univariable or multivariable analysis was <0.001, indicating that ART did not meet the proportional hazards assumption, further indicating that SHR may change with time and that the effect of ART varies at different follow-up time points. As shown in Figure 1C, approximately 40 months after ART, if the therapeutic effect is evaluated using SHR, no curative effect will be obtained. Therefore, the absolute measure of RMTLd was used to quantify the effect size. Compared with SHR, RMTLd can compensate for two major deficiencies in SHR: First, the method for estimating RMTLd does not need to take proportional hazards

assumptions into account. Second, RMTLd can be used to evaluate the effect even when the baseline is unknown. As shown in Figure 1D, although the RMTLd of different follow-up times varies, the estimated values of different follow-up times show that ART can reduce the survival time lost due to breast cancer death and does not provide completely different results due to the fluctuation of treatment effect, as does SHR.

Because survival times are generally longer in breast cancer patients without metastasis, especially in observational studies, competing risks are prevalent.[13] Therefore, to obtain a more accurate effect estimation in observational studies of LABC, not only covariate adjustment but also competing risks should be considered. In this study, the prognostic impact of ART was analyzed in 6358 female LABC patients with partial mastectomy collected from the SEER database, and the results of both univariable and multivariable-adjusted analyses showed that ART improved prognosis. Before interpreting the results, it is important to clarify that SHR describes the intensity of an event, not the risk of the event.[18,19] If SHR alone is reported in the results, the magnitude of the risk of death due to breast cancer cannot be determined, because the baseline risk remains unclear. For example, in this study, aSHR was 0.75 (95% CI 0.66–0.85). We can only determine whether ART is a protective factor against death due to breast cancer, but we cannot determine the actual effect size. Although the aSHR of 0.75 for patients who received ART compared with those who did not receive ART when the Fine-Gray model meets the proportional hazards assumption can be approximately interpreted as a 25% reduction in the risk of death due to breast cancer for the ART group compared with the NART group, a proper interpretation would be "the rate of death due to breast cancer was 0.75 times for the ART group than for the NART group." In the RMTL regression model, controlling for other covariates, the aRMTLd for patients who received ART at follow-up to 111 m was −4.15 m (95% CI −5.89 m to −2.42 m) compared with that for patients who did not receive ART, suggesting that ART after partial mastectomy in LABC patients reduces the survival time lost due to breast cancer death by an average of 4.15 m. In other words, ART was administered to increase survival time by an average of 4.15 months. The RMTLd is an absolute measure that directly quantifies the magnitude of the effect of ART and does not require the consideration of the proportional hazards assumption. Consequently, in cases where the proportional hazards assumption is not met and/or the baseline is unclear, we recommend using the absolute measure RMTLd to quantify the magnitude of the between-group difference in order to more accurately quantify the prognostic effect. Combining the relative measure SHR and the absolute measure RMTLd can provide an objective evaluation of the prognosis of ART and information, which is more consistent with the value in clinical practice.

The Fine-Gray and RMTL regression models can be used for both prognostic analysis and simple prediction. The Fine-Gray model is mostly used to predict the cumulative incidence of a specific event at follow-up to a specific time point in the presence of competing risks,[13,32] usually in conjunction with a nomogram to visualize the risk scores of different factors. Similarly, the RMTL regression model can be used to predict RMTL during the time window from 0 to τ, as well as with a nomogram to visualize the risk scores of different factors, which allows aRMTLd to be obtained between patients with different factors. The Fine-Gray model predicts the cumulative incidence of patients at different time points (maximum to τ), whereas the RMTL regression model only predicts RMTL at the moment of follow-up to τ, although τ can be chosen at different time points according to professional needs. Nevertheless, in studies considering competing risks, RMTL regression models can be used to predict the RMTL of patients and aRMTLd between patients, together with the difference (ratio) between the predicted risk of patients, to predict the prognosis of patients with certain factors after receiving different treatments; this will provide more appropriate and individualized treatment regimens for different patients.

This study has some limitations. First, the SEER database lacks the exact time of receiving a certain treatment; only the total follow-up time and time interval between diagnosis and treatment are mentioned in the database. The approximate follow-up time from the start of radiotherapy to the event of interest or the cutoff time in this study can only be calculated by subtracting the total follow-up time from the time interval between diagnosis and treatment. Patients in the ART group have to live until the time they receive ART. However, because the number of events that occurred during this period of waiting for ART was small and the gap time was generally 1 to 2 months, it had a minor effect on our main conclusions. Second, similar to other measures based on time scale, the τ value of RMTL-related methods should be carefully selected.[33] In case of few events in the late follow-up period, a too large τ value may overestimate the effect, and judgment should be made according to the actual occurrence of events of interest and

treatment effect. Finally, the SEER database lacks information related to the socio-economic status and biomarkers of LABC, etc. These variables might be important confounding factors. Therefore, the evaluation of prognostic effects in this study may be biased.

Conclusions

In studies considering competing risks, RMTLd can be used as a complement to SHR to quantify the between-group effect size and is reported together in the results. In this study, at 111 months of follow-up, the SHR of LABC patients who received ART was 0.75 (95% CI 0.66–0.85) compared with that of patients who did not receive ART, indicating that the rate (not risk) of death due to BC was 0.75 times for the ART group compared with the NART group. The aRMTLd of LABC patients who received ART was −4.15 m (95% CI −5.89 m to −2.42 m) compared with that of patients who did not receive ART, indicating that LABC patients who received ART after partial mastectomy had a reduced survival time loss by 4.15 m due to breast cancer death on average; thus, ART after partial mastectomy can increase the survival time by an average of 4.15 m. Therefore, in the presence of competing risks, the combined use of absolute measure RMTLd can more intuitively explain the prognostic effects, which is convenient for clinical practice and communication.

Data Sharing Statement

The SEER data were available upon request from the SEER website (https://seer.cancer.gov/). Sub-distribution hazard ratio can be calculated by crr function in R package cmprsk. Difference in crude restricted mean time lost can be calculated by RMTLd_test function in R package crRMTL. Multivariable regression of restricted mean time lost can be calculated by pseudoyl function in R package pseudo.

Ethics Approval and Consent to Participate

Data for the study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. No new clinical data were collected or used. We used datasets that maintained the anonymity of subjects. This study was granted exemption from ethical review approval under Items 1 and 2 of Article 32 of China's Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission Order No. 2, issued February 18, 2023), as it involved: (1) Evaluation of teaching methodologies and effectiveness in normal educational settings; (2) Analysis of publicly available, non-identifiable records and data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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