Establishment and verification of a nomogram for predicting survival in patients with triple-positive breast cancer

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Background: Triple-positive breast cancer (TPBC) is a specific type of breast cancer characterized by the positive expression of estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER-2). In recent years, the research on breast cancer has been increasing year by year, but there are few studies on TPBC, especially the lack of analysis with large sample size. In this study, sufficient samples were provided through the SEER database, explore the factors affecting the prognosis of TPBC, and construct a prediction model, in order to assess the individual survival of patients, and help clinicians accurately identify high-risk patients and develop personalized treatment plans.

Methods: Patients pathologically diagnosed with TPBC were recruited from Surveillance, Epidemiology, and End Results (SEER) database and randomly divided into training and validation groups (7:3 ratio). Univariate analysis was used to analyze the related factors affecting the prognosis of TPBC patients in the modeling group, and then multivariate Cox proportional hazards model was used to analyze the significant factors to screen out the independent risk factors affecting the 3- and 5-year overall survival (OS) rate and construct the prediction model. Using the concordance index (C-index) and calibration curve were performed to evaluate the predictive ability of the model.

Results: The results of the Cox risk-scale model showed that race, age, marital status, tumor grade, tumor, node, metastasis stage, surgical treatment, chemotherapy, and radiotherapy affected the prognosis of TPBC patients ($P<0.05$) in the training group, and the factors were used to construct a nomogram. The internal and external validation of the nomogram chart indicated that the C-index of the training group was 0.85 [95% confidence interval (CI): 0.836, 0.863] and that of the verification group was 0.833 (95% CI: 0.807, 0.858). The calibration curves of the 2 groups showed that the OS predicted by the model was consistent with the actual survival of the patients.

Conclusions: The prediction model accurately predicted the prognosis of and identified high-risk TPBC patients.

Keywords: Triple-positive breast cancer (TPBC); Surveillance; Epidemiology and End Result database (SEER database); prognostic factors; prediction model

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Introduction

Breast cancer is the most common malignant tumor affecting women worldwide, and its morbidity and mortality have been increasing annually; it poses a serious threat to women's health (1). As a special luminal B subtype, triple-positive breast cancer (TPBC) is characterized by the positive expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2), and accounts for about 10% of all breast cancer cases (2). It is pathologically characterized by infiltrating ductal carcinoma with complex karyotype. The most common histological grading is grade II and grade III (3). Vascular invasion and lymph node metastases are common in patients with TPBC, and the most likely site of distant metastasis is bone (4). Previous study has shown that the prognosis of TPBC patients is closer to that of patients with luminal A type and lower than that of patients with HER-2-positive type breast cancer (5). HER-2-positive patients often present with a low hormone receptor (HR) status, and patients with higher HER-2 expression have a worse prognosis. Notably, HR expression is inversely related to the prognosis of patients. Age, menopausal status at diagnosis, histological type of cancer, grade of primary tumor, and stage of diagnosis are important factors affecting the prognosis of TPBC patients (6).

In general, the proportion of breast cancer patients with TPBC is not small, but we found that there are few studies and reports on TPBC, and the total sample size was small, making the results unreliable. Currently, nomograms have been developed for the majority of cancer types (7-9), there is no prognostic model for patients with TPBC, so it is of great significance to understand the prognostic factors affecting the survival of patients with TPBC and establish a model to predict the prognosis of patients with TPBC.

In this study, we used the Surveillance, Epidemiology and End Result (SEER) database, established by the National Cancer Institute, which is also one of the most representative large tumor registries in North America, to gather valuable first-hand data (10). We extracted the data of TPBC patients from 2010 to 2016, analyzed the prognostic factors associated with TPBC, and established a prediction model to distinguish high-risk groups and guide clinicians in making treatment decisions. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3560/rc).

Methods

Patient eligibility and clinical features

This study took TPBC patients in SEER database as the research object, and established a prediction model to predict the prognosis of TPBC patients. Patients diagnosed with TPBC between 2010 to 2016 were identified from the SEER*Stat (version 8.3.8) database. Patients were eligible for inclusion in the study if they met the following inclusion criteria: (I) were diagnosed in the period of 2010 to 2016; (II) had a pathological diagnosis of infiltrating ductal carcinoma of the breast (8,500/3); and (III) were ER-, PR-, and HER-2-positive. Patients were excluded from the study if they met any of the following exclusion criteria: (I) were male; (II) had a survival period of 0 months; (III) had a non-primary cancer; (IV) were aged <18.5 years; and/or (V) had incomplete follow-up data. Overall survival (OS) is defined as the time from diagnosis of breast cancer to death from any cause. Clinical death was the end point of follow-up until December 31, 2016. Since any information in the SEER database does not require explicit consent from the patients, our study was not subject to the ethical approval requirements of the institutional review board. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data on the following clinical characteristics were collected: race, age, marital status, operation, chemotherapy, radiotherapy, survival status, survival time, etc. The tumor characteristics included were tumor grade, T stage, N stage, and M stage. The TNM staging of the tumors was performed according to the Staging System of the American Joint Committee on Cancer (AJCC, version 7). In relation to race, "Other" stands for American Indian/Alaskan Native or Asian/Pacific Islander.

Statistical analysis

Cases with missing data were removed directly using Excel 2007. The statistical analysis was performed using SPSS 18 software and R language (4.0.3). The sample function in R language software (4.0.3) was used to conduct a simple random sampling of the data. The data were divided into the training group (70%) and the verification group (30%). The Cox proportional hazards regression model was used to analyze the factors affecting the survival prognosis of patients in the training group, and factors with a P value <0.05 in the single-factor analysis were included in the multi-

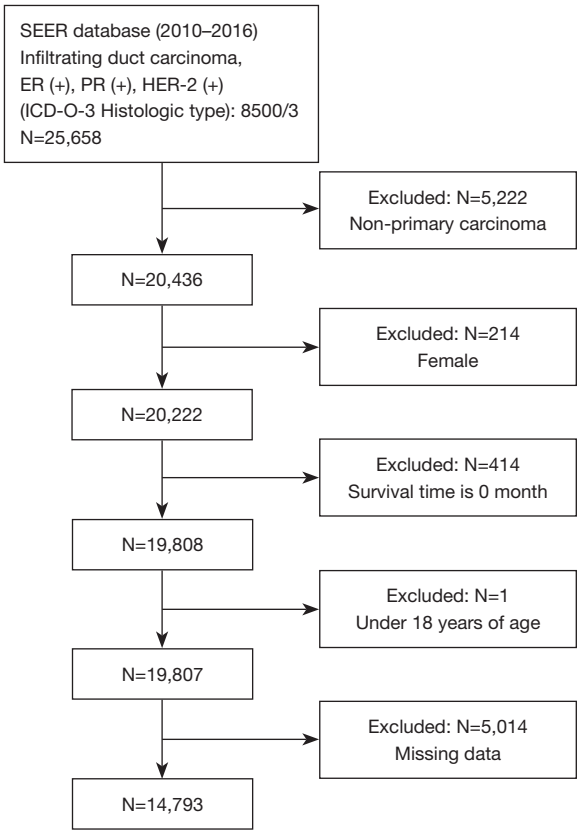

Figure 1 Diagram of the process used to exclude patients. SEER, Surveillance, Epidemiology and End Result; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

factor analysis to determine the final independent prognostic factors. The "RMS" package in R language was used to build a nomogram prediction model, calculate the concordance index (C-index) value, and draw the calibration curve. The internal validation of performance was estimated using the bootstrapping method (with 1,000 replications) (11).

Results

Patients' baseline characteristics

A total of 25,658 patients diagnosed with TPBC were enrolled in this study between 2010 and 2016, and for various reasons, 10,865 patients were excluded. Ultimately, 14,793 TPBC patients were deemed eligible for inclusion in the study. A filter flow chart of the study's process is shown in *Figure 1*. We selected extracted clinical data based on clinical observation and previous literature, including: race, age, marital status, tumor grade, tumor, node, metastasis stage, surgical treatment, chemotherapy, and radiotherapy. The clinicopathological characteristics of the training and validation sets are shown in *Table 1*. The median survival time for TPBC patients was 38 months in both the training and verification groups. During the follow-up period, a total of 1,193 patients died, of whom 874 patients were in the training group and 318 were in the verification group.

Independent prognostic factors in the training set and the construction of the nomogram

A training set was used to establish the nomogram. *Table 2* shows the results of the univariate and multivariate analyses for the potential predictors of OS. Race, age at diagnosis, marital status, breast cancer subtype, grade, T stage, N stage, M stage, radiation, chemotherapy, and surgery were found to be significant risk factors affecting OS in the univariate analysis. The multivariate analysis showed that the above factors were independent predictors of survival (*Table 2*). The independent factors were used to build a nomogram for predicting 3- and 5-year OS (*Figure 2*).

Nomogram validation

The nomogram map was validated internally and externally using the bootstrap method, and the number of self-sampling times was B =1,000. The validation results showed that the C-index of the training group was 0.85 [95% confidence interval (CI): 0.836, 0.863], while the C-index of the verification group was 0.833 (95% CI: 0.807, 0.858). A higher C-index indicates more accurate prognostic prediction (12). The correction lines of the 3- and 5-year survival rates of the modeling group and the verification group are shown in *Figure 3*. As *Figure 3* shows, the correction curves of the modeling group and the verification group are close to the ideal 45° dotted line, indicating a good consistency between the predicted value and the actual value (13). A score for each of the clinical pathological features of a TPBC patient can be obtained by projecting the patient's score upwards onto a small scale and summing the scores to obtain a total score, the higher the total score, the worse the survival prognosis, and the lower the OS rate at 3 and 5 years (14).

Discussion

Currently, the TNM staging system is the most commonly

Table 1 Basic demographic and clinical characteristics of patients with triple positive breast cancer

Characteristics	Training cohort (n=10,397)	Validation cohort (n=4,396)
Race, n (%)		
White	8,008 (77.0)	3,348 (76.2)
Black	1,206 (11.6)	544 (12.4)
Other	1,183 (11.4)	504 (11.5)
Age, n (%)		
18–39	1,175 (11.3)	506 (11.5)
40–59	5,331 (51.3)	2,252 (51.2)
60–79	3,351 (32.2)	1,436 (32.7)
≥80	540 (5.2)	202 (4.6)
Marital status, n (%)		
Yes	6,268 (60.3)	2,653 (60.4)
No	4,129 (39.7)	1,743 (39.6)
Grade, n (%)		
I–II	4,943 (47.5)	2,145 (48.8)
III–IV	5,454 (52.5)	2,251 (51.2)
T stage, n (%)		
T0–1	5,101 (49.1)	2,189 (49.8)
T2	4,019 (38.7)	1,688 (38.4)
T3	748 (7.2)	305 (6.9)
T4	529 (5.1)	214 (4.9)
N stage, n (%)		
N0	6,139 (59.0)	2,514 (57.2)
N1	3,112 (29.9)	1,379 (31.4)
N2	721 (6.9)	313 (7.1)
N3	425 (4.1)	190 (4.3)
M stage, n (%)		
M0	9,087 (87.4)	4,175 (95.0)
M1	590 (5.7)	221 (5.0)
Surgery, n (%)		
Yes	9,531 (91.7)	4,073 (92.7)
No/unknown	866 (8.33)	323 (7.3)
Radiation, n (%)		
Yes	5,133 (49.4)	2,190 (49.8)
No/unknown	5,264 (50.6)	2,206 (50.2)
Chemotherapy, n (%)		
Yes	7,839 (75.4)	3,335 (75.9)
No/unknown	2,558 (24.6)	1,061 (24.1)
Vital status, n (%)		
Alive	9,253 (89.0)	4,078 (92.7)
Dead	874 (8.4)	318 (7.3)

Table 2 Univariate and multivariate analyses of cancer-specific survival in the training cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Race				
White	Reference		Reference	
Black	1.58 (1.32, 1.89)	<0.01	1.39 (1.03, 1.86)	0.02
Other	0.74 (0.58, 0.94)	0.017	0.58 (0.37, 0.91)	0.01
Age, years				
18–39	Reference		Reference	
40–59	0.85 (0.65, 1.11)		1.25 (0.76, 2.07)	0.37
60–79	1.82 (1.40, 2.37)	<0.01	2.68 (1.63, 4.39)	<0.01
≥80	9.25 (7.02, 12.17)	<0.01	11.71 (6.97, 19.69)	<0.01
Marital status				
Yes	Reference		Reference	
No	2.32 (2.03, 2.66)	<0.01	2.50 (2.00, 3.13)	<0.01
Grade				
I + II	Reference		Reference	
III + IV	1.24 (1.08, 1.42)	<0.01	1.38 (1.108, 1.73)	0.04
T stage				
T0–1	Reference		Reference	
T2	2.29 (1.94, 2.71)	<0.01	2.47 (1.88, 3.25)	<0.01
T3	3.83 (3.05, 4.81)	<0.01	2.38 (1.92, 3.19)	<0.01
T4	9.78 (8.00, 11.94)	<0.01	10.98 (7.94, 15.1)	<0.01
N stage				
N0	Reference		Reference	
N1	1.83 (1.57, 2.14)	<0.01	1.72 (1.33, 2.22)	<0.01
N2	2.75 (2.22, 3.40)	<0.01	2.66 (1.87, 3.79)	<0.01
N3	4.84 (3.90, 6.00)	<0.01	4.68 (3.29, 6.67)	<0.01
M stage				
M0	Reference		Reference	
M1	9.06 (7.80, 10.52)	<0.01	8.97 (6.99, 11.51)	<0.01
Surgery				
Yes	Reference		Reference	
No/unknown	7.69 (6.65, 8.89)	<0.01	8.7 (6.84, 11.1)	<0.01
Radiation				
Yes	Reference		Reference	
No/unknown	1.94 (1.69, 2.23)	<0.01	1.83 (1.46, 2.30)	<0.01
Chemotherapy				
Yes	Reference		Reference	
No/unknown	2.57 (2.25, 2.94)	<0.01	2.29 (1.84,2.87)	<0.01

CI, confidence interval; HR, hazard rate.

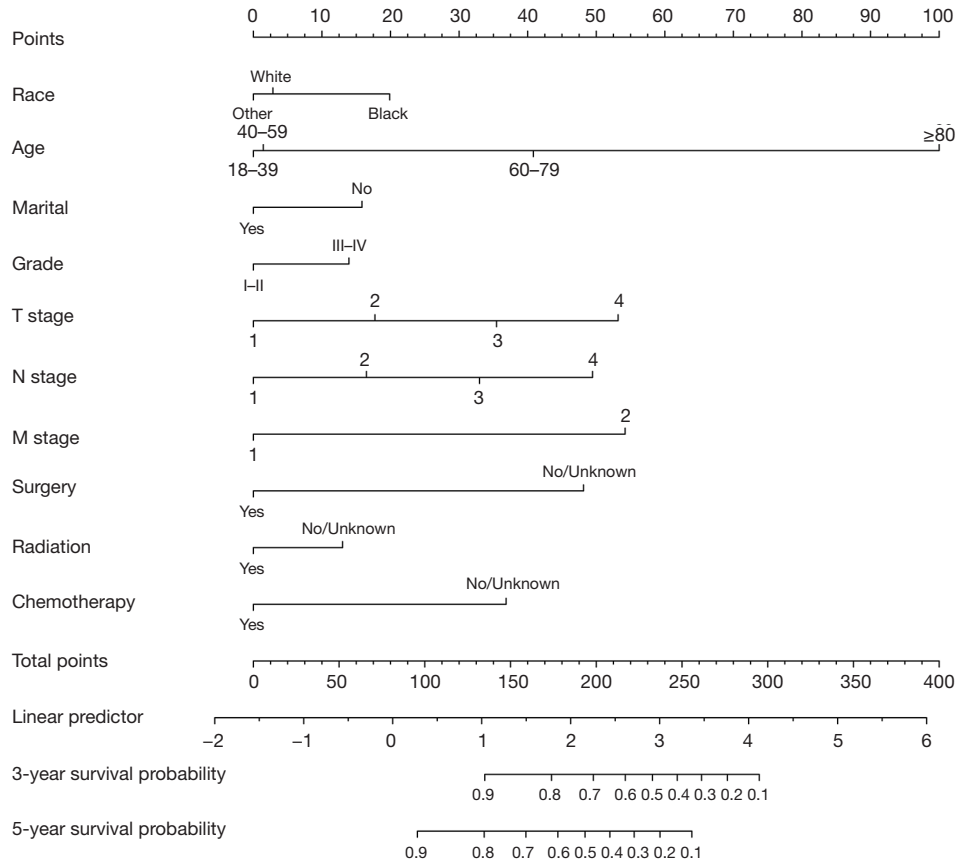

Figure 2 Nomogram to predict the 3- and 5-year OS of TPBC patients. Notes: A vertical line between each variable and points scale can be drawn to determine the points of each variable. The predicted survival rate was calculated according to the total points by drawing a vertical line from the Total Points scale to the OS scale. OS, overall survival; TPBC, triple-positive breast cancer.

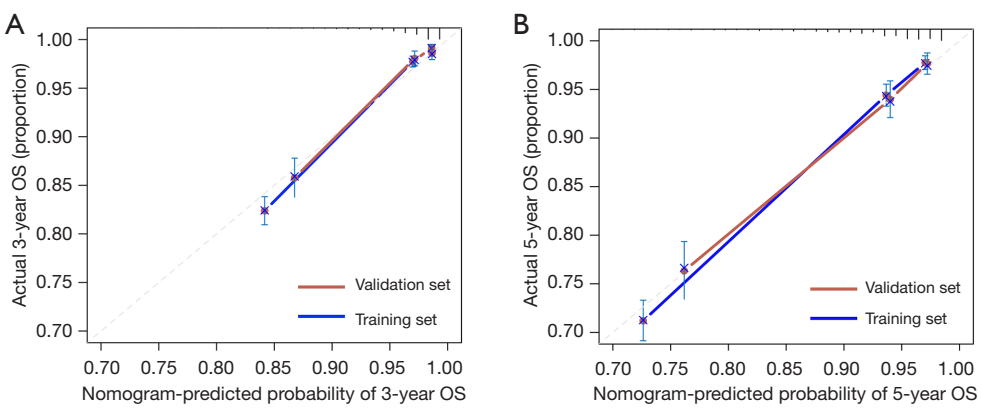

Figure 3 Calibration plots for predictions for the (A) 3- and (B) 5-year OS. The nomogram-predicted probability of OS is plotted on the X-axis, and the actual OS is plotted on the Y-axis. The predictions fall at a diagonal 45 line in the calibration plot, which indicates high prediction accuracy. OS, overall survival.

used method to predict the prognosis of patients (15,16). However, the TNM staging system is not always clinically accurate. A nomogram is a graphical representation of a clinical prediction model, and nomograms are widely used in the prediction of various cancers (17,18). Just like a scoring system, nomograms can also be used to calculate total scores based on the values of individual's predictive variables, and the probability is calculated based on the total score (19). In most cancers, nomograms are more accurate than the TNM staging system at predicting prognosis (20). As one of America's largest tumor registration database currently, the SEER database contains a large number of data of evidence-based medicine, including details of the basic situation of patients, the tumor size, the primary lesion, the treatment and follow-up situation, and the cause of death. Evidence-based clinical research provides evidence to support patient treatment. Thus, this study developed a prognostic prediction model for TPBC patients based on data from the SEER database.

TPBC is characterized by the positive expression of ER, PR, and HER-2, and accounts for about 10% of all breast cancer cases. Compared to other types of breast cancer, relatively few clinical studies on TPBC have currently been conducted. However, both basic and clinical studies suggest that it may be a subtype of interest in the classification and treatment of breast cancer and deserves further exploration (21). The prognosis of TPBC is slightly worse than that of HR (+) /HER-2 (–) patients, which is in turn better than that of patients with overexpressed HER-2. Among patients with advanced breast cancer, patients with TPBC have a better prognosis than patients with HR-/HER2+ (22).

To date, no reliable predictive model has been developed to predict the survival of TPBC patients. Thus, we developed a nomogram using a Cox regression model to the predict the 3- and 5-year OS of TPBC patients. The C-Index and calibration curve revealed that the nomogram could accurately predict the OS of TPBC patients. The univariate analysis suggested that race, age, marital status, tumor grade, T stage, N stage, M stage, surgery, chemotherapy, and radiotherapy were all independent risk factors affecting the survival rate of patients with TPBC. These independent risk factors were basically consistent with clinical observations.

Age has always been regarded as an independent risk factor affecting the prognosis of breast cancer patients. The results of this study showed that TPBC patients aged >60 years had a poor prognosis, and the older they were, the worse their prognosis (23,24). Conversely, patients aged <60 years had a better prognosis.

Previous study has confirmed that marital status can influence the incidence of breast cancer, and our results are consistent with those of previous study (25). This may be because women with terrible marital status often present with disorders of the endocrine system, high cortisol levels, an altered internal environment, and impaired anti-tumor function (26). The results of this study also suggested that black women have a poorer prognosis than white women and women from other racial groups. This finding has been reported previously (27,28).

In relation to TNM stage, most of the TPBC patients were in the T0–1, N0–1, and M0 stages, indicating that the TPBC patients were in the early stages at the time of their initial diagnoses. We also observed that TNM staging had a strong effect on OS. Further, we found that surgery, chemotherapy, and radiotherapy affected the prognosis of patients with TPBC. Notably, there was no significant difference in the survival of patients who received surgery and those who did not. This suggests that surgery is an effective treatment for patients with TPBC. Research has shown that there is no significant difference in the survival rate of patients with TPBC after breast preservation and total mastectomy (29).

At present, the main adjuvant therapy for TPBC is chemotherapy combined with targeted therapy, followed by endocrine therapy. Compared to ER-PR-HER2+ breast cancer, TPBC is less invasive and HER-2 expression levels are lower (30). Among all TNBC patients, male patients have a higher aggressiveness and are more likely to have metastases than female patients (31). Trastuzumab is a key treatment strategy for TPBC patients and is also the first-line treatment option for relapsed and metastatic patients. Recent studies suggest that the high expression of STC2, BCL2, and CDCA8 indicates a relatively good prognosis for TPBC patients. However, there is relatively little benefit from trastuzumab treatment (32). Previous study has shown that HR and a HER-2 status affect the treatment outcomes of TPBC patients. An ER level of 30% or higher, to chemotherapy reactivity is reduced, the joint by trastuzumab can improve the resistance to chemotherapy sensitivity, but when ER expression is >50%, the joint by trastuzumab resistance to treatment for patients with 5 years of PFS shows no obvious change, which may be related to its HER-2 and ER signaling pathways between cross-talk is related to the role (33).

The constructed nomogram showed good discrimination and performance. However, our study still had some

limitations. First, 10,865 of the initially identified 25,658 patients were excluded due to a lack of data, which may have a led to selection bias. Second, we did not include detailed treatment details, such as the surgical methods, and chemotherapy regimens. Third, several prognostic factors (e.g., fertility history, lactation history, and Ki-67 expression) were lacking. Fourth, the constructed nomogram was based on a set of reviews and needs to be further validated in prospective clinical trials. Despite these limitations, the prognostic nomogram presents an effective model for the accurate prediction of survival outcomes for TPBC patients.

To sum up, the results of this study indicated that race, age, marital status, tumor grade, TNM stage, surgical treatment, chemical treatment, and radiotherapy may be the major affecting factors the prognosis of TPBC patients. Early surgical interventions can lead to a relatively good long-term survival prognosis for patients. The predictive OS nomogram established in this study, the predictive performance and clinical application of which was evaluated by the C-index and calibration curve, effectively predicted the 3- and 5-year OS of TPBC patients in this data set, and accurately stratified their risk; thus, it may assist surgeons in making clinical decisions.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3560/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3560/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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. Since any information in the SEER database does not require explicit consent from the patients, the study was not subject to the ethical approval requirements of the institutional review board. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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