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BRIEF REPORT

Assessment of the prognostic and discriminating value of the novel bioscore system for breast cancer; a SEER database analysis

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Abstract
Background An updated bioscore has been proposed within the context of the 8th edition American Joint Committee on Cancer (AJCC) staging system for breast cancer. This study seeks to validate the discriminating value of this bioscore among non-metastatic breast cancer patients registered within the surveillance, epidemiology, and end results (SEER) database.
Methods Through SEER*Stat program, SEER database (2010–2013) was accessed and bioscore was formulated for each patient. Overall and cancer-specific survival analyses according to both bioscore and AJCC pathological stages were conducted through Kaplan–Meier analysis/log-rank testing, and multivariate analysis was conducted through a Cox proportional model.
Results A total of 181030 patients with non-metastatic, surgically treated breast cancer were identified in the period from 2010 to 2013. For overall and cancer-specific survival assessment according to the bioscore system, *P* values for pairwise comparisons among different score points were significant ($P < 0.0001$) except for the comparison between score 0 and score 1. For cancer-specific survival assessment according to the AJCC stages, P values for pairwise comparisons among different stages were significant ($P < 0.0001$) except for the comparison between stages IIIB and IIIC. For overall survival assessment according to the AJCC stages, P values for pairwise comparisons among different stages were significant ($P < 0.001$) except for the comparison between stages IA and IB. In a multivariate analysis, the following factors were associated with better cancer-specific survival (earlier stage disease, ER positivity, PR positivity, Her2 neu positivity, and nuclear grade) ($P < 0.0001$).
Conclusion The current analysis confirms the prognostic utility of the bioscore system and suggests it may be incorporated into decision-making algorithms for non-metastatic breast cancer.

Keywords Breast cancer · Prognosis · AJCC · SEER

Introduction

Almost one and half million cases of breast cancer were estimated to occur in 2012 according to globocan 2012 [1]. This makes breast cancer the second most common cancer in the world as well as the most common cancer among women both in developed and developing countries. Moreover, breast cancer is the 5th leading cause of cancer mortality, and while it is the first cause of cancer death among women living in developing countries, it is the second most common cause of death among women living in developed countries (after lung cancer) [2].

Treatment algorithms for breast cancer have incorporated a number of domains, namely, tumor domain (anatomical stage and biology) and patient domain (performance, age, and co-morbidity) [3]. The most commonly used staging system for breast cancer is the Tumor/Node/Metastasis (TNM)/American Joint Committee on Cancer (AJCC) system. Successive editions of this staging system have been released reflecting the advances in our knowledge of breast cancer prognosis and treatment approaches [4]. Despite the advances in understanding breast cancer biology, the AJCC breast cancer staging system has been

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restricted on anatomical/pathological description of the disease with no reference to tumor biology. Numerous publications suggested that within the same anatomical stage for breast cancer, different biological phenotypes may alter the prognosis [5]. Accordingly, the integration of both anatomical and biological classification into one staging system was an unmet need.

The MD-Anderson breast cancer team has proposed in 2011 a novel staging model for non-metastatic breast cancer patients treated with upfront surgery [6]. This proposed system incorporated grade and estrogen receptor (ER) status, and it provided a refined look to breast cancer staging. However, it did not include assessment of Her2 neu status as a portion of the patients evaluated in that model was in the pre-adjuvant trastuzumab era (1997–2006). More recently, an update of this model has been published within the context of the 8th AJCC staging system for breast cancer [7]. This update incorporated anatomical staging in conjunction with ER, Her2 neu and nuclear grade. It gives a score for each element of the above elements and a total "bioscore" for each patient according to these parameters (Table 1). Validation data for this updated model have been recently and concisely published within the context of discussion of AJCC 8th edition for breast cancer. However, these validation data were only based on MD-Anderson institutional database from 2007 to 2013 (incorporating only 3327 patients). Thus, it was fundamental to further validate the prognostic performance of this model within a larger scale cohort before it can be endorsed to clinical practice. Given the high quality and broad coverage of the surveillance, epidemiology, and end results (SEER) database, it was considered a good option for such a validation study.

Table 1 MD-Anderson prognostic bioscore system for breast cancer (As reported in Guiliano et al.)

Factor	Bio\score points assigned
Pathologic stage	
IA/IB	0
IIA	1
IIB	2
IIIA	3
IIIC	4
Estrogen receptor	
Positive	0
Negative	1
Her2 neu	
Positive	0
Negative	1
Nuclear grade	
1	0
2	0
3	1

Objective

The objective of this study is to assess the prognostic value of the proposed MD-Anderson bioscore for breast cancer in a cohort of patients recorded within the SEER database.

Methods

The cases evaluated in this analysis were extracted from the SEER-18 registry [8]; in order to achieve this, SEER*Stat software (Version 8.3.4) was queried. The date of SEER data submission was November 2015.

Selection of the study cohort

The SEER database search was limited to the duration from 2010 to 2013 (because Her2 status was not routinely recorded before 2010). To identify eligible invasive breast carcinoma patients, the ICD-O-3/WHO 2008 category of "breast" was chosen. The inclusion was further restricted to non-metastatic surgically treated patients. Cases with deficient information about estrogen receptor (ER), progesterone receptor (PR), Her2 neu status, nuclear grade, AJCC 7th stage or survival were excluded.

Data collection

Information extracted for each patient included age at diagnosis, race, gender, ER, PR, HER2 neu, breast cancer subtype, 7th edition T, N, and M stages, AJCC 7th edition stage group, nuclear grade, histological subtype, surgical treatment, radiotherapy, cause-specific death classification, survival months, and vital status. Bioscore was then reconstructed for each patient according to 7th edition AJCC stage, ER, HER2 neu and nuclear grade.

Cancer-specific survival was defined in this study as the time from diagnosis to death from breast cancer. Data about functional status of the patients (e.g., performance score) were not recorded in the SEER database. Data about systemic therapy were not recorded in the SEER database.

Statistical considerations

In this study, Kaplan–Meier analysis and log-rank testing were used for survival comparisons (including both overall survival and cancer-specific survival) according to both AJCC pathological stage and bioscore. Cox proportional hazard model was conducted to produce multivariate

analyses; and hazard ratios with corresponding 95% CI were generated for prognostic factors affecting cancer-specific survival. Statistical significance was declared with the achievement of a two-tailed P value <0.05. All the statistical analyses were performed using SPSS Statistics 20.0 (IBM, NY).

Results

Patients' characteristics

A total of 181,030 patients with non-metastatic, surgically treated breast cancer were identified in the period from 2010 to 2013 and were included into the analysis. Invasive duct carcinoma, not otherwise specified (NOS) represented the majority of cases (75.5%), lobular carcinoma, NOS (9%), and other variants (15.5%). The most frequent age group was 40–69 years (67.2%), followed by the group of >69 years (28.3%), while the age group <40 years was (4.5%). White race represented 80.5%, black race represented 10.2%, and other race groups represented 8.8%, while race was unknown in 0.5%. Male breast cancer represented only 0.8%. Distribution of patients according to AJCC stages and bioscore was reported in Table 2. ER was positive in 84% of cases, PR was positive in 73.6%, and HER2 neu was positive in 13.4%. Breast cancer subtype distribution was detailed in Table 2. Nuclear grade was grade 1 in 27.1%, 2 in 43.7%, and 3 in 29.2%. Breast conservative surgery was conducted in 55% of cases and breast (or chest wall) radiotherapy was received in 50.1%; however, technical details about technique or dose of radiotherapy were not available. Systemic therapy information was not available in the SEER database.

Survival outcomes according to AJCC 7th and bioscore systems

Overall and cancer-specific survivals were compared according to both AJCC 7th and bioscore systems. Log-rank testing with pairwise comparisons between all different stages was conducted. For overall and cancer-specific survival assessment according to the bioscore system, P values for pairwise comparisons among different score points were significant ($P < 0.0001$) except for the comparison between score 0 and score 1(Fig. 1a, b).

For cancer-specific survival assessment according to the AJCC 7th edition, P values for pairwise comparisons among different stages were significant ($P < 0.0001$) except for the comparison between stages IIIB and IIIC (Fig. 2a). For overall survival assessment according to the

Table 2 Baseline characteristics of included patients in the cohort ($N = 181,030$)

Parameters	N (%)
Age	
<40 years	8059 (4.5%)
40–69 years	121,723 (67.2%)
>69 years	51,248 (28.3%)
Race	
White	145,662 (80.5%)
Black	18,393 (10.2%)
Others	16,000 (8.8%)
Unknown	975 (0.5%)
Gender	
Female	179,670 (99.2%)
Male	1360 (0.8%)
Histology	
IDC, NOS	136,918 (75.5%)
Lobular carcinoma, NOS	16,279 (9%)
Other variants	27,833 (15.5%)
Pathological AJCC stage	
IA	94,555 (52.2%)
IB	4747 (2.7%)
IIA	41,417 (22.9%)
IIB	20,322 (11.2%)
IIIA	11,832 (6.5%)
IIIB	3017 (1.7%)
IIIC	5140 (2.8%)
Estrogen receptor	
Positive	152,040 (84%)
Negative	28,990 (16%)
Progesterone receptor	
Positive	133,170 (73.6%)
Negative	47,860 (26.4%)
Her2 neu	
Positive	24,294 (13.4%)
Negative	156,736 (86.6%)
Breast subtype	
HR+/Her2−	136,521 (75.4%)
HR+/Her2+	17,247 (9.5%)
HR−/Her2+	7047 (3.9%)
Triple-negative	20,215 (11.2%)
Nuclear grade	
1	49,106 (27.1%)
2	79,194 (43.7%)
3	52,730 (29.2%)
Bioscore	
0	4792 (2.6%)
1	77,587 (42.8%)
2	38,492 (21.3%)
3	27,853 (15.4%)

Table 2 continued

Parameters	*N* (%)
4	18,852 (10.4%)
5	9324 (5.2%)
6	3444 (1.9%)
7	686 (0.4%)
Type of surgery	
Breast conservative surgery	99,592 (55%)
Mastectomy	81,104 (44.8%)
Surgery, NOS	334 (0.2%)
Radiotherapy	
Yes	90,750 (50.1%)
No	82,867 (45.8%)
Unknown	7413 (4.1%)

IDC infiltrating duct carcinoma, *NOS* not otherwise specified, *AJCC* American Joint Committee on Cancer

AJCC 7th edition, P values for pairwise comparisons among different stages were significant ($P < 0.001$) except for the comparison between stages IA and IB (Fig. 2b).

Multivariate analysis for factors affecting cancer-specific survival was conducted (evaluating the following factors: age at diagnosis, AJCC stage, ER, PR, HER2 neu, nuclear grade). The following factors were associated with better cancer-specific survival (earlier stage disease, ER positivity, PR positivity, HER2 neu positivity, and nuclear grade) ($P < 0.0001$) (Table 3).

Discussion

The current study provides an assessment of the prognostic performance of the newly proposed MD-Anderson bioscore system for breast cancer. The current analysis confirms the prognostic utility of this system and suggests it may be incorporated into standard staging and therapeutic decision-making systems for breast cancer.

Potential limitations in this study include: (1) Systemic therapy data (chemotherapy, hormonal therapy, or anti-HER2 therapy) are not available in the SEER database. (2) Data about co-morbidities and performance status are not available; thus, the analysis has been conducted for both cancer-specific and overall survival to eliminate the potential confounding effect resulting from non cancer mortality. (3) Data about genomic biomarkers with potential prognostic impact are not available (e.g., oncotype Dx for luminal patients). (4) Relatively short period of follow-up (2010–2013) which may hide some minor long-term differences between different scores. (5) The bioscore has been devised and evaluated for patients pathologically staged and treated with surgery as an upfront treatment; thus, it is not possible to apply this system to patients clinically staged or to those who were treated with neo-adjuvant treatment before surgery. Alternatively, the Neo-Bioscore model proposed by the same MD-Anderson group and validated by subsequent groups may be working better in this context [9–12].

Overall, the multivariate analysis for factors affecting cancer-specific survival in this study generally goes in line with the recently published results from MD-Anderson

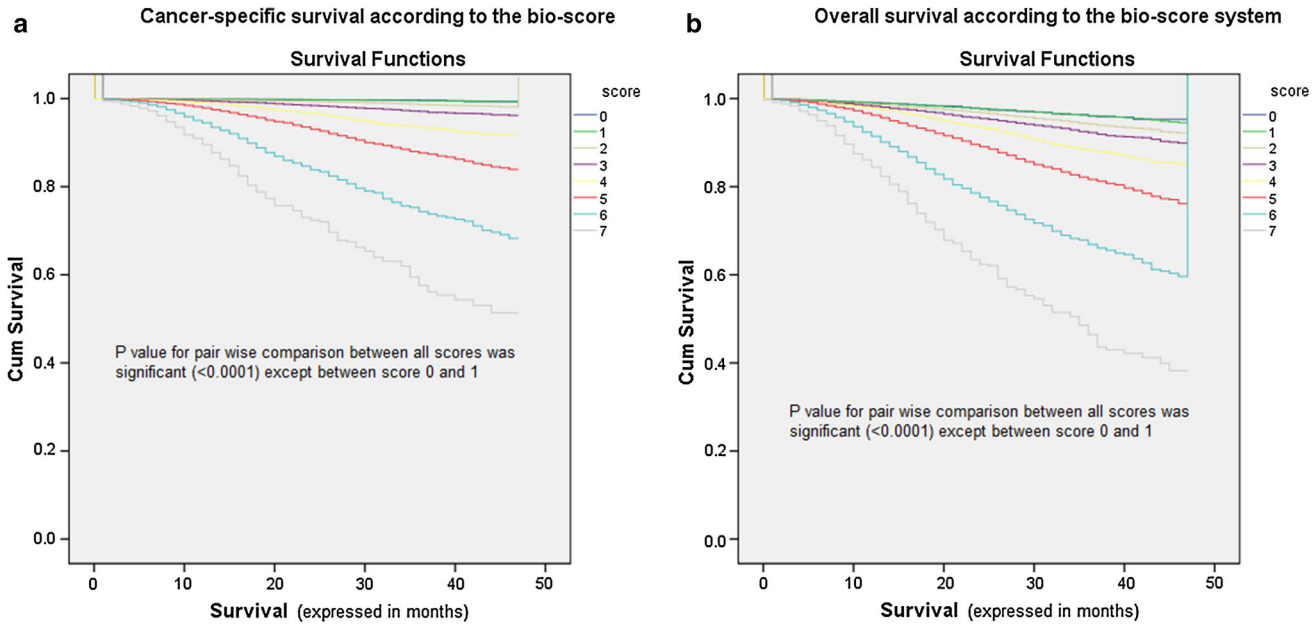

Fig. 1 Kaplan–Meier curve of: **a** Cancer-specific survival according to the bioscore; **b** Overall survival according to the bioscore

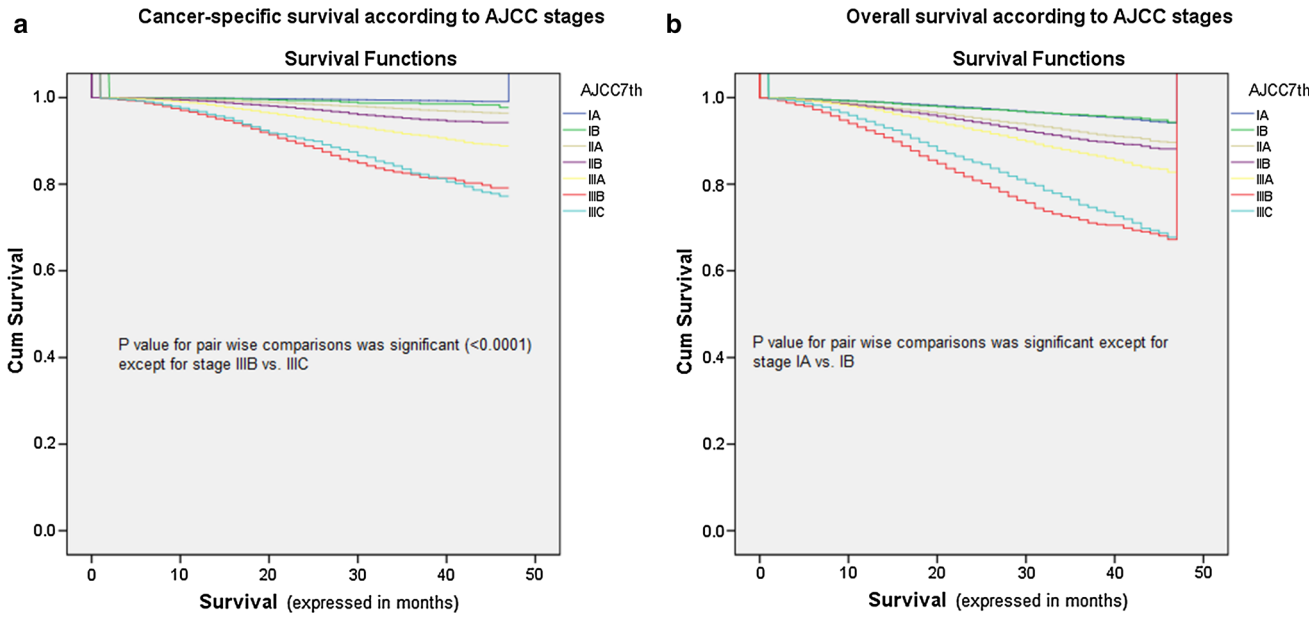

Fig. 2 Kaplan–Meier curve of: **a** Cancer-specific survival according to the 7th edition; **b** Overall survival according to the 7th edition

Table 3 Multivariate analysis for factors affecting cancer-specific survival

Parameter	HR (95% CI)	*P* value
Age		
<40 years	Reference	
≥40 years	1.012 (0.884–1.159)	0.861
AJCC 7th Stage		
IA	Reference	
IB	2.115 (0.493–0.2995)	<0.0001
IIA	2.955 (2.583–3.379)	<0.0001
IIB	5.272 (4.589–6.057)	<0.0001
IIIA	9.935 (8.668–11.386)	<0.0001
IIIB	18.650 (15.933–21.830)	<0.0001
IIIC	19.740 (17.166–22.700)	<0.0001
Estrogen receptor		
Negative	Reference	
Positive	0.543 (0.489–0.603)	<0.0001
Progesterone receptor		
Negative	Reference	
Positive	0.463 (0.416–0.515)	<0.0001
Her2 neu		
Negative	Reference	
Positive	0.553 (0.498–0.613)	<0.0001
Nuclear grade		
I	Reference	
II	1.254 (1082–1.452)	0.003
III	2.274 (1.968–2.628)	<0.0001

HR hazard ratio, *CI* confidence interval

institutional database. The only difference lies in the importance of PR status (which significantly affects cancer-specific survival in the current study, while it did not affect cancer-specific survival in the MD-Anderson study). Possible reason may lie in the huge difference in sample size between both studies (3327 patients in MD-Anderson study vs. 181,030 patients in the current SEER database).

Moreover, the multivariate model in the current study included also age at diagnosis (<40 vs. ≥40 years) which was not significant in multivariate analysis for factors affecting cancer-specific survival. This indicates that age at diagnosis—by itself—should not indicate that the disease has a worse prognosis if other anatomical and biological markers did not indicate so.

Although HER2 positivity has long been considered a marker of more aggressive disease and hence worse outcomes [13], the MD-Anderson data as well as the current SEER data indicate better outcomes for HER2-positive patients. One important caveat for the interpretation of this finding is that the vast majority of HER2-positive patients in both databases have been offered and mostly received adjuvant trastuzumab. This may indicate that in the context of anti-HER2 therapy, HER2-positive status should be considered a good rather than a poor prognostic indicator.

The 8th edition of the AJCC breast cancer staging manual has adopted a dual staging approach, incorporating anatomical stage groups and prognostic stage groups [7]. The anatomical stage groups are similar to the 7th stage groups and are directed to breast cancer global community where additional biomarkers may not be available everywhere. The prognostic stage groups incorporated biomarkers (like ER, PR, HER2 neu, nuclear grade,

Oncotype DX recurrence score in addition to the AJCC stage groups) and they are recommended for reporting patients within the United States. According to the prognostic stage groups, patients with triple-negative phenotype or grade 3 disease were upstaged. The AJCC 8th edition panel discussed also the incorporation of the MD-Anderson bioscore system but declined to adopt it pending large scale validation studies. The current study may provide such a large scale validation study which may support the incorporation of this system into future editions of the AJCC.

Compared to the proposed prognostic stage groups within the 8th AJCC, the bioscore model appears to be a more comprehensive and holistic tool which summarizes all the relevant prognostic factors of the patient in a single number. This shall facilitate reporting and comparison of treatment results among different institutions.

Numerous studies have suggested that incorporation of gene expression profiling (e.g., Oncotype DX) may improve the prognostic prediction of anatomical staging for hormone receptor positive/HER2-negative disease [14–16]. It remains to be seen what added value can be obtained by gene expression profiling when added to the bioscore system.

The current study showed also that AJCC pathological stage groups are still valid prognostic indicators for the outcomes of breast cancer patients. This goes in line with the recommendation of the AJCC panel that in areas of the world where the biomarkers are not available, it is still acceptable to report and compare results through the AJCC stage groups.

In conclusion, the current analysis confirms the prognostic utility of the bioscore system and suggests it may be incorporated into decision-making algorithms for non-metastatic breast cancer. Further studies are needed to evaluate whether gene expression profiling data could add meaningful prognostic information to the bioscore system.

Compliance with ethical standards

Conflict of interest The author declare that they have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

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