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Validation of a Risk Score Incorporating Tumor Characteristics into the American Joint Committee on Cancer Anatomic Stage for Breast Cancer

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Purpose: The American Joint Committee on Cancer 8th edition (AJCC8) prognostic stage (PS) was implemented January 1, 2018, but it is complex due to multiple permutations. A North American group proposed a simpler system using the anatomic stage with a risk score system (RSS) of 1 point each for grade 3 tumor and human epithelial growth factor receptor 2 (HER2) and estrogen receptor (ER) negativity. Here we aimed to evaluate this risk score system with our database of Asian breast cancer patients and compare it against the AJCC8 PS.
Methods: Patients diagnosed with breast cancer stage I–IV in 2006–2012 were identified in the SingHealth Joint Breast Cancer Registry. Five-year breast cancer-specific survival (CSS) and overall survival (OS) were calculated for each anatomic stage according to the risk score and compared with the AJCC8 PS.
Results: A total of 6,656 patients were analyzed. The median follow-up was 61 (interquartile range, 37–90) months. There was a high receipt of endocrine therapy (84.6% of ER+ patients), chemotherapy (84.3% of node-positive patients), and trastuzumab (86.0% of HER2+ patients). Within each anatomic stage, there were significant differences in survival in all sub-stages except IIIB. On multivariate analysis, the hazard ratio for negative ER was 1.74 (1.48–2.06), for negative HER2 was 1.49 (1.26–1.74), and for grade 3 was 1.84 (1.55–2.19). On multivariate analysis controlled for age, ethnicity, and receipt of chemotherapy, the RSS (Akaike information criterion [AIC] = 10,649.45; Harrell's Concordance Index [C] = 0.85) was not inferior to the AJCC8 PS (AIC = 10,726.65; C = 0.84) for CSS, nor was the RSS (AIC = 14,714.4; C = 0.82) inferior to the AJCC8 PS (AIC = 14,784.69; C = 0.81) for OS.
Conclusion: The RSS is comparable to the AJCC8 PS for a patient population receiving chemotherapy as well as endocrine- and HER2-targeted therapy and further stratifies stage IV patients.

Keywords: Biomarkers; Breast neoplasms; Neoplasm staging prognosis; Survival

INTRODUCTION

The 8th Edition of the American Joint Committee on Cancer Staging Manual (AJCC8) was implemented on January 1, 2018. The AJCC8 represented a significant change from previous

Author Contributions

Conceptualization: Wong RX, Wong FY; Data curation: Seow YH, Wong RX, Lim JHC, Lian W; Formal analysis: Seow YH, Wong RX, Lim JHC, Lian W; Investigation: Wong RX, Lian W; Methodology: Wong RX; Project administration: Wong RX, Wong FY; Software: Lim JHC, Lian W; Supervision: Wong RX, Yap YS, Wong FY; Validation: Seow YH, Wong RX, Lim JHC; Visualization: Wong RX, Lian W; Writing - original draft: Seow YH, Wong RX, Yap YS, Wong FY; Writing - review & editing: Seow YH, Wong RX, Yap YS, Wong FY.

editions as it incorporated biological markers into the prognostication of breast cancer [1]. Most validation studies have found that the new AJCC8 prognostic stage (AJCC8 PS) provides more accurate prognostication than the anatomic stage [2-5].

Notwithstanding the advantages provided by the new AJCC8 PS, many authors have expressed concerns regarding the complexity of the new system, which includes over 170 subgroups, making it impractical for routine use without references or electronic aids [5-8].

In 2017, Chavez-Macgregor et al. [9] proposed a simpler alternative to the AJCC8 PS in patients with breast cancer. The risk score system (RSS) calculated a risk score based on estrogen receptor (ER) status, human epithelial growth factor receptor 2 (HER2) receptor status, and tumor grade that was then incorporated into the anatomic stage for prognostication. Each anatomic stage would have 4 separate sub-stages with scores of 0–3. The authors verified the RSS using data from 43,938 patients in the California Cancer Registry and concluded that it provided accurate prognostic information. However, this alternative system has not yet been compared with the AJCC8 PS.

The present study was undertaken to determine the validity of the RSS, which has not been done using an external dataset at the time of this writing of this article, and explore the usefulness of the RSS compared to the AJCC8 PS.

METHODS

Study population

Patient information was obtained from the Singhealth Joint Breast Cancer Registry, a prospectively maintained database of patients from Singapore Health Services, a multi-institutional healthcare organization.

Patients diagnosed with invasive breast cancer between January 1, 2006, and December 31, 2014, were identified. This period was selected as routine HER2 testing and treatment with trastuzumab started in 2006. Patients for whom data were incomplete for ER status, HER2 receptor status, or tumor grade were excluded (n = 644). Those for whom data were missing for follow-up time, prognostic staging, or receipt of chemotherapy were also excluded (n = 114). Patients who received neoadjuvant chemotherapy were also excluded. Altogether, data for 6,656 patients were analyzed.

We defined ER, PR, and HER2 positivity in accordance with the recommendations of the 2010 and 2013 American Society of Clinical Oncology/College of American Pathologists [10,11].

Cancer-specific survival (CSS) was defined as the time from diagnosis to death from breast cancer, and deaths from other causes were assessed at the last follow-up. Overall survival (OS) was defined as time from diagnosis to death from any cause and assessed at the last follow-up.

Statistical analysis

Descriptive statistics were used to evaluate the characteristics of the study population.

A Cox proportional hazards model was used to identify factors independently associated with survival. The variables included were based on those previously identified by Chavez-

Table 1. Chavez-Macgregor et al. [9] risk score system components

Factors	Risk score assigned
Tumour grade	
1	0
2	0
3	1
ER status	
ER+	0
ER−	1
HER2 receptor status	
HER2+	0
HER2−	1

ER = estrogen receptor; ER+ = estrogen receptor positive; ER− = estrogen receptor negative; HER2 = human epidermal growth factor receptor 2; HER2+ = human epidermal growth factor receptor 2 positive; HER2− = human epidermal growth factor 2 negative.

Macgregor et al. [9] (anatomic stage, ER receptor status, HER2 receptor status, tumor grade, age, ethnicity, and treatment received).

Patients were classified according to their anatomic stage based on the 7th edition of the AJCC [12]. Risk scores for each patient was calculated as per the method followed by Chavez-Macgregor et al. [9]: 1 point was allocated each for ER receptor-negative status, HER2 receptor-negative status, and grade 3 tumor (**Table 1**). These points are totaled for the calculation of a risk score of 0–3. Patients in each anatomic stage were thus subdivided into 4 ordinal categories (risk score, 0–3). Survival analysis was performed for CSS and OS using the Kaplan-Meier method based on the anatomic stage and risk score. Log-rank tests were then performed to identify differences between the categories (risk score, 0–3) at each anatomical stage.

Akaike information criterion (AIC) and Harrell's concordance index (C-index) were used to compare the RSS and the AJCC8 PS. Adjustments were made for age, ethnicity, and receipt of chemotherapy since these factors affect survival outcomes [13-15].

The level of significance was set at 5% for all statistical tests. All statistical analyses were performed using STATA 15.0 (StataCorp LLC, College Station, USA).

Ethics statement

All procedures performed in studies involving human participants were done so in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Singapore Health Services Institutional Review Board (reference number 2017/2375). The institutional review board waived the need for informed consent due to the retrospective nature of this study.

RESULTS

Population characteristics

We analyzed a total of 6,656 patients from our database. Their clinicopathological characteristics are listed in **Table 2**. The median patient age at diagnosis was 54 (range, 19–97) years. The median follow-up was 61 (range, 0.1–43.0) months. Ductal carcinoma was the most common histology in the study cohort (87.0%). Overall, 64.0% of patients received chemotherapy and 84.3% of node-positive patients received adjuvant chemotherapy. Hormone receptor (HR) +/HER2− was the

Table 2. Patient characteristics and treatment information

Characteristics	Number of patients (n = 6,656)
Age (yr)	
< 40	595 (8.9)
≥ 40, < 50	1,772 (26.6)
≥ 50, < 60	2,119 (31.8)
≥ 60, < 70	1,397 (21.0)
≥ 70, < 80	641 (9.6)
≥ 80	132 (2.0)
Ethnicity	
Chinese	5,047 (75.8)
Malay	679 (10.2)
Indian	345 (5.2)
Others	585 (8.8)
Histological grade	
G1	962 (14.5)
G2	2,490 (37.4)
G3	3,204 (48.1)
Histology	
Ductal	5,794 (87.0)
Lobular	316 (4.7)
Others	546 (8.2)
Receptor status	
HR+/HER2+	1,014 (15.2)
HR+/HER2−	4,296 (64.5)
HR−/HER2+	626 (9.4)
TNBC	720 (10.8)
Risk score	
0	330 (5.0)
1	3,519 (52.9)
2	2,089 (31.4)
3	718 (10.8)
Surgery	
Mastectomy	4,216 (63.3)
Breast conserving surgery	2,258 (33.9)
No surgery	182 (2.7)
Axillary LN surgery	
Sentinel lymph node biopsy only	2,446 (36.7)
No	189 (2.8)
Axillary clearance	3,454 (51.9)
Axillary sampling	489 (7.3)
Unknown	78 (1.2)
Chemotherapy	
No	2,393 (36.0)
Yes	4,263 (64.0)
Chemotherapy (for node positive)	
No	434 (15.7)
Yes	2,325 (84.3)
Endocrine therapy	
No	345 (6.9)
Yes	4,252 (84.6)
Unknown	428 (8.5)
Targeted therapy	
No	176 (13.6)
Yes	1,116 (86.0)
Unknown	5 (0.4)

All data are presented as number (%).
HR = hormone receptor; HR+ = hormone receptor positive; HR− = hormone receptor negative; HER2 = human epidermal growth factor receptor 2; HER2+ = human epidermal growth factor receptor 2 positive; HER2− = human epidermal growth factor 2 negative; LN = lymph node.

most common tumor subtype (64.5%), followed by HR+/HER2+ (15.2%), triple-negative breast cancer (TNBC; 10.8%), and HR−/HER2+ (9.4%). Of the ER+ patients, 84.6% received endocrine therapy, while 86.0% of HER2+ patients who had chemotherapy received targeted therapy. Among our patients, 14.0% (n = 932) had ER+/PR− histology. Of these patients with discordant HR, 9.8% (n = 642) were ER+/PR−/HER2− and 4.4% (n = 290) were ER+/PR−/HER2+.

Survival analysis

Table 3 shows that on performing multivariate Cox regression analysis, anatomic stage, ER status, HER2 status, and tumor grade were independent predictors of both CSS and OS. The hazard ratio for CSS and OS increased with anatomic stage (with reference to anatomic stage I). ER− patients, compared to ER+ patients, had a hazard ratio of 1.74 and 1.62, respectively, for CSS and OS ($p < 0.001$ for both). HER2− patients, compared to HER2+ patients, had a hazard ratio of 1.49 and 1.50, respectively, for CSS and OS ($p < 0.001$ for both). Grade III patients, compared to grade I and II patients, had a hazard ratio of 1.84 and 1.59, respectively, for CSS and OS ($p < 0.001$ for both).

The CSS and OS survival curves for anatomical stages I–IV stratified by risk scores are shown in **Figures 1** and **2**. On performing the log-rank test, the risk score stratified well for all stages ($p < 0.05$) except stage IIIB ($p = 0.062$ for CSS, $p = 0.231$ for OS).

Table 3. Cox proportional hazards model evaluating determinants of CSS and OS amongst patients in this study

Covariate	CSS		OS	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Anatomic stage		< 0.001*		< 0.001*
I	1	-	1	-
IIA	2.15 (1.54–3.00)	< 0.001	1.86 (1.47–2.35)	< 0.001
IIB	4.22 (3.00–5.93)	< 0.001	2.84 (2.2–3.68)	< 0.001
IIIA	5.05 (3.58–7.12)	< 0.001	3.22 (2.47–4.19)	< 0.001
IIIB	5.53 (3.09–9.88)	< 0.001	3.34 (2.06–5.41)	< 0.001
IIIC	9.88 (7.02–13.9)	< 0.001	6.16 (4.74–8.01)	< 0.001
IV	44.89 (32.92–61.2)	< 0.001	26.87 (21.34–33.85)	< 0.001
ER status				
Positive	1	-	1	-
Negative	1.74 (1.48–2.06)	< 0.001	1.62 (1.4–1.88)	< 0.001
HER2 status				
Positive	1	-	1	-
Negative	1.49 (1.26–1.77)	< 0.001	1.50 (1.29–1.74)	< 0.001
Grade				
1, 2	1	-	1	-
3	1.84 (1.55–2.19)	< 0.001	1.59 (1.37–1.83)	< 0.001
Age at diagnosis (yr)		< 0.001*		< 0.001*
< 40	1	-	1	-
≥ 40, < 50	1.00 (0.73–1.38)	0.979	0.97 (0.73–1.28)	0.809
≥ 50, < 60	1.08 (0.80–1.47)	0.611	1.16 (0.88–1.52)	0.298
≥ 60, < 70	1.19 (0.87–1.64)	0.284	1.35 (1.02–1.79)	0.038
≥ 70, < 80	2.21 (1.55–3.14)	< 0.001	2.89 (2.14–3.92)	< 0.001
≥ 80	4.66 (2.88–7.53)	< 0.001	6.45 (4.4–9.46)	< 0.001
Ethnicity		< 0.001*		< 0.001*
Chinese	1	-	1	-
Malay	1.40 (1.13–1.72)	0.002	1.56 (1.30–1.88)	< 0.001
Indian	1.30 (0.96–1.76)	0.088	1.44 (1.11–1.85)	0.005
Others	0.38 (0.23–0.65)	< 0.001	0.63 (0.43–0.92)	0.016
Chemotherapy				
No	1	-	1	-
Yes	1.21 (0.97–1.52)	0.096	1.00 (0.83–1.19)	0.963

CSS = cancer specific survival; OS = overall survival; CI = confidence interval; ER = estrogen receptor; HER2 = human epithelial growth factor receptor 2.
*Based on likelihood ratio test.

A

CSS

Log rank *p* = 0.011

Years

No. at risk						
I risk score 0	47	41	39	34	13	0
I risk score 1	639	542	490	394	206	27
I risk score 2	209	165	147	116	64	4
I risk score 3	83	65	51	43	19	1

B

CSS

Log rank *p* < 0.001

Years

No. at risk						
IIA risk score 0	24	23	17	14	8	0
IIA risk score 1	408	339	296	245	138	11
IIA risk score 2	280	233	203	167	87	5
IIA risk score 3	121	104	88	71	36	2

C

CSS

Log rank *p* < 0.001

Years

No. at risk						
IIB risk score 0	15	12	9	8	5	0
IIB risk score 1	181	158	133	106	37	3
IIB risk score 2	149	120	99	81	43	6
IIB risk score 3	78	66	52	37	20	2

D

CSS

Log rank *p* = 0.002

Years

No. at risk						
IIIA risk score 0	24	20	18	10	7	0
IIIA risk score 1	152	130	111	77	38	5
IIIA risk score 2	131	108	88	75	37	2
IIIA risk score 3	38	28	21	18	10	0

E

CSS

Log rank *p* = 0.062

Years

No. at risk						
IIIB risk score 0	1	1	1	1	1	0
IIIB risk score 1	25	21	19	13	5	0
IIIB risk score 2	21	19	14	9	6	0
IIIB risk score 3	6	5	2	2	1	0

F

CSS

Log rank *p* < 0.001

Years

No. at risk						
IIIC risk score 0	3	3	3	2	0	0
IIIC risk score 1	81	68	53	42	21	0
IIIC risk score 2	126	101	78	56	31	2
IIIC risk score 3	44	33	16	10	3	0

G

CSS

Log rank *p* < 0.001

Years

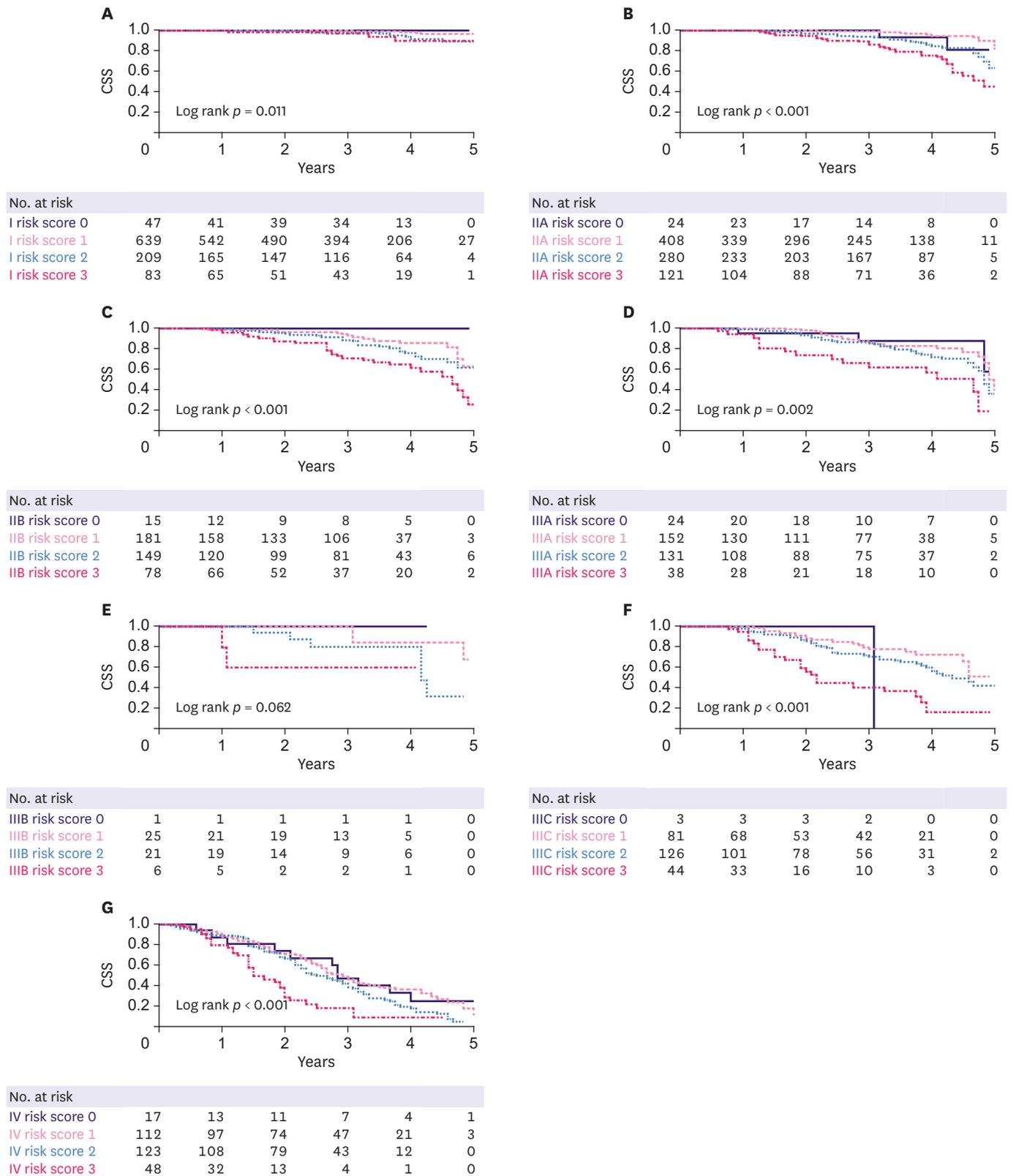| No. at risk						
IV risk score 0	17	13	11	7	4	1
IV risk score 1	112	97	74	47	21	3
IV risk score 2	123	108	79	43	12	0
IV risk score 3	48	32	13	4	1	0

Figure 1. Five-year CSS according to stage (I–IV) stratified by risk score. (a) I, (b) IIA, (c) IIB, (d) IIIA, (e) IIIB, (f) IIIC, (g) IV.
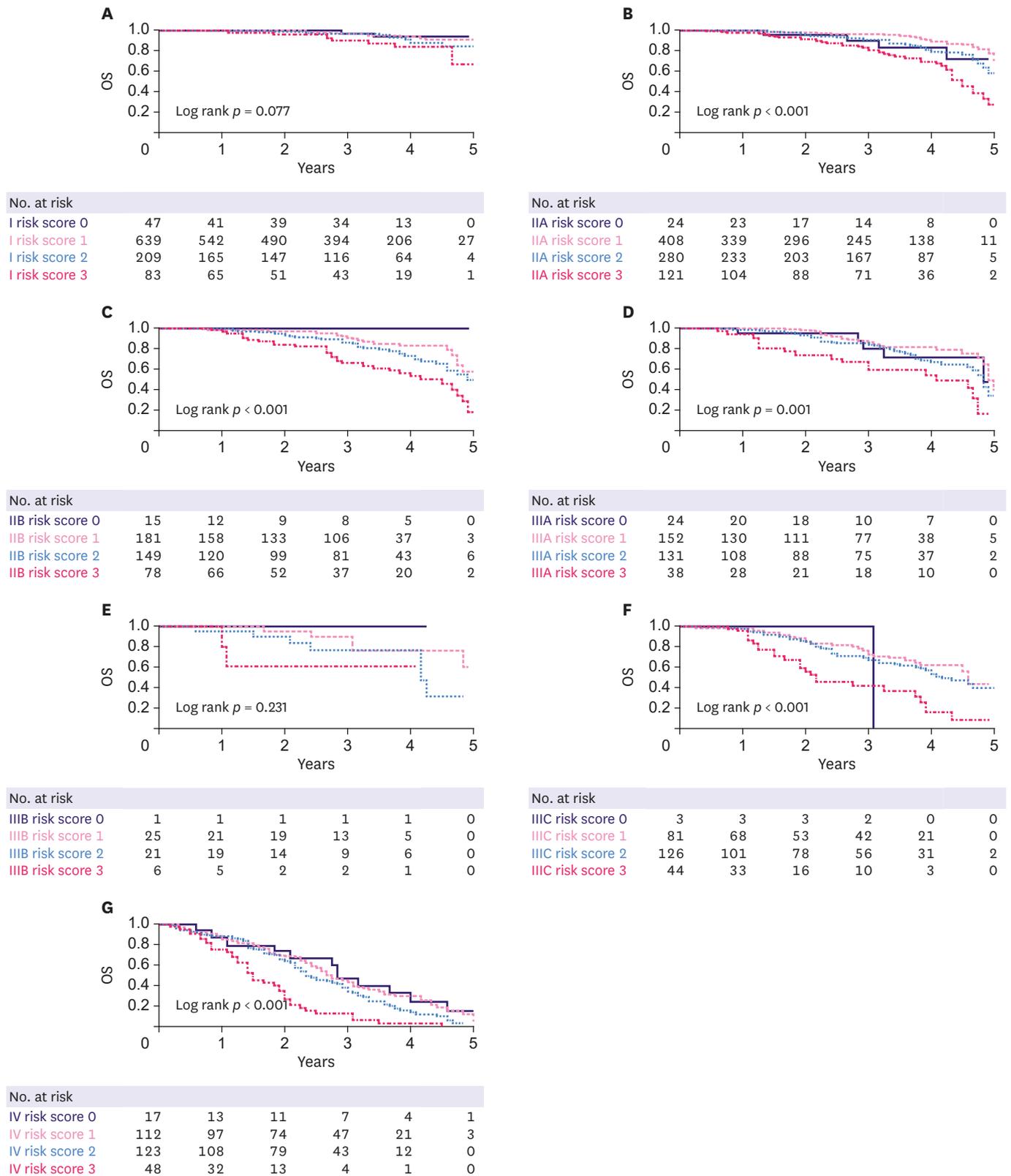CSS = cancer-specific survival.

Figure 2. Five-year OS according to stage (I–IV) stratified by risk score. (a) I, (b) IIA, (c) IIB, (d) IIIA, (e) IIIB, (f) IIIC, (g) IV.
OS = overall survival.

Table 4. Multivariable Cox models for CSS

Clinical variables	Prognostic stage		Anatomic stage + Number of risk factors	
	Hazard ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Anatomic stage				< 0.001*
I	-	-	1	-
IIA	-	-	2.15 (1.54–3.00)	< 0.001
IIB	-	-	4.23 (3.01–5.94)	< 0.001
IIIA	-	-	5.16 (3.67–7.27)	< 0.001
IIIB	-	-	5.61 (3.14–10.02)	< 0.001
IIIC	-	-	10.16 (7.22–14.3)	< 0.001
IV	-	-	45.78 (33.6–62.36)	< 0.001
Prognostic stage		< 0.001*		
I	1	-	-	-
IIA	2.86 (2.18–3.75)	< 0.001	-	-
IIB	4.04 (2.96–5.52)	< 0.001	-	-
IIIA	4.47 (3.33–6.00)	< 0.001	-	-
IIIB	6.30 (4.65–8.53)	< 0.001	-	-
IIIC	12.40 (9–17.09)	< 0.001	-	-
IV	30.75 (24.62–38.41)	< 0.001	-	-
Number of risk factors				< 0.001*
0	-	-	1	-
1	-	-	1.10 (0.76–1.60)	0.619
2	-	-	1.91 (1.32–2.77)	0.001
3	-	-	3.73 (2.52–5.53)	< 0.001
Age at diagnosis (yr)		< 0.001*		< 0.001*
< 40	1	-	1	-
≥ 40, < 50	1.00 (0.73–1.38)	0.989	1.01 (0.74–1.39)	0.938
≥ 50, < 60	1.06 (0.78–1.43)	0.720	1.10 (0.81–1.49)	0.558
≥ 60, < 70	1.19 (0.86–1.63)	0.293	1.21 (0.88–1.66)	0.245
≥ 70, < 80	2.27 (1.60–3.22)	< 0.001	2.26 (1.59–3.22)	< 0.001
≥ 80	4.69 (2.92–7.53)	< 0.001	4.58 (2.83–7.41)	< 0.001
Ethnicity		< 0.001*		< 0.001*
Chinese	1	-	1	-
Malay	1.50 (1.21–1.84)	< 0.001	1.41 (1.15–1.74)	0.001
Indian	1.36 (1.01–1.84)	0.045	1.30 (0.96–1.76)	0.090
Others	0.39 (0.23–0.65)	< 0.001	0.38 (0.23–0.64)	< 0.001
Receipt of chemotherapy				
No	1	-	1	-
Yes	1.49 (1.2–1.86)	< 0.001	1.25 (1.00–1.57)	0.047
AIC	10,726.65		10,649.45	
C-index	0.84		0.85	

CSS = cancer-specific survival; CI = confidence interval; AIC = Akaike information criterion; C-index = Harrell's concordance index.
*Based on likelihood ratio test.

The multivariate Cox model for CSS showed that compared to risk score 0, hazard ratio was 1.10, 1.91, and 3.73 for risk scores of 1, 2, and 3 respectively (**Table 4**). For OS, compared to risk score 0, hazard ratio was 1.28, 1.88, and 3.55 for risk scores of 1, 2, and 3, respectively (**Table 5**). The RSS and AJCC8 PS demonstrated excellent discrimination of CSS and OS for our study cohort. Thus, the RSS (AIC = 10,649.45; C-index = 0.85) is not inferior to the AJCC8 PS (AIC = 10,726.654; C-index = 0.84) for CSS, nor is the RSS (AIC = 14,714.4; C-index = 0.82) inferior to the AJCC8 PS (AIC = 14,784.69; C-index = 0.81) for OS.

Figure 3 displays the hazard ratio estimates for each combination of anatomic staging and risk score produced by a Cox proportional hazards model adjusted for age, ethnicity, and receipt of chemotherapy. This demonstrated that with more risk factors, hazard ratios generally increased within an anatomic stage; however, a patient with a lower stage but more risk factors may have a higher risk of breast cancer-related death than another patient with a higher stage of disease but fewer risk factors.

Table 5. Multivariable Cox models for OS

Clinical variables	Prognostic stage		Anatomic stage + Number of risk factors	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Anatomic stage				< 0.001*
I	-	-	1	-
IIA	-	-	1.86 (1.47–2.36)	< 0.001
IIB	-	-	2.85 (2.21–3.69)	< 0.001
IIIA	-	-	3.28 (2.52–4.27)	< 0.001
IIIB	-	-	3.41 (2.1–5.51)	< 0.001
IIIC	-	-	6.33 (4.87–8.23)	< 0.001
IV	-	-	27.28 (21.67–34.35)	< 0.001
Prognostic stage		< 0.001*		
I	1	-	-	-
IIA	2.17 (1.74–2.7)	< 0.001	-	-
IIB	2.78 (2.13–3.62)	< 0.001	-	-
IIIA	3.27 (2.57–4.16)	< 0.001	-	-
IIIB	4.22 (3.27–5.45)	< 0.001	-	-
IIIC	7.94 (5.99–10.53)	< 0.001	-	-
IV	19.95 (16.66–23.9)	< 0.001	-	-
Number of risk factors				< 0.001*
0	-	-	1	-
1	-	-	1.28 (0.93–1.77)	0.135
2	-	-	1.88 (1.36–2.6)	< 0.001
3	-	-	3.55 (2.52–5.01)	< 0.001
Age at diagnosis (yr)		< 0.001*		< 0.001*
< 40	1	-	1	-
≥ 40, < 50	0.95 (0.72–1.27)	0.734	0.97 (0.73–1.3)	0.855
≥ 50, < 60	1.12 (0.86–1.47)	0.401	1.17 (0.89–1.53)	0.267
≥ 60, < 70	1.33 (1.01–1.76)	0.046	1.37 (1.03–1.81)	0.030
≥ 70, < 80	2.93 (2.17–3.96)	< 0.001	2.93 (2.16–3.96)	< 0.001
≥ 80	6.55 (4.48–9.55)	< 0.001	6.34 (4.32–9.3)	< 0.001
Ethnicity		< 0.001*		< 0.001*
Chinese	1	-	1	-
Malay	1.63 (1.36–1.96)	< 0.001	1.56 (1.3–1.88)	< 0.001
Indian	1.50 (1.17–1.93)	0.002	1.42 (1.1–1.83)	0.007
Others	0.63 (0.44–0.92)	0.017	0.62 (0.43–0.91)	0.013
Chemotherapy				
No	1	-	1	-
Yes	1.18 (0.99–1.4)	0.064	1.01 (0.84–1.2)	0.949
AIC	14,784.69		14,714.40	
C-index	0.81		0.82	

OS = overall survival; CI = confidence interval; AIC = Akaike information criterion; C-index = Harrell's concordance index.
*Based on likelihood ratio test.

DISCUSSION

Our study of a large cohort of Asian breast cancer patients treated between 2006 and 2014 revealed that tumor grade, ER status, and HER2 receptor status were independent predictors of 5-year CSS and OS, supporting their use in the RSS. We further demonstrated that the addition of these risk factors into anatomical staging refines the prognostication of patients with breast cancer. These findings concur with those reported by Chavez-Macgregor et al. [9].

Chavez-Macgregor et al. [9] proposed a potentially simple and effective RSS, but it has not been validated by other datasets worldwide; thus, our study aimed to increase evidence of its usefulness.

To our knowledge, this is the first study comparing the RSS with the AJCC8 PS. Our analysis showed that the RSS is not inferior to the AJCC8 PS. This RSS may be a simpler and more
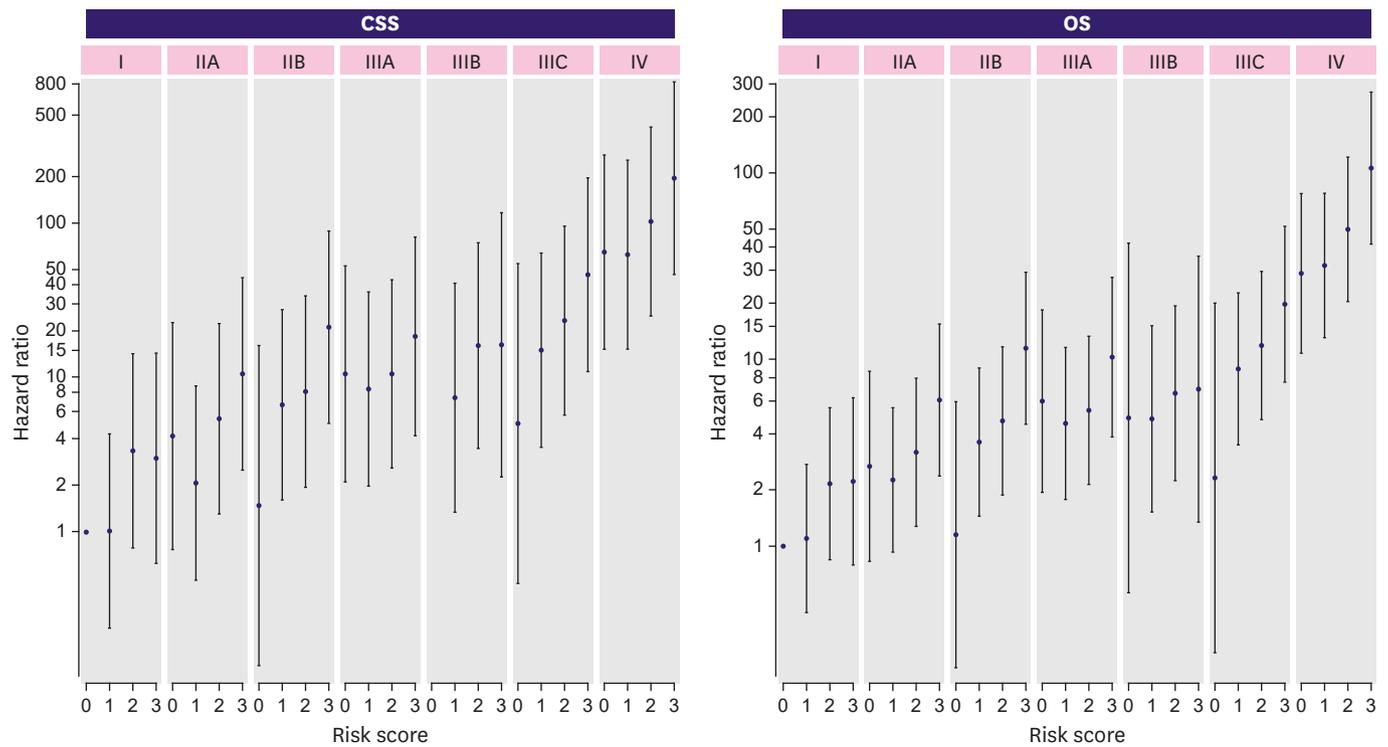
Figure 3. Hazard ratios of breast cancer patients according to stage and risk score. Reference group was stage I risk 0; bars represent 95% confidence intervals. Data are adjusted for age, ethnicity, and chemotherapy.
CSS = cancer-specific survival; OS = overall survival.

user-friendly alternative to the AJCC8 PS with similar discrimination in the prognostication of OS and CSS in breast cancer patients.

Our study did not manage to identify a statistically significant difference between stage IIIB patients. This is likely due to the small number of patients in our cohort with stage IIIB disease (n = 90). However, a visual analysis of the group revealed separation of the survival curves over 5 years.

While we obtained statistically significant results for the stage IIIA group of patients ($p < 0.05$) and there was good graphical discrimination for the first 4 years, stratification appeared to be lost at year 5. This is likely due to the small numbers of patients involved at year 5 (**Figure 1**).

An important distinction of the RSS compared to the AJCC8 PS is that stage IV patients are stratified into different subgroups, whereas these metastatic patients under the AJCC8 PS remain in the same group. This is clinically informative and reflects the observed differences in the survival of patients with metastatic breast cancer of different subtypes. It has been shown that that patients with metastatic disease of the HR+/HER2+ subtype have longer survival than those with the HR−/HER2− subtype [16-18].

As noted earlier, there have been challenges in the routine use of the AJCC8 PS. The RSS has several advantages as an alternative tool. First, it is simple and easy to calculate since it uses basic clinical information. Second, it capitalizes on the extensive knowledge of the anatomic staging system that underpins the common language between medical practitioners. It is simpler to build on this basis by incorporating the risk score into the anatomic stage rather

than the use of a cumbersome application to obtain the new AJCC8 PS. Third, it is easy to communicate risk and treatment to patients using this system. Clinicians can inform patients regarding the number of risk factors they have and could also associate treatment regimens such as endocrine therapy or targeted therapy with the risk factors. Finally, the RSS maintains a similar anatomic staging, allowing for comparison to previous legacy studies and registries.

Unfortunately, the RSS is not without its limitations. It does not incorporate the results of gene expression studies such as Oncotype DX™, unlike the AJCC8 PS [1]. Studies have verified the utility of gene expression studies in refining prognosis with potential implications on treatment [19,20]. This may result in difficulties applying the RSS in patients with the same anatomic score and risk factors but different Oncotype DX™ recurrence scores [21]. However, due to the current limited availability of results from these assays and the absence of long-term results from clinical trials, there is little evidence to guide the use of these assays in relation with risk factors [5]. Our study was limited by the lack of Oncotype DX™ data as well.

PR status was also not included in the current RSS. In our cohort, 14.0% (n = 932) of patients were ER+/PR−. Yi et al. [22] found that the staging system that included anatomic stage, grade, and ER had the highest C-index and lowest AIC. Other prognostic nomograms, the NHS predict for example, do not consider PR status either. On the other hand, the AJCC8 PS considers PR status, and in some circumstances, ER+ but PR− upstages a patient. St Gallens 2013 consensus recommended that ER+/PR−/HER2− patients be classified as luminal B, rather than A, reflecting the expert panel's opinion that ER+/PR− is a more aggressive variant [23,24]. Other studies have also shown that ER+ and PR− tumors generally have poorer outcomes. To complicate matters, Prat et al. [25] showed that more than 20% of PR-positive tumor cells were significant for predicting survival differences among luminal A patients. There is controversy regarding the clinical utility of PR testing. Studies have shown that ER−/PR+ tumors are not reproducible and that PR provides no actionable information for ER+ tumors such as reported by Hefti et al. [26]. It is beyond the scope of this study to decide whether PR should continue to be routinely tested. However, we have shown that even without PR, the RSS is not inferior to the AJCC8 PS.

The RSS is effective on the assumption that patients receive standard of care as per their biomarker status, e.g. a HER2+ patient should receive targeted therapy. HER2-positive status, which was initially recognized as a negative prognostic factor, has been reversed into a factor that prognosticates better survival with the advent of trastuzumab. Hence, this scoring system may not be applicable to cohorts of patients with HER2+ tumors who do not receive HER2-targeted therapy. This phenomenon has been observed in other studies as well, and it is a problem that the AJCC8 PS is not spared from [17,27]. This scoring system may also need to be modified in the future if there are any new breakthroughs that significantly improve the survival outcomes of subtypes associated with prognosis, such as the TNBC subtype.

The RSS does not re-stage a patient into a higher or low stage; hence, it is not immediately evident how comparable 2 patients are, such as one with a low anatomic stage but a high-risk scores and another with a high anatomic stage but lower risk scores. However, by simply building upon the existing anatomical staging system familiar to most oncologists, the RSS avoids the need for other inconvenient aids such as lengthy conversion tables, making it an attractive tool for everyday use.

We included age, ethnicity, and receipt of chemotherapy in the multivariate analysis as younger patients and Malay ethnicity have been shown in separate studies of the same cohort to be independent risk factors [13-15].

The strength of our study is that the database we used is prospectively maintained. Although not all patients received treatment, there was a high rate of chemotherapy (84.3% of node-positive patients received adjuvant chemotherapy), targeted agent therapy (86.0% of HER2+ breast cancer patients), and endocrine therapy (84.6% of ER+ breast cancer patients).

Our study is limited by its relatively short follow-up duration. We only included patients diagnosed after 2006 since our institution only started routine use of adjuvant trastuzumab for patients with HER2+ disease from that point onward. This is an issue since luminal cancer subtypes may relapse after a longer interval [28].

To allow for wider implementation, more centers should consider adopting the use of this RSS, which is simple yet accurate for refining the prognosis of stage I–IV breast cancers. Since this is a novel system, we recommend the following nomenclature: anatomic stage IA (RS + 1), stage IV (RS + 2), etc.

The RSS provides a simpler way to integrate biomarkers with the prevalent common language of the anatomic stage in breast cancer patients. It is comparable to the more complex AJCC8 PS in its ability to stage patients by 5-year CSS and OS. Furthermore, it provides meaningful stratification for metastatic patients. Our findings support the use of RSS as a simpler alternative to the AJCC8 PS.

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