Received: 10 June 2020 | Accepted: 10 June 2020 | Published online: 30 June 2020

DOI: 10.1002/ctm2.115

CLINICAL AND TRANSLATIONAL MEDICINE Open Access WILEY

LETTER TO EDITOR

Establishment of prognostic nomograms based on skeletal muscle index and serum biomarker in breast cancer patients receiving radiotherapy

Dear Editor

The precision medical model for breast cancer patients is the development of individualized treatment plans. One of its core principles is that cancer treatment needs to target the individual biological characteristics of different patients.[1-3] Therefore, besides the classic prognostic factors, novel clinical features and factors will be the key of future researches to improve the management and prognosis of breast cancer. In recent years, gene expression characteristics have been increasingly used to make better selection of patients who could benefit from intensive treatment.[4,5] However, these genetic tests are expensive, which limits its widespread use. Therefore, it is of great importance to explore cost-effective and convenient tools that can effectively predict patients' survival, so as to screen high-risk patients with poor prognosis and develop appropriate treatment plans. In this study, we first investigated the prognostic significance of a model consisting of monocyte-to-lymphocyte ratio (MLR) and the skeletal muscle index (SMI), which was then incorporated with other clinicopathological factors to establish nomograms for predicting the multiple prognosis in breast cancer.

There were 326 patients retrospectively retrieved in this study. Skeletal muscle area was measured according to our previous study.[6,7] The SMI was calculated as follows: SMI = skeletal muscle area (cm^2)/height (m^2).[8] Routine clinicopathological data were assembled within 1 week of treatment and the MLR was calculated as monocyte count (10^9/L)/lymphocyte count (10^9/L). According to the receiver operating characteristic (ROC) curve, the cut-point for L3SMI, T4SMI, and MLR was 44.9 cm^2/m^2, 10.6 cm^2/m^2, and 0.19, respectively. Based on these, the sarcopenia-MLR (S-M) grade was defined: Grade 1, none of the two markers elevated; Grade 2, either elevated; and Grade 3, both elevated.

The study flow chart is shown in Figure S1, and the baseline characteristics are shown in Table S1. The relation between SMI at T4 and L3 measurements is shown in Figure S2. Linear regression analysis demonstrated significant correlation between the SMI at T4 and L3 ($r = 0.553$, $P < .001$) and the prediction rule was established: SMI at L3 = 18.928 + 1.834 × SMI at T4. BMI was significant covariate, apart from SMI at T4, and a multivariate regression model was established (Table S2) based on which the following prediction rule was then established: SMI at L3 = 11.466 + 1.399 × SMI at T4 + 0.553 × BMI.

For L3SMI-MLR, patients with S-M grade 1, the median OS, LRFS, DMFS, and DFS time were as follows: 65.8 interquartile range [IQR]: 57.0–77.1; 65.8 IQR: 57.0–77.1; 63.4 IQR: 47.5–76.1; 63.4 IQR: 46.6–76.1 months, which for the S-M grade 2 (61.0 months, IQR: 44.7–71.6; 60.1 months, IQR: 42.5–71.3; 57.4 months, IQR: 33.1–70.5; 56.0 months, IQR: 31.2–70.5) and S-M grade 3 (59.7 months, IQR: 34.5–66.6; 59.7 months, IQR: 23.0–66.6; 51.8 months, IQR: 34.5–63.9; 51.8 months, IQR: 34.5–63.9). The OS, LRFS, DMFS, and DFS of patients with S-M grade 1 were significantly longer than that of S-M grade 2 or 3 ($P = .0015$ vs $P = .0130$ vs $P = .0150$ vs $P = .0170$, respectively; Figure 1). Similar results were found for T4SMI-MLR. For predicting OS, the AUC for L3 S-M grade, T4 S-M, and TNM stage were 0.700, 0.706, and 0.647, respectively. For predicting LRFS, the AUC for L3 S-M grade, T4 S-M, and TNM stage were 0.720, 0.627, and 0.705, respectively. Further, for predicting DMFS, the AUC for L3 S-M grade, T4 S-M, and TNM stage were 0.629, 0.625, and 0.600, respectively, and for predicting DFS, the AUC for L3 S-M grade, T4 S-M, and TNM stage were 0.622, 0.608, and 0.604, respectively (Figure S3). Similar findings for OS, LRFS, DMFS, and DFS were found in ROC analysis; L3S-M grade had highest AUC among the three assessment methods. L3S-M grade had better prediction ability than current staging system for different survival outcomes; T4S-M grade had slightly better prediction power than TNM stage except for LRFS.

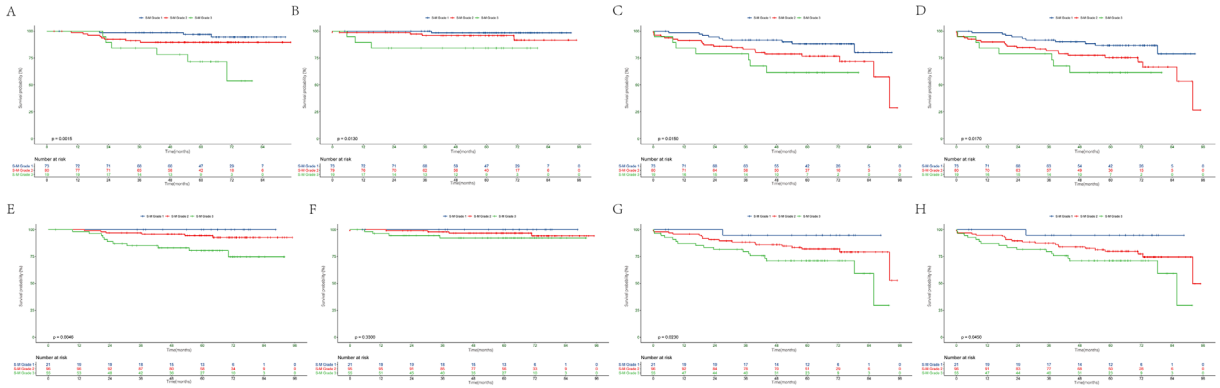

FIGURE 1 Comparing predictive ability by receiver-operating characteristic curve (ROC) analysis. Abbreviations: T4, the fourth thoracic vertebra); L3, the third lumbar vertebra; SMI-MLR, combined skeletal muscle index and monocyte-lymphocyte ratio; 95% CI, 95% confidence interval; AUC, area under the ROC curve. A, Comparing predictive ability of overall survival (OS). B, Comparing predictive ability of recurrence-free survival (RFS). C, Comparing predictive ability of distant metastasis-free survival (DMFS). D, Comparing predictive ability of diseases-free survival (DFS)

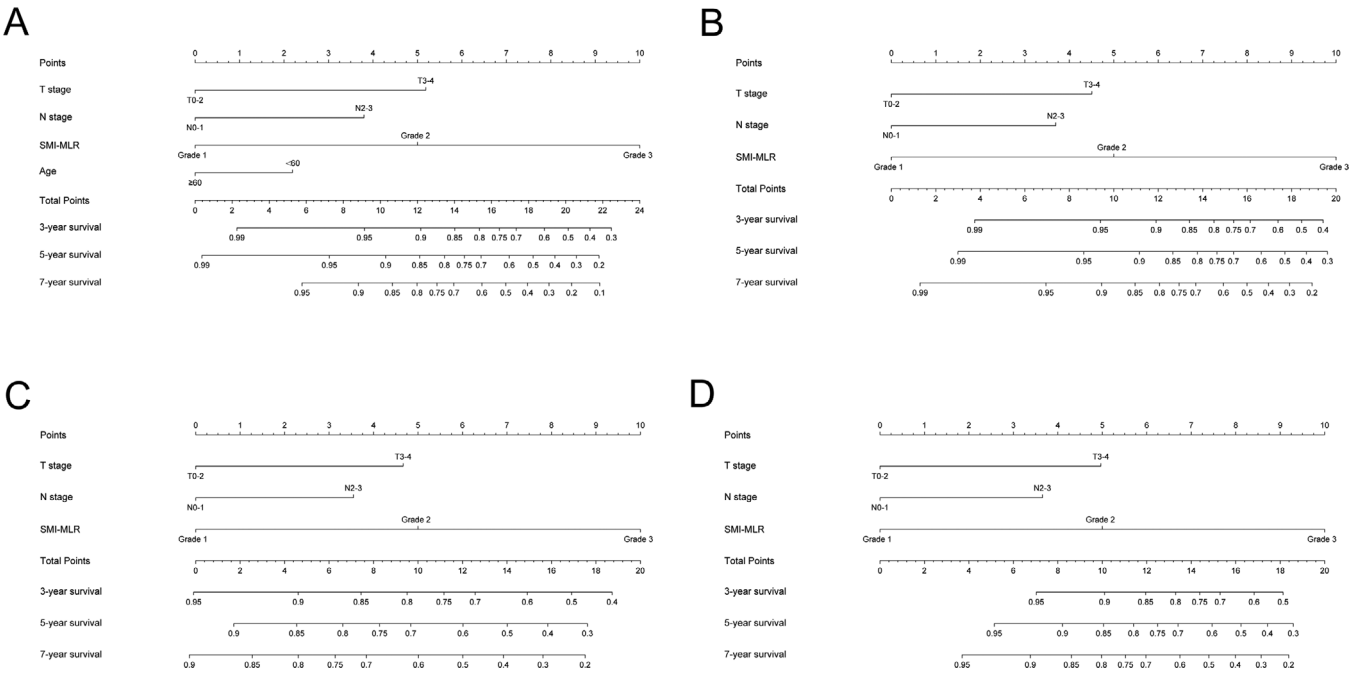

FIGURE 2 Nomograms for predicting 3-, 5-, and 7-year overall survival (OS), recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and diseases-free survival (DFS) by L3SMI-MLR. Nomograms for (A) OS, (B) RFS, (C) DMFS, and (D) DFS

We carried out nomogram analysis and included statistically significant parameters in the univariate analysis (Table S3) and constructed a nomogram that could predict the 3-, 5-, and 7-year OS (Figure 2). Similarly, we analyzed the other three survival outcomes and constructed corresponding nomograms. Considering that T4S-M had no significant statistical difference in RFS survival analysis, we only conducted univariate and multivariate Cox regression analyses of OS, DMFS, and DFS and established corresponding nomograms (Tables S4-S6 and Figure S5). Harrell's C-index after bootstrap correction was 0.743 (95% CI, 0.612–0.874), 0.823 (95% CI, 0.695–0.951), 0.661 (95% CI, 0.557–0.765), and 0.651 (95% CI, 0.552–0.750) of the established L3S-M-based nomogram for OS, RFS, DMFS, and DFS, which showed satisfactory accuracy in predicting the 3-, 5-, and 7-year survival. As shown in Figure S4, the actual values at each time point were in good agreement with the predicted values. Similar results were found for the established T4S-M-based nomogram of OS, DMFS, and DFS (Figure S6).

In this study, we reported a linear relationship between SMI at the T4 level, which is more practical in breast

cancer patients, and SMI at the L3 level, which is commonly used. By combing SMI and MLR, we developed a novel parameter named S-M grade to evaluate their association of multiple prognosis outcomes in breast cancer, and contrasted the prediction power of S-M grade with the traditional TNM stage system by ROC curve. The results showed that contrasted with the current staging system, L3S-M grade could better predict survival outcomes, and the T4S-M grade prediction ability was similar to that of the TNM stage. Based on the S-M grade, we established effective survival outcome predictive nomograms, which may allow accurate individualized survival prediction and therapy of future consultation.

ACKNOWLEDGMENTS

The authors thank the patients and their families for their support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Zhong-Yu Yuan and Xin Hua. Data curation: Xin Hua and Xin Huang. Formal analysis: Xin Hua and Xin Huang. Investigation: Jia-Peng Deng, Xin Huang, Zhang-Zan Huang, Chen-Ge Song, and Zhi-Qing Long: Methodology: Xin Hua and Xin Huang; Project administration: Zhong-Yu Yuan. Software: Xin Hua and Xin Huang. Supervision: Zhong-Yu Yuan and Huan-Xin Lin. Validation: Zhang-Zan Huang, Xin Huang, and Xin Hua. Visualization: Xin Huang. Writing and original draft: Xin Hua. Writing, review, and editing: all authors.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were 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. This study was approved by the Clinical Research Ethics Committee of SYSUCC (number: GZR2017-224). Informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Xin Hua[1,*]
Xin Huang[2,*]
Zhang-Zan Huang[1,*]
Chen-Ge Song[1]
Jia-Peng Deng[3]
Zhi-Qing Long[3]
Huan-Xin Lin[3]
Zhong-Yu Yuan[1]

[1] *Department of Medical Oncology, SunYat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China*
[2] *Department of Pancreatobiliary Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, China*
[3] *Department of Radiotherapy, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, China*

Correspondence
Zhong-Yu Yuan, Department of Medical Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, P. R. China.
Email: yuanzhy@sysucc.org.cn

*Xin Hua, Xin Huang, and Zhang-Zan Huang contributed equally to this work.

ORCID

Xin Hua https://orcid.org/0000-0002-2045-1293
Xin Huang https://orcid.org/0000-0002-0359-7290

REFERENCES

1. Tursz T, Andre F, Lazar V, Lacroix L, Soria JC. Implications of personalized medicine–perspective from a cancer center. *Nat Rev Clin Oncol*. 2011;8(3):177-183.
2. Scott JG, Berglund A, Schell MJ, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol*. 2017;18(2):202-211.
3. Zeng C, Stroup EK, Zhang Z, Chiu BC, Zhang W. Towards precision medicine: advances in 5-hydroxymethylcytosine cancer biomarker discovery in liquid biopsy. *Cancer Commun (Lond)*. 2019;39(1):12.
4. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817-2826.
5. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729.
6. Hua X, Deng JP, Long ZQ, et al. Prognostic significance of the skeletal muscle index and an inflammation biomarker in patients with breast cancer who underwent postoperative adjuvant radiotherapy. *Curr Probl Cancer*. 2020;44(2):100513.

7. Deng JP, Hua X, Long ZQ, Zhang WW, Lin HX, He ZY. Prognostic value of skeletal muscle index and monocyte-to-lymphocyte ratio for lymph node-positive breast cancer patients after mastectomy. *Ann Transl Med*. 2019;7(23):775.
8. Lee J, Chang CL, Lin JB, et al. Skeletal muscle loss is an imaging biomarker of outcome after definitive chemoradiotherapy for locally advanced cervical cancer. *Clin Cancer Res*. 2018;24(20):5028-5036.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.