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Original article

Development and validation of a nomogram for predicting survival on the base of modified lymph node ratio in breast cancer patients

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ABSTRACT

Background: Axillary lymph node status is one of the most important prognostic factors in breast cancer and previous studies indicated that lymph node ratio (LNR) could better predict the outcome than the counting of positive lymph nodes. In the current study, we evaluated the prognostic effect of modified LNR in breast cancer patients.
Methods: A total of 3339 breast cancer patients undergoing axillary lymph nodes dissection were enrolled and respectively analyzed. Seventy five percent of participants were randomly selected as training cohort and the remaining 25% were as validation cohort. Univariate and multivariate analyses were performed and the prognostic impact of mLNR was compared with pN staging. A prognostic nomogram was established and externally validated in the validation cohort.
Result: In multivariate analysis, both the mLNR and pN staging were independent prognostic factors for breast cancer patients, and the mLNR manifested superior discrimination power than the pN stages regardless of the total number of lymph nodes retrieved and the lymph node status. The nomogram was built including the identified independent prognostic factors and the calibration curves indicated optimal agreement between nomogram prediction and actual observation. The Concordance index (C-index) of the nomogram was statistically higher than that of the TNM system (0.747 vs. 0.711 in training cohort, 0.789 vs. 0.760 in validation cohort, both $p < 0.05$).
Conclusion: Modified LNR is an important prognostic parameter and can predict survival more accurately than pN staging. The novel nomogram could provide individual prediction for breast cancer patients and help clinicians in treatment option making and prognosis evaluation.

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1. Introduction

Breast cancer is the most common cancer and the main cause of cancer death in women. More than 230,000 new cases and 40,000

deaths were reported in the United States in 2015 [1]. Lymph nodes (LNs) assessment was an important indicator of disease severity and prognosis in breast cancer [2,3], which was commonly yielded through the axillary lymph node dissection (ALND).

Independently of tumor size, hormone receptor statuses and human epithelial growth factor receptor-2 (HER-2) status, increase of the positive LNs number is independently associated with higher recurrence risk and poor clinical outcomes [4]. Meanwhile, adjuvant chemotherapy and radiotherapy are recommended when lymphatic metastasis occurred. According to the TNM classification of the American Joint Committee on Cancer (AJCC) in breast cancer, the LNs status was assessed according to the number of positive LNs as pN0 (no positive nodes), pN1 (1—3 positive nodes), pN2 (4—9 positive nodes) and pN3 (10 or more positive nodes).

However, the current TNM classification does not consider the total number of LNs removed, and the latter could partly influence the identified numbers of positive LNs. Previous studies have found that inadequate ALND may lead to understaging of the LN status and higher regional recurrence [5]. Conversely, though excessive ALND guarantee sufficiently removed LNs, it would induce various postoperative complications, such as edema, numbness and movement disorder of affected limbs, which greatly decrease the quality of life.

Recently, ratio-based nodal categories were introduced and found to be superior than the traditional pN staging system [6–8]. Some studies have indicated that lymph nodes ratio (LNR), defined as the ratio of the number of positive LNs to the total number of LNs retrieved, was independent prognostic factor in several cancers, like lung cancer [9], head and neck cancer [10], bladder cancer [11] and breast cancer [12,13]. It could be in conjunction with the AJCC number-based pN staging in treatment decisions. However, But the LNR could not provide further prognostic information than the number-based pN staging when no positive lymph node is detected. Meanwhile, different cutoff points of LNR are proposed, varying between 0.1 and 0.65, to classify patients into various risk groups in different studies and no convincing consensus is available so far [12–15].

Here, we used the modified lymph node ratio (mLNR) as a continuous variable and compared its prognostic impact with number-based pN staging system in breast cancer patients undergoing ALND. We also developed and externally validated a predictive nomogram, which could provide individualized prognostic information based on a combination of parameters.

2. Materials and methods

2.1. Study population

Patients diagnosed as breast cancer from January 2002 to December 2008 in Sun Yat-sen University Cancer Center (SYSUCC) were retrospectively reviewed. The inclusion criteria were as follows: (1) female; (2) received surgical treatment; (3) pathologically diagnosed as invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). Exclusion criteria included: (1) received neoadjuvant chemotherapy or radiotherapy before surgery; (2) with previous or coexisting cancers other than breast cancer; (3) confirmed metastasis at the first visit; (4) only received sentinel lymph node biopsy; (5) bilateral breast cancer; (6) not enough data can be extracted. All patients were followed up to 31 of December 2014 or date of deaths. Seventy-five percent of enrolled patients were randomly selected as the training cohort to evaluate the prognostic value of parameters and to develop the nomogram for prognostic assessment. The remaining 25% of patients were grouped as the validation cohort for evaluation of the nomogram.

2.2. Clinical data collection

Age, menstrual status, menarche age, pathological diagnosis, histologic grade, tumor size, number of positive LNs, number of total retrieved LNs, hormone receptor and HER-2 status, family history and date of last follow-up or death were collected for subsequent analysis. The clinical stages were classified according to the AJCC TNM staging system (7th edition). The intrinsic subtypes were classified according to 2015 ESMO Clinical Practice Guidelines of breast cancer [16]. HER-2 positive was defined as "3+" in immunohistochemical test or "positive" in HER-2 fluorescence in situ hybridization test.

2.3. Statistical analyses

Categorical data were described using numbers and percentages, and Chi square test was performed to examine the differences between groups. Modified lymph node ratio (mLNR) was defined as $\frac{pLN+0.5}{tLN+0.5}$, where pLN is the number of positive LNs and tLN is the total number of retrieved LNs. Zero point five is added in both the numerator and denominator to avoid the occurrence of zero. The primary endpoint was cancer-specific survival (CSS), calculated from the time of pathological diagnosis to the date of cancer-related death or last follow-up. Univariate analysis and 3-steps multivariate analyses (Cox proportional hazards model) were performed to identify independent variables associated with CSS. In step 1 and step 2 multivariate analyses, pN stages and mLNR were included respectively, and both pN stages and mLNR were included in step 3 multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the Cox regression model. Subgroup survival analyses were performed based on the number of retrieved lymph nodes (<10 or ≥10) and the lymph node status. Receiver operating characteristics (ROC) curve analyses were applied to evaluate the discriminatory power of different nodal classifications. Likelihood ratio chi-square (LR chi^2) and Akaike's information criterion (AIC) in the Cox regression model were used to assess the model fitness of pN staging and mLNR.

A prognostic nomogram was established based on the independent prognostic factors identified, using backward step-down process. Concordance index (C-index) was calculated for the evaluation of the discrimination power and the comparison between the nomogram and TNM staging system. Bootstraps with 1000 resamples were used for internal validation of the training cohort and the external validation was performed by applying the nomogram to the validation cohort. Calibration of the nomogram was performed by comparing the predicted survival with the observed survival in both the training cohort and validation cohort. All the statistical analyses were performed using SPSS (version 19.0, Chicago, IL, USA) and R software (version 3.2.3) with the survival and *rms* package. A two-tailed *p* value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 3339 female patients with primary non-metastatic invasive breast cancer were enrolled in the current study (Fig. 1). Two thousand five hundred and two patients were randomly selected as training cohort and 837 patients were included in the validation cohort. Table 1 listed the patient characteristics and histopathological features, and no significant difference was observed between the training cohort and validation cohort. The mean age of the overall cohort was 47.9 (range 21–81) years old, and 408 (12.2%) patients were under the age of 35. Tumor sizes of T1, T2 and T3 were observed in 1371 (41.1%), 1755 (52.5%) and 213 (6.4%) patients, and stage I, II and III accounted for 25.0%, 50.5% and 24.5% of the study cohort, respectively. Axillary lymph node metastases were confirmed in 1622 (48.6%) patients, and 321 (9.6%) patients had less than 10 total lymph nodes retrieved. There were 2450 (73.4%) patients categorized as luminal subtype, among which 34.0% (1135) were luminal A subtype, 26.7% (891) were luminal B (HER-2 negative) subtype and 424 (12.7%) were luminal B (HER-2 positive) subtype. HER2 over-expressing subtype and triple-negative subtype comprised 11.1% (369) and 15.5% (520) of total participants respectively.