Low serum albumin levels and high neutrophil counts are predictive of a poorer prognosis in patients with metastatic breast cancer

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Abstract. Breast cancer is a severe disease with high incidence and mortality rates in menopausal women. Previous studies have shown that nutritional status and inflammation play a significant role in the development of breast cancer. However, whether serum albumin (ALB) and neutrophils (NE) accelerate the progression of this disease remains unclear. In the present study, a total of 94 cases of newly diagnosed metastatic breast cancer were assessed. For analysis, 26 risk factors including ALB and NE were assessed. Multivariate Cox proportional hazards regression analysis was then used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for continuous and categorical covariates. Compared with the control group, patients with disease progression, low levels of ALB, higher NE, counts, and higher neutrophil to lymphocyte ratio counts were associated with worse overall survival (OS). When these risk factors were fitted into a multivariate regression model, progression [P<0.001, HR=3.03 (1.62-5.66)], NE counts ≥$3.370x10^9$ [P=0.004, HR=2.15 (1.27-3.65)] and ALB levels <43.275 g/l [P=0.008, HR=0.47 (0.27-0.82)] remained statistically significant factors for a worse OS. These independently associated risk factors were used to form an OS estimation nomogram. The constructed nomogram demonstrated good accuracy in estimating risk, with a bootstrap-corrected C index of 0.686. We further collected data on 30 patients for external validation and found the nomogram had an accuracy of 83.3%. In conclusion, low serum ALB levels and increased NE counts were predictive of a poorer prognosis in patients with metastatic breast cancer. Nomograms based on the multivariate analysis showed a good predictive ability for estimating the risk of OS.

Introduction

Breast cancer is one of three malignant genital tumors. Although early breast cancer is considered a curable disease with surgical interventional therapy, metastatic breast cancer remains a considerable challenge. The symptoms of breast cancer during the early stages are often mild and thus missed, meaning patients are often diagnosed in the first instance with advanced-stage breast cancer. Worldwide, ~1/8 of women suffer from breast cancer during their lifetime (1). Every year, 1.7 million people worldwide are diagnosed with breast cancer, and among these patients, ~1/3 of them succumb to cancer. According to two recent investigations conducted by Esteva *et al* (2) and Stehle *et al* (3), the morbidity and mortality of this disease are rising annually. The risk and prevalence of breast cancer increase with age (1). Using current treatment regimens, it is difficult to eradicate advanced tumors, with treatments typically aimed at prolonging life, improving patients' quality of life, and alleviating patient suffering (2).

Growth by commandeering an individual's nutrients and energy is a significant feature of all malignant tumors (3). Malnutrition may result in immune dysfunction, blocking of wound healing, disease recovery, as well as an inability to fend off infections appropriately, and it is also a poor prognostic factor for patients with advanced cancer (4). Albumin (ALB) is the most abundant protein in plasma, and it plays an important role in several physiological processes due to its properties (5). The ALB concentration of peripheral blood is ~40 mg/ml and its molecular weight is ~67 kDa (6); it is regarded as one of the

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most important biomarkers for evaluating the nutrient status of patients (7). In recent years, ALB has been clinically used as an ideal carrier for improving anti-tumor pharmacokinetics as it can bind with chemotherapeutics and prolong their half-life in plasma (8). Several studies have revealed the association between nutrient status and breast cancer (9-11); however, to the best of the authors' knowledge, there are no studies assessing the association between ALB and the development of breast cancer.

Inflammatory cells play an important role in the tumor microenvironment especially neutrophils, which could activate cancer cells (12). Inflammatory cells are mediators that take part in tumor initiation and promotion. They also act as a source of cytokines for cancer cells, which enhance cell survival and proliferation (13). Recently, Yang *et al* (14) suggested that oncogene activation (such as RTKs, Ras, and p53) stimulates inflammation and tumor progression via the actions of cytokines, growth factors, chemokines, reactive oxygen species, prostaglandins, and nitrogen species, as well as recruitment of inflammatory cells. Neutrophils (NE) increase in production and release inflammatory factors during the inflammatory process (15). Previous studies have suggested that hypoxia, a common feature of solid tumors, targets multiple cell types in the tumor microenvironment including neutrophils by regulating the expression of multiple angiogenic genes (16-18). Expression of the immunosuppressive cytokine TGF-β is upregulated in tumors and plays a significant role in blocking immune responses and affecting tumor progression. TGF-β can also induce this type of blockade and increase NE attracting chemokines, resulting in increased local production of pro-inflammatory cytokines. Following TGF-β blockade, depletion of these NEs significantly suppresses the anti-tumor effects of treatment and reduces CD8+ T-cell activation (13). Previous studies have found that inflammation leads to a decrease in the levels of serum ALB (19-21). Artigas *et al* (22) showed that the inflammatory state (for example, sepsis) results in an increase in microvascular permeability. ALB distribution between intra- or extra-vascular compartments changes accordingly, causing ALB levels to decrease in the plasma. Kaysen *et al* (23) also suggested that the effect of inflammation on the vascular endothelium and lipoprotein structure was the leading cause of lower ALB levels in plasma. However, few studies have focused on the relationship between ALB and NE.

To investigate the influence of ALB and NE on the overall survival of patients with metastatic breast cancer, a retrospective analysis of 94 patients with this disease was performed, taking into account 26 risk factors.

Materials and methods

Patient characteristics. A total of 94 patients who were newly diagnosed with metastatic breast cancer were included in the present study. The median age was 64 years old [interquartile range (IQR) 58-70]. Patients who met the inclusion criteria and who visited between April 2008 and July 2014 in the First Affiliated Hospital of Soochow University were included in this study. A total of 30 patients was included from Sichuan Cancer Hospital and the median age was 61 years old (IQR 56-67). Informed consent was obtained from all patients prior to data collection. The median values were used as cut-off values. This study was approved by the Committee for the Ethical Review of Research at the First Affiliated Hospital of Soochow University and was conducted in accordance with institutional guidelines and the Declaration of Helsinki (24).

Blood samples. Peripheral venous blood (5-7 ml) was collected in a sterile EDTA tube. All patients were fasted for 12 h and samples were obtained between 6:30 and 7:30 a.m. to standardize the known impact of circulating hormones (circadian rhythm) on the number and subtype distribution of the various white blood cell indices. Hematological parameters were analyzed within 30 min of collection using a biochemical analyzer (Olympus AU5421+ISE, Olympus Corporation). Lymphocyte (LY), mononuclear leucocyte (MO), NE, eosinophilic granulocyte (EO), basophilic granulocyte (BA) and hemoglobin (HGB) level, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), thrombocyte count (PLT), thrombocytocrit (PCT), mean platelet ratio (MPV), platelet distribution width (PDW), C-reactive protein (CRP), ALB, globulin level (GLB), lactate dehydrogenase (LDH), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), count of leukocyte (WBC), erythrocyte (RBC), and albumin to globulin ratio (AGR) were recorded. The patients were divided into two groups according to the median values. The post/pre-chemotherapeutic ratio was defined as the pre-chemotherapeutic blood parameter value and the corresponding value obtained after chemotherapy.

Evaluation. Computed tomography (CT) scans were performed for the assessment of response every 2 months and evaluated according to the criteria of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (25).

Follow-up. We recorded responses to chemotherapy including partial response (PR), stable disease (SD), and progressive disease (PD). After first-line chemotherapy, disease progression was defined as a lack of response to chemotherapy. In contrast, SD or PR after chemotherapy was defined as response to chemotherapy. Survival time was measured from the date of chemotherapy until death or the last clinical evaluation. The prognostic analyses were performed regarding OS. OS was defined as the time from the diagnosed date to death from any cause.

Diagnostic criteria of metastatic breast cancer. Postmenopausal women with metastatic breast cancer in estrogen receptor-positive, progesterone-receptor-positive, or both were enrolled. All the patients were diagnosed according to local institutional standards (26). Women were eligible if they had received no hormonal therapy, prior chemotherapy, or immunotherapy for metastatic disease. Adjuvant or neoadjuvant chemotherapy had to have been completed more than 12 months before enrollment.

Statistical analysis. Statistical analysis was performed using the 'survival' and 'survminer' statistical packages in R version 3.6.0 (27). Covariates were compared before or

Table I. Patient characteristics at enrollment.

Factor	Before chemotherapy, n=94	After chemotherapy, n=94	P-value
Age	51.0 (46.0-62.0)	-	-
Smoking			-
Yes	31 (33.0)	-	
No	63 (67.0)	-	
Family history of cancer, n (%)			-
Yes	21 (22.3)	-	
No	73 (77.7)	-	
LY, $x10^9$/l, median (IQR)	1.505 (0.998-2.090)	1.215 (0.910-1.660)	0.022[a]
MO, $x10^9$/l, median (IQR)	0.330 (0.230-0.420)	0.330 (0.242-0.475)	0.440
NE, $x10^9$/l, median (IQR)	3.370 (2.665-4.388)	3.385 (2.435-4.478)	0.332
EO, $x10^9$/l, median (IQR)	0.080 (0.050-0.140)	0.080 (0.040-0.120)	0.398
BA, $x10^9$/l, median (IQR)	0.010 (0.000-0.020)	0.010 (0.000-0.020)	0.342
HGB, g/l, median (IQR)	126.2 (118.3-132.0)	114.8 (105.0-121.9)	<0.001[c]
HCT, l/l, median (IQR)	0.370 (0.340-0.390)	0.340 (0.320-0.368)	<0.001[c]
MCV, fl, median (IQR)	89.39 (84.83-92.75)	91.05 (88.53-94.29)	0.007[b]
MCH, pg, median (IQR)	30.00 (28.80-31.36)	30.48 (29.25-31.61)	0.129
MCHC, g/l, median (IQR)	338.9 (328.5-348.0)	333.6 (325.1-341.4)	0.019
RDW, %, median (IQR)	12.90 (12.34-13.43)	14.75 (13.71-16.21)	<0.001[c]
PLT, $x10^9$/l, median (IQR)	179.5 (151.8-227.9)	207.0 (160.9-241.5)	0.111
PCT, l/l, median (IQR)	0.180 (0.130-0.220)	0.190 (0.143-0.230)	0.381
MPV, fl, median (IQR)	10.40 (9.05-11.40)	9.950 (8.025-11.115)	0.104
PDW, %, median (IQR)	15.68 (12.80-16.99)	15.60 (12.70-16.93)	0.994
CRP, mg/l, median (IQR)	4.010 (1.427-8.572)	3.035 (1.780-5.245)	0.327
ALB, g/l, median (IQR)	43.27 (40.65-46.74)	43.95 (40.19-46.55)	0.873
GLB, g/l, median (IQR)	29.39 (25.90-32.38)	26.88 (23.55-30.72)	0.011
LDH, U/l, median (IQR)	199.4 (178.9-253.8)	216.6 (178.8-262.7)	0.542
NLR, median (IQR)	2.285 (1.575-3.627)	2.645 (1.950-3.362)	0.243
PLR, median (IQR)	132.7 (93.3-190.0)	172.5 (129.5-218.5)	0.004[b]
WBC, $x10^9$/l, median (IQR)	5.810 (4.445-6.997)	5.125 (3.757-6.452)	0.078
RBC, $x10^9$/l, median (IQR)	4.180 (3.950-4.367)	3.750 (3.502-4.128)	<0.001[c]
AGR, median (IQR)	1.480 (1.347-1.730)	1.630 (1.410-1.870)	0.029

[a]P<0.05, [b]P<0.01, [c]P<0.001. EO, eosinophilic granulocyte; BA, basophilic granulocyte; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; PLT, thrombocyte; PCT, thrombocytocrit; MPV, mean platelet ratio; PDW, platelet distribution width; CRP, c-reactive protein; NE, neutrophils; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, leukocyte; RBC, erythrocyte; AGR, albumin to globulin ratio.

after chemotherapy using a Wilcoxon rank sum test (27) for continuous variables.

Survival curves of patients with high or low levels of NE, ALB, or NLR and whether progression occurred for each of the primary endpoints were plotted. Multivariate Cox proportional hazards regression was then used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for the continuous and categorical covariates mentioned previously.

A nomogram was calculated based on the results of the multivariate Cox regression analysis and using the rms package of R, version 3.0 (http://www.r-project.org/). The nomogram is based on proportionally converting each regression coefficient in multivariate cox regression to a 0- to 100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned 100 points. The points are added across independent variables to derive total points, which are converted to predicted probabilities. The predictive performance of the nomogram was measured using the concordance index (C-index) and calibration with 1,000 Bootstrap samples to decrease the overfit bias. The conventional Bootstrap internal validity analysis method is to randomly sample a certain number of returnable cases in the original data set to build a model, and then use the original data set to verify the model. By doing random sampling, establishment, and validation 500-1,000 times, 500-1,000 models can be obtained, and the parameter distributions of the model can be summarized. Therefore, the final parameter values of the model can be determined (28).

Table II. Univariate Cox Regression Analysis of Overall Survival on metastatic breast cancer patients.

Factor	Hazard ratio (95% confidence interval)	P-value
Age, >63 vs. ≤63	1.04 (0.67-1.62)	0.868
PD, Yes vs. No	3.55 (2.03-6.21)	<0.001[c]
LY, ≥1.505 vs. <1.505	1.00 (0.65-1.56)	0.987
MO, ≥0.330 vs. <0.330	0.88 (0.56-1.37)	0.563
NE, ≥3.370 vs. <3.370	1.88 (1.20-2.93)	0.006[b]
EO, ≥0.080 vs. <0.080	1.30 (0.83-2.04)	0.246
BA, ≥0.010 vs. <0.010	1.41 (0.89-2.24)	0.141
HGB, ≥126.210 vs. <126.210	0.68 (0.43-1.06)	0.086
HCT, ≥0.370 vs. <0.370	0.94 (0.60-1.48)	0.804
MCV, ≥89.385 vs. <89.385	0.99 (0.63-1.54)	0.955
MCH, ≥29.995 vs. <29.995	0.89 (0.57-1.39)	0.616
MCHC, ≥338.860 vs. <338.860	1.06 (0.68-1.65)	0.797
RDW, ≥12.900 vs. <12.900	0.66 (0.42-1.03)	0.066
PLT, ≥179.500 vs. <179.500	1.29 (0.83-2.00)	0.264
PCT, ≥0.180 vs. <0.180	1.56 (1.00-2.42)	0.051
MPV, ≥10.400 vs. <10.400	1.04 (0.67-1.63)	0.860
PDW, ≥15.680 vs. <15.680	1.39 (0.89-2.17)	0.147
CRP, ≥4.010 vs. <4.010	1.39 (0.89-2.16)	0.145
ALB, ≥43.275 vs. <43.275	0.47 (0.30-0.73)	<0.001[c]
GLB, ≥29.390 vs. <29.390	1.06 (0.68-1.65)	0.785
LDH, ≥199.410 vs. <199.410	0.89 (0.57-1.39)	0.612
NLR, ≥2.285 vs. <2.285	1.56 (1.00-2.43)	0.05[a]
PLR, ≥132.710 vs. <132.710	1.27 (0.81-1.97)	0.298
WBC, ≥5.810 vs. <5.810	1.42 (0.91-2.21)	0.123
RBC, ≥4.180 vs. <4.180	0.84 (0.54-1.31)	0.450
AGR, ≥1.480 vs. <1.480	0.78 (0.50-1.22)	0.277

[a]P<0.05, [b]P<0.01, [c]P<0.001. EO, eosinophilic granulocyte; BA, basophilic granulocyte; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; PLT, thrombocyte; PCT, thrombocytocrit; MPV, mean platelet ratio; PDW, platelet distribution width; CRP, c-reactive protein; NE, neutrophils; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, leukocyte; RBC, erythrocyte; AGR, albumin to globulin ratio.

Results

Baseline characteristics. A total of 94 consecutive patients between April 2008 and July 2014 who were newly diagnosed with metastatic breast cancer were included in the present study. The median age of the enrolled patients was 51.0 years old (IQR, 46.0-62.0), and all patients (100%) were female; 31 (33.0%) patients had a history of smoking, and 21 (22.3%) patients had a family history of cancer. The LY, MO, NE, EO, and BA counts as well as HGB levels, HCT, MCV, MCH, MCHC, RDW, PLT, PCT, MPV, PDW, CRP, ALB, GLB, LDH, NLR, PLR, WBC, RBC, and AGR counts before and after chemotherapy. Among these factors, the LY count [1.505 (0.998-2.090) vs. 1.215 (0.910-1.660), P=0.022], RBC count [4.180 (3.950-4.367) vs. 3.750 (3.502-4.128), P<0.001], HGB levels [126.2 (118.3-132.0) vs. 114.8 (105.0-121.9), P<0.001] and the HCT [0.370 (0.340-0.390) vs. 0.340 (0.320-0.368), P<0.001] decreased after chemotherapy, while MCV [89.39 (84.83-92.75) vs. 91.05 (88.53-94.29), P=0.007], RDW [12.90 (12.34-13.43) vs. 14.75 (13.71-16.21), P<0.001] and PLR [132.7 (93.3-190.0) vs. 172.5 (129.5-218.5), P=0.004] increased. The baseline characteristics of the patients are listed in Table I. The more advanced the stage of breast cancer, the lower the patients' ALB levels were and the higher the NE levels were (Table SI). NE/ALB data were compared before and after chemotherapy in stage II and III breast cancer patients. After chemotherapy, ALB levels were lower in stage III patients than stage II patients [42.72 (41.94, 43.80) vs. 39.90 (38.81, 40.67), P<0.001]. In contrast, there was no significant difference in the indicators before chemotherapy (Table SII).

Prognosis and independent prognostic factors. The investigation was censored on Jan 10, 2019. The median follow-up time was 30.0 (range, 2.0-109.0) months. After 5-years, 84.0% of the patients enrolled died from cancer-associated factors. Univariate analysis of risk factors that influenced OS was analyzed. In the univariate analysis, PD, NE, ALB, and NLR were all predictive of an unfavorable prognosis (Table II).

Patients with disease progression, low levels of ALB, and higher NE and NLR counts had a worse OS. When these

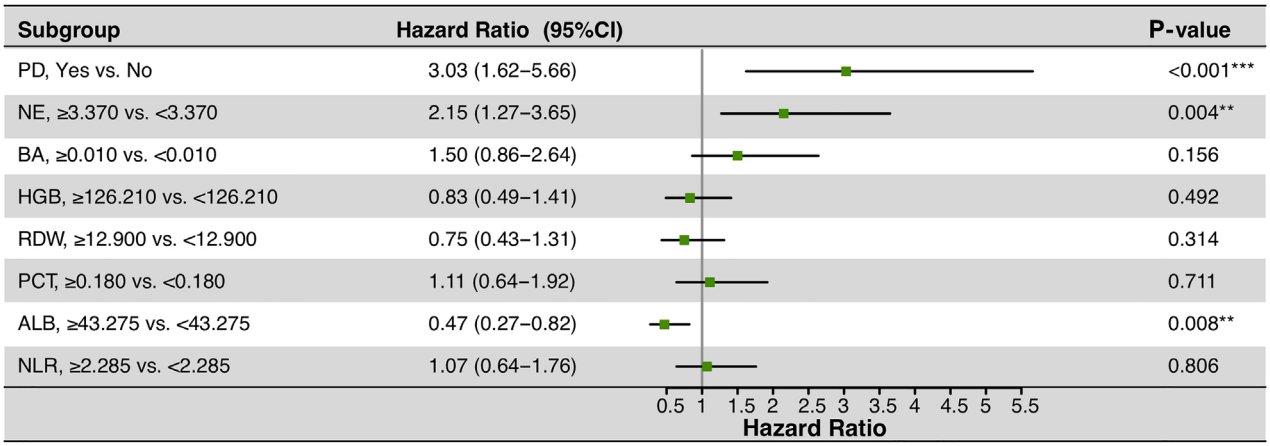

Figure 1. Multivariate Cox Regression analysis of 5-year OS in patients with metastatic breast cancer. OS, overall survival; PD, progressive disease; NE, neutrophils; BA, basophilic granulocyte; HGB, hemoglobin; RDW, red blood cell distribution width; PCT, thrombocytocrit; ALB, albumin; NLR, neutrophil to lymphocyte ratio.

risk factors were fitted into a multivariate regression model, patients with progression [3.03 (1.62-5.66), P<0.001], NE counts ≥3.370x10^9/l [2.15 (1.27-3.65), P=0.004], and ALB levels <43.275 g/l [0.47 (0.27-0.82), P=0.008] remained statistically significant factors for a worsened OS (Fig. 1).

The ALB, NE, and NLR levels were detected, and patients were divided into high and low groups based on the median level. Using survival analysis, we found that patients with progression (Fig. 2A), had higher NE counts (Fig. 2B), or low ALB levels (Fig. 2C) demonstrated a significantly poorer prognosis. There was no significant effect of NLR on prognosis (Fig. 2D). NE and ALB also had prognostic value for patients after chemotherapy, but no statistically significant value for patients before chemotherapy.

Development and validation of an OS-predicting nomogram. All variables used in this analysis were based on the data obtained preoperatively. The related variables included whether progression occurred, NE, and ALB.

We used these independent risk factors to form an OS estimation nomogram (Fig. 3A). The resulting model was finally validated using the bootstrap validation method. The nomogram demonstrated good accuracy in estimating the risk of mortality, with an unadjusted C index of 0.686 and a bootstrap-corrected C index of 0.686.

In the validation cohort, the nomogram displayed a C index of 0.686 for the estimation of OS. The calibration curve showed good accuracy for risk estimation (Fig. 3B).

Overall, 30 patients were collected as the external validation cohort for the model. The validation revealed that the predictive accuracy of the present constructed model was 95.0% (Fig. S1).

Discussion

The present study analyzed 26 factors, including ALB levels and NE counts, using data obtained from blood biochemical analyses and routine examinations of 94 samples collected between April 2008 and July 2014 in the First Affiliated Hospital of Soochow University. In the present study, both univariate and multivariate survival analyses showed that patients with low ALB levels and increased NE count had a poorer prognosis.

Serum ALB, an important biomarker for evaluating nutritional status, was shown to be associated with the development of advanced cancer. Multiple mechanisms explain the poor prognostic effect of low ALB levels in patients with advanced cancer. Hoogenboezem *et al* (6) showed that an increased nutrient supply and substantial energy production are required by cancerous cells due to their rapid proliferation and high levels of metabolism. In the tumor microenvironment, ALB is rapidly absorbed by a tumor to counter the relative lack of amino acids. This process allows the tumor to meet the high metabolic requirements of rapid tumor proliferation, resulting in a reduction in serum ALB levels (6). Another study by Sarett *et al* (29) showed that a loss of appetite caused by tumor chemotherapy or radiotherapy resulted in reduced protein intake and impaired synthesis. Furthermore, tissue damage and inflammation accelerate the process of catabolism, decreasing the levels of ALB in the plasma (29). In addition, cytokines such as IL-6 released by tumor cells inhibit ALB production in hepatocytes. Additionally, a reduction in ALB production results in an increase in a TNF-mediated increase in the permeability of microvessels causing the serum ALB levels to decrease (30). Moreover, a previous study also suggests that malnutrition in the serum of cancer patients can lead to a decrease in the rate of synthesis of serum ALB, accelerating degradation, and thus resulting in hypoproteinemia (31). Previous studies have also shown that low serum ALB levels are an independent predictor of a poor prognosis in patients with breast cancer as well as lung, rectal, and gastric cancer (7,30,32).

Chen *et al* (32) confirmed that preoperative ALB levels ≤37.6 g/l were associated with a poor prognosis in several kinds of cancer. Liu *et al* (33) analyzed 2,425 samples from patients with non-metastatic invasive breast cancer. They reached the conclusion that patients with a higher pre-treatment ALB level (>3.9 g/dl) had a 45% lower risk of death compared with those with a lower pre-treatment ALB level (≤3.9 g/dl). Lis *et al* (34) analyzed 180 breast cancer patients and found

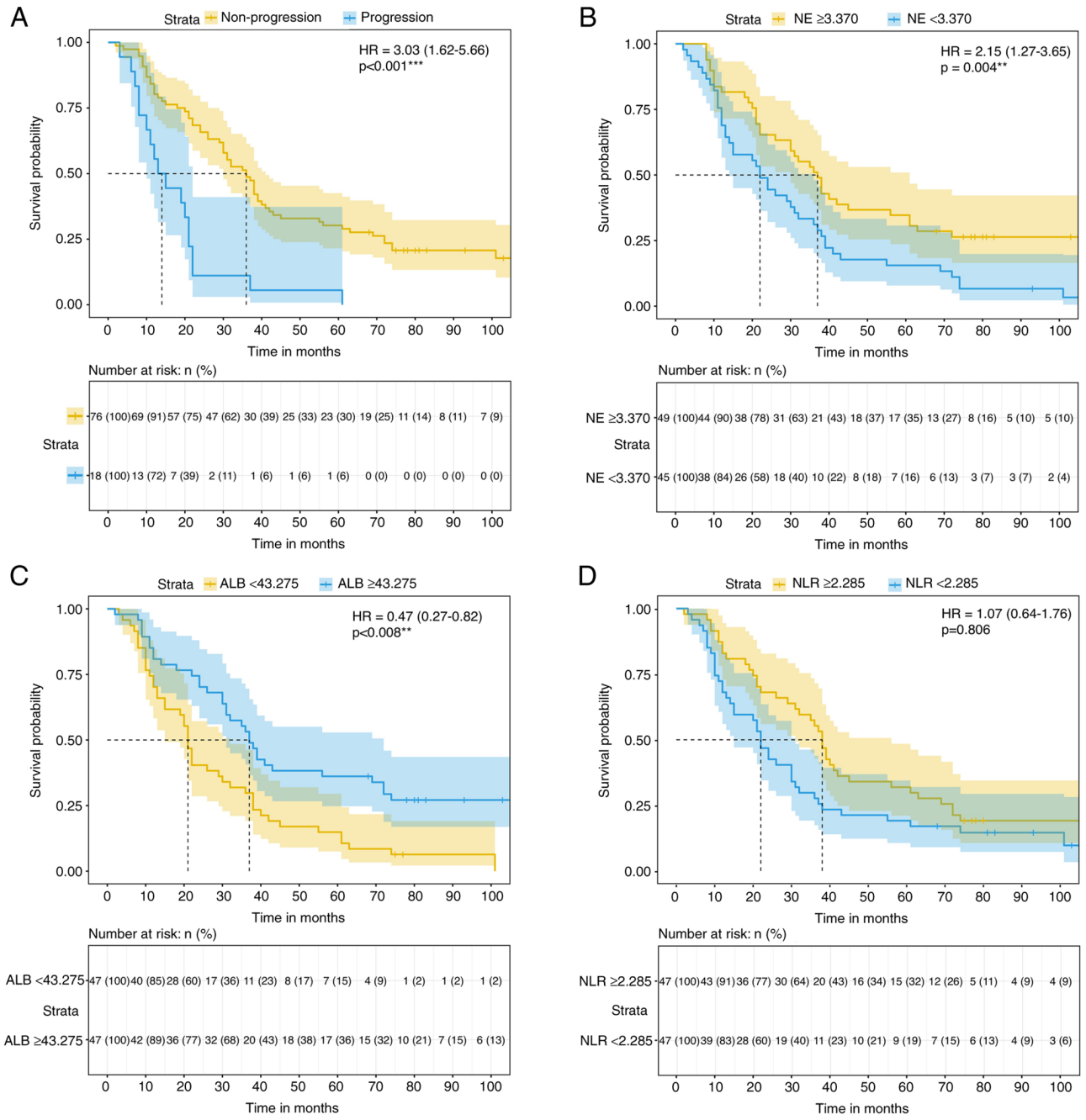

Figure 2. OS of patients with metastatic breast cancer stratified by the statistically significant factors. (A) OS of metastatic breast cancer patients stratified by progression. (B) OS of metastatic breast cancer patients stratified by NE counts. (C) OS of metastatic breast cancer patients stratified by ALB levels. (D) OS of metastatic breast cancer patients stratified by the NLR. OS, overall survival; NE, neutrophils; ALB, albumin; NLR, neutrophil to lymphocyte ratio; CI, confidence interval.

that normal levels of baseline serum ALB (>3.5 g/dl) had a 72% reduced risk of death compared with patients with lower levels (<3.5 g/dl). The present study showed that patients with low ALB levels had a poor prognosis at each stage of breast cancer. However, it has also been shown that serum ALB may not be meaningful in predicting the invasion or relapse of breast cancer (7).

In recent years, substantial clinical and laboratory evidence has supported the notion that inflammation is closely associated with malignant tumors, an independent risk factor in the occurrence and progression of malignant tumors (35). NE, as a leading biomarker of inflammation, plays an important role in the inflammatory tumor microenvironment (36). A study by Dumitru *et al* (37) showed that NEs have strong proangiogenic activities which were mediated by VEGF and the release of matrix metalloprotease-9. They also showed that NE trophozoites can increase the migration, invasion, and metastasis of a tumor. A study by Dumitru *et al* (38) found that NE-derived oncostatin M induced VEGF production from cancer cells when cocultured with blood and increased cancer cell detachment and invasive capacity, suggesting that NEs and oncostatin M may promote tumor progression *in vivo*. A recent study showed that NE extracellular traps (NETs) were associated with cancer progression (39). Multiple investigations

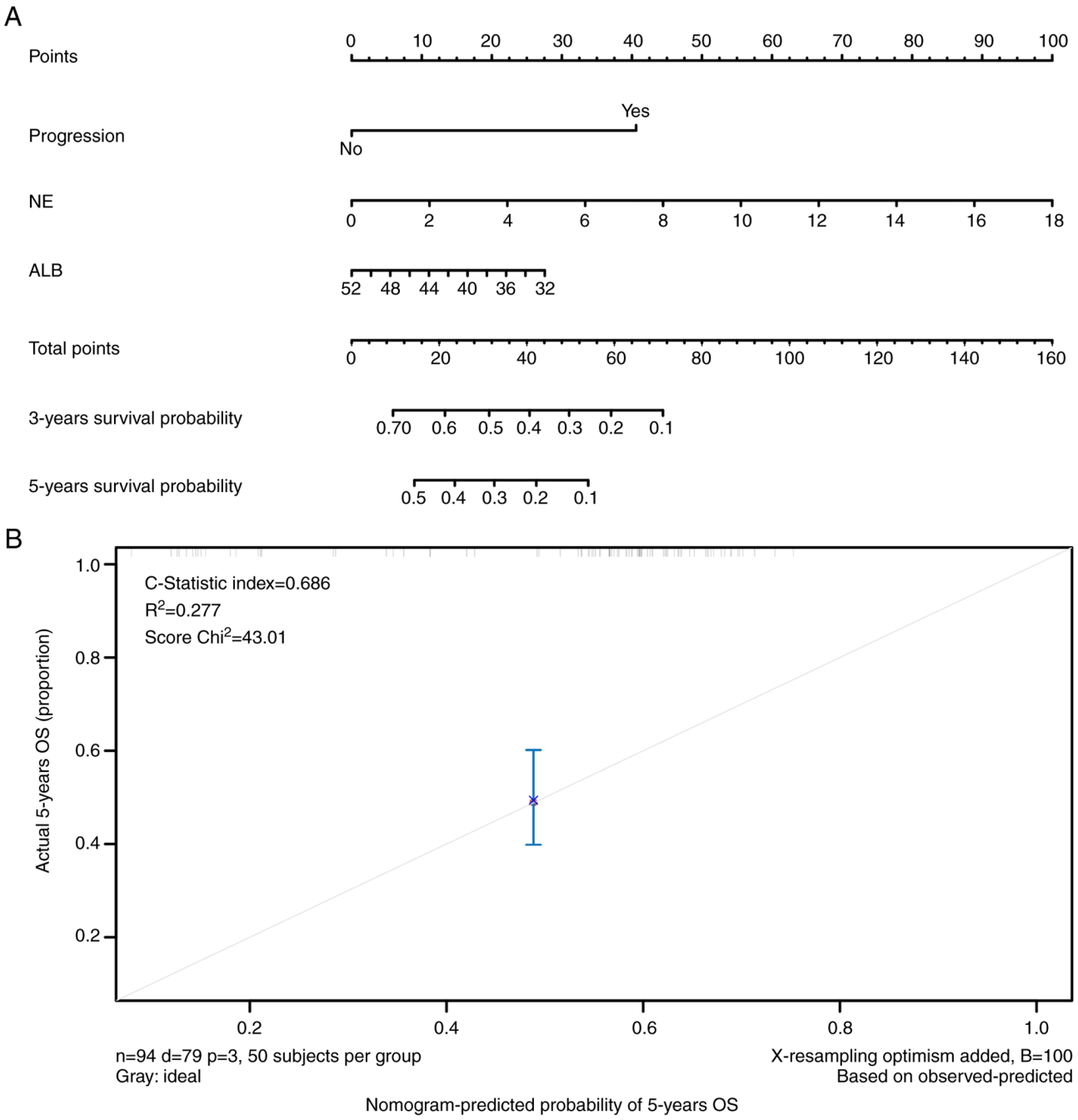

Figure 3. Nomogram for OS risk estimation of patients with metastatic breast cancer patients and its predictive performance. (A) Nomogram to estimate the OS risk of metastatic breast cancer patients in different factors. (B) Validity of the predictive performance of the nomogram in estimating the OS risk of metastatic breast cancer patients (n=94). OS, overall survival; NE, neutrophils; ALB, albumin.

have reported that mild neutropenia during chemotherapy was associated with a better OS in patients with breast cancer and other types of cancer (40-42). The present study also analyzed the correlation between survival and globulin levels and found that it was not statistically significant.

As an excellent anticancer drug carrier, ALB exhibits remarkable potential in the field of tumor therapy. Several ALB-mediated anticancer drugs have been developed with multiple advantages (43,44). For example, 130 nM ALB-bound (nab™) paclitaxel, also known as Abraxane, is being extensively applied clinically. It is now used primarily for metastatic breast cancer following a lack of response to combination chemotherapy or breast cancer that has recurred within 6 months of adjuvant chemotherapy. Compared with traditional solvent paclitaxel, Abraxane exhibits improved safety and efficacy (45).

The present study has some limitations. First, this study was retrospective, thus there may be some selection bias. Secondly, the sample size of this study is small. Moreover, this study did not include evaluation of genetic markers for breast cancer although genetic markers are important in oncology research for early diagnosis of disease and prediction of prognosis. Therefore, a prospective multi-center study with larger sample sizes, where additional varied factors are assessed is required to confirm the results of the present study.

In conclusion, the present study showed that low serum ALB levels and increased NE counts were predictive of a poorer prognosis in patients with metastatic breast cancer. The nomogram that was constructed based on multivariate analysis had good accuracy in estimating the risk of OS.

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Availability of data and materials

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

Authors' contributions

MX and HZ designed the study and performed the experiments. JC, HZ and YY collected and analyzed the data. ZX, MX, HZ, and JT contributed to research design, data analysis, writing the manuscript and supervision of the study. ZX and JC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Suzhou, China). The processing of clinical tissue samples was performed in strict compliance with the ethical standards described in the Declaration of Helsinki. All patients signed written informed consent forms.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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