Original Research Article

Prognostic Value of Combined Lactate Dehydrogenase, C-Reactive Protein, Cancer Antigen 153 and Cancer Antigen 125 in Metastatic Breast Cancer

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Abstract

Background: Breast cancer (BC), especially metastatic BC, is one of the most lethal diseases in women. CA 125 and CA 15-3 are commonly used indicators for diagnosis and prognosis of BC. Some serological indicators, such as lactate dehydrogenase (LDH) and C-reactive protein (CRP), can also be used to assess the prognosis and progression in BC.

Methods: Univariate Cox regression analysis and LASSO regression analysis were performed to identify prognostic factors and build prognostic models. We distributed the patients into 2 groups based on the median risk score, analyzed prognosis by Kaplan–Meier curve, and screened independent prognostic factors by multivariate Cox regression analysis.

Result: We identified 4 indicators-LDH, CRP, CA 15-3, and CA 125—related to the prognosis in BC and established a prognostic model. The high LDH group showed worse overall survival (OS) than low LDH group (P = .017; hazard ratio (HR), 1.528; 95% confidence interval (CI), 1.055-2.215). The high CRP group showed worse OS than low CRP group (P = .004; HR, 1.666; 95% CI, 1.143-2.429). The high CA153 group showed worse OS than low CA 15-3 group (P=.011; HR, 1.563; 95% CI, 1.075-2.274). The high CA 125 group showed worse OS than low CA 125 group (P = .021; HR, 1.499; 95% CI, 1.031-2.181). The area under the curve for risk score was .824, Ki-67 was .628, age was .511, and grade was .545. Risk score was found to be an independent prognostic factor using multivariate Cox regression analysis.

Conclusion: We successfully established an optimization model by combining 4 prognosis-related indicators to assess the prognosis in patients with metastatic BC.

Keywords

breast cancer, C-reactive protein, lactate dehydrogenase, prognosis, risk factors

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Introduction

Breast cancer (BC) is one of the most commonly diagnosed tumors in women. Approximately 272,400 new cases and 70,700 deaths with BC occur each year in China.[1] The main causes of death in patients with BC are recurrence and metastasis of the disease. According to molecular pathological classification, BC is primarily divided into 3 categories: hormone receptor (HR)-positive, HER2-positive, and triple-negative BC (TNBC).[2,3]

TNBC is a poor prognosis factor, the prognosis of patients is very poor, and the number of patients with TNBC is small. As we could not measure its weight in the model, we excluded patients with TNBC. Additionally, it is difficult to follow up the overall survival (OS) of patients with HER2-positive and early ER- and PR-positive tumors because of their long survival time. Therefore, we selected patients with stage IV tumors with ER-positive, PR-positive, and HER-2 negative status.

Some serum tumor indicators are correlated with prognosis in patients with BC Lactate dehydrogenase (LDH) is a key enzyme in the glucose metabolism pathway and catalyzes conversion of glucose to lactic acid.[4] LDH is associated with prognosis in various cancers, including breast cancer, cervical cancer, and lung cancer.[5-7] C-reactive protein (CRP) is an indicator of systemic inflammation,[8] and elevated levels of CRP indicate poor prognosis in several cancer types.[9] CA 15-3 is a soluble MUC1 mucin, which is a tumor indicator commonly used in the diagnosis of BC.[10] Moreover, serum CA 15-3 level is a recognized prognostic indicator of BC.[11] CA 125 is an important biomarker for the diagnosis of BC and can predict the course of the disease.[12] Researchers usually select one of these indicators or associate multiple indicators to help in the early diagnosis or evaluate efficacy and prognosis in BC.

As all the indicators have false positives and false negatives, we attempted to combine multiple indicators to analyze prognosis in each patient. In the present study, we combined 4 indicators to predict prognosis in patients with metastatic BC and established a prognostic model. We anticipate that a combination of different indicators can better analyze prognosis in patients with metastatic BC.

Material and Methods

Patients

The inclusion and exclusion criteria were shown in Supplementary Figure S1.

This retrospective study included 130 patients with metastatic BC who were admitted at the Suzhou Municipal Hospital, Jining Cancer Hospital, and Yijishan Hospital of Wannan Medical College, between 2014 and 2017. All patients were staged according to the criteria of the AJCC eighth edition. The study was approved by Institutional Ethics Committee of the Jining Cancer Hospital and the Affiliated Suzhou Hospital of Nanjing Medical University; and all patients or their relatives provided verbal informed consent after being told the significance of this study. The approval number of this study was KL901196, and the study was conducted in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are shown in Supplementary Figure S1.

The inclusion criteria for patients were as follows: (a) Aged 18-75 years; (b) Eastern Cooperative Oncology Group (ECOG) score of 0-1; (c) tumor molecular subtypes ER-positive, PR-positive, and HER-2–negative; (d) stage IV disease. The exclusion criteria for patients were as follows: (a) HER-2 positive and TNBC; (b) men with BC; (c) underwent a blood test for acute or chronic inflammation, fever, and abnormally elevated neutrophils.

Examination of Serum Indicators

Patients underwent fasting for 8 h at night before the blood test, and elbow venous blood was collected between 7 AM and 8 AM to avoid any effect of the circadian rhythm on the results. RBCs and WBCs were examined using a hematology analyzer (Sysmex XE-2100; Sysmex, Kobe, Japan). LDH, CRP, albumin (ALB), and globulin (GLB) levels were examined using a clinical chemistry analyzer (Hitachi 7600; Sysmex, Kobe, Japan). Levels of CA 15-3, CA 125, carcinoembryonic antigen (CEA), CA 19-9, and CA 72-4 were examined using the Immunology Analyzer (Roche cobas e601; Basel, Switzerland).

Evaluation and Follow-Up of Patients

Computed tomography (CT) was performed every 3 months to evaluate the response and patients were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[13] The survival duration was calculated from the time of diagnosis to death or the last follow-up. Patients were followed up for 13-48 months (median, 23 months). The first follow-up was 1 month after radiotherapy and continued until the patient died or the end of the study in August 2019. The first follow-up for patients who received first-line endocrine therapy was 3 months after treatment and for those who received first-line chemotherapy was 2-3 cycles after chemotherapy.

Construction of Prognostic and Validation Models

Prognostic risk scores were obtained for all patients by univariate Cox regression analysis and LASSO-penalized Cox regression.[14] To further verify the feasibility of the prognostic model, we randomly distributed the patients into 2 groups-test and training-using the edgeR package (v3.52). The survival of

Table 1 Clinicopathological Features of BC Patients.

Clinical Features		
Age (years)	Media	51
	Age	29-75
	Numbers of patients (n = 130)	Numbers of patients (%)
T	T1 (≤2 cm)	14 (10.77)
	T2 (2~5 cm)	56 (43.08)
	T3 (>5 cm)	45 (34.62)
	T4(chest wall or skin invasion)	15 (11.53)
N	Have	96 (73.85)
	None	34 (26.15)
Grade	G1	54 (41.54)
	G2	37 (28.46)
	G3	39 (30.00)
Ki-67	≤30	58 (44.62)
	>30	72 (55.38)
First-line effect	SD	20 (15.38)
	PR	57 (43.85)
	PD	53 (44.77)

Abbreviation: BC, breast cancer; PD, progressive disease, PR, partial response; SD, stable disease

patients in the 2 groups was analyzed using the Kaplan–Meier (KM) analysis. The risk score calculation formula is as follows

$$SurvivalRiskScore(SRS) = \sum_{i=1}^{k}(C_i \times V_i)$$

Statistical Analysis

All statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, La Jolla, CA, USA). For analysis of survival data, KM curves were constructed, and statistical analysis was performed using log-rank test. Univariate and multivariate Cox regression analyses were used to identify the independent risk factors associated with BC. The associations between risk score and clinicopathological features were evaluated using $\chi 2$ test. Statistical significance was set at $P < .05$.

Results

Clinical Features of Patients With BC

This study included 130 patients. The median age of patients was 51.0 years, and their ages ranged from 29 to 75 years. The patients had median survival duration of 19.05 months. Of the 130 patients, 14, 56, 45, and 15 had tumor stages T1, T2, T3, and T4, respectively. Ninety-six patients had lymphatic metastasis, and 34 had no lymphatic metastasis. Fifty-eight patients had high Ki-67 (>30) levels, and 72 had low Ki-67 (≤30) levels. At the time of diagnosis, 54, 37, and 39 patients had grade 1, grade 2, and grade 3 tumors, respectively. At the first evaluation, 20, 57, and 53 patients had stable disease (SD), partial response (PR), and progressive disease (PD), respectively. All patients received first-line chemotherapy or endocrine therapy. The clinicopathological features are summarized in Table 1. 2 separate tables were made for the test group and the train group named Supplementary Table S1 and Supplementary Table S2.

Prognostic Significance of Pretreatment Parameters in Patients With Metastatic BC

The patients were distributed into 2 groups according to median parameter levels. With univariate Cox regression analysis, prognostic factors are screened for BC patients, as shown in Figure 1.

The high LDH group showed worse OS than low LDH group (Figure 2A; $P = .017$; hazard ratio, (HR) 1.528; 95% confidence interval (CI), 1.055-2.215). The high CRP group showed worse OS than low CRP group (Figure 2B; $P = .004$; HR, 1.666; 95% CI, 1.143-2.429). The high CA 15-3 group showed worse OS than low CA 15-3 group (Figure 2C; $P = .011$; HR, 1.563; 95% CI, 1.075-2.274). The high CA 125 group had worse OS than low CA 125 group (Figure 2D; $P = .021$; HR, 1.499; 95% CI, 1.031-2.181).

Development of Prognostic and Validation Models

We used univariate Cox regression and LASSO regression analyses to build an optimization model (Figure 3A and 3B). The prognostic parameter signature was derived as a risk score using the following formula:

Risk score = (CA 15-3 value × .02248) + (CA 125 value × .01143) + (LDH value × .00025) + (CRP value × .07668).

We classified patients into high- and low-risk score groups based on the median risk score as the cutoff and analyzed the

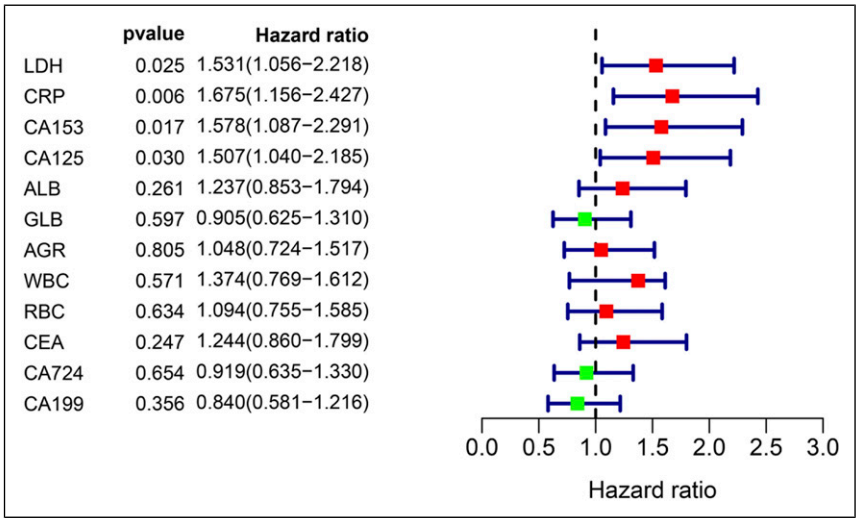

Figure 1. Univariate Cox regression analysis of clinical indicators.

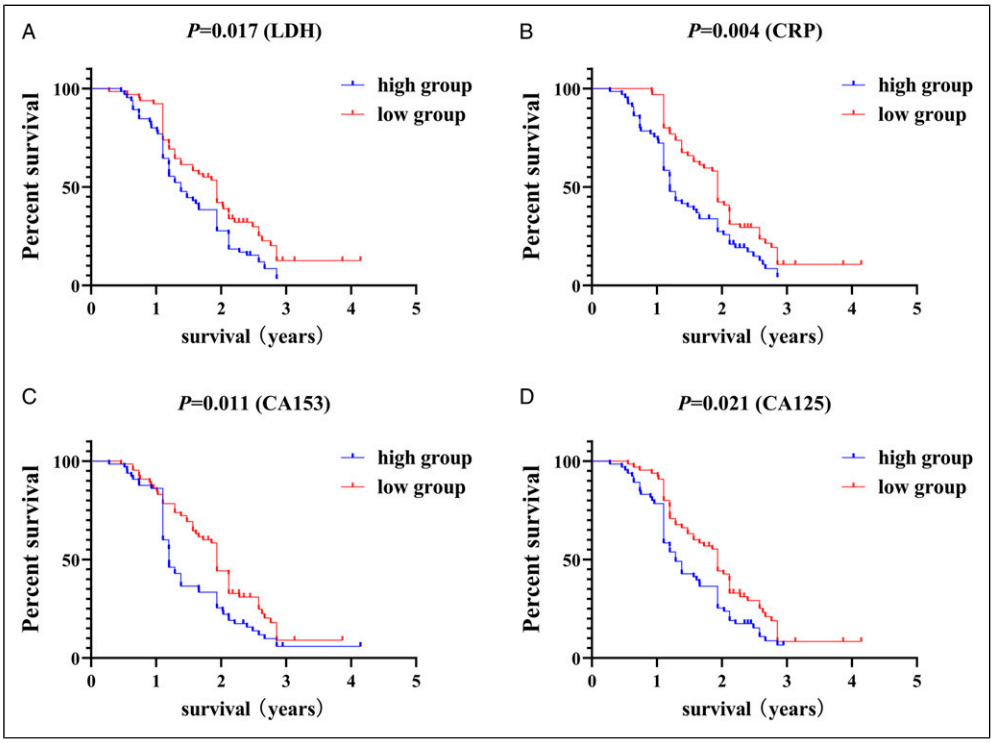

Figure 2. The Kaplan–Meier (KM) curve for clinical indicators related to prognosis: A, LDH; B, CRP; C, CA 15-3; and D, CA 125.

survival by KM curve. The high-risk score group showed worse OS than low-risk score group (Figure 4A; $P = .001$; HR, 1.835; 95% CI, 1.257-2.678).

To further verify the feasibility of the model, we used the edgeR package, which randomly distributed all patients into 2 groups—test and training to construct validation models (Figure 3C-F). Regardless of the test or training groups, the prognosis of the high-risk score group is shown in Figure 4B (test: P<.001; HR, 2.698; 95% CI, 1.546-4.708) and Figure 4C (training: $P = .030$; HR, 1.705; 95% CI, 1.002-2.900).

Clinical Outcome of Prognostic Models

The univariate analyses showed that high Ki-67 (HR, 1.508; 95% CI, 1.037-2.193; $P = .031$) and high-risk score (HR,

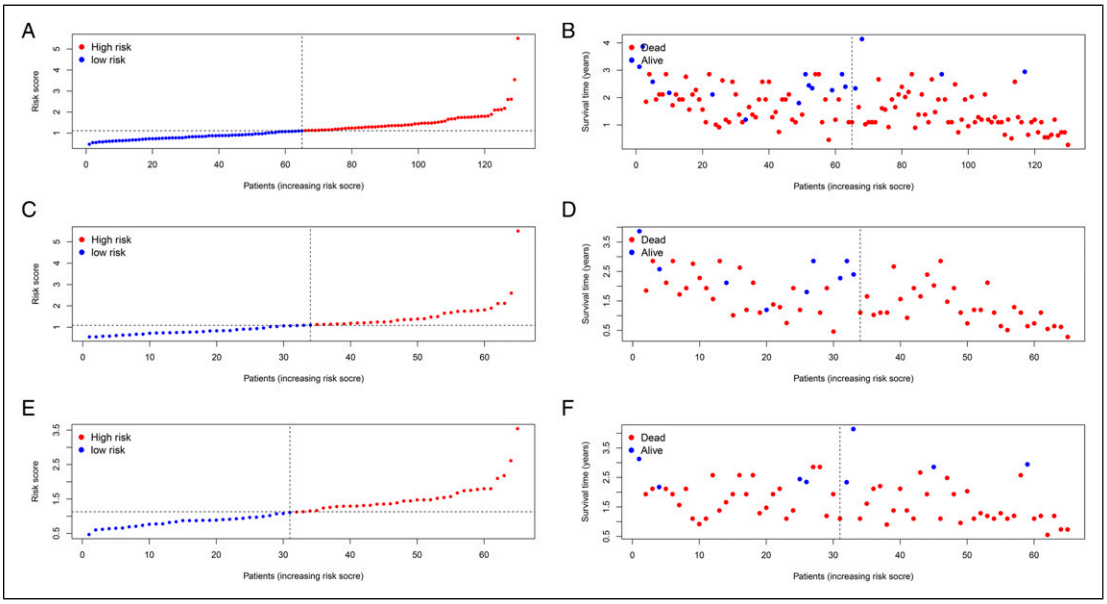

Figure 3. Construction of the prognostic and validation models. A, risk score and distribution of groups in all patients with breast cancer (BC). B, survival status of all patients with BC in different groups. C, risk score and distribution of patients with BC in the test group. D, survival status of patients with BC in different groups in the test group. E, risk score and distribution of patients with BC in the training group. F, survival status of patients with BC in different groups in the training group.

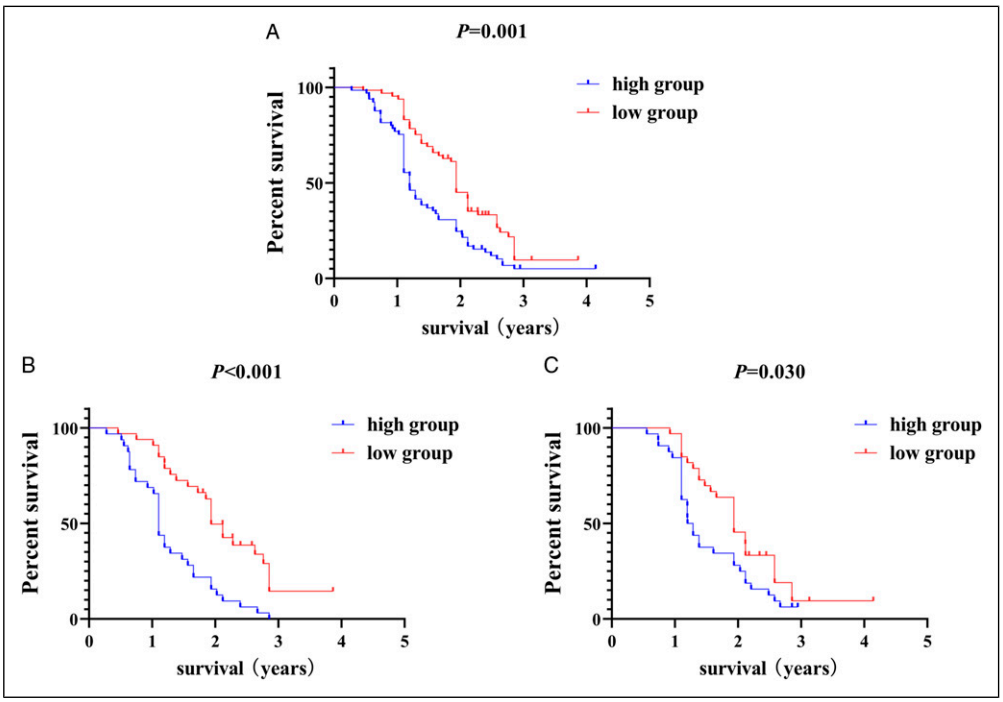

Figure 4. Prediction of prognosis using prognostic and validation models. A, Kaplan–Meier (KM) curves for all patients with BC using prognostic model. B, KM curve for patients with BC in the test group using validation model. C, KM curve for patients with BC in the training group using validation model.

1.863; 95% CI, 1.283-2.704; P = .001) were significant risk factors for worse prognosis (Figure 5A). In the multivariate analysis, high-risk score (HR, 1.800; 95% CI, 1.236-2.621; P = .002) was found to be independently associated with worse survival (Figure 5B). The outcomes of the multivariate analyses for OS are shown in Table 2.

The risk scores varied significantly between the different Ki-67 groups (Figure 6A) and different first-line treatment

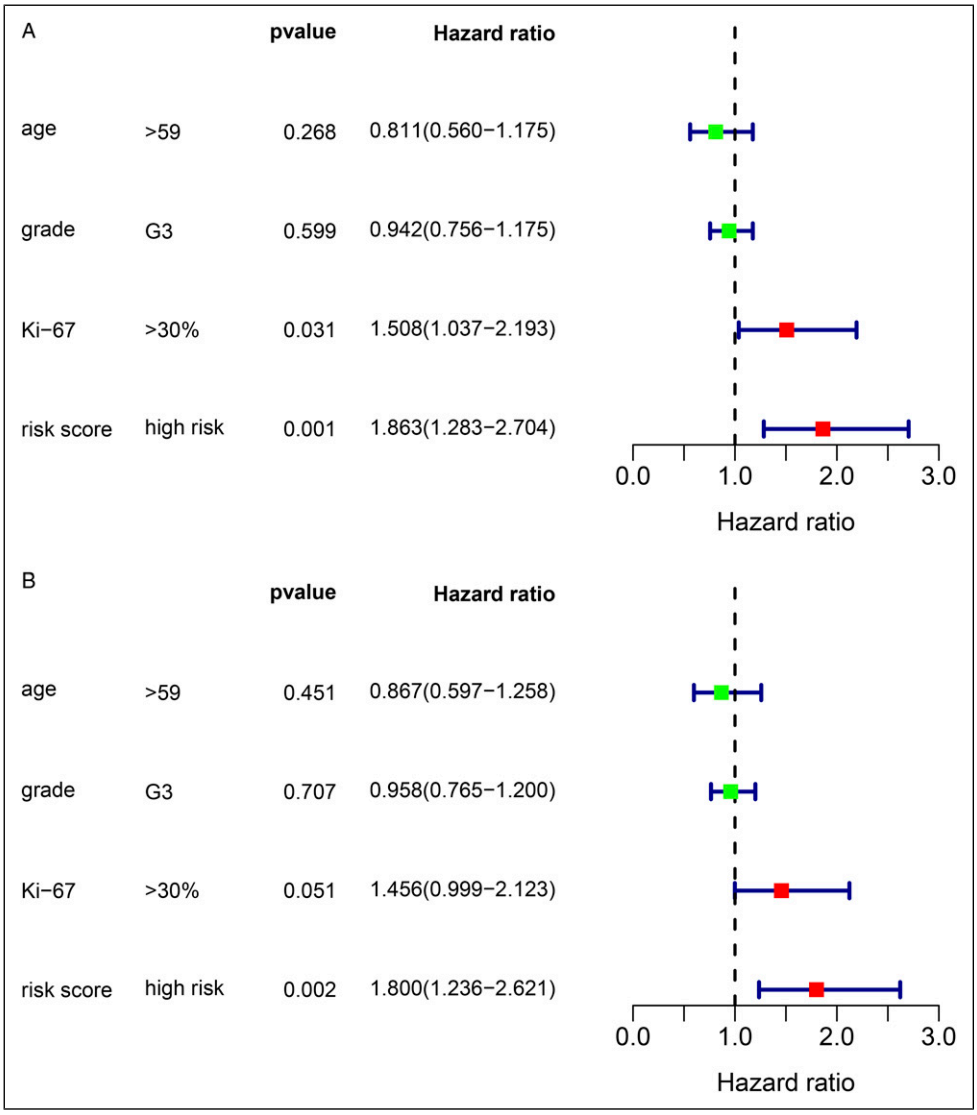

Figure 5. Cox regression analysis of prognostic model. A, univariate analyses; B, multivariate analyses.

Table 2. Univariate and multivariate logistic regression analysis of Breast cancer patients risk factors.

	Overall survival (OS)			
	Univariate Analysis		Multivariate Analysis	
Risk factors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (>59 years or ≤59 years)	.811 (.560-1.175)	.268	.867 (.597-1.258)	.451
Grade (G3 or G1-2)	.942 (.756-1.175)	.599	.958 (.765-1.200)	.707
Ki-67 (>30 or ≤30)	1.508 (1.037-2.193)	.031	1.456 (.999-2.123)	.051
Risk score (high or low)	1.863 (1.283-2.704)	.001	1.800 (1.236-2.621)	.002

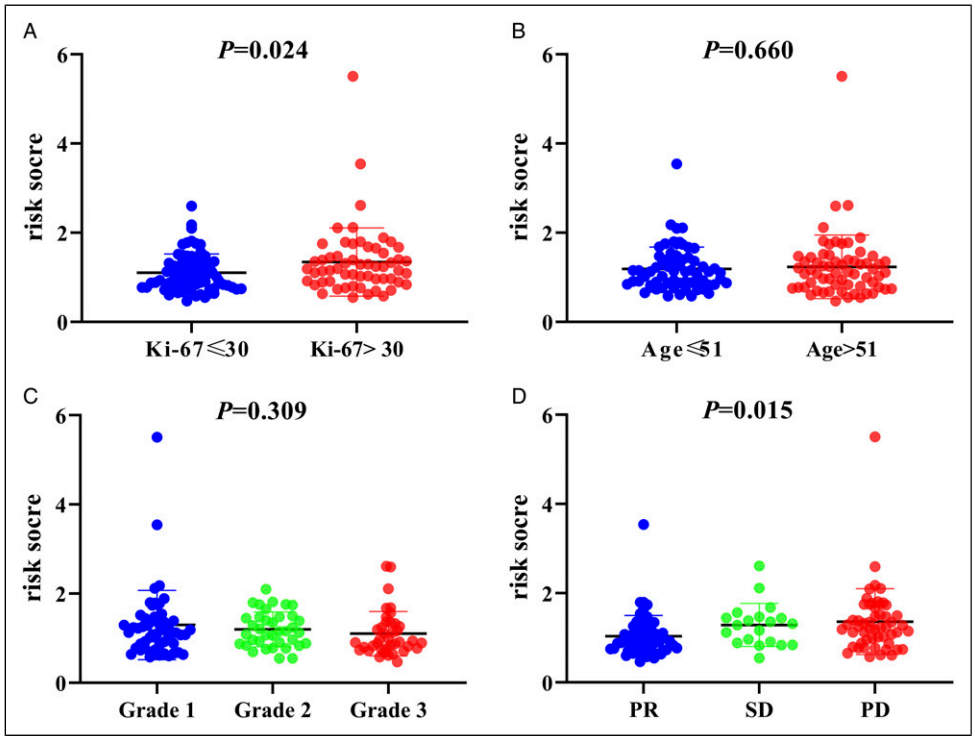

Figure 6. Relationship between risk score and clinicopathological features in prognostic model. A, Ki-67; B, age; C, grade; and D, first-line treatment effect.

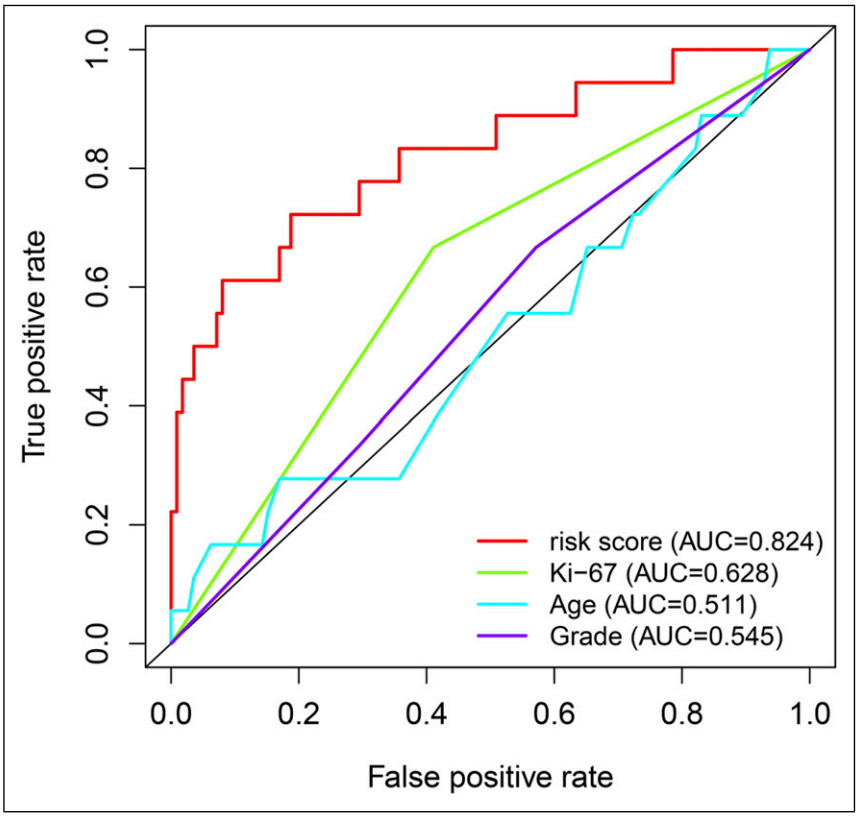

Figure 7. Receiver operating characteristic (ROC) curve for prognostic model and clinicopathological features.

effect groups (Figure 6D). The risk scores were not significantly different between the different age groups (Figure 6B) and different grade groups (Figure 6C).

Verification of the Accuracy of the Prognostic Model

To further verify the accuracy of the prognostic model, we constructed an ROC curve, as shown in Figure 7. The area under the curve for risk score was .824, for Ki-67 was .628, for age was .511, and for grade was .545.

Discussion

Breast cancer is the most common malignancy, and despite recent advances in diagnosis and treatment, it remains the second leading cause of death in women. Highly aggressive subtypes of TNBC and chemoresistance are 2 challenging areas of current research. However, tumor biomarkers have been found to assist in breast cancer diagnosis, prognosis, prediction of treatment response, and disease monitoring during and after treatment.[15]

In the present study, 4 indicators related to prognosis-LDH, CRP, CA 15-3, and CA 125-were identified to construct an optimization model with univariate Cox and LASSO Cox regression analyses. In the model, we distributed patients into 2 groups based on the median risk score, and patients with high-risk scores showed worse prognosis than those with low-risk scores. To further verify the model, the R language was used to randomly distribute the patients into 2 groups. We found that regardless of the group, the prognosis of patients with high-risk score had worse OS than those with low-risk score.

A few serum indicators are currently being used to predict prognosis in breast cancer. Studies have shown that CA 15-3 and CA 125 can assess the prognosis in patients with breast cancer. A study by Li et al. found that high levels of CA 15-3 (>13U/mL) are related to metastasis-free survival and recurrence-free survival in patients with luminal-A BC.[16] In another study, Li et al. found that levels of CA 15-3 (1 week and 6 months) and CA 125 (1 week after surgery) were significantly higher in patients with recurrent BC than those in patients without recurrent BC.[17] A study by Nazmeen et al.[18] suggested that levels of CA 125 are indicators for diagnosis and can also predict prognosis and disease progression in BC.[18] Taken together, these retrospective studies have shown that CA 15-3 and CA 125 can assess prognosis in patients with metastatic and recurrent BC. In the present study, patients with BC were distributed into 2 groups according to their median pretreatment CA 15-3 and CA 125 levels. Univariate analysis showed that CA 15-3 and CA 125 are prognostic indicators of metastatic BC. The KM curve showed that the high CA 15-3 and CA 125 groups have worse prognosis than low CA 15-3 and CA 125 groups.

LDH is a key enzyme in the lactic acid metabolism pathway, and its activity is closely related to injury, inflammation, and tumor growth.[4] Previous studies have identified LDH as a prognostic factor for metastatic BC. In a study involving 392 patients with advanced BC, Pelizzari et al. found that increased levels of LDH after first-line treatment in patients with BC are an independent prognostic factor for OS and progression-free survival (PFS).[19] A meta-analysis by Liu et al.[20] indicated that LDH is an independent prognostic factor for OS and PFS in patients with metastatic and non-metastatic BC.[20] Further, CRP is an indicator of inflammation and its levels are related to prognosis in many cancers. In contrast, Wulaningsih et al. suggested that pretreatment levels of CRP are associated with prognosis, but not with diagnosis, in BC.[9] A study by Villaseñor et al.[21] reported that levels of CRP are associated with 5-year and 10-year survival rates in patients with BC.[21] The present study indicated that high levels of LDH and CRP correlate with worse OS in patients with metastatic BC. The Ki-67 proliferative index (Ki-67) is a predictive and prognostic factor in BC. Tagliafico et al. showed that quantitative radiomic imaging features extracted from digital breast tomosynthesis images in breast tumors are associated with Ki-67 expression.[22] Aman et al. found that a high Ki-67 index is associated with adverse clinicopathological factors. Moreover, Ki-67 index is useful for the treatment in patients with primary BC.[23] Many studies have used at least one of the indicators to guide patient prognosis. Therefore, we intend to combine more indicators to more effectively evaluate prognosis in patients with metastatic BC.

There are a few limitations in the present study. First, it was a single-center retrospective study, and second, some other clinical features of BC were not considered. Therefore, we will increase the sample size and conduct multicenter research in the future.

Conclusion

In summary, single tumor indicators have limitations as assessment methods for prognosis in BC. The present study identified 4 indicators and constructed a prognostic model for HR-positive metastatic BC. The risk score and results of the first evaluation after treatment showed that patients with PD and SD had significantly higher risk scores than those with PR.

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Author Contributions

YW and SCS contributed conception and design of the study; YFL, JJW, and YQH collect the data; XYC, WDZ, and WJW performed the statistical analysis; YYM and HW wrote the first draft of the article. All authors contributed to article revision, read, and approved the submitted version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Statement

This work was approved by the Medical Ethics Committees of the Suzhou Municipal Hospital, Jining Cancer Hospital, and Yijishan Hospital of Wannan Medical College, and all patients or their relatives provided verbal informed consent after being told the significance of this study. The approval number of this study was KL901196, and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent

Verbal consent for publication was obtained from all participants.

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Supplemental material

Supplemental material for this article is available online.

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