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Erythrocyte modified controlling nutritional status as a biomarker for predicting poor prognosis in post-surgery breast cancer patients

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Nutrition and inflammation are closely related to prognosis in breast cancer patients. However, current nutritional and inflammatory measures predict disease free survival (DFS) of breast cancer are still different, and the most predictive measures remain unknown. This study aimed to compare the predictive effects of commonly used nutritional and inflammatory measures on DFS and to improve existing nutritional or inflammatory measures in order to develop a new model that is more effective for predicting postoperative recurrence and metastasis in breast cancer patients. The clinical data of 536 female breast cancer patients with invasive ductal carcinoma who underwent surgery at Shaoxing People's Hospital from January 2012 to December 2018 were retrospectively evaluated. The predictive effects of nutritional and inflammatory indicators on DFS were evaluated. Machine learning was used to evaluate and rank laboratory indicators, select relatively important variables to modify nutritional or inflammatory indicators with the best predictive power, and evaluate their predictive role in patients' postoperative recurrence and metastasis. Among various metrics predicting DFS, the CONUT score emerged paramount with an area under the curve (AUC) of 0.667. Interestingly, the combination of the erythrocyte levels with the CONUT score (ECONUT) achieved the highest AUC (0.722). The Kaplan-Meier survival analysis showed that the group exhibiting high ECONUT scores experiencing a notably poorer DFS. ECONUT was identified as an independent risk factor for postoperative DFS ($P < 0.001$). The ECONUT model could provide an effective assessment tool for predicting DFS in breast cancer patients.

Keywords Breast cancer, Nutrition, Inflammation, Recurrence, Metastasis, Prognosis

Abbreviations

AUC	Area under the curve
BCS	Breast conserving surgery
CONUT	Controlling Nutritional Status
DFS	Disease-free survival
ECONUT	Erythrocyte-modified Controlling Nutritional Status
HER2	Human epidermal growth factor receptor 2
MLR	Monocyte-to-lymphocyte ratio
NRI	Nutritional risk index
NLR	Neutrophil to lymphocyte ratio
PIV	Pan-immune-inflammation value
PLR	Platelet to lymphocyte ratio
PNI	Prognostic nutritional index
ROC	Receiver operating characteristic
SII	Systemic immune-inflammation index
SIRI	Systemic inflammation response index
TNBC	Triple negative breast cancer

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TG	Triglyceride
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
APO	Apolipoprotein

Metastasis of breast cancer, the most prevalent malignancy in women, remains a formidable adversary; it accounts for a significant proportion of cancer-related fatalities. Despite advancements in surgery, radiotherapy, chemotherapy, targeted therapy, and neoadjuvant chemotherapy, the mortality rate of breast cancer remains high, particularly in cases characterized by distant metastasis or postoperative resurgence[1]. Distant metastasis remains the main cause of mortality in breast cancer patients[2]. Therefore, there is a need to identify biomarkers that could be used to predict the risk of recurrence and metastasis to identify those patients who will benefit substantially from a more aggressive treatment strategy, thereby personalizing treatment and improving survival outcomes.

Studies have shown that the nutritional and inflammatory status may have an impact on disease progression and prognosis in cancer patients[3,4]. Poor nutritional status could trigger an inflammatory response and metabolic abnormalities, and inflammation affects the role of nutrition to varying degrees, ultimately leading to worse outcomes[5,6]. Numerous systemic inflammatory markers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), systemic inflammation score (SIS), pan-immune-inflammation value (PIV), and systemic inflammation response index (SIRI), are associated with tumor recurrence and metastasis[7–9]. Similarly, several nutritional indicators such as the Controlling Nutritional Status (CONUT), the Prognostic Nutritional Index (PNI), and the Nutritional Risk Index (NRI) have been identified as independent prognostic factors in gastrointestinal tumors[10–12]. Compared to the cumbersome, time-consuming, and subjective patient-generated subjective global assessment (PG-SGA), these nutritional and inflammatory markers are easily measurable, simple, and objective. However, there are still differences between these measures in predicting disease free survival (DFS) of breast cancer, and the most predictive measures remain unknown[13]. Therefore, further research is warranted to investigate the role of these markers in patients with breast cancer, especially in some specific subtypes.

In this study, we investigated the prognostic value of various nutritional and inflammatory assessment markers in breast cancer patients undergoing surgery. We compared the predictive effects of these markers on DFS and refined the existing markers to determine a more effective indicator for predicting postoperative recurrence and metastasis in patients with breast cancer. Additionally, we aimed to provide more accurate indicators for physicians and patients to assess the prognosis of each patient with breast cancer.

Methods

Study design

Invasive breast cancer patients who underwent primary tumor resection in Shaoxing People's Hospital from January 2012 to December 2018 were retrospectively retrieved from the patients' medical records. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shaoxing People's Hospital (064-Y-01). Due to the retrospective nature of the study, Ethics Committee of Shaoxing People's Hospital waived the need of obtaining informed consent. Only female patients with a histopathologically confirmed diagnosis of invasive breast cancer without distant metastasis who had complete medical records and peripheral venous blood measurements in the week prior to surgery were included in the study. Patients who received neoadjuvant therapy, had inflammatory or autoimmune diseases, and those who were diagnosed with other types of malignant tumors or serious diseases after surgery were excluded from the study. In addition, patients who received medications that could affect the blood cell count were also excluded. A flow chart detailing the study patients is provided in Supplementary Fig. 1.

Pathological features and molecular subtypes

Patients were staged according to the 8th Edition American Joint Committee on Cancer-Tumor, Node, and Metastases (AJCC-TNM) staging system[14]. The expression of estrogen receptor (ER) and progesterone receptor (PR) were scored using the St. Gallen criteria[15]. the human epidermal growth factor receptor (HER-2) status was assessed by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) assay. HER-2 negative status was defined as IHC HER-$2^{+}/^{++}$, or the FISH result was negative, or the FISH test was not performed; HER-2 positive status was defined as IHC = 3^{+}, or FISH-positive/chromogenic in situ hybridization-positive[16,17]. Ki-67 positive nuclear ≥ 14% was defined as high expression, < 14% as low expression[18].

Data collection process

The information on demographic (gender and age), clinical (surgical technique, menstrual status, height, weight, body mass index (BMI), blood biochemistry), and pathological subtype was extracted from the patients' medical records. The CONUT score was calculated based on the albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration The CONUT ranges from 0 (normal) to 12 (severe malnutrition). The formulas for calculating all nutritional scores and inflammatory evaluation indicators are described in detail in the Supplementary Table 1.

Follow-up assessment

In this investigation, the principal outcome measure was Disease-Free Survival (DFS), which denotes the interval from surgical intervention until the detection of recurrent or metastatic illness within the study's observation period. Recognition of disease recurrence and metastasis was determined by imaging examinations

(breast ultrasound, mammography, thoracic computed tomography, or osteoscintigraphy) or histological biopsy analysis.

Statistical analysis

The data were analyzed using R v.4.2.1. The categorical variables were expressed as numbers (percentages). The non-normally distributed variables were expressed as median (standard deviations). The area under the curve (AUC) of a time-dependent receiver operating characteristic (ROC) curve was used to assess the predictive ability of the models based on the nutritional score and inflammatory score. The random forest machine learning algorithm was utilized to rank the importance of laboratory indicators and screen out the relatively important indicators. The inflammatory markers or nutritional scores with the highest predictive power for DFS were combined with laboratory indicators to build a new predictive model. The survival curve of DFS was drawn by Kaplan-Meier method and tested using the log-rank test for comparisons. Univariate and multivariate Cox regression analyses with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to identify the independent factors linked with DFS. P value of < 0.05 was considered statistically significant.

Results

Patient baseline characteristics

Encompassing an extensive cohort of 536 breast cancer patients, this study delineates a median age of the afflicted at 52 years, spanning a broad spectrum from 23 to 82. The patients were followed up for an average of 90 months. The majority of the patients ($n = 319$, 60%) had Luminal B breast cancer. The rest of the patients were diagnosed with either Luminal A ($n = 72$, 13%), Her-2 positive ($n = 80$, 15%), or triple-negative (TNBC) ($n = 65$, 12%) breast cancer. Out of the 536 enrolled patients, 160 (30%) were diagnosed with pathological stage I, 316 (59%) with pathological stage II, and 60 (11%) with pathological stage III disease. In addition, 49% ($n = 262$) of the patients had lymph node involvement. Total mastectomy was performed in 444 patients (83%) and the rest ($n = 93$, 17%) underwent breast-conserving surgery. Following surgery 95 patients developed tumor recurrence and/or metastasis. 56% of the patients had a CONUT score ranging from 0 to 1. The fundamental attributes of the participating patients are listed in Table 1.

Predictive ability of the nutritional and inflammatory indicators for DFS

As depicted through time-dependent ROC of nutritional indicators PNI, NRI, and CONUT score along with inflammatory markers SII, SIRI, PIV, NLR, PLR, and MLR in breast cancer predictions, the CONUT score had the highest AUC (0.667), indicating the strongest predictive power for DFS, followed by PNI with an AUC of 0.620 (Fig. 1). Furthermore, when examining the AUC of the above nine indicators at 1 year, 3 years, and 5 years, PNI and CONUT demonstrated superior predictive value compared to other nutritional indicators (Supplementary Table 2). Conducting a Kaplan-Meier analysis, we observed that patients with low CONUT, MLR, PLR, NLR, SII, and SIRI had significantly better DFS than those in the high CONUT score group. Conversely, patients with a high PNI had a lower risk of postoperative recurrence or metastasis (Supplementary Fig. 2).

Construction of the novel predictive model

Individual indicators were extracted from the inflammation and laboratory indicators, and their predictive importance was assessed and ranked using a machine learning method (random forest). Notably, erythrocytes were considered to be the most important variables in this ranking (Supplementary Fig. 3). Therefore a new model based on the erythrocyte levels and CONUT score was developed. This novel model is referred to as ECONUT (Erythrocyte modified Controlling Nutritional Status). A nomogram was constructed to visualize the performance of the model, as shown in Fig. 2. The CONUT score and erythrocyte levels are each assigned a specific score on the dotted line. Based on the weighted average score for each variable, we then estimated an erythrocyte score threshold of 100, and a CONUT score of 42.87 as predictive of DFS. After combining these two factors the ECONUT score predictive of DFS was calculated as Erythrocyte score $\times$ (42.87/6) $\times$ CONUT + (100/-5) $\times$ (E-6), which simplifies to ECONUT = 7.145 CONUT – 20E + 120.

The optimal ECONUT cutoff score for predicting postoperative DFS was 54.263. The ECONUT model based on this cutoff achieved an AUC value of 0.722 (95% CI = 0.662 ~ 0.782) and notably surpassed alternative predictive markers, as shown in Fig. 3. Patients were categorized into high and low ECONUT cohorts utilizing this pivotal threshold. The tumor size ($P = 0.039$), lymphatic metastasis ($P = 0.010$), high-density lipoprotein cholesterol (HDL-C) ($P = 0.011$), low-density lipoprotein cholesterol (LDL-C) ($P = 0.001$), apolipoprotein A-1 (APOA-1) ($P < 0.001$) and apolipoprotein B (APOB) ($P < 0.001$) were influencing factors (Supplementary Table 3). The mean DFS was 131.9 months (range = 128.6-135.2 months) for patients with low ECONUT score and 102.9 months (range = 94.1-111.7 months) for patients with high ECONUT score. Concurrently, across varying histological grades encompassing Luminal B, HER2-enriched, and TNBC subtypes, as well as in pathologic stages I and II, the Kaplan-Meier survival analysis revealed a significant disparity in DFS, with the group exhibiting high ECONUT scores experiencing a notably poorer prognosis, as depicted in Fig. 4.

Random internal verification

Employing a stochastic numeral generator, the total population was divided into training (374 cases) and testing (162 cases) cohorts at a ratio of 7:3. The ROC curve shows that ECONUT scores in the training group (AUC = 0.715) and the test group (AUC = 0.727) (Supplementary Fig. 4), and the AUC values of 1 year, 3 years, and 5 years are significantly better than other indicators (Supplementary Table 2), and the calibration curve of the nomogram is in the Supplementary Fig. 5. The internally validated ECONUT score as the most effective indicator of DFS in breast cancer patients.

Characteristic	$N=536^1$
Time (months)	91 (79, 106)
Age (years)	52 (46, 60)
Height (cm)	160.0 (156.0, 162.0)
Weight (kg)	58 (53, 63)
BMI (kg/m^2)	22.9 (21.0, 24.8)
Menopause status	
NO	339 (63%)
YES	197 (37%)
Surgery type	
BCS	92 (17%)
Mastectomy	444 (83%)
Histological grade	
I	40 (7.5%)
II	217 (40%)
III	279 (52%)
Tumor size (cm)	
2≤	247 (46%)
>2且<5	260 (49%)
≥5	29 (5.4%)
Lymphatic metastasis	
NO	274 (51%)
YES	262 (49%)
Pathological stage	
I	160 (30%)
II	316 (59%)
III	60 (11%)
Molecular subtype	
Luminal A	72 (13%)
Luminal B	319 (60%)
HER2-enriched	80 (15%)
TNBC	65 (12%)
PNI	50.2 (47.4, 53.4)
CONUT	
0	129 (24%)
1	171 (32%)
2	134 (25%)
3	75 (14%)
4	20 (3.7%)
5	5 (0.9%)
6	2 (0.4%)
NRI	107 (102, 111)
PIV	162 (100, 264)
SIRI	0.76 (0.50, 1.15)
SII	454 (302, 648)
MLR	0.24 (0.19, 0.31)
NLR	2.05 (1.55, 2.75)
PLR	140 (109, 186)
Leukocyte ($10^9/L$)	5.34 (4.30, 6.42)
Neutrophil ($10^9/L$)	3.20 (2.35, 4.06)
Lymphocyte ($10^9/L$)	1.50 (1.20, 1.90)
Monocyte ($10^9/L$)	0.37 (0.30, 0.46)
Eosinophil ($10^9/L$)	0.07 (0.03, 0.12)
Basophil ($10^9/L$)	0.020 (0.010, 0.030)
Erythrocyte ($10^9/L$)	4.24 (4.00, 4.52)
Hemoglobin ($10^9/L$)	127 (118, 136)
Platelet ($10^9/L$)	219 (183, 258)
Continued	

Characteristic	$N=536^1$
Albumin (g/L)	42.5 (40.0, 44.8)
Cholesterol (mmol/L)	4.66 (4.09, 5.33)
TG (mmol/L)	1.14 (0.77, 1.60)
HDL-C (mmol/L)	1.24 (1.04, 1.49)
LDL-C (mmol/L)	2.92 (2.37, 3.42)
APOA-1 (g/L)	1.22 (1.09, 1.42)
APOB (g/L)	0.84 (0.69, 1.00)
[1]Median (IQR); n (%)	

Table 1. The baseline characteristics of the study population. *BMI* body mass index, *BCS* breast conserving surgery, *CONUT* controlling nutritional status, *NRI* nutritional risk index, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index, *PIV* pan-immune-inflammation value, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *TNBC* triple negative breast cancer, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *APO* apolipoprotein.

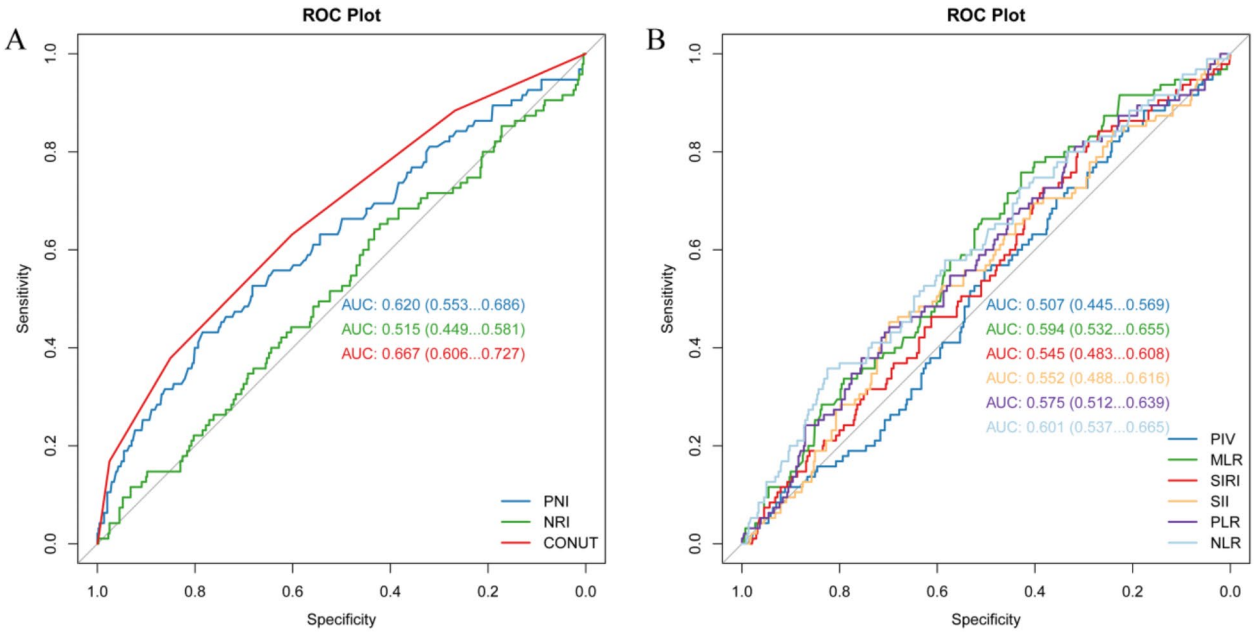

Fig. 1. The time-dependent ROC of nutritional and inflammatory indicators for predicting DFS of breast cancer patients. Notes: (A) Nutritional index. (B) Inflammatory index.

Relationship between nutritional and inflammatory indicators and the risk of DFS

Through univariate and multivariate Cox regression analysis, a high CONUT score ($P<0.001$) and pathological stage ($P<0.001$) were identified as independent predictive factors for DFS (Supplementary Table 4). Furthermore, in model a, there was a significant association between the PNI, CONUT, SIRI, SII, MLR, NLR, PLR, and ECONUT indices and breast cancer recurrence and metastasis (Table 2). However, after adjusting for height, weight, BMI, menopause status, surgery type, pathological stage staging, lymphatic metastasis, and tumor size, only the ECONUT score stood as a statistically significant marker in models b and c. The univariate and multivariate Cox regression analyses identified the ECONUT index as an independent predictor of postoperative recurrence and metastasis in breast cancer patients.

Discussion

Breast cancer is the most frequently diagnosed malignant tumor with high mortality in female, despite improvements in multidisciplinary treatment approaches in recent years, recurrence and metastasis remain major challenges in cancer management. Nutrition and inflammation are closely related to prognosis in breast cancer patients. However, the current nutritional and inflammatory measures that predict DFS in breast cancer are still different, and the most predictive measures remain unclear. In this study, we investigated the impact of nutritional indicators (CONUT, NRI, and PNI), and immune indicators (SII, SIRI, PIV, NLR, PLR, and MLR)

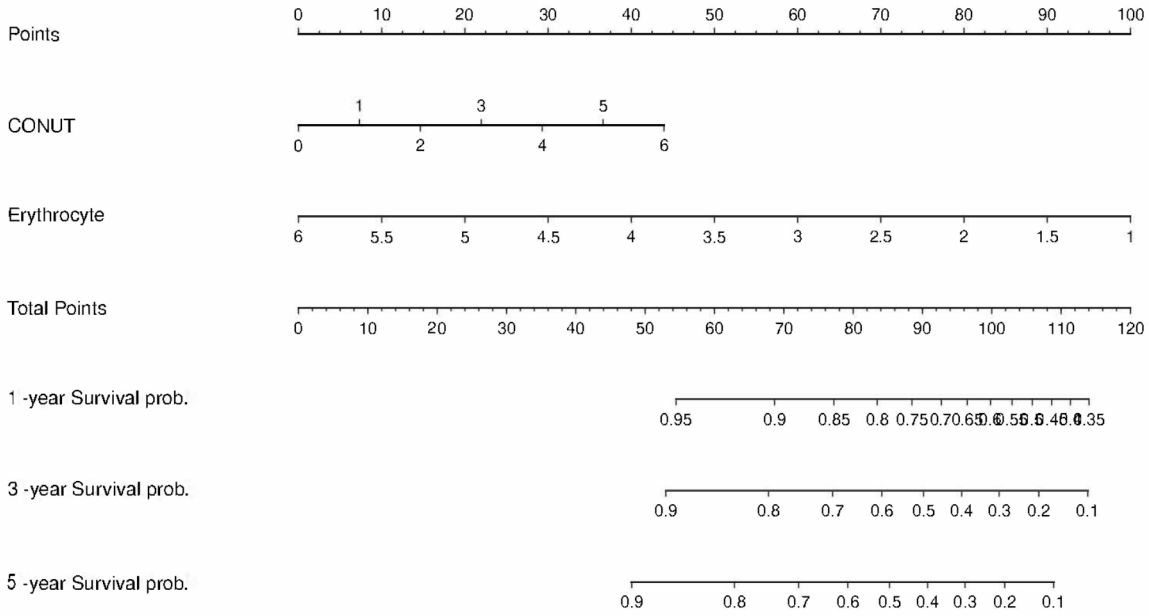

Fig. 2. Nomogram to predict the DFS of breast cancer patients.

on DFS in patients with breast cancer. Among these nine indicators, we found that the ROC curve of nutritional evaluation indicators (CONUT and PNI) was significantly better than that of inflammation-related indicators, indicating that preoperative nutritional status was a more important factor, which was basically consistent with the conclusion of Ahiko et al. in 1880 patients with colorectal cancer[19]. Studies have shown that perioperative nutritional interventions can improve clinical outcomes after surgery and are reflected in relevant guidelines[20].

Since the CONUT score has shown better performance than the other indicators in predicting DFS (AUC = 0.667), followed by the PNI (AUC = 0.620). The random forest method was then used to evaluate and rank the individual variables. In this analysis, the erythrocytes were identified as predictors of DFS and used to develop the ECONUT model. The time-dependent, 1-year, 3-year, and 5-year AUC demonstrated that ECONUT's predictive power was superior to CONUT and the other eight nutritional and immune measures described above. Our current findings indicate that higher ECONUT scores are associated with tumor size, lymphatic metastasis, HDL-C, LDL-C, APOA-1 and APOB. At the same time, across varying histological grades encompassing Luminal B, HER2-enriched, and TNBC subtypes, as well as in pathologic stages I and II, the Kaplan-Meier survival analysis revealed a significant disparity in DFS, with the group exhibiting high ECONUT scores experiencing a notably poorer prognosis. On the other hand, Cox proportional hazard regression models showed that the ECONUT score was identified as an independent prognostic factor for breast cancer.

The ECONUT index is a combination of the CONUT score and the erythrocyte weighting coefficient. The CONUT score was determined based on the total cholesterol, albumin, and lymphocyte levels. Cancer can lead to malnutrition and ultimately a reduction in the body's main energy storage protein albumin[21]. Low serum albumin levels are associated with a higher incidence of mortality in both solid and hematological tumors[22], such as colorectal cancer[23,24], lung cancer[25], and pancreatic cancer[26]. A decreased serum albumin concentration is thought to be associated with systemic inflammation that affects hepatocyte catabolism and anabolism[27,28]. As the main component of the human immune system, lymphocytes reflect the immune ability of the body to fight diseases. The infiltration of lymphocytes in tumors is a positive prognostic marker for many solid tumors[29–31]. Researches have also shown that lower peripheral lymphocyte counts may lead to suppression of the body's anti-tumor immune function. This immunological suppression can precipitate a cascade leading to tumor immune evasion, fostering disease progression and adversely impacting clinical outcomes for patients[32,33]. On the other hand, elevated cholesterol levels have been identified as strongly associated with breast cancer occurrence, recurrence, and metastasis[34–36]. Additionally, our study for the first time used erythrocytes to predict DFS in patients with breast cancer. Studies have shown that fatty acids on the erythrocyte membrane may play a role in regulating immunity, T cell function, and the formation of inflammatory[37,38]. In addition, it has been reported that erythrocyte membrane proteins play a diagnostic and predictive role in metastatic breast cancer[39]. Therefore the combination of the erythrocytes levels with nutritional markers could be used to better assess the extent of

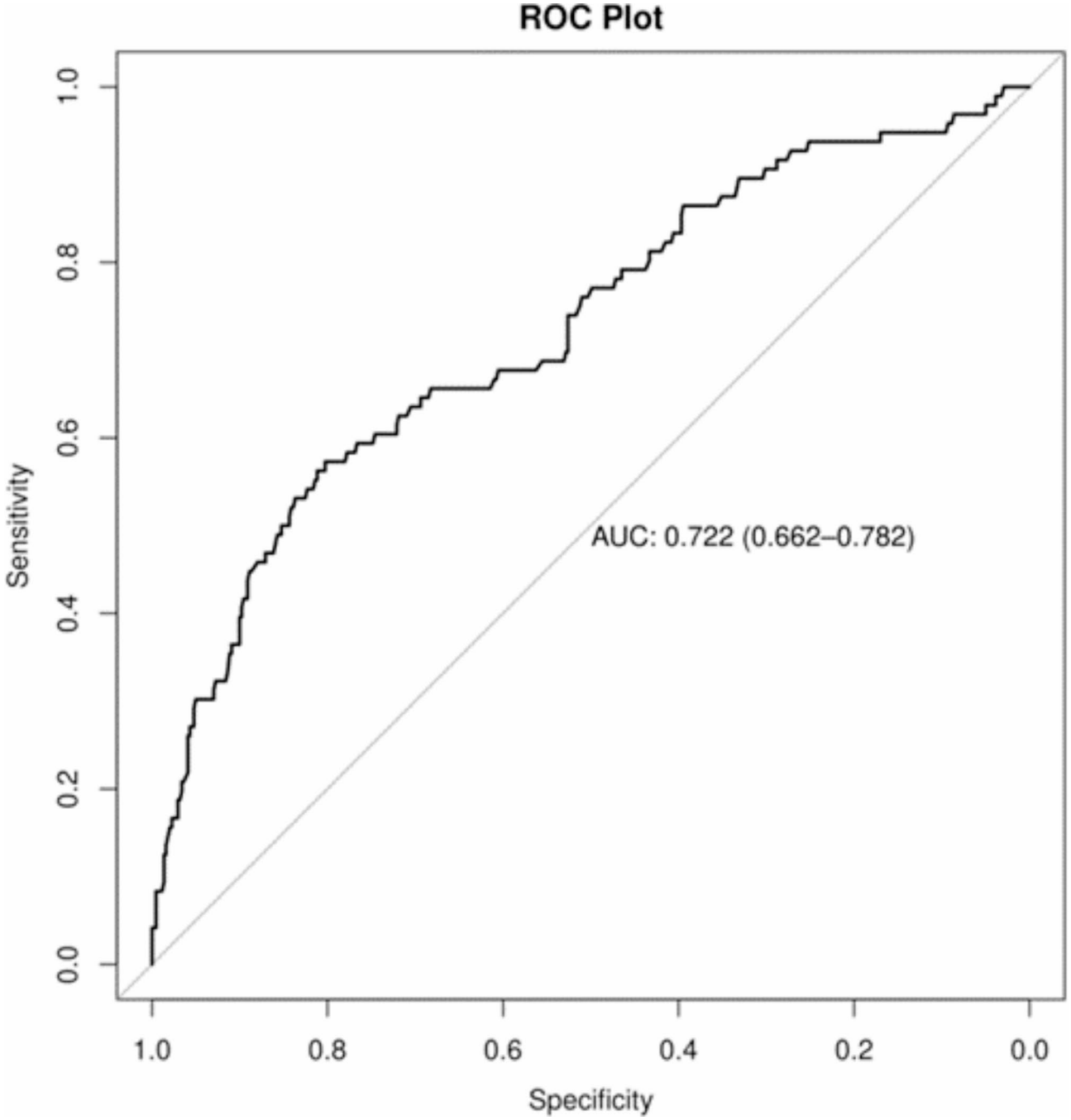

Fig. 3. The time-dependent ROC of ECONUT for predicting the DFS of breast cancer patients.

the inflammatory response and ultimately improve the predictive ability of the CONUT score for DFS in patients with breast cancer.

This study has some limitations that must be acknowledged. The sample used to develop the model in this study was small and was obtained retrospectively from a single center, thus limiting the generalisability of our research findings. The lack of external validation may have limited the accuracy of our results. Due to the absence of comprehensive databases investigating the hematological indicators in breast cancer patients, the predictive value of ECONUT for different molecular subtypes of breast cancer patients needs to be confirmed through large-scale, multi-center, prospective studies. In addition, due to the small number of deaths in the collected cases, this study focused on DFS as an endpoint outcome and did not analyze overall survival. The effect of ECONUT score on overall survival still requires further investigation. Finally, the potential mechanisms underlying the association between ECONUT score and the development of recurrence and metastasis have not been fully elucidated, and future studies are therefore necessary to investigate this relationship more deeply.

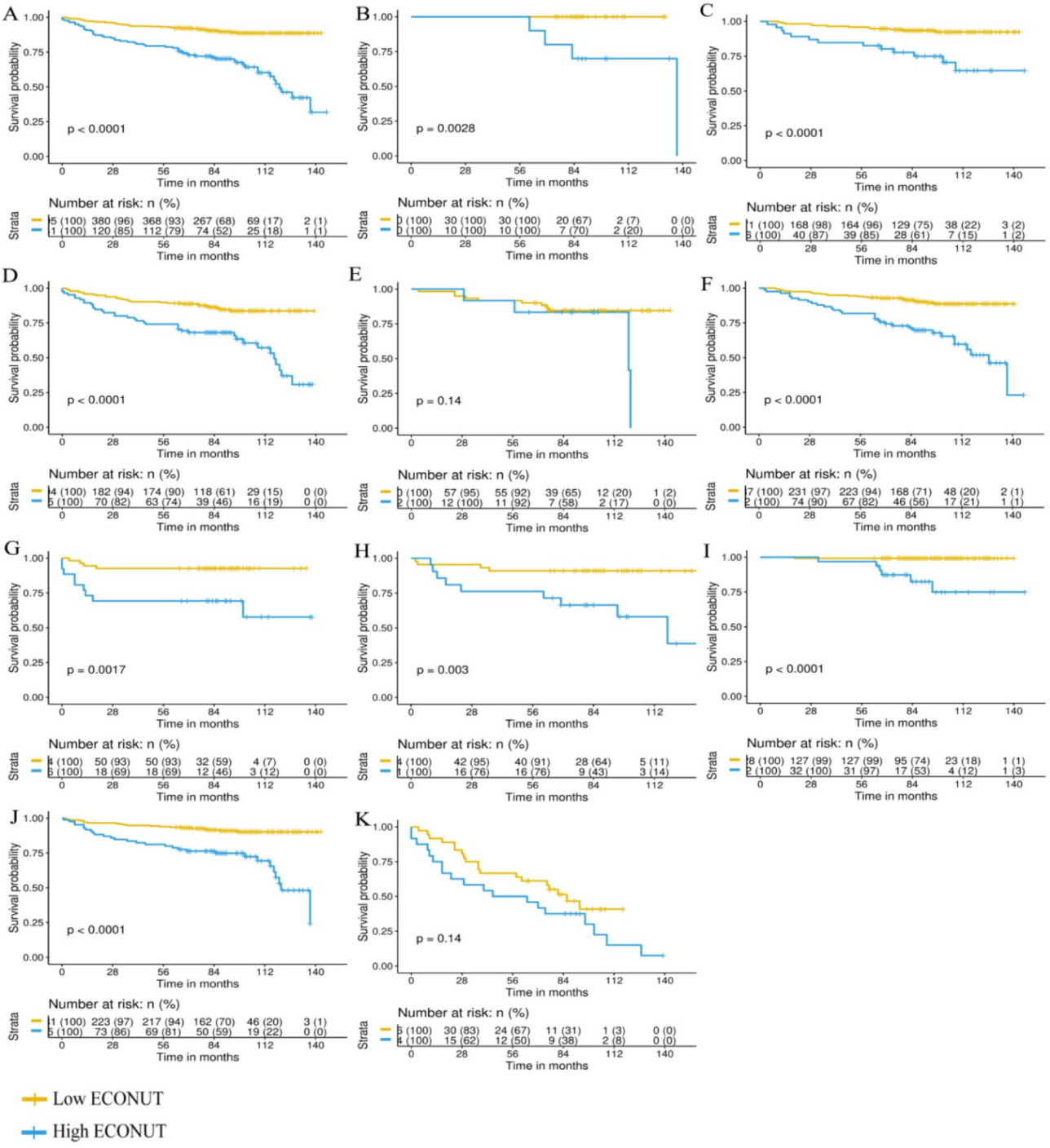

Fig. 4. The Kaplan–Meier curves of breast cancer patients based on the ECONUT grade. (**A**) Overall (**B**) Stage (I) (**C**) Stage (II) (**D**) Stage (III) (**E**) Luminal A (**F**) Luminal B (**G**) HER2-enriched (**H**) TNBC (**I**) pstage (I) (**J**) pstage (II) (**K**) pstage III.

Conclusion

Our novel model based on CONUT score and erythrocyte levels improved the ability to predict DFS in patients with breast cancer. This model can be used by clinicians to guide treatment interventions. However, further research is required to validate these findings.

	Model a		Model b		Model c	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
PNI	0.41 (0.27–0.61)	< 0.001	0.69 (0.41–1.16)	0.163	0.84 (0.46–1.53)	0.561
CONUT	2.26 (1.49–3.44)	< 0.001	0.73 (0.37–1.43)	0.361	0.75 (0.37–1.50)	0.410
NRI	0.80 (0.52–1.21)	0.289	1.16 (0.70–1.90)	0.565	0.86 (0.44–1.67)	0.660
PIV	1.40 (0.83–2.37)	0.207	0.87 (0.38–2.01)	0.746	0.81 (0.35–1.90)	0.628
SIRI	1.69 (1.02–2.80)	0.040	1.36 (0.57–3.29)	0.488	1.28 (0.52–3.16)	0.588
SII	1.75 (1.17–2.62)	0.007	(1.230.67–2.25)	0.503	(1.200.63–2.31)	0.582
MLR	2.04 (1.29–3.25)	0.002	1.25 (0.67–2.31)	0.482	1.41 (0.75–2.66)	0.288
NLR	2.17 (1.43–3.31)	< 0.001	1.33 (0.73–2.40)	0.350	1.57 (0.84–2.95)	0.157
PLR	1.68 (1.12–2.52)	0.012	0.80 (0.48–1.33)	0.390	0.79 (0.47–1.32)	0.364
ECONUT	4.12 (2.74–6.19)	< 0.001	3.47 (1.83–6.57)	< 0.001	3.61 (1.88–6.94)	< 0.001

Table 2. The univariate and multivariate Cox regression analysis evaluating the associations between each indicators and the DFS of breast cancer patients. Model a: No adjusted. Model b: Adjusted for p stage, surgery type. Model c: Adjusted for p stage, surgery type, height, weight, BMI, menopause, tumor size, lymphatic metastasis, molecular subtype.

Data availability

The datasets generated and analysed during the current study are not publicly available due to privacy but are available from the corresponding author on reasonable request.

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Author contributions

JJH designed research, analyzed data, and wrote the paper; JMD analyzed data; XY and ZYY collected data; GMH designed research. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shaoxing People's Hospital (064-Y-01). Due to the retrospective nature of the study, Ethics Committee of Shaoxing People's Hospital waived the need of obtaining informed consent.

Additional information

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