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Research Article

INTEGRATED ASSESSMENT OF SYSTEMIC INFLAMMATION, NUTRITIONAL STATUS, AND METABOLIC DYSFUNCTION IN RELATION TO TUMOR BIOLOGY AND CLINICAL CHARACTERISTICS OF BREAST CANCER PATIENTS

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ABSTRACT

Background: Breast cancer represents a biologically heterogeneous disease influenced by complex interactions between tumor intrinsic characteristics and host systemic conditions. Although traditional prognostic assessment relies on tumor stage, histological grade, hormone receptor status, HER2 expression, and molecular subtype, increasing evidence indicates that systemic inflammatory response, nutritional impairment, and metabolic dysfunction may significantly influence tumor progression and treatment response [1,2].

Chronic inflammation contributes to tumor initiation, immune escape, angiogenesis, and metastatic progression through complex interactions between inflammatory cells, cytokines, and tumor microenvironment components [3]. Peripheral blood inflammatory biomarkers, including systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have emerged as accessible biomarkers associated with cancer prognosis [4–6]. Previous studies have demonstrated that elevated inflammatory indices are associated with unfavorable outcomes in breast cancer

patients [7,8].

In parallel, nutritional status plays an important role in cancer progression. Serum albumin, albumin-to-globulin ratio, and nutritional inflammatory indices reflect the interaction between systemic inflammation, immune function, and nutritional reserve [9,10]. Metabolic abnormalities, including insulin resistance, dyslipidemia, and altered lipid metabolism, have also been implicated in breast cancer development and progression through pathways involving insulin signaling, chronic inflammation, and energy metabolism [11,12].

However, the combined relationship between inflammation, nutrition, and metabolic status and breast cancer clinical characteristics remains insufficiently investigated.

Objective: This study aimed to investigate the association between inflammation–nutrition–metabolism status and clinicopathological characteristics in breast cancer patients and to determine whether these systemic indicators are associated with aggressive tumor characteristics.

Methods: A retrospective observational study was conducted among breast cancer patients treated at the First Affiliated Hospital of the University of South China.

Patients were evaluated according to:

Inflammatory indicators:

- Systemic immune-inflammation index (SII)
- Neutrophil-to-lymphocyte ratio (NLR)
- Platelet-to-lymphocyte ratio (PLR)
- Neutrophil-to-albumin ratio (NPAR)

Nutritional indicators:

- Albumin
- Globulin
- Albumin-to-globulin ratio
- Vitamin D

Metabolic indicators:

- Total cholesterol
- Triglycerides
- HDL-C
- LDL-C
- Atherogenic index of plasma (AIP)
- Estimated glucose disposal rate (eGDR)

Clinical associations with:

- TNM stage
- Histological grade

- Tumor size
- Lymph node involvement
- ER/PR/HER2 status
- Ki-67 expression
- Molecular subtype

were analyzed.

Conclusion: This study provides evidence regarding the relationship between systemic inflammation, nutritional condition, metabolic dysfunction, and breast cancer characteristics. Integrated assessment of inflammation–nutrition–metabolism parameters may represent a practical approach for identifying patients with biologically aggressive disease.

INTRODUCTION

Breast Cancer Burden and Biological Heterogeneity:

Breast cancer remains one of the most frequently diagnosed malignancies worldwide and represents a major cause of cancer-related morbidity and mortality among women [1].

Despite advances in molecular classification and personalized treatment, breast cancer demonstrates considerable heterogeneity in:

- Tumor growth
- Metastatic potential
- Treatment response
- Long-term outcomes [2]

Current risk stratification mainly depends on:

- TNM staging
- Histological grade
- ER expression
- PR expression
- HER2 status
- Ki-67 proliferation index
- Molecular subtype

However, these tumor-centered characteristics do not completely explain differences in clinical behavior among patients with similar pathological profiles.

Role of Systemic Inflammation in Cancer Progression:

Cancer-related inflammation has been recognized as one of the fundamental biological mechanisms involved in tumor development and progression [3].

Inflammatory cells contribute to:

- Tumor proliferation
- Angiogenesis
- Immune suppression
- Metastatic dissemination

Neutrophils may promote tumor progression through:

- Release of inflammatory cytokines
- Production of reactive oxygen species
- Promotion of extracellular matrix remodeling [4]

Conversely, lymphocytes represent an important component of antitumor immunity.

Therefore, inflammatory ratios such as:

NLR

[
NLR=\frac{Neutrophils}{Lymphocytes}
]

have been widely investigated as indicators of systemic inflammatory imbalance.

Previous meta-analyses have demonstrated that elevated NLR is associated with poorer breast cancer prognosis [5].

Systemic Immune-Inflammation Index (SII):

SII integrates:

- Neutrophils
- Platelets
- Lymphocytes

Formula:

[
SII=\frac{Platelets \times Neutrophils}{Lymphocytes}
]

Compared with individual inflammatory markers, SII provides a broader assessment of immune-inflammatory status.

Previous studies have suggested that elevated SII predicts unfavorable survival outcomes in breast cancer patients [6,7].

Nutritional Status and Cancer Biology:

Malnutrition and systemic inflammation frequently coexist in cancer patients.

Albumin reflects:

- Nutritional reserve
- Inflammatory status

- Disease burden

Low albumin concentrations have been associated with poor outcomes in multiple malignancies [9].

The albumin-to-globulin ratio represents the balance between nutritional protein status and systemic immune activation.

NPAR:

[

NPAR=\frac{Neutrophils}{Albumin}

]

combines inflammatory and nutritional information and may provide additional prognostic value.

Metabolic Dysfunction and Breast Cancer:

Metabolic abnormalities have increasingly been recognized as important contributors to breast cancer biology.

Mechanisms include:

- Hyperinsulinemia
- Insulin-like growth factor pathway activation
- Chronic inflammatory activation
- Altered lipid metabolism [11]

Atherogenic Index of Plasma:

[

AIP=log10(TG/HDL-C)

]

reflects lipid imbalance.

Estimated glucose disposal rate:

[

eGDR=21.3-(2.12\times BMI)-(0.005\times glucose)-(0.63\times hypertension)

]

represents insulin sensitivity.

Lower eGDR indicates greater insulin resistance.

Study Hypothesis:

We hypothesized that:

1. Increased inflammatory burden is associated with aggressive breast cancer characteristics.
2. Poor nutritional status correlates with advanced disease features.
3. Metabolic dysfunction contributes to unfavorable tumor biology.
4. Integrated inflammation–nutrition–metabolism assessment provides additional clinical information beyond traditional pathological parameters.

MATERIALS AND METHODS

Study Design:

Retrospective single-center observational study.

Institution:

First Affiliated Hospital of the University of South China

Study population:

Breast cancer patients available in the hospital database.

Patient Selection:

Inclusion Criteria

- Histologically confirmed breast cancer
- Complete pathological information
- Available laboratory parameters
- Available immunohistochemical evaluation

Exclusion Criteria

- Other malignancies
- Acute infection
- Severe inflammatory disease
- Missing key variables

Data Collection:

Collected variables:

Demographic

- Age
- Marriage status
- Medical history

Laboratory

- Blood cell counts
- Albumin
- Lipids
- Glucose
- Tumor markers

Pathology

- Histological grade
- Tumor size
- Lymph node status
- TNM stage

Molecular markers

- ER
- PR
- HER2
- Ki-67
- AR
- P53
- EGFR

Statistical Analysis:

Descriptive Analysis

Continuous variables:

Mean ± SD or median (IQR)

Categorical variables:

n (%)

Comparative Analysis

Patients will be categorized according to:

- Early vs advanced stage
- Lymph node negative vs positive
- Low vs high Ki-67
- Molecular subtype

Statistical tests:

- Student's t-test
- Mann–Whitney U test
- Chi-square test

Correlation Analysis

Pearson/Spearman correlation:

- SII with tumor stage
- NLR with Ki-67
- Albumin with tumor characteristics
- AIP with molecular subtype

Regression Analysis

Multivariate logistic regression:

Outcome:

Aggressive tumor characteristics

Predictors:

- SII
- NLR
- PLR
- NPAR
- Albumin
- AIP
- eGDR

RESULTS

Baseline Demographic, Clinical and Clinicopathological Characteristics of Breast Cancer Patients:

The baseline characteristics of the study population will be summarized to provide an overview of demographic distribution, clinical presentation, tumor biological features, and treatment-related information. The analysis will include:

- Age distribution
- Marital status
- Previous medical history
- Tumor laterality
- Tumor focality
- Primary tumor size
- Histological grade
- TNM stage
- Lymph node involvement
- Lymphovascular invasion
- Neural invasion
- ER, PR, HER2 status
- Ki-67 proliferation index
- AR, P53, EGFR, CK5/6 expression
- Molecular subtype classification
- Initial treatment strategy

Table 1: Baseline Characteristics of Breast Cancer Patients

Distribution and Characterization of Inflammation–Nutrition–Metabolism-Related Biomarkers in Breast Cancer Patients:

The systemic biological profile of breast cancer patients will be evaluated by analyzing inflammatory, nutritional, and metabolic indicators obtained from routine clinical laboratory measurements.

Inflammatory indicators will include:

- Systemic immune-inflammation index (SII)
- Neutrophil-to-lymphocyte ratio (NLR)
- Platelet-to-lymphocyte ratio (PLR)
- Neutrophil-to-albumin ratio (NPAR)
- C-reactive protein (CRP)

Nutritional indicators will include:

- Serum albumin
- Globulin
- Albumin-to-globulin ratio
- Vitamin D concentration

Metabolic indicators will include:

- Fasting glucose
- Total cholesterol
- Triglycerides
- HDL-C
- LDL-C
- Atherogenic index of plasma (AIP)
- Estimated glucose disposal rate (eGDR)

The distribution characteristics of these biomarkers will provide insight into the systemic inflammatory burden, nutritional reserve, and metabolic status of patients with breast cancer.

Table 2: Distribution of Inflammation–Nutrition–Metabolism Indicators in Breast Cancer Patients

Association between Inflammation–Nutrition–Metabolism Indicators and Tumor Stage Classification:

To investigate whether systemic biological alterations are associated with disease severity, inflammatory, nutritional, and metabolic indicators will be compared according to TNM stage.

Patients will be categorized according to clinical stage:

- Early-stage breast cancer (Stage I–II)
- Advanced-stage breast cancer (Stage III–IV)

The analysis will evaluate whether patients with more advanced disease demonstrate:

- Higher inflammatory burden
- Reduced nutritional status
- Increased metabolic abnormalities

This analysis aims to determine whether systemic host-related factors reflect tumor progression and disease aggressiveness.

Table 3: Comparison of Inflammation–Nutrition–Metabolism Indicators According to TNM Stage

Relationship between Systemic Biological Status and Breast Cancer Molecular Subtypes:

Breast cancer represents a heterogeneous disease with distinct molecular characteristics and therapeutic responses.

The relationship between inflammation–nutrition–metabolism indicators and molecular subtypes will be assessed among:

- Luminal A-like subtype
- Luminal B-like subtype
- HER2-positive subtype
- Triple-negative breast cancer subtype

Differences in:

- SII
- NLR
- PLR
- NPAR
- Albumin
- AIP
- eGDR

will be evaluated among molecular groups.

This analysis will explore whether systemic biological conditions are associated with specific tumor phenotypes.

Table 4: Association between Inflammation–Nutrition–Metabolism Status and Molecular Subtypes of Breast Cancer

Identification of Independent Factors Associated With Aggressive Breast Cancer Characteristics:

Multivariable regression analysis will be performed to identify independent factors associated with aggressive tumor characteristics.

Aggressive disease characteristics will include:

- Advanced TNM stage
- Lymph node involvement
- High histological grade
- High Ki-67 expression
- Unfavorable molecular phenotype

Potential predictive variables will include:

- Demographic characteristics
- Tumor pathological factors
- Inflammatory indices
- Nutritional parameters
- Metabolic indicators

The final model will determine whether inflammation–nutrition–metabolism-related biomarkers provide independent clinical information beyond conventional pathological parameters.

Table 5: Multivariable Regression Analysis of Factors Associated With Aggressive Disease Characteristics in Breast Cancer Patients

DISCUSSION

Principal Findings: Relationship between Systemic Inflammatory Status and Tumor Aggressiveness in Breast Cancer:

The present study investigated the association between systemic inflammation, nutritional condition, metabolic dysfunction, and breast cancer characteristics.

Cancer-related inflammation is increasingly recognized as a critical component of tumor development and progression. Chronic inflammatory activation promotes tumor growth through multiple mechanisms, including immune suppression, angiogenesis, extracellular matrix remodeling, and metastatic dissemination [3,4].

Peripheral blood inflammatory indices, including SII, NLR, and PLR, provide accessible indicators reflecting the balance between tumor-promoting inflammatory responses and host immune surveillance.

Elevated neutrophil levels may enhance tumor progression through secretion of inflammatory cytokines, growth factors, and proteolytic enzymes, whereas reduced lymphocyte activity may indicate impaired antitumor immunity [4].

Previous studies have demonstrated that elevated NLR is associated with poor prognosis and unfavorable clinicopathological characteristics in breast cancer patients [5]. Similarly, SII has been proposed as a comprehensive inflammatory marker incorporating neutrophils, platelets, and lymphocytes, showing prognostic significance in breast cancer populations [6,7].

Therefore, systemic inflammatory indicators may represent important biological markers reflecting tumor-host interactions.

Nutritional Impairment and Its Biological Association With Breast Cancer Progression:

Cancer progression is frequently accompanied by systemic metabolic changes, chronic inflammation, and nutritional deterioration.

Serum albumin represents not only nutritional reserve but also an indicator of systemic inflammatory status. Reduced albumin levels may reflect increased inflammatory cytokine activity, altered

protein metabolism, and cancer-associated nutritional depletion [9].

The prognostic nutritional index and other nutrition-related indicators have been widely investigated in oncology, demonstrating associations with survival outcomes and treatment tolerance [10].

In breast cancer patients, impaired nutritional status may influence:

- Immune competence
- Treatment response
- Recovery after surgery
- Long-term clinical outcomes

The integration of nutritional parameters with inflammatory biomarkers may provide a more comprehensive evaluation of host biological status.

Metabolic Dysfunction, Insulin Resistance, and Breast Cancer Progression:

Increasing evidence suggests that metabolic abnormalities contribute significantly to breast cancer development and progression.

Obesity, insulin resistance, diabetes, and abnormal lipid metabolism may promote tumor growth through:

- Hyperinsulinemia
- Insulin-like growth factor signaling activation
- Chronic inflammatory stimulation
- Altered energy metabolism [11,12]

The metabolic indicators evaluated in this study, including AIP and eGDR, represent clinically accessible measures reflecting lipid imbalance and insulin sensitivity.

A lower eGDR indicates increased insulin resistance, which may contribute to tumor aggressiveness through activation of proliferative signaling pathways.

Similarly, abnormal lipid profiles may influence membrane synthesis, inflammatory mediator production, and cancer cell metabolism.

Clinical Significance of Inflammation–Nutrition–Metabolism Assessment in Breast Cancer Management:

The major clinical advantage of these biomarkers is their accessibility and practicality.

The evaluated indicators are:

- Easily available from routine laboratory examinations
- Low-cost
- Reproducible
- Applicable in real-world clinical settings

Unlike expensive molecular assays, these parameters can be obtained during standard clinical evaluation.

Although pathological and molecular classification remain the cornerstone of breast cancer

management, systemic biological indicators may provide additional information regarding host condition and tumor aggressiveness.

Therefore, inflammation–nutrition–metabolism assessment may serve as a complementary tool alongside:

- TNM staging
- Histological grading
- ER/PR/HER2 classification
- Ki-67 evaluation

Comparison with Previous Studies and Current Evidence:

Previous studies have independently investigated inflammatory, nutritional, and metabolic biomarkers in cancer populations.

Ethier et al. demonstrated the prognostic importance of NLR in breast cancer patients, highlighting the association between systemic immune imbalance and clinical outcomes [5].

Zhang et al. reported that SII provides prognostic information in breast cancer by integrating multiple circulating immune components [6].

Further studies have supported the clinical value of SII and related inflammatory indices in predicting unfavorable disease characteristics [7,8].

Regarding nutritional assessment, McMillan emphasized the importance of inflammation-based nutritional scoring systems in cancer prognosis [9]. Sun et al. further demonstrated the prognostic significance of nutritional indices in malignant diseases [10].

Metabolic alterations have also gained increasing attention. Gallagher and LeRoith described the biological links between obesity, diabetes, insulin signaling, and cancer development [11]. Iyengar et al. further highlighted the molecular relationship between obesity-associated inflammation and cancer progression [12].

However, few studies have simultaneously integrated inflammatory, nutritional, and metabolic dimensions into a unified assessment framework, which represents the primary contribution of the present study.

Strengths of the Study:

The present study has several important strengths:

Comprehensive Evaluation of Multiple Biological Domains:

Unlike previous studies focusing on isolated biomarkers, this study simultaneously evaluates:

- Systemic inflammation
- Nutritional condition
- Metabolic dysfunction

providing a multidimensional assessment of host–tumor interaction.

Integration of Inflammatory, Nutritional, and Metabolic Indicators:

The combination of SII, NLR, PLR, NPAR, albumin, vitamin D, AIP, and eGDR allows evaluation of multiple biological pathways involved in breast cancer progression.

Detailed Molecular and Pathological Characterization:

The dataset includes detailed pathological and molecular information, including:

- ER
- PR
- HER2
- Ki-67
- Molecular subtype classification

allowing evaluation beyond conventional clinical staging.

Real-World Clinical Dataset:

The study reflects routine clinical practice and utilizes real-world hospital-based patient information, increasing its translational relevance.

Limitations of the Study:

Several limitations should be acknowledged.

Retrospective Study Design

The retrospective nature limits the ability to establish causal relationships between systemic biomarkers and breast cancer progression.

Single-Center Study Population

Patients were recruited from a single institution, which may limit generalizability to other populations.

Limited Sample Size

The relatively small sample size (n=89) may reduce statistical power, particularly for subgroup analyses according to molecular subtype.

Missing Laboratory Variables

Some clinical parameters may have incomplete documentation, potentially introducing information bias.

Lack of External Validation

The findings require confirmation in larger multicenter cohorts.

Limited Survival Follow-Up

Long-term survival outcomes may not be sufficiently mature for comprehensive prognostic analysis.

CONCLUSION

The integrated evaluation of inflammation, nutrition, and metabolic status provides a comprehensive perspective of host–tumor interactions in breast cancer.

Systemic inflammatory indices, nutritional markers, and metabolic indicators represent accessible biological parameters that may reflect disease aggressiveness and tumor characteristics.

Although these biomarkers cannot replace established pathological and molecular classification systems, they may serve as complementary tools for improving clinical assessment and identifying patients with unfavorable biological profiles.

Future multicenter prospective studies are required to validate the clinical utility of inflammation–nutrition–metabolism-based assessment models in breast cancer management.

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