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ORIGINAL RESEARCH

Lactate Dehydrogenase as a Potential Mediator Between Immature Granulocytes and Tumor Burden in Breast Cancer

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Background: Chronic inflammation and metabolic dysregulation contribute to breast cancer initiation and progression. Immature granulocytes (IG) and lactate dehydrogenase (LDH) reflect systemic inflammation and metabolic activity, respectively, but their interplay in tumor growth remains unclear.

Objective: To investigate the associations among IG, LDH, and breast tumor size, and to evaluate whether LDH mediates the relationship between IG and tumor burden.

Methods: A total of 778 breast cancer patients undergoing primary surgery were included. Peripheral blood IG counts and LDH levels were measured within two weeks preoperatively, and tumor size was obtained from postoperative pathology reports. Associations were assessed using SHAP feature importance analysis, univariate and multivariate linear regression, weighted linear regression, and subgroup analyses. Mediation analysis evaluated the potential mediating role of LDH.

Results: In weighted and multivariable linear regression analyses, both IG count and LDH levels were significantly positively associated with tumor size. After full adjustment, IG remained an independent predictor of tumor size ($\beta = 6.09$, $P = 0.01$), and LDH showed a similar association ($\beta = 0.01$, $P = 0.014$). IG count was also strongly correlated with LDH levels ($\beta = 241.52$, 95% CI: 86.97–396.06, $P < 0.01$). Mediation analysis indicated that LDH partially mediated the IG–tumor size association, accounting for 9.86% of the total effect. Subgroup analysis suggested that the relationship between IG and tumor size is modulated by hypertension.

Conclusion: These findings suggest a potential interplay between systemic inflammation and tumor metabolism in breast cancer progression. IG and LDH may serve as accessible biomarkers associated with tumor burden and could assist in risk stratification and clinical decision-making. Multicenter prospective studies are required to validate these associations and further elucidate the underlying biological mechanisms.

Keywords: breast cancer, inflammation, lactate dehydrogenase, immature granulocytes, tumor size

Introduction

Breast cancer (BC) is a malignant tumor arising from mammary epithelial tissue, characterized by uncontrolled cellular proliferation and malignant transformation.[1] Despite extensive research, its precise etiology remains incompletely elucidated. According to the latest global cancer statistics, breast cancer accounts for 11.6% of all newly diagnosed cancer cases, ranking as the most prevalent malignancy and the leading cause of cancer-related death among women worldwide, thereby posing a substantial threat to women's health.[2]

Emerging evidence suggests that the development and progression of breast cancer are determined not only by the intrinsic biological characteristics of the tumor but also by host-related factors such as systemic inflammation and metabolic state.[3,4] Inflammation and tumors engage in a complex bidirectional interplay, and several inflammatory

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markers—such as the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and immature granulocyte (IG) count—have been applied in the prognostic evaluation of multiple malignancies.[5–8] Nevertheless, the specific association between systemic inflammation and breast cancer tumor burden, particularly tumor size, remains insufficiently explored.

In parallel, lactate dehydrogenase (LDH), a key metabolic enzyme in glycolysis, reflects both tumor metabolic activity and tissue injury.[9] Elevated LDH levels have been consistently associated with unfavorable prognosis in various cancers.[10,11] Importantly, tumor-associated inflammation and metabolic reprogramming are not independent processes but often act in concert to promote cancer progression. However, systematic investigations examining the interrelationship among inflammation, metabolism, and tum or burden in breast cancer remain limited.

Therefore, the present study aims to elucidate the associations between systemic inflammatory markers, LDH levels, and breast cancer tumor size. In addition, mediation analysis will be performed to determine whether LDH mediates the link between inflammation and tumor burden, thereby providing novel insights into the mechanistic interplay of inflammation and metabolism in breast cancer. This work seeks to contribute new evidence to refine risk stratification and advance precision management in breast cancer.

Materials and Methods

Study Population

A total of 778 patients with breast cancer who underwent surgery at the Department of Breast Surgery, The Second Affiliated Hospital of Fujian Medical University, between July 1, 2021, and June 30, 2025, were included in this study. Clinical data were extracted from the institutional electronic medical record system. All personal identifiers were removed to ensure compliance with patient privacy protection regulations.

Inclusion Criteria:

1. Female, aged >20 years;
2. Underwent primary breast cancer surgery;
3. Pathologically confirmed as the first and only primary malignant breast tumor;
4. No evidence of distant metastasis at diagnosis;
5. No history of neoadjuvant therapy.

Exclusion Criteria:

1. Missing or incomplete covariate data;
2. Severe inflammatory disease or acute infection within one month prior to diagnosis;
3. Significant dysfunction of major organs.

The detailed patient selection process is presented in Figure 1.

Tumor Size Measurement

To minimize the confounding effects of treatment on tumor growth, this study included only patients who had not received neoadjuvant therapy. Tumor size was defined as the maximum tumor diameter documented in the postoperative pathology report. For patients presenting with multiple lesions, the diameter of the largest lesion was recorded as the representative tumor size.

Assessment of Metabolic Levels and Systemic Inflammation

Peripheral blood samples were collected from each participant within two weeks prior to breast cancer surgery and analyzed in the hospital laboratory. To assess systemic inflammation, three hematological indicators were selected: immature granulocyte (IG) count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). These

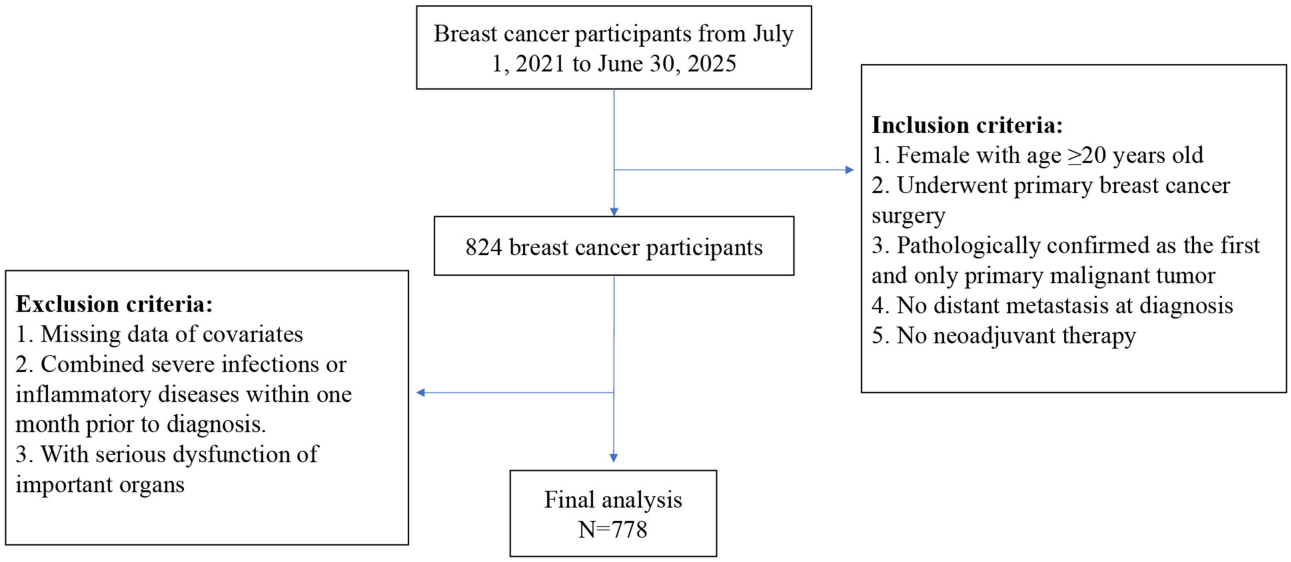

Figure 1 Flowchart of participant selection.

indices provide a comprehensive reflection of the host's inflammatory status and immune balance, thereby enabling a more accurate evaluation of systemic inflammation. The calculation formulas were as follows:

NLR = neutrophil count/lymphocyte count;

PLR = platelet count/lymphocyte count.

In addition, lactate dehydrogenase (LDH) levels were measured concurrently. As a key metabolic enzyme, LDH serves as an important biomarker of tumor cell metabolic activity and the degree of tissue injury.

Covariates

Based on previous studies, the following variables were included as covariates in this analysis: age, body mass index (BMI), hypertension (yes/no), diabetes (yes/no), marital status (unmarried/married), history of procreation (yes/no), pausimenia status (yes/no), tumor laterality (left/right), tumor count (single/multiple), histological grade (I, II, III), presence of perineural or vascular invasion (yes/no), estrogen receptor (ER) status (positive/negative), progesterone receptor (PR) status (positive/negative), human epidermal growth factor receptor 2 (HER2) status (positive/negative), and axillary lymph node metastasis (ALNM) (yes/no). Because fewer than ten participants reported a history of smoking or alcohol consumption, these two variables were excluded from the final analysis.

Statistical Analysis

Participants were stratified into two groups according to tumor size (Group 1: ≤2 cm; Group 2: >2 cm), and baseline characteristics were compared between the groups. Continuous variables that satisfied normality assumptions, evaluated using the Kolmogorov–Smirnov test, were expressed as mean ± standard deviation and compared using independent samples *t*-tests. Categorical variables were summarized as frequencies and percentages, with between-group differences assessed by chi-square tests or Fisher's exact tests, as appropriate.

To identify variables associated with tumor size, we first applied SHAP-based feature importance analysis in combination with univariate and multivariate linear regression. Based on these results, three weighted linear regression models were constructed to assess the associations among immature granulocyte (IG) count and tumor size, IG count and lactate dehydrogenase (LDH), and LDH and tumor size, respectively. Subgroup analyses were further conducted using fully adjusted models to evaluate the relationship between IG count and tumor size across different clinical subgroups.

Finally, mediation analysis was performed using the "mediation" package in R (v4.3.2) to test whether LDH acted as a mediator in the association between IG count and tumor size. A two-sided p-value < 0.05 was considered statistically significant.

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Results

Baseline Characteristics of Study Participants

A total of 778 patients with breast cancer were included in this study, and their baseline characteristics are summarized in Table 1. When stratified by tumor size (≥2 cm), patients in the larger tumor group (G2) exhibited significantly higher mean values of several continuous variables, including age, BMI, Ki-67, LDH, IG count, and NLR, compared with those in the smaller tumor group (G1) (all P-value < 0.05).

Table 1 The Baseline Characteristics of 778 Breast Cancer Participants

Variables	Total (n = 778)	Tumor Size		Statistic	P-value
		G1: ≤2cm (n = 429)	G2: >2cm (n = 349)		
Age, Mean ± SD	51.09 ± 10.97	50.18 ± 9.46	52.20 ± 12.50	t=−2.49	0.013
BMI (kg/m^2), Mean ± SD	23.45 ± 3.21	23.20 ± 3.02	23.76 ± 3.40	t=−2.42	0.016
Tumor size(cm), Mean ± SD	2.01 ± 1.06	1.29 ± 0.54	2.90 ± 0.84	t=−30.97	<0.001
KI67, Mean ± SD	37.04 ± 21.10	33.46 ± 19.64	41.44 ± 22.01	t=−5.28	<0.001
LDH (U/L), Mean ± SD	168.58 ± 35.72	165.05 ± 32.12	172.92 ± 39.31	t=−3.01	0.003
IG count (*10^9/L), Mean ± SD	0.01 ± 0.02	0.01 ± 0.01	0.01 ± 0.02	t=−2.91	0.004
NLR, Mean ± SD	2.23 ± 1.20	2.14 ± 1.18	2.34 ± 1.20	t=−2.35	0.019
PLR, Mean ± SD	150.05 ± 57.53	148.74 ± 51.30	151.65 ± 64.41	t=−0.68	0.494
Hypertension, n(%)				χ^2=9.78	0.002
No	655 (84.19)	377 (87.88)	278 (79.66)		
Yes	123 (15.81)	52 (12.12)	71 (20.34)		
Diabetes, n(%)				χ^2=5.94	0.015
No	714 (91.77)	403 (93.94)	311 (89.11)		
Yes	64 (8.23)	26 (6.06)	38 (10.89)		
Marital status, n(%)				χ^2=0.15	0.702
Unmarried	15 (1.93)	9 (2.10)	6 (1.72)		
Married	763 (98.07)	420 (97.90)	343 (98.28)		
Procreation, n(%)				χ^2=0.45	0.505
No	26 (3.34)	16 (3.73)	10 (2.87)		
Yes	752 (96.66)	413 (96.27)	339 (97.13)		
Pausimenia, n(%)				χ^2=0.10	0.752
No	395 (50.77)	220 (51.28)	175 (50.14)		
Yes	383 (49.23)	209 (48.72)	174 (49.86)		
Laterality, n(%)				χ^2=0.32	0.573
Left	397 (51.03)	215 (50.12)	182 (52.15)		
Right	381 (48.97)	214 (49.88)	167 (47.85)		
Tumor count, n(%)				χ^2=3.67	0.055
Single	710 (91.26)	384 (89.51)	326 (93.41)		
Multiple	68 (8.74)	45 (10.49)	23 (6.59)		
Histology, n(%)				χ^2=39.97	<0.001
I	45 (5.78)	38 (8.86)	7 (2.01)		
II	389 (50.00)	240 (55.94)	149 (42.69)		
III	344 (44.22)	151 (35.20)	193 (55.30)		
Nerve invasion, n(%)				χ^2=2.85	0.091
No	627 (80.59)	355 (82.75)	272 (77.94)		
Yes	151 (19.41)	74 (17.25)	77 (22.06)		
Vascular invasion, n(%)				χ^2=10.18	0.001
No	553 (71.08)	325 (75.76)	228 (65.33)		
Yes	225 (28.92)	104 (24.24)	121 (34.67)		

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 778)	Tumor Size		Statistic	P-value
		G1: ≤2cm (n = 429)	G2: >2cm (n = 349)		
ER, n(%)				χ^2=6.35	0.012
Negative	200 (25.71)	95 (22.14)	105 (30.09)		
Positive	578 (74.29)	334 (77.86)	244 (69.91)		
PR, n(%)				χ^2=3.48	0.062
Negative	243 (31.23)	122 (28.44)	121 (34.67)		
Positive	535 (68.77)	307 (71.56)	228 (65.33)		
HER2, n(%)				χ^2=0.83	0.361
Negative	572 (73.52)	321 (74.83)	251 (71.92)		
Positive	206 (26.48)	108 (25.17)	98 (28.08)		
ALNM, n(%)				χ^2=8.47	0.004
No	528 (67.87)	310 (72.26)	218 (62.46)		
Yes	250 (32.13)	119 (27.74)	131 (37.54)		

Notes: t: *t*-test, χ^2: Chi-square test.
Abbreviations: BMI, Body Mass Index; LDH, Lactate Dehydrogenase; IG count, Immature Granulocytes Count; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; ER, Estrogen Receptor; PR, Progesterone Receptor; HER2, Human Epidermal Growth Factor Receptor 2; ALNM, Axillary Lymph Node Metastasis; SD, standard deviation.

With respect to categorical variables, the G2 group demonstrated significantly higher proportions of vascular invasion, ER-negative status, axillary lymph node metastasis (ALNM) positivity, histological grade III, hypertension, and diabetes (all $P < 0.05$). In contrast, no significant differences were observed between the two groups in terms of tumor laterality, nerve invasion, PR status, HER2 status, parity, menopausal status, or marital status.

SHAP Feature Importance

In the machine learning–based SHAP interpretability analysis (Figure 2), LDH, IG count, NLR, and PLR were identified as the top predictors of tumor size among all evaluated variables. Notably, LDH ranked second in feature importance, underscoring its pivotal role in predicting tumor size.

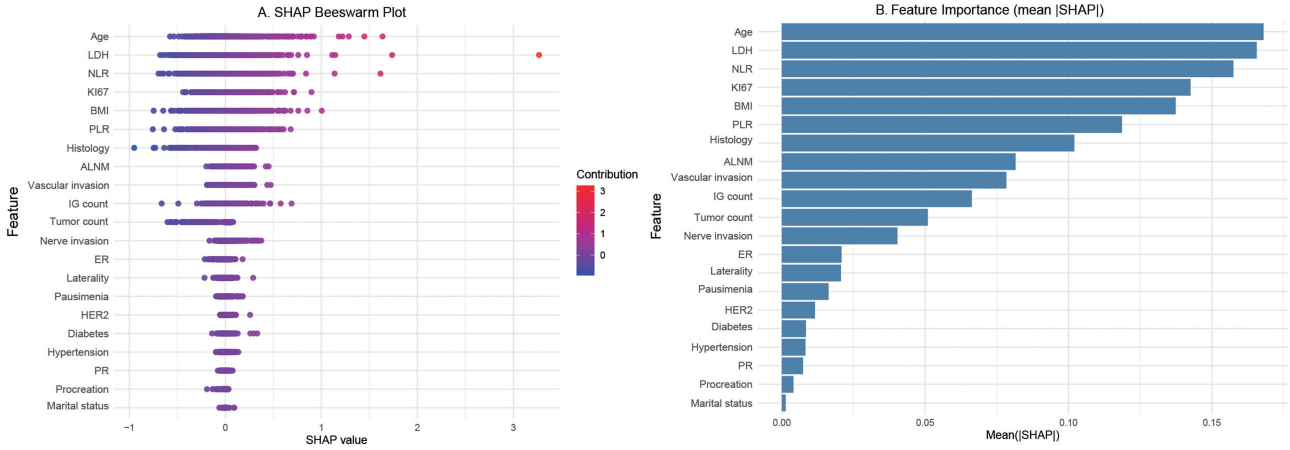

Figure 2 SHAP-based interpretation of the machine learning model for tumor size prediction. (**A**) SHAP beeswarm plot showing the distribution and magnitude of SHAP values for LDH, IG count, NLR, PLR, and other clinical variables, reflecting their individual contributions to tumor size prediction. (**B**) Feature importance plot ranking variables according to the mean absolute SHAP values, indicating their overall importance in the model.

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Univariate and Multivariate Linear Regression Analysis

The results of univariate and multivariate linear regression analyses indicate that, while NLR and PLR were not significantly associated with tumor size, both LDH and IG count exhibited strong positive correlations with tumor size (Table 2). In the multivariate model, LDH (β = 0.01, 95% CI: 0.01–0.01, P-value = 0.019) and IG count (β = 7.31, 95% CI: 2.89–11.73, P-value = 0.001) remained independent predictors. These findings suggest that increased tumor volume is directly associated with elevated LDH levels and higher immature granulocyte counts. Accordingly, LDH and IG count may serve as potential biological markers, warranting further investigation into their roles in tumor progression.

Table 2 Univariate and Multivariate Linear Regression Analysis for Tumor Size of 778 Breast Cancer Participants

Variables	Univariate					Multivariate				
	β	S.E	t	*P*	β (95% CI)	β	S.E	t	*P*	β (95% CI)
Age	0.01	0.00	2.73	0.006	0.01 (0.01 ~ 0.02)	0.01	0.00	1.90	0.058	0.01 (−0.00 ~ 0.01)
BMI (kg/m^2)	0.02	0.01	1.91	0.057	0.02 (−0.00 ~ 0.05)					
KI67	0.01	0.00	6.30	<0.001	0.01 (0.01 ~ 0.01)	0.01	0.00	4.01	<0.001	0.01 (0.01 ~ 0.01)
LDH (U/L)	0.01	0.00	3.63	<0.001	0.01 (0.01 ~ 0.01)	0.01	0.00	2.36	0.019	0.01 (0.01 ~ 0.01)
IG count (*10^9/L)	9.13	2.37	3.85	<0.001	9.13 (4.49 ~ 13.78)	7.31	2.26	3.24	0.001	7.31 (2.89 ~ 11.73)
NLR	0.05	0.03	1.43	0.154	0.05 (−0.02 ~ 0.11)					
PLR	−0.00	0.00	−0.24	0.810	−0.00 (−0.00 ~ 0.00)					
Hypertension										
No					0.00 (Reference)					
Yes	0.18	0.10	1.73	0.084	0.18 (−0.02 ~ 0.38)					
Diabetes										
No					0.00 (Reference)					0.00 (Reference)
Yes	0.37	0.14	2.68	0.008	0.37 (0.10 ~ 0.64)	0.23	0.13	1.71	0.087	0.23 (−0.03 ~ 0.49)
Marital status										
Unmarried					0.00 (Reference)					
Married	0.20	0.28	0.73	0.467	0.20 (−0.34 ~ 0.74)					
Procreation										
No					0.00 (Reference)					
Yes	0.21	0.21	0.99	0.322	0.21 (−0.20 ~ 0.62)					
Pausimenia										
No					0.00 (Reference)					
Yes	0.04	0.08	0.48	0.632	0.04 (−0.11 ~ 0.19)					
Laterality										
Left					0.00 (Reference)					
Right	0.03	0.08	0.36	0.718	0.03 (−0.12 ~ 0.18)					
Tumor count										
Single					0.00 (Reference)					0.00 (Reference)
Multiple	−0.40	0.13	−2.96	0.003	−0.40 (−0.66 ~ −0.13)	−0.37	0.13	−2.95	0.003	−0.37 (−0.62 ~ −0.13)
Histology										
I					0.00 (Reference)					0.00 (Reference)
II	0.60	0.16	3.70	<0.001	0.60 (0.28 ~ 0.92)	0.39	0.16	2.43	0.015	0.39 (0.08 ~ 0.70)
III	0.93	0.16	5.70	<0.001	0.93 (0.61 ~ 1.25)	0.57	0.17	3.35	<0.001	0.57 (0.24 ~ 0.91)
Nerve invasion										
No					0.00 (Reference)					0.00 (Reference)
Yes	0.32	0.10	3.36	<0.001	0.32 (0.13 ~ 0.51)	0.21	0.10	2.15	0.032	0.21 (0.02 ~ 0.39)
Vascular invasion										
No					0.00 (Reference)					0.00 (Reference)
Yes	0.39	0.08	4.74	<0.001	0.39 (0.23 ~ 0.55)	0.16	0.10	1.63	0.103	0.16 (−0.03 ~ 0.35)

(*Continued*)

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Table 2 (Continued).

Variables	Univariate					Multivariate				
	β	S.E	t	*P*	β (95% CI)	β	S.E	t	*P*	β (95% CI)
ER										
Negative					0.00 (Reference)					0.00 (Reference)
Positive	−0.20	0.09	−2.36	0.019	−0.20 (−0.37 ~ −0.03)	−0.02	0.13	−0.12	0.903	−0.02 (−0.27 ~ 0.24)
PR										
Negative					0.00 (Reference)					0.00 (Reference)
Positive	−0.18	0.08	−2.21	0.027	−0.18 (−0.34 ~ −0.02)	0.09	0.12	0.71	0.477	0.09 (−0.15 ~ 0.33)
HER2										
Negative					0.00 (Reference)					
Positive	0.08	0.09	0.89	0.373	0.08 (−0.09 ~ 0.25)					
ALNM										
No					0.00 (Reference)					0.00 (Reference)
Yes	0.35	0.08	4.30	<0.001	0.35 (0.19 ~ 0.50)	0.21	0.09	2.29	0.022	0.21 (0.03 ~ 0.38)

Abbreviations: BMI, Body Mass Index; LDH, Lactate Dehydrogenase; IG count, Immature Granulocytes Count; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; ER, Estrogen Receptor; PR, Progesterone Receptor; HER2, Human Epidermal Growth Factor Receptor 2; ALNM, Axillary Lymph Node Metastasis; CI, Confidence Interval.

Weighted Linear Regression (WLR)

Using weighted linear regression (WLR), we examined the associations between tumor size, lactate dehydrogenase (LDH) levels, and immature granulocyte (IG) count in 778 patients with breast cancer (Table 3). IG count, analyzed as a continuous variable, was significantly positively correlated with tumor size, and this association remained robust after multivariable adjustment (β = 6.09, 95% CI: 1.46–10.72, $P = 0.01$). When the IG count was treated as a categorical variable, tumors in the IG > 0 group were significantly larger than those in the IG = 0 group (β = 0.21, 95% CI: 0.06–0.35, $P = 0.005$). Similarly, LDH levels were positively associated with tumor size (β = 0.01, $P = 0.014$), suggesting that higher tumor burden is linked to both inflammatory activation and increased metabolic activity.

Further analysis revealed a strong positive linear relationship between IG count and LDH levels (Table 4). In continuous variable analysis, LDH levels increased substantially with each unit increase in IG count (β = 241.52, 95% CI: 86.97–396.06, P-value < 0.002). In subgroup analysis, LDH levels were significantly higher in the IG > 0 group compared with the IG = 0 group (β = 6.27, 95% CI: 1.45–11.08, P-value = 0.011).

Collectively, these findings suggest a potential synergistic interplay among systemic inflammation, metabolic activity, and tumor growth, as an elevated proportion of immature granulocytes in peripheral blood is associated with both increased tumor size and concomitant rises in LDH levels.

Table 3 Association of Tumor Size and IG Count/Lactate Dehydrogenase Among 778 Breast Cancer Participants

Variables	Model1		Model2		Model3		Model4	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
IG count (*10^9/L) (Continuous)	9.13 (4.49 ~ 13.78)	<0.001	7.90 (3.34 ~ 12.45)	<0.001	6.09 (1.46 ~ 10.72)	0.010	–	–
IG count (*10^9/L)								
IG count=0	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)		–	–
IG count>0	0.26 (0.11 ~ 0.41)	<0.001	0.24 (0.09 ~ 0.38)	0.001	0.21 (0.06 ~ 0.35)	0.005	–	–
LDH (U/L) (Continuous)	0.01 (0.01 ~ 0.01)	<0.001	0.01 (0.01 ~ 0.01)	<0.001	–	–	0.01 (0.01 ~ 0.01)	0.014

Notes: Model1: Crude, Model2: Adjust: Hypertension, Diabetes, Marital status, Procreation, Pausimenia, Laterality, Tumor count, Histology, Model3: Adjust: Hypertension, Diabetes, Marital status, Procreation, Pausimenia, Laterality, Tumor count, Histology, Nerve invasion, Vascular invasion, ER, PR, HER2, ALNM, Age, BMI, KI67, LDH, NLR, PLR, Model4: Adjust: Hypertension, Diabetes, Marital status, Procreation, Pausimenia, Laterality, Tumor count, Histology, Nerve invasion, Vascular invasion, ER, PR, HER2, ALNM, Age, BMI, KI67, IG count, NLR, PLR.
Abbreviations: CI, Confidence Interval.

Table 4 Association of Immature Granulocytes Count and Lactate Dehydrogenase Among 778 Breast Cancer Participants

Variables	Model1		Model2		Model3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
IG count (*10^9/L) (Continuous)	258.35 (101.07 ~ 415.63)	0.001	318.18 (166.84 ~ 469.52)	<0.001	241.52 (86.97 ~ 396.06)	0.002
IG count (*10^9/L)						
IG count=0	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
IG count>0	7.30 (2.23 ~ 12.37)	0.005	8.25 (3.39 ~ 13.10)	<0.001	6.27 (1.45 ~ 11.08)	0.011

Notes: Model1: Crude. Model2: Adjust: Hypertension, Diabetes, Marital status, Procreation, Pausimenia, Laterality, Tumor count, Histology. Model3: Adjust: Hypertension, Diabetes, Marital status, Procreation, Pausimenia, Laterality, Tumor count, Histology, Nerve invasion, Vascular invasion, ER, PR, HER2, ALNM, Age, BMI, Tumor size, KI67, LDH, NLR, PLR.
Abbreviation: CI, Confidence Interval.

Subgroup Analysis

Subgroup analyses were performed to assess the consistency of the association between IG count and tumor size across different clinical characteristics, including age, hypertension, diabetes, marital status, history of procreation, pausimenia status, BMI, histological type, and ER, PR, and HER2 status. A positive association between IG count and tumor size was observed in most subgroups. However, the relationship was significantly modified by hypertension (P-value for interaction = 0.012) (Table 5).

Table 5 Subgroup Analysis for the Association Between Immature Granulocytes Count and the Tumor Size in Breast Cancer Population

Variables	n (%)	β (95% CI)	P-value	P-value for interaction
All patients	778 (100.00)	6.09 (1.46 ~ 10.72)	0.010	
Age				0.878
≤40	129 (16.58)	9.31 (−6.70 ~ 25.32)	0.257	
40~60	508 (65.30)	6.72 (1.56 ~ 11.87)	0.011	
>60	141 (18.12)	0.70 (−14.79 ~ 16.18)	0.930	
Hypertension				0.012
No	655 (84.19)	9.35 (4.10 ~ 14.60)	<0.001	
Yes	123 (15.81)	−5.19 (−15.87 ~ 5.49)	0.343	
Diabetes				0.215
No	714 (91.77)	5.30 (0.50 ~ 10.11)	0.031	
Yes	64 (8.23)	14.10 (−6.70 ~ 34.89)	0.191	
Marital status				0.509
0	15 (1.93)	−39.17 (NA ~ NA)		
1	763 (98.07)	6.04 (1.37 ~ 10.71)	0.012	
Procreation				0.207
No	26 (3.34)	−33.54 (−115.28 ~ 48.20)	0.458	
Yes	752 (96.66)	6.21 (1.50 ~ 10.91)	0.010	
Pausimenia				0.442
No	395 (50.77)	6.19 (0.31 ~ 12.08)	0.040	
Yes	383 (49.23)	6.70 (−1.02 ~ 14.42)	0.090	
BMI				0.907
<18.5	33 (4.24)	26.90 (−56.00 ~ 109.80)	0.537	
18.5~23.9	431 (55.40)	7.45 (1.51 ~ 13.38)	0.014	
24~27.9	233 (29.95)	5.01 (−3.72 ~ 13.75)	0.262	
≥28	81 (10.41)	−7.67 (−31.76 ~ 16.43)	0.535	

(*Continued*)

Table 5 (Continued).

Variables	n (%)	β (95% CI)	P-value	P-value for interaction
Histology				0.267
I	45 (5.78)	−5.92 (−41.19 ~ 29.34)	0.744	
II	389 (50.00)	9.56 (2.73 ~ 16.40)	0.006	
III	344 (44.22)	1.28 (−5.42 ~ 7.98)	0.709	
ER				0.424
Negative	200 (25.71)	−1.26 (−12.00 ~ 9.48)	0.818	
Positive	578 (74.29)	8.71 (3.65 ~ 13.77)	<0.001	
PR				0.911
Negative	243 (31.23)	1.75 (−7.37 ~ 10.88)	0.707	
Positive	535 (68.77)	7.43 (2.10 ~ 12.76)	0.007	
HER2				0.299
Negative	572 (73.52)	6.01 (1.21 ~ 10.81)	0.015	
Positive	206 (26.48)	7.16 (−5.88 ~ 20.21)	0.283	

Abbreviations: BMI, Body Mass Index; ER, Estrogen Receptor; PR, Progesterone Receptor; HER2, Human Epidermal Growth Factor Receptor 2; CI, Confidence Interval.

Exploring Potential Mechanistic Links

To explore the potential underlying mechanisms linking IG count, LDH, and tumor growth, mediation analysis was performed. As shown in Figure 3, LDH partially mediated the association between IG count and tumor size, and this mediating effect was statistically significant. Specifically, LDH accounted for approximately 9.86% of the total effect, suggesting that it may serve as a biological mediator that partially explains the positive correlation between elevated IG levels and increased tumor size.

Discussion

In the present study, we demonstrated that immature granulocyte (IG) count and lactate dehydrogenase (LDH) levels were both positively associated with tumor size in patients with breast cancer. Mediation analysis revealed that LDH partially mediated the relationship between IG and tumor size, highlighting a potential interplay between systemic inflammation and metabolic activity in promoting tumor growth. Furthermore, subgroup analyses suggested that this association may be influenced by the presence of hypertension, indicating that host comorbidities could modulate the impact of inflammatory responses on tumor burden.

Accumulating evidence indicates that chronic inflammation plays a critical role in the onset and progression of various diseases, including cancer and cardiovascular disorders.[12–15] As early as the 19th century, researchers proposed a close association between chronic inflammation and carcinogenesis.[16] While inflammation represents a natural

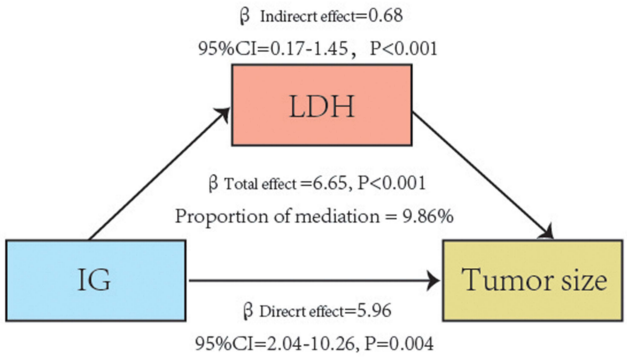

Figure 3 LDH as a mediator in the association between IG count and tumor size.

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protective response to tissue injury, its persistence can lead to a chronic state, which substantially increases the risk of cancer and other diseases.[17] The inflammatory tumor microenvironment, shaped by interactions among tumor cells, stromal cells, and inflammatory immune cells, provides a permissive milieu that fosters tumor initiation and progression through multiple mechanisms.[18,19]

Clinically, severe stressors such as sepsis, trauma, or viral infections can induce "emergency granulopoiesis", a hematopoietic response in which the bone marrow rapidly produces neutrophils to meet acute demands. This process, however, also results in the release of immature neutrophils into the peripheral blood.[20–22] Immature granulocytes (IG), as a novel inflammatory biomarker, are easily detectable and have been widely applied in the prognostic evaluation of various diseases.[23,24] Recent studies have shown that immature neutrophils are markedly enriched in bone metastasis tissues in various cancers, where they contribute to immunosuppressive processes.[25] Similarly, myeloid-derived suppressor cells (MDSCs), a well-recognized immunosuppressive cell population, are increased in the peripheral blood and tumor tissues of cancer patients, correlating with impaired T-cell function, resistance to immunotherapy, and unfavorable prognosis.[26] Consistent with these findings, Salma M Saed et al reported that breast cancer patients with tumors >2 cm exhibited significantly higher levels of g-MDSCs compared with those with tumors ≤2 cm, in line with the results of the present study.[27]

LDH plays a critical role in malignant tumor progression.[28] Elevated LDH levels have been consistently associated with poor prognosis in cancer patients and are considered a classical hallmark of the "Warburg effect", in which tumor cells preferentially utilize glycolysis even under normoxic conditions, producing excessive lactate.[29–31] The accumulation of lactic acid acidifies the tumor microenvironment, thereby promoting invasion, metastasis, angiogenesis, and immune evasion.[28] Moreover, LDH contributes to malignant progression by inducing epithelial–mesenchymal transition (EMT) and enhancing angiogenesis.[32,33] Recently, LDH has attracted increasing attention as both a prognostic biomarker and a potential therapeutic target.[34] Inhibiting LDH not only disrupts the Warburg effect and tumor energy metabolism but may also improve responsiveness to chemotherapy, immunotherapy, and radiotherapy, providing a promising avenue for combined cancer treatment strategies.[35,36]

Our findings indicate that LDH partially mediates the relationship between IG and breast tumor size. Consistently, a study on pancreatitis reported a positive correlation between immature granulocytes and LDH, supporting our observations.[37] Inflammation is known to upregulate LDH through multiple mechanisms. For example, inflammatory microenvironments can activate signaling pathways such as HIF-1α, which induces LDHA expression.[38,39] Additionally, doxorubicin-induced neutrophil extracellular traps (NETs) have been shown to regulate ferroptosis in cardiomyocytes via the HMGB1/TLR4/YAP axis, causing myocardial injury and subsequent elevation of peripheral LDH levels.[40] Inflammatory responses can also damage tumor or surrounding stromal cells, releasing intracellular LDH into the extracellular space and circulation, thereby increasing serum LDH levels. The concurrent elevation of IG and LDH may further acidify the tumor microenvironment, accelerating tumor progression and malignancy.

Our study indicates that the relationship between IG and tumor size is modulated by hypertension. In normotensive patients, IG counts and tumor size show a consistent positive correlation, whereas this association is not statistically significant in hypertensive individuals. Hypertension is characterized by dysregulated reactive oxygen species (ROS) production, a key contributor to oxidative stress, which also plays a pivotal role in inflammation-driven tumorigenesis and progression, potentially altering systemic inflammatory responses.[41,42] Moreover, hypertension-associated endothelial dysfunction, vascular injury, and cardiovascular remodeling may further impact tumor development.[43] The use of antihypertensive medications may additionally modulate inflammatory status, influencing tumor progression. However, studies specifically evaluating the impact of hypertension on tumor burden in breast cancer patients remain scarce, highlighting an important gap in the current evidence. These observations highlight the need for further studies to elucidate the complex interplay between hypertension, inflammation, and tumor growth.

Our findings carry important biological and clinical implications, highlighting the central roles of systemic inflammation and metabolic alterations in breast cancer progression. Both immature granulocytes and LDH reflect aspects of the host inflammatory response and tumor metabolic activity, and their elevations were consistently associated with larger tumor size. These markers may therefore provide valuable insights into tumor burden and could assist in the early identification of patients with more aggressive disease. In addition, IG and LDH represent biologically meaningful

pathways involving neutrophil-driven inflammation and glycolytic reprogramming, which have been increasingly recognized as contributors to tumor growth. These factors may serve not only as accessible biomarkers but also as potential entry points for therapeutic strategies that target inflammation–metabolism interactions in breast cancer.

Nevertheless, several limitations should be acknowledged. Due to the cross-sectional nature of this study, causal inference cannot be established, and the temporal relationship among IG, LDH, and tumor burden cannot be determined. The single-center design may also limit the generalizability of the findings. Furthermore, the distribution of IG counts restricted our ability to investigate more complex or nonlinear associations. Although multiple covariates were adjusted for, the possibility of residual confounding cannot be excluded. To address these limitations and further clarify the biological pathways linking inflammation, LDH elevation, and tumor growth, future research will require multicenter prospective studies as well as mechanistic investigations.

Conclusion

These findings suggest a potential interplay between systemic inflammation and tumor metabolism in breast cancer progression. IG and LDH may serve as accessible biomarkers associated with tumor burden and could assist in risk stratification and clinical decision-making. Multicenter prospective studies are required to validate these associations and further elucidate the underlying biological mechanisms.

Data Sharing Statement

The data are available from the corresponding author upon reasonable request.

Ethical Approval

This retrospective study was approved by the Clinical Research Ethics Committee, The Second Affiliated Hospital of Fujian Medical University (Approval No. 2025-105). All procedures were conducted in strict accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study and the complete removal of all patient-identifying information to ensure anonymity, the Ethics Committee granted a waiver of written informed consent. All data were analyzed in an anonymized manner. All operations in this study complied with relevant guidelines and regulatory requirements.

This study was conducted and reported in accordance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines.

Author Contributions

All authors have made substantial intellectual contributions to the work and approved it for publication. The specific contributions, following the CRediT taxonomy, are as follows:

Huikai Liang: Conceptualization, Investigation, Formal analysis, Writing – original draft.

Kelun Pan: Methodology, Investigation, Data curation, Writing – original draft.

Xinlan Liang: Formal analysis, Validation, Visualization, Writing – review & editing.

Jiayi Wang: Investigation, Resources, Data curation, Writing – review & editing.

Xinru Xie: Investigation, Resources, Writing – review & editing.

Ningning Wan: Conceptualization, Supervision, Project administration, Writing – review & editing.

Jianqing Lin: Supervision, Funding acquisition, Resources, Writing – review & editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Huikai Liang, Kelun Pan, and Xinlan Liang contributed equally to this work and are designated as co-first authors.

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Disclosure

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