SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-66466

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–10, 2026

Original paper
Originalni naučni rad

CIRCULATING STREM-1 AS A BIOMARKER OF MYELOID-DRIVEN INFLAMMATION IN BREAST CANCER: DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE

STREM-1 U CIRKULACIJI KAO BIOMARKER MIJELOIDNOG UPALA KOD RAKA DOJKE: DIJAGNOSTIČKI I PROGNOSTIČKI ZNAČAJ

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Summary

Background: Circulating biomarkers that reflect tumor-associated immune-inflammatory activation may help refine breast cancer assessment. Triggering receptor expressed on myeloid cells-1 (TREM-1) amplifies myeloid-driven inflammatory signaling, and its soluble form (sTREM-1) can be measured in serum. However, the diagnostic and prognostic relevance of pretreatment circulating sTREM-1 in breast cancer remains insufficiently defined.
Methods: This single-center retrospective observational study included 132 treatment-naive patients with stage I-III breast cancer, 68 patients with benign breast disease, and 60 healthy controls. Serum sTREM-1, conventional tumor markers, C-reactive protein (CRP), and derived inflammatory indices, including NLR, PLR, LMR, and SII, were analyzed. Associations with clinicopathological features, diagnostic performance, and disease-free survival (DFS) were evaluated using correlation analysis, receiver operating characteristic (ROC) curves, Kaplan-Meier analysis, and Cox regression models.
Results: Serum sTREM-1 was significantly elevated in breast cancer compared with benign disease and healthy controls ($P < 0.001$). Higher sTREM-1 levels were associated with larger tumor size, lymph node involvement, advanced stage, high histological grade, and elevated Ki-67 expression (all $P < 0.05$). sTREM-1 correlated positively with CRP, NLR, PLR, and SII and negatively with LMR (all

Kratak sadržaj

Uvod: Primarni hiperparatireoidizam (PHPT) je povezan je metaboličkim poremećajima, endotelijalnom disfunkcijom i povećanim kardiovaskularnim rizikom. Rastvorljivi endoglin (sENG), biomarker porekla iz endotela, predstavlja potencijalni pokazatelj vaskularnog stresa povezanog sa TGF-β. Cilj ovog istraživanja je bio da uporedi serumske nivoe sENG kod pacijenata sa asimptomatskim PHPT i zdravih kontrolnih ispitanika, kao i da ispita povezanost između sENG i metaboličkih parametara.
Metode: U ovu studiju preseka uključena su 42 pacijenta sa biohemijski potvrđenim asimptomatskim PHPT i 39 zdravih kontrolanih pacijenata uparenih po starosti i polu. Upoređeni su serumski nivoi sENG i metabolički parametri između grupa. Za procenu potencijalnih povezanosti korišćeni su Welchov t-test, hi-kvadrat test, korelacione i regresione analize.
Rezultati: Serumski nivoi sENG su bili slični između PHPT i kontrolne grupe (1,40±1,13 naspram 1,46±1,31 ng/mL, $p=0,83$). U PHPT grupi uočene su slabe, ali statistički neznačajne pozitivne povezanosti između sENG i indeksa telesne mase, glikemije natašte, insulina i HOMA-IR. Ove povezanosti su bile manje izražene u kontrolnoj grupi. U linearnoj regresionoj analizi telesna masa je identifikovana kao nezavisan determinanta sENG u PHPT grupi ($p=0,047$). U dvosmernoj ANOVA analizi nisu utvrđeni značajni glavni niti interakcioni efekti, a granične

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P < 0.001). For differentiating breast cancer from benign breast disease, sTREM-1 showed good diagnostic performance (AUC = 0.842), which improved when combined with CA15-3 and NLR (AUC = 0.889). Elevated sTREM-1 independently predicted shorter DFS in multivariate analysis (HR = 1.96, 95% CI: 1.01-3.80, P = 0.046).
Conclusion: Circulating sTREM-1 is elevated in breast cancer and reflects myeloid-driven immune-inflammatory activation. As a measurable serum biomarker, sTREM-1 may provide complementary information for auxiliary diagnosis and prognosis evaluation. Larger multicenter studies are needed to validate its clinical utility and define standardized assay thresholds.

Keywords: breast cancer, sTREM-1, diagnosis, prognosis, immune inflammation, biomarker

interakcije uočene za glikemiju i indeks telesne mase nisu dostigle statistički značaj.
Zaključak: Serumski nivoi sENG se nisu značajno razlikovali između pacijenata sa asimptomatskim PHPT i kontrolnih pacijenata. Nisu utvrđene statistički značajne povezanosti između sENG i metaboličkih parametara. Iako su regresioni dijagrami vizuelno ukazivali na određene trendove, ti nalazi nisu dostigli statistički značaj. Ove rezultate treba tumačiti sa oprezom, a neophodna su i dalja istraživanja sa većim uzorcima radi razjašnjenja povezanosti.

Ključne reči: primarni hiperparatireoidizam, rastvorljivi endoglin, endotelijalna disfunkcija, metabolički parametri, insulinska rezistencija

Introduction

Breast cancer is one of the most common malignant tumors in women and a major public health problem affecting quality of life and survival outcomes. According to GLOBOCAN 2022 data, breast cancer remains one of the leading contributors to the global burden of female malignancies (1). As a cancer characterized by both high incidence and marked clinical heterogeneity, breast cancer has imposed a continuously increasing medical burden worldwide and has raised the demands placed on patients' families, social support systems, and long-term health management (2,3). In recent years, with the wider use of breast imaging screening, improved public health awareness, and continual updates in treatment strategies, increasing numbers of patients have been identified at relatively early stages and have received standardized treatment. Even so, more accurate identification of underlying biological differences, recurrence risk, and long-term outcome variability among different patients remains one of the central issues in breast cancer research and precision management.

At present, the diagnosis of breast cancer still relies primarily on imaging and pathology. Ultrasonography, mammography, and magnetic resonance imaging play important roles in lesion detection, localization, and preoperative evaluation, but their results may still be influenced by lesion size, breast density, operator experience, and equipment conditions. Pathological examination is the diagnostic gold standard, but it is invasive and difficult to use for dynamic assessment of the overall biological changes of the tumor before and after treatment and throughout follow-up. Traditional serum markers such as CA15-3 have long been used in clinical practice, yet their sensitivity in early-stage or localized breast cancer is unsatisfactory (4). This means that when tumor burden remains limited and the lesion is still relatively localized, relying on conventional serum markers alone often cannot achieve satisfactory early identification or refined stratification. Existing reviews also suggest that CA15-3 and CEA are more suitable for treatment monitoring or recurrence surveillance than as ideal stand-alone screening tools (5). Therefore, beyond imaging and pathology, it remains clinically meaningful to explore new serum biomarkers that can reflect tumor-related host responses and that also have potential for dynamic monitoring.

In recent years, systemic inflammatory indices derived from peripheral blood have gradually become a focus of breast cancer research. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and C-reactive protein have been widely used for prognostic evaluation and risk stratification because they are easy to obtain and relatively inexpensive (6). The strength of these indices lies in their derivation from routine laboratory tests, which makes them readily accessible in clinical practice and reasonably reproducible; they have shown value in prognostic studies across multiple tumor types. In breast cancer, such indices can to some extent reflect the inflammatory burden, immune balance, and the intensity of tumor–host interaction at the systemic level. However, these markers are largely nonspecific indicators of inflammation (7). Although they can suggest the presence of inflammatory and immune dysregulation, they provide limited insight into the particular inflammatory signaling axes involved. In other words, they are better at answering whether inflammation exists than at explaining which type of inflammatory mechanism deserves attention or which immune regulatory steps may be most closely related to tumor behavior. For that reason, identifying biomarkers that are both detectable in serum and more informative at the pathway level has become an important direction in tumor inflammation research.

Breast cancer cannot be fully explained by malignant cell overgrowth alone (8,9). It arises within a highly interactive biological context in which tumor cells coexist with stromal elements, immune populations, cytokine networks, and extracellular matrix

components. Increasing evidence suggests that persistent inflammatory signaling contributes to several malignant traits, including phenotypic adaptability, resistance to therapy, and reawakening of dormant tumor cells (10). The impact of inflammation is not restricted to one pathway or one compartment. Instead, it extends across multiple dimensions, affecting cancer-cell function, reshaping the surrounding tissue environment, and altering host-wide responses. Continuous inflammatory exposure may modify tumor metabolic activity and growth dynamics, while also changing how cancer cells communicate with neighboring fibroblasts, endothelial cells, and immune populations. At the same time, interactions between infiltrating immune cells and cancer-associated fibroblasts can reinforce an immune-suppressive niche that favors disease progression (11). These observations indicate that the breast tumor microenvironment is constantly evolving, and that such remodeling is closely linked to invasive behavior, metastatic dissemination, and variability in treatment efficacy. Among the many cellular participants in this process, tumor-associated myeloid cells—particularly tumor-associated macrophages and myeloid-derived suppressor cells—have a central role in supporting immune evasion, invasion, and metastasis (12). Compared with the better-known lymphocyte-centered antitumor response, myeloid cells are more directly involved in inflammatory signal escalation, stromal remodeling, suppression of effective immunity, and preparation of premetastatic sites. For this reason, molecules associated with myeloid-cell activation may offer a useful window into the interconnected processes of inflammation, immune imbalance, and breast cancer progression.

In recent years, triggering receptor expressed on myeloid cells-1 (TREM-1) has attracted growing attention as a regulator of myeloid-cell-driven inflammation. This receptor is mainly present on neutrophils, monocytes, and macrophages, where it functions as an important enhancer of innate immune responses (13). Rather than serving simply as an initiating signal, TREM-1 primarily strengthens an existing inflammatory state by promoting effector-cell activation and augmenting the release of downstream inflammatory mediators. Previous studies have shown that this pathway participates in the amplification of myeloid inflammatory activity and is implicated in both inflammatory disorders and tumor-related processes (14). Across infectious diseases, sterile inflammatory conditions, and several malignancies, the TREM-1 axis has been associated with disease intensity and systemic inflammatory burden. A soluble form of this receptor, sTREM-1, is detectable in peripheral blood, which makes it a potentially useful circulating biomarker (15). In comparison with tissue-derived molecular indicators, serum soluble markers are more amenable to repeated measurement and longitudinal follow-up, giving them practical value in clinical evaluation. Although most earlier work on soluble TREM-1 has centered on infection and sepsis, its established role in inflammatory signal amplification also makes it highly relevant to cancer biology (16). This relevance is particularly important in tumors, where inflammation cannot be simply categorized as beneficial or detrimental; depending on the biological context, it may instead sustain tumor expansion, facilitate immune escape, and support metastatic spread.

Studies based on transcriptomic profiling and single-cell analysis have indicated that elevated TREM1 expression in breast cancer tissue is linked to worse clinical outcomes, greater infiltration of myeloid populations, and a more immunosuppressive tumor milieu (17). These observations imply that TREM-1 is unlikely to be only a secondary marker accompanying inflammation; rather, it may actively participate in the remodeling of myeloid immune responses in breast cancer. In other words, increased TREM-1 may point not merely to an inflammatory state, but to a tumor-promoting and immune-restrained inflammatory environment. Previous clinical investigations have also reported detectable serum sTREM-1 levels in patients with solid malignancies, including breast cancer, providing preliminary support for blood-based assessment (18). This point is of considerable translational importance, because it suggests that investigation of the TREM-1 pathway need not rely exclusively on tissue samples or expensive omics techniques, but may also be approached through peripheral blood analysis in routine practice. However, clinical evidence regarding serum sTREM-1 in untreated breast cancer remains insufficient. Its distribution pattern in breast cancer, its relationship with clinicopathological characteristics, its correlation with conventional inflammatory markers, and its prognostic relevance have not yet been fully clarified.

Against this background, the present study focused on pretreatment circulating sTREM-1 because it is directly linked to myeloid inflammatory signaling and can be assessed noninvasively in peripheral blood. Although tissue-based and transcriptomic studies have suggested a role for TREM-1 in breast cancer-related immune suppression, clinical evidence regarding serum sTREM-1 in treatment-naive breast cancer remains limited. In particular, it remains unclear whether serum sTREM-1 can distinguish breast cancer from benign breast disease, reflect systemic inflammatory activation beyond conventional tumor markers and routine inflammatory indices, and provide prognostic information for disease-free survival. Therefore, we quantified pretreatment serum sTREM-1 in patients with stage I-III breast cancer and included benign breast disease cases and healthy controls as comparison groups. The novelty of this study lies in the

integrated evaluation of sTREM-1 as an auxiliary diagnostic biomarker, an indicator of myeloid-driven systemic inflammation, and a potential prognostic factor in breast cancer. By adopting this approach, we sought to determine whether serum sTREM-1 provides additional clinical information beyond conventional tumor markers and nonspecific inflammatory indices.

Materials and Methods

Study population

This single-center retrospective observational study enrolled three groups of participants. The breast cancer group consisted of 132 women with newly diagnosed primary breast cancer at stage I–III who were admitted to the department of breast surgery between January 2022 and December 2024 and had pathological confirmation. During the same period, 68 women with benign breast disease confirmed by pathology or imaging were included as the benign breast disease group. In addition, 60 healthy women who underwent routine physical examination in the same time frame were recruited as the healthy control group.

Inclusion and exclusion criteria

For the breast cancer group, eligible participants were women aged 18 years or older with newly diagnosed primary breast cancer, pathologically confirmed stage I–III disease, no antitumor treatment before blood collection, including surgery, chemotherapy, radiotherapy, targeted therapy, or immunotherapy, complete clinical records, and the ability to undergo follow-up.

For the benign breast disease group, inclusion criteria were female sex, age of at least 18 years, a diagnosis of benign breast disease established by imaging or pathology, and complete clinical information.

For the healthy control group, women were eligible if they were 18 years of age or older, attended routine health screening during the same period, had no previous history of malignant disease, and showed no evident infection or inflammatory disorder.

The exclusion criteria for all groups included acute infection, fever, or confirmed inflammatory disease within the preceding 4 weeks; coexisting autoimmune disorders, hematologic diseases, or other malignant tumors; recent use of antibiotics, glucocorticoids, or immunosuppressive agents; severe liver or kidney dysfunction; and pregnancy or lactation.

Specimen collection and biochemical measurements

Peripheral venous blood samples were collected from all participants in the morning following an overnight fast (at least 8–10 hours) to minimize the influence of circadian and dietary variations on circulating biomarkers. Blood samples were drawn into standard serum-separating tubes and allowed to clot at room temperature for 30 minutes, followed by centrifugation at 3,000 rpm for 10 minutes. The obtained serum was immediately aliquoted and stored at −80 °C until analysis to avoid repeated freeze–thaw cycles.

Serum levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human sTREM-1 QuickTest ELISA Kit, FineTest, Wuhan, China; Cat. No. QT-EH3832; detection range: 31.25–2000 pg/mL; analytical sensitivity: 18.75 pg/mL) in accordance with the manufacturer's instructions. Briefly, serum samples and standards were added to antibody-precoated wells, incubated, washed, and reacted with enzyme-conjugated detection antibody and substrate solution. Optical density was measured at the wavelength recommended by the manufacturer, and concentrations were calculated from the standard curve. The intra-assay and inter-assay coefficients of variation (CVs) were both $<10\%$, ensuring acceptable analytical precision. All samples were measured in duplicate, and the mean value was used for statistical analysis. Laboratory personnel were blinded to clinical grouping to reduce measurement bias.

Routine hematological parameters, including neutrophil, lymphocyte, monocyte, and platelet counts, were measured using an automated hematology analyzer (e.g., Sysmex XN-series, Japan). Serum C-reactive protein (CRP) levels were determined by immunoturbidimetric assay, while carbohydrate antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) were measured using electrochemiluminescence immunoassay (ECLIA) on a fully automated analyzer (e.g., Roche Cobas 8000 system, Germany), following standardized laboratory protocols.

Derived inflammatory indices were calculated as follows: neutrophil-to-lymphocyte ratio (NLR = neutrophil count / lymphocyte count), platelet-to-lymphocyte ratio (PLR = platelet count / lymphocyte count), lymphocyte-to-monocyte ratio (LMR = lymphocyte count / monocyte count), and systemic immune-inflammation index (SII = platelet count × neutrophil count / lymphocyte count). All laboratory measurements were performed in the same certified clinical laboratory under standardized operating procedures.

For patients with breast cancer, detailed clinicopathological data were systematically recorded, including age, menopausal status, tumor size, lymph node involvement, clinical stage, histological grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Ki-67 proliferation index, and molecular subtype classification.

Outcome measures and laboratory endpoints

The primary objective of this study was to evaluate the clinical and biochemical significance of circulating sTREM-1 in breast cancer. The predefined laboratory and clinical endpoints were as follows: (1) Biochemical comparison: quantitative comparison of serum sTREM-1 levels among patients with breast cancer, benign breast disease, and healthy controls, to determine its potential as a circulating biomarker; (2) Clinicobiochemical associations: assessment of the relationships between serum sTREM-1 concentrations and clinicopathological characteristics, reflecting tumor burden and biological aggressiveness; (3) Inflammatory correlation analysis: evaluation of the correlations between sTREM-1 and established systemic inflammatory biomarkers (CRP, NLR, PLR, LMR, and SII), to explore its role within the myeloid-driven inflammatory response network; (4) Diagnostic performance: determination of the diagnostic accuracy of sTREM-1, alone and in combination with conventional tumor biomarkers (CA15-3, CEA) and inflammatory indices, using receiver operating characteristic (ROC) curve analysis; (5) Prognostic evaluation: investigation of the association between baseline serum sTREM-1 levels and disease-free survival (DFS), including its independent prognostic value assessed by multivariate Cox regression modeling.

Follow-up and endpoint events

Patients were followed through outpatient review and telephone interviews until December 2025. The primary endpoint was DFS, defined as the time from diagnosis to the occurrence of local recurrence, regional recurrence, distant metastasis, new contralateral breast cancer, or death. Cases without endpoint events at the last follow-up, as well as those lost to follow-up, were treated as censored observations.

Statistical analysis

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 26.0 and R version 4.3.0 (IBM, Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of distribution plots. Normally distributed continuous variables were described as mean +/- standard deviation, whereas non-normally distributed variables were presented as median with interquartile range. Categorical data were summarized as counts and percentages.

Differences among the three groups were examined using one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Comparisons between two groups were performed using the independent-samples t test or the Mann-Whitney U test. The chi-square test was applied for comparisons of categorical variables. Spearman correlation analysis was used to assess relationships between sTREM-1 and systemic inflammatory indices. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic efficacy, and the AUC, 95% confidence interval, optimal cutoff value, sensitivity, and specificity were calculated. Survival analysis was performed with the Kaplan-Meier method and compared using the log-rank test. For survival analysis, the median serum sTREM-1 value in the breast cancer cohort was used as the cutoff to avoid arbitrary threshold selection and to obtain balanced high- and low-sTREM-1 groups, because no externally validated cutoff is currently available. Multivariate prognostic analysis was conducted using the Cox proportional hazards model. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics and serum sTREM-1 levels in the three groups

Age did not differ significantly among the breast cancer group, benign breast disease group, and healthy control group ($P = 0.287$), suggesting that the three groups were generally comparable at baseline. In contrast, serum sTREM-1 levels showed clear between-group differences, with the highest levels observed in patients with breast cancer. Moreover, compared with the other two groups, patients with breast cancer exhibited increased NLR, PLR, CRP, and SII, together with decreased LMR, indicating a more evident systemic immune-inflammatory response in this population (*Table I*).

Association between serum sTREM-1 and clinicopathological features of breast cancer

Within the breast cancer cohort, higher serum sTREM-1 levels were found in patients with larger tumor size, lymph node metastasis, stage III disease, higher histological grade, and elevated Ki-67 expression. No statistically significant differences were detected according to ER, PR, or HER2 status.

Table I Comparison of baseline characteristics and inflammatory indices among the three groups.

Indicator	Breast cancer group (n=132)	Benign breast disease group (n=68)	Healthy control group (n=60)	P value
Age (years)	51.9 (46.2, 56.8)	50.7 (43.6, 54.8)	49.8 (42.9, 55.1)	0.287
sTREM-1 (pg/mL)	148.5 (126.7, 173.2)	96.4 (82.1, 110.6)	71.2 (61.8, 81.4)	<0.001
CA15-3 (U/mL)	23.7 (18.9, 29.4)	13.8 (11.2, 16.0)	12.4 (10.5, 14.2)	<0.001
CEA (ng/mL)	2.9 (2.1, 3.8)	1.9 (1.4, 2.5)	1.7 (1.3, 2.1)	<0.001
NLR	2.12 (1.63, 2.66)	1.73 (1.42, 2.06)	1.58 (1.29, 1.80)	<0.001
PLR	154.7 (128.6, 181.9)	117.4 (99.3, 135.1)	103.6 (89.5, 117.2)	<0.001
LMR	3.31 (2.85, 3.76)	4.05 (3.62, 4.41)	4.26 (3.88, 4.58)	<0.001
CRP (mg/L)	3.4 (2.2, 4.7)	1.2 (0.7, 1.8)	0.8 (0.4, 1.1)	<0.001
SII	684.5 (552.3, 856.7)	472.3 (366.1, 594.2)	395.8 (312.4, 487.9)	<0.001

Table II Relationship between serum sTREM-1 and clinicopathological characteristics of breast cancer.

Clinicopathological feature	n	sTREM-1 (pg/mL)	P value
Tumor size T1–2	103	143.1 (122.8, 164.5)	
Tumor size T3	29	165.7 (146.6, 187.4)	0.006
Node-negative	75	139.8 (121.5, 159.9)	
Node-positive	57	161.4 (141.9, 184.7)	0.003
Clinical stage I–II	96	140.7 (121.9, 159.4)	
Clinical stage III	36	169.2 (149.8, 189.6)	<0.001
Histologic grade G1–2	83	143.6 (123.4, 163.8)	
Histologic grade G3	49	158.2 (139.6, 181.1)	0.041
ER-positive	97	145.4 (124.8, 169.5)	
ER-negative	35	154.8 (134.2, 178.6)	0.233
PR-positive	88	144.9 (123.7, 168.9)	
PR-negative	44	155.7 (136.0, 180.2)	0.178
HER2-negative	101	145.8 (124.6, 170.7)	
HER2-positive	31	156.9 (136.7, 180.6)	0.189
Ki-67 <20%	59	139.4 (120.5, 160.8)	
Ki-67 ≥20%	73	157.9 (136.9, 180.5)	0.011
Luminal A	28	133.8 (117.1, 148.6)	
Luminal B	49	145.6 (124.3, 168.2)	
HER2-enriched	21	158.9 (141.7, 176.4)	
TNBC	34	162.8 (143.2, 183.9)	0.024

When analyzed by molecular subtype, the overall difference was significant, and relatively increased sTREM-1 levels were mainly observed in the HER2-enriched and TNBC subgroups (*Table II*).

Correlations between serum sTREM-1 and systemic inflammatory markers

Spearman correlation analysis demonstrated that, in patients with breast cancer, serum sTREM-1 was positively associated with NLR, PLR, CRP, and SII, whereas an inverse correlation was found with LMR. These findings suggest that sTREM-1 is broadly consistent with conventional indicators reflecting systemic inflammatory and immune activation (*Table III*).

Table III Correlation analysis between serum sTREM-1 and systemic inflammatory indices.

Indicator	r	P value
NLR	0.412	<0.001
PLR	0.358	<0.001
LMR	-0.327	<0.001
CRP	0.486	<0.001
SII	0.441	<0.001

Supportive diagnostic performance of serum sTREM-1 in breast cancer

ROC curve analysis indicated that serum sTREM-1 had good discriminatory ability for differentiating breast cancer from benign breast disease, with an AUC of 0.842. Its diagnostic performance was superior to that of CEA and NLR and was also better than CA15-3 used alone. Using 118.6 pg/mL as the optimal cutoff value, the corresponding sensitivity and specificity were 78.0% and 77.9%, respectively. In addition, when sTREM-1 was combined with CA15-3 and NLR, the AUC further increased to 0.889, implying that a combined model may offer better auxiliary diagnostic efficiency than a single marker alone (*Table IV*).

Table IV Diagnostic performance of serum sTREM-1 and related indices for breast cancer (breast cancer vs benign breast disease).

Indicator	AUC	95% CI	Optimal cutoff	Sensitivity (%)	Specificity (%)
sTREM-1	0.842	0.783–0.901	118.6 pg/mL	78.0	77.9
CA15-3	0.742	0.669–0.816	20.4 U/mL	60.6	75.0
CEA	0.684	0.607–0.762	2.60 ng/mL	50.8	73.5
NLR	0.703	0.628–0.778	1.95	62.9	67.6
sTREM-1 + CA15-3 + NLR	0.889	0.844–0.934	—	82.6	82.4

Table V Cox regression analysis of DFS in patients with breast cancer.

Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age ≥50 years	1.12 (0.58–2.16)	0.734	—	—
Tumor size T3	1.89 (1.01–3.54)	0.046	1.54 (0.82–2.91)	0.183
Positive lymph nodes	2.26 (1.19–4.28)	0.012	1.87 (0.95–3.69)	0.071
Histologic grade G3	1.67 (0.88–3.15)	0.116	—	—
Ki-67 ≥20%	1.92 (1.01–3.63)	0.045	1.48 (0.78–2.80)	0.249
HER2-positive	1.41 (0.70–2.86)	0.337	—	—
High sTREM-1	2.31 (1.22–4.37)	0.010	1.96 (1.01–3.80)	0.046

Relationship between serum sTREM-1 and prognosis in breast cancer

Based on the median serum sTREM-1 level of 147.0 pg/mL in the breast cancer cohort, patients were classified into low- and high-sTREM-1 groups; this median-based cutoff was selected to avoid arbitrary threshold selection and to ensure balanced group sizes for survival comparison. The median follow-up period was 30 months. Kaplan-Meier analysis showed that patients in the high-sTREM-1 group had a significantly lower 3-year DFS than those in the low-sTREM-1 group (68.2% vs 86.1%, log-rank P = 0.003). Univariate Cox regression analysis identified larger tumor size, lymph node positivity, high Ki-67 expression, and elevated sTREM-1 as factors associated with shorter DFS. After adjustment in multivariate analysis, high serum sTREM-1 remained an independent predictor of adverse DFS (*Table V*).

Discussion

The present study indicates that pretreatment circulating sTREM-1 is clinically relevant in breast cancer as a serum marker linked to myeloid-driven inflammation. Rather than simply restating the observed elevation of sTREM-1, the central implication is that this molecule may connect tumor burden, systemic inflammatory activation, and recurrence risk within a single measurable biomarker framework. These findings suggest that serum sTREM-1 may complement conventional tumor markers and routine inflammatory indices by providing information about the host immune-inflammatory response associated with breast cancer progression.

From the perspective of the tumor microenvironment, breast cancer is not a disease driven solely by tumor cells. Instead, it is a dynamic system jointly shaped by tumor cells, host immunity, stromal components, and vascular elements. Recent reviews of the breast cancer tumor microenvironment have shown clear differences among molecular subtypes in immune-cell infiltration, myeloid-cell enrichment, and immunosuppression within distant metastatic lesions (19). Thus, breast cancer heterogeneity is reflected not only by ER, PR, HER2, or proliferation status, but also by variation in immune composition and inflammatory background among patients (20). Some subtypes may be more prone to macrophage accumulation, expansion of myeloid-derived suppressor cells, and local immunosuppression, all of which can favor invasion and metastasis. Therefore, any peripheral blood marker that can indirectly reflect tumor-related myeloid immune activation may provide additional information for risk stratification. In this respect, the potential value of sTREM-1 may lie not simply in reflecting the overall burden of inflammation, but in more closely capturing the myeloid immune activation axis that is of particular importance in tumor progression.

In the present study, sTREM-1 was associated with tumor size, lymph node metastasis, and more advanced clinical stage, suggesting that its elevation does not merely indicate the presence of cancer, but may also be related to increased tumor burden and enhanced aggressiveness. Clinically, larger tumors and more extensive regional lymph node involvement usually imply more complex interactions between the tumor and the host, accompanied by stronger local inflammatory amplification and more pronounced systemic immune imbalance. Highly proliferative tumors are often characterized by more evident local hypoxia, metabolic reprogramming, and inflammatory amplification, and myeloid cells are key participants in these processes. They not only secrete proinflammatory cytokines and chemokines, but also participate in stromal remodeling, angiogenesis, and immune escape. Taken together with previous studies on TREM-1 in tumor-associated myeloid cells, it is reasonable to speculate that high sTREM-1 may represent a host response state skewed toward immunosuppression and protumor remodeling. Such a state may not be determined solely by tumor cell number, but it tends to coexist with more unfavorable biological behavior, which may explain the association observed here between high sTREM-1 and aggressive clinical features.

From the perspective of auxiliary diagnosis, sTREM-1 alone yielded an AUC of 0.842 for differentiating breast cancer from benign breast disease, and the AUC increased to 0.889 when sTREM-1 was combined with CA15-3 and NLR. This pattern supports the clinical interpretation that sTREM-1 is more appropriately viewed as an adjunctive biomarker rather than a replacement for existing diagnostic approaches. In routine practice, breast cancer assessment requires integration of imaging, pathology, tumor markers, and host-response information. Previous studies have shown that conventional serum markers such as CA15-3 and CEA have limited sensitivity and specificity, particularly in localized disease. The added value of sTREM-1 may therefore lie in introducing an immune-inflammatory dimension into existing marker panels. If confirmed in larger external cohorts, a combined model incorporating sTREM-1 may improve auxiliary diagnostic assessment and help identify patients whose tumor biology is accompanied by stronger systemic inflammatory activation.

It should be noted that the clinical performance of serum biomarkers is influenced not only by the disease itself, but also by differences in testing platforms and methodology. Reviews of laboratory methods for clinically used serum biomarkers in breast cancer have shown that the degree of

standardization across immunoassays, differences in reagents, and platform updates can all affect the consistency and comparability of results (21). This issue is especially important for studies of novel serum biomarkers. Even if a given molecule shows good performance in a single-center study, differences in experimental conditions, reagent sources, and assay batches may still influence threshold stability and the external validity of the findings. This highlights that future real-world studies will need to pay close attention to threshold determination and inter-platform consistency for sTREM-1. In addition, sample processing, timing of blood collection, storage conditions, and comorbid status may all affect measured values. Therefore, if sTREM-1 is to move toward higher-level evidence and broader clinical verification, methodological standardization will be an unavoidable prerequisite.

From a prognostic standpoint, patients with high sTREM-1 had a significantly lower 3-year DFS than those with low sTREM-1, and multivariate Cox analysis supported sTREM-1 as an independent prognostic factor. This finding suggests that sTREM-1 may capture risk information that is not fully explained by traditional clinicopathological variables. Because soluble biomarkers can be measured repeatedly, sTREM-1 may have potential value for longitudinal risk assessment if future studies confirm its stability across treatment periods and follow-up intervals. Its particular relevance lies in its biological connection with myeloid immune activation, which may provide a mechanistic context for adverse prognosis rather than serving only as a nonspecific risk signal.

The observed correlations between sTREM-1 and CRP, NLR, PLR, LMR, and SII further support its role within the systemic inflammatory network of breast cancer. Conventional inflammatory indices are inexpensive and clinically accessible, but they remain broad and nonspecific. By contrast, sTREM-1 is linked more closely to the myeloid inflammatory pathway. Therefore, these markers should be interpreted as complementary rather than interchangeable. In clinical application, sTREM-1 may be most useful when combined with routine tumor markers and inflammatory indices to identify patients with both tumor-associated inflammation and increased progression risk.

Several limitations of this study should be considered. First, this was a single-center retrospective observational study with a relatively modest sample size, which limits the external validity and generalizability of the findings. The proportions of molecular subtypes and clinical stages were also not evenly distributed, and this may have influenced subgroup comparisons. Second, although patients with recent infection or obvious inflammatory disorders were excluded, serum sTREM-1 may still be affected by subclinical inflammation or unrecognized comorbid conditions. Third, this study focused mainly on serum-level clinical associations and did not include tissue-based TREM-1 expression, immune-infiltration profiling, or experimental validation; therefore, mechanistic interpretation remains limited. Finally, postoperative adjuvant treatment strategies were not analyzed in a detailed stratified manner, and therapeutic heterogeneity may have affected follow-up outcomes. Future multicenter prospective studies with larger cohorts, standardized assay platforms, and integrated tissue and functional analyses are needed to validate these results.

In summary, serum sTREM-1 appears to provide clinically meaningful information at the intersection of auxiliary diagnosis, systemic immune-inflammatory activation, and prognosis assessment in breast cancer. Its value is unlikely to reside in use as a stand-alone screening test, but rather in its ability to complement existing tumor markers and inflammatory indices within a more integrated clinical evaluation framework. If validated in larger multicenter real-world populations, sTREM-1 may become a useful noninvasive biomarker for identifying patients with stronger myeloid-related inflammatory activation and higher disease progression risk.

Conclusion

Circulating sTREM-1 is significantly elevated in treatment-naive patients with stage I-III breast cancer and is closely associated with tumor burden, aggressive clinicopathological characteristics, and systemic inflammatory status. As a measurable serum biomarker, sTREM-1 may provide complementary value for the auxiliary diagnosis of breast cancer and independent prognostic information for disease-free survival. Its correlations with established inflammatory indices support its role in reflecting myeloid-driven immune-inflammatory activation. From a clinical biochemistry perspective, circulating sTREM-1 may serve as a noninvasive biomarker for assessing tumor-associated inflammatory responses and disease progression risk, although larger multicenter validation is required before routine clinical application.

Funding

This study was supported by Xinjiang Uygur Autonomous Region Natural Science Foundation (2025D01C440).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Received:
Accepted: