UKR Journal of Medicine and Medical Research (UKRJMMR)
Homepage: https://ukrpublisher.com/ukrjmmr/
Email: submit.ukrpublisher@gmail.com
Volume 2, Issue 2, March-April 2026
ISSN: 3107-5061 (Online)

Evaluation of Serum NLRP3 and ST2 Concentrations in Breast Cancer Patients: Potential Biomarkers of Inflammation and Tumor Progression

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DOI: *https://doi.org/10.5281/zenodo.18919943*

Article History
Original Research Article
Received: 15-02-2026
Accepted: 01-03-2026
Published: 09-03-2026

Citation: Sahar Saadi Karieb, Mustafa Riyadh Abdullah, Hazima Mossa Alabassi, Layla Mahmood Saeed. (2026). Evaluation of Serum NLRP3 and ST2 Concentrations in Breast Cancer Patients: Potential Biomarkers of Inflammation and Tumor Progression. UKR Journal of Medicine and Medical Research (UKRJMMR), Volume 2(2), 24-31.

Abstract

Background: *Breast cancer remains a leading malignancy worldwide, and inflammation-related pathways are increasingly recognized as contributors to tumor progression and immune modulation The NLRP3 inflammasome and the IL-33/ST2 axis have been implicated in breast cancer biology.*

Objective: *To assess serum NLRP3 and ST2 levels in breast cancer patients and their association with clinicopathological features.*

Methods: *A cross-sectional study was performed including 90 women with newly diagnosed breast cancer and 60 healthy controls. Serum NLRP3 and ST2 were measured using ELISA, and levels were compared between groups and across grade, stage, and hormonal receptor status.*

Results: *Serum NLRP3 was significantly higher in patients than controls (120.68±1.23 vs 80.13±2.79 pg/mL; $p<0.001$). Serum ST2 was also higher in patients (0.447±0.111 vs 0.143±0.013 ng/mL; $p=0.01$). NLRP3 differed across grades with significant differences between Grade I vs III ($p=0.03$) and Grade II vs III ($p=0.045$), while stage-wise differences were not significant ($p=0.75$). ST2 differed across grades (Grade I vs II $p=0.05$; Grade I vs III $p=0.05$) but not across stages ($p=0.9$). No significant differences were observed for NLRP3 or ST2 by L.M.N., ER, PR, or HER2 status, and there was no correlation between ST2 and NLRP3 ($r=0.046$; $p=0.68$).*

Conclusion: *Serum NLRP3 and ST2 were significantly higher in breast cancer patients than controls, supporting an association with systemic inflammation. NLRP3 varied significantly by tumor grade (lower in Grade III), while both biomarkers showed no significant differences by stage, lymph node status, or ER/PR/HER2 profile and were not correlated, suggesting they reflect broader inflammatory responses rather than tumor burden alone.*

Keywords: *Breast cancer; NLRP3; ST2; IL-33; inflammasome; inflammation.*

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and is a leading cause of cancer-related mortality (1). Despite major advances in screening and systemic therapy, outcomes still vary widely across patients because breast cancer is biologically heterogeneous and influenced by tumor burden, molecular subtype, and host-related factors (2).

The idea that the inflammatory tumour microenvironment is closely related to the development and progression of cancer is being more and more supported (3). Through intricate interactions between malignant cells and innate/adaptive immune pathways, inflammation is now understood to be a fundamental enabling characteristic of malignancy, influencing tumour growth, immune evasion, angiogenesis, and therapeutic response (4).

The NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome has garnered interest among important innate immune platforms because of its capacity to control caspase-1 activation and downstream inflammatory mediators (5). Higher tissue expression of NLRP3 (and related innate immune markers) in breast cancer has been linked to worse outcomes and more aggressive clinicopathological characteristics, indicating that inflammasome activity may have predictive significance (6, 7). Furthermore, research suggests that blocking NLRP3 signalling can improve the effectiveness of chemotherapy in triple-negative breast cancer models, indicating its possible clinical relevance (8).

Concurrently, another inflammation-related route connected to the biology of breast cancer is the (Interleukin-33/ Suppression of Tumorigenicity 2 (IL-33/ST2) axis (9). In the tumour microenvironment, ST2 functions as a transmembrane receptor and a soluble isoform (sST2) that can function as a decoy receptor (9), influencing IL-33 signalling and immune responses. While clinical evidence indicates that circulating sST2 may include predictive information in advanced disease, recent reviews emphasise the wide-ranging effects of IL-33/ST2 signalling on immunological polarisation, tumour growth, and metastasis in breast cancer (10, 11).

Although breast cancer is extensively studied, there remains a need for circulating biomarkers that reflect systemic inflammation and can be related to clinicopathological characteristics (grade, stage, and molecular subtype (12). Accordingly, assessing circulating inflammatory biomarkers such as NLRP3 and ST2/sST2 may provide useful insight into systemic inflammation in breast cancer and its relationship to disease characteristics. This study therefore aims to evaluate serum levels of NLRP3 and ST2 in breast cancer patients compared with healthy controls and to explore their associations with relevant clinicopathological features.

Materials and Methods

Study design and setting

This cross-sectional study was conducted at the Oncology Teaching Hospital, Iraqi Medical City (Baghdad, Iraq), between August 2023 and December 2023.

Study population

The study included 90 female patients with newly diagnosed breast cancer (treatment-naïve) and 60 age-matched healthy female controls. Breast cancer diagnosis was confirmed by mammography and histopathological examination. Patients were eligible if they were aged 25–75 years and had no prior history of other malignancies. Exclusion criteria included ongoing systemic infection, autoimmune disease, other major acute or chronic medical conditions, pregnancy, and breastfeeding.

Healthy controls were women with no history of cancer or other chronic diseases and were matched to the patient group by age and sex.

Clinical and pathological data

Demographic and clinical variables were obtained from medical records, including age, tumor grade, tumor stage, and immunohistochemical (IHC) receptor status. Tumor stage was assigned according to the TNM system consistent with AJCC 8th edition staging principles (13). Tumor grade was categorized as grade I–III based on histopathological differentiation.

Hormone receptor status was determined by IHC. Estrogen receptor (ER) and progesterone receptor (PR) positivity were defined as ≥1% of tumor nuclei staining positive (14). HER2 positivity was defined according to ASCO/CAP guidance (e.g., IHC 3+ or ISH amplification when applicable) (15). L.M.N. status was recorded as documented in the medical reports/your protocol (and should be explicitly defined in the manuscript to avoid ambiguity).

Blood sampling and serum handling

Fasting venous blood (5 mL) was collected from patients and controls in the morning. For patients, sampling was performed prior to initiation of any treatment. Blood was allowed to clot at room temperature for 30 minutes, centrifuged at 3000 rpm for 10 minutes, and serum was stored at −80°C until analysis.

Measurement of serum NLRP3 and ST2

Serum NLRP3 and ST2 concentrations were measured using commercial double-antibody sandwich ELISA kits (MBS3802246 and MBS9346824) from (Mybiosourcc,

USA). In brief, samples were added to antibody-coated microplates, followed by a detection antibody conjugated to an enzyme. After substrate addition, optical density was measured and concentrations were calculated from a standard curve, consistent with standard sandwich ELISA principles (16).

Statistical analysis

Data were analyzed using GraphPad Prism (version 10). Descriptive statistics were expressed as mean ± standard error (SE). Comparisons between two groups were performed using an independent t-test, and comparisons across multiple categories (e.g., grades/stages) were evaluated using one-way ANOVA with appropriate post-hoc tests. Pearson correlation was used to assess relationships between continuous variables. A p-value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Ethics Committee of Iraqi Medical City (Oncology Teaching Hospital (NO: 51 at 1/4/2025), Baghdad. All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants (17).

Results

As shown in Figure 1, the study revealed significant differences in the concentrations of NLRP3 and ST2 between control and patient groups. The mean concentration of NLRP3 was markedly elevated in patients (120.68 ± 1.23 pg/mL) compared to controls (80.13 ± 2.79 pg/mL), with a highly significant P-value of <0.001. Similarly, ST2 levels were higher in patients (0.447± 0.111 pg/mL) than in controls (0.143 ± 0.013 ng/mL), showing statistical significance with a P-value of 0.01. These findings suggest a potential role for both NLRP3 and ST2 in distinguishing patient groups from healthy controls.

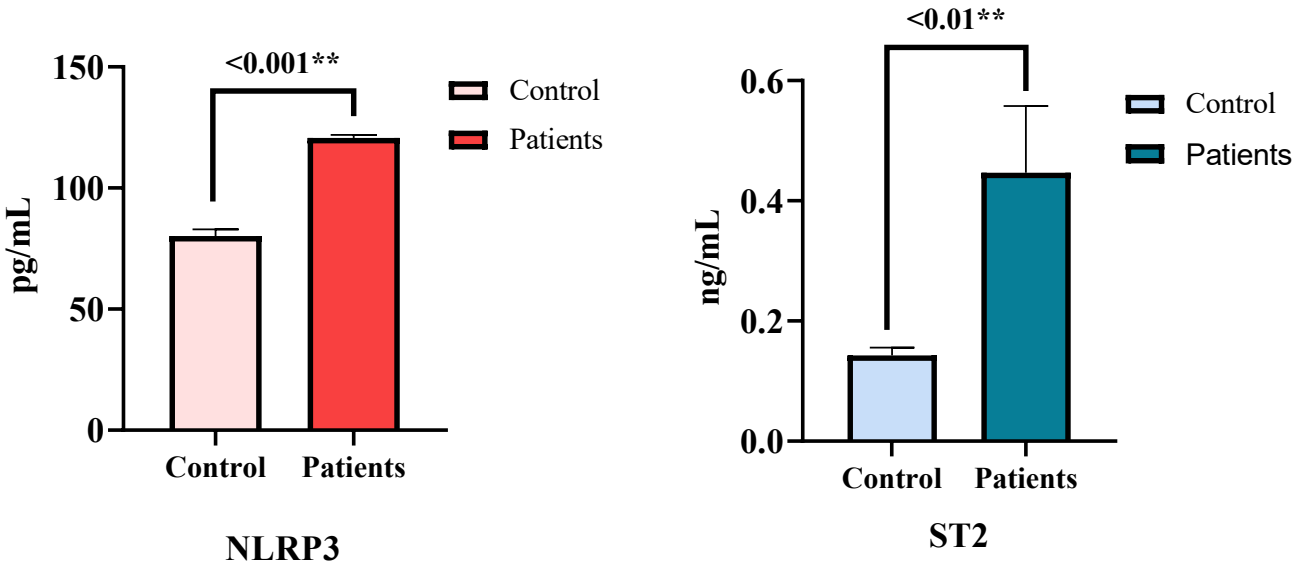

Figure 1: Comparison of NLRP3 and ST2 Concentrations between Control and Patient Groups

As shown in Figure 2, the analysis of NLRP3 and ST2 concentrations across different grades and stages of disease revealed significant variations. For NLRP3, the mean concentration decreased progressively with increasing grade, from 124.74 ± 1.95 pg/mL in Grade I to 115.36 ± 2.97 pg/mL in Grade III. Statistically significant differences were observed between Grade I and Grade III (p = 0.03) and between Grade II and Grade III (p = 0.045), while the difference between Grade I and Grade II was not significant (p = 0.32). Across stages, NLRP3 levels ranged from 119.46 ± 1.88 pg/mL in Stage II to 123.02 ± 3.09 pg/mL in Stage I, with no significant differences observed (p = 0.75).

For ST2, concentrations increased notably from Grade I (0.355 ± 0.2 ng/mL) to Grade III (0.837± 0.423 ng/mL), with significant differences between Grade I and both Grade II (p = 0.05) and Grade III (p = 0.05). In terms of stages, ST2 concentrations ranged from 0.361 ± 0.057 pg/mL in Stage I to 0.545 ± 0.258 ng/mL in Stage III, with no statistically significant differences observed among stages (p = 0.9). These findings suggest that NLRP3 and ST2 are more closely associated with disease grade than stage.

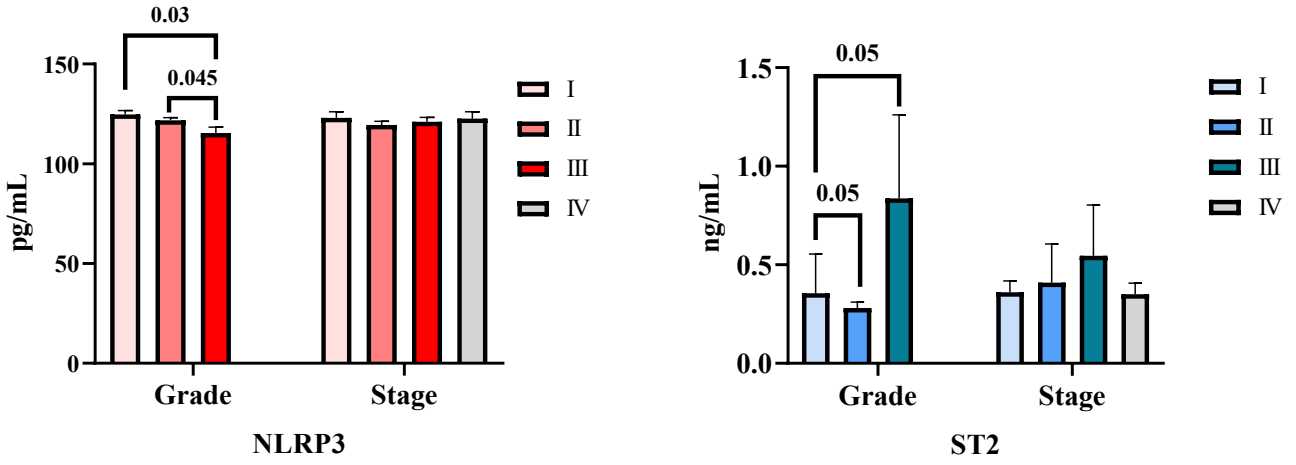

Figure 2: NLRP3 and ST2 Concentrations across Different Grades and Stages of Disease

As showed in Table 1, the analysis of NLRP3 and ST2 concentrations across various molecular subtypes of breast cancer showed no significant differences. For NLRP3, there were no significant differences observed between the negative and positive expression groups for L.M.N. (120.27 ± 1.62 pg/mL vs. 121.02 ± 1.83 pg/mL, p = 0.76), ER (119.74 ± 3.01 pg/mL vs. 120.90 ± 1.39 pg/mL, p = 0.71), PR (119.74 ± 2.56 pg/mL vs. 120.99 ± 1.41 pg/mL, p = 0.66), or Her2 (119.99 ± 1.35 pg/mL vs. 123.29 ± 2.85 pg/mL, p = 0.28).

Similarly, for ST2, no significant differences were observed between the L.M.N. negative and positive groups (0.50 ± 0.214 ng/mL vs. 0.363 ± 0.107 ng/mL, p = 0.5), ER negative and positive groups (0.549 ± 0.330 ng/mL vs. 0.280 ± 0.028 ng/mL, p = 0.1), PR negative and positive groups (0.498 ± 0.226 ng/mL vs. 0.398 ± 0.129 ng/mL, p = 0.7), or Her2 negative and positive groups (0.376 ± 0.122 ng/mL vs. 0.608 ± 0.273 ng/mL, p = 0.4). These results indicate that NLRP3 and ST2 concentrations are not significantly influenced by the molecular subtypes of breast cancer in this sample.

Table 1: NLRP3 and ST2 Concentrations Across Different hormonal states of Disease

Groups	Parameter concentration (Mean±S.E.)	
	NLRP3 (pg/mL)	**ST2** ng/mL
L.M.N. (-Ve)	120.27±1.62	0.50±0.214
L.M.N. (+Ve)	121.02±1.83	0.363±0.107
P value	0.76 NS	0.5 NS
ER (-Ve)	119.74±3.01	0.549±0.330
ER (+Ve)	120.90±1.39	0.280±0.028
P value	0.71 NS	0.1 NS
PR (-Ve)	119.74±2.56	0.498±0.226
PR (+Ve)	120.99±1.41	0.398±0.129
P value	0.66 NS	0.7 NS
Her2 (-Ve)	119.99±1.35	0.376±0.122
Her2 (+Ve)	123.29±2.85	0.608±0.273
P value	0.28 NS	0.4 NS
NS= no significant		

As showed in table 2, the Pearson correlation between ST2 and NLRP3 was found to be 0.046, with a p-value of 0.68, indicating no significant correlation between these two parameters. The lack of statistical significance suggests that ST2 and NLRP3 do not have a direct linear relationship in this dataset.

Table 2: Correlation between NLRP3 and ST2

Parameter		ST2	NLRP3
ST2	Pearson Correlation	1	0.046
	Sig. (2-tailed)	-	0.68
NLRP3	Pearson Correlation	0.046	1
	Sig. (2-tailed)	0.68	-

Discussion

In this cross-sectional study, serum NLRP3 and ST2 were significantly higher in breast cancer patients than healthy controls, supporting the concept that systemic inflammatory signaling accompanies breast cancer. These results align with broader evidence that innate immune and inflammatory programs can contribute to tumor-supportive microenvironments and systemic immune modulation (18, 19).

The inflammasome pathway has been increasingly implicated in breast cancer biology. In a clinical tissue-based study, higher tumor expression of NLRP3 was linked to worse prognosis in breast cancer patients (20). While this study measured serum levels rather than tumor expression, the marked elevation in patients compared with controls is consistent with a role for inflammasome-associated inflammation in the disease process. A mechanistic framework for this observation is provided by the central role of the NLRP3 inflammasome in linking danger signals to cytokine release and inflammatory cell death (6). NLRP3 inflammasome activation leads to caspase-1 activation with subsequent maturation of IL-1β and IL-18, and cleavage of gasdermin-D (GSDMD), resulting in pyroptosis—an inflammatory form of programmed cell death that amplifies cytokine leakage and danger-associated molecular pattern (DAMP) release (21). Importantly, inflammasome signaling in breast cancer is highly context-dependent and may arise from multiple cellular sources within (and outside) the tumor microenvironment (6). In breast cancer, IL-1β and NLRP3 overexpression has been reported in association with the accumulation of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), suggesting that inflammasome activity can coexist with an immunosuppressive milieu (22). Experimental data also indicate that tumor genetic/phenotypic features can indirectly drive IL-1β–dominated inflammation through stromal and myeloid crosstalk; for example, loss of p53 in tumor cells can stimulate TAM-derived IL-1β via WNT-related signaling and promote systemic inflammation and metastasis, while pharmacologic interruption of this loop reduced neutrophilic inflammation and metastatic spread (23). Cancer-associated fibroblasts may likewise sense DAMPs and activate NLRP3 pathways, producing IL-1β and promoting tumor progression through endothelial activation and adhesion-related remodeling (24). Collectively, these observations provide biologically plausible explanations for why circulating inflammasome-related signals may be detectable in serum in breast cancer patients.

Serum-based work has shown that NLRP3 can behave as a dynamic circulating marker in breast cancer settings. For example, Hewala et al. measured serum NLRP3 (together with IL-18 and GSDMD-CT) in breast cancer patients undergoing radiotherapy and reported that NLRP3 increased significantly after radiotherapy compared with pre-radiotherapy levels, indicating therapy-associated activation of pyroptosis/inflammasome signaling in the circulation (25). This aligns with the concept that NLRP3-related pathways are not confined to tumor tissue but can be reflected systemically and may be modulated by treatment-related oxidative stress and inflammatory signaling (25). Soltan et al. reported that serum NLRP3 levels were significantly lower in non-metastatic than metastatic cases, suggesting higher circulating NLRP3 in the context of metastatic disease, while also reporting strong diagnostic performance for NLRP3 across early and late stages (26).

ST2 is the receptor for IL-33 and exists as a membrane-bound signaling receptor (ST2L) and a soluble decoy receptor (sST2) measurable in serum (10). Studies and reviews emphasize that the IL-33/ST2 axis can reshape the tumor immune landscape by influencing myeloid polarization, regulatory T-cell biology, angiogenesis, and metastatic niches, although its net effect can be context-dependent (10). Consistent with this framework, we found higher circulating ST2 in patients than controls, and grade-related differences, suggesting that IL-33/ST2–related immunoregulation may be enhanced in subsets of more aggressive histology. At the same time, the absence of a stage-wise trend suggests that circulating ST2 may behave more like an inflammation/immune-regulatory marker rather than a direct measure of anatomical disease extent.

Our results align with several serum-based investigations. Lu et al. reported elevated serum sST2 (and IL-33) in breast cancer compared with controls, and noted clinicopathological associations in ER-positive disease (27). In advanced breast cancer, Chen et al. evaluated serum

sST2 as a prognostic biomarker and highlighted that sST2 is also linked to cardiotoxicity; notably, they reported no statistically significant differences in sST2 across ER, PR, and HER2 subgroups in their cohort, which is consistent with our lack of association by receptor status (11). These comparisons support the idea that serum ST2 can be elevated in breast cancer, but its clinicopathological correlations (stage, subtype) may vary across populations and may be modified by comorbidities and treatment exposures.

A key consideration is that sST2 is an established biomarker in cardiovascular stress and injury, and breast cancer therapies (especially anthracyclines and radiotherapy) can influence sST2 trajectories. The higher sST2 in patients with cardiotoxicity after chemotherapy, illustrating how treatment-related cardiac injury can confound interpretation if sampling is not standardized (28).

Serum NLRP3 levels showed a grade-dependent decline in our cohort, decreasing from Grade I and Grade II to Grade III, with statistically significant differences for Grade I vs III and Grade II vs III, while no significant variation was observed across clinical stages I–IV. This pattern suggests that circulating NLRP3 may be more closely related to tumor differentiation/biology (grade) than to anatomical extent (stage). Such dissociation is biologically plausible because inflammatory signaling is a recognized enabling feature of cancer progression and can be shaped by evolving tumor–immune interactions rather than by tumor size alone (4, 29). In particular, NLRP3 inflammasome activity is context-dependent and can promote tumor progression via IL-1β/IL-18–driven myeloid recruitment and immunomodulation, yet it can also participate in inflammatory cell-death programs (pyroptosis), meaning that net circulating signals can change direction as tumors become less differentiated and more immunosuppressive (6).

When compared with previous serum-based studies, the direction and clinicopathologic associations of circulating NLRP3 remain heterogeneous, supporting the interpretation that serum NLRP3 reflects a systemic inflammatory phenotype rather than a simple proxy for stage. In an Egyptian cohort, Soltan et al. reported altered serum NLRP3 in breast cancer and suggested relationships with metastatic status/diagnostic performance, implying that systemic inflammasome-related signals may vary by disease biology and cohort composition (metastatic vs non-metastatic, treatment status) (26). In another serum study, Hewala et al. demonstrated that radiotherapy significantly increased serum NLRP3 (together with IL-18 and GSDMD-CT), emphasizing that circulating NLRP3 is highly sensitive to inflammatory stressors and may change substantially with treatment exposure—an important confounder when interpreting stage/grade relationships (25). Conversely, tissue-based evidence indicates that higher intratumoral NLRP3 expression has been linked to poorer prognosis in breast cancer, underscoring that tissue expression and serum concentrations do not necessarily track in parallel due to compartmentalization, release/clearance kinetics, and systemic immune remodeling (6). Collectively, our finding—lower serum NLRP3 in Grade III despite stage invariance—may reflect a shift toward immune-evasive, less inflammasome-active systemic profiles in poorly differentiated tumors, or a dominance of local (tumor microenvironment) inflammasome signaling that is not proportionally mirrored in the circulation (20).

Our finding of higher ST2 in patients than controls is compatible with this biology, and the grade-associated differences observed for ST2 may suggest that ST2-related immune modulation increases with histologic aggressiveness in this cohort. Clinical literature also supports biomarker potential: a retrospective cohort study in advanced breast cancer reported associations between serum soluble ST2 and prognostic evaluation, supporting possible clinical utility in selected contexts (11). n addition, more recent experimental work has proposed IL-33–linked mechanisms in breast cancer aggressiveness and explored ST2-targeting strategies (e.g., ST2 silencing) in preclinical models (30).

In this study, serum NLRP3 and ST2 did not differ significantly when stratified by lymph node status (L.M.N.), ER, PR, or HER2 (all $p>0.05$). This suggests that, at least in treatment-naïve patients, these circulating markers may reflect a general systemic inflammatory/immune activation rather than being tightly linked to molecular subtype defined by hormone receptors or HER2. This interpretation is consistent with evidence that both the NLRP3 inflammasome and the IL-33/ST2 axis have context-dependent roles in breast cancer and can be driven by multiple cellular compartments (tumor cells, stromal cells, and circulating myeloid cells), so serum levels may not mirror receptor-defined tumor biology.

The lack of correlation between serum NLRP3 and ST2 in our cohort suggests that these biomarkers may represent partially independent inflammatory circuits. Mechanistically, IL-33 is an “alarmin” released upon cellular stress and tissue damage, while inflammasome/caspase pathways can modulate the inflammatory milieu through IL-1β/IL-18 and pyroptosis. Foundational work also indicates that IL-33 biology differs from IL-1β/IL-18 in terms of caspase processing and activation/inactivation dynamics, supporting the notion that IL-33/ST2 signals need not track linearly with

inflammasome markers in serum (31). Therefore, combined evaluation of NLRP3 and ST2 may provide complementary (rather than redundant) information about systemic inflammation in breast cancer.

Conclusion

Breast cancer patients exhibited significantly higher serum NLRP3 and ST2 levels than healthy controls, supporting their association with systemic inflammation. Within patients, NLRP3 decreased significantly with higher grade, whereas stage-related differences were not significant. In addition, NLRP3 and ST2 did not differ by lymph node status or ER/PR/HER2 profiles, and the two biomarkers were not correlated. Overall, these results imply that circulating NLRP3 and ST2 may represent broader inflammatory/immune responses in breast cancer rather than direct markers of tumor extent, warranting validation in larger prospective cohorts with outcome endpoints.

Acknowledgment: In this study, we would like to thanks Mustansiriyah University and University of Baghdad for supporting the present work.

Conflicts of Interest:

The authors declare no conflict of interest.

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