



Review Article



Hematological and Biochemical Serum Markers in Breast Cancer: Diagnostic, Therapeutic, and Prognostic Significance

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Abstract

Breast cancer remains one of the most common cancers affecting women globally, with late detection frequently contributing to its high mortality rate. Multiple factors drive these delays, including a lack of awareness, financial constraints in low-income countries, and limited access to non-invasive and accurate biomarkers. This review aims to introduce biomarkers, particularly hematological and biochemical serum markers, as essential, non-invasive, and accurate tools for improving the diagnosis, prognosis, and therapeutic management of breast cancer. Hematological markers are measurable blood parameters that reflect physiological and pathological processes such as inflammation, infection, cardiovascular stress, autoimmune conditions, and cancer. Routinely measured hematological markers, such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and red blood cell indices, are typically obtained from standard tests like the complete blood count. Regular monitoring through complete blood count is essential during cancer treatment to evaluate changes in blood cell counts and detect potential adverse effects. Because of their affordability, minimal infrastructure requirements, and broad accessibility, hematological parameters have been increasingly studied for their association with high-risk factors in breast cancer, particularly in resource-limited settings. Their utility underscores their critical role in improving patient outcomes across diverse healthcare environments. This review summarizes the clinical value of various hematological and serum-based biochemical markers in the screening and diagnosis of breast cancer. Prediction methods that incorporate hematological and serum-based biochemical parameters can support screening, diagnosis, and staging. Overall, individual or combined blood indicators hold significant potential to enhance diagnostic accuracy and effectiveness.

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide and is the second leading cause of cancer-related deaths in women.¹ In 2022, it remained the most common cancer in fe-

males and was one of the top five causes of cancer deaths. On average, four women are diagnosed with breast cancer every minute, and one woman dies from it.² According to the GLOBOCAN 2022 estimates published by the International Agency for Research on Cancer, breast cancer continues to pose a major global health burden.³ In 2022, breast cancer in women was the second most common cancer diagnosed globally, with about 2.3 million new cases, accounting for 11.6% of all cancer cases.³ It was also a major contributor to cancer mortality, with 665,684 deaths, representing 6.9% of all cancer-related deaths, making it the fourth leading cause of cancer death worldwide.³ Breast cancer ranked as the most frequently diagnosed cancer in women in 157 countries and was the leading cause of cancer death among women in 112 countries. The age-standardized incidence rate for breast cancer was

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46.8 per 100,000 women, and the cumulative risk of developing breast cancer before the age of 75 was 5.05%, with a mortality risk of 1.36%.⁴ Notably, the burden of breast cancer varied by region and human development index (HDI), with higher incidence rates in more developed regions but relatively higher mortality rates in lower-HDI regions, reflecting disparities in access to early detection and treatment.^{5,6} While breast cancer can develop at any age after puberty, the likelihood of diagnosis increases significantly with age, particularly in later life.^{2,6}

The impact of breast cancer varies greatly depending on a country's level of development. In countries with a very high HDI and strong healthcare systems, about one in 12 women is likely to develop breast cancer during their lifetime, and around one in 71 women will die from it. In contrast, in countries with a low HDI and limited medical resources, the risk of developing breast cancer is lower, i.e., about one in 27 women, but more women die from it, with about one in 48 losing their lives. This highlights the survival challenges faced in settings with limited healthcare.⁷⁻⁹

Early detection and treatment of breast cancer greatly improve survival outcomes. However, many women face barriers to early detection. Factors such as social conditions, financial constraints, geography, and related obstacles often limit timely, affordable, and adequate access to breast care services. Additionally, the limited availability of non-invasive, reliable diagnostic methods delays detection and treatment. The World Health Organization recommends two key approaches to promote early cancer detection. The first is early diagnosis, which involves recognizing cancer signs and symptoms at an early stage. The second is screening, which tests apparently healthy individuals to detect cancer before symptoms appear.¹⁰ In low- and middle-income countries, many women with breast cancer are diagnosed only at advanced stages, when the disease is more difficult to treat. In such settings, promoting early diagnosis should precede large-scale screening programs, as it can significantly improve outcomes for breast cancer patients.^{11,12} Therefore, prioritizing early diagnosis is essential.

Effective early detection is crucial for enhancing survival rates by enabling timely intervention and more favorable treatment outcomes, yet conventional diagnostic methods often fall short. To address this gap, there is a growing demand for more precise and sensitive diagnostic tools. In this context, biological markers (biomarkers) have emerged as transformative tools, offering the potential for earlier and more accurate identification of diseases, including breast cancer.

Biological markers such as hormone receptors (estrogen receptor and progesterone receptor), human epidermal growth factor receptor 2 (HER2), and Ki-67 provide insights into tumor characteristics, guide personalized treatment strategies, and offer minimally invasive methods for early detection and monitoring of disease progression.^{13,14} These markers help assess tumor aggressiveness and predict recurrence, enabling clinicians to make informed decisions and improve patient outcomes. However, in many developing countries such as India, where a large proportion of the population belongs to lower-income groups, the high cost of advanced diagnostic tools remains a major barrier to timely diagnosis. Many women, particularly those from economically disadvantaged backgrounds, may not seek diagnostic evaluations due to unaffordable expenses. This underscores the urgent need for accessible and cost-effective diagnostic strategies.^{15,16}

One promising approach is to focus on hematological markers—measurable blood parameters that may serve as early indicators of breast cancer. Blood tests are widely used in clinical settings, relatively inexpensive, and require minimal infrastructure

compared to imaging or molecular diagnostics. By identifying specific blood-based markers that signal cancerous changes or serve as warning indicators for future malignancies, early detection can become more accessible to women across all economic groups.

In this review, we emphasize the potential of hematological markers in breast cancer diagnosis, highlighting their role as accessible and cost-effective tools. Markers such as changes in complete blood count, as well as inflammatory indicators like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have shown significant promise in reflecting systemic inflammation and immune responses associated with cancer. Additionally, parameters such as hemoglobin (Hb) levels and red cell distribution width provide insights into chronic disease or inflammation, which may be linked to malignancy. While these hematological markers are not cancer-specific, their combined use can yield valuable information about cancer activity or an elevated risk of malignancy, offering a more nuanced approach to early detection and risk assessment. Importantly, blood tests are affordable, non-invasive, repeatable, and widely available, making them ideal for integration into routine healthcare practices, even in resource-constrained settings.

By focusing on hematological markers associated with breast cancer and exploring their diagnostic potential, this review attempts to bridge the gap between advanced, often costly cancer diagnostics and the real-world accessibility needs of underserved populations. It calls for a shift toward developing inclusive, cost-effective blood-based tools to reach those who might otherwise face barriers to early detection and treatment. Such approaches aim not only to improve outcomes but also to ensure diagnostic equity in the global fight against breast cancer.

While numerous studies have identified novel biomarkers for breast cancer, including genetic mutations (e.g., *BRCA1* and *BRCA2*) and protein markers (e.g., HER2, cancer antigen (CA) 15-3), comparatively less attention has been given to the role of blood parameters in diagnosing or understanding breast cancer and other cancers.^{17,18} This review addresses this gap by explicitly focusing on hematological parameters and their significance in breast cancer detection and management. It emphasizes the importance of blood cell-based markers in detecting and monitoring breast cancer. Additionally, it explores various blood biochemicals notably associated with breast cancer and examines serological markers, focusing primarily on their relevance and utility in breast cancer diagnosis and management. In doing so, it outlines an approach for more inclusive diagnostic strategies that can benefit both high-resource and low-resource healthcare settings.

Hematological markers associated with breast cancer

Hematological markers are blood components that reflect the physiological and pathological state of the body. These markers include parameters related to red blood cells (RBCs), white blood cells (WBCs), platelets, Hb levels, and various biochemical components.¹⁹⁻²² They are crucial in the early diagnosis, monitoring, and prognosis of multiple diseases, including cancer, by providing insights into inflammation, immune response, infection, anemia, and other systemic conditions. Based on their biological role and diagnostic utility, hematological markers can be classified into several categories: complete blood count parameters, inflammatory markers [NLR, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)], coagulation markers (D-dimer, fibrinogen), biochemical markers in blood [electrolytes (e.g., sodium, potassium), enzymes (e.g., liver enzymes), and glucose levels]. Inflam-

matory cells such as neutrophils, lymphocytes, monocytes, and platelets, along with ratios like NLR, PLR, and lymphocyte-to-monocyte ratio, can be measured through routine blood tests and are increasingly recognized for their prognostic value. Elevated NLR and PLR levels are associated with poor survival outcomes and more aggressive disease, while a higher lymphocyte-to-monocyte ratio often correlates with a better prognosis. These markers help predict treatment response, the likelihood of metastasis, and overall survival (OS), offering clinicians accessible and cost-effective means to assess disease progression and guide therapeutic decisions in cancer patients.²³⁻²⁵

Several studies have shown that tumors are closely associated with hematological parameters, as cancer significantly influences the composition, function, and behavior of blood cells and related markers. This relationship is valuable not only for diagnostic and prognostic purposes but also for monitoring cancer progression and treatment outcomes. For instance, leukocytosis (elevated WBC counts) commonly occurs, especially in advanced cancer stages.²⁶ Tumors frequently induce chronic inflammation, which supports growth by promoting angiogenesis and immune evasion, while also leading to dysregulated hematological changes. Anemia is another common finding in cancer patients, particularly in gastrointestinal cancers, where it may result from blood loss, impaired RBC production, or inflammatory cytokine-mediated suppression of erythropoiesis. Some cancers also promote increased platelet counts, a condition that facilitates tumor progression. Platelets shield circulating tumor cells from immune surveillance and aid metastasis. The PLR has been identified as a prognostic biomarker in cholangiocarcinoma,²⁶ while the absolute monocyte count has been reported as a prognostic factor for survival and recurrence-free survival in stomach cancer patients.²⁷

In breast cancer, hematological markers play a critical role in understanding and monitoring the disease. Many studies have reported significant changes in specific blood parameters, highlighting their potential as diagnostic and prognostic tools. Key markers include altered levels of Hb, RBCs, WBCs, lymphocytes, neutrophils, and monocytes, which consistently show statistically significant differences compared to healthy individuals. These alterations are linked to inflammatory responses, immune system activity, and tumor progression, all of which are commonly associated with breast cancer. The consistent changes in Hb, WBCs, and lymphocytes underscore their importance in breast cancer surveillance.

Formed element

Formed elements refer to the cellular parts of blood, which include RBCs, WBCs, and platelets. In breast cancer, their levels can fluctuate; for instance, anemia (low RBC count) and thrombocytosis (high platelet count) are often observed, while WBC levels may increase as a response to inflammation or tumor activity. In a recent study, 200 participants were divided into two groups: 100 women with breast cancer aged ≥ 26 years and 100 healthy controls aged ≥ 21 years. Eligible participants provided whole blood samples, which were promptly analyzed for complete blood count parameters. The serum was tested for CA 15-3 and CRP. This study aimed to compare hematological parameters between the breast cancer and control groups. The results revealed statistically significant differences in several hematological parameters, including Hb ($P = 0.0393$), RBCs ($P = 0.0045$), WBCs ($P = 0.0327$), lymphocytes ($P = 0.0098$), neutrophils ($P = 0.0441$), and monocytes ($P < 0.0001$). However, other parameters, such as packed cell volume ($P = 0.2393$), mean corpuscular volume ($P = 0.7193$), mean corpuscular Hb ($P = 0.1168$), mean corpuscular Hb concentration

($P = 0.6816$), eosinophils ($P = 0.5903$), basophils ($P = 0.2841$), and platelets ($P = 0.0893$), did not show significant differences between the two groups, indicating that Hb, RBCs, WBCs, neutrophils, lymphocytes, and monocytes, among other parameters, scored high points of evidence for breast cancer surveillance.²⁸

In a separate study, researchers investigated variations in hematological profiles, enzymatic activity, and oxidative stress indicators among women with breast cancer undergoing chemotherapy. The study compared these parameters between breast cancer patients and healthy individuals. Results from the hematological assessments revealed a significant reduction in erythrocyte-related parameters as Hematocrit, Hb and RBC in the patient group compared to the controls and standard reference ranges ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively).²⁹

NLR

NLR is a marker derived from a blood test measuring the ratio of neutrophils to lymphocytes. It is used as an indicator of systemic inflammation and immune response. The NLR is another important marker of inflammation, which plays a key role in cancer growth and spread. A meta-analysis was conducted to determine how well NLR could predict outcomes in breast cancer. The analysis included 12 studies that met the eligibility criteria. The results showed that patients with higher NLR levels had worse outcomes. Specifically, they had shorter disease-free survival (hazard ratio = 1.46, 95% confidence interval: 1.12–1.90, $P = 0.044$) and shorter OS (hazard ratio = 2.03, 95% confidence interval: 1.41–2.93, $P < 0.001$). Further analysis of breast cancer subtypes revealed that NLR was not linked to OS in patients with luminal A and luminal B subtypes. However, positive associations were found in patients with HER2-positive and triple-negative breast cancer subtypes. In summary, this meta-analysis concluded that NLR is a valuable marker for predicting outcomes in breast cancer. Patients with higher NLR tend to have a worse prognosis.³⁰

In a study of breast cancer patients with oligometastatic disease at the time of recurrence, researchers found that a low NLR was linked to better OS. Even after considering other important factors like hormone receptor status, number of metastases, and liver involvement, low NLR still showed a strong connection to longer survival ($P = 0.023$). The researchers built a prediction model using NLR and five other helpful factors. Patients who had all six favorable factors had a high eight-year survival rate of 90.9%. This shows that NLR can be a valuable marker to help predict long-term outcomes in breast cancer patients with oligometastatic disease.³¹

The NLR is becoming a valuable marker for predicting cancer outcomes because it is easy to measure using a simple blood test. It was first linked to inflammation in seriously ill patients, and many studies have found that a high NLR is often associated with worse outcomes in cancer. This may be because inflammation plays a key role in cancer growth, and specific immune cells like neutrophils can affect tumor behavior.³²

PLR

Among all blood tests, the PLR is considered a reliable and straightforward marker that can help predict cancer progression.²⁶ PLR is a hematological marker obtained from a blood test representing the ratio of platelets to lymphocytes. In one study, researchers analyzed the relationship between PLR and clinical characteristics in a patient cohort. The study reported an average platelets count of 271.2 ± 69.6 , an average lymphocyte counts of 1.7 ± 0.6 , and a mean PLR of 181.1 ± 131.0 . Preoperative PLR data were available for 747 patients, accounting for 94.2% of the

study cohort. Their analysis identified an optimal cutoff value of 292 for PLR to differentiate patients with varying cancer-specific survival. This threshold divided the cohort into two groups: 699 patients with a low PLR (<292) and 48 patients with a high PLR (≥ 292). Further statistical analysis revealed that a high PLR was significantly associated with lymph node involvement, higher tumor grades, and estrogen receptor-negative tumors, with all correlations reaching statistical significance ($P < 0.05$). However, PLR was not significantly associated with other factors, including age, advanced T stage, progesterone receptor status, or HER2 overexpression. These findings suggest that a high PLR may indicate more aggressive tumor features and potentially poorer prognosis, making it a valuable parameter for stratifying patient risk in subsequent analyses.³³

High PLR levels are significantly associated with poorer outcomes, including both OS and disease-free survival. Additionally, elevated PLR correlates with more advanced clinicopathological features such as tumor stage, lymph node involvement, and distant metastasis, reinforcing its potential role in breast cancer staging. Although the exact mechanisms behind PLR's prognostic value are not fully understood, several biological explanations have been proposed. High PLR may reflect increased platelet activity, which is known to support tumor growth and spread. Platelets can release growth factors such as platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor-beta, and platelet factor 4, which promote tumor angiogenesis and proliferation. They also aid tumor cell adhesion to blood vessels, support their escape into tissues, and help build tumor-supportive stroma. Moreover, platelets may protect tumor cells from immune system clearance, thereby facilitating metastasis. These findings underscore the role of PLR as a promising and accessible prognostic marker in breast cancer.³⁴

ESR

The ESR is another simple and low-cost test that can help detect chronic inflammation. It measures how quickly RBCs settle at the bottom of a test tube within one hour. ESR is a nonspecific marker of inflammation, with elevated levels often indicating the presence of inflammatory or autoimmune conditions, infections, or certain cancers. Elevated ESR has been linked to poor prognosis in certain types of cancer, including both solid tumors and hematologic malignancies.

The study evaluated ESR levels in 60 women diagnosed with breast cancer and compared them with 30 healthy female controls. Blood samples were collected in EDTA tubes, and ESR was measured using the Westergren method. The results showed a significantly higher ESR in breast cancer patients (47.5 ± 7.3 mm/h) compared to the control group (6.9 ± 0.5 mm/h), with $P < 0.05$, indicating statistical significance. Elevated ESR levels are commonly observed in malignancies and may reflect systemic inflammation and tumor progression. In breast cancer, high ESR has previously been linked to worse prognosis and poor treatment outcomes.³⁵

Biochemical serum markers associated with breast cancer

Biochemical markers found in blood are molecules such as proteins, enzymes, metabolites, or other substances that provide crucial insights into physiological and pathological conditions, including diseases like cancer. Standard biochemical components are regularly analyzed, including creatinine, urea, uric acid, alkaline phosphatase (ALP), albumin, calcium, sodium, potassium,

chloride, cholesterol, glucose, and others. These markers are often used for diagnosis, prognosis, and monitoring treatment responses. For instance, in cancer, markers like CA 15-3 and CA 27.29 are associated with breast cancer detection, while alpha-fetoprotein is linked to liver cancer. Carcinoembryonic antigen (CEA) is another marker elevated in colorectal and other cancers.^{36,37} These markers allow non-invasive assessment, enabling early disease detection, outcome prediction, treatment guidance, and monitoring of disease progression or recurrence, making them indispensable tools in modern clinical practice.

In a retrospective cohort study, it was observed that patients with advanced-stage breast cancer had higher levels of blood sugar, serum ALP, and urea compared to those with early-stage breast cancer.³⁸ The biochemical makeup of blood offers essential information about existing health issues or potential future complications. These parameters can be assessed through a blood chemistry panel, which measures concentrations of chemicals, enzymes, and organic waste products in the bloodstream. In individuals with breast cancer, abnormal blood chemistry panel results may indicate that the disease has spread to organs such as the bones, kidneys, or liver. Several studies have also explored the relationship between liver function tests, kidney function tests, and mortality in breast cancer patients.³⁹

Enzymes

A study investigated biochemical markers in breast cancer patients with and without metastasis to understand their diagnostic and prognostic significance. Blood samples from 58 non-metastatic and 44 metastatic breast cancer cases were analyzed both before and after mastectomy. The findings revealed notable differences in specific biochemical markers compared to standard controls. In non-metastatic breast cancer patients, a significant increase was observed in lactate dehydrogenase (LDH), glutathione (GSH), and ferritin levels. Additionally, this group showed a non-significant rise in ALP and gamma-glutamyl transferase levels. Among individual cases, 70% of non-metastatic patients exhibited LDH levels above the normal range, while elevated ferritin and GSH levels were found in 65% and 62% of these patients, respectively. These abnormalities were even more pronounced in patients with metastatic breast cancer. The study underscores the potential of LDH, GSH, and ferritin as reliable biochemical markers for assessing breast cancer progression, with higher levels correlating with metastasis. This research highlights the importance of these markers in monitoring disease status and tailoring treatment strategies effectively.^{40,41}

Creatine kinase

Creatine kinase BB is an isoenzyme of creatine kinase predominantly found in the brain and smooth muscle tissues. It plays a vital role in cellular energy homeostasis and is clinically significant in diagnosing conditions such as ischemic stroke, brain trauma, and certain cancers, including breast cancer. Creatine kinase BB serum levels were analyzed using radioimmunoassay in individuals with various breast conditions, including benign and malignant pathologies. Elevated levels of this enzyme were detected in 30% of patients (six out of 20) with primary breast cancer. Notably, after surgery, the levels returned to normal only in patients who did not have lymph node involvement. Among patients with benign breast lesions, 21% (six out of 28) showed increased enzyme levels, while 13% (four out of 38) of those with metastatic breast cancer exhibited similar elevations. A significant proportion of patients with high creatine kinase BB levels had tumors positive for estro-

gen and progesterone receptors. These results indicate that while creatine kinase BB cannot be reliably considered a marker for malignancy in breast diseases, it may serve as a potential indicator of hormone dependency in breast cancer.^{42,43}

Serum uric acid (SUA)

SUA is a metabolic byproduct of purine nucleotide breakdown, primarily excreted by the kidneys. Monitoring SUA provides crucial insights into metabolic health, aiding in diagnosing and managing gout, renal conditions, cardiovascular risks, and even cancer. SUA has been proposed as a biomarker in routine examinations at the early stages of breast cancer.⁴⁴ Studies suggest an association between SUA levels and the initiation and progression of breast cancer. High SUA levels have been associated with a decreased probability of developing breast cancer, indicating a potential protective effect. However, cohort studies have reported conflicting results, showing that high SUA levels may also be linked to increased breast cancer risk. Despite these contradictions, the inverse relationship between SUA levels and breast cancer risk underscores its potential protective role. Clinicians should focus on maintaining proper SUA levels in women for optimal health and potentially reduced breast cancer risk.⁴⁵

Transaminases

Research has shown that patients with malignant breast cancer tend to have higher activities of specific transaminases compared to those with benign breast cancer. The elevation in serum glutamic-oxaloacetic transaminase (SGOT) (aspartate transaminase) and serum glutamic-pyruvic transaminase (SGPT) (alanine transaminase) is thought to indicate liver and kidney dysfunction, potentially caused by tumor invasion. ALP levels were elevated beyond the normal range, whereas SGOT and SGPT levels remained within normal limits. However, the average values of SGOT and SGPT showed a significant increase, aligning with findings from other studies.⁴⁶

ALP

The rise in serum ALP levels in breast cancer patients serves as an important biochemical indicator, often suggesting metastasis. ALP is an enzyme primarily associated with bone and liver tissues, and elevated levels in the bloodstream are frequently linked to increased bone turnover or liver dysfunction. In breast cancer, metastasis to the bones is common, and heightened ALP activity reflects the body's response to bone tissue destruction and remodeling caused by cancerous lesions.⁴⁷

Additionally, liver metastases can contribute to elevated ALP levels due to impaired liver function and enzyme release from damaged liver cells. This progressive increase in ALP is therefore not only a marker of cancer spread but also a reflection of the systemic impact of metastasis on vital organs. Monitoring ALP levels in breast cancer patients provides valuable insights into disease progression, particularly the development of metastatic complications, and can guide further diagnostic and therapeutic strategies.⁴⁸

CRP

Another important marker is CRP, which is predominantly produced in the liver and is a sensitive, commonly used indicator of systemic inflammation. Its production is stimulated by cytokines such as interleukin-6, interleukin-1, and tumor necrosis factor- α . Unlike other inflammatory markers, CRP is particularly advantageous in epidemiological research due to its consistent temporal stability and the availability of reliable measurement techniques.

In the same study where ESR levels were compared between breast cancer patients and healthy controls, CRP levels were also evaluated. The results showed that breast cancer patients had markedly elevated CRP levels (73.8 ± 1.3 mg/L) compared to healthy controls (9.0 ± 0.7 mg/L), with $P < 0.05$. This significant rise in CRP suggests an active inflammatory response in breast cancer patients. As an acute-phase protein, CRP is a nonspecific but sensitive marker of systemic inflammation, and elevated levels have been associated with tumor burden, aggressive phenotypes, and poorer survival outcomes in breast cancer.³⁵ Elevated CRP levels have also been linked to various chronic diseases, including an overall increased cancer risk, with specific associations with lung, colorectal, endometrial, and ovarian cancers. However, research exploring the connection between CRP and breast cancer risk remains limited and yields inconsistent findings.⁴⁸ A meta-analysis concluded that higher CRP levels are linked to an increased risk of breast cancer, particularly among Asian populations. While the evidence for causation is limited, the findings suggest that chronic inflammation may contribute to breast cancer development. Further high-quality cohort studies involving larger numbers of breast cancer cases are essential to clarify whether CRP directly influences breast cancer development.⁴⁸

CA

Several studies, including a report from the City of Hope (a leading medical and research institution in Los Angeles), identified two serum-based tumor markers, CA 15-3 and CA 27.29, as important markers for breast cancer. CA 15-3 is a protein released into the bloodstream by tumor cells and can be measured by simple blood tests. These markers are primarily used to monitor cancer response to treatment, assessing tumor stability, growth, shrinkage, and recurrence rather than diagnosis or prognosis alone. CA 27.29 is a blood-based test measuring glycoprotein levels produced by the mucin-1 gene and is commonly used in advanced-stage breast cancer. Another study evaluated CA 15-3, CA 27.29, and CEA across distinct cohorts: healthy controls ($n = 82$), patients with benign breast diseases ($n = 42$), and breast cancer patients ($n = 499$).⁴⁹ Studies have shown that mucinous antigens such as CA 15-3, CA 27.29, MCA, and CA 549 outperform CEA in monitoring breast cancer. Among these, CA 27.29 demonstrated greater sensitivity than CA 15-3, particularly in detecting bone and organ metastases. Overall, CA 15-3 and CA 27.29 are considered the most reliable markers for breast cancer follow-up.⁴⁹

D-dimer

A prospective cohort study conducted at Baghdad Teaching Hospital from January 2014 to January 2016 evaluated plasma D-dimer levels in 70 patients divided into two groups: one with breast carcinoma and the other with benign breast tumors. D-dimer levels were normal (<0.25 mg/L) in the benign tumor group but elevated in the breast carcinoma group. Furthermore, patients with advanced breast cancer showed significantly elevated D-dimer levels, which were associated with larger tumor size, higher tumor stage and grade, lymphovascular invasion, and lymph node involvement. These findings indicate that plasma D-dimer serves as an important prognostic marker for breast cancer, especially in advanced stages, reflecting disease progression, lymphovascular spread, and metastasis.⁵⁰

Apart from blood cell-based markers, reactive oxygen species (ROS) are crucial indicators in breast cancer diagnosis and prognosis. ROS are highly reactive molecules generated as byproducts of cellular metabolism and are tightly regulated under normal physi-

ological conditions. In breast cancer, an imbalance in ROS levels leads to oxidative stress, which plays a pivotal role in tumor initiation, progression, and therapeutic response. ROS-induced oxidative damage to DNA, lipids, and proteins promotes genomic instability and alters cellular signaling pathways, contributing to cancer growth and metastasis. ROS-related markers, including malondialdehyde, GSH, and superoxide dismutase, are valuable tools for understanding the oxidative environment in breast cancer. Evaluating ROS levels helps assess tumor aggressiveness, predict therapeutic outcomes, and develop strategies to restore redox balance. These insights complement blood cell-based markers, offering a comprehensive approach to breast cancer management.^{51,52} Determination of catalase and 4-hydroxynonenal (4-HNE) has been used as a non-invasive biomarker for the early detection of breast cancer in Iraqi women.⁵³ ROS are oxygen-containing molecules with reactive properties, including radicals like O_2^- (superoxide), $HO\cdot$ (hydroxyl), as well as non-radicals like H_2O_2 (hydrogen peroxide). Excessive ROS production may induce lipid peroxidation, affecting polyunsaturated fatty acids in cell membranes and generating 4-HNE. 4-HNE can cause DNA damage by forming adducts with DNA bases, promoting genomic instability and carcinogenesis.^{54,55} Catalase is an antioxidant enzyme that prevents oxidative damage by converting hydrogen peroxide into water and oxygen.^{56,57} Catalase activity was decreased in breast cancer patients compared to controls, supporting previous observations,⁵⁸ while 4-HNE levels were elevated in the patient group.^{59,60} The significantly reduced catalase levels and increased serum 4-HNE serve as diagnostic markers for breast cancer.

Systemic biomarkers for breast cancer management

Hematological and serum-based biomarkers are gaining attention as tools for enhancing breast cancer diagnosis and prognosis, particularly in low-resource settings. Markers such as the NLR, PLR, ESR, and Hb provide insight into the systemic inflammatory and immune responses associated with cancer. These blood tests are affordable and widely accessible, making them especially useful where advanced diagnostics may be unavailable. They are also valuable for monitoring disease progression and treatment response during chemotherapy or radiotherapy.

In parallel, oxidative stress markers such as MDA, GSH, and superoxide dismutase provide insights into the internal oxidative balance of cancer patients. Elevated ROS drives genetic damage, tumor growth, and metastasis. Despite their value, these markers can be challenging to measure due to technical limitations in routine clinical settings.

Hematological markers such as NLR and PLR have been extensively studied in several cancers, including breast cancer. Although they can be influenced by factors such as circadian rhythm, infections, or stress, many studies confirm their prognostic value. A meta-analysis reported that high NLR is linked to poor survival across multiple solid tumors.⁶¹ Increased NLR and neutrophil percentages are associated with higher breast cancer risk, particularly in postmenopausal women.^{24,62} Although these markers fluctuate in breast cancer, they remain relevant for cancer stratification.

A recent study demonstrated that low baseline NLR was significantly associated with improved progression-free survival and OS in patients treated with trastuzumab and docetaxel. This trend also held true for patients receiving trastuzumab, pertuzumab, and docetaxel, especially in adjusted models such as propensity score matching and inverse probability of treatment weighting.⁶³ Evidence also supports combining systemic markers with tumor im-

mune features. A study using multiplex immunohistochemistry in triple-negative breast cancer found that patients with high PLR and NLR had greater infiltration of $CD4^+FOXP3^+$ regulatory T-cells, whereas those with high tumor-infiltrating lymphocytes and low PLR had better survival outcomes.⁶⁴ This combination approach may improve prognostic accuracy.

Real-world evidence from the UK Clinical Practice Research Datalink (CPRD) dataset, involving over 425,000 patients, supports the value of blood-based markers. Abnormalities in CRP, ESR, WBC, ferritin, and albumin increased significantly in the seven months preceding a cancer diagnosis, showing their potential as early warning signs when interpreted alongside symptoms.^{65,66}

Several host factors can influence inflammatory markers. For instance, obesity may induce inflammation through extracellular vesicles, inflammasome activation, and gene expression changes.^{67,68} Aging similarly remodels the immune environment.⁶⁹ These effects can mask cancer-specific signals, limiting diagnostic accuracy.

While markers like CA 15-3 and ALP have long been used in breast cancer care, their usefulness in early diagnosis is limited. CA 15-3 is more helpful in advanced cases.^{70,71} CA 15-3 and CEA are not suitable for primary detection but are effective for monitoring disease progression and recurrence.⁷² Regarding ALP, it is not helpful for early diagnosis but may help predict bone metastasis. Elevated ALP, combined with CA 15-3, low Hb, and lymph node status, strongly predicted bone metastases in breast cancer, with a high area under the curve of 0.900.⁷³ In this review, we focused on CA 15-3 and ALP in tracking disease progression and metastasis risk rather than initial diagnosis.

Markers of oxidative stress, like 4-HNE and catalase, though biologically important, require advanced techniques such as enzyme-linked immunosorbent assay or mass spectrometry, making them difficult to use in routine clinical settings. Their integration into standard care will depend on the development of simpler, more accessible testing methods. Blood-based biomarkers offer advantages such as ease of use and affordability but are not without limitations. Low specificity can result in false positives, leading to unnecessary follow-ups and biopsies. Most blood-based biomarkers are still in early research stages, with few having undergone validation for clinical implementation. Such limitations could offset their cost-saving appeal.^{74,75} Clinical relevance of these hematological and serum biomarkers across breast cancer progression is summarized in Table 1.^{23-26,29-31,33,34,39,41,46,48-50,71,76-80}

Therefore, these biomarkers should be viewed as complementary tools rather than stand-alone diagnostics. Their actual value lies in integration with imaging, clinical evaluation, and possibly genomic markers within structured diagnostic models assessing utility, safety, and cost-effectiveness. False-negative results are another concern; relying solely on these biomarkers may delay diagnosis in early-stage disease. Conversely, false positives can cause unnecessary emotional and financial burdens.⁸¹

SUA presents a complex case. It acts as both an antioxidant and a pro-inflammatory agent, depending on its level. Uric acid has been shown to have protective effects in breast cancer, whereas high uric acid levels could drive cancer progression through inflammation and activation of growth pathways.⁸²⁻⁸⁴ A J-shaped curve in uric acid-breast cancer risk suggests that both extremes may be harmful.⁸⁴ This dual role reinforces the need for a balanced interpretation of uric acid levels in cancer care.

NLR also holds prognostic value in different breast cancer subtypes. For example, high NLR is linked to worse survival in triple-negative breast cancer, likely due to immunosuppressive neutro-

Table 1. Clinical relevance of hematological and serum biomarkers across cancer progression: Roles in early detection, prognosis, therapeutic response, and recurrence monitoring

Biomarkers	Type	Early detection	Prognosis (DFS/OS)	Therapeutic response	Recurrence monitoring	Reference
Hb	Hematological marker	Nonspecific; low levels seen in many chronic conditions	Anemia (low Hb) is associated with poor prognosis and aggressive disease in cancer patients	Can reflect myelosuppression or response to chemotherapy	May indicate recurrence indirectly when anemia recurs post-treatment	29
RBCs	Hematological marker	Not useful alone for detection	Low RBC count reflects systemic inflammation, tumor burden, and poor nutritional status	Changes during therapy may reflect bone marrow response or suppression	Not specific, but could support surveillance when paired with other markers	29
WBCs	Hematological marker	Elevated levels are common in infections and inflammatory states, not specific	Leukocytosis is associated with systemic inflammation and a worse prognosis in many cancers	May fluctuate during chemotherapy; leukopenia can indicate marrow suppression	Can support recurrence monitoring in conjunction with clinical status	29
Lymphocytes	Hematological marker	Not specific for early detection; may be suppressed in multiple conditions	Low lymphocyte counts are associated with poor immune surveillance and worse prognosis in Breast and cervical cancer	Recovery of lymphocytes post-treatment may indicate good immune recovery	Persistently low levels may indicate immune exhaustion and higher recurrence risk	23–25
Neutrophils	Hematological marker	Elevated in many non-cancer conditions (infection, stress)	High neutrophil counts are associated with systemic inflammation and adverse survival outcomes	Changes in neutrophils during therapy may indicate treatment effect or myelosuppression	May support recurrence monitoring when included in NLR or CBC trends	23–25
Monocytes	Hematological marker	Not diagnostic; modestly raised in cancer-related inflammation	Elevated monocyte counts may indicate tumor-associated macrophage (TAM) recruitment and poor prognosis	A decrease post-treatment may reflect reduced tumor burden or inflammation	Could aid recurrence monitoring when combined with NLR or LMR	23–25
HCT	Hematological marker	Not diagnostic; reductions may occur due to anemia of chronic disease or treatment	Low HCT levels observed in BC patients, especially post-chemotherapy, may reflect nutritional and inflammatory status	A decrease in HCT during chemotherapy may indicate treatment-induced anemia	Not specific for recurrence; trends may support surveillance when interpreted with clinical context	29
HGB	Hematological marker	Not suitable alone for early detection	Anemia (low HGB) is commonly seen in BC patients and is linked to fatigue, poor functional status, and worse outcomes	HGB levels drop during chemotherapy; recovery indicates hematological response	Persistent anemia post-treatment may signal marrow suppression or systemic disease	29
NLR	Hematological marker	Limited – not useful for primary detection; influenced by inflammation and stress	Strong prognostic indicator across stages, including early and metastatic breast cancer	Predicts chemotherapy response and progression, especially in oligometastatic disease	Elevated NLR correlates with poor outcomes and relapse risk	30,31
PLR	Hematological marker	Limited – not reliable for early screening; influenced by inflammation	Elevated PLR is a consistent predictor of poor prognosis and adverse tumor characteristics	Not widely used to predict therapy response	May be associated with relapse risk or poor post-treatment survival	26,33,34
LMR	Hematological marker	Limited – not validated for early detection in Breast or cervical cancer	Lower LMR is associated with poor prognosis and higher tumor burden	Not yet established in breast cancer; limited evidence in cervical cancer	May reflect post-treatment hematologic changes	23–25
ESR	Hematological marker	Not specific or sensitive for early detection	Elevated levels indicate systemic inflammation in breast cancer patients	Potentially useful for tracking response to therapy	Not directly assessed, but may indicate disease activity	76,77
CA15-3	Biochemical marker	Low sensitivity for early detection; more reliable in advanced stages	Associated with metastatic and progressive disease; higher levels reflect poor prognosis	Widely used to monitor treatment response, especially in metastatic BC	Helpful in identifying recurrence and distant metastasis	48,49,71

(continued)

Table 1. (continued)

Biomarkers	Type	Early detection	Prognosis (DFS/OS)	Therapeutic response	Recurrence monitoring	Reference
CA27.29	Biochemical marker	Not suitable for early diagnosis; similar profile to CA 15-3	Elevated in patients with progressive/metastatic disease	Effective for tracking therapy effectiveness and adjusting treatment plans	Can help predict recurrence risk in high-risk patients	49
CEA	Biochemical marker	Low sensitivity and specificity for early-stage breast cancer; not reliable for screening	Elevated levels correlate with advanced disease stage and tumor burden	Useful in monitoring therapeutic response, particularly in metastatic or advanced cases	Effective in identifying recurrence or progression, mainly when used with CA 15-3 or CA 27.29	49
LDH	Biochemical marker	Nonspecific; not reliable for early detection	Elevated LDH is associated with tumor progression, metastasis, and poor prognosis	May indicate tumor lysis or burden reduction during treatment	Rising LDH levels post-treatment can suggest recurrence or residual disease	39,41
GSH	Biochemical marker	Not suitable for screening; decreased levels suggest oxidative stress, but not specific to BC	Lower GSH in BC patients, especially with metastasis, indicates higher oxidative damage and worse prognosis	GSH depletion reflects redox imbalance during treatment; it may correlate with treatment toxicity and burden	Not specifically validated for recurrence monitoring	78
Ferritin	Biochemical marker	Limited diagnostic value alone; elevated in multiple non-cancer conditions	Higher levels found in metastatic BC patients; correlates with tumor burden and inflammation	Not a standard marker for monitoring response	May suggest residual or recurrent disease if levels remain elevated post-treatment	78
ALP	Biochemical marker	Not useful for early detection in isolation; elevation often occurs later	Significantly elevated in patients with bone or liver metastases; associated with poor prognosis	Limited use in tracking treatment efficacy alone	A sensitive indicator for bone metastasis recurrence or progression	46,41
GGT	Biochemical marker	Not specific; may be elevated in hepatic conditions	Elevated in advanced stages and liver involvement; indicates increased oxidative stress and tumor activity	Not routinely used for therapy response, but may reflect hepatic toxicity	May support recurrence monitoring when metastasis involves the liver	46
Creatine Kinase-BB	Biochemical marker	Elevated serum/tumor cytosol levels observed even in early stages; potential for early detection	Higher levels are associated with tumor aggressiveness and burden	May reflect tumor metabolic activity, showing a reduction post-therapy	Limited data on use for recurrence tracking; promising but not yet validated	78,79
SGPT	Biochemical marker	Not specific to breast cancer; typically, normal unless hepatic involvement	Mild elevation may occur with advanced/metastatic disease; not a strong prognostic marker	Elevated post-therapy may suggest hepatic stress or drug toxicity	Not validated for recurrence detection; possible role in liver metastasis	46
SGOT	Biochemical marker	Not suitable for early cancer detection	Similar to ALT, elevated levels may indicate hepatic involvement in late stages	May reflect liver stress or adverse effects of chemotherapy	Unclear utility in recurrence monitoring	46
CRP	Biochemical marker	Not specific to early detection	Elevated levels in both localized and metastatic disease indicate systemic inflammation	May reflect treatment response indirectly	Useful as a supportive marker for monitoring disease activity	80
D-dimer	Biochemical marker	Nonspecific for early breast cancer; elevated in various conditions (e.g., thrombosis, infection)	Significantly elevated in patients with advanced-stage breast cancer; correlates with tumor burden and coagulation activation	May decrease with effective therapy, reflecting reduced tumor burden and hypercoagulability	Rising levels post-treatment may suggest recurrence or progression, especially in metastatic disease	50

ALP, alkaline phosphatase; ALT, alanine aminotransferase; BC, breast cancer; CA, cancer antigen; CBC, complete blood count; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DFS, disease-free survival; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; GSH, glutathione; Hb, hemoglobin; HCT, hematocrit; HGB, hemoglobin (sometimes used interchangeably with Hb in lab reports); LDH, lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; TAM, tumor-associated macrophage; WBC, white blood cell.

phil activity.⁸⁵ Conversely, high NLR is associated with poorer treatment response in hormone receptor-positive, HER2-negative patients receiving neoadjuvant therapy.⁸⁶ This shows that NLR reflects systemic inflammation, which impacts prognosis in various subtypes, albeit through different biological mechanisms.

Hematologic and serum-based markers such as NLR, PLR, CA 15-3, and oxidative stress indicators provide valuable insights into cancer biology, treatment response, and prognosis. However, their application in early diagnosis or screening must be approached with caution. These markers hold promise when used as part of a broader, multi-modal strategy incorporating clinical assessment, imaging, and molecular profiling. Various hematological and blood biochemical parameters that have been notably associated with breast cancer can be studied, with a primary focus on their relevance and utility in breast cancer diagnosis and management. Machine learning algorithms can be applied to large datasets obtained from breast cancer patients. Together, these insights contribute to a more comprehensive understanding of how affordable and accessible diagnostic tools can be developed to benefit diverse populations and improve early detection, screening, and cancer staging.

Future directions

Integrating hematological, serum biochemical, and ROS-related markers into breast cancer management strategies holds promise for transforming early detection and personalized therapy. Future research should focus on developing standardized protocols for assessing these markers, ensuring reproducibility and consistency in clinical practice. Emerging technologies, such as liquid biopsy and advanced bioinformatics tools, can be leveraged to analyze multiple biomarkers simultaneously, improving diagnostic precision. Investigating the interplay between hematological markers, oxidative stress, and genetic predisposition may uncover novel prognostic signatures and therapeutic targets. Exploring antioxidant-based therapies tailored to ROS profiles offers another avenue for innovation, potentially mitigating treatment side effects and improving outcomes. Expanding access to these affordable diagnostic tools, particularly in low-resource settings, can help bridge disparities in breast cancer care and reduce mortality rates globally.

Conclusions

Hematological and serum-based biomarkers present promising avenues for improving breast cancer detection, monitoring, and prognostication, especially in resource-limited settings. Markers such as NLR, PLR, CA 15-3, and oxidative stress indicators provide insight into tumor-associated inflammation, systemic immune response, and disease progression. While these markers are non-invasive, accessible, and cost-effective, challenges such as low specificity, influence from non-cancerous conditions, and limited validation hinder their use as stand-alone diagnostic tools. Their real value lies in integration within multi-modal diagnostic frameworks that combine clinical examination, imaging, and molecular profiling. Further research and standardization are needed to validate their clinical utility, minimize false positives and negatives, and refine risk prediction models. Ultimately, incorporating such biomarkers into structured screening strategies could contribute to earlier diagnosis and more equitable cancer care across populations.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Study concept and design (BPJ), Writing (YM, SJ), drafting of the manuscript (BPJ, YM), review and editing (YM, SJ, BPJ), critical revision of the manuscript for important intellectual content (PJ, KCM, NK, BPJ), administrative, technical, or material support, and study supervision (BPJ). All authors have made a significant contribution to this study and have approved the final manuscript.

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