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Article

Complex Analysis of Morphophysiological, Biochemical, and Cytohistological Changes in Peripheral Blood of Patients with Breast Cancer

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Abstract: Breast cancer is one of the most common oncological diseases among women and is characterized by high mortality rates. There is an increasing need for non-invasive, repeatable, and cost-effective diagnostic methods for early detection and prognosis assessment. Peripheral blood serves as a sensitive biological medium reflecting systemic morphophysiological, biochemical, and immunological changes associated with tumor progression. The present study aimed at a comprehensive evaluation of morphophysiological, biochemical, and cytohistological changes in the peripheral blood of patients with breast cancer. The study involved 200 histologically confirmed breast cancer patients (stages I–IV) and 150 healthy control subjects. Hematological, biochemical, and cytohistological parameters were analyzed using modern laboratory techniques and multivariate statistical modeling. The results revealed decreased erythrocyte indices, increased RDW, neutrophilia, lymphopenia, and thrombocytosis in patients. Biochemically, significant increases in CRP, LDH, and oxidative stress markers were observed, which were directly correlated with disease stage. Cytohistological examinations showed erythrocyte anisopoikilocytosis, nuclear atypia of leukocytes, and enhanced lymphocyte apoptosis. These findings indicate that peripheral blood–based biomarkers have high diagnostic and prognostic value.

Keywords: breast cancer; peripheral blood; hematological parameters; biochemical markers; cytohistological changes

Introduction

Breast cancer (BC) currently remains one of the most pressing global health issues affecting women. According to the World Health Organization, BC ranks first among all female malignancies and is a leading cause of cancer-related mortality. Although early detection of the disease ensures higher survival rates, diagnosis is often delayed in many cases. In recent years, interest has grown not only in understanding local tumor biology but also in studying systemic responses of the body[1]. Peripheral blood parameters are considered an important source reflecting tumor-associated inflammation, immune dysregulation, and metabolic reprogramming processes[2].

Literature Review

Numerous studies describe breast cancer as a disease associated with systemic inflammation. Changes in hematological parameters, particularly decreased hemoglobin levels and increased RDW, reflect tumor-associated anemia and impaired bone marrow function. Research has shown that

elevated RDW values are associated with poor prognosis and lower survival rates[3]. Changes in the leukocyte profile, such as neutrophilia and lymphopenia, and the neutrophil-to-lymphocyte ratio (NLR) are widely recognized as independent prognostic factors in breast cancer. High NLR indicates immune suppression and an inflammatory character of the tumor microenvironment. Elevated platelet-to-lymphocyte ratio (PLR) reflects the involvement of platelets in angiogenesis and metastasis processes[4].

Among biochemical markers, C-reactive protein (CRP) and lactate dehydrogenase (LDH) are particularly important. Increased CRP serves as an indirect marker of chronic inflammation and tumor activity, while LDH reflects the shift of tumor cells to anaerobic metabolism. Furthermore, elevated oxidative stress markers lead to cellular membrane and DNA damage[5].

Cytohistological studies allow for the detection of morphological atypia in peripheral blood cells. Alterations in erythrocyte shape and size, disruption of leukocyte nuclear structures, and lymphocyte apoptosis have been confirmed in multiple studies to correlate with disease severity[6].

Materials and Methods

The study was conducted using a prospective case–control design. Peripheral venous blood samples were collected from all participants after overnight fasting. Hematological analyses were performed using automated analyzers, while biochemical parameters were determined using standard enzymatic and ELISA methods. Cytohistological evaluation was carried out using Wright–Giemsa staining. Statistical analysis considered $p < 0.05$ as significant[7].

Results and Discussion

The obtained results demonstrate that breast cancer (BC) is accompanied by pronounced systemic changes in peripheral blood. The identified hematological, biochemical, and cytohistological alterations were closely associated with tumor progression, immune dysregulation, and metabolic reprogramming[8].

Comparative morphophysiological analysis revealed significant hematological disturbances in BC patients compared to healthy controls[9].

Table 1. Hematological Parameters.

Parameter	Control Group	Disease Group (Stages III–IV)	β / Additional Info	P-value
Hemoglobin (g/dL)	13.4 ± 0.9	10.8 ± 1.3	−0.62 (95% CI: −0.71 to −0.53)	<0.001
Hematocrit (%)	Normal	Normocytic-hypochromic anemia	—	—
MCV (fL)	Normal	Normocytic-hypochromic	—	—
RDW (%)	12.6 ± 1.4	15.8 ± 2.1	—	<0.001
Leukocytes (×10⁹/L)	7.2 ± 1.8	9.6 ± 2.4	—	0.004
NLR	<3.5	>3.5 (68% of patients)	OR = 2.47	0.002
Platelets (×10⁹/L)	Normal	384 ± 96	Thrombocytosis in 31% of patients	—
PLR	Normal	>180	Associated with lymph node involvement	<0.01

Analysis of the leukocyte profile showed a statistically significant increase in leukocyte counts in advanced-stage patients compared to early-stage disease. Pronounced neutrophilia accompanied by relative lymphopenia resulted in elevated neutrophil-to-lymphocyte ratio (NLR), exceeding 3.5 in 68% of metastatic patients[10]. Logistic regression analysis identified NLR as an independent predictor of tumor progression (OR = 2.47, p = 0.002), reflecting systemic inflammatory activation[11].

Table 2. Biochemical Parameters.

Parameter	Control Group	Disease Group	Correlation / Additional Info	P-value
LDH (U/L)	312 ± 74	486 ± 128	Tumor volume: r = 0.69; Metastatic load: r = 0.73	<0.001
CRP (mg/L)	2.6 ± 1.1	14.2 ± 6.8	HR = 1.89 (95% CI: 1.32–2.71)	<0.001
MDA	—	1.8-fold increase	—	<0.001
TAC	—	32% decrease	—	—
Albumin (g/L)	Normal	β = −0.44	Hypoalbuminemia <35 g/L → 5-year mortality risk +40%	0.006

Biochemical profiling revealed significant metabolic and inflammatory dysregulation in BC patients. LDH levels showed strong positive correlations with tumor volume and metastatic burden. Alterations in CRP and albumin reflected chronic inflammation and cancer-associated cachexia[12].

Table 3. Cytohistological Parameters.

Parameter	Control Group	Disease Group	Additional Info / Remarks	P-value
Erythrocytes	Normocytosis	Anisocytosis, poikilocytosis, target cells, ovalocytes	2.3-fold increase	<0.001
Leukocytes	Normal	Nuclear asymmetry, chromatin condensation, vacuolization	Increased immature forms in stages III–IV	<0.001
Lymphocyte apoptosis	Low	22% TUNEL-positive	Associated with lymphopenia	—

Cytohistological evaluation of peripheral blood smears revealed significant qualitative cellular abnormalities in BC patients. Erythrocytes exhibited marked anisocytosis and poikilocytosis, with frequent target cells and ovalocytes observed in advanced stages. Leukocyte morphology showed nuclear asymmetry, chromatin condensation, and cytoplasmic vacuolization, particularly in neutrophils and monocytes. The frequency of immature leukocyte forms significantly increased in stages III–IV, indicating bone marrow stress and altered hematopoiesis[13].

Apoptotic indices of circulating lymphocytes were markedly elevated, with up to 22% TUNEL-positive cells in metastatic patient samples. These findings were strongly correlated with lymphopenia ($r = -0.61$) and markers of immune suppression. Global oncological datasets suggest that such cytohistological changes predict reduced chemotherapy responsiveness and decreased immunological resilience[14].

Integrated multivariate modeling combining morphophysiological, biochemical, and cytohistological parameters achieved high discriminative accuracy. Disease stage classification demonstrated an innovative precision with AUC = 0.87. Among all variables, NLR, LDH, CRP, and erythrocyte morphological anomalies contributed most significantly to predictive power ($p < 0.001$)[15].

Extrapolation using international survival trends indicated that patients presenting with high NLR (>3.5), elevated LDH (>450 U/L), and distinct cytohistological abnormalities had approximately 25–35% lower 5-year survival compared to patients without these alterations. These findings support the clinical utility of blood-based integrated biomarkers as non-invasive tools for early detection, disease monitoring, and prognostic stratification in breast cancer[16].

This study provides a comprehensive evaluation of morphophysiological, biochemical, and cytohistological changes in the peripheral blood associated with BC, emphasizing their systemic relevance and potential clinical benefits. The findings support the concept that breast cancer is not

merely a localized malignancy but a systemic disease capable of inducing profound hematological, metabolic, and cellular disruptions in parallel with tumor progression[17].

The observed morphophysiological changes, including anemia, leukocytosis, neutrophilia, and thrombocytosis, correspond to cancer-associated hematologic syndromes reported in large oncological cohorts. Statistically significant decreases in hemoglobin and increases in RDW indicate inflammation-driven dysregulation of erythropoiesis. Meta-analyses encompassing over 40,000 BC patients report anemia prevalence ranging from 30% in early stages to >65% in advanced disease, with hemoglobin decline independently associated with 20–30% increased mortality risk. The strong negative regression coefficient between hemoglobin concentration and tumor stage in this study aligns with these global trends[18].

Elevated NLR and PLR further highlight the role of systemic inflammation in BC pathogenesis. International pooled analyses indicate that NLR values above 3.0–3.5 are associated with a 1.8–2.6-fold increased risk of disease recurrence and reduced overall survival. The high prevalence of elevated NLR in metastatic disease and its strong predictive value in multivariate models supports the hypothesis that redistribution of inflammatory cells reflects tumor-induced immune imbalance.

Mechanistically, neutrophil predominance facilitates tumor growth via secretion of vascular endothelial growth factors, matrix metalloproteinases, and immunosuppressive cytokines, while lymphopenia impairs anti-tumor immune surveillance[19].

Biochemical alterations observed in this study reflect significant metabolic reprogramming in aggressive disease. Elevated serum lactate dehydrogenase (LDH) indicates enhanced anaerobic glycolysis and tumor hypoxia, consistent with the Warburg effect. Large population studies report that LDH levels above 450 U/L correlate with 35–50% reduction in 5-year survival among BC patients. Strong correlations between LDH, tumor burden, and metastatic status suggest that LDH may serve as a robust surrogate marker of tumor aggressiveness.

Significant increases in C-reactive protein (CRP) underscore chronic systemic inflammation as a central driver of disease progression. Epidemiological data from international cancer registries indicate that CRP concentrations above 10 mg/L are associated with nearly twofold increased cancer-specific mortality. The independent prognostic value of CRP observed here supports its integration into routine risk stratification models.

Concomitant hypoalbuminemia, frequently observed in advanced aggressive tumors, reflects both inflammatory liver reprioritization and cancer-associated cachexia, with albumin levels below 35 g/L associated with ~40% increased mortality risk.

Oxidative stress imbalance represents another key pathogenic mechanism identified in this study. Observed increases in lipid peroxidation markers and decreases in total antioxidant capacity indicate a shift toward a pro-oxidant state, promoting DNA damage, genomic instability, and tumor progression. International comparative studies report significantly elevated oxidative stress markers in hormone receptor-negative and triple-negative BC, subtypes known for aggressive clinical behavior and poor prognosis. Predictive modeling based on these data suggests that patients with marked oxidative imbalance may exhibit reduced responsiveness to chemotherapy and radiotherapy due to enhanced cellular resistance mechanisms.

Cytohistological evaluation identified qualitative cellular anomalies indicative of bone marrow dysfunction and immune suppression. Increased anisocytosis and poikilocytosis reflect impaired erythrocyte maturation, while leukocyte nuclear atypia and elevated immature forms indicate stress hematopoiesis driven by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α. High levels of lymphocyte apoptosis observed in advanced disease stages were mutually correlated with immune dysregulation[20].

Conclusion

The results of this study demonstrate that morphophysiological, biochemical, and cytohistological alterations in peripheral blood of patients with breast cancer have significant clinical and scientific relevance. Decreased erythrocyte indices, elevated RDW, neutrophilia, lymphopenia, and thrombocytosis indicate the systemic nature of the disease. Biochemical markers, including CRP and LDH, confirm associations with chronic inflammation, metabolic activity of tumor cells, and disease

aggressiveness. Elevated oxidative stress markers reflect the depth of pathological processes occurring at the cellular level.

Cytohistological analyses revealed erythrocyte anisopoikilocytosis, leukocyte nuclear atypia, and increased lymphocyte apoptosis, indicating impaired bone marrow function and compromised immune system activity. These parameters were closely correlated with disease stage and prognosis, highlighting their high diagnostic and prognostic value.

Overall, integrated peripheral blood–based biomarkers can serve as promising, non-invasive, and cost-effective tools for early detection of breast cancer, monitoring disease progression, and guiding individualized treatment strategies. Implementation of this approach in clinical practice may significantly enhance the effectiveness of breast cancer management.

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