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Exploring RDW as a predictive marker for 5-year overall and progression-free survival in breast cancer; a retrospective, diagnostic cohort study

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Abstract

Introduction: Red cell distribution width (RDW), a parameter traditionally used to assess anemia, has emerged as a potential prognostic biomarker in various cancers, including breast cancer. Studies suggested that elevated RDW levels are associated with worse outcomes in terms of overall survival (OS) and progression-free survival (PFS).
Objectives: This study aims to explore the utility of RDW as a predictive marker for 5-year OS and PFS in breast cancer patients.
Patients and Methods: This retrospective cohort study investigated the prognostic significance of RDW as a predictive marker for 5-year OS and PFS in breast cancer patients. Conducted on 144 women treated at Shariati hospital and the cancer institute of Imam Khomeini hospital in Tehran, Iran, between 2011 and 2016, the study collected demographic, clinical, and pathological data from patient records and pathology reports. RDW values were derived from routine blood tests, while survival outcomes were assessed through phone interviews with patients or their families. The primary outcome focused on the association between RDW levels and 5-year OS, while the secondary outcome examined its correlation with 5-year PFS.
Results: The results revealed that higher RDW was significantly associated with poorer outcomes of both OS and PFS, with an odds ratio (OR) of 1.89 and 1.41, respectively. The receiver operating characteristic (ROC) curve analysis indicated that, for patients with no 5-year OS, RDW demonstrated an area under the curve (AUC) of 0.783, ranging from 0.671 to 0.895. Similarly, for patients with no 5-year PFS, RDW showed an AUC of 0.679 (0.576–0.783).
Conclusion: These findings highlight RDW as a potential prognostic biomarker for breast cancer survival outcomes, with higher RDW values correlating with poorer prognosis in terms of both OS and PFS.

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Introduction

Breast cancer is the most common malignancy globally, with over 2.26 million new cases reported in 2020, and its diagnosis relies heavily on histological evaluation of biopsy specimens, which can be labor-intensive and prone to errors. Advances in artificial intelligence (AI) have significantly improved diagnostic accuracy by identifying clinical and morphological features with high sensitivity and specificity, aiding in the differentiation between invasive and non-invasive subtypes (1). Breast cancer is a heterogeneous disease, with subtypes such as human epidermal growth factor receptor 2 (HER2) low breast cancer, characterized by low HER2 expression, posing unique challenges for detection and treatment due to tumor heterogeneity and analytical limitations (2). Additionally, dormant metastatic breast cancer cells, which can remain inactive for years before recurrence, exhibit distinct gene expression profiles that correlate with disease-free survival (DFS), offering potential predictive biomarkers for recurrence risk (3). Treatment responses and survival outcomes are influenced by factors such as DNA methylation changes following neoadjuvant chemotherapy, highlighting the role of epigenetic mechanisms in prognosis (4).

Breast cancer is the most common cancer among women worldwide and a leading cause of cancer-related mortality. Its incidence varies significantly across regions, with higher rates observed in developed countries compared to less developed regions, where mortality rates are disproportionately higher due to limited access to healthcare resources. Risk factors include demographic variables such as age,

Key point

In a diagnostic cohort study, we found that higher red blood cell distribution width was significantly linked to poorer outcomes in both overall survival (OS) and progression-free survival (PFS). The ROC curve analysis revealed that red cell distribution width (RDW) had strong predictive accuracy for identifying patients without 5-year OS, while also showing predictive value for those without 5-year PFS. These findings suggest that red blood cell distribution width, a readily available parameter from routine blood tests, could serve as a valuable prognostic tool in cancer management. Clinically, this may help in identifying high-risk patients who could benefit from more intensive monitoring or treatment strategies, potentially enhancing personalized care and outcomes.

race, and socioeconomic status, reproductive factors like age at menarche and parity, genetic predispositions such as BRCA mutations, and lifestyle factors including diet, physical activity, alcohol consumption, and tobacco use. The median age of diagnosis has risen in recent years, reflecting increasing longevity and improved healthcare access. Despite advancements in screening and treatment, disparities in survival persist, particularly among racial groups, with black women experiencing higher mortality rates and lower survival rates compared to White women (5,6).

Overall survival (OS) and progression-free survival (PFS) are critical metrics in understanding breast cancer outcomes. For metastatic breast cancer (MBC), the median OS has improved over time with advancements in treatment, reaching approximately 25 months, while PFS varies significantly depending on tumor subtype and treatment response; triple-negative breast cancer (TNBC) has the poorest prognosis, with a 5-year OS of only 9% for patients with multiple metastatic sites, compared to 31% for those with single-site metastases (7). High-dose chemotherapy with autologous stem-cell support has shown that up to 21% of patients achieve prolonged PFS at five years, particularly those with chemosensitive disease and minimal tumor burden (8). PFS is often used as a surrogate for OS in clinical trials, with studies suggesting that a 50% improvement in median PFS is predictive of significant OS benefits when sufficient events are analyzed (9). However, survival outcomes remain influenced by factors such as age, disease stage, and tumor biology (7,10).

Recently, red cell distribution width (RDW) has emerged as a significant prognostic marker for OS and PFS in breast cancer patients. Studies indicated that elevated RDW levels are associated with aggressive tumor characteristics, including larger tumor size, advanced stage, lymph node metastases, and higher rates of recurrence (11-13). A retrospective cohort study of 825 patients demonstrated that high RDW (>13.82) correlated with poorer OS (HR = 2.43) and DFS (HR = 1.89), even after adjusting for confounding factors (13). Similarly, in young women (<40 years), pretreatment RDW>13.75% predicted markedly reduced OS (HR=11.67) and DFS, particularly in advanced-stage disease (11). Meta-analyses of 4,884 patients confirmed these findings, showing high RDW linked to worse OS (HR = 2.12) and DFS (HR = 1.77), with stronger prognostic value in surgery-only subgroups (12). Post-treatment RDW elevation, especially when increasing from baseline after adjuvant therapy, further predicts inferior survival outcomes (14). The medical information mart for intensive care IV (MIMIC-IV) database analysis reinforced RDW's association with all-cause mortality at 6 months, one year, and 3 years, while a critical threshold of RDW>13.5 increased recurrence and death risks by 1.7-fold (15). These findings position RDW as an accessible, cost-effective biomarker for stratifying survival risk in breast cancer management.

Objectives

This study aimed to evaluate the prognostic value of RDW as a predictive marker for 5-year OS and PFS in breast cancer patients, using a retrospective diagnostic cohort study design, and to determine its potential utility as a preoperative cost-effective and accessible biomarker for risk stratification and clinical decision-making.

Patients and Methods

Study design and participants

This retrospective diagnostic cohort study was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (16). This study examined 144 women diagnosed with breast cancer who were treated at Shariati hospital and the cancer institute of Imam Khomeini hospital in Tehran, Iran, between 2011 and 2016. The study aimed to assess the prognostic role of RDW as a predictive marker for 5-year OS and PFS in breast cancer patients.

Inclusion and exclusion criteria

The inclusion criteria for the study were a confirmed diagnosis of breast cancer based on pathology results, availability of RDW test results, breast sample pathology report, and access to necessary data for evaluating OS and PFS over a 5-year period. Patients with concurrent malignancies, myeloproliferative disorders, or other conditions affecting RDW were excluded from the study.

Data collection

Demographic information, including patients' age, was extracted from patients' clinical documents. RDW values were determined based on routine laboratory tests performed on venous blood samples. Clinical and pathological data, such as whether or not patients received chemotherapy and radiotherapy, the status of estrogen and progesterone receptors, luminal and HER2 status, malignancy type (invasive ductal carcinoma [IDC] or other malignancy type), and tumor stage (I, II, and III), were obtained from breast tissue pathology reports. Five-year survival outcomes, including OS and PFS, were assessed through phone interviews with patients, their

families, or their first-degree relatives.

Outcomes

The primary outcome of this study is the evaluation of 5-year OS in breast cancer patients based on their RDW levels. The secondary outcome is assessing the correlation between 5-year PFS and RDW values. Both outcomes aim to determine the prognostic significance of RDW as a predictive marker in breast cancer patients, to establish its potential as a cost-effective and readily available preoperative biomarker for risk stratification and treatment planning

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 27. The Kolmogorov-Smirnov test was applied to assess the normality of data distribution, while chi-square test, Fisher's exact test, and independent T-test were utilized to compare frequency distributions across groups. Logistic regression models were employed to examine the relationship between RDW and 5-year OS and PFS. Receiver operating characteristic (ROC) curve analysis was conducted to identify optimal RDW cut-off values, with the area under the curve (AUC) used to evaluate its predictive accuracy for breast cancer survival. Additionally, sensitivity and specificity metrics were calculated for RDW, and statistical significance was defined as a *P* value below 0.05.

Results

This study involved 144 women with an average age of 49.51±11.51 years. Among these participants, 124 patients (86.11%) achieved a five-year OS rate, while 20 patients (13.89%) did not achieve it. Additionally, 104 patients (72.22%) achieved a five-year PFS rate, whereas 40 patients (27.78%) did not. The evaluation of demographic and clinical data between patients with and without 5-year OS revealed that the distribution of HER2 status showed a significant difference, with a higher proportion of HER2-positive cases in the group without survival. Similarly, the frequency of luminal subtypes and malignant types differed significantly between the groups, with notable variations in the distribution of luminal B and HER2-enriched subtypes, as well as IDC. Disease stage also exhibited a significant association, with advanced stages being more prevalent among those without survival. Additionally, RDW demonstrated a significant difference, being higher in the non-surviving group. Conversely, factors such as radiotherapy, chemotherapy, estrogen receptor, progesterone receptor status, and patient age did not show statistically significant differences between the groups (Table 1).

The results demonstrated that the distribution of HER2 status, luminal subtypes, and malignant types showed statistically significant variations between the groups with and without PFS. Specifically, the HER2-negative status and IDC were more prevalent among those with

Table 1. Frequency distribution of demographic characteristics and clinical data between patients with and without 5-year overall survival

Variable		5-Year overall survival				*P* value
		Yes (n = 124)		No (n = 20)		
		No.	%	No.	%	
Receiving radiotherapy	No	34	27.4	6	30	0.811*
	Yes	90	72.6	14	70	
Receiving chemotherapy	No	5	4	0	0	0.361*
	Yes	119	96	20	100	
Estrogen receptor	No	29	23.4	8	40	0.115*
	Yes	95	76.6	12	60	
Progesterone receptor	No	42	33.9	9	45	0.334*
	Yes	82	66.1	11	55	
HER2 status	No	99	79.8	9	45	<0.001*
	Yes	25	20.2	11	55	
Luminal	A	84	67.7	8	40	0.006**
	B	15	12.1	5	25	
	HER2-enriched	10	8.1	6	30	
	Triple negative	15	12.1	1	5	
Malignant type	IDC	114	91.9	14	70	0.004*
	Other type	10	8.1	6	30	
Stage	I	27	21.8	0	0	<0.001**
	II	78	62.9	6	30	
	III	19	15.3	14	70	
Variable		**Mean**	**SD**	**Mean**	**SD**	***P* value**
Age (year)		48.93	10.24	53.15	17.40	0.303***
RDW (%)		13.15	1.86	15.13	1.74	<0.001***

SD, standard deviation; HER2, Human epidermal growth factor receptor 2; IDC, Invasive ductal carcinoma; RDW, Red cell distribution width,
*Chi-square, **Fisher's exact test, ***Independent T-test.

PFS, while the HER2-positive status and other malignant types were more common in those without. Disease stage also exhibited a significant association, with earlier stages being more prevalent among those with PFS. Additionally, the RDW demonstrated a significant difference, being higher in the group without PFS. In contrast, variables including radiotherapy, chemotherapy, estrogen receptor status, progesterone receptor status, and patient age did not exhibit significant differences between the two groups (Table 2).

The correlation between RDW and the 5-year OS and PFS in breast cancer patients was assessed using logistic regression analysis. For OS, unadjusted analysis revealed that higher RDW was significantly associated with reduced survival, with an odds ratio (OR) of 1.89. After adjusting for potential confounders such as HER2 status, luminal subtypes, tumor stage, and malignant types, the association remained significant, with an OR of 1.76. In contrast, for PFS, the unadjusted analysis showed a significant association between elevated RDW and poorer outcomes, with an OR of 1.41. However, after adjustment in terms of HER2 status, luminal subtypes, tumor stage, and malignant types, this association was not statistically significant, with an OR of 1.14. These findings suggest that RDW is a stronger independent predictor of OS compared to PFS in breast cancer patients (Table 3).

The diagnostic value of RDW in predicting OS and PFS in breast cancer patients was assessed using ROC curve analysis. For patients with no 5-year OS, RDW demonstrated an AUC of 0.783, ranging from 0.671 to 0.895. Various RDW cut-off values were evaluated, with sensitivities and specificities increasing at higher thresholds: for RDW ≥ 13.35%, sensitivity was 80% and specificity 54%; for RDW ≥ 14.70%, sensitivity was 65% and specificity reached 78%. Similarly, for patients with no 5-year PFS, RDW showed an AUC of 0.679 (0.576–0.783). Sensitivity and specificity varied across cut-off points: at RDW ≥ 13.35%, sensitivity was 65% and specificity 54%; at RDW ≥ 14.70%, sensitivity dropped to 47%, but specificity rose to 79% (Figure 1 and Table 4).

Discussion

The analysis demonstrates that elevated RDW exhibits a clinically meaningful association with long-term survival outcomes in breast cancer patients. After accounting for key clinical variables, RDW was independently predictive of OS; however, its association with PFS was not an independent predictor but was also significant, suggesting distinct biological or prognostic influences on these endpoints. The association between elevated RDW and survival outcomes in breast cancer aligns with existing literature. Previous studies consistently identify RDW as an independent prognostic marker for OS, corroborating the current findings. For instance, a retrospective cohort study of 825 patients by Yao et al demonstrated that elevated RDW correlated with advanced tumor stage, lymph node metastasis, and poorer OS, even after adjusting for clinical variables (HR = 2.43 for OS) (13). Similarly, a 2024 analysis

Table 2. Demographic characteristics and clinical data frequency distribution among patients with and without 5-year progression-free survival

Variable		5-Year progression-free survival				*P* value
		Yes (n = 104)		No (n = 40)		
		No.	%	No.	%	
Receiving radiotherapy	No	31	29.8	9	22.5	0.381*
	Yes	73	70.2	31	77.5	
Receiving chemotherapy	No	5	4.8	0	0	0.158*
	Yes	99	95.2	40	100	
Estrogen receptor	No	23	22.1	14	35	0.113*
	Yes	81	77.9	26	65	
Progesterone receptor	No	35	33.7	16	40	0.476*
	Yes	69	66.3	24	60	
HER2 status	No	85	81.7	23	57.5	0.003*
	Yes	19	18.3	17	42.5	
Luminal	A	71	68.3	21	52.5	0.012**
	B	12	11.5	8	20	
	HER2-enriched	7	6.7	9	22.5	
	Triple negative	14	13.5	2	5	
Malignant type	IDC	99	95.2	29	72.5	<0.001*
	Other type	5	4.8	11	27.5	
Stage	I	26	25	1	2.5	<0.001*
	II	64	61.5	20	50	
	III	14	13.5	19	47.5	
Variable		**Mean**	**SD**	**Mean**	**SD**	***P* value**
Age (year)		49.35	10.58	49.95	14.21	0.808***
RDW (%)		13.08	1.82	14.32	2.07	<0.001***

SD, standard deviation; HER2, Human epidermal growth factor receptor 2; IDC, Invasive ductal carcinoma; RDW, Red cell distribution width,
*Chi-square, **Fisher's exact test, ***Independent T-test.

Table 3. The correlation of RDW with OS and PFS of patients with breast cancer using logistic regression

Variable		Having no 5-year overall survival			
		P value	OR	95% CI	
				Lower	Upper
RDW (%)	Unadjusted	<0.001	1.89	1.35	2.65
	Adjusted	0.013	1.76	1.13	2.76
Variable		**Having no 5-year progression-free survival**			
		***P* value**	**OR**	**95% CI**	
				Lower	**Lower**
RDW (%)	Unadjusted	0.001	1.41	1.14	1.73
	Adjusted	0.271	1.14	0.88	1.47

OR, Odds ratio; CI, Confidence interval; RDW, Red cell distribution width.

Table 4. Diagnostic value of RDW in the prediction of OS and PFS of patients with breast cancer

Survival type	Diagnostic value of RDW						
	AUC (0-1)	*P* value	95% CI		Cut off (%)	Sensitivity (%)	Specificity (%)
			Lower	Upper			
Having no 5-year OS	0.783	<0.001	0.671	0.895	13.35	80	54
					13.75	80	59
					14.05	70	63
					14.45	65	72
					14.70	65	78
Having no 5-year PFS	0.679	0.001	0.576	0.783	13.35	65	54
					13.75	65	40
					14.05	55	65
					14.45	50	74
					14.70	47	79

AUC; Area under curve, CI, Confidence interval; RDW, Red cell distribution width; OS, Overall survival; PFS, Progression-free survival.

of 939 patients by Xiao et al confirmed RDW's autonomous association with increased all-cause mortality at 6 months, 1 year, and 3 years (adjusted HRs = 3.20–2.53) (15). These results mirror the observed persistent OS association post-adjustment in the present analysis.

The diminished prognostic significance of RDW for PFS in adjusted models contrasts with some earlier reports. While one study linked high RDW to reduced DFS (HR = 1.89) (13), others, such as a 2019 investigation of RDW-to-platelet ratio by Takeuchi et al, noted associations between RDW-derived metrics and DFS but emphasized confounding by HER2 status and age (17). This discrepancy may reflect differences in cohort characteristics, adjusted variables, or distinct biological mechanisms influencing OS versus PFS. For example, OS may capture systemic effects of RDW-linked pathways (e.g., chronic inflammation, oxidative stress) (13,18), whereas PFS could depend more on tumor-specific factors less modulated by RDW.

A 2016 meta-analysis by Hu et al of 4,267 cancer patients further contextualizes these findings, identifying elevated RDW as a pan-cancer predictor of poor OS (HR = 1.47) and DFS (HR = 1.91) (18). The stronger OS association in breast cancer-specific studies (13, 15) underscores its utility in this population. Mechanistically, RDW's correlation

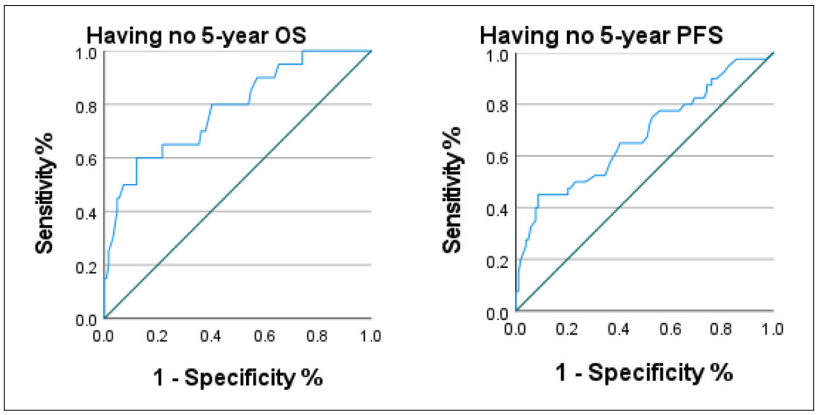

Figure 1. Diagnostic value of RDW in the prediction of OS and PFS of patients with breast cancer using ROC curve.

with tumor aggressiveness (e.g., larger size, advanced stage) (13,17) and inflammatory markers (13) supports its role in OS, which may integrate broader systemic decline rather than solely tumor progression.

Overall, these findings highlight RDW as a potential prognostic biomarker for breast cancer survival outcomes, where higher RDW values correlate with poorer prognosis in terms of both OS and PFS. Elevated RDW consistently associates with advanced tumor characteristics and systemic inflammation, which may drive OS decline through pathways like oxidative stress or impaired immune response. While RDW's role in PFS is less robust, its stronger association with OS underscores its utility as a marker of cumulative physiological decline rather than direct tumor progression. This positions RDW as an accessible, cost-effective prognostic tool, but further research is needed to optimize thresholds and clarify its clinical applicability across survival endpoints.

Conclusion

This study provides compelling evidence that elevated RDW is significantly associated with adverse outcomes in breast cancer, specifically poorer OS and PFS. The observed ORs of 1.89 for OS and 1.41 for PFS underscore the predictive value of RDW in identifying patients at higher risk of unfavorable survival outcomes. Furthermore, the ROC curve analysis demonstrated that RDW has a moderate to high discriminatory power for predicting 5-year OS (AUC = 0.783) and PFS (AUC = 0.679), suggesting its utility as a prognostic biomarker. These findings support the integration of RDW into clinical practice as a cost-effective and readily available tool for risk stratification and personalized treatment planning in breast cancer management.

Limitations of the study

Firstly, the study's retrospective design may introduce biases related to data quality and availability, as well as potential inconsistencies in how data were collected over time. Additionally, the reliance on phone interviews for assessing survival outcomes could lead to inaccuracies or incomplete data, particularly if not all patients or their families were reachable or willing to participate. The study's focus on a specific population treated at two hospitals in Tehran may limit the generalizability of findings to other populations or healthcare settings. Furthermore, the exclusion of patients with conditions affecting RDW, while necessary for isolating the effect of RDW on breast cancer outcomes, means that the results may not apply to patients with these comorbidities. Lastly, the study did not explore the underlying biological mechanisms linking RDW to cancer outcomes, which could provide deeper insights into its prognostic value.

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Authors' contribution

Conceptualization: Ali Mir.
Data curation: Ehsan Habibi.
Formal analysis: Marzieh Lashkari.
Investigation: Ali Mir and Marzieh Lashkari.
Methodology: Ehsan Habibi and Marzieh Lashkari.
Project management: Ehsan Habibi.
Resources: All authors.
Supervision: Ali Mir.
Validation: Ali Mir.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

The research was conducted under the principles of the Declaration of Helsinki. This study resulted from the General Surgery residency thesis of Ehsan Habibi (Thesis #47801), with ethical approval (IR.TUMS.MEDICINE.REC.1399.062; https://ethics.research.ac.ir/EthicsProposalView.php?id=131833), approved by Tehran University of Medical Sciences, Tehran, Iran. Prior to any intervention, all participants provided written informed consent. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized AI (Perplexity.ai and grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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