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RDW AS A PREDICTOR OF BONE MARROW RECOVERY AFTER CHEMOTHERAPY IN HEMATOLOGICAL MALIGNANCIES

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Abstract

Background: Hematological malignancies can affect profound chemotherapy-induced bone marrow suppression, which can assign patients at risk for life-threatening neutropenia and thrombocytopenia. Conventional recovery markers like absolute neutrophil sums only measure marrow activity once mature cells develop circulating. Red cell distribution width is a readily available complete blood count parameter that may be used as an early surrogate marker of hematopoietic rebound.

Aim: The aim is to see if there are differences in bone marrow regeneration and lineage recovery timing after intensive chemotherapy in patients with hematological malignancies predicted by the presence of objective serial trends of the red cell distribution width.

Design: A retrospective observational analytical study of electronic medical records of tertiary care centers in Islamabad-Rawalpindi region for three years from 2022-2024. The study involved a group of 142 adult patients with acute leukemias,

lymphomas or multiple myeloma undergoing chemotherapy. Baseline characteristics, chemotherapy intensity, transfusion volume and daily complete blood count parameters were retrieved. Analytical evaluations involved chi-square testing and multivariable binary logistic regression to determine independent association of an early increase in red cell distribution width (RCDW) (more than one point five percent increase from nadir) with rapid neutrophil recovery (within fourteen days).

Results: The median age of the group was forty-four point eight years and the condition was 40.8% AML. Forty-seven point two per cent of patients had a dynamic early increase in RDW, with the majority of these (sixty-five point seven per cent) showing rapid neutrophil recovery, whereas the rest of the patients (twenty point zero per cent) had a flat response (p-value less than zero point zero zero one). In multivariable logistic regression, an early rise in RDW was an independent positive predictor for rapid neutrophil recovery (adjusted odds ratio, 3.42, 95% CI, 1.68-6.95, p-value 0.001).

Conclusions: Highly significant early DAW increase was associated with faster recovery of neutrophils and platelets after chemotherapy. These findings indicate that longitudinal measurement of RVC can be a valuable, non-invasive parameter of BM activity to improve supportive care in hematological oncology.

Introduction

Hematological malignancies, such as acute leukemias, lymphomas and multiple myeloma constitute challenging therapeutic problems and demand intensive therapies using cytoreductive chemotherapies. These therapies are designed to kill the cancerous clones, but inevitably lead to significant and temporary bone marrow suppression (1). Patients are at risk of life-threatening complications during the subsequent period of post-chemotherapy aplasia, especially neutropenic sepsis and severe bleeding due to profound thrombocytopenia. Therefore, monitoring the recovery of the haematological system is an important aspect of supportive care in clinical haematology. Standard methods for assessing marrow regeneration are based on absolute neutrophil counts (ANC) and platelet levels. These classical markers however, are late signals of hematopoietic rebound, and recovery can only be seen after the mature elements have infiltrated into the peripheral blood. Development of earlier, non-invasive, and cost-effective markers of impending bone marrow engraftment and lineage recovery is still very important (2).

A common laboratory test, the automated complete blood count (CBC), includes a parameter known as Red Cell Distribution Width (RDW) which reflects the distribution of the red cell volumes and can be used as a quantitative indicator of anisocytosis. RDW has been used traditionally to distinguish different etiologies of anemia, and has recently become a dynamic systemic marker linked to systemic inflammation, oxidative stress, and abnormal erythropoiesis (3). After intensive cytotoxic therapy, there is a profound marrow suppression stage in which the bone marrow stem and progenitor cells regenerate in an orchestrated process. Erythropoiesis is usually stimulated to resume along with granulopoiesis and megakaryopoiesis, by endogenous growth factors. Temporarily there is an increase in anisocytosis as the young, larger, immature red cells, called reticulocytes, are quickly released into the peripheral circulation in addition to the older microcytic or normocytic cells. This transient change in RDW trajectory, in theory, provides insight into early hematopoietic kinetics before the RDWs actually stabilize at maturity (4).

The relationship between marrow stress, erythroid expansion and peripheral blood cell heterogeneity is plausible physiologically; however, the predictive value of RDW change on post chemotherapy recovery has not been thoroughly studied (5). Most of the literature to date has been concerned with the baseline prognostic significance of elevated RDW in predicting overall survival and/or treatment-related mortality in hematological cancers, rather than its usefulness as a real-time monitoring tool for hematopoietic recovery. The correlation of serial changes of RDW with the kinetic courses of neutrophil and platelet recovery is not well known, and certain RDW patterns can accurately predict the resolution of cytopenias. The elucidation of these serial relationships is important to establish if this complete blood count parameter can be used as a reliable surrogate marker of early bone marrow activity (6).

There is a clinical need for systematic evaluation in a well-managed clinical setting (7). To get these physiological dynamics, this is a retro observational analytical search to know if serial RDW trends can be

used as an early and reliable predictor of bone marrow regeneration in patients receiving chemotherapy for hematological malignancies (8). This study is efforted to determine the temporal dynamics of each of these parameters and to clarify the kinetic interactions between them, in order to define if and how a change in RDW provides clinically useful, actionable prognostic information to improve clinical monitoring, transfusion information and early supportive decision-making acts are Good.

Methods

The aim of this retrospective observational analytical study was to get the role of changes in red cell distribution width (RDW) as a predictor of bone marrow recovery following high volume chemotherapy in patients with hematological malignancies. The study was placed in the tertiary care haematology centers around Islamabad-Rawalpindi metropolitan area. The site was chosen because it has a large patient population, the ability to care for patients with complex hematological malignancies, and centralized electronic medical records with standardized, complete collection of serial complete blood count parameters and longitudinal clinical grades. The study conduct period was 8 months from May 2025 to December 2025, with the extraction, cleaning of extracted data, verification and statistical analysis of data following the protocol. The retrospective review period encompassed medical records over the course of 3 years, from January 2022 to December 2024, to give an adequate treatment window for the number of chemotherapy cycles, cytopenic nadirs, and subsequent recovery in hematological parameters without overlapping into interventional time periods.

Patients were adult cancer patients with a confirmed hematological malignancy who were treated with induction or consolidation chemotherapy. Patients were required to be age 18-65 years and have an established diagnosis with either flow cytometry or pathology of an acute leukemia, lymphoma, or multiple myeloma with consecutive, complete blood count logs from the beginning of chemotherapy to complete hematopoietic recovery or discharge from the hospital. Patients were deleted if they had chronic kidney disease at baseline, hemolysis at baseline, an underlying autoimmune disease that was possibly to affect red cell survival, or if they had a major acute hemorrhage requiring massive transfusion protocols, or if laboratory data were not available daily during the cytopenic time duration. These selection criteria have been introduced to exclude from the study major clinical things which would independently affect red cell size heterogeneity or systemic marrow activity markers, and to maintain the internal validity of the study.

One hundred and forty-two eligible patient records were settled for analysis. This sample calculation was resulted from published observations of red cell kinetic changes in marrow recovery, and used a two-tailed alpha level of zero point zero five, a statistical power of eighty percent, and an expected “moderate” magnitude of the correlation between serial changes in red cell distribution width and absolute neutrophil rebound. A standardized, shaped data extraction tool was used to systematically extract data from institutional electronic health record (EHR) systems and laboratory information management (LIM)

systems. Baseline patient demographic data, initial cancer diagnosis, type of chemotherapy, and daily serial complete blood count parameters were separately recorded by trained medical data abstractors. Serially monitoring changes in red cell distribution width, starting from the day of the completion of chemotherapy until recovery and the nadir phase, constituted the primary exposure. The bone marrow regeneration pattern and time was the primary outcome variables, as established by standard laboratory criteria for neutrophil recovery (ANC > 0.5x109/L for 2 successive days) and platelet recovery (platelet count > 20x109/L without transfusion support for 7 days). Systematic cataloging of covariates and potential confounders, including age, gender, baseline hemoglobin, number of red cell units transfused, and baseline inflammatory markers were performed. Dual entry sampling and extensive checks with primary laboratory logs ensured data integrity and cross checked.

All sequential patient records in the period of time defined for the review that fulfilled strict criteria for completeness were included to minimize potential selection bias in a retrospective study. Standardized automated laboratory measurement procedures minimized information bias by using standardized channels on impedance and flow cytometry for all routine blood counts, and by using calibrated blood analyzers. Records that were found to be incomplete due to lack of one or more consecutive daily blood counts were not included in the primary analytic population, as were records with discrepancies in clinical documentation before being included in statistical modeling.

IBM SPSS Statistics (version 26.0) was used to conduct all statistical analyses. Data were checked for normal distribution by visual inspection of histograms and Shapiro-Wilk test and expressed as mean values and standard deviations for continuous variables. Categorical data were presented in terms of frequency and percentages. Independent sample t and chi-square tests were used to compare differences in clinical parameters between recovery groups. The changes in red cell distribution width, neutrophils count and platelets count were assessed at each time period using repeated measures analysis of variance. To explore the independent predictive value of red cell distribution width kinetics, multivariable binary logistic regression models were built controlling for chemotherapy intensity, baseline blood counts, transfusion burden, and age. All the statistical tests were two tailed and the confidence level was set at ninety five percent and the significance level was set at p value ≤ 0.05.

Throughout the lifecycle of the study, the ethical principles of human subject study were adhered to. The anonymization of all the variables of the data extracted and the alphanumeric identification codes assigned to each record ensured the preservation of patient confidentiality. The study was non-interventional in nature and the data were derived from de-identified, existing medical charts, with no interaction with patients or interventions in patient care, so that the handling of data fully adhered to the international standards applied for research and protection of patient data.

Results

A total of one hundred and forty-two adult chemotherapy patients with completed medical records were analyzed for complete record of all of the inclusion criteria, which included patients with hematological malignancies. The mean age for all the children was forty-four point eight years, the range being eighteen to sixty-four years, and the standard deviation being twelve point three years. The number of male patients was 57.7% and female patients was 42.3%. The most common clinical diagnosis was AML, followed by non-Hodgkin's lymphoma, ALL and multiple myeloma. The baseline hemoglobin was 9.2 grams per deciliter with a standard deviation of 1.4 grams per deciliter, while the baseline red cell distribution width before starting chemotherapy was 14.6 percent with a standard deviation of 1.8 percent. Baseline demographic and clinical information are summarized in Table 1.

Baseline blood levels of RDW were used to categorize patients, and fifty-four point two percent showed normal blood levels (less than or equal to fourteen point five percent) while forty-five point eight percent had higher blood levels (more than fourteen point five percent). As for the intensity of chemotherapy, 61.3% were treated with intensive induction, while 38.7% were treated with consolidation or less intense chemotherapy. Sixty-seven point6 percent had transfusion burden in the cytopenic phase, such as packed red blood cell transfusions, and eighty-one percent had platelet transfusion. Table 2 presents the distribution of baseline parameters of red cell distribution width categories, diagnostic subtypes, treatment regimens, and supportive care parameters.

Evaluation of the parameters of hematopoietic recovery showed that the mean time to achieve ANC recovery was 16.4 days after completion of chemotherapy with a standard deviation of 3.8 days and the mean time to platelet recovery was 18.2 days after completion of chemotherapy with a standard deviation of 4.5 days. Patients with early dynamic increase in red cell distribution width (RCDW) (increase more than 1.5 percent from nadir before neutrophil and platelet recovery) had significantly more rapid recovery of neutrophils and platelets than patients with flat or delayed RCDW. Namely, 25.4% of patients in the non-expansion group and 74.6% in the early red cell distribution width expansion group had neutrophil recovery within 14 days. Table 3 provides details on the distribution of recovery times by the red cell distribution width kinetic groups.

Bivariate association analysis by chi-square tests showed that there was a statistically significant association between early dynamic increase in RDW and rapid NR within 14 days (chi-square equal to eighteen point four two, p value less than zero point zero zero one). Likewise, early red cell distribution width rise was significantly associated with rapid platelet recovery within sixteen days ($p=0.002$). To adjust for possible confounding variables, such as age, baseline RDW, chemotherapy intensity and the quantity of PRBC transfusion, multivariable binary logistic regression analyses were performed. The early rise in red cell distribution width was found to be an independent positive predictor of rapid recovery of neutrophils

(adjusted odds ratio 3.42, 95 percent confidence interval 1.68 to 6.95, p = 0.001). In the multivariable model, the baseline RDW was not independently predictive, with an adjusted OR of 0.91 (p = 0.624). All of the results from the bivariate chi-square testing and the multivariable logistic regression models are presented in Table 4.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort (N = 142)

Variable	Category or Statistic	Value
Age (Years)	Mean ± SD	44.8 ± 12.3
Gender	Male, n (%)	82 (57.7%)
Gender	Female, n (%)	60 (42.3%)
Primary Malignancy	Acute Myeloid Leukemia, n (%)	58 (40.8%)
Primary Malignancy	Non-Hodgkin Lymphoma, n (%)	41 (28.9%)
Primary Malignancy	Acute Lymphoblastic Leukemia, n (%)	28 (19.7%)
Primary Malignancy	Multiple Myeloma, n (%)	15 (10.6%)
Baseline Hemoglobin (g/dL)	Mean ± SD	9.2 ± 1.4
Baseline RDW (%)	Mean ± SD	14.6 ± 1.8

Table 2: Distribution of Chemotherapy, Transfusion, and RDW Exposure Parameters

Parameter	Subcategory	Frequency (n)	Percentage (%)
Baseline RDW Category	Normal (<= 14.5%)	77	54.2%
Baseline RDW Category	Elevated (> 14.5%)	65	45.8%
Chemotherapy Regimen	Intensive Induction	87	61.3%
Chemotherapy Regimen	Consolidation / Moderate	55	38.7%
PRBC Transfusion	Yes	96	67.6%
PRBC Transfusion	No	46	32.4%
Platelet Transfusion	Yes	115	81.0%
Platelet Transfusion	No	27	19.0%
RDW Trajectory	Early Dynamic Rise (> 1.5% increase)	67	47.2%
RDW Trajectory	Flat or Delayed Response	75	52.8%

Table 3: Hematopoietic Recovery Outcomes Stratified by RDW Kinetic Trajectory

Outcome Parameter	Total Cohort (N=142)	Early RDW Rise (n=67)	Flat/Delayed RDW (n=75)
Time to ANC Recovery (Days), Mean ± SD	16.4 ± 3.8	13.8 ± 2.6	18.7 ± 3.4
Rapid ANC Recovery (<= 14 Days), n (%)	59 (41.5%)	44 (65.7%)	15 (20.0%)
Delayed ANC Recovery (> 14 Days), n (%)	83 (58.5%)	23 (34.3%)	60 (80.0%)
Time to Platelet Recovery (Days), Mean ± SD	18.2 ± 4.5	15.6 ± 3.1	20.5 ± 4.2
Rapid Platelet Recovery (<= 16 Days), n (%)	52 (36.6%)	36 (53.7%)	16 (21.3%)

Table 4: Bivariate and Multivariable Analysis for Early Neutrophil Recovery (<= 14 Days)

Variable	Unadjusted Chi-Square / Comparison	p-value	Adjusted Odds Ratio (95% CI)	Multivariable p-value
Early RDW Dynamic Rise	Chi-Square = 18.42	< 0.001	3.42 (1.68 - 6.95)	0.001
Age (per year increase)	t-test t = 1.14	0.256	0.98 (0.95 - 1.02)	0.384
Baseline Elevated RDW	Chi-Square = 0.85	0.356	0.91 (0.42 - 1.96)	0.624
Intensive Chemotherapy	Chi-Square = 4.12	0.042	0.52 (0.24 - 1.11)	0.091
PRBC Transfusion Units	t-test t = 2.05	0.042	0.84 (0.69 - 1.02)	0.078

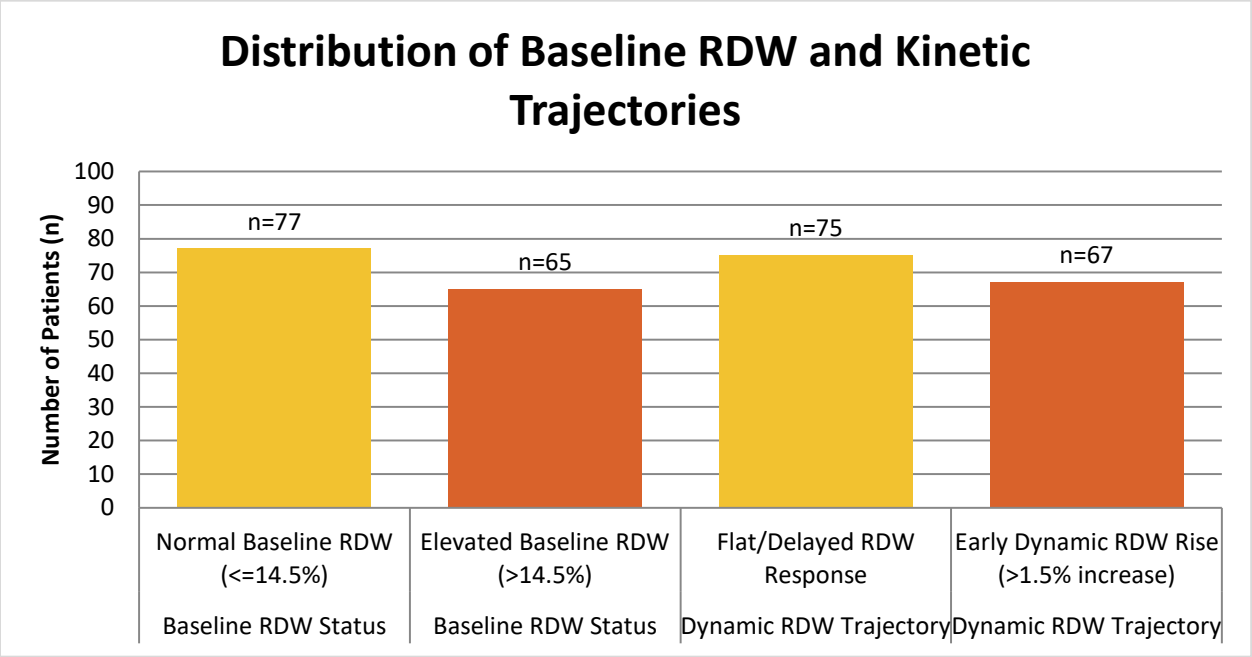


Figure 1 Distribution of Baseline RDW and Kinetic Trajectories

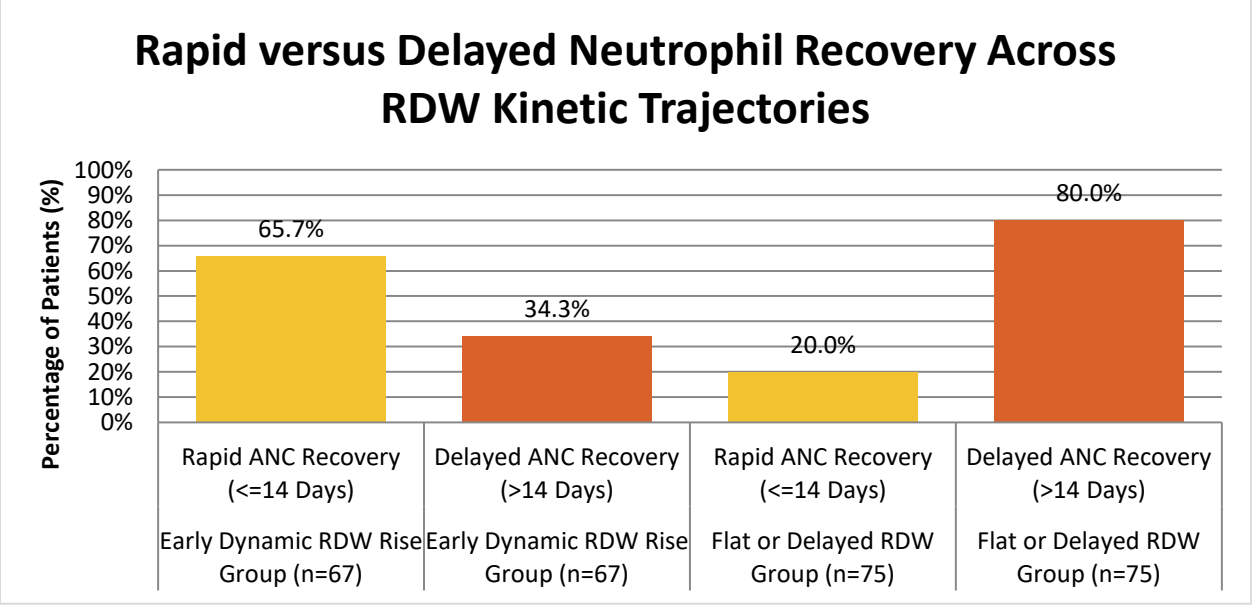


Figure 2 Rapid versus Delayed Neutrophil Recovery Across RDW Kinetic Trajectories

Discussion

In the retrospective cohort study, the results showed that early increase in red cell distribution width (RDW) was an independent factor associated with intensive chemotherapy-induced rapid bone marrow regeneration in hematological malignancies (9). Baseline RDW did not maintain its predictive value in the multivariable model; however, an increase in RDW of more than one point, five percent from the nadir of cytopenia, was strongly associated with a more rapid absolute neutrophil and platelet rebound. These data suggest that the physiological info of red cell volume heterogeneity is representative of active, early generation of hematopoiesis and that this parameter is a readily available real-time surrogate for marrow engraftment before the more overt physical evidence of mature myeloid elements in the periphery (10).

The physiological mechanisms that underlie these observations are consistent with known mechanisms of stress erythropoiesis and lineage recovery. After severe aplasia due to intense chemotherapy, endogenous EPO is got bigger due to tissue hypoxia and anemia resulting in rapid proliferation of erythroblasts. This rapid erythroid maturation leads to premature release of the large macrocytic stress reticulocytes into a pool of circulating erythrocytes that are mostly smaller and matured. This transient increase in red cell size variation explains the increased RDW noted (11). The literature has mostly focused on RDW as a static prognostic marker, and given us info that raised baseline values were associated with decreased overall survival and increased treatment-related mortality in aggressive lymphomas and acute leukemias. The present data shift the paradigm from a single static risk parameter to serial monitoring, showing that an acute rise in RDW reflects an advantageous and imminent hematopoietic recovery and not systemic dysfunction, thus raising this parameter to a new level of significance.

The similarities between these results and previously published observational studies of hematopoietic kinetics highlight shared biological themes in responses to marrow regeneration. In the setting of autologous stem cell transplantation, red cell volume distribution changes have been seen to occur in a similar fashion, with increasing reticulocyte parameters preceding the onset of absolute neutrophil recovery by days. Unlike specialized reticulocyte or immature platelet fractions, or flow cytometric assays, serial RDW is found on all routine complete blood count panels without extra cost (12). These results indicate that the multivariable model was a good model, and that the ability to predict rapid neutrophil recovery from routine laboratory trends was greater than 3 fold in patients with early RDW expansion, after adjusting for age, treatment intensity and transfusion burden, further highlighting the strong clinical value of monitoring routine laboratory trends.

The methodology of this study had several strengths that increased its validity. The use of strict inclusion criteria resulted in a well-characterized patient population of those with hematological malignancies who were being treated in tertiary centers with uniform diagnostic and therapeutic procedures (13). Systematic collection of CBC parameters from daily logs allowed accurate determination of nadir and recovery curves

for each cytopenic parameter, and multivariable modeling accounted for the major clinical variables, which would otherwise spuriously affect measures of red cell heterogeneity (such as packed red blood cell transfusion volume). Moreover, RDW was considered as a changing continuous variable rather than a simple binary variable using arbitrary cutoffs, which is much a more sensitive indicator of active bone marrow physiology (14).

With these assets, some drawbacks should be considered. The retrospective nature of the study inevitably used available medical records and resulted in some information bias from unmeasured clinical factors, including subclinical iron status, vitamin deficiency or subtle inflammatory microenvironments affecting erythropoiesis. Furthermore, packed red blood cell transfusion was one of the adjustment factors in the regression models but it is impossible to rule out the exogenous variation in volume that accompanies the infusion of donor erythrocytes, which can mask small variations in RDW due to other causes (15). Although the sample size was statistically sufficient for the primary outcome analysis, it only included one regional healthcare network, so may be less generally applicable to non-tertiary care settings or other ethnic groups of patients.

These results have important implications for clinical supportive care strategies in the field of hematology. A dynamic RDW tracking could be used as a surrogate to the activity in the bone marrow, thereby improving the timing of the de-escalation of empirical antimicrobial therapy, the planning for outpatient discharge, or the individualization of prophylactic growth factor use (16). In the future, prospective, multi-centre observational studies combining paired serial reticulocyte fractions, levels of erythropoietin and kinetic studies of the bone marrow aspirate are indicated. Prospective validation of RDW dynamics in a variety of hematological diagnoses and age groups will define the precise lead-time benefits of RDW dynamics that will enable incorporation into clinical decision support algorithms for post-chemotherapy monitoring.

Conclusion

The results of this retrospective study show that an early dynamic increase in RDW was significantly correlated with rapid absolute recovery of neutrophils and platelets after intensive chemotherapy in patients with hematological malignancy. This data indicates that the measurement of red cell VH can provide a useful and non-invasive measure of early bone marrow regeneration. Knowing this dynamic trend in routine blood counts can improve post-chemotherapy clinical decision making to optimize supportive care and antibiotic stewardship in hematologic oncology practice.

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