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Red blood cell distribution width at diagnosis as a predictor factor in chronic phase-chronic myeloid leukemia patients treated with first-generation tyrosine kinase inhibitors

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Abstract:

BACKGROUND: Chronic myelogenous leukemia is a hematological disorder of stem cells resulting from uncontrolled and unregulated growth of myeloid cells in the bone marrow. Since the introduction of tyrosine kinase inhibitors (TKIs), therapy has dramatically improved survival in these patients. TKIs treatment targeting BCR-ABL significantly improves the prognosis of patients with chronic myelogenous leukemia. To date, the validity of scoring systems is insufficient for predicting prognosis, and there are few studies of scoring systems for predicting treatment response and clinical efficacy of TKIs.

OBJECTIVES: The objective of this study was to evaluate the ability of the red blood cell distribution width (RDW) to predict treatment response in chronic myeloid leukemia-chronic phase (CP) patients treated with first-generation TKI.

PATIENTS AND METHODS: A prospective and retroprospective cohort study was conducted on chronic myeloid leukemia-CP patients treated with first-generation TKI at Iraqi Hematological Centers. The collection period was from December 2020 to November 2021. Patients were treated with first-generation TKIs as initial therapy and were followed up to assess the response by polymerase chain reaction (PCR). The assessment of RDW was done at baseline and then at 3, 6, 12, and 18 months after initiation of therapy.

RESULTS: There were 150 patients included in this study. The mean age of patients was 43.7 ± 14 years (range: 18–84 years). Males were representing 48.6% and females 51.3%. The classification of baseline RDW showed that the majority of patients (53%) had high RDW. The RDW showed significant change over time, in which, it was significantly decreasing over time ($P < 0.05$). Association between PCR over time and baseline RDW category showed that the high baseline RDW was associated with higher mean PCR at 3, 6, 12, and 18 months ($P < 0.05$). The correlation between RDW at baseline and PCR at 3, 6, 12, and 18 months showed that there was a significant positive weak correlation between baseline RDW and PCR at 6, 12, and 18 months. The association between baseline RDW and the response showed that high baseline RDW was associated with higher failure rate at 6 and 12 months ($P < 0.05$).

CONCLUSION: RDW could be used in the prediction of response to treatment. Furthermore, high RDW showed significant association with high disease activity score, high white blood cell count, and lower hemoglobin, in addition to association and correlation with PCR level.

Keywords:

Acute promyelocytic leukemia, arsenic trioxide, cardiac toxicity

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Introduction

Chronic myeloid leukemia (CML) is clonal disorder of pluripotent stem cells that accounts for around 15% of leukemia and may occur at any age. It is characterized by increased and unregulated growth of myeloid cells in the bone marrow and the accumulation of excessive white blood cells (WBCs).[1]

Since the introduction of tyrosine kinase inhibitors (TKIs), therapy has dramatically improved survival in these patients. TKI treatment targeting BCR-ABL significantly improves the prognosis of patients with chronic myelogenous leukemia. To date, the validity of scoring systems is insufficient for predicting prognosis, and there are few studies of scoring systems for predicting treatment response and clinical efficacy of TKIs.[2]

The red blood cell distribution width (RDW), a measure of heterogeneity size of red blood cell size,[3] is an independent prognostic factor for many disorders, including cancers (lung, colon, breast, and prostate) as well as in several types of hematologic malignancies (multiple myeloma, natural killer/T-cell lymphoma, diffuse large B-cell lymphoma, and CML).[4,5] In a study conducted by Iriyama *et al*., they found that patients with a higher RDW had poorer overall survival and progress-free survival.[4] However, the RDW could be affected by the widely used hematological analyzers that could interpret with RDW cutoff value.[6] Therefore, we conducted this study to evaluate the ability of the RDW to predict treatment response in chronic myeloid leukemia-chronic phase (CP) patients treated with first-generation TKI.

Patients and Methods

A prospective and retrospective cohort study was conducted on chronic myeloid leukemia (CML)- CP patients treated with first-generation TKI at Iraqi Hematological Centers. The collection period was from December 2020 to November 2021. The study was approved by review ethical committee of Iraqi council for medical specializations in Baghdad. Written informed consent was obtained from patients who enrolled in the study.

The study population consisted of 150 patients (100 patients were retrospective and the other 50 patients were retrospective) with diagnosed CML-CP with the following inclusion criteria:

Inclusion criteria

1. Confirmed diagnosis of CML patients (bone marrow and polymerase chain reaction [PCR] or FISH study for BCR-ABL transcript)
2. Age 18 years old and above
3. Patients were treated with first-generation TKI as initial therapy.

Exclusion criteria

1. Use of interferon-α or any chemotherapy before or in combination with TKIs treatment
2. Age <18 years at diagnosis
3. Prior blood transfusion
4. Iron-deficiency anemic patients
5. Patients who had an NYHA Grade of III/IV.

Patients' risk and response assessment

Sokal and Eutos scores have been used to assess patients' risk and the assessment.

Reverse transcriptase quantitative PCR for BCR-ABL was conducted on peripheral blood (PB) at various time points during the patient's treatment journey, including baseline, 3 months after treatment initiation, 6 months after treatment initiation, 12 months after treatment initiation, and 18 months after treatment initiation. It should be noted that not all patients underwent PCR at the 3-month mark, and some patients lacked results during specific follow-up periods.

Red blood cell distribution width categorization

The RDW normal range was calculated based on the normal range for red cell distribution width which is 12.2%–16.1% in adult females and 11.8%–14.5% in adult males.[7]

Patients have been divided for two groups:

- Group A: Included patients with high RDW at baseline
- Group B: Included patients with normal RDW at baseline.

Monitoring response

The assessment of response was based on PCR results from patients who had available data during each assessment period. Optimal, warning, and failure scales were utilized to evaluate responses at different time points. For the 3-month assessment, an optimal response was defined as BCR-ABL <10%, a warning response as BCR-ABL >10%, and failure as the absence of hematological response. At 6 months, an optimal response was indicated by BCR-ABL <1%, a warning response by BCR-ABL between 1% and 10%, and failure by BCR-ABL >10%. By the 12-month mark, an optimal response was characterized by BCR-ABL <0.1%, a warning response by BCR-ABL between 0.1% and 1%, and failure by BCR-ABL >1%. Ultimately, at any time, an optimal response was defined as BCR-ABL <0.1%.

Results

The mean age of patients was 43.7 ± 14 years (range: 17–84 years). Males were representing 48.6% and females 51.3%. Regarding the classification of disease, the majority of patients (68.7%) had intermediate disease scores by Sokal, and 94.7% of patients had low disease scores by Eutos. Regarding spleen size, the mean size was 5.2 ± 4 cm (range: 0–15 cm) [Table 1].

The classification of baseline RDW showed that the majority of patients had high RDW [Figure 1].

The distribution of RDW category showed that there was significant higher RDW frequency among high/intermediate Sokal score in comparison to low Sokal score patients (P = 0.003). Furthermore, high Eutos score show a significant association with high RDW at baseline (P = 0.046), while gender did not showed a significant difference with baseline RDW [Table 2].

Red blood cell distribution width changes

The RDW showed significant change over time, in which, it was significantly decreasing over time [$P < 0.05$, Table 3].

Association between PCR over time and baseline RDW category showed that the high baseline RDW was associated with higher mean PCR at 3, 6, 12, and 18 months [$P < 0.05$, Table 4].

The correlation between RDW at baseline and PCR at 3, 6, 12, and 18 months showed that there was a significant positive weak correlation between baseline RDW and PCR at 6, 12, and 18 months [Figure 2].

The association between baseline RDW and response showed that high baseline RDW was associated with higher failure rate at 6 and 12 months [$P < 0.05$, Table 5].

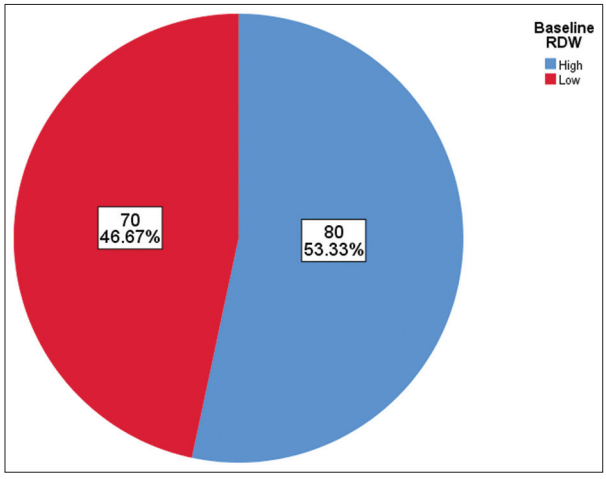

Figure 1: Red blood cell distribution width category distribution across patients. RDW = Red blood cell distribution width

Discussion

The baseline RDW among all CML patients was 16.7 with range from 12 to 23. This baseline RDW value was in line with another study by Li *et al*. that showed the median RDW at admission was 16.6 (range from 13 to 23).[8] While a recent study by Mao *et al*. showed that the median RDW at baseline was 18 with range from 17 to 28.[5] Despite the

Table 1: Demographic characteristics of patients

Variable	Data
Age (years), mean±SD	43.7±14
Gender, *n* (%)	
Male	73 (48.6)
Female	77 (51.4)
Sokal, *n* (%)	
Low	41 (27.3)
Intermediate	103 (68.7)
High	6 (4.0)
EUTOS, *n* (%)	
Low	142 (94.7)
High	8 (5.3)
RDW	16.7±2.1
WBC	187.55±131
Hb	10.68±1.85
MCV	87.16±4.6
Platelet	418.20±212
Eosinophils (%)	6±0.3
Basophile (%)	8±0.3
PB blast (%)	5±0.33
BM blast (%)	3±0.1
PCR-ABL (%)	90.09±15.9
Spleen size (cm)	17.5±4

SD=Standard deviation, RDW=Red blood cell distribution width, WBC=White blood cell, Hb=Hemoglobin, MCV=Mean corpuscular volume, PB=Peripheral blood, BM=Bone marrow, PCR=Polymerase chain reaction, ABL=Abelson tyrosine-protein kinase, EUTOS=European treatment and outcome study for CML score

Table 2: Red blood cell distribution width distribution across gender, Sokal, and Eutos

	RDW cat				*P**
	Normal		High		
	Count	Layer, *n* (%)	Count	Layer, *n* (%)	
Gender					
Female	37	48.1	40	51.9	0.77
Male	33	45.2	40	54.8	
Sokal					
High	1	16.7	5	83.3	0.003
Intermediate	1	39.8	62	60.2	
Low	28	68.3	13	31.7	
EUTOS					
High	1	12.5	7	87.5	0.046
Low	69	48.6	73	51.4	

*Chi-square and Fisher's exact tests. RDW=Red blood cell distribution width, EUTOS=European treatment and outcome study for CML score

Table 3: Change in red blood cell distribution width

	Mean±SD	*P**
Pair 1		
RDW 1	16.707±2.0542	0.001
RDW 3	15.865±2.1988	
Pair 2		
RDW 3	15.865±2.1988	0.0001
RDW 6	14.792±1.6340	
Pair 3		
RDW 6	14.792±1.6340	0.0001
RDW 12	13.975±1.5353	
Pair 4		
RDW 12	13.975±1.5353	0.0001
RDW 18	13.511±1.5316	
Pair 5		
RDW 1	16.707±2.0542	0.0001
RDW 18	13.511±1.5316	

*Paired sample *t*-test. SD=Standard deviation, RDW=Red blood cell distribution width

Table 4: Association between polymerase chain reaction over time and baseline red blood cell distribution width category

Group statistics			
Baseline RDW	***n***	**Mean±SD**	***P****
PCR 1			
High	80	89.8±16.97	0.84
Low	70	90.3±14.79	
PCR 3			
High	17	11.3±11.51	0.04
Low	21	5.09±7.49	
PCR 6			
High	74	9.04±13.22	0.001
Low	62	5.40±12.98	
PCR 12			
High	75	2.97±7.75	0.003
Low	69	0.10±0.37	
PCR 18			
High	78	1.30±4.52	0.02
Low	67	0.03±0.18	

*Independent sample *t*-test. RDW=Red blood cell distribution width, PCR=Polymerase chain reaction, SD=Standard deviation

difference in baseline RDW between studies, later study used their RDW of 18.65% determined by receiver operating characteristic curve analysis to discriminate between high and low RDW groups from retrospective data.

The classification of patients for low and high RDW showed that there was 53% of patients had high RDW and 46% of patients with lower RDW. This was in reverse to Mao *et al*. study that showed nearly 38% of patients had high RDW.[5]

The distribution of RDW category showed that there was significant higher RDW frequency among high/intermediate Sokal score in comparison to low Sokal score patients. This was in line with Mao *et al*. study that showed an association between higher RDW scores and Sokal scores.[5] Furthermore, in this study, the high Eutos score shows a significant association with high RDW at baseline. In a recent study by Pfirrmann *et al*. showed that Eutos score was superior to Sokal score in the predication of overall survival.[9] This association of our study between high RDW with Sokal and Eutos scores indicated that RDW and independent predictor factor for high-risk CML irrespective to higher identification of high-risk group by Sokal score based on Pfirrmann *et al*. study.[9]

While in this study, gender did not showed a significant difference with baseline RDW. No other study evaluated the role of gender in CML with RDW difference; however, a study from Germany showed that the female gender was associated with favorable intermediate-risk score in comparison to the male gender.[10]

Regarding the baseline laboratory results, only WBC and hemoglobin (Hb) showed a significant association with high RDW, in which, higher RDW showed significant association with higher WBC and lower Hb. No significant difference in the mean baseline of laboratory results, spleen size, and PCR between normal and high baseline RDW. This was in line with Mao *et al*. study that showed both WBC and Hb showed significant association with higher RDW.[5] While Li *et al*. showed in addition to WBC and Hb, the RBC count, eosinophil, and PB blasts were significant association with higher RDW.[8]

Lower Hb and higher WBC are associated with bad prognosis, in which higher WBC are leading factors for faster transformation of chronic CML phase to blast phase.[11] This indicates that RDW could play further role in the prognosis of CML patients.

Importantly, in this study, the RDW showed significant change over time, in which, it was significantly decreasing over time, in which RDW decreased from 16.7 to 13.5 after 18 months of treatment. This was in line with Bessman *et al*. study that showed RDW progressively declined during the first 3 months after treatment and reached an asymptote at that time and hematopoiesis normalizes qualitatively as well as quantitatively after successful imatinib therapy of CML.[12] Furthermore, another study by Jbireal *et al*. showed that patients with imatinib mesylate induced a significant decrease in RDW 16 doses of treatment, respectively, as compared with untreated patients.[13]

Association between PCR over time and baseline RDW category showed that the high baseline RDW was associated with higher mean PCR at 3, 6, 12, and 18 months ($P < 0.05$). This was partially agreed with

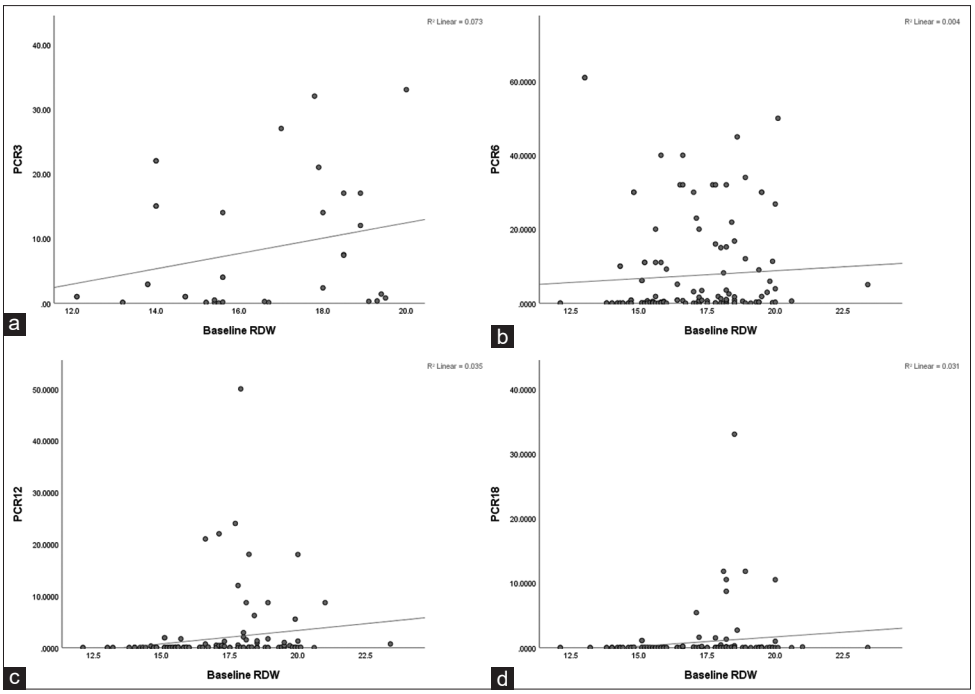

Figure 2: Correlation between baseline red blood cell distribution width (RDW) and polymerase chain reaction (PCR) at 3, 6, 12, and 18 months. (a) RDW with PCR 3 (P = 0.1, r = 0.27). (b) RDW and PCR 6 (P = 0.047, r = 0.06). (c) RDW and PCR 12 (P = 0.02, r = 0.18). (d) RDW and PCR 18 (P = 0.03, r = 0.17). RDW = Red blood cell distribution width, PCR = Polymerase chain reaction

Table 5: Association between baseline red blood cell distribution width and response

	Baseline RDW, count (%)		*P*
	High	Low	
PCR 3			
Optimal	9 (36.0)	16 (64.0)	0.15
Warning	8 (61.5)	5 (38.5)	
PCR 6			
Failure	16 (88.9)	2 (11.1)	0.005
Optimal	36 (43.9)	46 (56.1)	
Warning	21 (60.0)	14 (40.0)	
PCR 12			
Failure	17 (81.0)	4 (19.0)	0.007
Optimal	44 (44.9)	54 (55.1)	
Warning	13 (54.2)	11 (45.8)	
PCR 18			
Failure	9 (69.2)	4 (30.8)	0.54
Optimal	61 (50.8)	59 (49.2)	
Warning	7 (63.6)	4 (36.4)	

PCR=Polymerase chain reaction, RDW=Red blood cell distribution width

Mao *et al*. study that showed the high RDW group had significantly worse treatment responses at 3 and 6 months, whereas there was no significant difference in treatment responses between the 2 groups at 12 months.[9] Furthermore, Li *et al*. showed that a progressive decline in RDW started at 3 months after treatment till 60 months of follow-up.[8]

Furthermore, the correlation between RDW at baseline and PCR at 3, 6, 12, and 18 months showed that there was a significant positive weak correlation between baseline RDW and PCR at 6, 12, and 18 months.

The NCCN guidelines state that patients who achieve early molecular response (EMR) by 3 or 6 months generally have favorable outcomes, but major molecular response (MMR) is not a significant prognosticator of long-term outcomes in patients who achieve stable complete cytogenetic response (CCyR).[14] In this study, the RDW could predict the treatment responses at 6 and 12 months but not 3 months, and the RDW at diagnosis was significantly lower in patients who achieved 6M-EMR and 12M-CCyR. However, the RDW was not significantly different in patients who did not achieve 18M-MMR. Iriyama *et al*. observed dynamic changes in the RDW before TKIs treatment and 1, 3, and 6 months after TKIs treatment. They found that the RDW was transiently elevated after 1 month but declined at 3 and 6 months. They found no change at 12 months.[4]

Furthermore, a study by Khani and Karimi showed that examined the significance of RDW in patients with CML that an important role in the classification of patients to predict the responses and treatment outcomes; In fact, the RDW value in CML patients is higher than normal in most cases, it may predict the treatment response, this type of classification facilitates the planning of treatment.[6]

Furthermore, a meta-analysis by Ai *et al*. studied the prognostic role of RDW in hematological malignancies and showed that in seven trials with 1031 patients suffering from hematological malignancies with increased pretreatment RDW predicted poor overall survival and they concluded that for hematologic malignancies, patients with higher RDW are more likely to have poorer prognosis than those with lower RDW.[15]

Conclusion

RDW could be used in the prediction of response to treatment. Furthermore, high RDW showed significant association with high disease activity score, high WBC count, and lower Hb, in addition to association and correlation with PCR level.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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