Original Article

Some Hematological Indices as Predictors of Survival in Chronic Myeloid Leukemia Patients

Yusur Falah Faraj[1,2], Khalid Mahdi Salih[3], Abderrahim Khelif[2]

[1]National Center of Hematology, Mustansiriyah University, Baghdad, Iraq, [2]The National Center of Hematology, Ibn El Jazzar Faculty of Medicine, University of Sousse, Sousse, Tunisia, [3]Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

Abstract

Background: Despite the promising of introduction of tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) remains a significant cause of annual mortality. Red blood cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) are parameters derived from a complete blood count (CBC) commonly used to diagnose anemia, autoimmune diseases, and inflammation. These parameters have been reported to have a strong association with various diseases, including hematologic malignancies. **Objectives:** The study aims to identify whether RDW, NLR, and PLR can act as predictors of survival in newly diagnosed and treated CML patients. **Materials and Methods:** The study involved 60 Iraqi patients (37 males, 23 females, aged 17–69 years) with CML at chronic phase, who were referred to the National Center of Hematology/Mustansiriyah University, Baghdad, from February 2022 to December 2022. Twenty were newly diagnosed (T0), and 40 were under TKI treatment (T+), with 20 on imatinib and 20 on nilotinib. Additionally, a control group of 20 age- and gender-matched healthy subjects was included. CBC assessed red blood cell (RBC) indices across all groups. **Results:** There was no significant difference in the age of CML patients at the onset of disease between males (34.5 ± 11.7 years) and females (34 ± 11.9 years). Likewise, there was no significant difference in the treatment of CML patients with imatinib or nilotinib between males (48% and 52%) and females (53.3% and 47.7%), respectively. Most RBC indices for patients and controls were within normal ranges without significant differences. However, RDW% in T0 was markedly elevated (20.4%), with about 80% showing anisocytosis, surpassing both T+ and controls, and exceeding the upper limit of normal. The total and differential white blood cell (WBC) counts were significantly higher in T0 compared to T+, exceeding their normal ranges. Additionally, the NLR was significantly higher in T0 (8.13) compared with T+ and controls (1.80 and 1.87, respectively). Platelet count, mean platelet volume, and platelet distribution width (PDW%) differed significantly among the three groups but remained within the normal range. However, PLR in T0 (31 ± 24) was significantly lower than those in T+ and controls (130 ± 43 and 102 ± 27, respectively). **Conclusion:** It can be concluded that the monitoring of some parameters in peripheral blood in CBC test (as a simple and inexpensive test) such as RDW%, NLR%, and PLR% during the therapy course of CML patients may act as predictive markers to evaluate the prognosis of disease in CML patients and the degree of response to certain TKI treatment.

Keywords: Anisocytosis, chronic myeloid leukemia, imatinib, nilotinib, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, red blood cell distribution width

Introduction

Chronic myeloid leukemia (CML) is a hematological malignancy characterized by uncontrolled proliferation and upregulation of myeloid cells within the bone marrow due to the fusion of ABL1 gene on chromosome 9q34 with BCR gene on chromosome 22q11 forming what's known as Philadelphia chromosome, resulting an overactive tyrosine kinase enzyme that triggers various signaling pathways leading to the transformation of normal cells into a cancerous state.[1-3] In the realm of leukemia, CML holds a notable position accounting for approximately 15% of newly diagnosed cases in adults.[4] Predominantly, this leukemia occurs in individuals within the fifth and sixth decades of life in developed and Western countries, rising with age.[5] Furthermore, there exists a slight male predominance with the ratio of male to female ranging

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_14_24

Address for correspondence: Dr. Yusur Falah Faraj, National Center of Hematology, Mustansiriyah University, Baghdad, Iraq. E-mail: yusur_falah@uomustansiriyah.edu.iq

Submitted: 21-May-2024 **Revised:** 11-Jun-2024 **Accepted:** 12-Jun-2024 **Published:** 22-Jul-2024

How to cite this article: Faraj YF, Salih KM, Khelif A. Some hematological indices as predictors of survival in chronic myeloid leukemia patients. Mustansiriya Med J 2024;23:38-44.

between 1.3 and 1.8:1.[6] A study in Iraq from 2002 to 2006 with 669 patients found that the median age of CML patients was 37. It also showed a higher predisposition of males to CML compared to females.[7] Similarly, a retrospective study on Tunisian CML patients from January 2011 to December 2019 found that the median age at diagnosis was 49 years, and most of the patients were diagnosed during the chronic phase of the disease.[8] The introduction of tyrosine kinase inhibitors (TKIs), starting with imatinib, has markedly transformed the treatment approach for CML.[9] A breakthrough in targeted therapy marked a new era. Imatinib was effective, but some patients developed resistance. This led to the development of second-generation TKIs (bosutinib, dasatinib, and nilotinib), initially for imatinib-resistant patients and later as frontline therapy.[10,11] While TKI therapy brought hope, a considerable number still die from CML annually.[12] Moreover, the current scoring system has limitations in predicting treatment response and TKIs' clinical efficacies.[13]

In this context, the red blood cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), and PLT are routinely measured as part of complete blood count (CBC) for diagnosing hematological diseases. They have gained attention for their intriguing associations with various diseases.[14,15] It has been identified as having relevance in a diverse array of clinical contexts, spanning numerous types of solid tumor[16-18] and several types of hematologic malignancies.[19-21] Based on these observations, this study aims to investigate if RDW, NLR, and platelet/lymphocyte ratio (PLR) may serve as reliable predictors of survival in newly diagnosed and treated CML patients. This could provide a promising method for prognostic assessments in CML management.

Materials and Methods

Sixty Iraqi patients (37 males and 23 females) with CML at chronic phase (CML-CP), aged 17–69 years, were included in this study. They were referred to the National Center of Hematology at Mustansiriyah University in Baghdad during the duration spanning from February 2022 to December 2022. The diagnosis of disease is confirmed by polymerase chain reaction to identify the Philadelphia chromosome containing BCR-ABL gene. Medical history of all patients including disease duration, type of treatment, and refractory response to certain drug was recorded from their profile. Twenty of them are newly diagnosed (abbreviated as T0), and the rest 40 patients are under treatment with TKIs (abbreviated as T+), 20 of them treated with imatinib (daily dose of 400 mg) and 20 with nilotinib (dose escalated from 300 to 400 mg twice daily). Along with patients, 20 healthy subjects (with matched age and gender) were enrolled to act as a control group.

CBC was performed to assess red blood cell (RBC), white blood cell (WBC), and platelet indices in all groups. A vein puncture procedure was employed to obtain 2 ml of blood sample from each subject. These samples were then transferred into anticoagulant tubes containing ethylenediaminetetraacetic acid (AFICO-DISP, Jordan) for directly examination of CBC using five-differential full automated Hematology Analyzer DxH 500 (Beckman Coulter, USA) based manufacturer company procedures (M-52D diluent, M-52LH lyse, and M-52DIFF lyse). The values of RBC count, hemoglobin content (Hb), hematocrit (Hct), mean corpuscle volume (MCV), mean corpuscle hemoglobin concentration (MCHC), RDW, total and differential WBC count, NLR, platelet count, and PLR were recorded.

The statistical analysis was performed utilizing VassarStats Website for Statistical Computation. Numerical values are expressed as mean ± standard deviation. Categorical variables are reported as percentages, and the Chi-square test is used to examine differences between several groups. The differences among three independent samples are analyzed with the use of the analysis of variance and Tukey's honestly significant difference test. Additionally, the Pearson's calculator test is used to examine the correlation between two variables. Two-tail $P < 0.05$ is used to measure the significance of differences.

Results

Table 1 shows nonsignificant difference in the age between control group (39.2 ± 12.1 years) and patients of T0 and T+ (35.6 ± 12.2 and 43.3 ± 13.9 years, respectively). Furthermore, this table shows that the male-female ratio in CML patients is 1.6: 1, thus the distribution of male: female in the control group (1.5:1) is conducted to be matched with that in patients and with nonsignificant difference.

Furthermore, Figure 1 reveals that there is no significant difference in the age of CML patients at onset of disease between males (34.5 ± 11.7 years) and females (34 ± 11.9 years). Furthermore, there is no significant difference in the treatment of CML patients with imatinib or nilotinib between males (48% and 52%, respectively) and females (53.3% and 47.7%, respectively), as shown in Figure 2.

Moreover, Table 2 reveals that the values of RBC count, Hb, Hct, MCV, and MCHC are within the normal range in males and females of patients and control groups. However,

Table 1: Age and gender of patients and control groups

Character	Control ($n=20$)	Patients		*P*
		T0 ($n=20$)	T+ ($n=40$)	
Age (years)				
Range	19–61	17–55	14–65	0.103
Mean±SD	39.2±12.1	35.6±12.2	43.3±13.9	
Gender, *n* (%)				
Male	12 (60)	12 (60)	25 (62.5)	0.975
Female	8 (40)	8 (40)	15 (37.5)	
MFR	1.5	1.6		

SD: Standard deviation, MFR: Male/female ratio

the value of RDW% in newly diagnosed patients (20.4%) is significantly ($P < 0.0001$) higher than those in treated patients and control group (13% and 13.1%, respectively) as well as higher than the upper limit of the normal range (16%). Based on RDW, Figure 3 shows that the majority (80%) of newly diagnosed patients have anisocytosis RBCs.

On the other hand, the absolute values of total and differential count of WBCs in newly diagnosed patients are significantly higher than those in treated patients and control group and also higher than the upper limit of their normal range. Furthermore, NLR in newly diagnosed patients (8.13) is significantly higher than in treated patients and control group (1.80 and 1.87, respectively). Regarding platelet count, although there was a significant difference in platelet count among all groups, all values are within normal ranges. However, PLR in newly diagnosed patients (31 ± 24) is significantly lower than in treated patients and control group (130 ± 43 and 102 ± 27, respectively) [Table 3].

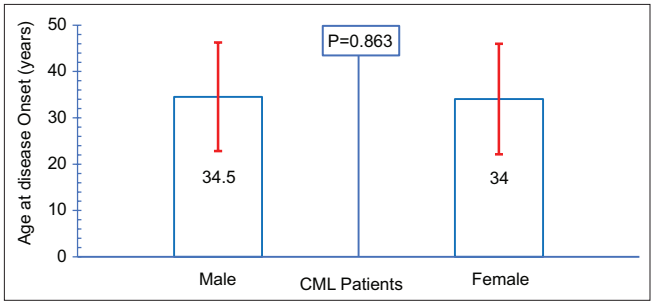

Figure 1: Age of chronic myeloid leukemia patients at the onset of disease. CML: Chronic myeloid leukemia

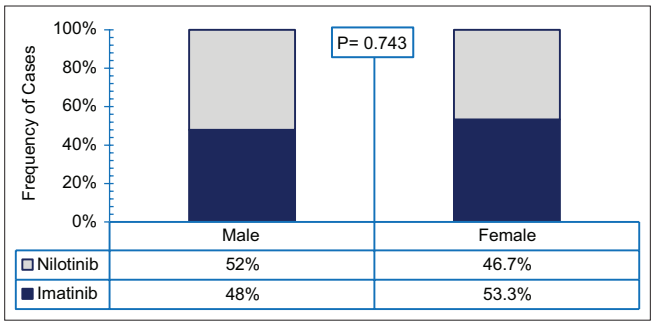

Figure 2: Frequency of cases of chronic myeloid leukemia with different treatments

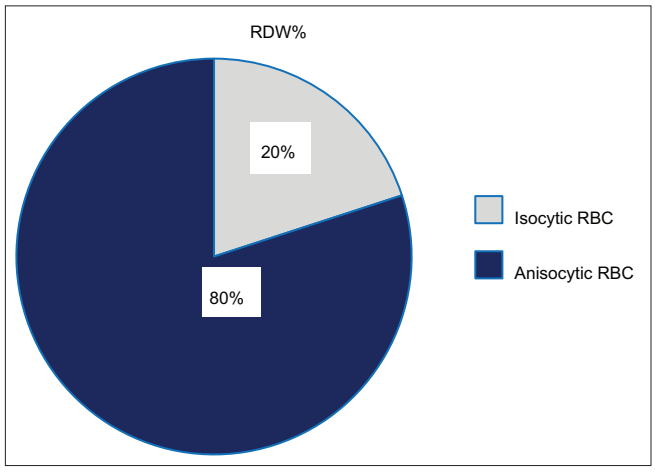

Figure 3: Frequency of anisocytosis red blood cells in newly diagnosed chronic myeloid leukemia patients. RBC: Red blood cell, RDW: Red blood cell distribution width

Discussion

According to the findings of this study, the mean age of patients at the onset of disease was 34 years [Figure 1]. This aligns closely with a prior study in Iraq conducted between 2002 and 2006 which reported that the median age on the onset of disease was 37 years.[7] A recent Iraqi study indicated that 216 CML patients attended the National Center of Hematology between 2005 and 2020; the mean age at diagnosis was in the final years of the fourth decade of life.[22] In neighboring Jordan, a study underscored a comparable trend, revealing that the mean age of CML patients at the onset of disease was in the fifth decade of life.[23] Similarly, a 2022 study involving 801 CML patients in Tunisia found that the average age at diagnosis was 47 years.[8] Additionally, in Brazil, CML patients were typically diagnosed in their fifth decade.[24] In contrast, reports from the United States show a significantly higher median age at diagnosis for CML, which is 65 years.[25] These collective observations underscore the variability in age at the time of diagnosis across diverse geographical and demographic contexts shedding light on the epidemiological characteristics in distinct populations.

Additionally, the present study determined a male-to-female ratio of 1.6:1 among CML patients, as elucidated in Table 1. This finding aligns harmoniously with multitude of prior studies which consistently indicating a higher incidence of CML among males.[7,8] Moreover, a study conducted in the United States reported a slightly elevated prevalence in males with a male-to-female ratio of 1.4:1.[25] Conversely, an Iraqi study assessed 216 CML patients and found that 163 are still alive, while 53 have unfortunately passed away. The study observed a slightly higher proportion of female patients overall, with a male-to-female ratio of 1:1.16 among all patients and 1:1.76 among surviving patients. However, the deceased group had a reverse ratio of 3.41:1, favoring males.[22] These findings confirm the demographic factors in shaping the gender distribution of CML cases.

In concerning with treated CML patients in the present study, 20 individuals received imatinib treatment while the other 20 patients were administered nilotinib, as delineated in Figure 2. Imatinib operates as a protein-TKI that inhibits the BCR-ABL tyrosine kinase, selectively targets c-Kit, Abl, and "platelet-derived growth factor receptor."[26] Imatinib treatment, as a front-line therapy in patients with chronic phase of CML, has been associated with high rates of complete cytogenetic and major molecular response (MMR).[27] However, nilotinib is a new oral TKIs, rationally designed to overcome imatinib

Table 2: Red blood cell indices in different groups of patients and control

RBC indices	Reference	Control C ($n=20$)	Patients		*P*
			T0 ($n=20$)	T+($n=40$)	
Count ($\times10^{12}$/L)					
Male	4.2–5.8	4.3±0.3	4.7±0.4	4.8±0.7	0.157
Female	3.5–5	4.3±0.2	4.1±0.3	4.4±0.3	0.193
Hb (g/dL)					
Male	12–16	12.9±0.9	13.2±1.2	14±1.7	0.121
Female	11–15	12.7±0.3[a]	11.4±1.5[b]	12.5±0.7[a,b]	0.023
Hct (%)					
Male	38–54	39.2±2.6	40.9±3.1	41.5±4.9	0.362
Female	37–47	38.9±1.2	35.5±5.7	37.7±1.9	0.158
MCV (fl)	80–100	89.9±3.4	86.8±5.8	86.7±4.8	0.084
MCHC (g/dL)	32–36	32.7±0.5	32.8±1.9	33.4±0.7	0.076
RDW (%)	11–16	13.1±0.5[b]	20.4±4.0[a]	13±0.8[b]	<0.0001

Different small letters indicate significant difference between columns. RBC: Red blood cell, Hb: Hemoglobin, MCV: Mean corpuscle volume, MCHC: Mean corpuscle hemoglobin concentration, Hct: Hematocrit, RDW: Red blood cell distribution width

Table 3: White blood cell and platelet parameters in different groups of patients and control

Parameters ($\times10^9$/L)	Reference	Control ($n=20$)	Patients		*P*
			T0 ($n=20$)	T+($n=40$)	
WBC total count ($\times10^9$/L)	4–12	7.5±1.4[b]	156.8±90.4[a]	7.4±2.8[b]	<0.0001
N ($\times10^9$/L)	2–7	4.5±1.02[b]	125.4±73.1[a]	4.2±2.1[b]	<0.0001
L ($\times10^9$/L)	0.8–4	2.4±0.46[b]	16.6±11.5[a]	2.4±0.74[b]	<0.0001
E ($\times10^9$/L)	0.02–0.5	0.13±0.09[b]	2.4±1.7[a]	0.29±0.19[b]	<0.0001
B ($\times10^9$/L)	0–0.2	0.021±0.013[b]	0.365±0.746[a]	0.053±0.065[b]	0.008
M ($\times10^9$/L)	0.12–1.2	0.45±0.08[b]	1.5±0.92[a]	0.44±0.24[b]	<0.0001
NLR	NA	1.87±0.37[b]	8.13±5.5[a]	1.80±0.73[b]	<0.0001
Plt count ($\times10^9$/L)	100–400	241±45.4[b]	347±143[a]	292±72[b]	0.004
PLR	NA	102±27[b]	31±24[c]	130±43[a]	<0.0001

Different small letters indicate significant difference between columns. NLR: Neutrophil/lymphocyte ratio, PLR: Platelet lymphocyte ratio, NA: Not available, WBC: White blood cell

resistance in CML.[28,29] Although there are no significant safety differences between the two drugs, Zhang *et al*. demonstrated that nilotinib is more effective than imatinib in treating CML. Additionally, Yu *et al*. found that nilotinib achieves cytogenetic and molecular responses more quickly and thoroughly.[30,31] Since the ultimate goal of CML treatment is to minimize long-term toxicities and maximize deeper remissions in order to achieve treatment-free remissions,[32] the treatment of newly diagnosed chronic phase CML with nilotinib has resulted in a higher rate of MMR and "complete cytogenetic response" compared to imatinib but at a higher cumulative cost.[33]

In concerning to the results obtained from CBC, this study elucidates that the majority of RBC indices in both patient and control groups fall within normal range and without significant difference. However, RDW% in newly diagnosed patients was significantly higher compared to treated patients and the control group, exceeding the normal upper limit of 20.4%, as shown in Table 2. This pronounced elevation in RDW% is indicative of a condition known as anisocytosis where a substantial majority (80%) of newly diagnosed patients manifest a discernible heterogeneity in the size and volume of their RBCs, as shown in Figure 3. As is well known, anisocytosis is defined as the presence of RBCs with significant heterogeneity in size and volume in the peripheral blood. Anisocytosis may arise from a spectrum of pathological conditions including "congenital erythrocyte disorders" (like β-thalassemia, sickle cell disease, and hereditary spherocytosis), anemia (due to iron, folate, or Vitamin B deficiencies), some forms of hemolytic anemia, oxidative stress, inflammation, and impaired renal function.[34] Therefore, it can be inferred that RDW serves as more accessible, rapid, and cost-effective diagnostic test compared to other potentially useful biomarkers.[35] In line with this, several studies demonstrated that the stratification of CML patients based on their RDW value can offer a valuable insight into prognosis, survival outcomes, and progression to advanced stage of the disease. This stratification is beneficial to subsequent treatment and to avoid CML-CP transforming into more advanced phase.[36] Furthermore, a retrospective study conducted by Mao *et al.,* 2021, showed that high RDW at the time of diagnosis could predict poor prognosis of CML-CP and RDW was associated with treatment responses, ultimately establishing it as a better predictor of prognosis when compared

to other laboratory parameters in the general population.[37] Lippi *et al.* reported that a higher RDW% is linked to a higher risk of mortality since there is a positive correlation between the RDW% and a number of inflammatory markers.[38] Additionally, according to Demirkol *et al.*, inflammation impairs erythropoiesis and alters RBC maturation, both of which help to raise the percentage of RDW.[39] Consequently, an increased RDW may serve as a link between inflammation and carcinogenesis and be associated with a bad prognosis for cancer patients.[40] Furthermore, Iriyama *et al.* concluded that most cases of CML patients show anisocytosis at diagnosis that improved after TKI treatment and the RDW has an essential role in risk stratification of CML-CP patients for predicting treatment responses and outcomes.[19] Recently, Mao *et al.* in 2021 evaluated the ability of RDW to predict prognosis and treatment response in CML-CP patients, treated with TKIs and demonstrating that high RDW was an adverse predictor of overall survival and progression-free survival.[37]

This study also reveals that the absolute values of total and differential count of WBCs in newly diagnosed patients are higher than the upper limit of their normal range and significantly higher than treated patients and control group. While the platelet counts are within the normal range, there is a significant difference between the patients and the control group [Table 3].

Since CML is a form of malignancy that affects the bone marrow, all newly diagnosed CML patients are presented with high WBCs count, these malignant cells crowd the bone marrow and prevent the production of nonmalignant blood cells. Previously, Hayran *et al.*[41] showed that leucocyte count >18 × 10^9/L along with neutrophil proportion >72.6% is the best combination of peripheral blood counts for predicting CML, so counts above these thresholds should be carefully investigated for CML, particularly the early, chronic phase of the disease, which is usually not associated with any symptoms. However, Schiffer *et al.*[42] demonstrated that lymphocyte count >3.6 × 10^9/L is an indicator of lymphocytosis which can be developed in a minimum of 32% of CML patients and persists for more than 1 year in at least 50% of such patients. As it is well known, the clinical hallmark of CML is the uncontrolled production of maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils.[43] On the other hand, results in Table 3 demonstrated that NLR in newly diagnosed patients (8.13) is significantly higher than those in treated patients and control group (1.80 and 1.87, respectively); however, the values of NLR are decreased in patients treated with both types of drug. The PLR in newly diagnosed patients is significantly lower compared to both treated patients and the control group. A variety of prior studies have reported that higher NLR is correlated with a worse survival outcome, stages of disease, and courses of treatment in both solid tumor and hematopoietic tumor.[44,45] Stefaniuk *et al.* considered NLR as a tumor microenvironment biomarker and can be used as a prognostic factor, not only in solid tumors, but also in hematological malignancies because high NLR reflects a decrease in the number of lymphocytes and an elevated number of neutrophils in tumor microenvironment.[46] In fact, NLR has previously reported as a good prognostic marker of inflammatory conditions[47] and infectious diseases.[48] Moreover, several studies have revealed the significance of NLR as a prognostic factor in patients with solid tumors such as colon cancer,[49] ovarian cancer,[50] gastric cancer,[51] and breast cancer.[52] Furthermore, the role of this ratio has been well confirmed in some hematological malignancies such as diffuse large B-cell lymphoma,[53] Hodgkin lymphoma[54] and multiple myeloma,[55] but until now, the prognostic significance of NLR in leukemias has not been widely reported.[46] Recently, it has been reported that NLR is correlated with prognosis and response to chemotherapy in patients with acute myeloid leukemia.[56] Although many studies have defined the role of platelet-to-lymphocyte in lymphoid malignancies, few applications exist for myeloid neoplasm or hematopoietic stem cell transplantation procedures.[57] For instance, evaluation of inflammatory status in cancerous diseases using some hematological indices including NLR, LMR, or PLR is widely investigated for the prognostic assessment of the patients with numerous tumors because they are low cost and can be easily determined only on the basis of the CBC.[58,59] PLR is widely recognized as a valuable prognostic predictor, especially in solid tumors such as gastric cancer[60] and breast cancer.[61] Recently, Li *et al.* demonstrated that PLR is associated with poor prognosis in the case of acute myeloid leukemia patients and may represent a novel independent prognostic factor.[62]

Conclusion

It can be concluded that RDW monitoring during the therapeutic course proves to be a vital strategy in managing CML. Furthermore, NLR and PLR can represent a simple and inexpensive test that establishes RDW as an indispensable predictive tool. The accessibility and simplicity of the RDW, NLR, and PLR tests make them act as predictive markers to estimate and evaluate the prognosis of CML patients and the degree of response to certain TKI drug.

Acknowledgments

I would like to acknowledge the patients and the control group for their collaboration in acquiring the research samples. I extend my appreciation and gratitude to colleagues and friends in the National Center of Hematology for their help.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Algahtani FH, Alqahtany FS. Evaluation and characterisation of chronic myeloid leukemia and various treatments in Saudi Arabia: A retrospective study. J Infect Public Health 2020;13:295-8.
2. Porazzi P, De Dominici M, Salvino J, Calabretta B. Targeting the CDK6 dependence of Ph+ acute lymphoblastic leukemia. Genes (Basel) 2021;12:1355.

3. Osman AE, Deininger MW. Chronic myeloid leukemia: Modern therapies, current challenges and future directions. Blood Rev 2021;49:100825.
4. Pandrala M, Bruyneel AA, Hnatiuk AP, Mercola M, Malhotra SV. Designing novel BCR-ABL inhibitors for chronic myeloid leukemia with improved cardiac safety. J Med Chem 2022;65:10898-919.
5. Malhotra H, Radich J, Garcia-Gonzalez P. Meeting the needs of CML patients in resource-poor countries. Hematology Am Soc Hematol Educ Program 2019;2019:433-42
6. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). Best Pract Res Clin Haematol 2009;22:295-302.
7. Alameri A, Al-Khudhair M, Batool G, Al-Mudhafer A, Murad N. Epidemiology of chronic myeloid leukemia in Iraqi patients. 14th Congress of the European Hematology Association Abstract Book. Haematologica 2009;94 Suppl 2:578.
8. Menif S, Bettaieb J, Belakhal R, Manai Z, Msaddek F, Elloumi M. Epidemiology of chronic myeloid leukemia in Tunisias. Am J Biomed Sci Res 2022;7:167-70.
9. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, *et al.* Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: Results from the randomized BFORE trial. J Clin Oncol 2018;36:231-7.
10. Bavaro L, Martelli M, Cavo M, Soverini S. Mechanisms of disease progression and resistance to tyrosine kinase inhibitor therapy in chronic myeloid leukemia: An update. Int J Mol Sci 2019;20:6141.
11. Westerweel PE, Te Boekhorst PA, Levin MD, Cornelissen JJ. New approaches and treatment combinations for the management of chronic myeloid leukemia. Front Oncol 2019;9:665.
12. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
13. Gurrea Salas D, Glauche I, Tauer JT, Thiede C, Suttorp M. Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? Ann Hematol 2015;94:1363-71.
14. Lippi G, Dipalo M, Teti L, Cervellin G. Relationship between red blood cell distribution width and prognostic biomarkers in patients admitted to the emergency department with acute infections. Eur J Intern Med 2013;24:e15-6.
15. Mozos I. Mechanisms linking red blood cell disorders and cardiovascular diseases. Biomed Res Int 2015;2015:682054.
16. Seretis C, Seretis F, Lagoudianakis E, Gemenetzis G, Salemis NS. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013;5:121-6.
17. Albayrak S, Zengin K, Tanik S, Bakirtas H, Imamoglu A, Gurdal M. Red cell distribution width as a predictor of prostate cancer progression. Asian Pac J Cancer Prev 2014;15:7781-4.
18. Serden AY, Eryilmaz MA, Aksoy N, Okus A, Unlu Y, Sevinc B. Is early detection of colon cancer possible with red blood cell distribution width? Asian Pac J Cancer Prev 2015;16:753-6.
19. Iriyama N, Hatta Y, Kobayashi S, Uchino Y, Miura K, Kurita D, *et al.* Higher red blood cell distribution width is an adverse prognostic factor in chronic-phase chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. Anticancer Res 2015;35:5473-8.
20. Zhou S, Fang F, Chen H, Zhang W, Chen Y, Shi Y, *et al.* Prognostic significance of the red blood cell distribution width in diffuse large B-cell lymphoma patients. Oncotarget 2017;8:40724-31.
21. Wang J, Xie X, Cheng F, Zhou X, Xia J, Qian X, *et al.* Evaluation of pretreatment red cell distribution width in patients with multiple myeloma. Cancer Biomark 2017;20:267-72.
22. Anwer Ahmed A, Khaleel KJ, Abbas Fadhel A, Laftaah Al-Rubaii BA. Chronic myeloid leukemia: A retrospective study of clinical and pathological features. Rev Bionatura 2022;7:41.
23. Awidi A, Abbasi S, Alrabi K, Kheirallah KA. Generic imatinib therapy among Jordanians: An observational assessment of efficacy and safety in routine clinical practice. Clin Lymphoma Myeloma Leuk 2017;17:e55-61.
24. Godoy CR, Levy D, Giampaoli V, Chamone DA, Bydlowski SP, Pereira J. Circulating endothelial cells are increased in chronic myeloid leukemia blast crisis. Braz J Med Biol Res 2015;48:509-14.
25. Mandal A. Chronic Myelogenous Leukemia Epidemiology. Iraq: News-Medical; 2023.
26. Iqbal N, Iqbal N. Imatinib: A breakthrough of targeted therapy in cancer. Chemother Res Pract 2014;2014:357027.
27. Pavkovic M, Angelkovic R, Popova-Simjanovska M, Genadieva-Stavric S, Cevreska L, Stojanovic A, *et al*. Molecular response in patients with chronic myeloid leukemia treated with imatinib – Single centre experience. Prilozi 2015;36:179-86.
28. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD. AMN107 (nilotinib): A novel and selective inhibitor of BCR-ABL. Br J Cancer 2006;94:1765-9.
29. le Coutre P, Ottmann OG, Giles F, Kim DW, Cortes J, Gattermann N, *et al.* Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. Blood 2008;111:1834-9.
30. Zhang BS, Chen YP, Lv JL, Yang Y. Comparison of the efficacy of nilotinib and imatinib in the treatment of chronic myeloid leukemia. J Coll Physicians Surg Pak 2019;29:631-4.
31. Yu L, Qin YZ, Lai YY, Shi HX, Huang XJ, Hou Y, *et al.* Comparison of nilotinib versus imatinib as frontline therapy in newly diagnosed patients with chronic myeloid leukemia in chronic phase. Zhonghua Xue Ye Xue Za Zhi 2019;40:996-1002.
32. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, *et al.* European leukemianet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-84.
33. Ibrahim A, Moukalled N, Mahfouz R, El Cheikh J, Bazarbachi A, Abou Dalle I. Safety and efficacy of elective switch from nilotinib to imatinib in newly diagnosed chronic phase chronic myeloid leukemia. Clin Hematol Int 2022;4:30-4.
34. Lippi G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width and cardiovascular disorders. Does it really matter which comes first, the chicken or the egg? Int J Cardiol 2016;206:129-30.
35. Lippi G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation. World J Cardiol 2019;11:292-304.
36. Li T, Li X, Chen H, Huang KZ, Xie Q, Ge HY, *et al.* Higher red blood cell distribution width is a poor prognostic factor for patients with chronic myeloid leukemia. Cancer Manag Res 2021;13:1233-43.
37. Mao XL, Xi YM, Li ZJ, Jia MF, Li M, Wang LN, *et al.* Higher red blood cell distribution width at diagnose is a simple negative prognostic factor in chronic phase-chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: A retrospective study. Medicine (Baltimore) 2021;100:e24003.
38. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
39. Demirkol S, Balta S, Cakar M, Unlu M, Arslan Z, Kucuk U. Red cell distribution width: A novel inflammatory marker in clinical practice. Cardiol J 2013;20:209.
40. Ai L, Mu S, Hu Y. Prognostic role of RDW in hematological malignancies: A systematic review and meta-analysis. Cancer Cell Int 2018;18:61.
41. Hayran M, Koca E, Haznedaroglu IC, Unsal I, Durgun B, Guvenc F, *et al.* Predicting chronic leukaemias from assessment of complete peripheral blood counts. J Int Med Res 2006;34:640-7.
42. Schiffer CA, Cortes JE, Hochhaus A, Saglio G, le Coutre P, Porkka K, *et al.* Lymphocytosis after treatment with dasatinib in chronic myeloid leukemia: Effects on response and toxicity. Cancer 2016;122:1398-407.
43. Al Ghasham NS. Neutrophilic-chronic myeloid leukemia: A case report. Int J Health Sci (Qassim) 2015;9:87-90.
44. Song Y, Yang Y, Gao P, Chen X, Yu D, Xu Y, *et al.* The preoperative neutrophil to lymphocyte ratio is a superior indicator of prognosis compared with other inflammatory biomarkers in resectable colorectal cancer. BMC Cancer 2017;17:744.
45. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020;18:360.
46. Stefaniuk P, Szymczyk A, Podhorecka M. The neutrophil to lymphocyte and lymphocyte to monocyte ratios as new prognostic factors in

hematological malignancies – A narrative review. Cancer Manag Res 2020;12:2961-77.
47. Sarikaya M, Dogan Z, Ergul B, Filik L. Neutrophil-to-lymphocyte ratio as a sensitive marker in diagnosis of celiac disease. Ann Gastroenterol 2014;27:431-2.
48. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CP, *et al.* The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. J Infect 2019;78:339-48.
49. Absenger G, Szkandera J, Stotz M, Postlmayr U, Pichler M, Ress AL, *et al.* Preoperative neutrophil-to-lymphocyte ratio predicts clinical outcome in patients with stage II and III colon cancer. Anticancer Res 2013;33:4591-4.
50. Williams KA, Labidi-Galy SI, Terry KL, Vitonis AF, Welch WR, Goodman A, *et al.* Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. Gynecol Oncol 2014;132:542-50.
51. Sun X, Liu X, Liu J, Chen S, Xu D, Li W, *et al.* Preoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio in predicting survival for patients with stage I-II gastric cancer. Chin J Cancer 2016;35:57.
52. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: A systematic review and meta-analysis. Breast Cancer Res 2017;19:2.
53. Mu S, Ai L, Fan F, Qin Y, Sun C, Hu Y. Prognostic role of neutrophil-to-lymphocyte ratio in diffuse large B cell lymphoma patients: An updated dose-response meta-analysis. Cancer Cell Int 2018;18:119.
54. Dogan A, Demircioglu S. Assessment of the neutrophil-lymphocyte ratio in classic Hodgkin lymphoma patients. Pak J Med Sci 2019;35:1270-5.
55. Zeng Q, Liu Z, Li Q, Liu T. Prognostic value of neutrophil to lymphocyte ratio and clinicopathological characteristics for multiple myeloma: A meta-analysis. Medicine (Baltimore) 2018;97:e12678.
56. Zhang Q, Yang Q, Weng Y, Huang Z, Chen R, Zhu Y, *et al.* Neutrophil-to-lymphocyte ratio correlates with prognosis and response to chemotherapy in patients with non-M3 de novo acute myeloid leukemia. Transl Cancer Res 2021;10:1013-24.
57. Mulas O, Mola B, Madeddu C, Caocci G, Macciò A, Nasa G. Prognostic role of cell blood count in chronic myeloid neoplasm and acute myeloid leukemia and its possible implications in hematopoietic stem cell transplantation. Diagnostics (Basel) 2022;12:2493.
58. Yang YT, Jiang JH, Yang HJ, Wu ZJ, Xiao ZM, Xiang BD. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival compared to established biomarkers in HCC patients undergoing liver resection. Sci Rep 2018;8:2535.
59. Sun Y, Zhang L. The clinical use of pretreatment NLR, PLR, and LMR in patients with esophageal squamous cell carcinoma: Evidence from a meta-analysis. Cancer Manag Res 2018;10:6167-79.
60. Hirahara T, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, *et al.* Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer 2019;19:672.
61. Chen L, Kong X, Yan C, Fang Y, Wang J. The research progress on the prognostic value of the common hematological parameters in peripheral venous blood in breast cancer. Onco Targets Ther 2020;13:1397-412.
62. Li Y, Wang S, Xiao H, Lu F, Zhang B, Zhou T. Evaluation and validation of the prognostic value of platelet indices in patients with leukemia. Clin Exp Med 2023;23:1835-44.