Clinico-Hematological Profile in Patients with Chronic Myeloid Leukemia

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a clonal malignant neoplasms of pluripotent hematopoietic stem cell described by the excessive proliferation of mature granulocytes and their precursors in the bone marrow and peripheral blood. It is characterized by the presence of Philadelphia chromosome, a translocation between chromosome 9 and 22 or BCR-ABL1 gene.

Objectives: To evaluate clinical and hematological parameters in patients with chronic myeloid leukemia and to assess the risk stratification of these patients according to Sokal and European Treatment Outcome Study (EUTOS) scoring systems.

Setting: This case series study conducted at Ibn-Sina Teaching Hospital/Outpatients Hematology Department from November 2019 to April 2020.

Patients and methods: Total seventy patients with chronic myeloid leukemia included in this study. They involved 64 old cases and 6 new cases. The records of old cases were reviewed for clinical history, clinical examination, previous blood counts, bone marrow study and genetic study, where ever it was available. For new cases clinical history and physical examinations were noted. Complete blood pictures, biochemical tests and molecular study (BCR-ABL) were done at private laboratory. The BCR-ABL done by real-time reverse transcription polymerase chain reaction using Xpert BCR-ABL Ultra test on Cepheid GeneXpert® Dx System. All patients were categorized into different risk groups by using Sokal and European Treatment Outcome Study scores that calculated according to standard formulae.

Results: The males were (57.1%) of patients and females were (42.9%) with male to female ratio was 1.33:1, their age ranged from 16-82 years with a mean of 41.9 years. The most common complains were fatigue (87.1%), fullness in the abdomen (78.6%) and constitutional symptoms (64.3-74.3%). About 96% of patients had splenomegaly at presentation. The mean total leucocyte count was 153.7 $x10^9$/L, basophilia found in (72.9%) of patients and anemia in (85.7%) of them. By Sokal score, (25.7%) of patients were categorized as low risk, (52.8%) as intermediate risk and (21.4%) as high risk. According to EUTOS score, (60%) of patients were categorized as low risk, while (40%) of them as high risk. There were significant differences in high and low risk groups between two scoring systems (P-values 0.016, 0.000).

Conclusion: Middle age groups (35-54 years) were commonly affected by chronic myeloid leukemia and males were predominance over females. Fatigue, fullness in the abdomen were the most common complains, while splenomegaly was the most common clinical sign. Majority of the patients, when categorized by the Sokal score, fall under the low- and intermediate-risk groups, the same is true for the EUTOS score, which, however, does not have an intermediate risk category.

Keywords: chronic myeloid leukemia ; clinical parameters; hematological parameters; EUTOS; Sokal .

الملف السريرى المختبرى لدى المرضى المصابين بسرطان الدم النقوى المزمن

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الخلاصة

الخلفية: سرطان الدم النقوي المزمن (CML) هو أورام خبيثة نسيلي من الخلايا الجذعية المكونة للدم متعددة القدرات التي تتصف بالانتشار المفرط للخلايا الحبيبية الناضجة وسلائفها في نخاع العظام والدم المحيطي. يتميز بوجود كروموسوم فيلادلفيا ، وهو انتقال بين الكروموسوم ٩ و ٢٢ أو جين BCR-ABL1.

الأهداف: لتقييم المعايير السريرية والدموية في المرضى الذين يعانون من سرطان الدم النخاعي المزمن (CML) ولتقييم طبقات المخاطر لهؤلاء المرضى وفقًا لأنظمة تسجيل نتائج دراسة سوكال والأوروبية (EUTOS).

المكان والزمان: اجريت دراسة سلسلة الحالات هذه في مستشفى ابن سينا التعليمي/ قسم امراض الدم في العيادة الخارجية من شهر نوفمبر ٢٠١٩ الى أبريل ٢٠٢٠ .

طرق البحث: تضمنت هذه الدراسة ٧٠ مريضا مصابا بسرطان الدم النقوي المزمن, كان ٦٤ منهم حالة قديمة و٦ حالات جديدة. تم مراجعة سجلات الحالات القديمة من حيث الملاحظات السريرية والفحص السريري, تعداد الدم السابق, دراسة نخاع العظم والدراسة الجينية حيثما كانت متاحة. اما بالنسبة للحالات الجديدة فقد تم تدوين التاريخ السريري والفحص السريري وتم اجراء فحص صورة الدم , الاختبارات الكيميائية الحيوية والدراسة الجينية في مختبر خاص. يتضمن الفحص الجيني فحص BCR-ABL الذي تم اجرائه عن طريق تفاعل البوليمراز المتسلسل في الوقت الحقيقي باستخدام Xpert BCR-ABL على نظام Cephid. تم تصنيف جميع المرضى إلى مجموعات خطر مختلفة باستخدام درجات دراسة نتائج سوكال والأوروبية التي تم حسابها وفقًا للصيغ القياسية.

النتائج: كان الذكور (٥٧.١٪) من المرضى والإناث (٤٢.٩٪) وكانت نسبة الذكور إلى الإناث ١.٣٣: ١ وأعمارهم تتراوح بين ١٦-٨٢ سنة بمتوسط ٤١.٩ سنة. كانت الشكاوى الأكثر شيوعًا هي التعب والامتلاء في البطن والأعراض البنيوية. حوالي ٩٦ ٪ من المرضى يعانون من تضخم الطحال في وقت التشخيص. كان متوسط عدد الكريات البيض الكلي ١٥٣.٧ × ١٠ ^{٩} / لتر ، ولوحظت زيادة في الخلايا القاعدية لدى (٧٣ ٪) من المرضى وفقر الدم في (٨٥.٧ ٪) منهم. حسب درجة سوكال ، تم تصنيف (٢٥.٧٪) من المرضى على أنهم منخفضو الخطورة، (٥٢.٨٪) على أنهم متوسطو الخطورة و (٢١.٤٪) على أنهم ذات خطورة عالية. وفقًا لدرجة EUTOS ، تم تصنيف (٦٠٪) من المرضى على أنهم منخفضو الخطورة ، بينما (٤٠٪) منهم عالي الخطورة. كانت هناك فروق ذات دلالة إحصائية في مجموعات المخاطر العالية والمنخفضة بين نظامي تسجيل (P-values 0.016, 0.000).

الاستنتاج: تأثرت الفئات العمرية المتوسطة (٣٥-٥٤ سنة) بشكل شائع بسرطان الدم النقوي المزمن. كان التعب والامتلاء في البطن من أكثر الشكاوى شيوعًا ، في حين كان تضخم الطحال هو أكثر العلامات السريرية شيوعًا. غالبية المرضى، عند تصنيفهم حسب درجة سوكال ، يندرجون تحت المجموعات ذات المخاطر المنخفضة والمتوسطة ، وينطبق الشيء نفسه على درجة EUTOS ، والتي ، مع ذلك ، لا تحتوي على فئة مخاطر متوسطة.

الكلمات المفتاحية: سرطان الدم النقوي المزمن, المعايير السريرية, المعايير الدموية, نظام EUTOS وSokal .

INTRODUCTION

Chronic myeloid leukemia is the most common type of the myeloprofilerative neoplasms (MPNs) described by overproduction of mature and immature blood cells in the peripheral blood, spleen and bone marrow [1]. It associated with reciprocal translocation between chromosome 9 and 22 which is cytogenetically noticeable as Philadelphia chromosome (Ph) [2] , consequences in a fusion *BCR- ABL* [3] . The outcome of this fusion *BCR-ABL* gene is a constitutively active tyrosine kinase protein, *p210 BCR- ABL,* resulting in the stimulation of numerous downstream signals that transmute hematopoietic stem cells, encourages cellular growing and overwhelms apoptosis, changes adhesion of the cell to bone marrow stroma and induces genetic instability [2,4-6] . Positive *BCR-ABL* cells are unbalanced predisposed to develop numerous heterogeneous genomic aberrations, leading to the evolution from chronic phase to accelerated and blast phases as a result of alteration in the leukemic phenotype from chronic to acute [7] . Chronic myeloid leukemia records around 15% of totally leukemia cases in adult [8] . The average age at the time of diagnosis varies between sixty and sixty five years [9] , 10% of CML patients are children and adolescents [10] , It is slightly higher in males than females [11] .

Various prognostic systems have been used to stratify the risk of patients with CML, from which Sokal score and newly established scoring system named the EUTOS score [12,13] . These systems can guide treatment decisions, also useful for predicting survival in patients receiving tyrosine kinase inhibitors (TKIs) and cytogenetic response to treatment [12,17] . The Sokal score is based on age, spleen size, and peripheral blood platelet count and blast count. Patients are classified as being high-risk (Sokal score >1.2), intermediate-risk (0.8 to 1.2), or low-risk (<0.8) [14-16] . While

EUTOS score is based on the percentage of basophils in the peripheral blood and the spleen size at diagnosis, the patients are classified as a high risk (EUTOS score of ≥87 %) or low risk (<87%) [17].

AIMS OF STUDY

1.To evaluate the hematological parameters of cases with CML and their clinical manifestation.

2. To assess the risk stratification of CML patients using Sokal and EUTOS scoring systems.

PATIENTS AND METHODS

This case series study was conducted on seventy patients with CML (6 new cases and 64 old cases) at Ibn-Sina Teaching Hospital/ Outpatient Hematology Department from November 2019 to April 2020. The records of old cases were reviewed for clinical notes, clinical examination, previous blood counts, bone marrow study and genetic study, where ever it was available. For new cases clinical history and physical examinations were noted, complete blood pictures, biochemical testes and genetic study were done at private laboratory.

Ten mLs of venous blood were aspirated from patients (new cases) by clean venipuncture and delivered into sterile EDTA tubes (3ml), then stored at 4◦C to be used within three days for molecular study, second EDTA tubes (2ml) for doing complete blood pictures using (NIHON KOHDEN and Hycount 3N Hycel Coulter counter) and (5mls) in gel tubes for biochemical tests.

Stratification of risk groups calculated using the following formula. The Sokal score formula is as follows: Exp [0.0116 x (age in years - 43.4) + 0.0345 x (spleen size cm below costal margin - 7.51) + 0.188 x (platelet count ⁄ 700)^2 - 0.563) + 0.0887 x (blast cell % in peripheral blood - 2.10)] [(24)], while EUTOS score formula is (7 x basophils % in peripheral blood) + (4 x spleen size cm below costal margin) [17] .

Molecular Study for BCR-ABL1 Translocation

Done by real-time reverse transcription polymerase chain reaction using Xpert BCR-ABL Ultra test on Cepheid GeneXpert® Dx System. The procedure was done according to instruction of the kit.

The results are interpreted automatically by the GeneXpert system from measured fluorescent signals and embedded calculation algorithms that are shown in the View Results window [18,19] .

RESULTS

A total of 70 patients with documented CML were enrolled in this study. Their ages ranged between 16 and 82 years, mean age was 41.9 years. Forty (57.1%) were males with mean age 38.6 ranged from 16-72 years and 30 (42.9%) were females with mean age 46.3 ranged from 18-82 years. Male :Female ratio was 1.33:1. Overall most common age group affected was between 35-54 years (Figure 1).

The most common complain among males was fatigue, followed by fullness in the abdomen and constitutional symptoms, while in females the more common complain was bone pain. Among the enrolled CML patients: 67 patients (95.7%) had splenomegaly at the time of presentation while hepatomegaly found in 15 patients (21.4%) only (Table 1).

The mean total leucocyte counts was 153.7x10^9/L ranged from 29- 436 x 10^9/L. Twenty four patients (34.3 %) had neutrophilia and 51(72.9 %) had basophilia. The majority of immature WBCs in the peripheral blood were myelocytes and metamyelocytes (Table 2). Sixty patients (85.7 %) had anemia, 35 of them were males (50%) and 25 were females (35.7%), normochromic normocytic type was the most common. Thrombocytosis had been observed in 15 (21.2 %) of patients. The mean LDH level was 792 U/L with a range of 312-1812 U/L, seven patients (10%) had elevated serum LDH level. The mean uric acid was 4.8 mg/dl with a range of 2-12.6 mg/dl, serum uric acid was increased in eleven (15.7%) of cases. (normal range of serum uric acid is 3.5-7.2 mg/dl in males and 2.6-6 mg/dl in females, while normal LDH levels range from 140-280 unit/liter U/L).

The results of bone marrow examination of 46 CML patients were available, 44 (95.7 %) of them were in chronic phase while 2 (4.3 %) patients were in accelerated phase at the time of diagnosis. All patients had hypercellular bone marrow with myeloid hyperplasia, the higher level of Myeloid / Erythroid ratio was 30/1. The erythropoiesis was decreased in 17 patients (36.9 %), while megakaryopoiesis was increased in 8 of them (17.4 %).

By Sokal score, 18(25.7%) of patients were categorized as low risk , 37(52.8%) as intermediate risk and 15(21.4%) as high risk . By EUTOS score, 42(60%) of patients were categorized as low risk, while 28(40%) of them as high risk. There were significant differences in high and low risk groups between two scoring systems (P-values 0.016, 0.000).

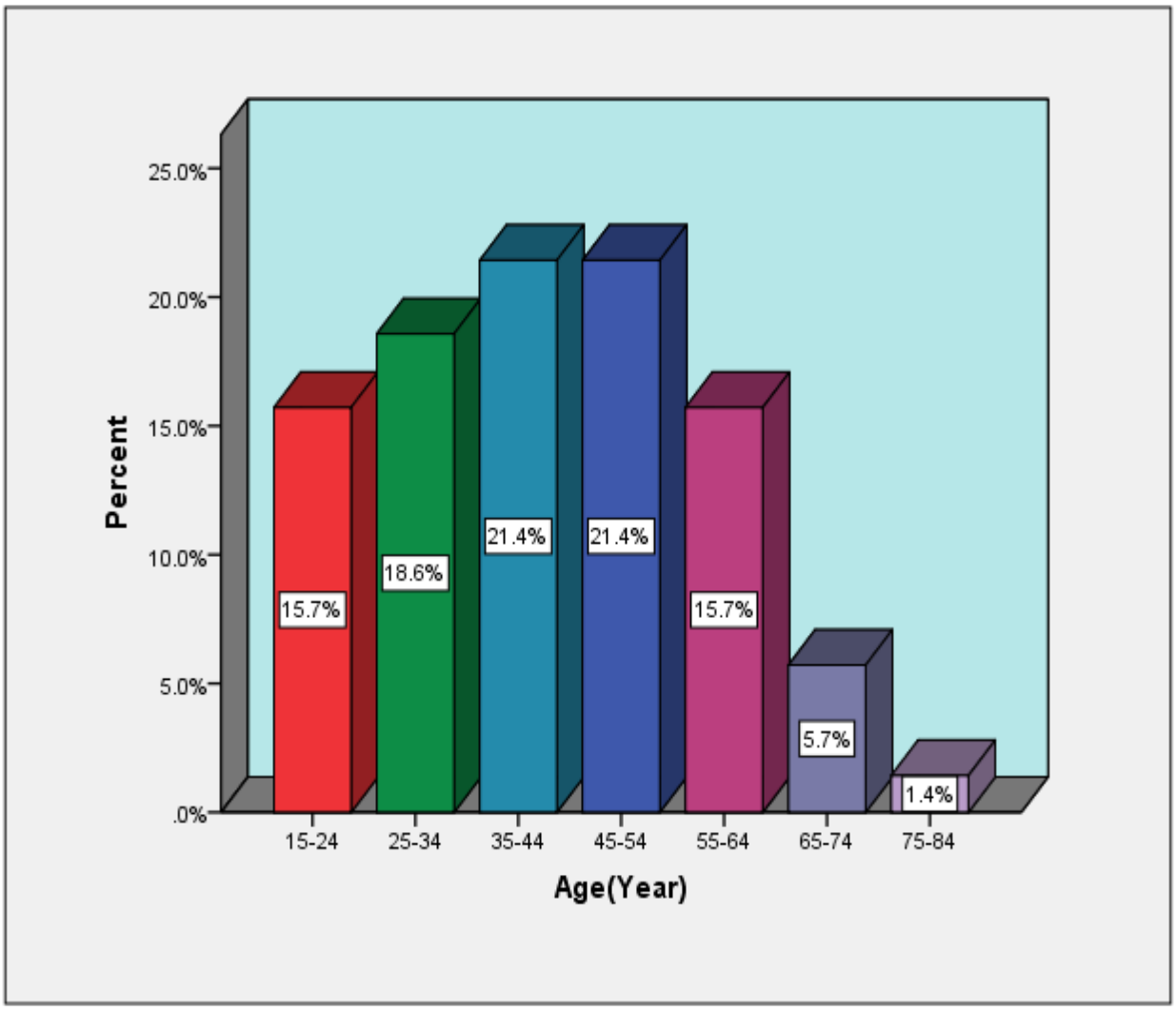

Figure 1: Age distribution of patients with CML

Table (1) : Symptomatic presentation and clinical observation of patients with CML

		Sex		Total (n=70)
		Male(n=40)	Female(n=30)	
Fatigue	Number	32	29	61
	% of Total	45.7%	41.4%	87.1%
Palpitation	Number	14	16	30
	% of Total	20.0%	22.9%	42.9%
Dyspnea	Number	10	14	24
	% of Total	14.3%	20.0%	34.3%
Headache	Number	14	22	36
	% of Total	20.0%	31.4%	51.4%
Dizziness	Number	19	20	39
	% of Total	27.1%	28.6%	55.7%
Blurred vision	Number	15	13	28
	% of Total	21.4%	18.6%	40.0%
Burning pain in hands and feet after hot bath	Number	8	13	21
	% of Total	11.4%	18.6%	30.0%
Thrombosis	Number	0	2	2
	% of Total	0.0%	2.9%	2.9%
Bleeding	Number	11	11	22
	% of Total	15.7%	15.7%	31.4%
Pruritus	Number	8	9	17
	% of Total	11.4%	12.9%	24.3%
Bone pain	Number	21	27	48
	% of Total	30.0%	38.6%	68.6%
Fullness in the abdomen	Number	30	25	55
	% of Total	42.9%	35.7%	78.6%
Left hypochondrial pain	Number	8	4	12
	% of Total	11.4%	5.7%	17.1%
Fever	Number	27	19	46
	% of Total	38.6%	27.1%	65.7%
Night sweats	Number	26	19	45
	% of Total	37.1%	27.1%	64.3%
Weight Loss	Number	29	23	52
	% of Total	41.4%	32.9%	74.3%
Anorexia	Number	29	20	49
	% of Total	41.4%	28.6%	70.0%
Pallor	Number	35	25	60
	% of Total	50.0%	35.7%	85.7%
Splenomegaly	Number	37	30	67
	% of Total	52.9%	42.9%	95.7%
Hepatomegaly	Number	9	6	15
	% of Total	12.9%	8.6%	21.4%

Table (2) : Hematological parameters for patients with CML

	Sex								
	Male (n=40)			Female (n=30)			Total (n=70)		
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
HB g/dl	10.4	6.3 - 16.0	2	9.8	7 – 14.3	1.7	10.1	6.3 – 16	1
HCT %	31.7	19 – 48	6.3	30.3	20.4 – 45	5.5	31.1	19 – 48	6
RBC 10^6/Ml	5.2	2.4 – 31.3	6.8	3.6	2.7 – 5.8	.6	4.2	2.4 – 31.3	4.4
MCV fl	85.4	29.7 – 114.8	18.2	86	64 -119.3	12.3	85.7	29.7-119.3	15.1
MCH Pg	30.7	26 – 38.3	3.2	28	19.5 -35.5	3.7	29.2	19.5 -38.3	3.7
MCHC g/dl	34.4	26.3 – 45.5	4.2	33.5	25.2- 46.4	5.2	33.9	25. - 46.4	4.7
WBC 10^9/L	162.1	36 – 436	96.1	142.4	29 – 365	79.4	153.7	29 - 436	89.2
Neutrophils %	53.3	15 – 88	18.4	55.5	11 – 80	16.3	54.2	11 – 88	17.4
Lymphocytes %	6.4	1 – 30	6.5	6.9	1 –24	5.2	6.6	1 – 30	5.9
Monocytes %	2.5	.0 – 14	2.6	3.9	.0 – 15	3.9	3.1	.0 – 15.0	3.3
Basophiles %	4.4	.0 – 21	3.9	6.9	.0 – 15	4.9	5.5	.0 – 21.0	4.5
Eosinophils %	3.6	.0 – 23	4.4	3.7	.0 – 11	2.9	3.7	.0 – 23.0	3.8
Promyelocytes %	15.2	3 – 30	7.8	8.5	1 – 22	5.5	12.5	1 – 30	7.6
Myelocytes %	24.3	.0 – 35	9.4	20.9	2 – 44	11.7	22.9	.0 – 44	10.5
Band %	9.0	5 – 17	6.9	28	28 – 28	.	13.8	5 – 28	11.1
Metamyelocytes %	14.8	6 – 28	8.7	14.3	10 – 20	5.1	14.7	6- 28	6.9
Blast %	2.9	1- 6	2	2.3	1 – 6	1.6	2.6	1 – 6	1.8
PLT 10^9/L	359	98 – 1051	198.5	401.3	154 -1188	247.7	377.1	98 – 1188	220.2
MPV fl	7.8	5.7 – 9.9	1.1	8	5.1 – 10.3	1.2	7.9	5.1 – 10.3	1.1
PDW %	15.4	9.2 – 19.7	3.4	15.6	10.3 -18.7	2	15.6	9.2 – 19.7	2.6

(HB: Hemoglobin; HCT: Hematocrit; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; WBC: White blood cell ; PLT: Platelets; MPV: Mean platelets volume; PDW: Platelet distribution width; SD: standard deviation)

DISCUSION

Seventy patients with CML included in this study with mean age was 41.9 years, a higher mean age 54, 50.4 years reported in Iraqi and Indian studies [20,21] , while Iraqi studies in Mosul conducted by AL-Khero, 2018 and AL-Khero, 2004 revealed mean age 41.2, 46.2 years [22,23] , that is consistent with our result. The young age of onset may be attributed to the effect of carcinogenic material and radiation that Iraqi people exposed to it from wars. In the other hand, studies in Iran, Western Libya, Pakistan and India reported mean age of 45.8, 41.8, 39.5 and 38.6 years [24-27] .

Reports from India and Pakistan demonstrated males predominance among the enrolled CML patients with M:F ratio were (1.4:1, 1.6:1) [26,27] . This finding may be due to greater exposure of males to environmental or occupational hazard. Anyway, females were predominate in Libyan study conducted by Jbireal *et al*., 2019 [25] with M:F ratio of 0.6:1.

Majority of CML patients in this study were in the 4th and 5th decade of life that corresponding to study obtained by Gupta and Kanetkar, 2020 [21] **,** who found that (45.94%) of their Indian patients were in the 5th decade.

All CML patients in the present study were symptomatic at the time of presentation and the most common complaint was fatigue (87.1%) followed by fullness in the abdomen (74.3%), constitutional symptoms (weight loss 74.3%, anorexia 70%, fever 65.7% and night sweats 64.3%). This was higher when compared with the Indian study which revealed common presentation were fatigue (62.2%), fever (40.5%) and fullness in the abdomen (35.1%) [21] . Another Indian study revealed fullness in abdomen 66.6%, fever 59%, and fatigue 55.5% [27] , this can be attributed to diverse sample size among studies, environmental factors and late presentation of our patients.

Splenomegaly and anemia were the most common clinical signs in our patients, these findings consistent with that obtained by Kumar *et al*., 2019; Jameel and Jamil, 2006 [27,28] . The Indian study revealed splenomegaly 54% and anemia 13.5% [28] . In the research done by Srinivas *et al*., 2013 [29] , 70% of patients had splenomegaly and 38% of them had anemia, the last two studies are disagree with the present study, this is may be due to late presentation of our patients who had high percentage of splenomegaly and anemia at the time of diagnosis.

Hepatomegaly account 21.4% of our patients, this observation was similar to studies conducted by Gupta and Kanetkar, 2020; Srinivas *et al*., 2013 [21,29] , who reported hepatomegaly in 32.4%, 20% respectively, while Jameel and Jamil, 2006; Kumar *et al*., 2019 [27,28] had revealed hepatomegaly 57%, 58%, this may attributed to larger sample size of this study.

Bleeding was reported in 31.4% of the CML patients, this finding inconsistent with two studies in Pakistan that reported bleeding in 14.4% and 13.4% of cases [26, 30] .

In a large multi-centered French study, at the time of diagnosis, the frequency of chronic phase and accelerated phase were 96.8%, 2.2% [31] , this finding was similar to the current study. However, studies conducted by Ahmed *et al*., 2009 and Kumar *et al*.,2019 [27,32] , reported frequencies of chronic phase 77.8%, 83%, and accelerated phase 15.5%, 12%. The possible explanation can be either, late presentation of the patients in our locality or the natural behavior of disease is different.

In this study, total mean WBCs count, HB and platelets count were 153.7 $x10^9$/L , 12.3 g/dl, 377.1 $x10^9$/L respectively. Majority of patients (72.9%) had basophilia with mean basophiles was 5.5 %. Myelocytes and metamyelocytes were the most common type of immature WBCs in the peripheral blood with mean 22.9 %, 14.7%. In Chang *et al*. study in Pakistan, the mean WBCs, HB and platelets were 121 $x10^9$, 9.5 g/dl, 285 $x10^9$/L respectively, that disagree with our results. In the same study, the myelocytes was the prominent immature WBCs in the peripheral blood with mean was 25 % [26] . Gupta and Kanetkar study,2020 in India [21] showed mean WBCs, HB and platelets were 153.3 $x10^9$/L, 9.7 g/dl, 448 $x10^9$/L, absolute basophilia in the peripheral smear with mean was 3.27%, accordingly mean WBCs and basophilia were shared to our finding. Kumar *et al*., 2019 [27] revealed mean WBCs, HB and platelets were 182 $x10^9$/L, 9.4 g/dl, 328 $x10^9$/L respectively, thus mean platelets agree with that revealed in our study. The same study reported mean basophiles was 5.27 % .

The present study obtained elevated level of mean serum LDH, that attributed to disintegration of an increased number of leucocytes, while mean serum uric acid was found to be reasonable. These findings are similar to study conducted by Gupta and Kanetkar, 2020 [21] .

The six collected new cases in our study had no BM examination, however it is indicated for identification of the disease phase, the presence of myelofibrosis and to determining karyotype of patient [33] **.**

In the current study, a high percentage of patients assign under low and intermediate risk category by using Sokal score, this finding is in line with another studies in Iraq, Turkey, Egypt, India and Nigeria [34-39] , another studies reported a high percentage of patients were under high risk category by the same score [40-42] . This can be explained by ethnic variation, nature of disease and differences in sample size.

A high percentage of patients were under low risk category according to EUTOS score [(39,40)] **,** this is similar to the finding of this study. Other two studies conducted by UZ *et al*., 2013; Elbedewy and Elashtokhy, 2016, which revealed majority of patients were assign under low risk category (88%, 85%) using EUTOS score [35,36] .

The differences in percentage of LR and HR between the two scores can be explained that EUTOS score does not have an intermediate risk category and it depends on two variables only.

CONCLUSION

Most common age groups affected by CML were middle age (35-54 years). Males were more commonly affected than females. Fatigue, fullness in the abdomen and constitutional symptoms were the commonest complains, while splenomegaly and anemia were the most common clinical signs at presentation. Majority of patients had basophilia. By sokal score, most of patients fall under the low- and intermediate-risk categories, the similar is true for the EUTOS score, which, however, does not have an intermediate risk category**.**

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