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Risk Stratification of Chronic Myeloid Leukaemia Patients with ELTS Risk Score at a Tertiary Care Hospital in Bangladesh

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ABSTRACT

Introduction: *Chronic Myeloid Leukaemia (CML) is a myeloproliferative neoplasm characterised by uncontrolled proliferation of white blood cells and its precursors. Various risk scoring systems have been formulated for risk stratification of CML patients at diagnosis. European Treatment Outcome Study (EUTOS) Long Term Survival (ELTS) score has been recommended for use by European LeukaemiaNet.* ***Objective:*** *The objective of the study was to stratify the Chronic Myeloid Leukaemia patients in chronic phase into different risk categories using ELTS scoring system.* ***Materials and Methods:*** *This observational cross-sectional study was conducted among CML patients at Bangabandhu Sheikh Mujib Medical University (BSMMU) between September 2020 and October 2021. A total of fifty adult chronic myeloid leukaemia patients were enrolled using purposive sampling technique. CML patients with confounding comorbidities and CML patients in accelerated and blast phases were excluded. Clinical information and haematological parameters were recorded. Bone marrow study was conducted to confirm phase of the disease. ELTS risk score was calculated, and risk stratification was done. Chi-square test was done to find out statistical association between variables.* ***Results:*** *Among study participants, 14% were identified as high-risk cases using ELTS score. 40% of patients were intermediate-risk and 46% were low-risk disease. Presence of hepatomegaly and splenomegaly were significantly more common among high-risk CML patients. Significantly increased eosinophil percentages and blast percentages and significantly lower haemoglobin level were found in high-risk patients.* ***Conclusion:*** *A fair proportion of the CML patients were identified as high-risk patients. Hepatomegaly, splenomegaly, lower haemoglobin, higher eosinophil and higher blast percentages in peripheral blood were identified to be associated with higher risk status of patients.*

Key words: *Bangladesh, CML, Chronic Myeloid Leukaemia, ELTS score, Risk Stratification*

Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm characterized by the presence of Philadelphia chromosome (Ph). The resultant mutation BCR-ABL[1] mutation underlies the pathophysiology of this disease. The natural history of untreated Chronic Myeloid Leukaemia (CML) consists of a chronic phase (CP), accelerated phase (AP) and blastic phase (BP).[1] If appropriate treatment is not provided, most cases of chronic phase of CML usually progress to blastic Phase (directly or after developing accelerated phase) within 3-5 years after diagnosis.[2] In recent years, prognosis of CML has improved significantly. CML patients now have 10-year overall survival rate of 80-90%.[3]

Four prognostic scoring systems, Sokal, Euro, EUTOS, and ELTS have been formulated for risk categorization of Chronic Phase-Chronic Myeloid Leukaemia (CP-CML) patients at diagnosis.[4-9.] Newer treatment strategies have gradually improved the outcome of CML and CML patients may now expect to have a survival almost similar to general population.[10] The EUTOS Long-Term Survival (ELTS) score (Table-I) was introduced in 2016 as a prognostic tool for patients receiving Tyrosine Kinase Inhibitor (TKI) based therapy. It distinguished three risk groups based upon significant differences in probabilities of dying of CML itself.[11] Several studies have concluded that ELTS score is superior for risk stratification in chronic phase CML patients compared to the Sokal score.[12–13]

Risk stratification of CML patients is important prior to treatment initiation. The European LeukaemiaNet (ELN), in its most recent guideline on CML in 2020, has suggested use of ELTS score as the preferred tool for prognostic risk stratification.[4] Choice of first or newer generation tyrosine kinase inhibitor as initial treatment depends primarily upon risk stratum of the patient while keeping affordability and comorbidities in consideration.[14-16] National Comprehensive Cancer Network in its latest guideline has suggested use of second-generation Tyrosine Kinase Inhibitors for initiating therapy in intermediate and high risk patients based on findings from BFORE, DASISION and ENESTnd trials.[14,17-19] This study aimed to assess the risk of dying from CML itself among patients in chronic phase using The ELTS scoring system.

Methods

The observational cross-sectional study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU) between September 2020 and October 2021. Fifty adult chronic myeloid leukaemia patients irrespective of sex were enrolled in this study. CML patients with confounding comorbidities like Chronic Liver Diseases and CML Patients in Accelerated and Blast Phases were excluded from the study. Purposive sampling technique was used for patient enrolment. Clinical information and haematological parameters were recorded in a pre-designed data collection sheet. Bone marrow examination was done to confirm the phase of the disease. ELTS Risk score was calculated among patients according to the following equation:

ELTS Risk Score11= 0.0025 × (age/10)3 + 0.0615 × spleen size + 0.1052 × peripheral blood blasts + 0.4104 × (platelet count/1000)-0.5

According to ELTS Score, Low Risk, Intermediate Risk and High risk are defined by ELTS Risk Scores of <1.5680, 1.5680 – 2.2185 and >2.2185 respectively.[11]

Risk category was assigned to each individual patients and proportion of high-risk, intermediate-risk and low-risk cases was calculated. Relations between patients' clinical features and haematological parameters were explored. The collected data were analysed with SPSS software for Windows version 26. Association between variables were assessed using chi-square test. Statistical significance was defined as p-value < 0.05.

Results

The mean age of study participants was 38.7 (±14.4) years and median age was 35.5 (IQR 27 – 51) years. Majority belonged to age group of 31 – 45 years. Majority of the study participants (78%) were male, and the rest (22%) were female. Common symptoms of the patients included fatigue, bone pain, weight loss, fever and abdominal lump (Figure-1). About 10% of participants were diagnosed incidentally. Rarely, in 4% of participants, mucosal bleed including gum bleeding was present.

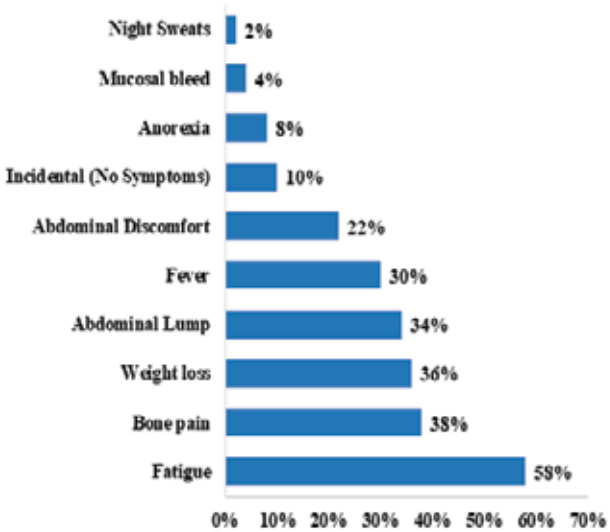

Figure 1: Pattern of Symptoms among Study Participants

On clinical examination, anaemia was found in 86% of participants. 82% and 26% of participants had splenomegaly and hepatomegaly respectively. Median spleen size was 7 cm from left costal margin. Median size of palpable liver was 2.5 cm from right costal margin.

Mean bone marrow blast percentage was 4.7% with a standard deviation of 2.6%. Median White Blood Cell (WBC) count was 212.5 (140.8 - 319) × 10^9/L. Median haemoglobin was 9.6 (IQR 8.6–10.8) g/dL. Median platelet count was 410 (IQR 258.3 – 583.5) ×10^9/L. Median eosinophil and basophil percentage was 2 (IQR 2–4)% and 4 (IQR 2–5)% respectively. Median blast percentage in peripheral blood was 3 (IQR 2–5)%. (Table I)

Table I: Peripheral Blood Parameters in Study Participants

Parameters in Peripheral Blood	Median	Interquartile Range
Haemoglobin (g/dL)	9.6	8.6 – 10.8
WBC Count (× 10^9/L)	212.5	140.8 - 319
Platelet Count (× 10^9/L)	410	258.3 – 583.5
Eosinophil (%)	2	2 - 4
Basophil (%)	4	2 - 5
Blast (%)	3	2 - 5

Study participants were stratified into three risk groups according to ELTS score. Among study participants, 14% were identified as having high risk disease. Two-fifth of participants (40%) had intermediate risk disease and almost half (46%) had low risk disease according to ELTS prognostic scoring system (figure 2).

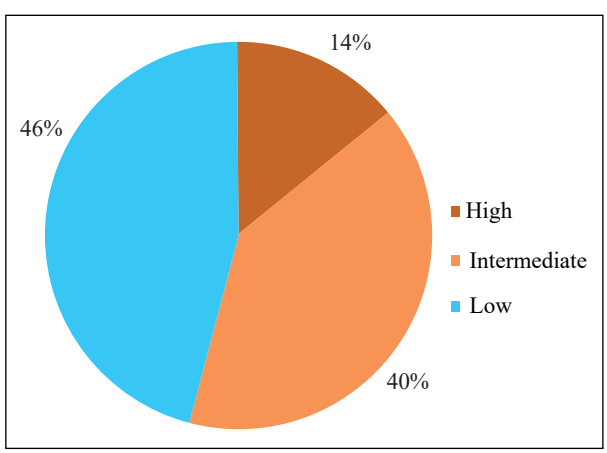

Figure-2: Risk Stratification of Study Participants

Hepatomegaly and Splenomegaly were found more commonly among high-risk patients compared to low-risk patients and the relationships were found to be statistically significant (Table II).

Table-II: Distribution of Clinical Signs among Study Participants in Different ELTS Risk Categories (Number and Percentage)

		ELTS Risk Category			Total	p value
		High	**Intermediate**	**Low**		
Hepatomegaly	Present	3 42.9%	8 40%	2 8.7%	13 26%	0.038[s]
	Absent	4 57.1%	12 60%	21 91.3%	37 74%	
Splenomegaly	Present	7 100%	19 95%	15 65.2%	41 82%	0.024[s]
	Absent	0 0%	1 5%	8 34.8%	9 18%	
Total		**7** **100%**	**20** **100%**	**23** **100%**	**50** **100%**	

High-risk and intermediate-risk patients had relatively higher percentage of eosinophils in peripheral blood compared to low-risk CML patients. Blasts percentage was higher among high-risk patients. Haemoglobin level was lowest among high-risk patients and highest among low-risk patients. These relationships were found to be statistically significant (Table III).

Table-III: Distribution of Haematological Parameters in Participants with Different Risk Categories

	ELTS Risk Category				P-value
	High	Intermediate	Low	Total	
WBC (× 109 / L)	296.7 ± 143.1	259.3 ± 115.9	192.8 ± 132.3	234 ± 131.2	0.098ns
Neutrophil (%)	38.1 ± 9.9	47.3 ± 10.4	50.4 ± 13.6	47.4 ± 12.4	0.071ns
Lymphocyte (%)	6.6 ± 2.3	8.7 ± 4.8	12 ± 8.3	9.9 ± 6.7	0.098ns
Eosinophil (%)	3.3 ± 1.4	3.2 ± 1.5	2 ± 1.8	2.7 ± 1.7	0.042s
Monocyte (%)	2.3 ± 2	3.5 ± 2.3	2.9 ± 2.3	3.1 ± 2.2	0.430ns
Basophil (%)	5.7 ± 2.6	4.1 ± 2.6	3.4 ± 2.2	4 ± 2.5	0.105 ns
Blast (%)	5.4 ± 3	4.3 ± 1.9	2.3 ± 2	3.5 ± 2.4	0.001s
Myelocyte (%)	37.9 ± 8	27 ± 10.1	26.7 ± 14.7	28.4 ± 12.6	0.101 ns
Platelet (× 106 / L)	285 ± 126.8	462.3 ± 233.3	540 ± 338.6	473.2 ± 286	0.114 ns
Haemoglobin (g/dL)	8.3 ± 1.3	9.8 ± 1.4	10.5 ± 2.5	9.9 ± 2.1	0.047 s

s = significant; ns= not significant

Discussion

The age distribution of the participants revealed that a significant proportion of our patients were relatively young. Chronic Myeloid Leukaemia is usually considered more common in sixties and seventies. But, in developing countries, it is more common among relatively younger persons.[2] Our study and a previous study have revealed a similar picture in Bangladesh.[20] The median age of participants in this study was 35.5 years while another study found median age of CML patients in Bangladesh to be 40.20 The Median age of CML patients in neighbouring India was between 38 and 40 years and in Saudi Arabia was 40.21 years.[20-22] CML patients in two studies from China found that median age of CML patients were 40 years and 49 years.[23,24] Our study participants' mean and median age was lower than that found in studies conducted in the western world.[5,19] The median age of CML patients in German and US population was found to be 52 and 60 years respectively.[5,20]

Nonspecific symptoms like fatigue, bone pain, weight loss, and fever were found were more common among symptoms. Hasford J et al. also reported similar symptoms in chronic myeloid leukaemia patients.[7] In his study, Fatigue and general ill feeling was the most common symptoms, present in about 48% of CML population, 22% had organomegaly related complications, 18% had weight loss more than 10% and only 7% had fever.[7] In this study, 58% of participants complained of fatigue, 34% complained of abdominal lump and 22% had abdominal discomfort, 30% complained of fever and 36% complained of weight loss. In this study, only one-tenth of the participants were diagnosed incidentally while doing routine check-up or when undergoing investigations for other health complains. It has been estimated that up to half of the chronic myeloid leukaemia patients in chronic phase are diagnosed incidentally in the United States.[25,26] Among Indian population, <5% CML patients presented without symptoms, while 60% had fever or other constitutional symptoms.[21]

Among clinical signs, splenomegaly and anaemia were very common. Hepatomegaly was found in about one-quarter of the participants in this study. Hasford J. et al.[7] found hepatomegaly in about one third of chronic phase CML patients. Other investigators also found hepatomegaly less commonly among chronic myeloid leukaemia patients in chronic phase than splenomegaly.[25,26] About 93% of Indian CML patients had hepatomegaly, while only 18% of CML patients had hepatomegaly in the United States of America.[21]

Splenomegaly is a relatively common sign for chronic myeloid leukaemia. It also has prognostic value. Majority of prognostic scoring systems utilize maximum spleen size from left costal margin on palpation as one factor in calculation of the risk scores. Splenomegaly can be found in more than half of chronic phase CML patients in western countries.[25,26] Mean and median spleen size in our study participants (7.6 cm) were slightly higher than those found by Hasford J. et al. (5.4 cm).[7] Among Indian CML patients, splenomegaly was found in around 95% of patients, while it was found in 54% of a center in the United States.[21] Among indian population, 33% had massive splenomegaly.[21] Among Chinese CML patients, 62.8% had splenomegaly.[24] Median spleen size was 8 cm below left costal margin among Chinese population.[24] In comparison, Saudi CML patients had median spleen size of 8.33 cm.[22]

CML patients from India had a mean blast percentage of 2%, mean haemoglobin 11.2-11.4 g/dL.[21] CML patients from Saudi arabia had median platelet count 510×10^9 / L, median peripheral blood basophil 1.32%, median blood eosinophil 0.83%, median peripheral blood blasts 1.50%.[22] Among Chinese CML patients, Yang X et al found that median WBC count was 90.57×10^6 / L, median

haemoglobin 10.3 g/dL, median platelet count 473 × 10^9 / L, median basophil 4%, median peripheral blood 0% and median bone marrow blast 3%, while Zhang X et al. found Median haemoglobin 11.5 g/dL, median WBC count 120 × 10^6 / L, median platelet count 406 × 10^9 / L, median blast in peripheral blood 1%, median basophil in blood 4%.[23-24]

Presence of hepatomegaly and splenomegaly was significantly more common among high-risk patients. Haemoglobin level was significantly lower among patients stratified into higher risk categories. Eosinophil and blast percentages in peripheral blood were significantly different across different risk groups. Hasford J et al. found age, spleen size, haemoglobin, white blood cell count, percentages of blasts, promyelocytes, eosinophils and basophils, platelet count, weight loss, hepatomegaly and erythroblasts percentage as independent prognostic factors in univariate analysis.[7]

In this study, 14% cases were identified as high-risk disease, 40% cases as intermediate-risk disease and 46% cases as low-risk disease. ELTS score was utilized to obtain this risk stratification. ELTS scoring system has been recommended as the preferable risk stratification system for chronic phase chronic myeloid leukaemia patients as it reflects the disease related mortality with the most recent management strategies.

Pfirmmann M et al. analysed CML patients treated with imatinib from six clinical trial from ELN/EUTOS CML registry and found that ELTS score stratified 12%, 27% and 61% patients as high-risk, intermediate-risk and low-risk patients respectively compared to 23%, 37% and 40% by using Sokal score.[11] This finding of ELTS risk proportions is comparable to the findings of 14% high-risk patients in this current study. Banjar H and Alsobhi E stratified 95 patients of CML from Saudi Arabia using ELTS score. Proportion of high-, intermediate- and low risk patient was 18%, 26% and 56% respectively.[22] In China, Zhang X et al. found that 9%, 24.9% and 66.1% of CML patients had high-risk, intermediate-risk and low-risk ELTS score, while Yang X et al. found that 13.8%, 36.4% and 49.8% had high-risk, intermediate-risk and low-risk ELTS score.23-24 In 185 Turkish CML patients, the proportion of patients with high-, intermediate- and low-risk ELTS scores were 13.5%, 25.9% and 60.5% respectively.[27]

ELTS score puts less emphasis on patients' age in this era of therapy with TKI and assigns relatively smaller proportion of patients in the high-risk group.4 Wide availability and application of newer treatment strategies have resulted in significant improvement of survival and outdated previous prognostic systems. Therefore, it has become necessary to adopt the most recent and validated scoring system in clinical practice.

Conclusion

Application of ELTS risk score in risk categorization of Chronic Phase Chronic Myeloid Leukaemia patients have identified a fair proportion (14%) of patients as suffering from high-risk disease. Hepatomegaly and splenomegaly were more common among high-risk patients. High-risk patients had significantly higher eosinophil and blast percentage in peripheral blood and significantly lower haemoglobin level. Further study can be undertaken for exploring long term outcome and treatment response among chronic phase- chronic myeloid leukaemia patients of different risk categories.

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Conflicts of Interest

None

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