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To Determine the Prognostic scoring systems (Sokal, Hasford and ELTS) in CML-CP patients and correlation between Haematological parameters

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Abstract:

Introduction: The primary goal of CML management is to stratify patient's risk to identify the most optimal therapeutic regimen. The Sokal, Hasford and ELTS risk ratings were developed to predict patients on treatment. **Aim**: To perform a comparative study of CML prognostic indicators (Sokal, Haslford, and ELTS) at Swami Rama Himalayan University CML-CP patients with their demographical and haematological parameters. **Method:** This is a retrospective study performed on 71 Ph+ CML-CP patients who were never administered imatinib orally and study their demographical and haematological data. 30/71 were females and 41/71 were males with median age 38 years (range 18-75 years). 3(4.22%), 27(38.02%) and 41(57.75) patients were discriminated into low, intermediate and high risk in Sokal score respectively. 12(16.90%), 37(52.11%) and 22(30.99%) patients were discriminated into low, intermediate and high risk of Hasford score respectively and 5(7.04%), 28(39.44%), 38(53.52%) were patients divided into low, intermediate and high respectively of ELTS. **Conclusion**: The study found that Sokal and ELTS significantly predict treatment outcomes for CML-CP patients taking imatinib, and patients aged 20-39 are highly effective.

Keywords: CML Prognosis, CML, Sokal, Hasford, ELTS Scoring system

Introduction

Chronic myeloid leukemia (CML) is a malignancy that develops in the bone marrow's blood-forming cells and spreads throughout the bloodstream. It's also known as Chronic myelogenous leukemia. The World Health Organization (WHO) defines CML as a "Myeloproliferative neoplasm (MPN), " a condition in which the bone marrow produces an excess of white blood cells.(1) New version of classification, MPN comprises eight diseases: CML due to breakpoint cluster region (BCR)-Abelson oncogene (ABL) 1 positive, Chronic eosinophilic leukemia (CEL), Chronic neutrophilic leukemia (CNL), Essential thrombocytosis (ET), Masto cytosis, Polycythemia vera (PV), Primary myelofibrosis (PMF) and unclassified MPN.(2–4) CML is the first neoplasm in humans to be associated with a single, specific, acquired genetic lesion, is one of the best understanding in myeloproliferative disorders at the molecular level.(5,6) At presentation, it has three separate phase: the early chronic phase (CML-CP) has the best results, while the mid-accelerated phase (CML-AP) and the blast phase (CML-BP) have inferior outcomes with conventional therapy.(7)

In CML, the fusion of ABL1 on chromosome 9q34 with the BCR on chromosome 22q11.2 results in translocation t(9;22) (q34;q11.2), which creates a new chromosome known as the Philadelphia chromosome (Ph).(8–10) i.e. ABL1 gene breaks off from chromosome 9 and BCR gene breaks off from chromosome 22 and these two translocate and fuse with each other and make a new oncogene (BCR::ABL1) known as Ph+.(1) This oncogene produce a dysregulated tyrosine kinase.(11) TKI inhibits the enzyme leukemogenic kinase activity of BCR-ABL1 oncoprotein which is responsible for the cell functions, cell signaling, division with growth and this small targeted molecule demonstrated high efficacy and was good tolerated.(1,12) Several TKI are approved for treating CML, with best therapy choice like factor on efficacy, toxicity, tolerability and cost. Currently, there has been a growing emphasis on quality of life, avoiding long-term organ toxicities, and searching new strategies to result of "treatment-free remission" (TFR). Where, participants can stop TKI therapy. However, in resource-poor countries, available to effective drugs and essential monitoring shifts the primary treatment goal to survival.(13) In 2001, United States Food and Drug Administration (FDA) approved the first-generation TKI Imatinib mesylate (Gleevec), second-generation TKI dasatinib (Sprycel) in 2006, nilotinib (Tasingna) in 2007 and bosutinib (Bosulif) in 2012 similarly third-generation drugs is ponatinib (Iclusig) in 2012 for CML treatment. In 2021, Asciminib (Scemlix), which binds to a different part of the Kinase.(1) After using first-generation TKI as first-line treatment, imatinib, significantly improved the survival rate from 57% and 42% to 83-89% when compare with intensive chemotherapy and the interferon.(14–17)

CML is characterized by progressive symptoms, splenomegaly, anemia, and high WBCs counts. Without therapy, it advances over a period of 3-5 years from a CML-CP to CML-AP and finally to a last phase of CML-BP.(18,19) With a median survival of 5-6 years without

treatment, the majority of patients with CML are identified during the CP of the disease. Ignoring the treatment, the BP occurs in 2-15 months with a three to six month of median survival rate.(20) There have been several prognostic scoring models for CML, including Sokal, Hasford and European Treatment and Outcome Study (EUTOS). The Sokal score was developed during the chemotherapy period, the Euro or Hasford score during interferon-alpha treatment, and the EUTOS score during the TKI era. Sokal and Euro define patients as high, moderate, or low risk, whereas EUTOS labels them as high or low risk.(21–24)

Worldwide, Prognostic scoring systems of CML yielding conflicting findings. Some research concluded that the EUTOS score was more accurate in predicting CML prognosis, whereas other preferred the Sokal and Euro ratings. The Sokal and Euro rating were useful in predicting 5-year overall survival in imatinib patients, however the EUTOS score was originally successful in predicting full cytogenetic response and progression-free survival within 18 months of therapy. Since EUTOS was created during the TKI period, its confirmation is critical for CML management.(7,25–27)

Materials and Methods

In this study, the cases of Philadelphia chromosome positive (Ph+) CML-CP collected from the Department of Oncology, Swami Rama Himalayan University from 2022 to 2023. In this study, all the participant were newly diagnosed who have never taken imatinib, were enrolled (Figure 1). This study was authorized by the Institute's Ethical Committee (SRHU/HIMS/ETHICS/2022/150) and written informed consent was taken from all enrolled patients.

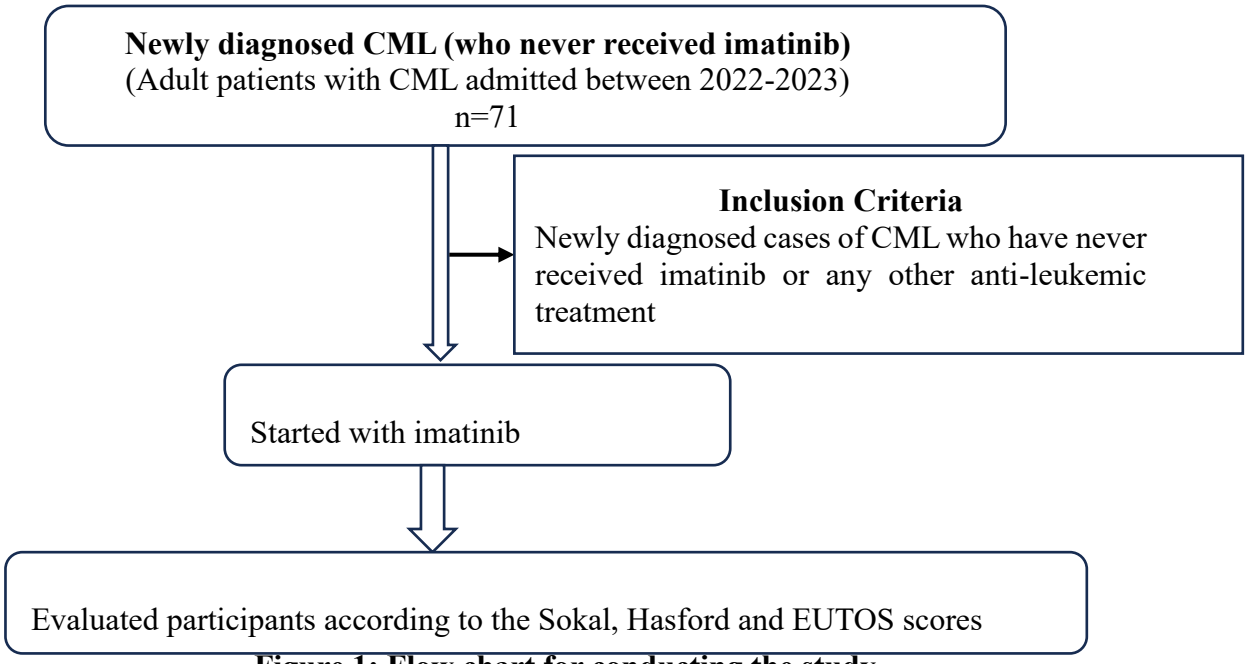

Figure 1: Flow chart for conducting the study.

Table 1: Method of Calculation for Sokal, Hasford and ELTS scoring systems.(28)

Scoring System	**Calculation**	Risk Definition
"Sokal Score"	"Exp. 0.0116 × (age -43.4) +0.0345 × (spleen – 7.51) + 0.1880 × [(platelets count/700)^2 – 0.563] + 0.0887 × (blasts – 2.10)"	Low risk: - < 0.08 Intermediate risk : - 0.8 -1.2 High risk: - > 1.2
"Hasford Score"	"[0.6666 × age (0 when age < 50 years;1), otherwise] + 0.0413 × spleen + 0.0584 × blasts + 0.0413 × eosinophils + 0.2039 × basophils [0 when basophils < 3%; 1, otherwise] + 1.0956 × platelet count [0 when platelets < 1500 × 10^9/L; 1, otherwise] × 1000"	Low risk: - ≤ 780 Intermediate risk: - 781-1480 High risk: - >1480
"ELTS Score"	"0.0025 × (age/10)^3 + 0.0615 × spleen + 0.1052 × blasts + 0.4104 × (platelet count/1000)$^{-0.5}$"	Low risk: - ≤ 1.5680 Intermediate risk: - 1.5680- 2.2184 High risk: - > 2.2185

Note: Exponential function; age is measured in years. The spleen is located below the costal margin, the platelet count is in × 10^9/L; basophils, eosinophils and blasts make up a percentage of the peripheral blood.

The cases were diagnosed according the WHO 2008 guideline and criteria and the techniques used for diagnosis of these cases was reverse transcriptase polymerase chain reaction (qPCR) for Ph chromosome. The total number of cases enrolled in this study were 71 including 41 male and 30 female cases. The clinical and demographic parameters of the cases which are recorded in this study are age, gender, spleen size, Hemoglobin (Hb), Total leukocyte count (TLC), Platelets counts and Differential leucocyte counts (DLC). In this study, the sample type was peripheral blood and bone marrow aspirate. The calculation method and risk categorization used at baseline or diagnosis were Sokal, Hasford and ELTS scoring system. (Table 1.)

Results:

The data obtained from CML cases were analyzed using MS-excel, mean ± SD were used. Pearson co-relation test was used to find out the co-relation between different parameters. The level of significant i.e. $p \leq 0.05$ was considered as significant value.

Table 2: Clinical features of new diagnosed CML patients.

Complaints	**Chronic Phase**	**Total Percentage**
Abdomen pain	31	43.66%
Abdominal fullness	40	56.34%
Black stool or diarrhoea	5	7.04%

Body pain Breathlessness	12	16.90%
Decreased appetite	2	2.82%
Easy bruising	31	43.66%
Fatigue	4	5.63%
Fever	34	47.89%
Headache	45	66.38%
Joint pain	5	7.04%
Night sweat	2	2.82%
Vomiting	10	14.08%
Weakness Weigh loss	6	8.45%
	30	42.25%

Total number of patients participated were 71, 41(57.7%) and 30 (42.3%), ratio is 1.37:1 male and female respectively. The median age of the patients were 38 years (18-76 years) and most common age group affected were between 30 to 40 years.

Table 3: Correlation of parameters

Variables		**p value**	**Pearson correlation®**
Spleen	TLC	0.95	0.2015
	Hb	0.426	-0.023
	Platelets	0.5108	0.003
TLC	Hb	0.02	-0.2336

In this study, most of the patients were symptomatic at the time of diagnosis. The common symptoms of the patients were fever (66.38%), abdominal fullness (56.31%) and fatigue (47.89%). (Table 2). Similarly, most of the patients were suffered from splenomegaly moderate (22.54%) and massive (77.42%) and 78.87 % cases had anaemia. (Table 3). The mid value of Basophil percentage was 2 (range: 0-17), median Hb 10.21 (range: 6.6-14.82), median TLC 92.5 (range: 2.1-477) with median blast percentage 3 (0-10). Most of the patient was suffered from Splenomegaly.

Table 4. Baseline Characteristics and Demographics of Patients (N=71)

Age (years)		No.	Percentage (%)
Median	38	-	-
Range	(18-76)		
Gender			
Male		41	57.75
Female		30	42.25
Haemoglobin (Hb), gm/dl			
<7		5	7.04
7-10		29	40.58
>10		37	52.11
Median	10.21		
Range	(6.6-14.82)		
Leukocyte, (10^3/µl)			
<100		37	52.11
100-250		21	29.58
>250		13	18.31
Median	92.5		
Range	(2.1-477)		
Platelets count, (10^3/µl)			
<100		3	4.23
100-450		46	64.79
>450		22	0.99
Median	342		
Range	(46-1087.9)		
Peripheral Blasts (%)			
0-2		31	43.66
3-10		40	56.34
Median	3		
Range	(0-10)		
Eosinophils (%)			
<4		51	71.83
4-10		19	26.76
>10		1	1.41
Median	3		
Range	(0.15)		
Basophils (%)			
>10		69	97.18
10-19		2	2.82
≥20		0	0
Median	2		
Range	(0-17)		
Spleen (cm)			
Moderate (≤11.9)		16	22.54
Massive (≥12)		55	77.46
Median	13.5		
Range	(6-27.2)		

Table 5: Signs at the time of diagnosis.

Signs at the time of diagnosis			
Signs		**CML**	**Percentage (%)**
Splenomegaly	Massive (≥12)	55	77.46
	Moderate (≤11.9)	46	22.54
Anaemia (>11.5)		56	78.87

Table 6 : Chronic Phase patient's distribution to risk scores			
Risk group	**Sokal Score**	**Hasford Score**	**ELTS Score**
Low, n (%)	3 (4.22)	12 (16.90)	5 (7.04)
Intermediate, n (%)	27 (38.02)	37 (52.11)	28 (39.44)
High, n (%)	41 (57.75)	22 (30.99)	38 (53.52)

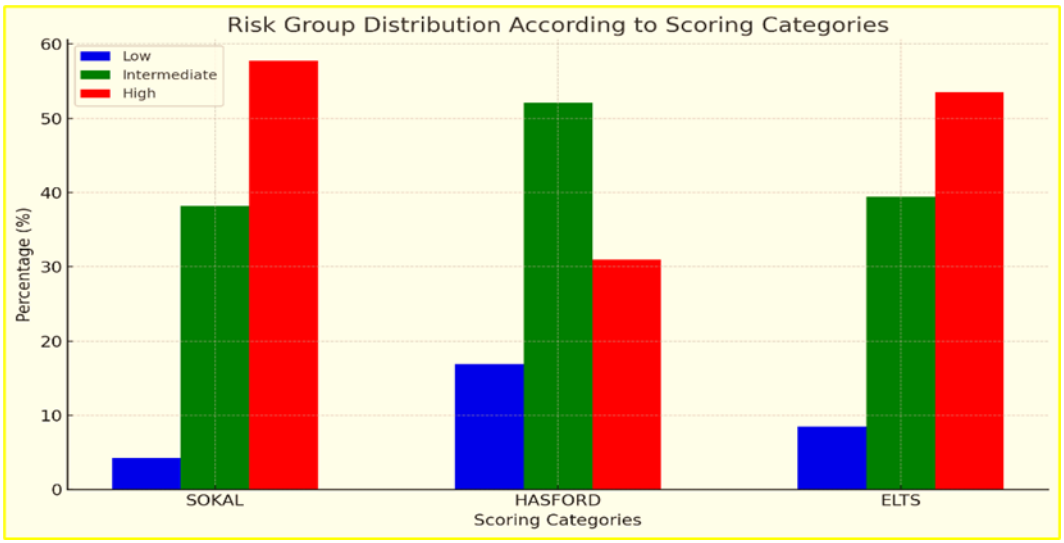

Figure 2. Risk Group Distribution According to Scoring Categories

This is a study performed on 71 Ph+ CML-CP patients who received oral imatinib therapy after diagnosis with CML were observed (Table 5), their demographical and hematological data were also recorded (Table 4). 30/71 were females and 41/71 were males with median age 38 years (range 18-75 years). Out of these 71 cases, 3 (4.22%), 27 (38.02%) and 41 (57.75) patients were discriminated into low, intermediate and high risk Sokal score respectively. 12 (16.90%), 37 (52.11%) and 22 (30.99%) patients were discriminated into low, intermediate and high risk of Hasford score respectively and 6 (8.45%), 28 (39.44%), 38 (53.52%) were patients divided into low, intermediate and high respectively (Table 6 and Figure 2).

Discussion:

Several scoring models have been developed based on the prognostic assessment of CML at the time of diagnosis. SOKAL, HASFORD, and ELTS are risks stratification-based scoring systems for CML patients that were created in 1984 and 1988, respectively. Later, in 2011, the EUTOS score was created using data from over 2000 CML-CP patients treated with TKI (imatinib). The purpose of this study was to collect clinical and hematological data from CML patients and examine any relationship with various grading little published or available information on the pattern of CML in India and other Asian nations.

This research has 71 CML patients, with a male-to-female ratio of 1.37:1 (40 men and 31 females). The median age was 38 (range: 18-76). According to the WHO, the typical age for CML diagnosis is in the fifth decade, however other Indian research suggest a median age of 42. This shows that CML development in Indian and Asian people occurs around a decade sooner than in western ones.(29,30)

All CML patients described in these studies were in CML-CP Phase, 66.38% of cases indicate fever, which is consistent with previous Indian research, however in the Savage et al study, just 6.2% of cases mention fever as a CML symptom. This might be one of the reasons for the high infection rate in the Indian population. The second symptom reported in our study was abdominal fullness (56.34%), which was followed by fatigue (47.89%).

Because karyotyping and molecular testing are not accessible at this clinic and many patients are unable to pay them, we only used molecular testing in a few cases. Indeed, the bulk of our patients come from a poor socioeconomic background. The WHO recommends detecting the Ph chromosome and/ or BCR-ABL1 fusion gene as a baseline study to conform CML diagnosis. In 71 instances, we performed three separate BCR-ABL fusion protein tests: P210 (e13a2, e14a2 major), P190 (e1a2, minor), and P230 (e19a2 micro). All CML-CP patients were positive for P210 (e13a2, e14 a2 Major), in my study. We are unable to proper follow up on the quantitative test for EFS (event-free survival) due to funding constraints but we show 85-90 % cases were survived with the imatinib at CML-CP in my study.

According to the USG data from this study, 22.54% of patients had moderate splenomegaly, while 77.46% had major splenomegaly. This data is consistent with the findings of the research by Ghalaut et al.(31) Furthermore, 52.11% of patients had mild anemia, with a median hemoglobin level of 10.21g/dl. Other Indian research found that splenomegaly and anemia occurred at rates ranging from 95% to 100% and 88.5% to 100%. Ghalaut et al. and Savage et al. reported 100% and 75.8% splenomegaly, respectively.

In this study, 78.87% of patients were anemic, although Singh et al. reported 97.4% of cases with anemia, and Raghuvanshi et al..(32,33)discovered an even greater incidence. Chang et al. found that only 46.9% of CML patient had significand anemia.(34)

In this investigation, we found cases of CML-CP when categorized using several risk stratification methods, such as Sokal, Hasford, and ELTS scoring system, as Low, Intermediate, and High-risk categories. Sokal and ELTS scores outperformed Hasford scores under the circumstances of abnormal and several parameters (such as high platelets, larger spleen size,

low Hb, and other parameters). This conclusion was similar to other studies from European population and Western population, however Tao et. al. found a different outcome in the Chinese population.(35)

Conclusion:

This study revealed that the Sokal and ELTS scores are helpful in predicting treatment outcomes for individuals with chronic myeloid leukaemia (CML-CP), most likely because they employ comparable parameters such as age, platelet count, and blast cell count. However, it did not verify the ELTS score's efficacy, presumably due to its dependence on only two indicators (basophil count and splenomegaly) and a lower number or high-risk individuals. These constraints many explain why the EUTOS score performed less well in this study that the Sokal and ELTS. The Study suggests utilizing Sokal and ELTS scores on a regular basis to predict the prognosis of CML-CP patients on imatinib. Future models may enhance early prognosis and aid in the selection of suitable medicines for improved results in the present TKI era.

Conflicts of interest

There are no conflicts of interest.

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