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The Utility and Applicability of Chronic Myeloid Leukemia Scoring Systems for Predicting the Prognosis of Egyptian Patients on Imatinib: Retrospective Study

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Abstract

Background: Chronic myeloid leukemia (CML) is myeloproliferative clonal neoplasm. Imatinib has greatly improved CML prognosis. Many prognostic scoring systems have been developed for CML risk stratification. In clinical practice, 3 systems are widely used: Sokal, Hasford and European Treatment Outcome Study (EUTOS). Recently, EUTOS long-term survival (ELTS) score is the first long-term scoring system that considered specifically CML-related death. Therefore, the aim of the present study was to validate the effectiveness of Sokal, Hasford, EUTOS and ELTS scoring systems in predicting the outcome in Egyptian CML-chronic phase (CML-CP) patients treated with imatinib.

Patients and methods: Retrospective study performed on 167 patients with CML-CP who were treated with imatinib. Using the Sokal, Hasford, EUTOS and ELTS scores, we divided the patients into each risk groups.

Results: Significant differences in event free survival (EFS), time without progression (TWP) and overall survival (OS) prediction between the Sokal, Hasford and ELTS risk groups, but no significant difference among the EUTOS score risk groups.

Conclusion: Our study indicates that Sokal, Hasford and ELTS scoring systems but not the EUTOS score are effective in predicting early treatment response, EFS, TWP and OS for Egyptian CML patients treated with imatinib.

Keywords: Chronic myeloid leukemia; Prognosis; Sokal; Hasford; EUTOS; ELTS

Introduction

Chronic myeloid leukemia (CML) is myeloproliferative clonal neoplasm with pluripotent hematopoietic stem cell origin. *BCR-ABL* fusion gene results from a balanced reciprocal translocation between *BCR* (Breakpoint cluster region) and ABL (Abelson) genes is the main finding in CML. Transposition of ABL proto-oncogene from chromosome 9 to BCR on chromosome 22 is either at chromosome level [Philadelphia (Ph) chromosome t(9;22)(q34;q11)] or cryptic at gene level. BCR-ABL encodes an unregulated, cytoplasm-targeted tyrosine kinase, leading to uninhibited cell proliferation [1,2]. CML is a triphasic disease, chronic-phase (CP), accelerated-phase (AP), and blast-phase (BP). Most patients are asymptomatic and diagnosed in CP; most patients will progress to rapidly fatal BP within 3–5 years if untreated [3].

Tyrosine kinase inhibitors (TKIs) including imatinib have greatly improved CML prognosis. In the pre TKI era, the 5-year CML overall survival (OS) with chemotherapy and interferon was 42% and 57%, respectively [4]. With imatinib the 5-year CML OS was 89–93% [5,6].

Many prognostic scoring systems have been developed for CML risk stratification. In clinical practice, 3 systems are widely used: Sokal et al. [7], Hasford et al. [8], and European Treatment Outcome Study (EUTOS) [9]. Sokal et al. [7] and Hasford et al. [8] were developed in the era of chemotherapy and interferon-α respectively. The Sokal score is based on patient age, spleen size, platelet count, and peripheral blasts % [7], and Hasford also includes peripheral eosinophil % and basophil % [8].

The Sokal and Hasford scores categorize patients as low, intermediate, or high risk and were developed to predict overall survival. In 2011, European Leukemia Network (ELN) [9] developed the European Treatment and Outcome Study (EUTOS) scoring system after doubts about the use of the 2 old systems in the TKI era to predict complete cytogenetic response (CCyR) at 18 months. EUTOS score is easy to use based only on peripheral basophil % and spleen size and categorize patients as low or high risk [10-12].

Recently, EUTOS long-term survival (ELTS) score is the first long-term scoring system that considered specifically CML-related death and categorizes patients as low, intermediate, or high risk. The authors of ELTS wrote "We hope that the ELTS score will be considered for the risk-stratified planning, analysis, and outcome interpretation of clinical trials" [13].

Therefore, the aim of the present study was to validate the effectiveness of Sokal, Hasford, EUTOS, and ELTS scoring systems in predicting the outcome in Egyptian CP-CML patients treated with imatinib.

Methods

Patients

This was a retrospective study performed on 167 patients with CML-CP selected consecutively who were treated with imatinib and diagnosed between January 2008 and December 2013 at Hematology Unit, Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta Health Insurance Hospital and other centers. The diagnosis of CML was based on characteristic peripheral blood smear and bone marrow examination findings and was confirmed by presence of Philadelphia chromosome on bone marrow cytogenetic studies or detection of BCR/ABL translocation by polymerase chain reaction (PCR) [3]. We used the previously defined diagnostic criteria for CML-CP according to ELN 2013 recommendations [14].

Treatment protocol

Imatinib mesylate (Gleevec, Novartis Pharma, Bale, Switzerland) was started at dose of 400 mg/day. The dose was adjusted according to their tolerance and response.

The patients had endured a maximum of six months from diagnosis to the imatinib treatment. Patients who received any cytoreductive treatment except for hydroxyurea and/or interferon-α (be used less than 3 months) before imatinib were excluded from the study.

Risk stratification

Sokal and Hasford scores were calculated using an online link (http://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/index_eng.html). EUTOS score was also calculated using an online link (http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html). ELTS score was also calculated using an online link (http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html). Using the Sokal, Hasford, EUTOS, and ELTS scores, we divided the patients into each risk groups. The calculation forms of each 4 scoring systems are summarized in Table 1.

Data collection

Data were collected by reviewing patients' records. Records with incomplete data (nine patients) were omitted from the study. All patients' data were handled according to ethical standards in accordance with the Declaration of Helsinki.

Scoring system	Calculation method	Risk definition
Sokal score [7]	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)]	Low risk (score < 0.8) Intermediate risk (score 0.8–1.2) High risk (score >1.2)
Hasford score [8]	[0.666 (when age ≥ 50 years) + (0.042 x spleen size cm below costal margin) + 1.0956 (when platelet count >1500 x 10^9 / L) + (0.0584 x blast cell % in peripheral blood) + 0.20399 (when basophil % in peripheral blood ≥3%) + (0.0413 x eosinophil % in peripheral blood)] x 1000.	Low risk (score ≤ 780) Intermediate risk (score > 780 but ≤1480) High risk (score > 1480)
EUTOS score [9]	(7 x basophils % in peripheral blood) + (4 x spleen size cm below costal margin)	Low risk (score ≤ 87) High risk (score > 87)
ELTS score [13]	0.0025 x (age in completed years/10)^3 + 0.0615 x spleen size cm below costal margin + 0.1052 x blasts % in peripheral blood + 0.4104 x (platelet count/1000)$^{-0.5}$	Low-risk (score ≤ 1.5680) Intermediate-risk (score > 1.5680 but ≤ 2.2185) High-risk (score > 2.2185)

Table 1: Method of calculation of Sokal, Hasford, EUTOS and ELTS scores.
ELTS: EUTOS Long-term Survival; EUTOS: European Treatment and Outcome Study; Exp: Exponential Function

Follow-up

While on therapy complete blood counts were monitored weekly for the first month and then every 2 weeks thereafter till patient achieved hematological response and then monthly. BCR-ABL was done using quantitative real time- polymerase chain reaction (RT-PCR) of blood cells in our study in the most of the cases for monitoring the molecular response every 3 months. In some cases, bone marrow aspiration for cytogenetics was performed every three or six months for the first year and then every six or twelve months in the following years. Cytogenetic response was measured in bone marrow cells and determined by proportion of the Ph-positive metaphases among at least 20 metaphases analyses with R-banding technique after short-term culture and was defined as complete cytogenetic response; CCyR (Ph-positive 0%), partial cytogenetic response; PCyR (Ph-positive 1-35%), and no cytogenetic response (>35% Ph-positive). Cytogenetic response was not assessed in patients with overt hematologic progression [15].

The definitions of accelerated-phase (AP), or blast-phase (BP), complete hematologic response (CHR), major cytogenetic response (MCyR), CCyR, major molecular response (MMR) and early treatment failure were made according to ELN 2013 recommendations [14].

Complete Hematologic response (CHR) was defined as platelet count <450 × 10^9/L, WBC count <10 × 10^9/L, differential without immature granulocytes, less than 5% basophils, and in addition to the disappearance of all signs and symptoms of CML including non-palpable spleen. MCyR was characterized as combination of both complete and partial cytogenetic responses. MMR was defined as BCR-ABL ≤ 0.1% in the quantitative RT-PCR of blood cells [14,16,17].

Outcomes

Different definitions, as published in previous studies, were used with minor modifications. The definition of event free survival (EFS) on the IRIS trial referred to an event as any of the following: progression to AP or BP; CML-related death; early treatment failure or loss of CHR, MCyR or MMR [5]. The definition of time without progression (TWP) by ENEST-nd referred to progression as any of the following: development of AP or BP or CML-related death [18]. Overall survival (OS) was calculated from the date of therapy initiation to the date of death or final follow up (December 2015). OS, EFS, TWP were calculated from the start of imatinib therapy.

Statistical analysis

The collected data were analyzed using SPSS version 17 software (SPSS Inc, Chicago, ILL Company). Non-parameteric data are expressed as median. Categorical variables are expressed as proportions. Fisher's exact and Chi-square tests were used for comparison between categorical data. Cumulative Incidence of EFS, TWP and OS were estimated using Kaplan-Meier method and compared using the log rank test. The Cox regression analysis was used for multivariate analyses for factors associated with survival using the forward selection method to determine hazard ratios (HRs) and 95% confidence intervals (95% CIs). P-value ≤ 0.05 was considered statistically significant.

Results

Characteristics of the CP-CML patients

This study recruited 167 patients, with median age of 49 years (Range, 23-74) at diagnosis. There were 108 males (64.7%) and 59 females (35.3%). 109 patients (65.3%) received hydroxyurea before commencing imatinib. Other parameters at diagnosis are shown in Table 2.

Variables	Range	Median
Age (years)	23-74	49
Peripheral blood blast (%)	0-7	2
Peripheral blood Eosinophil (%)	0-15	2
Peripheral blood Basophil (%)	1-15	4
Platelet count (X 10^9/L)	152-812	341
Spleen size (cm below the costal margin)	2-14	5
	Number	%
Sex (male/female)	108/59	64.7/35.3
Sokal score (low/intermediate/high)	36/95/36	21.6/56.8/21.6
Hasford score (low/intermediate/high)	65/82/20	38.9/49.1/12
EUTOS score (low/high)	142/25	85/15
ELTS score (low/intermediate/high)	76/78/13	45.5/46.7/7.8

Table 2: Characteristics of the study population.

ELTS: EUTOS Long-term Survival; EUTOS: European Treatment and Outcome Study

Sixty nine patients (41.3%) had early treatment failure with median time of 18 months (range: 3–18 months) with 95% confidence interval (14.73-17.01 months). Reasons of early treatment failure included no CHR at the 3rd month (5 patients), no cytogenetic response at the 6th month (4 patients), no complete cytogenetic response at the 12th month (4 patients), failure to achieve MMR at the 18th month (56 patients).

At the end of study; 36 patients (21.6%) died and 20 patients (12%) were lost to follow-up. 29 patients (17.4%) passed to AP, 18 of the previous 29 patients (10.8%) passed to BP up to the end of our study. 19 patients (11.4%) had MMR lose and were managed with imatinib dose escalation. All the patients were followed up for a period ranged from 26 to 81 months (median 46 months) with 95% confidence interval (45.3-49.3 months).

Sokal, Hasford, EUTOS and ELTS scores

At diagnosis, 36 (21.6%), 95 (56.8%) and 36 (21.6%) patients were in the Sokal low, intermediate and high risk groups respectively; while 65 (38.9%), 82 (49.1%) and 20 (12%) patients were in the Hasford low, intermediate and high risk groups respectively. According to the EUTOS score, 142 patients (85%) were low risk and 25 patients (15%) were high risk. 76 (45.5%), 78 (46.7%) and 13 (7.8%) patients were in the ELTS low, intermediate and high risk groups respectively (Table 2).

Variables		Early treatment failure	
		No (N: 98)	Yes (N: 69)
Sokal Score	Low (N: 36)	29 (80.6%)	7 (19.4%)
	Intermediate(N: 95)	56 (58.9%)	39 (41.1%)
	High (N: 36)	13 (36.1%)	23 (63.9%)
P-value		< 0.0001*	
Hasford Score	Low (N: 65)	54 (83.1%)	11 (16.9%)
	Intermediate (N: 82)	38 (46.3%)	44 (53.7%)
	High (N: 20)	6 (30%)	14 (70%)
P-value		< 0.0001*	
EUTOS Score	Low (N: 142)	87 (61.3%)	55 (38.7%)
	High (N: 25)	11 (44%)	14 (56%)
P-value		0.125	
ELTS Score	Low (N: 76)	62 (81.6%)	14 (18.4%)
	Intermediate (N: 78)	34 (43.6%)	44 (56.4%)
	High (N: 13)	2 (15.4%)	11 (84.6%)
P-value		< 0.0001*	

Table 3: Comparison of Sokal, Hasford, EUTOS and ELTS for Early treatment failure.
*: significant; ELTS: EUTOS Long-term Survival; EUTOS: European Treatment and Outcome Study; N: Number

Comparison between Sokal, Hasford, EUTOS and ELTS risk groups as regard incidence of early treatment failure showed that higher percentages of high Sokal, Hasford and ELTS score patients and lower percentages of low Sokal, Hasford, and ELTS score patients in patients with early treatment failure when compared with patients with no early treatment failure patients. EUTOS score risk group showed insignificant differences as regard early treatment failure incidence (Table 3).

Kaplan–Meier analysis

According to risk stratifications, there were significant differences in EFS, TWP and OS prediction between the Sokal, Hasford and ELTS risk groups, but insignificant difference among the EUTOS score risk groups (Table 4) (Figures 1-3).

Group (N) (%)	Event free survival (EFS)			Time without progression (TWP)			Overall survival (OS)		
	Events (N)	5 years EFS (%)	P-value Log rank	Events (N)	5 years TWP (%)	P-value Log rank	Events (N)	5 years OS (%)	P-value Log rank
Low Sokal score (N: 36) (21.6%)	10	65.5	<0.0001*	1	97	<0.0001*	0	100	<0.0001*
Intermediate Sokal score (N: 95) (56.8%)	49	42.4		8	85.1		9	88.5	
High Sokal score (N: 36) (21.6%)	34	3.2		24	27		27	18.3	
Low Hasford score (N: 65) (38.9%)	17	65.5	<0.0001*	3	93	<0.0001*	2	92.9	<0.0001*
Intermediate Hasford score (N: 82) (49.1%)	59	23.3		21	60.1		22	56.9	
High Hasford score (N: 20) (12%)	17	15		9	54		12	37.9	
Low EUTOS score (N: 142) (85%)	75	40	0.056	27	72.5	0.719	30	67.9	0.929
High EUTOS score (N: 25) (15%)	18	26.7		6	71.9		6	68.2	
Low ELTS score (N: 76) (45.5%)	28	52.9	<0.0001*	10	79.9	0.01*	9	81.8	<0.0001*
Intermediate ELTS score (N: 78) (46.7%)	52	31		16	72.6		17	65.6	
High ELTS score (N: 13) (7.8%)	13	0		33	43.5		10	26.4	

Table 4: Event free survival (EFS), time without progression (TWP) and overall survival (OS) probability for different groups of patients.
*: significant; ELTS: EUTOS Long-term survival; EUTOS: European Treatment and Outcome Study; N: Number

Our results also showed that the comparisons between every 2 subgroups in each score (Sokal, Hasford, and ELTS) for EFS, TWP, and OS had significant differences in all comparisons except (low Sokal vs. intermediate Sokal) for prediction of TWP, (intermediate Hasford vs. high Hasford) for prediction of EFS, TWP, and OS and (low ELTS vs. intermediate ELTS) for prediction of TWP and OS.

Multivariate Cox regression analysis

Multivariate Cox regression analyses were performed and showed that age (HR=1.445, 95% CI: 1.022-1.069, P<0.0001), splenic size below the costal margin (HR=1.101, 95% CI: 1.017–1.91, P=0.018), and peripheral blast % (HR=1.229, 95% CI: 1.099-1.373, P<0.0001) were independently associated with EFS. Peripheral blast % (HR=1.418, 95% CI: 1.182-1.702, P<0.0001), and platelet count (HR=1.002, 95% CI: 1.000-1.005, P=0.035) were independently associated with TWP. Peripheral blast % (HR=1.637, 95% CI: 1.345-1.992, P<0.0001) and peripheral eosinophil % (HR=1.165, 95% CI: 1.031-1.316, P=0.014) were independently associated with OS (Table 5).

Discussion

Therapy with TKIs is needed almost for the entire life span of CML patients, and this demands the development of new scoring system and assessment of old scoring system for risk categorization and predicting the survival and response at an early stage of CML patients. Various attempts have been made to validate the superiority of the available three old scores [12,19-21].

Identifying the right scoring system for the prognosis of patients with CP-CML undergoing imatinib therapy is controversial. Therefore, the aim of the present study was to validate the effectiveness of Sokal, Hasford, EUTOS and ELTS scoring systems in predicting the outcome in Egyptian CP-CML patients treated with imatinib.

To our knowledge, this is the first study to use data from Egyptian patients for comparing different score systems for CML prognosis and the first study to assess the ELTS score worldwide after the original paper by Pfirrmann et al. [13] who developed the ELTS score.

In our study, at diagnosis, 36 (21.6%), 95 (56.8%) and 36 (21.6%) patients were in the Sokal low, intermediate and high risk groups respectively; while 65 (38.9%), 82 (49.1%) and 20 (12%) patients were in the Hasford low, intermediate and high risk groups respectively.

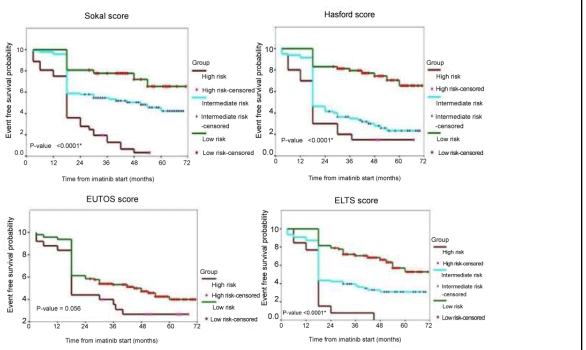

Figure 1: Kaplan–Meier analysis of the event free survival (EFS) probability.

According to the EUTOS score, 142 patients (85%) were low risk and 25 patients (15%) were high risk. 76 (45.5%), 78 (46.7%) and 13 (7.8%) patients were in the ELTS low, intermediate and high risk groups respectively.

The percentages of different risk groups among different scoring systems had many different figures in different studies [11,13,19-32]. In Egypt, Heiba and Elshazly [22] showed that 17 (30%), 24 (43%) and 15 (27%) patients were in the Sokal low, intermediate and high risk groups respectively in a study including 56 CML-CP patients. Also in Egypt, Edesa and Abdel-malek [23] showed that the majority of the cases had low risk (75%) according to EUTOS scoring system in a study including 60 CML-CP patients. The discrepancy in the reported figures between several studies, including our study, could be due to several factors. One could be the differences in the ethnicity of the studied groups, sample size, and different age distributions in different countries.

In this study, comparison between Sokal, Hasford, EUTOS and ELTS risk groups as regard incidence of early treatment failure showed that higher percentages of high Sokal, Hasford and ELTS score patients and lower percentages of low Sokal, Hasford and ELTS score patients in patients with early treatment failure when compared with patients with no early treatment failure. EUTOS score risk group showed insignificant differences as regard early treatment failure incidence.

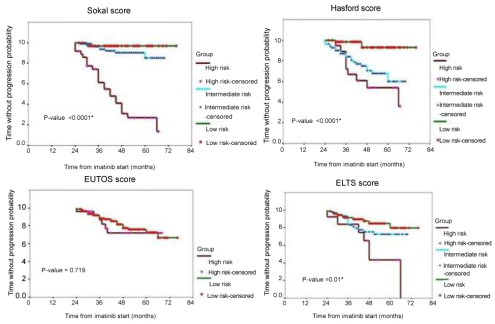

Figure 2: Kaplan–Meier analysis of the time without progression (TWP) probability.

Also in our study, according to risk stratifications, there were significant differences in EFS, TWP and OS prediction between the Sokal, Hasford and ELTS risk groups, but insignificant difference among the EUTOS score risk groups.

Variables	EFS			TWP			OS		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	1.045	1.022-1.069	<0.0001*	1.027	0.989-1.065	0.166	1.026	0.990-1.064	0.166
Spleen size (cm below the costal margin)	1.101	1.017-1.191	0.018*	1.014	0.889-1.158	0.831	0.957	0.840-1.090	0.505
Peripheral blood blast (%)	1.229	1.099-1.373	<0.0001*	1.418	1.182-1.702	<0.0001*	1.637	1.345-1.992	<0.0001*
Platelet count (x 10^9/L)	0.999	0.998-1.001	0.866	1.002	1.000-1.005	0.035*	1.001	0.999-1.004	0.205
Peripheral blood Eosinophil (%)	1.074	0.995-1.60	0.068	1.125	0.992-1.277	0.067	1.165	1.031-1.316	0.014*
Peripheral blood Basophil (%)	1.030	0.974-1.089	0.299	0.945	0.840-1.064	0.352	0.949	0.851-1.059	0.351

Table 5: Multivariate Cox regression analyses of clinicopathological variables and EFS, TWP, and OS.
*: significant; CI: Confidence Interval; EFS: Event Free Survival; HR: Hazard Ratio; OS: Overall Survival; TWP: Time Without Progression

Different studies had been done in patients with CML for identifying the right scoring system for the prognosis of patients with CP-CML undergoing imatinib therapy. Some of these studies were with our results and the others were against our results (Table 6). Our

results are comparable and completely agreement with the following studies. In Pakistan, Usman et al. [24] carried their study on 136 patients and found that the response was higher in patients who had low Sokal score at the time of presentation. In another study, Aziz et al. [25] carried their study on 304 patients and reported that low Sokal score was a significant predictive factor for event-free survival (EFS). In United Kingdom, de Lavallade et al. [26] found that the Sokal score can significantly predict for (OS, progression free survival (PFS), CCyR, and MMR) in 282 patients. In Japan, Yamamoto et al. [27] found in 145 CML patients that both the Sokal and Hasford scores, but not the EUTOS score, were clinically effective prognostic indicators (CCyR at 12 and 18 months, EFS, PFS and OS). In India, Francis et al. [28] who carried their study on 111 patients and found that the Sokal, Hasford but not EUTOS scoring systems were significantly associated with OS. In Egypt, Heiba and Elshazly [22] showed that Sokal score was highly significantly correlated with the response to treatment in the form of achievement of MMR at 18 months.

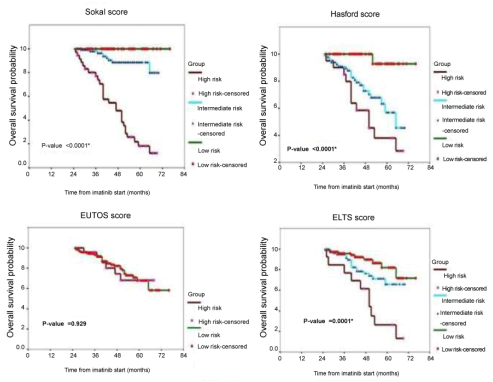

Figure 3: Kaplan–Meier analysis of the overall survival (OS) probability.

Study	Country	Type of study	Number of patients	Scores tested	Drug used	Results
Usman et al. [24]	Pakistan	Prospective	136	Sokal	Imatinib	Low Sokal score predict the higher hematologic as well as cytogenetic response.
de Lavallade et al. [26]	United Kingdom	Prospective	282	Sokal	Imatinib	Sokal score significantly predicted for CCyR and loss of CHR, but failed to predict for PFS and OS.
Aziz et al. [25]	Pakistan	Prospective	304	Sokal	Imatinib	Low Sokal score is significant predictive for EFS.
Marin et al. [19]	United Kingdom	Prospective	282	Sokal EUTOS	Imatinib	EUTOS score failed to predict for (OS, PFS, CCyR and MMR). Conversely, Sokal score significantly predicted for of these outcomes.
Jabbour et al. [29]	United states of America	Prospective	465	EUTOS	Imatinib or 2nd generation TKI	EUTOS score was not predictive for MMR, TFS, EFS, and OS.
Oyekunle et al. [30]	Nigeria	Prospective	134	Sokal Hasford	Imatinib	Sokal and Hasford predict significantly for PFS especially low- and intermediate-risk patients. However, neither of the scores was predictive for differences in OS or CCyR.
Hoffmann et al. [11]	Several European countries	Prospective	3140	EUTOS	Imatinib	EUTOS score was predictive for CCyR, PFS and OS.
Yamamoto et al. [27]	Japan	Retrospective	145	Sokal Hasford EUTOS	Imatinib	Sokal and Hasford Scores but not EUTOS score can predict the CCyR, EFS, PFS and OS. MMR can't be by the 3 scores
Tao et al. [31]	Chain	Retrospective	220	Sokal Hasford EUTOS	Imatinib	EUTOS can predict CCyR, PFS and OS. However, Sokal and Hasford scores could not discriminate the intermediate-risk from high-risk group in either survival or CCyR.
Francis et al. [28]	India	Prospective	111	Sokal Hasford EUTOS	Imatinib	Sokal and Hasford scores but no EUTOS tend to influence the OS.
Xia et al. [32]	Chain	Retrospective	210	Sokal Hasford EUTOS	Imatinib	The 3 scoring systems were associated with EFS, PFS, and 3-month and 12-month CCyR (except EFS with EUTOS).

Table 6: Different studies for evaluation of different scoring systems for the prognosis of patients with chronic phase-chronic myeloid leukemia.

CCyR: Complete Cytogenetic Response; CHR: Complete Hematologic Response; EFS: Event Free Survival; EUTOS: European Treatment and Outcome Study; MMR: Major Molecular Response; OS: Overall Survival; PFS: Progression Free Survival; TFS: Transformation Free Survival; TKI: Tyrosine Kinase Inhibitor.

Edesa and Abdel-malek [23] showed no statistically significant difference was observed in PFS according to EUTOS score. Marin et al. [19] and Jabbour et al. [29] evaluated the clinical significance of the EUTOS score and reported both negative findings. Pfirrmann et al. [13] showed that the ELTS score was successfully validated in an independent sample of 1120 patients. The ELTS score differentiated probabilities of dying of CML better than the Sokal, Hasford and EUTOS scores.

Other following studies had some points of agreement and some points of disagreement especially as regard the EUTOS score. In Nigeria, Oyekunle et al. [30] studied 134 CML patients and found that Sokal and Hasford risk groups predicted significantly better PFS for low- and intermediate-risk patients. However, neither of the scores was predictive for differences in OS or CCyR. In China, Tao et al. [31] made their study on 222 patients with CML and demonstrated that, EUTOS score predicted the OS, CCyR and PFS. Also, Xia et al. [32] stated that Sokal, Hasford and EUTOS scoring systems were associated with EFS, PFS, and 3-month and 12-month CCyR (except EFS with EUTOS). Using data from 3160 CML patients, Hoffmann et al. [11] recently reported that the EUTOS scoring system can predict CCyR at 18 months, PFS and OS. Also, several studies evaluated EUTOS score clinical significance and reported positive findings [12,20,21,31,32].

Our results showed that the cumulative differences between every 2 subgroups in each score (Sokal, Hasford, and ELTS) for EFS, TWP, and OS showed significant differences in all comparisons except (low Sokal vs. intermediate Sokal) for prediction of TWP, (intermediate Hasford vs. high Hasford) for prediction of EFS, TWP, and OS and (low ELTS vs. intermediate ELTS) for prediction of TWP and OS. Tao et al. [31] revealed that in the case of OS, Sokal score failed to stratify the low- and intermediate-risk groups. In the case of PFS, Sokal score could discriminate the patients of 3 risk groups significantly. Hasford score resulted in statistically significant difference between the low-risk and intermediate-risk groups in both OS and PFS, but not between the intermediate-risk and high-risk groups. The explanation of our results and the other study results are not clear and need more multicenter studies.

Our results also showed by multivariate Cox regression analyses that age, splenic size below the costal margin, and peripheral blast % were independently associated with EFS. Peripheral blast %, and platelet count were independently associated with TWP. Peripheral blast % and peripheral eosinophil %were independently associated with OS.

In comparison to the original articles which validate the original scores, Sokal et al. [7] showed in multivariate analysis that splenic size and peripheral blasts % in addition to age were the most important prognostic factors. The platelet count was only influence survival significantly when the count above 700 X 10^9/L. Also, Hasford et al. [8] showed in univariate and multivariate analysis age, spleen size, blasts %, basophils %, and eosinophils % correlated with survival. Hasford et al. [9] (EUTOS score) found in univariate analysis that splenic size, blasts, eosinophils, and basophils were statistically significant influence on CCyR at 18 months but the age, and platelets had no effect. Pfirrmann et al. [13] (ELTS score),showed that the cumulative incidence probabilities of CML death were significantly increased by higher age, bigger splenic size, higher peripheral blasts % and lower platelet counts.

Also, Xia et al. [32] showed that age, proportion of blasts, and platelet counts were independently associated with EFS. Age, proportion of blasts, and white blood cell count were independently associated with PFS.

The discrepancy in the reported results between several studies, including our study, could be due to several factors. One could be the differences in number and the second is ethnicity of the studied groups including environmental and genetic variations. The 3rd factor is different end points. The 4th factor is the duration of follow up.

In the present study, the EUTOS high-risk patients did not share the risk group with the other 3 scoring systems. The factors included in the Sokal, Hasford and ELTS scores are similar with small differences, but the EUTOS score includes only peripheral basophil count and the size of spleen. Age, platelet count, peripheral eosinophil and peripheral blast count, which are not included in the EUTOS score, might have a prognostic influence on CML patients.

The present study had some limitations such as, few patients were included. Also, we have not been able to objectively assess drug adherence as poor patient adherence to the CML therapy might be the predominant reason for the inability to obtain adequate molecular responses [33]. Also, this was a retrospective study with higher frequencies of biases. In general, the CML scoring systems had some limitations as, the validation of the CML risk scoring system were assessed using different end-points and the parameters used to calculate the scores, had no molecular or genetic factors.

Accordingly, further prospective, larger, multicenter, longer studies are necessary to overcome these limitations. Further studies will be required to assess the potential geographical and genetic differences between different populations as inter-racial differences in the pharmacokinetics of imatinib have been reported [34].

Conclusion

Our study indicates that Sokal, Hasford and ELTS scoring systems but not the EUTOS score are effective in predicting early treatment response, EFS, TWP and OS for Egyptian CML patients treated with imatinib.

Conflicts of Interest

The authors report no conflict of interest.

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Author's contributions:

1. Concept, design, definition of intellectual content, and statistical analysis: Tamer A. Elbedewy.

2. Literature search, manuscript preparation, manuscript editing, manuscript review, data acquisition, and data analysis: Tamer A. Elbedewy, Hossam Eldin A. Elashtokhy.
3. All authors have been read and approved the final version of the manuscript.

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