Sys Rev Pharm 2021;12(1):987-992
A multifaceted review journal in the field of pharmacy

Prognostic Implications of Sokal, Hasford, and EUTOS scores on Complete Hematologic and Early Molecular Responses in Newly Diagnosed Chronic Myeloid Leukemia Patients: A Prospective Cohort Study

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ABSTRACT

Sokal, Hasford, and EUTOS prognostic scoring systems are widely used for chronic myeloid leukemia (CML) patients. However, whether one of these scoring systems was better predicting therapeutic responses among patients treated with tyrosine kinase inhibitor (TKI) remains elusive. This study was aimed to assess the correlation of each prognostic score with therapeutic responses—complete hematologic response (CHR) and early molecular response (EMR) after treated with Imatinib mesylate. 40 CML patients with the mean of age of 40 ± 11 years from Indonesian population were followed-up prospectively. The CHR at 3 months was seen in 40.7%, 18.6%, and 40.7% in Sokal low-, intermediate- and high-risk groups respectively, 26.0%, 40.7%, and 33.3% in Hasford low-, intermediate- and high-risk groups respectively, 100% and 0% EUTOS low- and high-risk groups respectively. The EMR at 3 months was seen in 41.7%, 16.6%, and 41.7% in Sokal low-, intermediate- and high-risk groups respectively, 29.2%, 37.5% and 33.3% in Hasford low-, intermediate- and high-risk groups respectively, 100% and 0% in EUTOS low- and high-risk groups respectively. However, none of these scoring systems predicted CHR and EMR at 3 months among CML patients treated with Imatinib.

Keywords: Chronic Myeloid Leukemia, Complete hematologic response, Early molecular response, EUTOS, Hasford, Sokal

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INTRODUCTION

An oral targeted therapy of tyrosine kinase inhibitor (TKI) has shifted the paradigm of chronic myeloid leukemia (CML) treatment since the discovery of the role of BCR-ABL in the disease progression.[1,2] The first generation of TKI such as imatinib mesylate has been widely used as the first-line therapy of CML patients.[3,4] However, some patients developed resistance to the treatment as indicated by the unachieved therapeutic responses—early molecular response (EMR) and complete hematological response (CHR).[3] Predicting therapeutic response in CML patients ought to be investigated further especially using prognostic scoring models.

CML accounts for 10% of all leukemia new cases.[3] The establishment and validation of several prognostic systems have been long-way endeavors to measure treatment outcomes. Sokal and Hasford prognostic scoring systems have been used since the use of chemotherapy and interferon.[2,5] The current prognostic scoring system called the European Treatment and Outcome Study (EUTOS) was established after the era of imatinib mesylate.[2,6,7]

Several studies have investigated widely the clinical significance of these prognostic scoring systems and the results were also varied worldwide across different regions. Some studies found EUTOS score demonstrates better predictive efficacy for progression-free survival (PFS) and overall survival (OS) compared to Sokal and Hasford scores.[5,8–10] However, other studies found EUTOS score was not predictive for PFS and OS in CML patients.[6,11] In addition, studies that investigated the predictive correlation of various prognostic scoring systems with therapeutic responses also pose different results. While some studies showed EUTOS scoring system was better to predict the complete cytogenetic response (CCyR) and molecular response, others proved that Sokal and Hasford demonstrate a better predictive correlation.[5,6,8,9,11–13] Interestingly, a previous study reports that none of these prognostic scoring systems shows a predictive correlation with therapeutic response.[2]

To the best of our knowledge, there are very limited studies that analyzed the comparison of these prognostic scoring systems in patients with CML whom in imatinib treatment prospectively.[14] Furthermore few studies investigated these comparative relationships—all widely-used prognostic scoring systems and therapeutic responses—in the Asian population setting.[2,8,9,15] Also, there is no study involving the Indonesian population among above listed previous studies.

Therefore, we aimed to assess the correlation of patient early therapeutic responses after imatinib treatment with prognostic scoring system risk categories on different prognostic models—Sokal score, Hasford score, and EUTOS score in a cohort of Indonesian CML patients on imatinib treatment.

METHODS

The study was a prospective cohort, single-centered study evaluating the correlation of therapeutic response status (complete hematologic response and early molecular response) with prognostic scores (Sokal score, Hasford score, and EUTOS score) in CML patients who were treated with imatinib. The study was conducted in the Hematology and Medical Oncology Division, Department of Internal Medicine, Hasan Sadikin Hospital, Bandung; and Biology Molecular Division, Department of Clinical Pathology, Hasan Sadikin Hospital, Bandung. Written consent was obtained from the subject prior to enrollment in the study. The study was approved by the Health Research Ethics Committee-Universitas Padjadjaran and Hasan Sadikin Hospital.

Study subjects

We prospectively assessed all CML patients—treated with imatinib who admitted to the Hematology and Medical Oncology clinics between Match 2019 to December 2019. The study subjects were CML patients who were confirmed of the presence of BCR-ABL gene by reverse transcriptase polymerase chain reaction assay (RT-PCR). Subjects were treated with imatinib mesylate 400mg and evaluated for therapeutic responses. Subjects who showed sign of infection, were on corticosteroid treatment, and inadequate medical data were excluded from further analysis. This study was powered to have a 90% chance of detecting a 0.14 difference in fold change, with a standard deviation of 0,22 on a maximum fold change of JAK2 gene expression of 1.

We used a two-sided test with a 5% significance level and allowing for a 10% dropout rate. We recorded subjects characteristics including age, gender, spleen size, total leucocyte count, platelet count, percentage of myeloblasts, basophils, and eosinophils in peripheral blood. At the time of diagnosis, Sokal score, Hasford score, and EUTOS risk score were calculated and categorized according to the formula in **Table 1**.[16–18]

Table 1. Calculation and risk categories of Sokal score, Hasford score, and European Treatment and Outcome Study score

Scoring system	Calculation	Risk stratification
Sokal	Exponential function [0.0116 (age (years) – 43.4) + 0.0345 (spleen size (cm) – 7.51) + 0.188 ([platelet count /700]^2 – 0.563) + 0.0887 (blast cell counts (%) – 2.1)]	Low risk: < 0.8 Intermediate risk: 0.8 – 1.2 High risk: > 1.2
Hasford	0.666 (when age > 50 tahun + (0.042 x spleen size (cm) + 1.0956 (when platelet count > 1,500 x 10^9L) + (0.0584 x blast cell counts (%)) + 0.20399 (when basophil counts (%) > 3%) + (0,0413 x eosinophil counts (%)) x 100	Low risk: < 1.4 Intermediate risk: 1.4 – 2.0 High risk: > 2.0
EUTOS	(7x basophils (%)) + (4x spleen size (cm))	Low risk: ≤87 High risk: > 87
EUTOS: European Treatment and Outcome Study		

Follow-up

The hematologic and molecular responses of subjects after 3 months from the onset of imatinib treatment were follow-up. The hematologic and molecular responses were defined based on European LekemiaNet (ELN), National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO).[4,19,20]

The complete hematologic response (CHR) was defined as leukocyte count less than 10,000/mL, platelet count less than 450,000 cells/mL, the presence of myelocytes plus metamyelocytes less than 5%, the presence of basophils below 20%, the absence of blasts and promyelocytes in peripheral blood, and the absence of extramedullary involvement/non-palpable spleen and any other signs and symptoms related to leukemia.[21,22]

The molecular responses (MR) was examined by detecting the presence of BCR-ABL mRNA using real-time quantitative polymerase chain reaction (RQ-PCR). Early molecular response (EMR) was defined as BCR-ABL ≤ 10% on the third or sixth month of follow-up.[22,23]

Statistical analysis

Categorical variables were presented as percentages (age, Sokal score, Hasford score, and EUTOS score), whereas numerical variables as mean and range (age, spleen size, hemoglobin, total leucocyte count, basophil, eosinophil, platelet, and blast). Comparison of categorical variables was analyzed using Pearson's $\chi 2$ or Fisher's exact test, as appropriate. Analysis of numerical variables was done using unpaired student t-test or Mann Whitney test, as appropriate. Statistical significance was defined by a one-sided α of less than 0.05. Analyses were performed using IBM SPSS for *Windows* version 25.

RESULTS

During the study period, there were 43 subjects involved in the study, but 3 subjects were lost to follow-up. Hence, 40 patients were eligible for analysis. The characteristics of patients are shown in **Table 2**.

The median age of enrolled subjects was 40 years, with 60% male and 40% female. On the prognostic scores using Sokal score, there were 42.5%, 17.5%, and 40.0% of patients with low-, moderate-, and High-risk, respectively. Based on the Hasford score, there were 30.0%, 37.5%, and 32.5% of patients with low-, moderate-, and High-risk, respectively. There were 95.0% of patients with low-risk and 5.0% with high-risk based on EUTOS score.

Table 2. Characteristics of the subjects (n=40)

Characteristics	Subjects mean ± or n (%) or median (range)
Age (years)	40 ± 11
Sex	
- Male	24 (60%)
- Female	16 (40%)
Spleen (cm)	8 ± 3
Hematologic profile	
- Hemoglobin (g/dL)	9.5 ± 2.6
- Leukocyte (/µL)	111,585 (20,390 – 498,470)
- Basophil (%)	1 (0 – 8)
- Eosinophil (%)	1 (0 – 5)
- Platelet (x10^3/ µL)	294 (31 – 1,123)
- Blast (%)	8 (2 – 20)
Sokal score - Low (<0.8) - Moderate (0.8 –1.2) - High (>1.2)	 17 (42.5%) 7 (17.5%) 16 (40.0%)
Hasford score - Low (≤780) - Moderate (781–1,480) - High (>1,480)	 12 (30.0%) 15 (37.5%) 13 (32.5%)
EUTOS score - Low risk (<= 87) - High risk (> 87)	 38 (95.0%) 2 (5.0%)

The prognostic scores were analyzed based on their complete hematologic response status (**Table 3**). There was no difference in patients' characteristics of age, sex disparities, spleen size, and hematologic profile (hemoglobin, leukocyte, basophil, eosinophil, platelet, and blast). The analysis based on Sokal score results, there was no correlation between Sokal score result and complete hematologic response status with $p > 0.05$. Similarly, the Hasford score result was not correlated with compete hematologic response status with $p > 0.05$. EUTOS score was also found not correlated with complete hematologic response status ($p > 0.05$)

Table 3. Patients characteristics based on complete hematologic response status.

Characteristics	Complete Hematologic Response		p value
	Yes (n=27)	No (n=13)	
Age (years)	42 ± 12	37 ± 8	0.261[a]
Sex			
Male	16 (59.3)	8 (61.5)	0.895[c]
Female	11 (40.7)	5 (38.5)	
Spleen (cm)	9 ± 3	7 ± 2	0.167[a]
Hematologic profile			
- Hemoglobin (g/dL)	9.8 ± 2.5	8.7 ± 2.6	0.208[a]
- Leukocyte (/µL)	92,000 (20,390 – 498,000)	142,250 (33,000 – 344,130)	0.231[b]
- Basophil (%)	1 (0 – 8)	1 (0 – 7)	0.467[b]
- Eosinophil (%)	1 (0 – 5)	1 (0 – 4)	0.285[b]
- Platelet (x10^3/µL)	223 (31 – 1.123)	445 (49 – 960)	0.153[b]
- Blast (%)	8 (4 – 19)	8 (2 – 20)	0.685[b]
Sokal score			
- Low (<0.8) - Moderate (0.8 – 1.2) - High (>1.2)	11 (40.7) 5 (18.6) 11 (40.7)	6 (46.2) 2 (15.4) 5 (38.4)	0.941[c]
Hasford score - Low (≤780) - Moderate (781 – 1,480) - High (>1,480)	 7 (26.0) 11 (40.7) 9 (33.3)	 5 (38.4) 4 (30.8) 4 (30.8)	0.701[c]
EUTOS score - Low risk (≤87) - High risk (> 87)	 27 (100.0) 0 (0.0)	 11 (84.6) 2 (15.4)	0.100[d]
[a]*unpaired t-test*, [b]*Mann Whitney test*, [c]*chi square test*, [d]*Fisher Exact test*			

Next, we analyzed the prognostic scores based on the early molecular response status of subjects (**Table 4**). There was no difference in subjects' characteristics of age, sex disparities, spleen size, and hematologic profile (hemoglobin, leukocyte, basophil, eosinophil, and blast) between the two groups. However, the platelet count was higher among patients who did not achieve early molecular response. Based on the Sokal score, there was no correlation between the Sokal score result and early molecular response status with $p > 0.05$. Similarly, the Hasford score result was not correlated with early molecular response status with $p > 0.05$. EUTOS score was also found not correlated with early molecular response status ($p > 0.05$)

Table 4. Patients characteristics based on early molecular response status.

Characteristics	Early Molecular Response		p value
	Yes (n=24)	No (n=16)	
Age (years)	40 ± 12	40 ± 10	0.986[a]
Sex			
Male	14 (58.3)	10 (62.5)	0.792[c]
Female	10 (41.7)	6 (37.5)	
Spleen (cm)	9 ± 3	7 ± 2	0,104[a]
Hematologic profile			
- Hemoglobin (g/dL)	9.4 ± 2.1	9.5 ± 3.2	0.892[a]
- Leukocyte (/µL)	100,150 (20,390 – 498,470)	131,475 (33,000 – 344,130)	0.456[b]
- Basophil (%)	1 (0 – 8)	1 (0 – 7)	0.836[b]
- Eosinophil (%)	1 (0 – 5)	1 (0 – 5)	0.614[b]
- Platelet (x10³/µL)	199 (31 – 803)	462 (49 – 1,123)	**0.024[b]**
- Blast (%)	8 (4 – 19)	9 (2 – 20)	0.709[b]
Sokal score			
- Low (<0.8) - Moderate (0.8 – 1.2) - High (>1.2)	10 (41.7) 4 (16.6) 10 (41.7)	7 (43.8) 3 (18.8) 6 (37.4)	0.936[c]
Hasford score - Low (≤780) - Moderate (781 – 1,480) - High (>1,480)	7 (29.2) 9 (37.5) 8 (33.3)	5 (31.3) 6 (37.4) 5 (31.3)	0.987[c]
EUTOS score - Low risk (≤87) - High risk (> 87)	24 (100.0) 0 (0.0)	14 (87.5) 2 (12.5)	0.154[d]

[a]*unpaired t-test*, [b]*Mann Whitney test*, [c]*Chi square test*, [d]*Fisher exact test*

DISCUSSION

The emerging of Imatinib use as the treatment for CML patients drives the need to refine prognostic scoring systems precision as it changed the treatment approach in recent clinical practice. The risk stratification should be well-discriminated by a good prognostic scoring system. Determining a good prognostic scoring system to use is imperative as it may be used to predict treatment response for treatment adjustment. Therefore, a comparison of each presence scoring system should be done to determine whether they can be applied to monitor patient progression to establish definitive guidelines in the future.

In this present study, we compared the number of patients who attained CHR with the results of each prognostic scoring system. Although the results were not statistically significant, we found that the percentage of patients who were categorized as low risk on Sokal, Hasford, and EUTOS scoring systems is higher among patients who did not achieve CHR compared to patients with good CHR after 3 months. Although our finding shows that all patients with low EUTOS score achieved CHR, the difference was not significant statistically. Therefore, the small number of this present study subjects may influence the statistical significance of the results. On the other hand, this study result was similar to other previous studies in Indian, Algerian, Pakistan and Chinese populations that showed a low-risk Sokal score was associated with attained CHR after 3 months, although not statistically significant.[1,2,24,25]

Similarly, our result shows that among patients who achieved EMR after 3 months of Imatinib treatment, the proportions of the low-risk group based on Sokal, Hasford, and EUTOS scoring systems were higher compared to patients with poor EMR, although not statistically significant. Similarly, although our finding shows that all patients with low EUTOS score achieved EMR, the difference was not significant statistically. Hence, the number of subjects in this present study may influence the statistical significance of the results. Also, whether our result was influenced by the shorter follow-up period of 3 months remains elusive. To date, there is no study comparing each CML prognostic scoring system with a single date of molecular response follow-up of 3 months (EMR). Instead, several studies with a longer period of follow-up showed varied results. A previous study found that EUTOS was not correlated with major molecular response (MMR) at 8 years, whereas Sokal score predicted

the MMR at 8 years.[6] In a study among the Poland population, the Hasford scoring system was correlated with long-term MMR with a median of the follow-up period of 47 months.[26] Similarly, a study of the South Korean population also found Sokal, Hasford, and EUTOS scoring systems were significantly correlated with MMR rate at 8 months.[7]

Nevertheless, the insignificant result of this present study findings may also demonstrate the efficacy of Imatinib as a CML treatment. A study by Dybko et al showed that the number of patients treated with second-generation TKI who attained MMR after 3 months was significantly higher within the low-risk Hasford group compared to the intermediate-risk group.[26] Also, CML patients underwent second-generation TKI were likely to attain 18 months MMR among patients who were categorized as low-risk in the Hasford scoring system.[27] There are multiple factors affecting the therapeutic response among CML patients. A previous multivariate analysis showed discontinuation of Imatinib treatment for 4 weeks was associated with poor cytogenetic outcome. In addition, a higher platelet count with a cut-off point of more than 450 x 10^3/µL was significantly associated with poor major cytogenetic outcome.[28] This may explain a higher platelet count among is found among patients with poor EMR in this study compared to good EMR (Table 4). Importantly, adequate evaluation of patient compliance who are on Imatinib treatment should be implemented.
However, this study has several limitations. Relatively small sample size from a single center may influence the results of this present study. In addition, examiners' error on manual spleen size measurement and a wide range of treatment adherence variation among patients may also contribute to the poor therapeutic response.

CONCLUSION

Determining a predictable prognostic scoring system to be used for CML patients is needed. In this study, we did not validate the efficacy of three most-used prognostic scoring systems to predict therapeutic response among CML patients receiving Imatinib treatment. However, the low-risk prognostic score may result in better therapeutic responses. As study findings among different centers worldwide are still inconsistent, an international multi-centered study to validate these prognostic scoring systems is imperative for future study.

CONFLICT OF INTEREST

None

Author Contributions

Conceptualization: IW, RMAR, LR, MHB; Data curation: IW, FAD; Formal analysis: FAD; Funding acquisition: LR; Investigation: IW, MHB; Methodology: IW, RMAR, LR, MHB; Project administration: IW; Resources; Software; Supervision: RMAR, LR, MHB; Validation; Visualization: FAD; Roles/Writing - original draft: IW, FAD; Writing - review & editing: FAD, MHB

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