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Moderate anemia at diagnosis is an independent prognostic marker of the EUTOS, Sokal, and Hasford scores for survival and treatment response in chronic-phase, chronic myeloid leukemia patients with frontline imatinib

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ORIGINAL ARTICLE

Moderate anemia at diagnosis is an independent prognostic marker of the EUTOS, Sokal, and Hasford scores for survival and treatment response in chronic-phase, chronic myeloid leukemia patients with frontline imatinib

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ABSTRACT

Objectives: This study aimed to examine the prognostic value of anemia for the diagnosis of chronic myeloid leukemia in the chronic phase (CML-CP) receiving imatinib.

Methods: One hundred and fifty-four CML-CP patients were enrolled. The influences of moderate anemia with hemoglobin (Hb) < 10 g/dl, four scoring systems, and the early molecular response at 3 months (BCR-ABL $\leq$10%; 3M-EMR) on the achievement of a deep molecular response (DMR, MR4.5), progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) were compared.

Results: Moderate anemia was identified in 44 (28.6%) patients. These patients had more aggressive baseline features and higher risks, as assessed by scoring systems, and less favorable treatment responses vs those without anemia, including 3M-EMR (50.0% vs 69.1%), a complete cytogenetic response at 6 months (20.5% vs 50.9%), and a major molecular response at 12 months (22.5% vs 45.2%), with a median follow-up of 54.0 months. Furthermore, an Hb of 10 g/dl better distinguished DMR, EFS, PFS, and OS than the EUTOS, Sokal, and Hasford scores, and better predicted the responses and survivals in combination with 3M-EMR than 3M-EMR alone.

Conclusions: This finding highlights the significance of anemia in CML-CP, and suggests that patients with anemia at diagnosis should be carefully monitored and might benefit from more potent TKIs if not achieving 3M-EMR.

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Chronic myeloid leukemia; anemia; scoring systems; prognosis

Introduction

The prognosis of chronic myeloid leukemia (CML) has improved dramatically since the introduction of imatinib and other tyrosine kinase inhibitors (TKIs)[1–3]. The 5-year overall survival (OS) of patients with chronic myeloid leukemia in the chronic phase (CML-CP) receiving first-line therapy with imatinib is currently ~83–89%[2,4]. The second-generation TKIs, nilotinib and dasatinib, are known for their stronger potencies in inhibiting BCR-ABL oncoprotein, and have been approved as the choice of first-line therapy for CML-CP. The two major randomized studies on the second-generation TKIs, ENESTnd and DASISION, showed that frontline nilotinib and dasatinib were more efficacious in achieving optimal responses than imatinib[5,6]. Patients who achieved an early molecular response (EMR; BCR-ABL $\leq$10% on the international scale [BCR-ABL^{IS}]) at 3 months (3M-EMR) were proven to have better survival outcomes[2,4]. Thus, currently, a deeper and more rapid molecular response is the treatment goal, and 3M-EMR is recommended as a landmark of an optimal treatment response[7]. However, CML-CP patients continue to face treatment failure, disease progression, or drug intolerance.

To predict the outcomes of CML-CP patients in the TKI era, several predictive prognostic scores and markers at diagnosis were used to identify those with less-favorable treatment responses and outcomes. The Sokal score is one such marker proposed for chemotherapy[8], and was revised once for patients less than 45 years of age despite fewer applications[9]. The Hasford score is another marker developed for interferon-alpha[10]. Hasford *et al.*[11] established the European Treatment and Outcome Study (EUTOS) score, based on

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Supplemental data for this article can be accessed here.

spleen size and the blood basophil percentage, which predicts a complete cytogenetic response (CCyR) and progression-free survival (PFS) better than the Sokal and Hasford scores in CML-CP patients receiving front-line imatinib. Recently, Pfirrmann *et al.*[12] published a more specific score, namely the EUTOS long-term survival (ELTS) score, considering disease-specific deaths. Additionally, Lautti *et al.*[13] found that additional chromosomal abnormalities (ACAs) in the Philadelphia-positive clone were an adverse prognostic marker for front-line imatinib therapy. In addition, comorbidities might also be associated with patient adherence to TKI treatment and, hence, might affect survival outcomes[14]. Although the ENESTnd and DASISION trials have already shown that high-risk and intermediate-risk patients (as determined by the Sokal or Hasford scores) may preferentially benefit from nilotinib or dasatinib relative to imatinib in terms of the treatment response and disease progression, no survival improvement was reported, and imatinib is still highly effective in CML-CP patients. Choosing a suitable frontline TKI is important in consideration of adverse events, comorbidities, and cost, especially since a generic formulation of imatinib will become available this year.

Patients with co-existing anemia at the diagnosis of CML-CP are not rare. Anemia might be related to CML itself, due to ineffective hematopoiesis secondary to leukemia cell infiltration of the bone marrow or dilutional anemia due to massive splenomegaly[15], or anemia may be related to other comorbidities. During the establishment of the Sokal scores, the hemoglobin levels were prognostic in univariate analysis, but not significant in a multivariate regression for survival. Hence, hemoglobin levels were not included in the subsequent widely used prognostic scoring systems, and are rarely discussed as a baseline prognostic surrogate. However, anemia at diagnosis was recently reported to be associated with higher white blood cell counts, more frequent splenomegaly, and more CML-related deaths[16], and is a significant independent parameter of the achievement of a deep molecular response (DMR; MR4.5)[17]. Moreover, two other studies in the literature reported that the hemoglobin level was a marker associated with the outcomes of CML patients after imatinib failure[18,19]. In addition, reports have shown that a combination of baseline parameters at the diagnosis of CML with 3M-EMR better predicts patient outcomes and responses[20,21].

This study aimed to examine the role of baseline hemoglobin levels in predicting survival outcomes and DMR, and aimed to verify that the combination of prognostic surrogates with 3M-EMR is a better prediction model in patients with CML-CP who received a standard dose of imatinib.

Materials and methods

Patients and treatment

From January 2001 to April 2014, we conducted a retrospective review of patients from our hospital who were consecutively newly diagnosed as Philadelphia chromosome-positive (Ph+) CML-CP, and were treated with imatinib as the front-line therapy in accordance with the ELN 2013 recommendation. Patients who previously received interferon-α (INF-α) or any chemotherapeutic agent, or any agent in combination with TKI treatment, and patients who were lost to follow-up within 6 months of diagnosis were excluded from the study. The enrolment process is illustrated in Figure 1. A total of 154 CML-CP patients were included in the analysis. We performed data collection, captured the baseline general characteristics, and calculated the EUTOS, Sokal, and Hasford scores on the ELN work site (http://www.leukemia-net.org) according to the published formulae. The study was approved by the institutional review board of Taipei Veterans General Hospital, and was conducted in accordance with the Declaration of Helsinki.

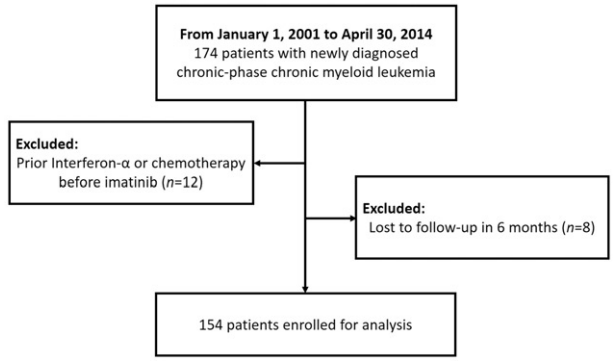

Figure 1. Patient selection ($n = 154$).

Cytogenetic and molecular analyses

The cytogenetic response was measured in bone marrow cells and was determined by metaphase analyses with the G-banding technique after short-term culture. At least 20 metaphases were required. We used the real-time PCR technique to quantify the BCR-ABL levels from the patients' peripheral blood samples at our hospital. The BCR-ABL/ABL1 transcript copy number was expressed as the copy number ratio of BCR-ABL to ABL1 in international scale (IS) units after multiplication by conversion factors. The conversion factors are validated by laboratories of the Institute of Medical and Veterinary Science, and the Leukemia Research Unit, Hanson Centre for Cancer Research in Adelaide, South Australia. The molecular response was defined as a reduction in the transcript level.

Definitions

Chronic phase (CP), complete hematologic response (CHR), complete cytogenetic response (CCyR), early molecular response (EMR), major molecular response (MMR), and complete molecular response (DMR) were defined in accordance with the ELN 2013 recommendations[7]. OS was measured from the date of TKI initiation to the date of death from any cause, last follow-up date, or last date of data collection (August 14, 2014). PFS was measured from the date of TKI initiation to the date of disease progression to an accelerated phase (AP)/blast crisis (BC) or death from any cause. Event-free survival (EFS) was measured from the date of TKI

initiation to the date of the first encountered event. The definition of events included disease progression, death, treatment failure according to the definition of the ELN 2013 recommendations, and first-line TKI discontinuation due to intolerance.

Defining the cut-off value of baseline hemoglobin levels

The cut-off value of the baseline hemoglobin level of CML-CP patients was decided by ROC analysis for EFS, PFS, OS, and MR4.5 achievement. The cut-off value with the largest Youden's index was 10.20 g/dl for MR4.5 achievement and OS, and 10.45 g/dl for EFS and PFS. To use a more simplified clinical surrogate than 10.20 g/dl or 10.45 g/dl, we used 10 g/dl as our arbitrary cut-off value.

Statistical analysis

Differences among variables were tested using either a Chi-squared test for categorical data or Mann-Whitney *U*-test for continuous data. EFS, PFS, and OS were estimated using Kaplan-Meier methods and were compared using the log-rank test. The cumulative incidence rates for cytogenetic and major molecular responses were estimated by considering death as the competing event. The discriminatory abilities of the four prognostic models and baseline characteristics were examined by the Cox proportional hazards model, and the results of the Cox model were expressed with the Akaike information criterion (AIC), which revealed how EFS, PFS, and OS were affected. The AIC was first developed by Akaike[22] as a way to compare different models on a given outcome. Akaike[22] showed that the selection of the "best" model is determined by an AIC score: $AIC = 2K\text{-}2\log(£(\theta|\ y))$, where K is the number of estimable parameters (degrees of freedom), and $\log£(\theta|\ y)$ is the log-likelihood at its maximum point of the model estimated. The model with the lowest *AIC* is more explanatory and informative[23,24]. A Cox proportional hazards model was used to analyze the predictive value of factors for survival outcomes. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 21.0 (SPSS. Inc., Chicago, IL). A *p*-value less than 0.05 was considered statistically significant.

Results

Patients

Between January 2001 and April 2014, 174 consecutive patients with CML-CP receiving frontline imatinib were screened. After excluding 12 patients who received INF-α or chemotherapy before TKI treatment and eight patients who were lost to follow-up within 6 months of diagnosis, 154 patients were enrolled in the study (Figure 1).

Baseline characteristics and treatments

The baseline characteristics of the 154 patients with CML-CP are shown in Table 1.

Table 1. Clinical characteristics of patients at presentation ($n = 154$).

Clinical characteristics	Median (range)	No. patients (%)
Age (years)	51 (18–86)	
Spleen size[a] (cm)	2.0 (0–14.0)	
WBC (10^9/L)	111.06 (3.0–610.3)	
Blast (%)	1.0 (0–10.0)	
Eosinophil (%)	2.0 (0–15.0)	
Basophils (%)	5.0 (0–19.0)	
Hemoglobin (g/dL)	10.9 (5.6–18.0)	
MCV	90.9 (80.2–102.0)	
Platelet counts (10^9/L)	415.0 (88.0–2412.0)	
Sex		
Male		89 (57.8)
Female		65 (42.2)
ACAs		
Yes		25 (16.2)
No		129 (83.8)
EUTOS score		
Low-risk		120 (77.9)
High-risk		34 (22.1)
Sokal score		
Low-risk		52 (33.8)
Intermediate-risk		56 (36.3)
High-risk		46 (29.9)
Hasford score		
Low-risk		62 (40.3)
Intermediate-risk		72 (46.7)
High-risk		20 (13.0)
ELTS score		
Low-risk		81 (52.6)
Intermediate-risk		50 (32.5)
High-risk		23 (14.9)

Abbreviations. ACAs, additional chromosomal abnormalities in Ph^+ cells; EUTOS, European treatment and outcome study; WBC, white blood cell; MCV, mean corpuscular volume; ELTS, The EUTOS long-term survival.
[a]Maximum distance from the costal margin by manual evaluation.

General outcomes

After a median follow-up period of 54 months (range = 3–144 months), the estimated OS, PFS, and EFS of the 154 patients at 5 years was 87.8%, 85.9%, and 66.9%, respectively (Supplemental Figure 1(A)). A total 15 patients died, including 11 deaths related to disease progression (either to AP or BC), three deaths related to infection with stable CML (two with pneumonia, and one with fungemia of *Candida tropicalis*), and one death related to hepatitis B virus reactivation. The cumulative incidence rates of CCyR and MMR at 5 years were 76.2% and 65.7% in all patients, respectively. The DMR (MR4.5) at 5 years was 40.1% (Supplemental Figure 1(B)). The 49 events counted as first-occurring events and included 10 events of imatinib discontinuation due to intolerance, 22 events of treatment failure, 13 events of disease progression, and four events of death unrelated to CML.

Association between the hemoglobin level and four scoring systems, baseline characteristics, and treatment responses

An analysis of our patients with low and high hemoglobin (Hb) levels was conducted, and the results are shown in Table 2. Patients with moderate anemia (Hb < 10 g/dl) had more splenomegaly, higher white blood cell counts, higher percentages of blasts and eosinophils in the peripheral blood,

Table 2. Characteristics and treatment responses of CML-CP patients with high and low hemoglobin levels at presentation ($n = 154$).

	Hb ≥10.0 g/dL ($n = 110$)	Hb <10 g/dL ($n = 44$)	p value
Sex, *n* (%)			
Male	64 (58.2)	25 (56.8)	.877
Female	46 (41.8)	19 (43.2)	
Age, *n* (%)			
≥60	81 (73.6)	26 (59.1)	.077
<60	29 (26.4)	18 (40.9)	
Splenomegaly, *n* (%)			
Yes	57 (51.8)	34 (77.3)	.004
No	53 (48.2)	10 (22.7)	
MCV			
Median, fL (range)	90.9 (80.2–100.6)	91.3 (80.3–102.0)	.717
WBC			
Median (10^9/L) (range)	88.6 (3.0–471.0)	177.4 (4.9–610.3)	<.001
Blast in PB			
Median (%) (range)	1.0 (0–10.0)	2.0 (0–10.0)	
Basophil in PB			
Median (%) (range)	5.0 (0–17.0)	6.0 (0–19.0)	.002
Eosinophil in PB			
Median (%) (range)	2.0 (0–9.0)	2.0 (0–15.0)	.068
Platelets			
Median (10^9/L) (range)	408.0 (98–1186.0)	422.0 (88–2412.0)	.038
EUTOS, *n* (%)			
High risk	18 (16.4)	16 (36.4)	.939
Low risk	92 (83.6)	28 (63.6)	.007
Sokal, *n* (%)			
High risk	25 (22.7)	22 (50.0)	.001
Intermediate/low risk	85 (77.3)	22 (50.0)	
Hasford, *n* (%)			
High risk	8 (7.3)	13 (29.5)	.001
Intermediate/low risk	102 (92.7)	31 (70.5)	
ELTS, *n* (%)			
High risk	12 (10.9)	11 (25.0)	.021
Intermediate/low risk	98 (89.1)	33 (75.0)	
ACAs status, *n* (%)			
Positive	14 (12.7)	11 (25.0)	.049
Negative	96 (87.3)	33 (75.0)	
Optimal responses			
3M-EMR, *n* (%)	76 (69.1)	22 (50.0)	.031
6M-CCyR, *n* (%)	56 (50.9)	9 (20.5)	<.001
12M-MMR§, *n* (%)	47 (44.3)	9 (22.5)	.006

Abbreviations. Hb, hemoglobin; MCV, mean corpuscular volume; WBC, white blood cell; PB, peripheral blood; LR, low-risk; IR, intermediate risk; HR, high risk; ELTS, The EUTOS long-term survival; ACAs, additional chromosomal abnormalities in Ph + cells; 3M-EMR, early molecular response with BCR-ABL ≤10% at 3 months; 6M-CCyR, complete cytogenetic response at 6 months; 12M-MMR, major molecular response at 12 months; 10 patients followed <12 months had no data for molecular response (six in Hb ≥10.0 g/dl; four in Hb <10 g/dl).

a high EUTOS risk, a high Sokal risk, a high Hasford risk, a high ELTS score, and more additional chromosomal abnormalities than patients with Hb ≥10 g/dl. Patients with moderate anemia had less favorable treatment responses, including 3M-EMR (50.0% vs 69.1% in Hb ≥10 g/dl, $p = .031$), a complete cytogenetic response at 6 months (20.5% vs 50.9% in Hb ≥ 10 g/dl, $p < .001$), and a major molecular response at 12 months (22.5% vs 44.3% in Hb ≥10 g/dl, $p = .006$).

Predictive roles of the baseline hemoglobin level, four scoring systems, and ACA status for DMR, EFS, PFS, and OS

The predictive roles of the baseline hemoglobin level, four scoring systems, and ACA status by the EUTOS for DMR achievement and survival outcomes are presented in Tables 3 and 4, respectively. Moderate anemia is a significant predictor of DMR achievement ($p = .026$), the Sokal score is a significant predictor ($p = .049$), and 3M-EMR is a significant predictor ($p = .006$). However, being ACA-positive, the EUTOS score, and the Hasford score are not significant predictors. Moderate anemia ($p = .003$), being ACA-positive ($p = .020$), the Sokal score ($p = .001$), the Hasford score ($p = .001$), and 3M-EMR ($p < .001$) are significant predictors of EFS. Moderate anemia ($p = .006$), being ACA-positive ($p = .022$), the Sokal score ($p = .016$), the Hasford score ($p = .003$), and 3M-EMR ($p = .004$) are significantly predictive of PFS, while the EUTOS score is not. Moderate anemia ($p = .015$) and 3M-EMR ($p = .031$) are predictive of OS, while being ACA-positive, the EUTOS score, the Sokal score, and the Hasford score are not. Regarding the quality of each model, 3M-EMR is predictive for differences with the lowest AIC in MR4.5, EFS prediction, and PFS prediction, in contrast to moderate anemia, which had the lowest AIC for the prediction of OS (Tables 3 and 4). Significant factors (Tables 3 and 4, $p < .1$) including ACA positivity and a scoring system with the lowest AIC at the time of diagnosis and with the lowest AIC for MR4.5 and survival outcomes in the univariate Cox regression were entered into further multivariate Cox regression analyses. As shown in Table 5, moderate anemia independently predicted EFS and PFS, but not OS, after multivariate adjustment. To predict DMR achievement, moderate anemia tended to predict a failure of achievement.

Combination of the hemoglobin level and score systems for detecting differences in DMR, EFS, PFS, and OS

As a significant risk factor at diagnosis, moderate anemia was further combined with achieving 3M-EMR to stratify patients into four groups to predict patient outcomes. For the achievement of DMR, patients without moderate anemia and with 3M-EMR had the best results. DMR achievement did not differ between patients without moderate anemia and without 3M-EMR, and patients with moderate anemia and with 3M-EMR. DMR achievement between patients with moderate anemia and without 3M-EMR was the most unlikely (Supplemental Figure 2(A)). Using this stratification system, similar survival prediction results were demonstrated (Supplemental Figures 2(B–D)). To simplify the stratification process, the patients were divided into two groups: (1) those without moderate anemia at diagnosis and with 3M-EMR and (2) those with moderate anemia or without 3M-EMR. This simplified stratification is a significant predictor of DMR, EFS, PFS, and OS (Figures 2–5) with the lowest AIC compared with other baseline prognostic surrogates and 3M-EMR (Tables 3 and 4).

Discussion

In this study, the patients with moderate anemia at the time of diagnosis also tended to have splenomegaly, higher white blood cell counts, higher percentages of blasts and eosinophils, and a high risk, as evaluated by the four

Table 3. Hazard ratio of different prediction models of DMR achievement.

	DMR achievement		AIC[b]
	HR (95% CI)	*p* value	
At presentation			
Hb (<10 vs. ≥10 g/dl)	0.47 (0.25–0.91)	.026	482.68
ACAs positive (yes vs. no)	0.57 (0.26–1.25)	.158	486.11
EUTOS score (high vs. low)	0.69 (0.37–1.31)	.257	487.04
Sokal score (high vs. low[a])	0.53 (0.28–0.98)	.049	484.08
Hasford score (high vs. low[a])	0.71 (0.32–1.56)	.388	487.59
ELTS score (high vs. low[a])	0.57 (0.24–1.34)	.196	486.48
Treatment response			
3M-EMR (>10% vs. ≤10%)	0.45 (0.24–0.78)	.006	479.88
Combination of Hb and 3M-EMR			
[(Hb <10 g/dl or 3M-EMR >10%) vs. (Hb ≥10 g/dl and 3M-EMR ≤10%)]	0.44 (0.26–0.75)	.002	478.99

Abbreviations. DMR, complete molecular response; MR4.5, Hb, hemoglobin; ACAs, additional chromosomal abnormalities in Ph + cells; EUTOS, European treatment and outcome study; ELTS, The EUTOS long-term survival; 3M-EMR, early molecular response with BCR-ABL ≤10% at 3 months; HR, hazard ratio; AIC, Akaike information criterion.
[a]Including intermediate-risk and low-risk.
[b]Akaike information criterion, a lower AIC is more explanatory and informative.

Table 4. Hazard ratio of different prediction models of survival outcomes.

	Event-free survival		AIC[b]	Progression-free survival		AIC[b]	Overall survival		AIC[b]
	HR (95% CI)	*p* value		HR (95% CI)	*p* value		HR (95% CI)	*p* value	
At presentation									
Hb (<10 vs ≥10 g/dl)	2.32 (1.33–4.08)	.003	440.70	3.62 (1.46–9.01)	.006	169.15	3.62 (1.29–10.18)	.015	125.04
ACAs positive (yes vs no)	2.10 (1.13–3.90)	.020	444.13	2.97 (1.17–7.56)	.022	172.22	2.30 (0.78–6.75)	.130	133.06
EUTOS score (high vs low)	0.99 (0.51–1.89)	.965	448.98	1.09 (0.39–3.04)	.864	176.78	0.71 (0.20–2.52)	.592	134.81
Sokal score (high vs low[a])	2.64 (1.51–4.63)	.001	437.99	3.02 (1.23–7.45)	.016	171.21	2.63 (0.95–7.29)	.064	131.73
Hasford score (high vs low[a])	2.85 (1.53–5.31)	.001	439.76	4.10 (1.61–10.41)	.003	169.50	2.72 (0.92–8.02)	.070	132.25
ELTS score (high vs low[a])	1.65 (0.82–3.30)	.160	447.19	3.68 (1.45–9.35)	.006	170.46	2.72 (0.92–8.02)	.070	132.24
Treatment response									
3M-EMR (>10% vs ≤10%)	3.38 (1.89–6.05)	<.001	431.28	4.15 (1.58–10.93)	.004	167.67	3.28 (1.12–9.60)	.031	130.07
Combination of Hb and 3M-EMR									
[(Hb <10 g/dl or 3M-EMR >10%) vs (Hb ≥10 g/dl and 3M-EMR ≤10%)]	4.04 (2.01–8.09)	<.001	429.66	8.66 (2.00–37.50)	.001	163.01	12.21 (1.61–93.92)	.002	123.40

Abbreviations. Hb, haemoglobin; ACAs, additional chromosomal abnormalities in Ph + cells; EUTOS, European treatment and outcome study; 3M-EMR, early molecular response with BCR-ABL ≤ 10% at 3 months; HR, hazard ration; AIC, Akaike information criterion.
[a]Including intermediate-risk and low-risk.
[b]Akaike information criterion, a lower AIC is more explanatory and informative.

Table 5. Multivariate Cox regression for survival outcomes.

	HR (95% CI)	*p*
Event-free survival*		
Hb (<10 vs ≥10 g/dl)	2.06 (1.09–3.87)	.026
Sokal score (high vs low[a])	1.47 (0.78–2.76)	.233
ACAs positive (yes vs no)	1.49 (0.77–2.89)	.233
Progression-free survival*		
Hb (<10 vs ≥10 g/dl)	2.79 (1.05–7.41)	.040
Hasford score (high vs low[a])	2.45 (0.90–6.68)	.079
ACAs positive (yes vs no)	2.13 (0.83–6.28)	.121
Overall survival*		
Hb (<10 vs ≥10 g/dl)	2.93 (0.96–8.99)	.060
Sokal score (high vs low[a])	1.74 (0.57–5.28)	.329
DMR achievement*		
Hb (<10 vs ≥10 g/dl)	0.48 (0.25–1.00)	.051
Sokal score (high vs low[a])	0.84 (0.33–2.17)	.725

Abbreviations. HR, hazard ratio; DMR, MR4.5.
[a]For DMR and survival outcomes, hemoglobin, ACAs positivity (if $p < .1$) and the scoring system with the lowest AIC in Table 3 entered further multivariate Cox regression analysis.
[b]Including intermediate-risk and low-risk.

scoring systems. Our analysis identified the association between moderate anemia and the aggressiveness of CML-CP. Hence, patients with moderate anemia had less favorable treatment responses at 3, 6, and 12 months. The prognostic value of the baseline hemoglobin level for DMR achievement and survival outcomes was confirmed and is even better if combined with 3M-EMR. Our findings highlight the value of using a cut-off baseline hemoglobin level of 10 g/dl, and suggest we consider combining prognostic surrogates with 3M-EMR results after imatinib treatment to better predict the outcomes of CML-CP.

In a setting outside of a clinical trial, our cohort demonstrated a comparable 5-year OS of 87.8% and PFS of 85.9% compared with patients in the IRIS trial[4]. The events observed for EFS in our cohort included imatinib discontinuation due to intolerance and treatment failure under the latest 2013 ELN guidelines, which could explain the lower 5-year EFS of 66.9%.

Anemia is common among CML-CP patients, and might be related to the nature of the disease or other comorbidities. In a review of previous studies, we found that anemia at the diagnosis of CML-CP (baseline haemoglobin <12.0 g/dl) was associated with high-risk features and CML-related deaths, but was not related to the treatment response[16]. Anemia was also considered a poor prognostic factor associated with PFS in CML patients receiving nilotinib after imatinib failure, and was

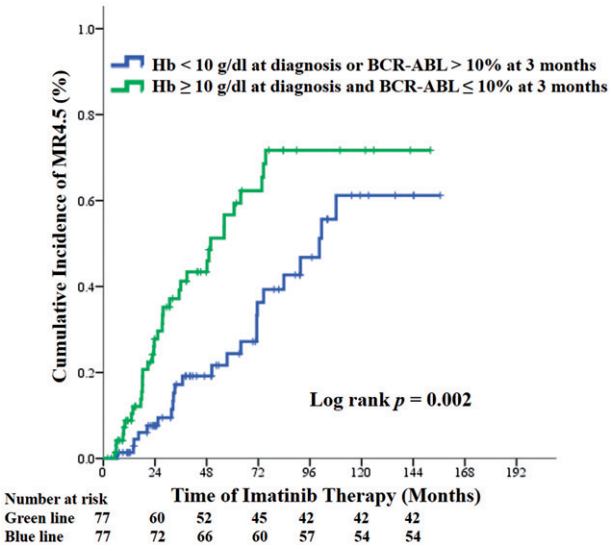

Figure 2. Cumulative incidence of DMR (MR4.5) in CML-CP patients receiving imatinib stratified by hemoglobin level with a cut-off value of 10 g/dl and 3M-EMR (two groups).

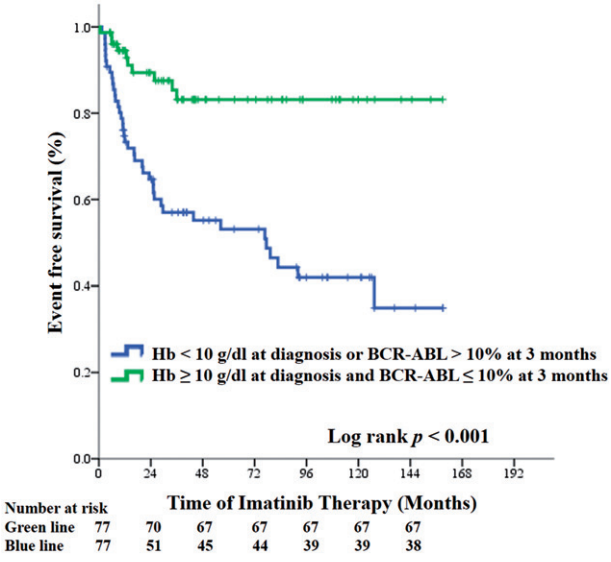

Figure 3. Event-free survival in CML-CP patients receiving imatinib stratified by hemoglobin level with a cut-off value of 10 g/dl and 3M-EMR (two groups).

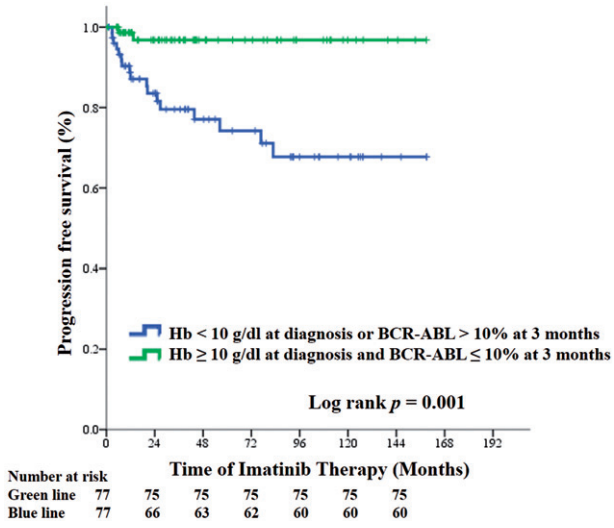

Figure 4. Progression-free survival in CML-CP patients receiving imatinib stratified by hemoglobin level with a cut-off value of 10 g/dl and 3M-EMR (two groups).

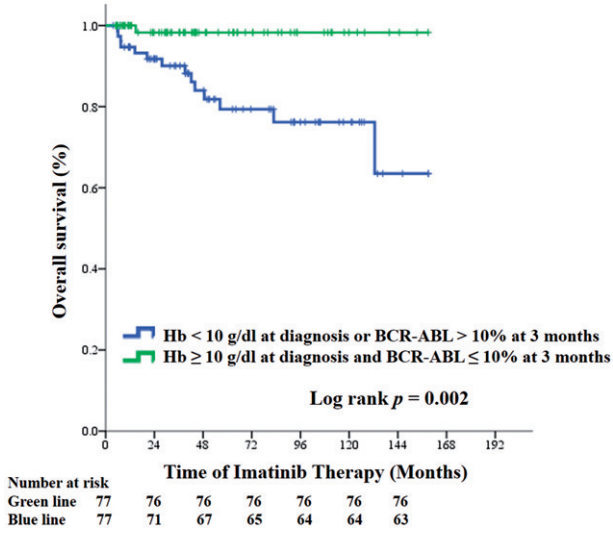

Figure 5. Overall survival in CML-CP patients receiving imatinib stratified by hemoglobin level with a cut-off value of 10 g/dl and 3M-EMR (two groups).

described as a negative factor associated with 3-month CCyR to 2nd line TKI in CML patients after imatinib failure[18,19]. Nonetheless, after the introduction of three widely used scoring systems, anemia has rarely been discussed as a baseline prognostic surrogate for CML patients before TKI treatment. It is worth mentioning that the revised Sokal score in 1985 added the prognostic value of the hematocrit, but the revised score was recommended for patients younger than 45 years of age. Because the original Sokal and Hasford scores were developed in the pre-TKI era, and hemoglobin levels were not included in either of these assessments, our focus on re-visiting the prognostic value of co-existent anemia at baseline at the time of the CML diagnosis is not a conflicting theory. Anemia levels <12.0 g/dl have been studied before, and were found not to be significant predictors of treatment response[16]. Additionally, the cut-off value of the hemoglobin level in the present study to define anemia as 10 g/dl by ROC analysis was scarcely reported previously, except by Oyekunle *et al.*[25], who validated it to predict overall survival. Anemia levels of 10 g/dl are a component of the Dynamic International Prognostic Scoring System plus (DIPSS plus), which effectively provides prognostic information for primary myelofibrosis (PMF). As an entity in myeloproliferative neoplasms, CML shares some clinical features with PMF such as anemia and bone marrow fibrosis. Bone marrow fibrosis in patients with myelofibrosis has been reported to be of prognostic significance[26], and was also reported to be related to poor outcomes in CML patients receiving imatinib[27,28]. Hence, the choice of a cut-off of 10 g/dl seemed reasonable. Outside of the nature of CML, anemia might be related to other comorbidities or invariable characteristics such as age or gender. All of the above factors might be confounding factors in the analysis of outcomes. As shown in Table 2, the patients' RBCs in our cohort were mainly normocytic, and the patients' MCVs did not differ between those without and with moderate anemia. This result might suggest

that the patients in our cohort with moderate anemia were less likely to have comorbidity-related anemia, such as iron-deficiency anemia or renal anemia. According to the results of Berger *et al.*[29], male CML patients had the worst outcomes. Additionally, while the number of male patients in our cohort with moderate anemia was larger than that of female patients with moderate anemia, the difference was not significant. Additionally, more patients with moderate anemia in the present study were in high-risk groups and had more moderate features such as splenomegaly, higher white blood cell counts, and higher percentages of peripheral blasts and eosinophils. This finding suggests that anemia itself in this cohort was directly related to CML.

In validating the CML risk scoring systems in our patient cohort, we found that the Hasford and Sokal scores, but not the EUTOS score, were clinically effective prognostic indicators for EFS and PFS. The EUTOS score was the most recently developed score system and the only system developed in the TKI-era, and it is widely used due to its simplicity. However, its usefulness is still uncertain. From the limited studies that included Asian patients similar to our cohort, Yahng *et al.*[30], Iriyama *et al.*[31], and Tao *et al.*[32] used the EUTOS score in patients from Korea, Japan, and China, respectively, and reported its clinical value. However, Yamamoto *et al.*[33] demonstrated the negative value of the EUTOS score, similar to the findings of the present study. The inconclusive results of the predictive capacity of the EUTOS might be due to the discordance between the scoring systems mentioned in the previous studies[30,32–39]. In the present cohort, only eight patients (25.8%) in the EUTOS high-risk group also belonged to the high-risk group defined by the other two scoring systems. Moreover, bias due to possible inter-observer error in the measurement of the spleen size could also affect the reliability of using the EUTOS score to predict outcomes in the present cohort. Moreover, a large study including 2,784 adult patients conducted by Castagnetti *et al.*[21] found that differences, such as the baseline spleen size and distribution in the EUTOS score, exist among young adults, adults, and elderly CML patients, and the authors concluded that young adolescent (age 18–29 years) patients might have relatively larger spleens and higher EUTOS scores. Therefore, a reconsideration of developing a novel prognostic risk model that could overcome this discrepancy is important. Hence, the significant prognostic role of hemoglobin levels at the time of diagnosis in our patients is worthy of further evaluation in larger studies.

Previous studies have researched the influence of combining baseline parameters at the diagnosis of CML with 3M-EMR to better predict patient outcomes and responses[15]. Qin *et al.*[17] found that combining the WBC count at presentation with the molecular response at 3 months predicts deep molecular responses to imatinib in newly diagnosed CP-CML patients. Castagnetti *et al.*[21] found that combining the EUTOS score and 3-month BCR-ABL transcript level identifies a group of low-risk CML patients with favorable responses to frontline imatinib therapy. In contrast, our study found that Hb $<$10 g/dl is associated with high-risk CML, and combining Hb $<$10 g/dl with no 3M-EMR predicts a less favorable response to frontline imatinib, as well as worse survival outcomes in CP-CML patients with the lowest AIC (Tables 3 and 4). Interestingly, in our study, the low hemoglobin level ($<$10 g/dl) is associated with a higher WBC count and higher proportions of high-risk categories among each CML risk score (the EUTOS, Sokal, and Hasford scores) (Table 2), which may partly explain our finding that combining the hemoglobin level with the 3-month molecular response had good discriminative power. Given that heterogeneity may exist among different patient populations, further larger prospective studies are necessary to validate the combination of models with the optimal prediction abilities.

In this study, the retrospective nature and data from one single center are potential limitations. Additionally, we could not effectively evaluate the patients' adherence to treatment, which might contribute to a bias in the outcome analysis. Furthermore, although no event that determined imatinib discontinuation was due to anemia in the course of disease progression, we could not determine whether anemia at the time of diagnosis affected the patients' adherence to treatment. Finally, some patients who were lost to follow-up had no 12-month MMR data, so there may be some bias in the evaluation of treatment response.

In conclusion, the present study not only confirmed the prognostic role of hemoglobin levels at the diagnosis of CML-CP, but also identified a possible better prediction model for MR4.5 and survival outcomes using a combination of baseline hemoglobin levels with 3M-EMR after imatinib treatment. This study warrants highly desirable prospective studies for validation.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The authors declare that they have no conflict of interest. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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