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Bcr::Abl1 B2A2 And B3A2 Transcripts And Longitudinal Hematologic And Splenic Response To Tyrosine Kinase Inhibitors In Chronic Myeloid Leukemia: A Prospective Cohort Study

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ABSTRACT: The clinical significance of major BCR::ABL1 transcript subtypes in chronic myeloid leukemia (CML) remains incompletely defined, particularly regarding longitudinal hematologic and splenic responses to tyrosine kinase inhibitor (TKI) therapy. This prospective cohort study included 59 adults with CML carrying b3a2 (n=45) or b2a2 (n=14) transcripts who received imatinib or nilotinib and completed six months of follow-up. Hematologic parameters and Schuffner-equivalent spleen size were assessed at baseline and at months 3 and 6. Longitudinal hematologic trajectories were evaluated using linear mixed-effects models, whereas splenic trajectories were analyzed using generalized estimating equations. Models were adjusted for age, sex, and TKI type. Significant changes over time occurred in all hematologic parameters. Time-by-transcript interactions were observed for platelet count ($p=0.010$) and basophil percentage ($p=0.041$), but not for other hematologic parameters. Splenic regression also differed by transcript type (time-by-transcript interaction, $p<0.001$). At month 6, adjusted Schuffner-equivalent spleen size was lower in the b3a2 group than in the b2a2 group (2.61 vs 5.97 cm; adjusted mean difference −3.36 cm, 95% CI −5.57 to −1.15; $p=0.003$). In multivariable analysis, b2a2 was associated with a 4.27-cm higher month-6 Schuffner-equivalent spleen size ($p<0.001$), whereas transcript type was not associated with month-6 leukocyte count, platelet count, or hemoglobin concentration. Both transcript groups showed substantial hematologic improvement during TKI therapy, but selected hematologic trajectories and splenic regression differed between b2a2 and b3a2. The more pronounced splenic regression observed with b3a2 warrants validation in larger multicenter cohorts.

1. INTRODUCTION

Chronic myeloid leukemia (CML) is a BCR::ABL1-driven myeloproliferative neoplasm in which tyrosine kinase inhibitors (TKIs) have transformed long-term disease control [1]. Management relies on serial molecular response milestones, and European LeukemiaNet guidance recommends identifying the BCR::ABL1 transcript type at diagnosis to enable follow-up [2,3].

The standard b2a2 and b3a2 transcripts account for approximately 98% of CML and both encode p210 BCR::ABL1; b3a2 contains an additional 75-base-pair exon encoding 25 extra amino acids [4]. Whether this structural difference confers clinically meaningful variation remains unsettled. In 1,124 patients, Su et al. [5] found higher optimal response rates and greater cumulative major molecular response with b3a2 during frontline imatinib or nilotinib, but not dasatinib; deep molecular responses were similar between transcript groups. A meta-analysis of 5,411 patients nevertheless favored b3a2 for major and deep molecular responses [6]. Heterogeneity persists: Marcé et al. [7] found an early molecular advantage for b3a2 but no significant differences in deep molecular response or treatment-free remission, whereas Laabidi et al. [8] found better cytogenetic and molecular responses with b3a2 but no significant survival difference. Transcript-dependent RT-qPCR measurement bias may also contribute modestly to apparent molecular-response differences [4,9].

Splenic involvement is a recognized feature of CML, and spleen size remains part of baseline clinical assessment [2]. Experimental work shows that splenic red-pulp macrophages support CML stem-cell maintenance and TKI resistance [10]. Prior transcript-type studies have largely emphasized molecular, cytogenetic, and survival outcomes; Laabidi et al. [8] assessed spleen size at diagnosis but not serial regression. This prospective Indonesian cohort therefore evaluated six-month serial hematologic changes and Schuffner-derived changes in splenomegaly according to b2a2 versus b3a2 during TKI therapy.

2. MATERIALS AND METHODS

2.1 Study design and setting

This prospective cohort study was conducted at the Hematology and Medical Oncology Clinic of Dr. Wahidin Sudirohusodo General Hospital, a tertiary referral hospital in Makassar, Indonesia. Participants were recruited from November 2025 to March 2026 and were followed for six months after initiation of tyrosine kinase inhibitor (TKI) therapy. The final follow-up was completed in September 2026. The study evaluated the association between BCR::ABL1 transcript type, b2a2 versus b3a2, and longitudinal hematologic changes and changes in splenomegaly during TKI therapy. Assessments were performed at baseline and at months 3 and 6.

2.2 Study participants and sampling

Eligible participants were men and women aged ≥18 years with chronic myeloid leukemia (CML), documented BCR::ABL1 b2a2 or b3a2 transcript, and written informed consent. Participants were required to receive either imatinib or nilotinib continuously during the six-month follow-up. Treatment continuity was assessed from medication history, routine clinical visits, and medication-dispensing records.

Patients were excluded if the required hematologic data were unavailable at baseline or during follow-up; spleen assessment was unavailable at baseline, month 3, or month 6; six-month follow-up was not completed, including loss to follow-up; or TKI therapy was discontinued or changed before the month-6 evaluation.

Participants were recruited using consecutive sampling. The minimum sample size was calculated for comparison of two independent proportions using prespecified response proportions of 0.76 for b3a2 and 0.23 for b2a2, informed by the between-transcript response difference reported by Laabidi et al. [8], with a 95% confidence level and 80% statistical power. The calculation yielded 13 participants per group. After allowing for 20% attrition or incomplete data, the planned minimum was increased to 17 participants per group, corresponding to 34 participants overall. A total of 59 participants completed the required assessments and were included in the final analysis.

2.3 Data collection tool and technique

Demographic, clinical, treatment, and laboratory data were obtained from routine clinical assessments and hospital medical records. Recorded variables included age, sex, BCR::ABL1 transcript type, TKI type and dose, peripheral-blood blast percentage, hematologic parameters, and spleen enlargement. Hematologic parameters included white blood cell count, platelet count, hemoglobin concentration, and differential percentages of neutrophils, lymphocytes, monocytes, and basophils. All hematologic measurements were obtained from routine hospital laboratory examinations and recorded at baseline and at months 3 and 6 of TKI therapy.

BCR::ABL1 transcript type was obtained from routine molecular testing documented in the medical record using quantitative reverse-transcription polymerase chain reaction (qRT-PCR). Participants were classified as having either the p210 b2a2 or p210 b3a2 transcript. TKI therapy was categorized as imatinib or nilotinib according to the treatment received during follow-up.

Hematologic changes were evaluated longitudinally for each parameter. For baseline-to-month-6 analyses, change was calculated as the month-6 value minus the baseline value. Negative values represented decreases, whereas positive values represented increases.

Spleen enlargement was assessed clinically using the Schuffner grading system at baseline and at months 3 and 6. For quantitative analysis, Schuffner grades were converted to equivalent spleen-size values using the conversion applied by Mulyani [11], in which grades I–VIII corresponded to 4, 8, 12, 16, 20, 24, 28, and 32 cm, respectively; grade 0 indicated a non-palpable spleen. These converted values were treated as Schuffner-equivalent measurements rather than direct imaging-based anatomical measurements. Change in spleen enlargement was calculated as: Δ Schuffner-equivalent spleen size = month-6 value − baseline value. Negative values indicated regression of palpable splenomegaly.

2.4 Statistical analysis method

Categorical variables were presented as frequencies and percentages. Continuous variables were summarized as mean ± standard deviation for normally distributed data or median with interquartile range (Q1–Q3) for non-normally distributed data. Normality was assessed using the Shapiro–Wilk test. Baseline characteristics were compared between the b2a2 and b3a2 groups using the independent-samples t test or Mann–Whitney U test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate.

Changes in hematologic parameters across baseline, month 3, and month 6 were initially assessed using repeated-measures analysis of variance for variables satisfying parametric assumptions or the Friedman test for non-normally distributed variables. When the overall time effect was significant, post-hoc comparisons were performed using paired t tests or Wilcoxon signed-rank tests, as appropriate, with Bonferroni correction.

Longitudinal hematologic trajectories were further evaluated using linear mixed-effects models incorporating time, transcript type, and the time × transcript interaction as fixed effects, with adjustment for age, sex, and TKI type. Within-participant repeated measurements were modeled using a first-order autoregressive covariance structure [AR(1)] with restricted maximum likelihood estimation. When the time × transcript interaction was statistically significant, post-hoc comparisons of estimated marginal means were performed with Bonferroni correction.

Changes in Schuffner-equivalent spleen size across the three time points were analyzed using the Friedman test followed by Bonferroni-adjusted Wilcoxon signed-rank tests. Baseline-to-month-6 changes in Schuffner-equivalent spleen size were compared between transcript groups using the Mann–Whitney U test.

Longitudinal changes in Schuffner-equivalent spleen size were additionally evaluated using generalized estimating equations (GEE) with a normal distribution, identity link, first-order autoregressive [AR(1)] working correlation structure, and robust covariance estimator. The model included time, transcript type, and the time × transcript interaction and was adjusted for age, sex, and TKI type. Adjusted estimated marginal means with 95% Wald confidence intervals were obtained at each time point, and pairwise comparisons were performed with Bonferroni correction.

Separate multivariable linear regression models were used to evaluate the association between BCR::ABL1 transcript type and month-6 white blood cell count, platelet count, hemoglobin concentration, and Schuffner-equivalent spleen size. Each model was adjusted for the corresponding baseline value, age, sex, and TKI type, with b3a2 as the reference group. Results were reported as regression coefficients (B) with 95% confidence intervals.

As an exploratory sensitivity analysis, month-6 clinically estimated spleen size was dichotomized as 0–4 cm versus 8–12 cm and analyzed using binary logistic regression adjusted for baseline clinically estimated spleen size, age, sex, and TKI type. Baseline spleen size was entered in 4-cm increments, consistent with the predefined clinical conversion. Results were reported as adjusted odds ratios with 95% confidence intervals. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Mac, version 30.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS AND DISCUSSION

3.1 Study population and baseline characteristics

A total of 59 patients with chronic myeloid leukemia completed the required assessments and were included in the analysis. Of these, 45 (76.3%) had the b3a2 transcript and 14 (23.7%) had the b2a2 transcript. Baseline age, sex distribution, Schuffner-equivalent spleen size, peripheral-blood blast percentage, leukocyte count, hemoglobin concentration, and differential leukocyte percentages were comparable between transcript groups. In contrast, TKI distribution differed substantially between groups: 88.9% of patients with b3a2 received imatinib, whereas 78.6% of those with b2a2 received nilotinib ($p<0.001$). Baseline platelet count was also higher in the b3a2 group than in the b2a2 group [514 (340–634) vs 325 (213–473) $\times 10^3/\mu L$; $p=0.011$] (Table 1).

Table 1. Baseline characteristics according to BCR::ABL1 transcript type

Characteristic	b3a2, n=45	b2a2, n=14	p value
Sex, n (%)			0.078
Male	25 (55.6)	4 (28.6)	
Female	20 (44.4)	10 (71.4)	
Age, years	41.0 (27.0–56.5)	36.5 (30.5–49.0)	0.986
TKI, n (%)			<0.001
Imatinib	40 (88.9)	3 (21.4)	
Nilotinib	5 (11.1)	11 (78.6)	
Schuffner-equivalent spleen size, cm	16.0 (12.0–24.0)	12.0 (8.0–20.0)	0.103
Peripheral-blood blasts, %	8.0 (8.0–9.0)	8.0 (7.5–9.75)	0.858
Leukocyte count, $\times 10^3/\mu L$	368.49 ± 166.46	345.12 ± 151.94	0.642
Platelet count, $\times 10^3/\mu L$	514 (340–634)	325 (213–473)	0.011
Hemoglobin, g/dL	8.78 ± 1.61	8.66 ± 2.10	0.822
Neutrophils, %	84.30 (77.60–87.55)	83.50 (77.73–86.53)	0.533
Lymphocytes, %	4.20 (2.80–6.90)	4.10 (3.03–5.80)	0.702
Monocytes, %	4.00 (3.00–6.15)	3.90 (2.35–4.58)	0.265
Basophils, %	3.80 (1.65–5.30)	4.75 (3.35–5.80)	0.156

Note: Data are presented as mean ± standard deviation, median (Q1–Q3), or n (%), as appropriate. Schuffner-equivalent spleen size was derived from the predefined conversion of clinical Schuffner grades. Continuous variables were compared using the independent-samples t test or Mann–Whitney U test, and categorical variables using Pearson's chi-square or Fisher's exact test, as appropriate. TKI, tyrosine kinase inhibitor.

3.2 Longitudinal hematologic response

Substantial hematologic improvement occurred during the six-month treatment period in both transcript groups. In the adjusted linear mixed-effects models, a significant effect of time was observed for all hematologic parameters, including leukocytes, platelets, hemoglobin, neutrophils, lymphocytes, and basophils (all $p<0.001$), as well as monocytes ($p=0.025$). However, the time-by-transcript interaction was significant only for platelet count ($p=0.010$) and basophil percentage ($p=0.041$), indicating transcript-specific differences in the longitudinal trajectories of these two parameters (Table 2).

For platelet count, the adjusted mean at baseline was higher in the b3a2 group than in the b2a2 group (536 vs 353 ×10³/μL; p=0.016), whereas no significant between-group differences remained at month 3 (242 vs 293 ×10³/μL; p=0.498) or month 6 (241 vs 230 ×10³/μL; p=0.890). For basophils, the adjusted means differed at baseline (3.61% vs 5.61%; p=0.004), converged at month 3 (1.48% vs 1.55%; p=0.920), and diverged again by month 6, when the b3a2 group had a lower adjusted basophil percentage than the b2a2 group (0.55% vs 2.47%; p=0.006). These differential trajectories are illustrated in Figure 1.

Table 2. Longitudinal hematologic changes according to BCR::ABL1 transcript type

Parameter	Transcript	Baseline	Month 3	Month 6	Time effect, p	Transcript effect, p	Time × transcript, p
Leukocytes, ×10³/μL	b3a2	368.49 ± 166.46	9.74 ± 4.13	8.33 ± 2.95	<0.001	0.433	0.825
	b2a2	345.12 ± 151.94	7.11 ± 3.40	8.16 ± 3.56			
Platelets, ×10³/μL	b3a2	514 (340–634)	190 (105–356)	223 (159–308)	<0.001	0.424	0.010
	b2a2	325 (213–473)	242 (154–338)	181 (142–269)			
Hemoglobin, g/dL	b3a2	8.78 ± 1.61	12.10 ± 2.14	12.57 ± 1.47	<0.001	0.543	0.820
	b2a2	8.66 ± 2.10	11.59 ± 1.74	12.14 ± 1.52			
Neutrophils, %	b3a2	84.30 (77.60–87.55)	55.20 (45.25–63.20)	56.10 (49.70–63.00)	<0.001	0.158	0.139
	b2a2	83.50 (77.73–86.53)	61.40 (50.90–68.30)	58.10 (53.50–67.63)			
Lymphocytes, %	b3a2	4.20 (2.80–6.90)	31.00 (24.15–44.55)	32.20 (26.90–38.70)	<0.001	0.016	0.365
	b2a2	4.10 (3.03–5.80)	28.20 (14.88–37.85)	29.20 (19.58–34.28)			
Monocytes, %	b3a2	4.00 (3.00–6.15)	5.60 (4.45–7.75)	7.00 (6.00–7.95)	0.025	0.039	0.924
	b2a2	3.90 (2.35–4.58)	6.90 (5.15–8.95)	7.10 (6.25–8.35)			
Basophils, %	b3a2	3.80 (1.65–5.30)	0.90 (0.40–1.95)	0.50 (0.00–1.25)	<0.001	0.007	0.041
	b2a2	4.75 (3.35–5.80)	0.50 (0.30–1.65)	2.30 (1.53–2.70)			

Note: Descriptive values are presented as mean ± standard deviation or median (Q1–Q3), according to distribution. P values for time, transcript, and time × transcript were obtained from linear mixed-effects models adjusted for age, sex, and TKI type, using a first-order autoregressive [AR(1)] covariance structure and restricted maximum likelihood estimation. Bold values indicate p<0.05. TKI, tyrosine kinase inhibitor.

For platelet count, the adjusted mean at baseline was higher in the b3a2 group than in the b2a2 group (536 vs 353 $\times 10^3/\mu L$; p=0.016), whereas no significant between-group differences remained at month 3 (242 vs 293 $\times 10^3/\mu L$; p=0.498) or month 6 (241 vs 230 $\times 10^3/\mu L$; p=0.890). For basophils, the adjusted means differed at baseline (3.61% vs 5.61%; p=0.004), converged at month 3 (1.48% vs 1.55%; p=0.920), and diverged again by month 6, when the b3a2 group had a lower adjusted basophil percentage than the b2a2 group (0.55% vs 2.47%; p=0.006). These adjusted longitudinal trajectories are shown in Figure 1.

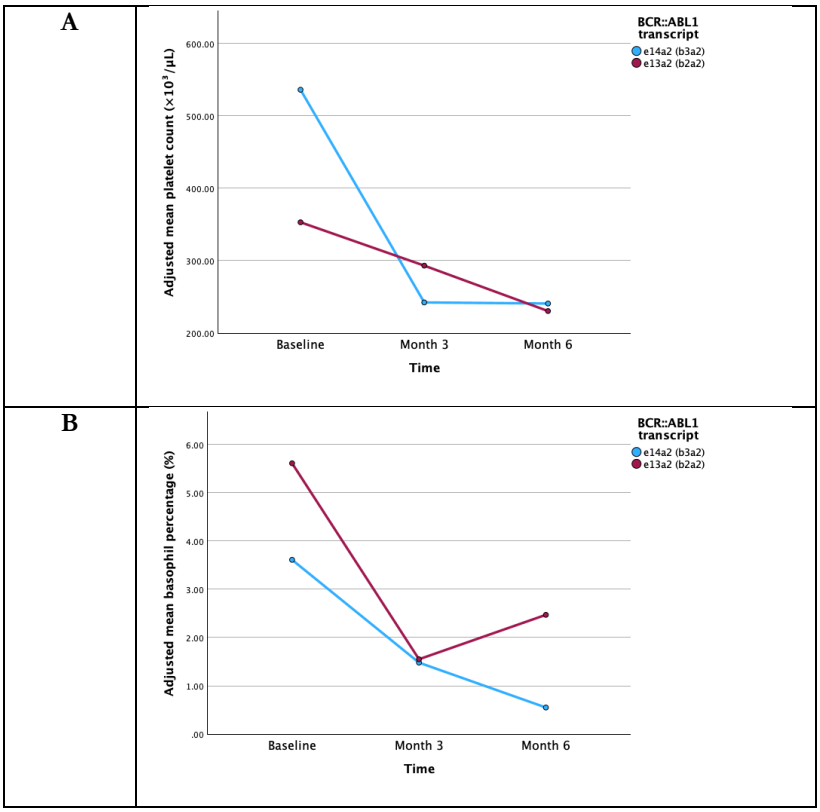


Figure 1. Adjusted longitudinal trajectories of platelet count and basophil percentage according to BCR::ABL1 transcript type. (A) Adjusted mean platelet count and (B) adjusted mean basophil percentage at baseline, month 3, and month 6 in patients with b3a2 and b2a2 transcripts.

3.3 Longitudinal splenic response

Schuffner-equivalent spleen size decreased progressively during TKI treatment, from a median of 16.0 (12.0–24.0) cm at baseline to 8.0 (4.0–8.0) cm at month 3 and 4.0 (0.0–4.0) cm at month 6 (p<0.001). Pairwise comparisons confirmed significant reductions between baseline and month 3, baseline and month 6, and month 3 and month 6 (all Bonferroni-adjusted p<0.001). The unadjusted baseline-to-month-6 reduction was greater in the b3a2 group than in the b2a2 group [−16.0 (−20.0 to −12.0) vs −8.0 (−12.0 to −4.0) cm; p<0.001].

Longitudinal GEE analysis further demonstrated a strong effect of time (Wald χ^2=264.22, df=2; p<0.001) and a significant time-by-transcript interaction (Wald χ^2=27.17, df=2; p<0.001), indicating different patterns of splenic regression between transcript groups after adjustment for age, sex, and TKI type. Adjusted Schuffner-equivalent spleen size did not differ significantly at baseline (17.10 vs 13.97 cm; p=0.140). By month 3, the adjusted means were 5.19 cm for b3a2 and 7.97 cm for b2a2 (p=0.056). At month 6, however, the b3a2 group had a significantly lower adjusted spleen size than the b2a2 group (2.61 vs 5.97 cm; mean difference −3.36 cm, 95% CI −5.57 to −1.15; p=0.003) (Table 3). The adjusted longitudinal splenic trajectories are illustrated in Figure 2.

Table 3. Longitudinal splenic response according to BCR::ABL1 transcript type

Time point/outcome	b3a2	b2a2	Between-group difference	p value
Adjusted Schuffner-equivalent spleen size, cm				
Baseline	17.10 (14.89–19.30)	13.97 (10.72–17.22)	3.13 (−1.02 to 7.27)	0.140
Month 3	5.19 (3.94–6.43)	7.97 (5.88–10.06)	−2.78 (−5.64 to 0.07)	0.056
Month 6	**2.61 (1.47–3.74)**	**5.97 (4.32–7.63)**	**−3.36 (−5.57 to −1.15)**	**0.003**
Unadjusted baseline-to-month-6 change, cm	−16.0 (−20.0 to −12.0)	−8.0 (−12.0 to −4.0)	—	**<0.001**

Note: Adjusted values are estimated marginal means (95% Wald confidence intervals) derived from a generalized estimating equation model with a normal distribution, identity link, AR(1) working correlation structure, and robust covariance estimator. The model was adjusted for age, sex, and TKI type. The overall time effect was significant (Wald χ^2=264.22, df=2; p<0.001), as was the time × transcript interaction (Wald χ^2=27.17, df=2; p<0.001). Between-group differences are calculated as b3a2 minus b2a2. Baseline-to-month-6 change is presented as median (Q1–Q3); negative values indicate regression of palpable splenomegaly.

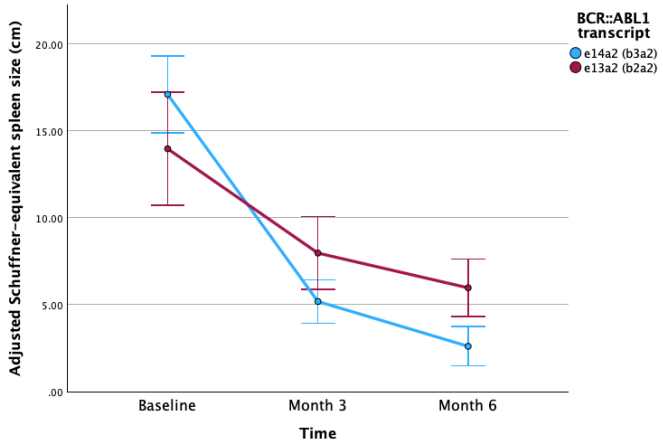


Figure 2. Adjusted longitudinal changes in Schuffner-equivalent spleen size according to BCR::ABL1 transcript type.

3.4 Adjusted associations with six-month outcomes

In multivariable linear regression, BCR::ABL1 transcript type was not independently associated with month-6 leukocyte count (B=−0.400; 95% CI −2.960 to 2.159; p=0.755), platelet count (B=13.425; 95% CI −96.830 to 123.679; p=0.808), or hemoglobin concentration (B=−0.787; 95% CI −2.047 to 0.473; p=0.216). In contrast, transcript type remained independently associated with month-6 Schuffner-equivalent spleen size. With b3a2 as the reference group, patients with b2a2 had an adjusted month-6 value 4.27 cm higher (B=4.274; 95% CI 2.487–6.061; p<0.001). Baseline Schuffner-equivalent spleen size (B=0.287; 95% CI 0.210–0.364; p<0.001) and age (B=0.040; 95% CI 0.002–0.079; p=0.040) were also independently associated with the month-6 value, whereas sex and TKI type were not.

An exploratory sensitivity analysis using residual clinically estimated spleen size of 8–12 cm at month 6 as the binary outcome showed a consistent direction of association. After adjustment for baseline spleen size, age, sex, and TKI type, the odds of having a residual spleen size of 8–12 cm were lower in the b3a2 group than in the b2a2 group (adjusted OR 0.014; 95% CI 0.001–0.340; p=0.009). Baseline spleen size was also associated with the outcome (adjusted OR 3.278 per 4-cm increase; 95%

CI 1.548–6.942; p=0.002). These sensitivity estimates should be interpreted cautiously because of the small number of participants with residual spleen enlargement of 8–12 cm and the resulting wide confidence intervals (Table 4).

Table 4. Adjusted associations between BCR::ABL1 transcript type and six-month outcomes

Panel A. Multivariable linear regression

Month-6 outcome	Adjusted B[1]	95% CI	p value	Adjusted R²
Leukocytes, ×10³/μL	−0.400	−2.960 to 2.159	0.755	0.001
Platelets, ×10³/μL	13.425	−96.830 to 123.679	0.808	−0.017
Hemoglobin, g/dL	−0.787	−2.047 to 0.473	0.216	−0.049
Schuffner-equivalent spleen size, cm	4.274	2.487 to 6.061	<0.001	0.570

Panel B. Exploratory sensitivity analysis for residual spleen size of 8–12 cm at month 6

Predictor	Adjusted OR	95% CI	p value
b3a2 vs b2a2	0.014	0.001–0.340	0.009
Baseline spleen size, per 4-cm increase	3.278	1.548–6.942	0.002
Age, per year	1.037	0.979–1.099	0.218
Male vs female	5.282	0.744–37.483	0.096
Imatinib vs nilotinib	0.754	0.054–10.550	0.834

Note: In Panel B, b2a2 was the reference transcript group; the binary outcome was residual clinically estimated spleen size of 8–12 cm versus 0–4 cm at month 6. The model was adjusted for baseline spleen size, age, sex, and TKI type. Baseline spleen size was entered per 4-cm increase. Because relatively few participants remained in the 8–12 cm category, the sensitivity analysis was considered exploratory. CI, confidence interval; OR, odds ratio; TKI, tyrosine kinase inhibitor.

3.5 Discussion

This prospective cohort showed marked hematologic improvement during the first six months of TKI therapy in both BCR::ABL1 transcript groups, while transcript-specific differences were confined to selected response trajectories. Platelet and basophil counts showed significant time-by-transcript interactions, whereas leukocyte count, hemoglobin, neutrophils, lymphocytes, and monocytes did not. The most prominent difference involved splenic response: despite no significant difference in baseline Schuffner-equivalent spleen size, patients with b3a2 experienced a steeper decline and had a lower adjusted spleen size at month 6 than those with b2a2. The predominance of b3a2 in the present cohort (76.3%) is consistent with Indonesian data from Yogyakarta, where b3a2 and b2a2 represented 74.3% and 22.4% of BCR::ABL1-positive CML cases, respectively [12].

The higher baseline platelet count observed in the b3a2 group is concordant with Laabidi et al. [8], who reported a significant association between b3a2 and thrombocytosis. However, this phenotype has not been consistently reproduced. In an Indonesian cohort, Mulyani et al. [13] found no significant differences in platelet count, leukocyte count, hemoglobin, basophils, or eosinophils between b3a2 and b2a2. In the present study, platelet values converged during treatment, and transcript type was not independently associated with platelet count at month 6. The significant interaction therefore appears to reflect different longitudinal trajectories, influenced in part by unequal baseline levels, rather than persistent transcript-dependent thrombocytosis.

Basophils also demonstrated a transcript-dependent trajectory, with lower adjusted values in b3a2 at month 6. Basophilia is an established feature of CML biology, and Sadovnik et al. [14] demonstrated that circulating CML basophils decrease substantially following successful treatment with BCR::ABL1 inhibitors. Their study did not compare b2a2 and b3a2, however, so the

transcript-specific pattern identified here should be regarded as an observational finding requiring confirmation rather than evidence of a known transcript-dependent basophil mechanism.

The broader literature more consistently associates transcript subtype with molecular response than with routine hematologic recovery. Su et al. [5] reported better milestone molecular responses for b3a2 during frontline imatinib and nilotinib, although this advantage was not observed consistently with dasatinib and early deep molecular responses were comparable between transcript groups. Chen et al. [6], in a meta-analysis of 16 cohorts, similarly found higher MMR rates among patients with b3a2. During frontline nilotinib, Genthon et al. [15] observed faster and deeper molecular responses with b3a2, while complete hematologic and cytogenetic response rates were similar. Nachi et al. [16] found a more modest pattern, with broadly comparable molecular kinetics and only a tendency toward better responses with b3a2. A review by Molica et al. [17] similarly concluded that b3a2 is generally associated with faster and deeper molecular responses, particularly during imatinib therapy, whereas its influence on long-term survival outcomes remains inconsistent. Taken together, these findings illustrate substantial heterogeneity in the magnitude of transcript-related effects across populations and treatment settings [5,6,15,16].

The finding of differential splenic regression is particularly relevant because previous transcript studies have predominantly assessed spleen size as a baseline disease characteristic rather than as a serial treatment outcome. Laabidi et al. [8] found no significant association between transcript type and spleen-size category at diagnosis, which parallels the absence of a significant baseline difference in the present cohort. Lee et al. [18], specifically among patients receiving imatinib who failed to achieve a three-month early molecular response, found that b2a2 and larger spleen size independently predicted poorer subsequent MMR. Although that selected population differs from ours, the finding indicates that transcript subtype and splenic disease burden can carry complementary clinical information. Our longitudinal results extend this observation by suggesting that differences may emerge in the rate of splenic regression during therapy, even when baseline spleen size is similar.

A direct mechanism linking b2a2/b3a2 subtype to splenic regression cannot be inferred from these data. Nevertheless, experimental work provides biological grounds for considering the spleen an active component of CML disease biology. Bührer et al. [10] demonstrated that splenic red-pulp macrophages form a niche capable of maintaining quiescent CML leukemic stem cells and promoting resistance to therapy. This finding supports the biological relevance of persistent splenic disease but does not establish that such microenvironmental effects differ according to BCR::ABL1 transcript subtype.

Interpretation of transcript-associated response also requires recognition of methodological factors. Both Dominy et al. [9] and Salmon et al. [4] demonstrated transcript-dependent effects on RT-qPCR measurement, indicating that technical amplification characteristics may partly contribute to apparent differences in molecular response. These effects do not, however, fully account for clinical differences, and the present splenic outcome is independent of BCR::ABL1 quantification.

The clinical implications should therefore remain cautious. Current ELN recommendations base treatment decisions primarily on molecular response milestones, treatment tolerance, comorbidities, resistance, and individual therapeutic goals rather than on b2a2/b3a2 subtype alone [2]. Contemporary reviews similarly emphasize that frontline TKI selection should balance response goals, toxicity, comorbidities, and treatment accessibility [19,20]. Thus, transcript type should not presently be used in isolation to direct TKI selection, but it may contribute additional biological or phenotypic information that warrants prospective validation.

The principal limitations are the single-center design, modest sample size, particularly the smaller b2a2 group, and the marked imbalance in TKI distribution between transcript groups. Although multivariable models adjusted for TKI type, residual confounding cannot be excluded because treatment overlap was limited. Splenic enlargement was assessed clinically using Schuffner grading and converted to Schuffner-equivalent centimeters rather than measured by imaging; these values therefore represent standardized clinical estimates rather than direct anatomical dimensions. Conversely, prospective assessment at three predefined time points and the concordant findings from longitudinal GEE and adjusted month-6 analyses strengthen the internal consistency of the observed splenic signal.

Overall, these findings suggest that b2a2 and b3a2 CML may differ in selected early treatment-response patterns rather than across hematologic recovery uniformly. The most consistent signal was less pronounced resolution of splenomegaly in b2a2. Larger multicenter studies incorporating standardized imaging, serial molecular kinetics, and adequately powered TKI-stratified analyses are required to determine whether transcript-specific splenic regression provides prognostic information beyond established molecular monitoring.

4. CONCLUSION

In this prospective cohort of patients with chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy, both b2a2 and b3a2 transcript groups showed substantial hematologic improvement over six months. However, longitudinal trajectories differed for platelet count and basophil percentage, and a more pronounced difference was observed in splenic response. Patients with b3a2 demonstrated greater regression of Schuffner-equivalent splenomegaly and a lower adjusted month-6 spleen size than those with b2a2, whereas transcript type was not independently associated with month-6 leukocyte count, platelet count, or hemoglobin concentration. These findings suggest that BCR::ABL1 transcript subtype may be associated with selected early phenotypic response patterns, particularly splenic regression, but should not be used in isolation to guide treatment decisions. Larger multicenter studies with standardized imaging and integrated molecular monitoring are needed to confirm the prognostic significance of these transcript-specific clinical trajectories.

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AUTHOR CONTRIBUTIONS

LADT contributed to the conceptualization and methodology of the study, participant recruitment and data collection, data curation, formal analysis, visualization, project administration, and preparation of the original manuscript draft. TH and AFB contributed to study conceptualization, methodology, supervision, validation, interpretation of the findings, and critical revision of the manuscript. SB, HR, RM, DB, and SS contributed to methodological evaluation, clinical interpretation, validation of the findings, and critical revision of the manuscript for important intellectual content. IJP contributed to statistical methodology, formal analysis, validation, interpretation of the results, visualization, and critical revision of the manuscript. All authors contributed to the final interpretation of the findings, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

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Ethics Statement

The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University (Ethical Clearance No. 259/UN4.6.4.5.31/PP36/2025). Permission to conduct the study was also obtained from the Clinical Research Unit of Dr. Wahidin Sudirohusodo General Hospital, Makassar (No. PK.02.04/D.XIX/2065/2025). Written informed consent was obtained from all participants before enrollment.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

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