RESEARCH ARTICLE

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Clinical Significance of the S348l Mutation in BCR-ABL as a Dominant Variant in Indonesian CML Patients Under Tyrosine Kinase Inhibitor Therapy: A Cohort Study

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Abstract

Objective: Chronic myeloid leukemia (CML) is characterized by the translocation of chromosomes 9 and 22, resulting in the *BCR-ABL* fusion gene. Tyrosine kinase inhibitors (TKIs) have markedly improved CML outcomes. Yet, resistance may develop due to mutations in the *BCR-ABL* kinase domain, particularly in the ATP-binding loop (P-loop), activation loop (A-loop), catalytic domain, and direct binding site. This study aimed to evaluate the relationship between *BCR-ABL* kinase domain mutations, hematological response, and overall survival among CML patients receiving TKI therapy at Wahidin Sudirohusodo General Hospital, Makassar. **Methods:** A prospective cohort study was conducted from March 2022 to July 2023 at the Hematology-Oncology outpatient clinic. Among 312 patients, 22 were classified as non-responders (no hematological response within three months) and 290 as responders. Forty-four patients (22 responders and 22 non-responders) underwent mutation analysis, and survival outcomes were compared. Statistical analysis was performed using SPSS. **Results:** Of the 44 patients, 11 harbored *BCR-ABL* mutations: S348L (n=6), T315I (n=4), and Y253F (n=1). All mutations were identified exclusively in the non-responder group. Mortality was significantly higher in non-responders than responders ($p<0.05$), and among non-responders with mutations compared to those without ($p<0.01$). Six-month survival rates were 65% for S348L, 50% for T315I, and 0% for Y253F, though survival differences between mutation types were not statistically significant (p=0,641). **Conclusion:** CML patients achieving early hematological response to TKI therapy had significantly better survival outcomes. In contrast, non-responders, particularly those harboring *BCR-ABL* kinase domain mutations, demonstrated poorer survival. The S348L mutation was the most common variant in this cohort. Early mutation detection may help guide therapeutic adjustments and improve outcomes in TKI-resistant CML.

Keywords: CML- *BCR-ABL* gene kinase dominant mutation- survival

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Introduction

Chronic myelocytic leukemia (CML) is a clonal hematopoietic disorder characterized by the presence of the Philadelphia chromosome (Ph), resulting from a translocation between chromosomes 9 and 22. This chromosomal rearrangement generates the *BCR-ABL* fusion gene, which encodes a constitutively active tyrosine kinase that drives uncontrolled proliferation and inhibits apoptosis [1]. CML constitutes 15% of all newly diagnosed leukemia cases, with an incidence rate of 1 to 2 cases per 100,000 individuals [2]. In Western nations, the mean age at which CML is diagnosed is approximately 56-57 years [3]. In Asia, Indonesia, and Makassar, reports indicate a younger demographic with an average age of 45-50 years [4].

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML by specifically targeting and inhibiting the activity of the *BCR-ABL* fusion protein. These therapies have significantly improved the prognosis of CML patients, with most achieving a sustained molecular response and an extended overall survival (OS) [5].

Despite the success of TKI therapy, a subset of patients develops resistance to treatment, which is often driven by mutations in the *BCR-ABL* gene, particularly within the kinase domain. These mutations alter the conformation of the *BCR-ABL* protein and reduce the binding efficiency of TKIs, resulting in treatment failure. Previous research has discovered over 100 mutations in the kinase domain

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of the *BCR-ABL* gene, with the most prevalent being T315I, Y253K, Y253H, E255K, E255V, and M315T [6]. Changes in the TKI direct binding site (T315I) are frequently accompanied by changes in the P-loop (Y253K, Y253H, E255K, and E255V) and mutations in the A-Loop (M315T) [7]. Numerous studies indicate that mutations in the P-loop correlate with accelerated development and reduced life expectancy. Mutations in the A-Loop result in reduced sensitivity to first and second generation TKIs [6-8].

The presence of these mutations is a key factor influencing clinical outcomes, with patients exhibiting poorer OS and progression-free survival (PFS) when mutations are detected [9].

TKIs can be classified into three generations based on their development and efficacy. The first-generation TKI, Imatinib, remains the cornerstone of CML treatment and has significantly improved patient survival since its introduction [1]. However, resistance due to mutations such as T315I and others in the kinase domain has led to the development of second-generation TKIs, including Dasatinib and Nilotinib [10]. These drugs are more potent and effective against certain mutations, including those that confer resistance to imatinib. Third-generation TKIs, such as Ponatinib, have been introduced as a treatment option for patients harboring the T315I mutation and those who fail second-line therapies. Ponatinib is particularly valuable for treating patients with the T315I mutation, which is largely resistant to other TKIs [1].

While these advanced TKIs have shown promise in improving outcomes for patients with resistant mutations, access to these medications remains a significant issue, particularly in developing countries like Indonesia. The Indonesian government currently provides coverage for Imatinib and Nilotinib, but the availability and affordability of second- and third-generation TKIs such as Dasatinib and Ponatinib are limited [11]. This restriction poses a challenge for patients who develop resistance to first-line treatments who may not benefit from the government-covered drugs. As a result, many patients in Indonesia may face suboptimal treatment options, leading to a higher risk of disease progression and poor survival outcomes [12].

This study aimed to investigate the relationship between *BCR-ABL* kinase domain mutations and overall survival in CML patients receiving TKI therapy [7]. Specifically, it will focus on how the type of mutation influences the efficacy of first- and second-generation TKIs and the implications for patient survival. The research will also explore the impact of the limited availability of advanced TKI options in Indonesia on patient outcomes, highlighting the need for expanded access to newer therapies [11]. Understanding the role of specific mutations in TKI resistance, as well as the barriers to accessing second- and third-generation TKIs, could lead to improved treatment strategies and outcomes for CML patients in Indonesia and similar regions with limited healthcare resources [1].

Materials and Methods

This research was a prospective cohort design from March to October 2022 at RSUP Dr. Wahidin Sudirohusodo Makassar, with follow-up extending until August 2024. The subjects consisted of individuals who satisfied the diagnostic criteria for Chronic Myeloid Leukemia (CML), specifically: (1) diagnosed with CML based on Bone Marrow Pathology (BMP) (2) *BCR-ABL* positive (3) aged 18 years or older (4) consenting to participate in the study. 2. Obtain data at the time of CML diagnosis, including standard hematological assessment, bone marrow aspiration with CML morphology, and *BCR-ABL* testing, all conducted prior to the initiation of TKI therapy.

Administration of TKI (Imatinib or Nilotinib) is evidenced by the medication adherence protocol and patient acknowledgment [10]. Three months post-initiation of TKI therapy, the patient underwent standard blood analysis to assess for the presence of a *BCR-ABL* gene mutation.1 TKI is a pharmaceutical agent that inhibits Abl protein activity by competitively binding to the ATP binding site, hence obstructing its functional processes. This trial contained the TKIs imatinib and nilotinib. Only these two categories of TKI are accessible under the National Health Insurance in Indonesia [11]. Exclusion criteria: (1) The patient is unreachable via telephone; (2) The data is inadequate. Additionally, the patient was monitored about general condition, adherence to TKI treatment, necessity for other symptomatic therapies, and survival status until June 2024. [12].

The Kinase Domain mutation of the *BCR-ABL* gene comprises point mutations T315I, Y253H/F, E255K/V, and M315T, which were evaluated through molecular investigation with the Sanger sequencing method. Mutations arise from translocation, and these mutations are identified. No mutation is indicated if there is an absence of translocation or single nucleotide alteration, whereas the result is deemed inconclusive if no transcribed RNA is identified [10]. Complete hematological response as per ESMO guidelines, specifically leukocyte count <10,000/L, absence of immature cells including myelocytes, promyelocytes, or blasts in peripheral blood, basophils <5%, platelet count <450x10^3/L, and no clinical symptoms of disease or lymphatic reduction after 3 months of TKI therapy [1]. The mutated and non-mutated groups were monitored until the conclusion of the research based on the results of the mutase examination.

The CML population consisted of 312 patients; during the course of therapy, 22 individuals demonstrated a non-hematological response (non-responders), while 290 individuals demonstrated a hematological response (responders). Among the 44 patients who were recruited and administered TKI for three months, routine blood tests and *BCR-ABL* gene mutation analyses were conducted randomly. Individuals who did not attain a full hematological response with imatinib were substituted with nilotinib.

Statistical Analysis

The data analysis was conducted with SPSS version

25. Kolmogorov-Smirnov test was used to evaluate data normality. Bivariate analysis was done with Chi-Square test, Independent t-test, Mann-Whitney test. Kaplan-Meier survival analysis was used to evaluated overall survival. Statistical test findings are deemed significant if the p-value is less than 0.05 [10].

Results

The study included a total of 44 participants, comprising 22 patients in responder group and 22 patient in non-responder group. Among these, 11 individuals were found to have *BCR-ABL* kinase domain mutations. The specific variants identified were S348L in six patients, T315I in four patients, and Y253F in one patient (Table 1).

Mutation analysis of the *BCR-ABL* gene was performed for both groups. Although the overall frequency of mutations was higher in the non-responder group compared to the responder group, this difference did not reach statistical significance (p>0.05). Specifically, eight patients (36.4%) in the non-responder group and three patients (13.6%) in the responder group exhibited detectable mutations (Table 2, Figure 1).

Regarding survival outcomes, patients who achieved an early haematological response to TKI therapy within three months demonstrated longer survival. All responders (100%) remained alive after 44 months of follow-up. In contrast, among the non-responders, five patients (22.7%) had died by a median follow-up of eight months. The mortality rate was notable higher in the non-responder group, and this difference was statistically significant (p<0.05). This indicates a substantial correlation between therapeutic response and outcome, as illustrated in Table 3 and Figure 2.

When survival was compared based on mutation status, individuals without mutations showed consistently higher survival rates, with 100% survival observed throughout the follow-up period. In contrast, the survival rate among patients harbouring mutations declined to approximately 75% at two months and 60% at six months after initiating therapy. Mortality appeared more frequent in the mutation-positive group, particularly among non-responders, where this difference reached statistical significance (p<0.01). This indicates a substantial correlation between mutations and outcomes. In the responder group, testing was not feasible as there were no fatalities (Table 4, Figure 3).

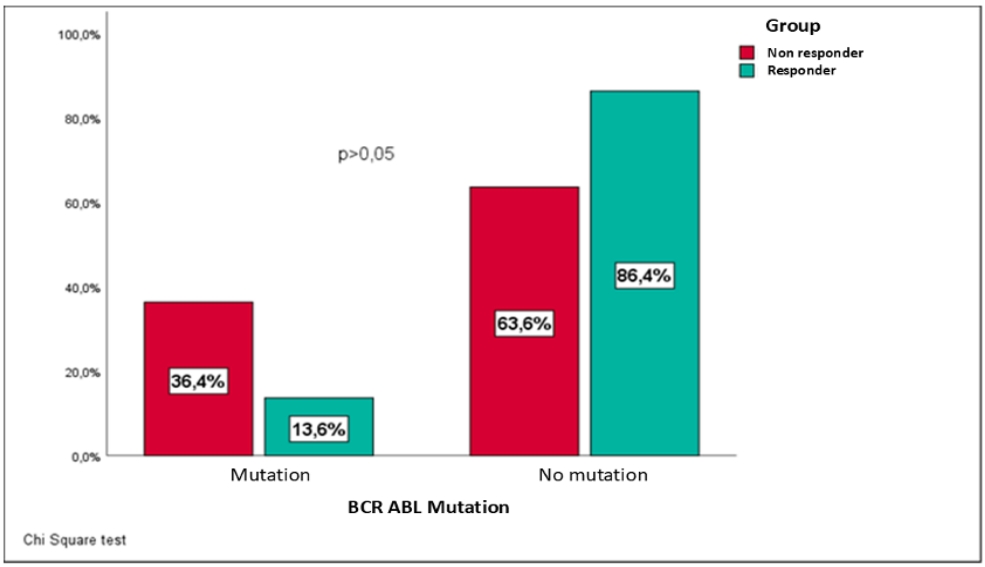

Figure 1. Comparison of Mutations According to Therapy Response Groups

Table 1. Characteristics of the Patients

Variable		N 44	%	Min	Max	Mean	SD
Therapeutic Response	Non Responser	22	50				
	Responder	22	50				
BCR-ABL Mutation	Yes	11	25				
	No	33	75				
Type Mutation	S348L	6	54.5				
	T315I	4	36.4				
	Y253F	1	9.1				
Outcome	Die	5	11.4				
	Life	39	88.6				
Follow-up duration of all samples (months) (n=44)				2	26	23.5	7.2
Duration of follow-up for mutations samples (months) (n=8)				2	26	12	11.7

Table 2. Comparison of Mutations and Therapy Response

Groups			Mutation BCR-ABL		Total
			Yes	No	
	Non-responder	N	8	14	22
		%	36.40%	63.60%	100.00%
	Responder	N	3	19	22
		%	13.60%	86.40%	100.00%
Total		N	11	33	44
		%	25.00%	75.00%	100.00%

Chi Square test (p=0.082)

Table 3. Comparison of Outcomes by Therapy Response Group

Groups			Survival		Total
			Die	Life	
	Non-responder	N	5	17	22
		%	22.70%	77.30%	100.00%
	Responder	N	0	22	22
		%	0.00%	100.00%	100.00%
Total		N	5	39	44
		%	11.40%	88.60%	100.00%

Chi Square test (p=0.018)

Further analysis according to mutation type (S348L, T315I, and Y253F) revealed variation in short-term survival. At six months after therapy initiation, survival rates were 0% for Y253F, 50% for T315I, and 65% for S348L. Although these observation suggest differences in outcomes across mutation types, the variation was not statistically significant (p=0.641) (Table 5, Figure 4).

Discussion

Chronic Myelocytic Leukemia (CML) is a hematological malignancy characterized by the presence of the *BCR-ABL* fusion gene, which drives uncontrolled proliferation of myeloid cells [13]. The treatment of CML has dramatically improved with the introduction of tyrosine kinase inhibitors (TKIs) such as Imatinib, Nilotinib, Dasatinib, Bosutinib, and Ponatinib [14]. These therapies have been shown to significantly enhance overall survival (OS) and progression-free survival (PFS) in CML patients. Despite these advances, resistance to TKIs remains a persistent clinical challenge, commonly associated with mutations in the *BCR-ABL* kinase domain [15]. This study examined the relationship between these mutations and patient outcomes among CML patients in Makassar, Indonesia.

Prevalence of BCR-ABL Gene Mutations and Survival Rates

In this cohort, 11 patients in non-responder group and three patients in the responder group exhibited mutations

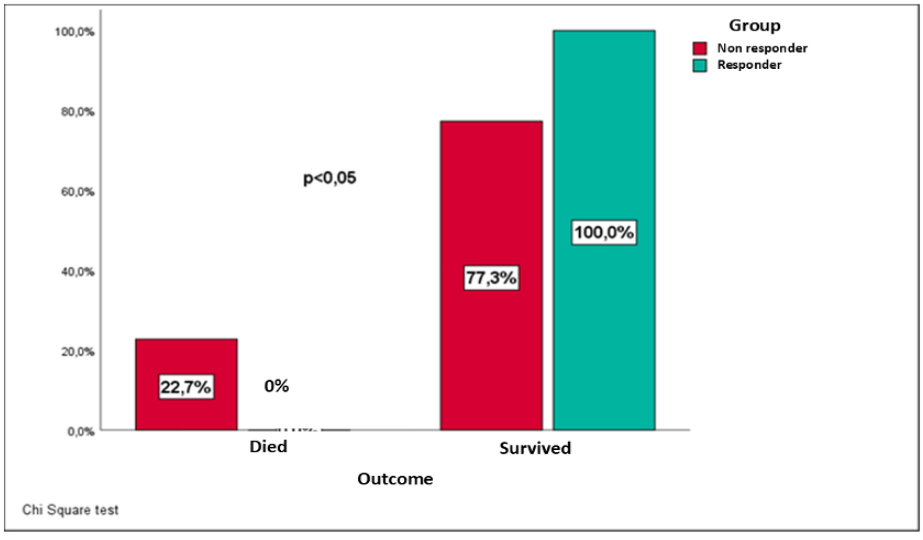

Figure 2. Comparison of Life Expectancy According to Mutation and Response to Therapy

Table 4. Comparison of Outcomes by Therapy Response Group

Groups	Mutation *BCR-ABL*		Survival		Total
			Die	life	
Non Response*	Yes	N	5	3	8
		%	62.50%	37.50%	100.00%
	No	N	0	14	14
		%	0.00%	100.00%	100.00%
Response**	Yes	N	0	3	3
		%	0.00%	100.00%	100.00%
	No	N	0	19	19
		%	0.00%	100.00%	100.00%

*Chi Square test (p=0,001); **Statistical analysis was not feasible due to the absence of mortality events in this group.

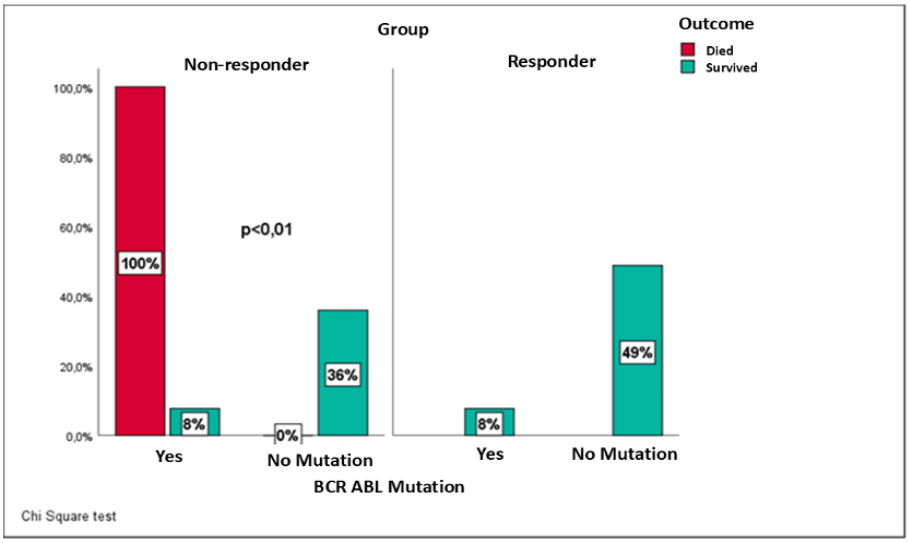

Figure 3. Comparison of Life Expectancy According to Mutation Type

in the *BCR-ABL* kinase domain. The mutations identified were S348L (6 cases), T315I (4 cases), and Y253F (1 case). Interestingly, although the non-responder group had a higher incidence of mutations, this difference did not reach statistical significance ($p > 0.05$).

It is important to note that S348L is considered a rare mutation. Studies such as those by Misyurin et al. and Jones et al. have reported this mutation in cases of imatinib resistance, with a particular focus on its occurrence in individuals who had intermittent imatinib use [16]. In this study, patients with S348L mutation tended to have shorter survival durations, suggesting a potential link between this mutation and reduced therapeutic response. The identification of this mutation in Indonesian patients

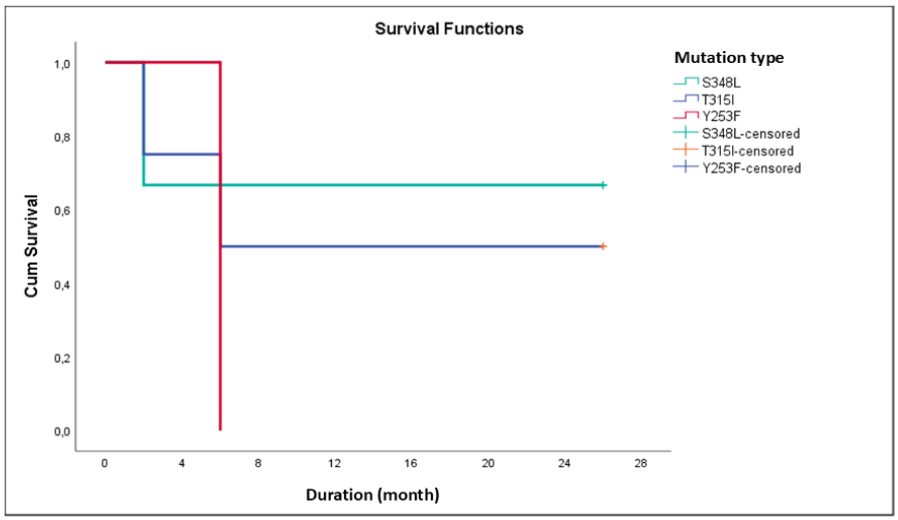

Figure 4. Overall Survival According to Mutation Type

Table 5. Comparison of Life Expectancy According to Mutation Type

Mutation Type			Outcome		Total
			Died	Survived	
	S348L	n	5	1	6
		%	83.30%	16.70%	100.00%
	T315I	n	2	2	4
		%	50.00%	50.00%	100.00%
	Y253F	n	1	0	1
		%	100.00%	0.00%	100.00%
Total		n	5	3	8
		%	62.50%	37.50%	100.00%

*Chi Square test (p=0.641)

suggests that regional variations in mutation patterns may exist and may contribute to varying clinical outcomes.

In contrast, patients with T315I and Y253F mutations had a similarly poor prognosis, as the Y253F mutation was associated with a 0% survival rate at six months post-therapy. The T315I mutation, which is known to be resistant to first and second-generation TKIs, showed a 50% survival rate at six months. These results are consistent with findings from other studies, including those by Pankaj Gadhia and Lavallade, where the T315I mutation was associated with resistance to multiple TKIs, including imatinib, dasatinib, and nilotinib [10, 17].

This finding indicates that while *BCR-ABL* mutations are more frequent in non-responders, other factors beyond mutations may contribute to treatment response. It is possible that additional genetic factors, or variations in patient adherence to therapy, could influence therapeutic outcomes. However, it remains clear that the presence of mutations like S348L, T315I, and Y253F warrants closer monitoring, as they are indicative of potential resistance mechanisms in CML.

The Role of Mutation Types in Survival Outcomes

One of the striking findings in this study was the correlation between mutational status and life expectancy. The Y253F mutation is known for its severe resistance to multiple TKIs, which could explain the 0% survival rate in patients harboring this mutation within six months of therapy. The T315I mutation, although less severe in terms of resistance, is also associated with a poor response to imatinib, dasatinib, and nilotinib, which could explain the 50% survival rate observed in our study at six months.

The S348L mutation's presence in 13.6% of the sample size is significant because this mutation has been linked to resistance to TKIs like imatinib, but its effects on survival remain less clear in other cohorts. In our study, 65% of patients with this mutation died within six months, which suggests that S348L mutations could be indicative of aggressive disease progression. The structural modification caused by the S348L mutation likely enhances the stability of the active *BCR-ABL* protein, thus interfering with the binding of TKIs. This could explain the diminished therapeutic efficacy observed in patients harboring this mutation.

These mutation-specific findings align with the global body of literature on the role of *BCR-ABL* mutations in CML. In particular, the study by Anthony and Harjianti (2020) emphasized that CML patients with mutations in the *BCR-ABL* kinase domain tend to have a poorer prognosis compared to mutation-negative individuals, further corroborating our findings [18].

Our findings indicate that therapeutic response plays a central role in determining life expectancy. Patients who responded positively to TKI therapy by the third month showed an impressive 100% survival rate after 44 months of follow-up. This result is consistent with the findings by Deininger et al., who documented that prompt therapeutic responses in CML patients are associated with improved survival rates and less recurrence. This underscores the importance of early treatment initiation and adherence in ensuring favorable outcomes for CML patients.

On the other hand, patients who did not respond to therapy had significantly lower survival rates, with the mortality rate being markedly higher in the non-responder group ($p < 0.05$). This is in line with the poor prognosis observed in patients who progress to the accelerated or blast phase of CML. These patients often experience a rapid deterioration of health despite intensive therapy, as highlighted in the literature and corroborated by the results of our study. These findings emphasize the critical role of early response monitoring and adjusting therapy in improving survival outcomes for CML patients.

The survival rates observed in our study are comparable to those found in other regions, although some differences exist in the response to specific TKIs. For instance, the Sumantri A.F. study (2019) in Indonesia showed that a significant proportion of patients on imatinib therapy achieved a complete hematological response, while those on nilotinib showed a slightly lower response rate [15]. Similarly, Anthony and Harjianti's study indicated that imatinib therapy was associated with improved hematological response in patients with low blast cell counts within the first three months of treatment [18]. This highlights the need for personalized treatment strategies, considering both mutation status and blast cell counts to optimize therapy.

Furthermore, the varying survival outcomes observed in Indonesian patients (mean survival of 30.4 ± 16.3 months) underline the importance of addressing regional factors such as access to healthcare and medication

adherence. The study also revealed a decline in patient adherence to therapy over time, which may contribute to the reduced survival rate in some patients. The progressive decline in adherence observed between the first and third years of treatment suggests that strategies to improve patient education, motivation, and long-term care support are essential to improve survival rates in the Indonesian population.

This study highlights the importance of molecular monitoring in the management of CML patients. The presence of mutations such as T315I, Y253F, and S348L is closely linked to treatment resistance, suggesting that routine mutation testing should be an essential part of clinical practice, especially for patients who are not responding to standard TKI therapy. For patients harboring these mutations, switching to third-generation TKIs like ponatinib (which is effective against T315I) or considering stem cell transplantation may improve survival outcomes.

Additionally, the significant difference in survival between the responder and non-responder groups emphasizes the need for early identification of treatment failures. By detecting mutations and adjusting therapies accordingly, healthcare providers can better tailor treatments to individual patients, improving long-term survival prospects.

Limitations and Future Research

This study has a few limitations that should be taken into account when interpreting the results. First, the number of patients included was relatively small, which reduces the statistical strength of the analysis and may not capture the full range of clinical variation among CML patients. Second, this was a single-center study carried out in Makassar, and therefore the findings might not represent the overall pattern seen in other hospitals or regions across Indonesia, where patient characteristics and treatment access can differ.

Another limitation is that mutation testing was performed using standard sequencing methods instead of next-generation sequencing (NGS). While the approach we used was adequate for detecting common *BCR-ABL* mutations, it might have missed rare or minor subclonal variants that could also play a role in resistance. Future research with larger, multicenter studies and more comprehensive molecular testing is needed to confirm these findings and provide a clearer picture of mutation profiles in Indonesian patients with CML.

Even with these limitations, our study still offers meaningful preliminary information on *BCR-ABL* mutation patterns and their possible influence on treatment outcomes. The results can serve as an early reference for clinicians and highlight the importance of routine molecular monitoring, early identification of treatment failure, and better access to advanced TKIs for patients who develop resistance.

In conclusion, this study provides preliminary evidence that mutations in the *BCR-ABL* kinase domain, particularly S348L, T315I, and Y253F, may be linked to reduced response to TKI therapy and shorter survival among CML patients in Makassar, Indonesia. Although the study was limited in size and scope, the trends observed suggest that certain mutations could influence treatment outcomes and deserve closer attention in clinical practice.

Early hematologic response continues to be one of the most important predictors of long-term survival, and incorporating regular molecular monitoring may help identify resistance earlier and guide timely therapeutic adjustments. These findings also point to broader issues that affect patient outcomes, including adherence to therapy and unequal access to advanced TKIs in Indonesia.

Overall, this study should be viewed as an exploratory step toward understanding mutation-related resistance patterns in Indonesian CML patients. Larger, multicenter studies using more comprehensive molecular tools will be essential to confirm these observations and support the development of more personalized and equitable treatment strategies in the future.

Author Contribution Statement

TH: Conceptualization, methodology, formal analysis, data curation, writing – original draft, visualization. WP: Conceptualization, methodology, formal analysis, data curation, software, writing & editing. AS: Methodology, software. FB: Conceptualization, methodology. SS : Writing-review & editing, supervision, project administration. RM: Writing-review & editing, supervision, project administration. DB: Writing-review & editing, supervision, project administration. All authors read and approved the final manuscript

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Institutional Approval

This study was conducted within the Hematology-Oncology subspecialty program at the Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia. It was reviewed and approved by the Faculty's Scientific and Ethical Committee prior to data collection.

Ethical Considerations

All research procedures were performed in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin. Written informed consent was obtained from all participants prior to enrollment.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Study Registration

This study was an observational cohort investigation and was not prospectively registered in any clinical trial

or registry database.

Conflict of Interest

The authors declare that there are no conflicts of interest related to the publication of this study.

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