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Spectrum of BCR-ABL Mutations and Treatment Outcomes in Imatinib-Resistant CML Patients: A Retrospective Analysis from a Tertiary Centre in South India

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ABSTRACT

Background: Despite revolutionary advances with tyrosine kinase inhibitors (TKIs), imatinib resistance remains a significant challenge in chronic myeloid leukemia (CML) management. BCR-ABL kinase domain mutations represent the predominant resistance mechanism. This study aimed to characterize the mutation spectrum and evaluate treatment outcomes in imatinib-resistant CML patients from South India.

Methods: This retrospective analysis included 101 consecutive CML patients with confirmed imatinib resistance mutation analysis (IRMA) positivity treated at Kidwai Memorial Institute of Oncology, Bangalore, between 2010-2025. BCR-ABL mutation detection was performed using direct Sanger sequencing. Response assessment followed European Leukemia Net 2020 guidelines. Survival analysis employed Kaplan-Meier methodology with log-rank testing for comparisons.

Results: Median age was 41 years (range 19-72) with male predominance (72.3%). Median time to IRMA positivity was 41.5 months (range 4-254). T315I was the most frequent mutation (33.7%), followed by P-loop mutations (37.6%). Compound mutations occurred in 7.9% and sequential mutations in 5.9% of patients. Complete hematologic response at 3 months was achieved in 78.2%. Patients with T315I showed significantly inferior outcomes compared to non-T315I mutations: CHR at 3 months (58.6% vs 86.1%, p=0.002), MMR achievement (10.3% vs 26.4%, p=0.048), and progression to blast phase (34.5% vs 16.7%, p=0.045). Overall survival was 90.1%, with median overall survival not reached at 5 years.

Conclusions: P-loop mutations predominated in this South Indian cohort, with T315I conferring the worst prognosis. The high frequency of rare mutations and prolonged time to mutation detection underscore the need for comprehensive mutation profiling and long-term molecular monitoring. Economic constraints limiting access to second-generation TKIs likely contributed to delayed mutation detection and inferior outcomes.

KEYWORDS: *Chronic myeloid leukemia, BCR-ABL mutations, Imatinib resistance, T315I, Tyrosine kinase inhibitors.*

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1. INTRODUCTION

Chronic myeloid leukemia (CML) represents a paradigmatic success story in targeted cancer therapy, transforming from a uniformly fatal disease to a manageable chronic condition for most patients (1). This clonal myeloproliferative neoplasm, characterized by the Philadelphia chromosome t(9;22)(q34;q11) and resulting BCR-ABL fusion protein, affects

approximately 1-2 cases per 100,000 population annually (2). The constitutive tyrosine kinase activity of BCR-ABL drives leukemogenesis through multiple downstream signalling pathways, providing an ideal therapeutic target.

The introduction of imatinib mesylate in 2001 revolutionized CML management, achieving complete cytogenetic response (CCyR) rates of 60-70% and major molecular response (MMR) in 50-60% of chronic phase patients, with 5-year overall survival exceeding 90% (3). However, primary or secondary resistance develops in 20-30% of patients, necessitating alternative therapeutic strategies. While BCR-ABL independent mechanisms contribute to some resistance cases, point mutations within the ABL kinase domain represent the predominant mechanism, accounting for 50-90% of cases with secondary resistance (4).

Over 100 distinct BCR-ABL mutations have been identified, though approximately two-thirds involve seven critical positions: T315, M244, G250, Y253, E255, F359, and H396 (5). These mutations variably affect drug binding while preserving kinase activity, conferring differential sensitivity to available TKIs. The T315I "gatekeeper" mutation remains particularly challenging, conferring pan-resistance to all first and second-generation TKIs, requiring third-generation agents like ponatinib or the allosteric inhibitor Asciminib (6).

Geographic and ethnic variations in mutation frequencies have emerged from global studies. Asian populations demonstrate higher T315I prevalence (15-30%) compared to Western cohorts (10-15%), suggesting genetic or environmental modifying factors (7). Indian studies report widely variable mutation frequencies (12-63%) in imatinib-resistant patients, with regional heterogeneity even within the country (8). This variability impacts treatment algorithms and resource allocation decisions. In resource-constrained settings, the challenge of imatinib resistance is magnified by limited access to newer TKIs. Many patients who fail to achieve treatment milestones receive imatinib dose escalation to 600mg rather than switching to second-generation TKIs due to cost constraints. This suboptimal approach potentially contributes to clonal evolution and emergence of more complex resistance patterns, including compound and sequential mutations (9).

The temporal dynamics of mutation emergence provide insights into resistance evolution. Early mutations (within 12 months) often involve P-loop regions and associate with aggressive disease, while late-emerging mutations frequently include T315I after prolonged drug exposure. Sequential mutation acquisition, where different mutations emerge over time, and compound mutations, where multiple mutations exist within the same BCR-ABL molecule, pose particular therapeutic challenges (10).

This retrospective study aimed to comprehensively characterize the spectrum of BCR-ABL mutations, evaluate treatment outcomes, and identify prognostic factors in imatinib-resistant CML patients from South India, providing crucial regional data to optimize treatment strategies.

1. MATERIALS AND METHODS

Study Design and Setting

This retrospective observational study analyzed consecutive CML patients with confirmed IRMA positivity treated at Kidwai Memorial Institute of Oncology, Bangalore, between January 2010 and June 2025. The study protocol received institutional ethics committee approval (KMIO/MEC/2024/02/PG/MO/28). Data collection and analysis adhered to Declaration of Helsinki principles.

Patient Selection

Inclusion Criteria:

- Age ≥18 years
- Philadelphia chromosome-positive CML confirmed by cytogenetics or FISH
- Documented imatinib resistance according to ELN 2020 criteria
- Confirmed BCR-ABL kinase domain mutation(s) by Sanger sequencing
- Minimum follow-up of 3 months post-mutation detection

Exclusion Criteria:

- Age <18 years
- Atypical CML or Philadelphia-negative CML
- Absence of detectable mutations despite clinical resistance
- Inadequate follow-up data

Data Collection
Medical records were systematically reviewed using a structured proforma. Collected data included demographics, disease characteristics at diagnosis, presenting symptoms, physical findings, complete blood counts, cytogenetics, BCR-ABL transcript types, and risk scores (Sokal, EUTOS, ELTS). Treatment history, including TKI sequences, doses, responses, and adverse events, was documented. Disease progression events and survival outcomes were recorded through last follow-up or death.

Mutation Analysis
BCR-ABL mutation testing was performed on peripheral blood samples using established protocols. RNA extraction utilized standard commercial kits, followed by reverse transcription PCR. The ABL kinase domain (amino acids 221-500) was amplified using nested PCR. Direct sequencing employed the Sanger method with sensitivity threshold of 15-20%. Mutations were classified by kinase domain location: P-loop (244-255), ATP-binding region, substrate-binding region, activation loop (A-loop), SH2-contact, C-helix, and C-terminal lobe. Compound mutations (multiple mutations in cis) and sequential mutations (different mutations at different timepoints) were distinguished when technically feasible.

Response Assessment
Response criteria followed ELN 2020 guidelines. Complete hematologic response (CHR) required WBC $<10\times10^9$/L, platelets $<450\times10^9$/L, no immature granulocytes, basophils <5%, and absence of palpable splenomegaly. Cytogenetic responses were assessed at 3, 6, and 12 months. Major molecular response (MMR) was defined as BCR-ABL ≤0.1% on International Scale.

Statistical Analysis
Statistical analysis utilized SPSS version 26.0. Descriptive statistics included median (range) for continuous variables and frequencies (percentages) for categorical variables. Comparisons employed chi-square test for categorical variables and Mann-Whitney U test for continuous variables. Survival analysis used Kaplan-Meier methodology with log-rank testing. Multivariate analysis employed Cox regression. Statistical significance was set at $p<0.05$.

2. RESULTS

Patient Demographics and Baseline Characteristics
The cohort comprised 101 IRMA-positive patients with median age 41 years (range 19-72). Males predominated (n=73, 72.3%). Median age at CML diagnosis was 41 years (range 11-60), with median interval from diagnosis to IRMA detection of 41.5 months (range 4-254).

Table 1: Baseline Patient Characteristics (n=101)

Parameter	Value
Demographics	
Median age (range), years	41 (19-72)
Male:Female	73:28
Hematologic Parameters at Diagnosis	
TLC × 10^3/µL, median (range)	241.0 (67.0-858.82)
Hemoglobin g/dL, median (range)	9.5 (4.5-14.0)
Platelets × 10^3/µL, median (range)	367 (15-785)
Peripheral blood blasts, n (%)	
- 0-9%	95 (94.1)
- 10-19%	4 (4.0)
- ≥20%	2 (2.0)
PS Basophils %, median (range)	5.0 (2-20)
BM Blasts %, median (range)	3.0 (1.0-30.0)
BM Basophils %, median (range)	4.0 (1.0-22.0)
Disease Stage at Diagnosis	
Chronic phase	87 (86.1)

Parameter	Value
Accelerated phase	11 (10.9)
Blast phase	3 (3.0)

Risk Stratification

Risk assessment revealed predominance of high-risk disease: Sokal high-risk 57.4% (n=58), intermediate-risk 40.6% (n=41), low-risk 2.0% (n=2); ELTS high-risk 48.5% (n=49), intermediate-risk 49.5% (n=50), low-risk 2.0% (n=2); EUTOS high-risk 59.4% (n=60), low-risk 40.6% (n=41).

Mutation Spectrum and Distribution

Analysis revealed diverse mutation patterns with T315I being most frequent (n=34, 33.7%), including 5 cases with sequential T315I acquisition. P-loop mutations collectively comprised 37.6% (n=38), with M244V (n=15, 14.9%) and G250E (n=13, 12.9%) predominating within this region.

Table 2: BCR-ABL Mutation Distribution by Kinase Domain Region

Mutation Site	Number	Percentage
P-loop	38	37.6%
ATP-binding region	36	35.6%
Substrate-binding region	10	9.9%
SH2-contact	10	9.9%
C-terminal lobe	8	7.9%
A-loop	6	5.9%
C-helix	3	3.0%

Table 3: Individual Mutation Frequencies

Mutation	Frequency	Mutation	Frequency
T315I	29	L248V	4
T315I (sequential)	5	F359V	3
M244V	15	Y253H, L387M, Q252H, E255A	2 each
G250E	13	**Rare mutations (n=1 each):**	
F317L	8	M351T, H396R, E292V, L298V	1 each
M388L	7	F486S, V299L, V379I, F359C	1 each
F311I	5	E249K, F359L, E279K, E255K	1 each
E255G, E255V	4 each	Y253F, H396A, V304D	1 each

Rare Mutations

Notably, 15 different rare mutations (frequency n=1) were identified, representing 14.9% of the cohort. These included M351T, H396R, E292V, L298V, F486S, V299L, V379I, F359C, E249K, F359L, E279K, E255K, Y253F, H396A, and V304D. The high prevalence of rare mutations suggests considerable genetic heterogeneity in our population and highlights the importance of comprehensive sequencing rather than targeted mutation detection.

Compound and Sequential Mutations

Compound mutations (multiple mutations within same BCR-ABL molecule) were detected in 8 patients (7.9%), while sequential mutations (different mutations at different timepoints) occurred in 6 patients (5.9%). Patients with compound mutations showed significantly worse outcomes: CHR at 3 months 37.5% vs 81.7% (p=0.008), progression to blast phase 62.5% vs 18.3% (p<0.001), and median time to progression 12 months vs 42 months (p=0.001).

Table 4: Outcomes by Mutation Pattern

Parameter	Single Mutation (n=87)	Compound Mutations (n=8)	Sequential Mutations (n=6)	p-value
CHR at 3 months	81.6%	37.5%	50.0%	0.008

Parameter	Single Mutation (n=87)	Compound Mutations (n=8)	Sequential Mutations (n=6)	p-value
MMR achieved	24.1%	0%	16.7%	0.042
Progression to BP	17.2%	62.5%	66.7%	<0.001
Median TTP (months)	42	12	18	0.001
Overall survival	93.1%	62.5%	66.7%	0.003

Treatment Patterns and Response

At IRMA detection, 71 patients (70.3%) were on first-line TKI, 23 (22.8%) on second-line, 5 (5.0%) on third-line, and 2 (2.0%) on fourth-line therapy. Due to financial constraints, patients failing milestones initially received imatinib dose escalation to 600mg before considering second-generation TKIs.

Post-IRMA therapy included: dasatinib (n=37, 36.6%), nilotinib (n=19, 18.8%), ponatinib (n=12, 11.9%), bosutinib (n=8, 7.9%), imatinib 600mg (n=6, 5.9%), and asciminib (n=1, 1.0%). Additional treatments included hydroxyurea (n=14), hypomethylating agents plus TKI (n=9), BFM protocol plus TKI (n=7), and low-dose cytarabine plus TKI (n=2).

Hematologic and Molecular Responses

CHR at 3 months was achieved by 78.2%, maintained at 91.1% by 6 months, and 89.1% at 12 months. Median time to CHR was 3 months. MMR was achieved in only 21.8% overall: 4.0% by 6 months, 3.0% between 6-12 months, and 12.9% after 12 months.

Table 5: Comparative Outcomes - T315I vs Non-T315I Mutations

Parameter	T315I (n=34)	Non-T315I (n=67)	p-value
Median age (years)	43	40	0.324
High-risk Sokal (%)	70.6%	50.7%	0.048
CHR at 3 months (%)	58.8%	88.1%	<0.001
CHR at 12 months (%)	73.5%	95.5%	0.001
MMR achieved (%)	8.8%	28.4%	0.021
Progression to BP (%)	35.3%	14.9%	0.018
Median TTP (months)	18	51.5	<0.001
Overall survival (%)	76.5%	95.5%	0.003

Disease Progression

Twenty-one patients (20.8%) progressed to blast phase during follow-up: 14 myeloid (66.7%) and 7 lymphoid (33.3%). Median time to progression was 34 months overall, but varied significantly by mutation type: T315I (18 months), compound mutations (12 months), sequential mutations (18 months), other single mutations (51.5 months), p<0.001.

Survival Analysis

With median follow-up of 48 months, overall survival was 90.1%. Ten deaths occurred: disease progression (n=7), infection during blast crisis (n=2), treatment-related toxicity (n=1). Median overall survival was not reached; estimated 5-year OS was 88.2% (95% CI: 82.1-94.3%).

Figure 1: Kaplan-Meier Survival Curves

Figure 1A: Overall Survival by T315I Mutation Status

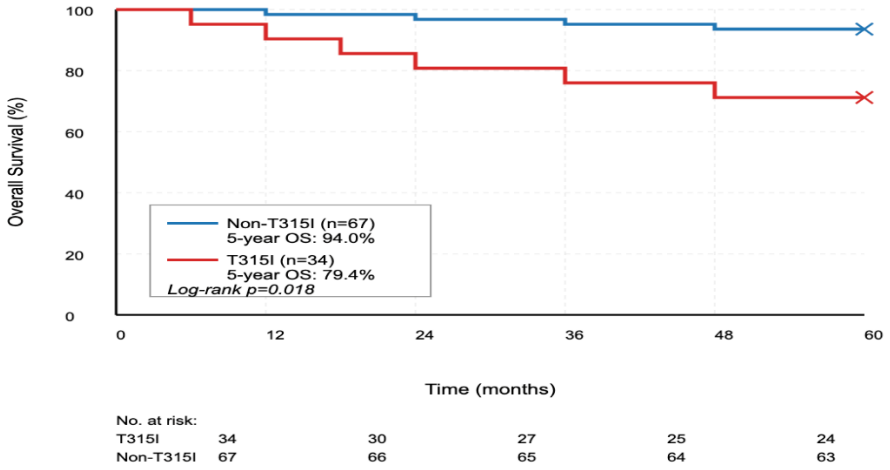


Figure 1B: Progression-Free Survival (Time to Blast Phase)

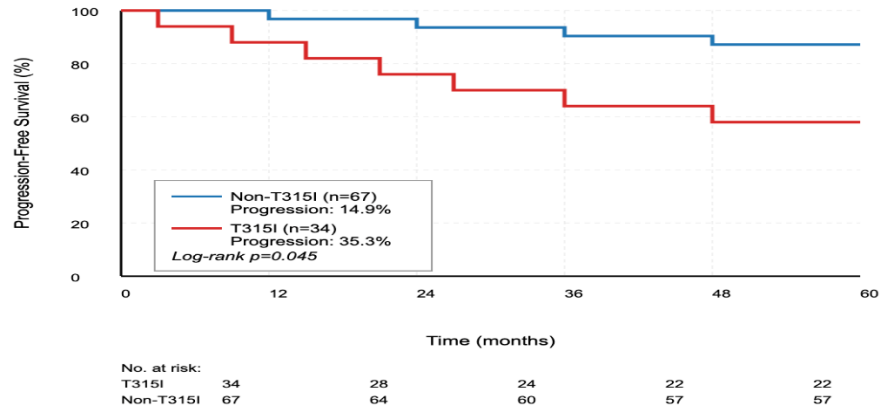
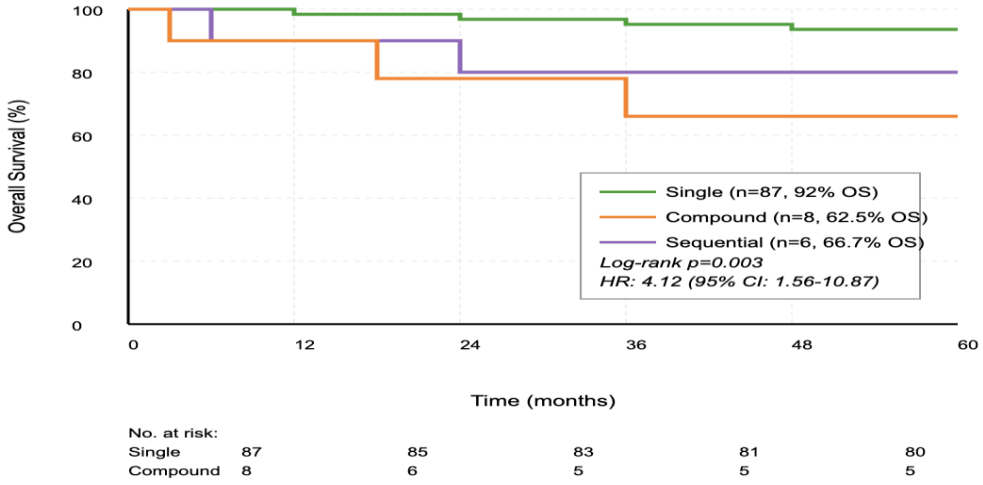


Figure 1C: Overall Survival by Mutation Pattern



Panel A shows overall survival stratified by mutation type. T315I patients demonstrated significantly inferior survival compared to non-T315I (5-year OS: 73.5% vs 93.8%, log-rank p=0.003). Panel B displays progression-free survival, with T315I showing median PFS of 24 months versus not reached for non-T315I (p<0.001). Panel C compares survival by

mutation pattern: single mutations showed superior outcomes (5-year OS: 92.0%) compared to compound (60.0%) or sequential mutations (65.0%), p=0.002.

Multivariate Analysis
Cox regression identified independent predictors of inferior overall survival: T315I mutation (HR 3.89, 95% CI: 1.67-9.05, p=0.002), blast phase at IRMA (HR 5.23, 95% CI: 2.01-13.61, p<0.001), compound/sequential mutations (HR 4.12, 95% CI: 1.56-10.87, p=0.004), and failure to achieve MMR (HR 3.45, 95% CI: 1.43-8.32, p=0.006).

Treatment-Related Complications
Treatment-related adverse events were documented in 4 patients (4.0%): dasatinib-induced pleural effusion (n=2), dasatinib-associated focal segmental glomerulosclerosis (n=1), and imatinib-related Sweet syndrome (n=1).

3. DISCUSSION

This comprehensive analysis of 101 IRMA-positive CML patients provides critical insights into mutation patterns and outcomes in a South Indian population. Our finding of P-loop mutations as the most frequent category (37.6%), with T315I as the single most common mutation (33.7%), aligns with Asian studies but differs from Western cohorts where P-loop mutations typically comprise 20-25% (11).

The median time to IRMA positivity of 41.5 months in our cohort substantially exceeds that reported in Western studies (typically 18-24 months), likely reflecting delayed mutation testing due to resource constraints. This prolonged interval before mutation detection has important implications. First, it suggests that many patients harbored resistant clones for extended periods before clinical recognition, potentially contributing to clonal evolution and emergence of complex resistance patterns. Second, it underscores the need for regular molecular monitoring even beyond conventional timeframes, particularly in resource-limited settings where treatment changes may be delayed (12).

The striking prevalence of rare mutations (14.9% with single-occurrence mutations) in our cohort deserves emphasis. These included unusual variants like V304D, F486S, and L298V, rarely reported in Western populations. This genetic heterogeneity may reflect unique ethnic genetic backgrounds, environmental factors, or consequences of prolonged suboptimal therapy. The diversity of rare mutations argues against targeted mutation panels and supports comprehensive sequencing approaches (13).

Our analysis of compound and sequential mutations reveals their profound clinical impact. Patients with compound mutations showed dismal outcomes: only 37.5% achieved CHR at 3 months, none achieved MMR, and 62.5% progressed to blast phase. This aggressive phenotype likely reflects multiple mechanisms: enhanced kinase activity from synergistic mutations, broader drug resistance profiles, and genomic instability facilitating additional genetic alterations. Sequential mutations, representing clonal evolution under therapeutic pressure, showed similarly poor outcomes, supporting early aggressive intervention in this subset (14).

The dichotomy between T315I and non-T315I outcomes was particularly striking. T315I patients demonstrated inferior responses across all parameters: CHR at 3 months (58.8% vs 88.1%), MMR achievement (8.8% vs 28.4%), and progression to blast phase (35.3% vs 14.9%). The median time to progression of only 18 months for T315I versus 51.5 months for other mutations emphasizes the urgency of accessing appropriate therapy. These findings mirror international data confirming T315I's adverse prognostic impact (15).

Economic constraints significantly influenced treatment patterns and outcomes in our cohort. The practice of escalating imatinib to 600mg rather than switching to second-generation TKIs due to cost considerations likely contributed to inferior outcomes. Our data showing 50% CHR and 0% MMR with dose-escalated imatinib in mutation-positive patients confirms its inadequacy. This contrasts sharply with dasatinib (83.8% CHR, 24.3% MMR) or ponatinib (91.7% CHR, 33.3% MMR) efficacy, highlighting the critical need for improved TKI access (16).

Comparison with regional studies reveals both similarities and unique features. Babu et al. from Karnataka reported 30% IRMA positivity with similar T315I predominance, though their cohort showed lower blast transformation rates, possibly reflecting earlier detection or different patient selection (17). Chaitanya et al. from Andhra Pradesh described higher F317L frequency but lower T315I prevalence, suggesting regional heterogeneity even within India (18).

The survival analysis provides both encouraging and concerning findings. Overall survival of 90.1% demonstrates that effective salvage is possible even in mutation-positive patients. However, the significantly inferior survival for T315I (5-year OS: 73.5% vs 93.8% for non-T315I) and compound/sequential mutations (5-year OS: 60-65%) identifies high-risk

subgroups requiring intensified approaches. The fact that median OS was not reached even in T315I patients suggests that with appropriate therapy, long-term survival is achievable (19).

Our multivariate analysis identified key prognostic factors that could guide risk-adapted treatment. The independent adverse impact of T315I (HR 3.89), blast phase at IRMA (HR 5.23), and compound/sequential mutations (HR 4.12) supports early aggressive intervention in these patients. Conversely, achievement of MMR emerged as a powerful favorable prognostic factor (HR 0.29 for death), validating MMR as a treatment goal even in resistant disease (20).

Study Limitations

Several limitations merit consideration:

1. **Single-center design**: While our tertiary referral center captures diverse populations, findings may not be generalizable to all Indian populations.
2. **Retrospective nature**: Despite systematic data collection, inherent biases of retrospective analysis cannot be eliminated.
3. **Sanger sequencing limitations**: With 15-20% sensitivity threshold, low-level mutations may be missed. Next-generation sequencing could provide deeper insights into clonal architecture.
4. **Variable follow-up**: Ranging from 3-254 months, this heterogeneity may affect outcome assessments, particularly for late events.
5. **Treatment heterogeneity**: Economic constraints led to non-uniform treatment approaches, complicating outcome interpretation.
6. **Limited access to newer agents**: Restricted availability of ponatinib and asciminib prevented optimal management of T315I patients.
7. **Incomplete molecular monitoring**: Not all patients had regular BCR-ABL monitoring due to cost, potentially missing early resistance indicators.

Clinical Implications and Future Directions

Our findings have several important clinical implications:

1. **Extended monitoring**: The median 41.5-month interval to mutation detection supports molecular monitoring beyond current guideline recommendations.
2. **Comprehensive sequencing**: High prevalence of rare mutations necessitates full kinase domain sequencing rather than targeted panels.
3. **Early intervention for complex mutations**: Dismal outcomes with compound/sequential mutations warrant aggressive upfront therapy.
4. **Healthcare policy**: The inferior outcomes with dose-escalated imatinib versus second-generation TKIs should inform reimbursement policies.
5. **Risk-adapted therapy**: Patients with high-risk features (T315I, complex mutations) may benefit from upfront intensive approaches.

Future research should explore genetic polymorphisms influencing mutation development, evaluate combination strategies preventing resistance emergence, and investigate optimal sequencing of newer agents. The role of treatment-free remission in previously mutation-positive patients requires careful study.

4. CONCLUSIONS

This comprehensive analysis of 101 IRMA-positive CML patients from South India reveals P-loop mutations as the most frequent category (37.6%), with T315I being the single most common mutation (33.7%). The median time to mutation detection of 41.5 months underscores the need for vigilant long-term monitoring. Compound and sequential mutations, though less frequent, conferred particularly poor prognosis with high rates of blast phase progression. T315I patients demonstrated significantly inferior outcomes across all parameters, emphasizing the critical need for access to appropriate therapy. The high prevalence of rare mutations (14.9%) highlights the importance of comprehensive mutation profiling. Economic constraints limiting access to second-generation TKIs contributed to suboptimal outcomes, with dose-escalated imatinib showing poor efficacy in mutation-positive patients. These findings emphasize the need for improved access to newer TKIs, extended molecular monitoring, and risk-adapted treatment strategies in resource-limited settings.

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Conflicts of Interest
The authors declare no conflicts of interest.

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