Section: Community Medicine

Original Research Article

# EARLY MOLECULAR RESPONSE AT THREE MONTHS AND ITS ASSOCIATION WITH LONG-TERM MOLECULAR RESPONSE AND SURVIVAL OUTCOMES IN CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH IMATINIB: AN AMBISPECTIVE COHORT STUDY

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***Received*** *: 28/09/2026*
***Received in revised form*** *: 23/10/2026*
***Accepted*** *: 05/11/2026*

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**DOI:** 10.70034/ijmedph.2026.4.327

**Source of Support:** Nil,
**Conflict of Interest:** None declared

**Int J Med Pub Health**
2026; 16 (4); 2171-2179

ABSTRACT

**Background:** Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the BCR-ABL1 fusion gene. Imatinib mesylate has substantially improved treatment outcomes, while early molecular response has emerged as an important indicator of subsequent therapeutic efficacy. However, its association with long-term molecular outcomes and overall survival requires further evaluation. **Objectives:** To assess the association between molecular response at three months and three-year overall survival among patients with chronic-phase CML receiving imatinib mesylate and to evaluate baseline predictors and subsequent molecular outcomes.

**Materials and Methods:** This ambispective observational cohort study included 67 patients with chronic-phase CML treated with imatinib mesylate at PGIMER, Chandigarh. Baseline demographic, clinical, hematological, and prognostic characteristics were assessed using Sokal, Hasford, and EUTOS scores. Molecular response was evaluated through quantitative BCR-ABL1 transcript assessment at predefined intervals up to 36 months. Early molecular response was defined as BCR-ABL1 ≤10% on the International Scale at three months. Statistical analysis included independent-samples t-tests, chi-square or Fisher's exact tests, and correlation analysis, as appropriate. Survival and follow-up outcomes were summarized descriptively. All statistical tests were two-sided, with $p<0.05$ considered statistically significant.

**Results:** Early molecular response was achieved in 50 of 67 patients (74.63%). Major molecular response was observed in 36/63 patients (57.14%) at 12 months, 38/54 (70.37%) at 24 months, and 39/52 (75.00%) at 36 months. At 36 months, major molecular response was observed in 33/39 (84.62%) patients with early molecular response and 6/13 (46.15%) patients without early molecular response. Baseline spleen size ($p=0.014$), total leukocyte count ($p=0.034$), and Hasford score ($p=0.001$) were significantly associated with early molecular response. During follow-up, 51 patients (76.12%) were recorded as alive, six (8.96%) died, eight (11.94%) were lost to follow-up, and two (2.99%) switched to nilotinib. The association between early molecular response and three-year overall survival could not be conclusively established.

**Conclusion:** Early molecular response was associated with favorable subsequent molecular outcomes among patients receiving imatinib mesylate. Baseline prognostic assessment combined with serial molecular monitoring may improve risk stratification and facilitate identification of patients requiring closer follow-up. The relationship between early molecular response and three-year overall survival remained inconclusive.
**Keywords:** Chronic myeloid leukemia; Imatinib mesylate; BCR-ABL1; Early molecular response; Major molecular response; Overall survival; Prognostic scores.

## INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm arising from the malignant transformation of a pluripotent hematopoietic stem cell. It is characterized by uncontrolled proliferation of myeloid cells and the presence of the Philadelphia chromosome, resulting from the reciprocal translocation t(9;22)(q34;q11.2). This chromosomal rearrangement generates the BCR-ABL1 fusion gene, which encodes a constitutively active tyrosine kinase responsible for abnormal cellular proliferation, impaired apoptosis, and altered hematopoietic differentiation. The disease typically progresses through chronic, accelerated, and blast phases if inadequately treated. Most patients are diagnosed during the chronic phase, when effective treatment offers the greatest opportunity for sustained disease control and prolonged survival.[1]

The introduction of tyrosine kinase inhibitors (TKIs) has substantially transformed the management and prognosis of CML. Imatinib mesylate, a selective inhibitor of BCR-ABL1 tyrosine kinase, was the first targeted agent to demonstrate superior hematological and cytogenetic responses compared with conventional interferon-based therapy. The landmark International Randomized Study of Interferon versus STI571 (IRIS) established imatinib as an effective first-line treatment for newly diagnosed chronic-phase CML.[2] Subsequent long-term studies demonstrated durable cytogenetic and molecular responses, reduced disease progression, and substantially improved survival. Five-year follow-up demonstrated an estimated overall survival of 89%, while extended follow-up confirmed sustained clinical benefits in patients receiving imatinib [3,4].

Despite these therapeutic advances, considerable variability exists in the depth and timing of molecular responses among patients receiving imatinib. Molecular monitoring using quantitative reverse-transcription polymerase chain reaction (RQ-PCR) allows sensitive measurement of residual leukemic burden through BCR-ABL1 transcript quantification. Standardization of molecular results on the International Scale (IS) has facilitated comparisons across laboratories and established clinically relevant response milestones. Major molecular response (MMR), defined as BCR-ABL1 ≤0.1% IS, represents an important therapeutic endpoint associated with durable disease control. Earlier investigations demonstrated that achieving deeper molecular responses during imatinib therapy was associated with improved long-term outcomes.[5]

Early molecular response (EMR), assessed approximately three months after initiating TKI therapy, has emerged as a clinically important prognostic indicator. The European LeukemiaNet recommendations published in 2013 defined an optimal molecular response at three months as BCR-ABL1 ≤10% IS, while values exceeding this threshold indicated a warning response requiring closer surveillance.[1] Marin et al. demonstrated that three-month BCR-ABL1 transcript levels were strongly associated with overall survival, progression-free survival, and subsequent molecular response in patients receiving TKI therapy. Their findings highlighted the prognostic importance of early treatment assessment and its potential contribution to individualized clinical management.[6]

Nevertheless, the interpretation of early molecular response requires consideration of the subsequent kinetics of leukemic burden reduction. Branford et al. observed that patients with BCR-ABL1 transcript levels exceeding 10% at three months did not constitute a homogeneous prognostic group. The rate of transcript decline from baseline provided additional prognostic information, suggesting that an isolated molecular measurement may not adequately characterize all patients with delayed responses.[7] These observations emphasize the importance of longitudinal monitoring and assessment of molecular response beyond the initial treatment period.

Alongside molecular monitoring, conventional prognostic scoring systems remain relevant for evaluating baseline disease characteristics. The Sokal and Hasford scores incorporate clinical and hematological variables to categorize patients according to their expected outcomes.[8,9] The European Treatment and Outcome Study (EUTOS) score was subsequently developed specifically for patients receiving imatinib and demonstrated an association with complete cytogenetic response and progression-free survival.[10] However, differences in their predictive performance and the relative contribution of baseline risk stratification and early molecular response warrant further investigation in different clinical populations.

Although international studies have established the prognostic importance of early molecular response, its relationship with three-year survival and subsequent molecular outcomes requires evaluation

in routine clinical settings, particularly where patient characteristics, treatment adherence, and monitoring practices may differ from controlled clinical trials. Therefore, the present study aimed to evaluate the association between molecular response at three months and overall survival at three years among patients with chronic-phase CML receiving imatinib mesylate. Additionally, the study assessed molecular responses at 24 and 36 months and examined baseline clinical characteristics and prognostic risk scores as potential predictors of long-term molecular outcomes.

## MATERIALS AND METHODS

**Study Design and Setting:** This was an ambispective observational cohort study conducted at the Hematology Clinic of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The study included patients diagnosed with chronic-phase chronic myeloid leukemia (CML-CP) who received imatinib mesylate therapy.

**Study Population and Sample Size:** A total of 67 patients with chronic-phase CML were included in the study. Patients were aged more than 12 years and had received imatinib mesylate as their initial tyrosine kinase inhibitor therapy. Clinical and laboratory information was obtained through retrospective review of available records and prospective follow-up. Patients were followed for up to 36 months to assess molecular response, disease status, and survival outcomes.

**Eligibility Criteria:** Patients aged more than 12 years with confirmed chronic-phase CML, diagnosed according to World Health Organization criteria, were eligible for inclusion. Diagnosis was established through characteristic peripheral blood and bone marrow findings, including leukocytosis, granulocytic proliferation with immature myeloid precursors, basophilia, and bone marrow hypercellularity, together with detection of the Philadelphia chromosome or BCR-ABL1 fusion transcript. Patients were required to have documented molecular response assessments at three and six months following initiation of imatinib therapy. Chronic-phase disease was established after excluding features of accelerated phase and blast crisis. Patients presenting with accelerated-phase CML, blast crisis, or known hypersensitivity to imatinib mesylate were excluded.

**Clinical and Hematological Evaluation:** Baseline clinical assessment included demographic characteristics, age, sex, duration of symptoms, physical examination findings, spleen and liver size, lymphadenopathy, and Eastern Cooperative Oncology Group (ECOG) performance status. Hematological evaluation included hemoglobin concentration, total leukocyte count, platelet count, differential leukocyte count, percentage of peripheral blood blasts, and basophil and eosinophil percentages. Clinical examinations and complete blood counts were performed during follow-up to assess disease control and hematological response.

Complete hematological response was defined by normalization of peripheral blood counts, leukocyte count below 10,000/mm³, platelet count below 450,000/mm³, absence of circulating immature myeloid cells, resolution of disease-related clinical manifestations, and disappearance of palpable splenomegaly. Partial hematological response was characterized by improvement in hematological and clinical parameters without fulfilling all criteria for complete hematological response.

**Baseline Prognostic Risk Assessment:** Patients were stratified at baseline using the Sokal, Hasford, and European Treatment and Outcome Study (EUTOS) prognostic scoring systems. The Sokal score was calculated using age, spleen size below the costal margin, platelet count, and peripheral blood blast percentage. Patients were classified into low-risk (score below 0.8), intermediate-risk (0.8–1.2), and high-risk (above 1.2) categories.

The Hasford score incorporated age, spleen size, peripheral blood blast percentage, eosinophil percentage, basophil percentage, and platelet count. Patients were categorized as low risk (≤780), intermediate risk (>780–1480), or high risk (>1480). The EUTOS score was calculated using the formula: 7 × peripheral blood basophil percentage + 4 × spleen size in centimeters below the costal margin. Patients with scores ≤87 were categorized as low risk, whereas those with scores >87 were categorized as high risk. Associations between these baseline prognostic classifications and subsequent molecular outcomes were evaluated.

**Molecular Response Assessment:** Molecular response was assessed by quantification of BCR-ABL1 fusion transcripts using real-time quantitative reverse-transcription polymerase chain reaction (RQ-PCR). Baseline molecular assessment was performed at PGIMER, Chandigarh. Subsequent molecular response was evaluated at 3, 6, 12, 18, 24, and 36 months following initiation of imatinib therapy.

Quantitative molecular testing at 24 and 36 months was performed using the GeneXpert system, an automated cartridge-based platform integrating nucleic acid extraction, reverse transcription, amplification, and detection. The assay quantified BCR-ABL1 transcripts relative to the ABL control gene, with results expressed as a percentage on the International Scale (IS).

Early molecular response at three months was evaluated using the BCR-ABL1 transcript threshold of 10% IS. Patients achieving transcript levels ≤10% were classified as having an optimal early molecular response, whereas those with levels >10% were classified as having an inadequate early molecular response. Major molecular response was defined as BCR-ABL1 transcript levels ≤0.1% IS. Molecular response at 24 and 36 months was assessed to determine the relationship between early treatment response and subsequent molecular outcomes.

**Outcome Measures:** The primary outcome was overall survival through 36 months following initiation of imatinib therapy in relation to early molecular response status at three months. Overall survival was defined as the time from initiation of imatinib therapy to death from any cause. Recorded survival and follow-up outcomes were assessed according to early molecular response status. Secondary outcomes included molecular response at subsequent follow-up intervals, the association between early molecular response and later major molecular response, and the prognostic relevance of baseline Sokal, Hasford, and EUTOS risk classifications. Baseline clinical and hematological characteristics were also evaluated for their associations with early molecular response.

**Follow-up and Outcome Assessment:** Patients underwent clinical, hematological, and molecular monitoring for up to 36 months following initiation of imatinib therapy. Follow-up information included clinical disease status, hematological response, molecular response, survival status, and changes in tyrosine kinase inhibitor therapy. Among the 67 patients, 51 were recorded as alive, six died during follow-up, eight were lost to follow-up, and two switched from imatinib to nilotinib. Follow-up outcomes were categorized according to the last recorded patient status. Treatment switching was considered a separate treatment-related outcome and was not classified as a mortality event.

**Statistical Analysis:** Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 20.0. Continuous variables were summarized using means and standard deviations or medians and ranges, as appropriate, while categorical variables were expressed as frequencies and percentages. Welch's independent-samples t-test was used to compare continuous variables between the early molecular response groups. Associations between categorical variables were assessed using Pearson's chi-square test or Fisher's exact test, as appropriate. Pearson's correlation coefficient was used to assess relationships between quantitative variables using available paired observations. Molecular response rates were calculated using the number of patients with available assessments at each follow-up interval. Survival and follow-up outcomes were summarized descriptively according to early molecular response status. The association between early molecular response and subsequent molecular outcomes was evaluated using appropriate categorical statistical tests. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

# RESULTS

The study included 67 patients with chronic-phase chronic myeloid leukemia (CML-CP) receiving imatinib mesylate.

**Baseline Demographic and Clinical Characteristics**

The demographic and clinical profile of the study population is summarized in Table 1. The cohort consisted predominantly of middle-aged adults, with a male predominance. Splenomegaly was the most frequent clinical manifestation, while functional performance status was generally well preserved at presentation.

**Table 1: Baseline Demographic and Clinical Characteristics of Patients with Chronic-Phase Chronic Myeloid Leukemia (N=67)**

| Characteristic | Value |
|---|---|
| **Demographic characteristics** | |
| Age, median (range), years | 42 (13–72) |
| Male | 40 (59.70%) |
| Female | 27 (40.30%) |
| Male-to-female ratio | 1.48:1 |
| **Age distribution** | |
| Young age group | 28 (41.80%) |
| Middle age group | 33 (49.25%) |
| Older age group | 6 (8.95%) |
| **Clinical characteristics** | |
| Symptom duration, median (range), days | 64 (0–1931) |
| Symptom duration in males, median, days | 62 |
| Symptom duration in females, median, days | 65 |
| Splenomegaly | 57 (85.07%) |
| Spleen size, median, cm below left costal margin | 8 |
| Hepatomegaly | 26 (38.80%) |
| Lymphadenopathy | 8 (11.94%) |
| **ECOG performance status** | |
| Grade 0–1 | 65 (97.01%) |
| Grade 2 | 2 (2.99%) |

Values are expressed as frequency (percentage) unless otherwise specified. ECOG: Eastern Cooperative Oncology Group.

**Baseline Hematological Profile and Prognostic Risk Stratification**

Baseline hematological evaluation demonstrated considerable variability in leukocyte and platelet counts. Prognostic assessment using the Sokal,

Hasford, and EUTOS scoring systems identified different risk distributions, highlighting the variation in patient classification across the three prognostic models. [Table 2]

**Table 2: Baseline Hematological Parameters and Prognostic Risk Classification (N=67)**

| Parameter | Value |
|---|---|
| **Hematological parameters** | |
| Hemoglobin, mean, g/dL | 10.78 |
| Total leukocyte count, mean, ×10³/mm³ | 168.72 |
| Platelet count, mean, ×10³/mm³ | 418.63 |
| Neutrophils, mean (%) | 49.57 |
| Lymphocytes, mean (%) | 7.19 |
| Monocytes, mean (%) | 1.90 |
| Eosinophils, mean (%) | 3.40 |
| Basophils, mean (%) | 4.48 |
| Peripheral blood blasts, mean (%) | 2.63 |
| Bone marrow blasts, mean (%) | 3.54 |
| **Sokal risk classification** | |
| Low risk | 15 (22.39%) |
| Intermediate risk | 32 (47.76%) |
| High risk | 20 (29.85%) |
| **Hasford risk classification** | |
| Low risk | 21 (31.34%) |
| Intermediate risk | 36 (53.73%) |
| High risk | 10 (14.93%) |
| **EUTOS risk classification** | |
| Low risk | 51 (76.12%) |
| High risk | 16 (23.88%) |

*Values are expressed as mean for continuous variables and n (%) for categorical variables. EUTOS: European Treatment and Outcome Study.*

Correlation analysis demonstrated significant positive associations between Sokal and Hasford scores (r=0.545, p<0.001) and between Hasford and EUTOS scores (r=0.462, p<0.001). No statistically significant correlation was observed between Sokal and EUTOS scores (r=0.042, p=0.735).

**Early Molecular Response and Associated Baseline Factors**

The association of early molecular response with clinical, hematological, and prognostic parameters is presented in Table 3. Patients achieving early molecular response had significantly smaller baseline spleen size (p=0.014), lower total leukocyte count (p=0.034), and lower Hasford score (p=0.001). Age, symptom duration, time to complete hematological response, hemoglobin concentration, bone marrow blast percentage, bone marrow eosinophil percentage, Sokal score, and EUTOS score were not significantly associated with early molecular response.

**Table 3: Association of Clinical, Hematological, and Prognostic Characteristics with Early Molecular Response at Three Months (N=67)**

| Parameter | BCR-ABL1 ≤10% (n=50) | BCR-ABL1 >10% (n=17) | p-value |
|---|---|---|---|
| Age, mean ± SD (years) | 41.08 ± 14.77 | 42.18 ± 13.45 | 0.779 |
| **Clinical characteristics** | | | |
| Symptom duration, mean ± SD (days) | 170.20 ± 330.27 | 170.24 ± 259.61 | 1.000 |
| Spleen size, mean ± SD (cm) | 7.30 ± 6.34 | 11.24 ± 5.06 | **0.014** |
| Time to complete hematological response, mean ± SD (days) | 41.98 ± 41.45 | 78.07 ± 84.53 | 0.145 |
| **Hematological parameters** | | | |
| Hemoglobin, mean ± SD (g/dL) | 10.74 ± 1.72 | 10.35 ± 1.97 | 0.477 |
| Total leukocyte count, mean ± SD (×10⁵/mm³) | 1.48 ± 0.94 | 2.33 ± 1.44 | 0.034 |
| Bone marrow blasts, mean ± SD (%) | 3.64 ± 2.16 | 4.29 ± 2.59 | 0.359 |
| Bone marrow eosinophils, mean ± SD (%) | 3.94 ± 2.59 | 3.24 ± 2.56 | 0.339 |
| **Baseline prognostic scores** | | | |
| Sokal score, mean ± SD | 1.009 ± 0.299 | 2.006 ± 2.116 | 0.070 |
| Hasford score, mean ± SD | 911.56 ± 396.94 | 1371.47 ± 474.02 | **0.001** |
| EUTOS score, mean ± SD | 59.26 ± 40.26 | 83.00 ± 44.72 | 0.064 |

*Values are expressed as mean ±standard deviation. P-values were calculated using Welch's independent-samples t-test. Bold p-values indicate statistical significance at p<0.05. Time to complete hematological response was available for 42 early responders and 14 non-responders; bone marrow eosinophil measurements were available for 49 early responders and 17 non-responders. BCR-ABL1: breakpoint cluster region–Abelson 1 fusion transcript.*

**Longitudinal Molecular Response During Treatment**

Serial molecular monitoring demonstrated an increase in the proportion of evaluable patients achieving major molecular response during follow-

up. Major molecular response was observed in 36 of 63 patients (57.14%) at 12 months, 41 of 62 (66.13%) at 18 months, 38 of 54 (70.37%) at 24 months, and 39 of 52 (75.00%) at 36 months. These proportions were calculated using the number of patients with available molecular assessments at the respective follow-up intervals. The varying numbers of evaluable patients were considered when interpreting longitudinal molecular-response patterns.

**Table 4: Longitudinal Molecular Response Following Imatinib Mesylate Therapy**

| Follow-up | Patients evaluated (n) | Molecular response threshold | Achieved, n (%) | Not achieved, n (%) |
|---|---|---|---|---|
| 3 months | 67 | BCR-ABL1 ≤10% | 50 (74.63%) | 17 (25.37%) |
| 6 months | 67 | BCR-ABL1 ≤1% | 37 (55.22%) | 30 (44.78%) |
| 12 months | 63 | BCR-ABL1 ≤0.1% | 36 (57.14%) | 27 (42.86%) |
| 18 months | 62 | BCR-ABL1 ≤0.1% | 41 (66.13%) | 21 (33.87%) |
| 24 months | 54 | BCR-ABL1 ≤0.1% | 38 (70.37%) | 16 (29.63%) |
| 36 months | 52 | BCR-ABL1 ≤0.1% | 39 (75.00%) | 13 (25.00%) |
| **Depth of molecular response at 36 months** | | | | |
| MR3 | 52 | BCR-ABL1 ≤0.1% | 39 (75.00%) | 13 (25.00%) |
| MR3.5 | 52 | BCR-ABL1 ≤0.032% | 35 (67.31%) | 17 (32.69%) |
| MR4 | 52 | BCR-ABL1 ≤0.01% | 28 (53.85%) | 24 (46.15%) |
| MR4.5 | 52 | BCR-ABL1 ≤0.0032% | 21 (40.38%) | 31 (59.62%) |

*Percentages were calculated using the number of patients with available molecular measurements at each follow-up interval. Molecular response was classified using quantitative BCR-ABL1 transcript measurements on the International Scale. MR3, MR3.5, MR4 and MR4.5 represent nested response thresholds and are not mutually exclusive.*

Quantitative analysis demonstrated a reduction in mean BCR-ABL1 transcript levels during follow-up, reflecting a decrease in molecular disease burden among evaluable patients. Molecular response proportions increased across successive assessments, although the number of patients with available molecular measurements varied between follow-up intervals. These findings indicate favorable molecular response patterns during imatinib treatment.

**Association Between Early and Subsequent Molecular Response**

The association between three-month molecular response status and subsequent molecular outcomes is presented in Table 5. Patients achieving early molecular response generally demonstrated higher proportions of subsequent major molecular response than patients who did not achieve the three-month target. At 36 months, major molecular response was observed in 33 of 39 patients (84.62%) who achieved early molecular response, compared with six of 13 patients (46.15%) who did not achieve early molecular response.

**Table 5: Association Between Three-Month Molecular Response and Subsequent Molecular Outcomes**

| Follow-up | Three-month EMR | Response achieved, n (%) | Not achieved, n (%) | Total |
|---|---|---|---|---|
| 6 months | Achieved | 37 (74.00%) | 13 (26.00%) | 50 |
| | Not achieved | 0 (0.00%) | 17 (100.00%) | 17 |
| 12 months | Achieved | 35 (72.92%) | 13 (27.08%) | 48 |
| | Not achieved | 1 (6.67%) | 14 (93.33%) | 15 |
| 18 months | Achieved | 38 (80.85%) | 9 (19.15%) | 47 |
| | Not achieved | 3 (20.00%) | 12 (80.00%) | 15 |
| 24 months | Achieved | 33 (82.50%) | 7 (17.50%) | 40 |
| | Not achieved | 5 (35.71%) | 9 (64.29%) | 14 |
| 36 months | Achieved | 33 (84.62%) | 6 (15.38%) | 39 |
| | Not achieved | 6 (46.15%) | 7 (53.85%) | 13 |

*Percentages were calculated within each three-month molecular response category using the number of patients evaluated at the corresponding follow-up interval. Early molecular response was defined as BCR-ABL1 ≤10% on the International Scale at three months. The six-month molecular response threshold was BCR-ABL1 ≤1%, whereas major molecular response at subsequent assessments was defined as BCR-ABL1 ≤0.1%.*

Correlation analysis demonstrated a significant positive association between BCR-ABL1 transcript levels at three months and those at 12 months ($r=0.511$, $p<0.001$) and 36 months ($r=0.315$, $p=0.023$). The correlation between three-month and 24-month transcript levels was not statistically significant ($r=0.228$, $p=0.098$). A strong positive correlation was observed between transcript levels at 24 and 36 months ($r=0.938$, $p<0.001$).

**Three-Year Survival Outcomes**

Survival and follow-up outcomes were assessed among 67 patients with chronic-phase chronic myeloid leukemia during a maximum follow-up period of 36 months. The distribution of recorded outcomes according to three-month molecular response status is presented in Table 6. Six deaths occurred during follow-up, while eight patients were lost to follow-up and two switched to nilotinib. Recorded mortality proportions were 10.00% among

patients achieving early molecular response and 5.88% among those not achieving early molecular response.

**Table 6: Distribution of Survival and Follow-up Outcomes According to Three-Month Molecular Response Status (N=67)**

| Follow-up outcome | EMR achieved (n=50) | EMR not achieved (n=17) | Total (N=67) |
|---|---|---|---|
| Alive | 39 (78.0%) | 12 (70.6%) | 51 (76.1%) |
| Death | 5 (10.0%) | 1 (5.9%) | 6 (9.0%) |
| Lost to follow-up | 6 (12.0%) | 2 (11.8%) | 8 (11.9%) |
| Switched to nilotinib | 0 (0.0%) | 2 (11.8%) | 2 (3.0%) |
| Total | 50 (100%) | 17 (100%) | 67 (100%) |

*Values are expressed as frequency (percentage). Percentages were calculated using the respective early molecular response group denominators (n=50 and n=17), with overall percentages calculated using N=67. Early molecular response (EMR) was defined as BCR-ABL1 ≤10% on the International Scale at three months. Survival and follow-up categories represent the last recorded patient outcomes during the observation period.*

Among the 67 patients, 51 (76.12%) were recorded as alive, six (8.96%) died during follow-up, eight (11.94%) were lost to follow-up, and two (2.99%) were switched to nilotinib. Five deaths occurred among the 50 patients who achieved early molecular response (10.00%), compared with one death among the 17 patients who did not achieve early molecular response (5.88%). These findings represent the distribution of recorded outcomes rather than estimated three-year overall survival probabilities. As individual event times and censoring dates were not available for verification, Kaplan–Meier survival estimates and between-group survival comparisons could not be reliably established from the available aggregate data. Therefore, the relationship between early molecular response and three-year overall survival remains inconclusive.

## DISCUSSION

The present study evaluated the association of early molecular response at three months with subsequent molecular and survival outcomes among 67 patients with chronic-phase chronic myeloid leukemia receiving imatinib mesylate. Early molecular response was achieved in 74.63% of patients, while major molecular response at 36 months was observed in 75.00% of evaluable patients. Baseline spleen size, total leukocyte count, and Hasford score were significantly associated with early molecular response. Patients achieving early molecular response demonstrated more favorable subsequent molecular outcomes. However, the relationship between early molecular response and three-year overall survival could not be conclusively established.

The achievement of early molecular response in approximately three-fourths of patients supports the effectiveness of imatinib in achieving early disease control. Marin et al,[6] in a study involving 282 patients receiving imatinib, demonstrated that three-month BCR-ABL1 transcript levels were strongly predictive of long-term outcomes. Patients with transcript levels exceeding 9.84% had substantially lower eight-year overall survival than those achieving the molecular target (56.9% versus 93.3%, $p<0.001$). The present findings similarly demonstrate the prognostic relevance of early molecular response for subsequent molecular outcomes. The European LeukemiaNet recommendations also emphasize the importance of assessing BCR-ABL1 transcript levels at three months to guide response monitoring and clinical decisions.[1]

Longitudinal molecular assessment demonstrated increasing proportions of evaluable patients achieving major molecular response, from 57.14% at 12 months to 70.37% at 24 months and 75.00% at 36 months. Among patients achieving early molecular response, 84.62% attained major molecular response at 36 months, compared with 46.15% among patients who did not achieve the initial molecular target. These findings are consistent with the long-term benefits of imatinib treatment demonstrated by Druker et al,[3] and Hochhaus et al.[4] Significant positive correlations were observed between three-month BCR-ABL1 levels and subsequent measurements at 12 and 36 months, whereas the correlation with 24-month measurements was not statistically significant. A strong positive correlation was also observed between the 24- and 36-month measurements. These findings support the clinical relevance of serial molecular monitoring. Hughes et al,[5] similarly emphasized the importance of molecular response in assessing therapeutic efficacy. Although early molecular response was associated with favorable subsequent molecular outcomes, its relationship with three-year overall survival remained inconclusive. Six deaths were recorded among the 67 patients, comprising five deaths among patients achieving early molecular response and one among those not achieving the early molecular target. Eight patients were lost to follow-up, and two switched to nilotinib. The limited number of mortality events and incomplete follow-up restricted the interpretation of long-term survival outcomes. Marin et al,[6] previously demonstrated a significant association between three-month BCR-ABL1 transcript levels and long-term survival. Differences in sample size, duration of follow-up, and clinical

characteristics may influence the observed relationships between early response and survival across studies. Branford et al,[7] further demonstrated that patients exceeding the three-month molecular threshold represent a heterogeneous group, with subsequent response kinetics providing additional prognostic information.

Baseline prognostic assessment demonstrated that Hasford score was significantly associated with early molecular response (p=0.001), whereas Sokal and EUTOS scores were not significantly associated with early molecular response (p=0.070 and p=0.064, respectively). Baseline spleen size (p=0.014) and total leukocyte count (p=0.034) were also significantly associated with early molecular response. The Sokal and Hasford scoring systems were originally developed to predict outcomes using baseline clinical and hematological characteristics.[8,9] Hasford et al,[10] subsequently developed the EUTOS score specifically for imatinib-treated patients and demonstrated better five-year progression-free survival among low-risk patients than high-risk patients (90% versus 82%, p=0.006). The present findings highlight the potential complementary role of baseline clinical characteristics, prognostic assessment, and early molecular monitoring in identifying patients requiring closer surveillance.

The clinical significance of these findings lies in the value of combining baseline prognostic assessment with serial quantitative molecular monitoring. Early identification of patients with delayed responses may facilitate closer evaluation of treatment adherence, response kinetics, and the need for further therapeutic assessment. The inclusion of three established prognostic scoring systems and longitudinal molecular evaluations extending to 36 months strengthens the clinical relevance of the study.

The study has several limitations. Its single-center observational design and relatively small sample size restrict generalizability and statistical power. Only six deaths were recorded during follow-up, limiting the precision of mortality comparisons. Eight patients were lost to follow-up, while two switched to nilotinib, potentially affecting the assessment of long-term treatment outcomes. The number of patients undergoing molecular assessment varied across follow-up intervals, introducing the possibility of attrition bias. Additional factors, including treatment adherence, dose modifications, comorbidities, and molecular response kinetics, were not comprehensively evaluated. Furthermore, the observational nature of the study precludes causal inference. Larger multicenter prospective studies with standardized molecular monitoring and longer follow-up are warranted to validate these findings.

## CONCLUSION

The present study highlights the clinical relevance of early molecular response in patients with chronic-phase chronic myeloid leukemia receiving imatinib mesylate. Approximately three-fourths of patients achieved early molecular response at three months, while major molecular response was observed in 75.00% of evaluable patients at 36 months. Patients achieving early molecular response demonstrated more favorable subsequent molecular outcomes, emphasizing the importance of early and serial molecular monitoring. Baseline spleen size, total leukocyte count, and Hasford score were significantly associated with early molecular response. Six deaths were recorded during follow-up, while the association between early molecular response and three-year overall survival remained inconclusive. These findings support the integration of baseline clinical assessment, prognostic stratification, and standardized molecular monitoring to identify patients requiring closer follow-up. Larger prospective multicenter studies with comprehensive follow-up are warranted to clarify the long-term prognostic implications of early molecular response.

**Declarations**

**Ethical Approval:** The study was conducted after obtaining approval from the Institutional Ethics Committee of PGIMER, Chandigarh, India.

**Informed Consent:** Informed consent was obtained from all study participants or their legally authorized representatives, as applicable.

**Funding:** The study received no external funding.

**Conflicts of Interest:** The authors declare no conflicts of interest.

**Data Availability:** The datasets generated and/or analyzed during the study are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

**Author Contributions:** All authors contributed significantly to the study, participated in manuscript preparation and critical revision, and approved the final version for publication.

**Acknowledgements:** The authors express their sincere gratitude to the faculty, residents, nursing staff, laboratory personnel, and supporting staff of the Department of Hematology, PGIMER, Chandigarh, for their valuable assistance and cooperation. The authors also thank all study participants for their participation and contribution to the research.

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