

16-Year Epidemiologic Study of Chronic Myeloid Leukemia in Azerbaijan: Clinical and Molecular Insights

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Received: 2026-01-18.

Accepted: 2026-02-24.



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J Clin Med Kaz 2026; 23(2): 6-18

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Abstract

Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with a global incidence of 0.5–2 per 100,000 population. However, comprehensive epidemiologic data from Azerbaijan remain limited.

Methods: A retrospective nationwide cohort study was conducted at the National Hematology and Blood Transfusion Center, the sole hematology referral center in Azerbaijan. All patients diagnosed with CML between 2008 and 2023 were included. Demographic, clinical, molecular, and treatment data were extracted from medical records. Descriptive analyses assessed temporal trends, age and sex distribution, seasonal and geographic patterns, ABO/Rh blood groups, kinase domain mutations, treatment response, and survival.

Results: Study included 766 patients, with a female predominance (54%) and the highest disease burden observed in individuals aged 50–59 years. CML incidence increased from 0.31 to 0.86 per 100,000 population between 2008 and 2023, while prevalence rose more than twelve-fold. Following the introduction of tyrosine kinase inhibitors (TKIs), five-year overall survival exceeded 80%. Most patients resided in the Absheron region, suggesting possible environmental or industrial influences. New diagnoses were more frequent during summer months (29.6%). Blood group A was more prevalent among patients compared with controls (40.3% vs 35.4%). First-line imatinib achieved optimal molecular responses in approximately 80% of patients, while 15% experienced treatment failure. Among 115 patients tested, T315I was the most common BCR-ABL mutation.

Conclusions: This nationwide CML analysis from Azerbaijan reveals a rising disease burden, female predominance, and favorable survival outcomes with TKI therapy. The findings emphasize the need for sustained access to molecular diagnostics and support national strategies for equitable CML care.

Keywords: chronic myeloid leukemia; epidemiology; Azerbaijan; molecular mutations; treatment response.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome, resulting from a reciprocal translocation between chromosomes 9

and 22, which creates the BCR-ABL1 fusion oncogene. This molecular alteration drives constitutive tyrosine kinase activity and uncontrolled proliferation of myeloid precursors [1]. Globally, CML accounts for about 15% of adult leukemia, with an annual incidence ranging between

0.5 and 2 per 100,000, depending on local diagnostic infrastructure, registry coverage, and population demographics [2, 3].

Historically, most studies have documented a modest male predominance in CML, with a male-to-female ratio typically between 1.2–1.7 [4]. Nevertheless, some regional data have shown a female predominance in certain ethnic or geographic populations [5][6]. Age distribution generally peaks between 40 and 60 years, although the introduction of tyrosine kinase inhibitors (TKIs) has dramatically changed outcomes, extending life expectancy and transforming CML into a chronic, manageable disease [7].

In Azerbaijan, epidemiological data remain sparse apart from limited reports on leukemia incidence in general [6]. Given Azerbaijan's unique industrial and environmental landscape, regional studies are crucial to detect possible influences on leukemia occurrence. Local analyses are therefore essential to identify patterns in gender distribution, age at diagnosis, Sokal risk stratification, and molecular features, which could influence both public health policy and clinical treatment approaches. In addition, factors such as seasonal diagnosis trends, ABO/Rh blood group associations, and molecular mutations in TKI-resistant patients are poorly described in this population.

Global Context and Rationale: Over the past two decades, the treatment landscape of chronic myeloid leukemia has been revolutionized by tyrosine kinase inhibitors (TKIs) [1,7]. Imatinib, the first-generation TKI, transformed CML from a fatal disease into a chronic, controllable condition. Subsequent second- and third-generation TKIs such as nilotinib, dasatinib, bosutinib, and ponatinib have further improved response depth, durability, and outcomes, particularly among patients harboring resistant clones [1]. Despite these advances, the emergence of ABL kinase domain mutations remains a key mechanism of therapeutic resistance. Among these, the T315I mutation is clinically the most relevant, conferring high-level resistance to first- and second-generation TKIs and often necessitating treatment with third-generation agents such as ponatinib. Evaluating the frequency of such mutations provides essential insight into molecular resistance profiles within a population and informs national treatment strategies.

In addition to molecular mechanisms, several epidemiological and biological factors have been proposed to influence CML occurrence and presentation. These include environmental exposures, population-level variations in blood group distribution, and possible seasonal patterns in diagnosis. ABO and Rhesus blood group antigens have been hypothesized to modulate immune and inflammatory responses, which could contribute to leukaemogenesis, whereas seasonal variation may reflect environmental, infectious, or behavioral influences affecting detection rates. Assessing these variables in a nationwide cohort helps to contextualize disease characteristics and identify potential avenues for future research.

This study aimed to characterize the epidemiology of chronic myeloid leukemia (CML) in Azerbaijan using nationwide data collected over a 16-year period (2008–2023). The primary objective was to describe national trends in incidence, prevalence, and survival outcomes within a unified healthcare system. Secondary aims were to explore demographic and regional patterns—including gender distribution, age at diagnosis, and geographic clustering—as well as to assess treatment responses and common resistance-associated molecular mutations among patients receiving tyrosine kinase inhibitors. By focusing on these core outcomes, the study provides a structured overview of disease burden and treatment effectiveness across the Azerbaijani CML population.

Methods

This study was conducted following best practices for observational epidemiologic research, ensuring methodological transparency and reproducibility. Detailed descriptions of the study design, patient selection, diagnostic procedures, data collection, and statistical analysis are provided below to allow independent replication of all steps undertaken.

Study Design and Setting

This was a nationwide retrospective cohort study designed to evaluate the epidemiology, clinical characteristics, treatment response, and survival outcomes of patients diagnosed with chronic myeloid leukemia (CML) in Azerbaijan over a 16-year period (2008–2023).

The study was conducted at the National Hematology and Blood Transfusion Center (NHBTC) in Baku, which serves as the country's only authorised tertiary reference centre for the diagnosis, treatment, and follow-up of patients with CML.

Within the national healthcare system, patients with suspected hematologic malignancies are referred to the NHBTC from regional hospitals and outpatient clinics. At this centre, diagnostic confirmation is performed using standardized cytogenetic and molecular testing, including BCR-ABL1 detection by quantitative RT-PCR and karyotyping. All confirmed cases are registered in the national CML database.

The NHBTC also coordinates the national tyrosine kinase inhibitor (TKI) distribution programme under the Ministry of Health. Treatment initiation, response monitoring, mutation testing, and long-term follow-up are therefore centralized at this institution. This structure ensures uniform diagnostic criteria, standardized treatment protocols, and near-complete national coverage of CML cases.

Although a small proportion of patients may initially seek diagnostic confirmation or second opinions abroad, these individuals are routinely re-registered at the NHBTC upon return to continue therapy within the national programme. Consequently, the registry is considered representative of nearly all CML cases nationwide. Some degree of under-diagnosis in remote regions cannot be entirely excluded; however, its impact is likely minimal because molecular and cytogenetic testing have been routinely available through the central programme since 2008.

Follow-up was defined from the date of initial CML diagnosis (first documented positive BCR-ABL1 test or bone marrow confirmation) to the date of last recorded clinical visit, death, or 31 December 2023, whichever occurred first. Patients alive at the end of this period were censored at their last documented follow-up. Survival analyses therefore reflect observation intervals ranging from 1 month to 16 years, depending on the year of diagnosis.

Patient Population

All patients with a confirmed diagnosis of chronic myeloid leukaemia (CML) between 1 January 2008 and 31 December 2023 were included in the registry-based cohort. Diagnosis was established according to World Health Organization (WHO) criteria [13], requiring detection of the BCR-ABL1 fusion transcript by quantitative RT-PCR and/or the presence of the Philadelphia chromosome on karyotyping.

Inclusion criteria: Confirmed diagnosis of CML with documented BCR-ABL1 positivity, age ≥ 18 years at diagnosis (paediatric cases were registered separately but excluded from adult analyses), availability of complete baseline demographic and clinical data.

Exclusion criteria: Patients with incomplete diagnostic confirmation (missing cytogenetic or molecular data), patients who were initially misclassified or referred with other myeloproliferative neoplasms, patients lost to follow-up immediately after diagnosis with no treatment or outcome data available.

During the study period, a total of 812 patients with confirmed CML were identified in the national registry. After applying the predefined inclusion and exclusion criteria, 766 patients fulfilled all eligibility requirements and were included in the final analysis.

A total of 766 patients fulfilled these criteria and were included in the main analysis.

Of these, 249 patients had adequate serial molecular monitoring data to evaluate treatment response to first-line imatinib according to ELN guidelines. Patients without consistent quantitative BCR-ABL1 measurements were not included in this sub-analysis to avoid measurement bias. Similarly, 115 patients underwent ABL kinase domain mutation testing due to clinical or molecular evidence of TKI resistance; this subset reflects all cases with available stored samples and formal resistance evaluation during the study period.

The remaining patients continued first-line or subsequent-line TKI therapy (nilotinib, dasatinib, or bosutinib) under standard national protocols but were excluded from those sub-analyses due to insufficient longitudinal molecular data or absence of resistance work-up.

To evaluate the distribution of ABO blood groups and Rhesus factor among patients with CML, a control population was used for comparison. Anonymized data from 7,086 healthy blood donors were obtained from the NHBTC Blood Bank database. Controls were matched to patients by sex and broad age categories (± 10 years) to minimize demographic bias. This control cohort represents the general healthy donor population in Azerbaijan and serves as the national reference for blood group distribution.

Data Collection

Demographic data comprised age, sex, and place of residence. Clinical data included Sokal risk category at diagnosis, disease phase (chronic, accelerated, or blast crisis), hematologic parameters (hemoglobin, leukocyte counts, platelet counts, basophil percentages), treatment responses to tyrosine kinase inhibitors, and molecular analyses (including ABL kinase domain mutations in patients with treatment resistance). Seasonal patterns and ABO/Rh blood group distributions were also extracted from the patient records.

Outcome Measures

The primary outcome was to describe the epidemiological profile of CML in Azerbaijan, including incidence, prevalence, age and gender distribution, regional distribution, seasonal patterns, and treatment responses. Secondary outcomes included evaluation of survival trends before and after TKI therapy and analysis of molecular resistance patterns.

Genetic and Molecular Analysis

Molecular testing for BCR-ABL1 transcript quantification was performed using real-time quantitative PCR at baseline and during follow-up according to ELN guidelines. ABL kinase domain mutation analyses were performed in patients who demonstrated suboptimal response or resistance to imatinib ($n=115$), using PCR amplification and pyrosequencing techniques. Confirmatory testing was performed at Ankara ATQ Biotechnology Laboratories for less common variants.

Follow-up for Outcomes: All outcome measures were evaluated over the defined follow-up period, beginning at the date of confirmed CML diagnosis and ending at death, last clinical contact, or 31 December 2023, whichever occurred first. Patients alive at the last available follow-up were treated as censored observations in survival analyses. Overall survival and treatment-response outcomes were therefore calculated within observation intervals ranging from 1 month to 16 years, depending on year of diagnosis and completeness of follow-up data.

Statistical Analysis

Descriptive statistics were used to summarize demographic, clinical, and molecular characteristics. Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. Incidence and prevalence rates were standardized to national population data from the State Statistical Committee of Azerbaijan for each calendar year.

Incidence and prevalence rates reported in this study are crude population-based rates. Age-standardized rates were not calculated because the primary objective was to describe national trends using complete registry data rather than to perform international comparative analyses. Annual incidence and prevalence rates were calculated with 95% confidence intervals using Poisson distribution methods.

Survival analyses were performed using the Kaplan–Meier method. Follow-up was defined from the date of diagnosis to death, last clinical contact, or 31 December 2023, whichever occurred first. Patients alive at last follow-up or lost to follow-up were censored at the date of their last documented clinical contact and were included in the analysis up to the time of censoring. Median overall survival (OS) and progression-free survival (PFS) were estimated with 95% confidence intervals (CIs) using Greenwood’s formula. One-, three-, and five-year overall survival probabilities were also estimated. Survival curves were compared using the log-rank test, with p-values reported descriptively.

Annual mortality incidence rates were summarized, and the average annual percent change (AAPC) was calculated using log-linear regression. The AAPC and its 95% confidence interval were derived from the regression slope, and statistical significance was assessed using two-sided p-values.

Comparisons across categorical variables were analyzed using chi-square (χ^2) tests. For analyses involving multiple categorical comparisons, such as seasonal distribution and ABO/Rh blood-group frequencies, results were adjusted using the Holm–Bonferroni correction to control for multiple testing. All results are expressed descriptively or as effect estimates with 95% CIs.

Multivariable modeling was not performed because several key confounding variables—including comorbidity profiles, treatment adherence, socioeconomic indicators, and environmental exposure data—were not consistently available across the national registry, particularly for earlier years of the cohort. The study was therefore designed as a primarily descriptive national epidemiological analysis.

All analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and independently cross-checked by two investigators to ensure reproducibility.^{2,7}

Treatment Response Assessment

Treatment response to imatinib was assessed according to the European LeukemiaNet (ELN) 2020 criteria. Optimal molecular response was defined as BCR-ABL1 $\leq 10\%$ at

3 months, $\leq 1\%$ at 6 months, and $\leq 0.1\%$ (major molecular response, MMR) at 12 months. Patients who did not achieve these milestones, lost a previously achieved response, or developed BCR-ABL kinase-domain mutations conferring resistance (e.g., T315I, F359C/V) were categorised as imatinib-resistant. For descriptive subgroup analyses, patients were stratified by achievement of early molecular response (EMR) and major molecular response (MMR) to explore trends in long-term outcomes.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of the National Hematology and Blood Transfusion Center. All analyses were performed on anonymized data extracted from the center’s registry in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of enrollment for data collection and future research purposes.

Results

Gender Distribution of CML Patients

A total of 766 patients with chronic myeloid leukemia were included in the study cohort. As illustrated in Figure 1, there was

a slight female predominance, with females comprising 54% of cases and males 46%.

Temporal Trends in CML Incidence

The incidence of chronic myeloid leukemia demonstrated an overall increasing trend in Azerbaijan between 2008 and 2023 (Figure 2). In 2008, the recorded incidence was 0.31 per 100,000 population, rising to 0.86 per 100,000 in 2023. The most pronounced growth occurred between 2010 and 2011, with incidence nearly doubling from 0.42 to 0.83 per 100,000.

When stratified by gender, female incidence generally exceeded that of males across most years. Female incidence ranged from 0.15 per 100,000 in 2009 to a peak of 0.58 per 100,000 in 2022. Male incidence varied between 0.14 per 100,000 in 2008 and 0.46 per 100,000 in 2021. These patterns align with the overall observed female predominance in the cohort.

Annual incidence rates with 95% confidence intervals were calculated for each year and sex. Among females, incidence ranged from 0.27 per 100,000 (95% CI: 0.12–0.42) in 2008 to 1.15 per 100,000 (95% CI: 0.85–1.44) in 2022. Among males, incidence ranged from 0.29 per 100,000 (95% CI: 0.13–0.46) in 2009 to 1.16 per 100,000 (95% CI: 0.86–1.46) in 2016. Confidence intervals for all annual rates were calculated using Poisson methods.

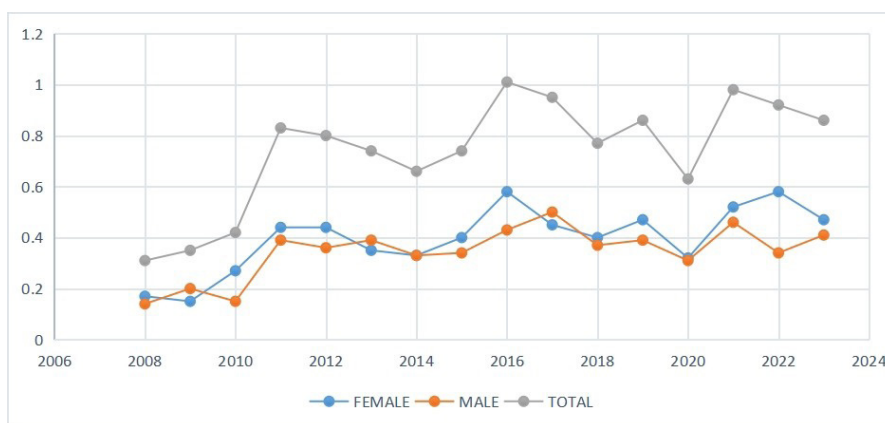


Figure 1 – Incidence of CML by years

The figure shows annual incidence rates of CML stratified by sex (female and male) and total population. Trends demonstrate year-to-year variation with generally higher total incidence driven by contributions from both sexes. Female and male incidence rates follow similar temporal patterns, with fluctuations observed across the study period.

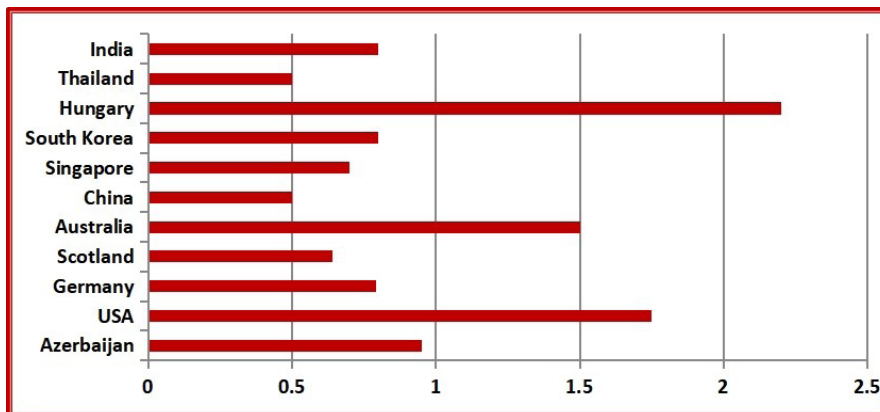


Figure 2 – Incidence of CML among different countries

The figure compares reported CML incidence rates among different countries, highlighting international variability in disease burden. Differences may reflect population structure, diagnostic practices, and registry coverage.

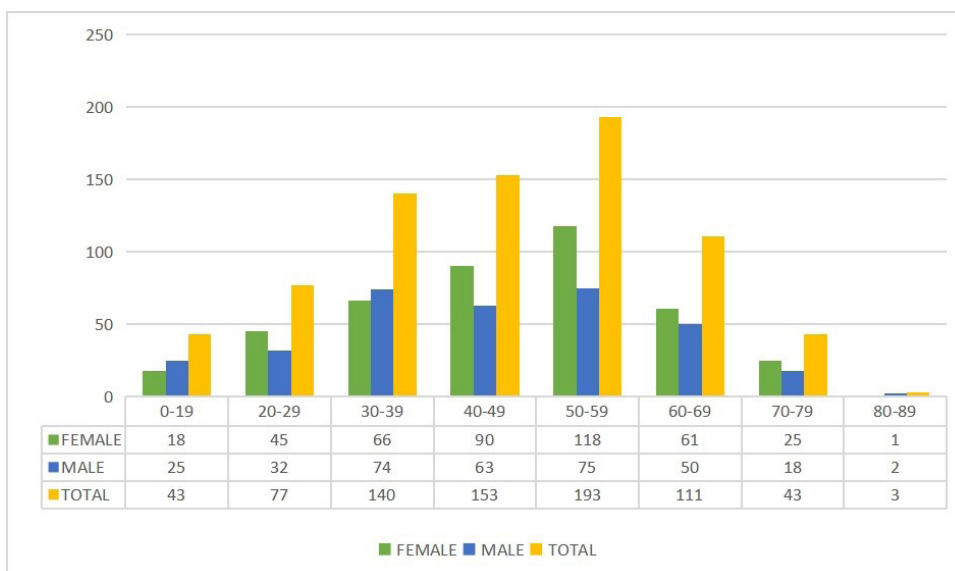


Figure 3 – Age-gender distribution

The figure illustrates the distribution of CML cases across age groups stratified by sex. The highest number of cases was observed in middle-aged and older adults, with comparable patterns between females and males across most age categories.

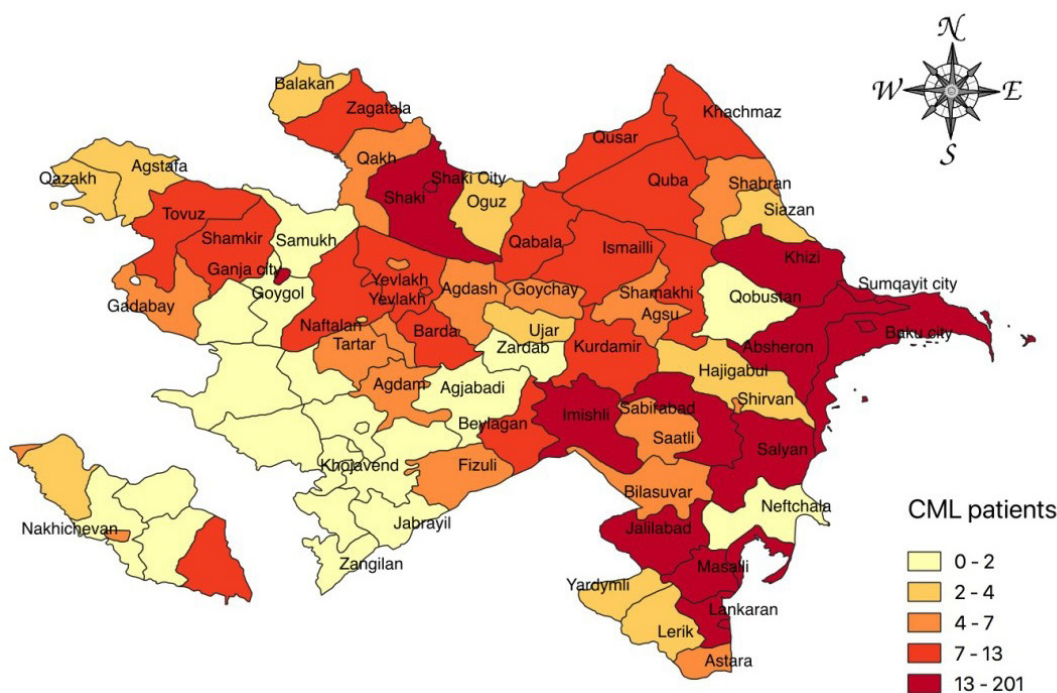


Figure 4 – Distribution of CML patients among regions of Azerbaijan

The map illustrates the regional distribution of CML patients in Azerbaijan, with darker shading indicating a higher number of cases. Variation across regions likely reflects differences in population density, referral patterns, and access to specialized hematology services.

International Comparison of CML Incidence

Figure 3 presents an international comparison of chronic myeloid leukemia incidence, allowing contextualization of the Azerbaijani data within a global epidemiological framework. In Azerbaijan, the incidence was approximately 0.9 per 100,000, similar to that reported in Germany and South Korea. In contrast, the incidence was notably higher in Hungary (2.3 per 100,000), Australia (1.5 per 100,000), and the United States (1.7 per 100,000). Lower incidence rates were observed in Thailand (0.4 per 100,000) and China (0.5 per 100,000).

Prevalence Trends in CML

The prevalence of chronic myeloid leukemia in Azerbaijan showed a consistent and notable rise over the period 2008–2023 (Figure 4). The total number of patients living with CML increased from 99 in 2008 to 1,219 in 2023, representing a more than twelve-fold increase over sixteen years.

When stratified by sex, the number of prevalent female cases grew from 43 in 2008 to 617 in 2023, while male prevalent cases increased from 56 to 602 during the same period. The consistently higher cumulative number of female

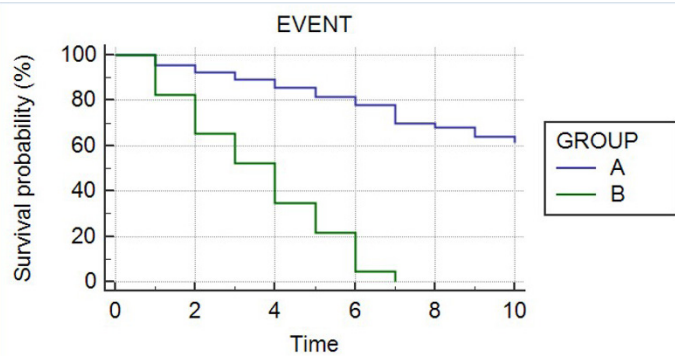


Figure 5 – Kaplan–Meier Survival Curves Comparing CML Patients Treated Before and After Introduction of TKI Therapy

Kaplan–Meier curves illustrate event-free survival over time for two study groups (Group A and Group B). Group A demonstrates a consistently higher survival probability throughout the follow-up period compared with Group B.

patients supports the female predominance observed in this cohort.

Annual prevalence rates with 95% confidence intervals were also calculated for each year and sex. Among females, prevalence increased from approximately 0.97 per 100,000 (95% CI: 0.68–1.30) in 2008 to 12.13 per 100,000 (95% CI: 11.16–13.12) in 2023. Among males, prevalence increased from approximately 1.29 per 100,000 (95% CI: 0.96–1.67) in 2008 to 11.95 per 100,000 (95% CI: 11.02–12.92) in 2023. Confidence intervals for all annual prevalence rates were calculated using Poisson methods.

Number of Newly Diagnosed CML Patients

Figure 5 illustrates the annual number of patients newly diagnosed with chronic myeloid leukemia from 2008 to 2023. Over this sixteen-year period, there was a general upward trend in new diagnoses, with some year-to-year fluctuations.

In 2008, 27 new CML cases were identified (12 female, 15 male). The number of new diagnoses rose sharply to 76 cases in 2011, followed by a stable period where annual new diagnoses ranged between 63 and 99 cases from 2012 to 2023.

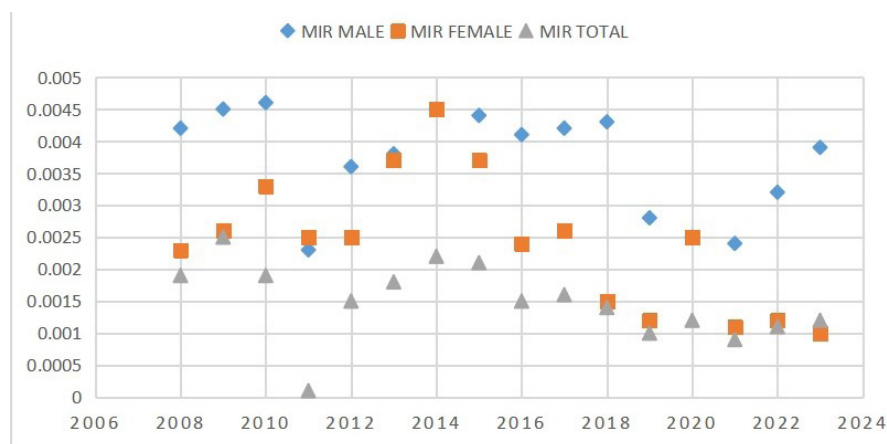


Figure 6 – Mortality rate of CML patients.

The figure presents annual mortality rates of CML stratified by sex (male and female) and for the total population. Male mortality rates were consistently higher than female rates across most years, while overall mortality demonstrated temporal fluctuations during the study period.

The highest annual count was recorded in 2021 with 98 new cases.

Age and Gender Distribution of CML Patients

Analysis of age groups (Figure 6) revealed the highest disease burden in the 50–59 age group, with female predominance evident in several decades. Most patients were diagnosed between the ages of 30 and 69 years, accounting for approximately 72% of the total cohort, with clear peaks in the 50–59 and 40–49 age groups. Specifically, the highest burden was observed in patients aged 50–59 years, accounting for 193 cases (118 female and 75 male). Although age categories are presented in decades starting from 0–19 years, only patients aged 18 years and older were included in the study. Therefore, the 0–19 group represents only patients aged 18–19 years.

In younger age groups (under 30 years), the incidence of CML was substantially lower, with only 43 cases in the 0–19 group and 77 cases in the 20–29 group. Likewise, the prevalence sharply declined after age 70, reflecting both lower life expectancy and lower disease detection in advanced age.

Female predominance was apparent in several key age brackets, particularly in the 50–59 group (118 females vs. 75 males) and 40–49 group (90 females vs. 63 males), supporting the gender pattern noted in the overall cohort.

Geographic Distribution of CML Patients

Figure 7 illustrates the geographic distribution of chronic myeloid leukemia patients across the administrative regions of Azerbaijan. The map shows a clear concentration of CML cases in the Absheron economic region, including Baku and Sumgayit, which reported the highest burden (up to 201 cases) and are indicated in dark red.

Moderate case densities (7–13 patients) were observed in districts such as Ganja, Mingachevir, and parts of Lankaran, while low-prevalence areas (0–2 patients) were mainly located in rural western and southern regions, including parts of Qazakh and Zangilan.

Seasonal Patterns of CML

Table 1 presents the distribution of chronic myeloid leukemia (CML) diagnoses across the four seasons in Azerbaijan. The highest proportion of cases occurred during summer (June–August) (29.6%), followed by spring (March–May) (25.4%), autumn (September–November) (23.5%), and winter (December–February) (21.5%).

Table 1

Distribution of Disease Phase and Sokal Risk Groups among CML Patients

Category	Subcategory	Male, n (%)	Female, n (%)	Total, n (%)	P value
Disease phase	Chronic	290 (80.6)	322 (79.3)	612 (79.9)	0.63
	Accelerated	60 (16.7)	75 (18.5)	135 (17.6)	
	Blast crisis	10 (2.7)	9 (2.2)	19 (2.5)	
Sokal risk group	Low	79 (22.2)	105 (25.5)	184 (24.0)	0.41
	Intermediate	220 (62.0)	255 (62.0)	475 (62.0)	
	High	56 (15.8)	51 (12.5)	107 (14.0)	

This table summarizes the distribution of chronic myeloid leukemia patients by disease phase and Sokal risk category, stratified by sex. Most patients were diagnosed in the chronic phase, and the majority belonged to the intermediate Sokal risk group, with similar distributions observed between male and female patients.

Table 2

Comparison of Imatinib Responders and Resistant Patients

Variable	Imatinib responders (n = 651)	Imatinib resistant (n = 115)	OR	95% CI	p-value
Age, years	Range: 4–84; mean: 47.3	Range: 16–80; mean: 45.3	-	-	-
Sex distribution	Male: 42.0%; Female: 58.0%	Male: 55.7%; Female: 44.3%	1.74	1.16–2.61	0.007
Disease phase	Chronic: 84.8% Accelerated: 15.2% Blast crisis: 0%	Chronic: 78.3% Accelerated: 16.5% Blast crisis: 5.2%	1.55	0.94–2.55	0.080
Sokal risk group	Low: 51.9% Intermediate: 40.4% High: 7.7%	Low: 30.4% Intermediate: 58.3% High: 11.3%	2.51	1.27–4.95	0.008

Odds ratios were calculated comparing resistant versus responder groups. Confidence intervals were derived using standard logistic methods. This table presents demographic and disease-related variables in patients who achieved an optimal response to first-line imatinib (n = 651) and those who were classified as imatinib-resistant (n = 115). Age distribution was comparable between the two groups, with similar mean ages (47.3 vs. 45.3 years). A significantly higher proportion of males was observed among imatinib-resistant patients compared with responders (55.7% vs. 42.0%), corresponding to an odds ratio (OR) of 1.74 (95% CI: 1.16–2.61; p = 0.007). Regarding disease phase at diagnosis, resistant patients more frequently presented with advanced phases, including accelerated phase and blast crisis (21.7% vs. 15.2% in responders), although this difference did not reach statistical significance (OR: 1.55; 95% CI: 0.94–2.55; p = 0.080). Risk stratification according to the Sokal score showed a significantly higher proportion of intermediate- and high-risk patients in the imatinib-resistant group. The odds of resistance were significantly increased among patients with higher Sokal risk (OR: 2.51; 95% CI: 1.27–4.95; p = 0.008).

Association of ABO Blood Groups and Rhesus factor with CML

Table 2 summarises the distribution of ABO blood groups and Rhesus factor among patients with CML and among healthy controls. Blood group A was more frequent among patients (40.3 %) than among controls (35.4 %), whereas blood group B was less common (14.6 % vs 20.2 %). Blood group A was significantly more frequent among CML patients than controls, and this association remained statistically significant after Bonferroni correction for multiple ABO group comparisons

(adjusted p = 0.024). The proportions of groups O and AB were similar between the two populations.

Regarding Rhesus factor, Rh-positive individuals predominated in both groups (about 92 % of patients and 90 % of controls).

Disease Phase and Risk Group Distribution

Table 3 summarizes the distribution of disease phases and risk groups among CML patients according to Sokal classification. Risk stratification was performed using the Sokal scoring system, as this was the only risk model consistently applicable throughout the entire 2008–2023 dataset. Variables required for the ELTS score (EUTOS Long-Term Survival) were not uniformly available for earlier cases; thus, the Sokal score was adopted for standardization and longitudinal comparability. At presentation, the majority of patients were diagnosed in the chronic phase (79.9%), with 80.6% of males and 79.3% of females falling into this category. The accelerated phase was identified in 17.6% of patients overall (16.7% male and 18.5% female), while only 2.5% presented in blast crisis (2.7% male and 2.2% female).

Risk stratification by the Sokal scoring system revealed that 24% of patients were classified as low risk, 62% as intermediate risk, and 14% as high risk. The proportion of low-risk patients was slightly higher among women (25.5%) compared to men (22.2%). Conversely, high-risk disease was marginally more frequent among males (15.8%) than females (12.5%).

Table 3

Distribution of BCR-ABL Kinase Domain Mutations among Imatinib-Resistant Patients by Gender

Mutation	Male, n (%)	Female, n (%)	Total, n (%)
E255K	1 (7.1)	0 (0.0)	1 (5.3)
F359C	2 (14.3)	1 (20.0)	3 (15.8)
F317L (TTA)	1 (7.1)	0 (0.0)	1 (5.3)
F317L (TTG)	1 (7.1)	1 (20.0)	2 (10.5)
F359V	2 (14.3)	1 (20.0)	3 (15.8)
Y253H	2 (14.3)	0 (0.0)	2 (10.5)
T315I	5 (35.7)	2 (40.0)	7 (36.8)

This table presents the frequency and distribution of BCR-ABL1 kinase domain mutations in imatinib-resistant patients, stratified by sex. The T315I mutation was the most frequently detected mutation in both male and female patients.

Table 4

Distribution of BCR-ABL Kinase Domain Mutations by Disease Phase and Sokal Risk Group

Group	Patients with mutations, n	Proportion (%)	p-value
Disease phase			
Chronic phase	10	11.1	
Accelerated phase	5	26.3	
Blast crisis phase	4	66.7	0.0008
Sokal risk group			
Low risk	5	14.3	
Intermediate risk	12	17.9	
High risk	2	15.4	0.890

This table shows the proportion of patients harboring BCR-ABL1 kinase domain mutations according to disease phase and Sokal risk category. Mutation frequency increased significantly with disease progression, being highest in blast crisis, while no significant association was observed between mutation frequency and Sokal risk group.

Hematologic Parameters across Disease Phases

Table 4 presents hemoglobin levels and leukocyte counts stratified by disease phase among CML patients.

In terms of hemoglobin levels, the majority of patients in the chronic phase had moderate anemia, with 47.7% having hemoglobin between 7.1–10 g/dL and 27.1% between 10.1–12 g/dL. Severe anemia (Hb 4–7 g/dL) was present in 8.7% of chronic-phase patients. Among patients in the accelerated phase, 67.4% had hemoglobin above 7 g/dL, while 10.4% had severe anemia. In blast crisis, severe anemia was more frequent, with nearly half (47.4%) of patients showing hemoglobin levels in the 4–7 g/dL range.

Regarding leukocyte counts, chronic-phase patients most commonly had counts between 21–100 $\times 10^9/L$, representing 20.1% in the 21–50 range and 20.9% in the 51–100 range. Very high leukocyte counts ($>300 \times 10^9/L$) were seen in only 13.5% of chronic-phase patients. In contrast, 26.7% of patients in the accelerated phase and 42.1% in blast crisis had extremely elevated leukocyte counts above 100 $\times 10^9/L$, consistent with disease progression.

Table 5 details the distribution of basophil percentages and platelet counts among chronic myeloid leukemia patients, stratified by disease phase.

In chronic-phase patients, the majority had basophil percentages between 0–1 % (57.0%) or 2–7% (36.6%), with only 3.4% showing basophil counts above 8%. In contrast, patients in the accelerated phase showed a shift toward higher basophil levels, with 8.9% having basophils between 8–20% and 7.0% exceeding 21%. Among those in blast crisis, elevated basophil percentages were common, with 42.1% in the 8–20% category and 21% above 21%, reflecting progressive disease activity.

Regarding platelet counts, most chronic-phase patients had counts in the normal-to-moderately elevated range (150–450 $\times 10^9/L$ in 67.3%, 451–1000 $\times 10^9/L$ in 15.0%). Thrombocytosis exceeding 1000 $\times 10^9/L$ was seen in 7.9% of chronic-phase patients. In the accelerated phase, 57.0% had platelet counts of 150–450 $\times 10^9/L$, while 18% showed elevated counts between 451–1000 $\times 10^9/L$. Notably, in blast crisis, 10.5% of patients presented with severe thrombocytopenia ($<20 \times 10^9/L$), indicating advanced marrow failure.

Survival of CML Patients Before and After TKI Therapy

Figure 8 presents the Kaplan–Meier survival analysis comparing chronic myeloid leukemia patients treated before the introduction of tyrosine kinase inhibitors (TKIs) (Group B, green curve) and those treated after TKI availability (Group A, blue curve).

Patients receiving TKI therapy (Group A) demonstrated markedly improved survival outcomes, with an estimated 5-year survival probability exceeding 80% and maintaining above 60% even at 10 years of follow-up. In contrast, patients managed before TKI availability (Group B) showed a steep decline in survival, with median survival below 4 years and 10-year survival approaching 0%. The difference between the two survival curves was statistically significant according to the log-rank test ($p < 0.001$).

In the TKI-treated cohort, the estimated overall survival was approximately 95% at 1 year, 89% at 3 years, and 81% at 5 years. Median overall survival was not reached during the observation period.

In contrast, the pre-TKI cohort showed substantially lower survival, with estimated survival of approximately 84% at 1 year, 53% at 3 years, and 23% at 5 years. The median overall survival in the pre-TKI group was approximately 3.5–4 years. The difference between survival curves was statistically significant according to the log-rank test ($p < 0.001$).

CML Mortality Trends Over Time

Figure 9 shows annual mortality incidence rates (MIR) for chronic myeloid leukemia patients in Azerbaijan from 2008 to 2023, stratified by sex. Overall, the mortality rate has declined over the study period, reflecting improvements in early diagnosis, monitoring, and treatment with tyrosine kinase inhibitors.

In the early observation years (2008–2011), the total mortality incidence rate ranged between 0.002 and 0.0045, with similar patterns across males and females. Peak mortality was observed around 2010–2014, where MIR values for males approached 0.0045 and for females reached 0.004. After 2015, a steady downward trend was evident, with the total MIR stabilizing below 0.0015 after 2020.

The mortality incidence rate (MIR) increased from 0.057 to 0.165 per 100,000 population between 2008 and 2016, after which it stabilized and showed a modest decline. Log-linear regression demonstrated an average annual percent change (AAPC) of +7.0% per year (95% CI: 4.0–9.0; $p < 0.001$).

First-Line Imatinib Response in CML Patients

Table 6 summarizes treatment responses to first-line imatinib therapy among 249 patients with chronic myeloid leukemia. At the 3-month evaluation, 198 patients (79.5%) achieved an optimal response, defined as BCR-ABL1 $\leq 10\%$, while 12 patients (4.8%) showed a suboptimal response (BCR-ABL1 $> 10\%$). A total of 39 patients (15.7%) failed to achieve complete hematologic remission (CHR) at this time point.

At 6 months, 195 patients (78.3%) achieved BCR-ABL1 $\leq 1\%$, fulfilling criteria for optimal response, whereas 16 patients (6.4%) remained suboptimal (BCR-ABL1 $> 1\%$), and 38 patients (15.3%) had BCR-ABL1 levels above 10%, indicating treatment failure.

By 12 months, 200 patients (80.3%) achieved major molecular response (MMR, BCR-ABL1 $\leq 0.1\%$), while 9 patients (3.6%) continued to show suboptimal response. In contrast, 40 patients (16.1%) failed treatment with BCR-ABL1 $> 1\%$ at 12 months.

ABL Kinase Domain Mutation Analysis

Mutation analysis of the ABL kinase domain was performed in 115 patients with chronic myeloid leukaemia who showed suboptimal response or resistance to imatinib. Fourteen distinct mutations were detected, most commonly affecting the P-loop and ATP-binding regions. The T315I mutation was the predominant variant, followed by substitutions at codons F359, Y253, E255, and F317.

A detailed list of all mutations, including nucleotide and amino-acid changes, is provided in Table 8. Several uncommon variants were confirmed by pyrosequencing in an external reference laboratory (Ankara ATQ Biotechnology Laboratories).

BCR-ABL Kinase Domain Mutations in Imatinib-Resistant Patients

BCR-ABL1 kinase domain mutation analysis was performed in 115 patients with suspected resistance or suboptimal response. Among these, 19 patients (16.5%) were found to harbor mutations. When expressed relative to the entire cohort of 766 patients, the overall mutation prevalence was 2.5%.

Among mutation-positive cases, the most frequent mutation was T315I, detected in 7 patients (36.8%), followed by F359C and F359V in 3 patients each (15.8%), Y253H and F317L (TTG) in 2 patients each (10.5%), and E255K and F317L (TTA) in 1 patient each (5.3%).

Comparison of Responders vs. Imatinib-Resistant Patients

Table 7 compares clinical characteristics between patients who responded to imatinib therapy (n=651) and those who were resistant (n=115).

Among imatinib responders, the median age was 47.3 years (range 4–84), with a female predominance (58% female, 42% male). In contrast, the imatinib-resistant group had a median age of 45.3 years (range 16–80) and a male predominance (55.7% male, 44.3% female).

Phase distribution showed that most responders were in chronic phase (84.8%), with 15.2% in accelerated phase and none in blast crisis. For the imatinib-resistant group, 78.3% were in chronic phase, 16.5% in accelerated phase, and 5.2% in blast crisis, indicating more advanced disease among resistant patients.

Risk stratification by the Sokal score revealed that among responders, 51.9% were low risk, 40.4% intermediate risk, and 7.7% high risk. Conversely, imatinib-resistant patients had a higher proportion of intermediate (58.3%) and high-risk (11.3%) profiles, with only 30.4% classified as low risk.

Characteristics of BCR-ABL Mutations in Imatinib-Resistant Patients

Table 8 provides a detailed breakdown of mutation characteristics among imatinib-resistant CML patients. The overall mutation detection rate was higher in patients over the age of 50 years (20.45%) compared to those under 50 years (14.08%), with a p-value of 0.045.

Mutation frequency was also higher in males (24.5%) than in females (7.8%), a difference observed. Among mutation-positive patients, T315I remained the predominant variant, detected in seven males (35.7%) and two females (40%). When calculated relative to the entire group of imatinib-resistant patients, this corresponded to approximately 9% of males and 3% of females overall.

Distribution of Detected Mutations by Disease Phase and Risk Group

Figure 20 shows how BCR-ABL mutations among imatinib-resistant patients were distributed according to disease phase and Sokal risk categories.

By disease phase, mutations were identified in approximately 11% of patients in the chronic phase, 26% in the accelerated phase, and 67% in blast crisis.

By Sokal risk group, mutations were found in 15.4% of high-risk patients, 17.9% of intermediate-risk patients, and 14.3% of low-risk patients, without a difference.

Discussion

This study provides the first comprehensive epidemiological evaluation of chronic myeloid leukemia in Azerbaijan over a 16-year period. The variability in CML incidence across different countries likely reflects differences in genetic background, environmental exposures, population age structure, diagnostic infrastructure, and reporting standards [2]. For example, previous studies have reported CML incidence rates of around 1.5 per 100,000 in the United Kingdom [8], 1.2–1.5 per 100,000 in Italy [9], and about 1 per 100,000 in Japan [10]. Placing Azerbaijan's incidence within this international context suggests it is in the mid-range globally, consistent with patterns observed in other upper-middle-income countries with developing hematology services. Continued improvement of cancer registries and diagnostic capacity will be essential to fully understand national trends.

The upward trend in prevalence likely reflects both increasing annual diagnoses and improved survival with tyrosine kinase inhibitor (TKI) therapy, which has transformed CML into a chronic, manageable condition [11]. These findings indicate a growing long-term care burden in Azerbaijan.

Although the national population increased from about 8 million in 2008 to nearly 10 million in 2023, all prevalence estimates were standardized per 100,000 population; therefore, the rise cannot be explained by population growth alone. It more likely reflects improved survival and accumulation of long-term treated patients.

Compared internationally, CML prevalence in Azerbaijan remains lower than in some Western European regions, such as Lombardy, Italy [12], likely due to differences in registry maturity, diagnostic access, and population age structure.

Risk group analyzing results are consistent with international patterns in which most patients are diagnosed in the chronic phase and classified into intermediate-risk groups, though the relatively low proportion presenting in blast crisis highlights the benefits of improved early detection and treatment access in this population [13]. The use of the Sokal score rather than more contemporary prognostic systems such as the ELTS score represents a limitation of the present study. Complete data required for ELTS calculation were not consistently available in the earlier years of the national registry, and therefore Sokal scoring was used to ensure uniformity across the full 16-year cohort. Future analyses of more recent patient subsets, where complete variables are available, may allow incorporation of ELTS-based risk stratification to improve contemporary prognostic assessment and international comparability.

The hematologic parameters highlight typical disease evolution in CML, with increasing basophilia and a trend toward thrombocytopenia as patient progress from chronic phase to blast crisis. These patterns illustrate typical hematologic features of CML at various stages, with lower

hemoglobin and higher leukocyte burdens observed in advanced phases [14,15].

One of the most striking features was a slight female predominance, contrary to the modest male predominance described in many global studies [17]. A similar female predominance has been noted in some local studies on leukemia in Azerbaijan [6]. The observed female predominance in this national cohort may reflect complex biological and sociocultural factors. Hormonal influences on immune modulation and tyrosine-kinase inhibitor metabolism, as well as differences in health-seeking behavior and occupational exposure, could contribute to the observed pattern. Estrogens have been shown to modulate hematopoietic stem and progenitor cell function, potentially influencing disease incidence and progression [18]. However, these explanations remain speculative and should be regarded as hypothesis-generating. Future mechanistic and population-based studies are needed to clarify the biological and environmental underpinnings of gender-related variations in CML. This finding should be interpreted with caution. Differences in healthcare access, referral patterns, health-seeking behavior, or occupational exposure profiles between men and women may contribute to the observed distribution and cannot be excluded. Because the present study was observational and registry-based, it was not designed to evaluate biological mechanisms underlying sex differences. Therefore, speculative explanations related to hormonal influences on hematopoiesis cannot be supported by the current data. Future population-based studies incorporating detailed occupational, environmental, and healthcare utilization variables will be necessary to clarify the determinants of sex-specific patterns in CML. The consistent increase in both incidence and prevalence observed across the study period is likely related to improved molecular diagnostics, greater disease awareness, and stronger referral pathways [19]. However, a true increase in CML burden cannot be ruled out, potentially associated with environmental exposures, lifestyle factors, and aging of the population, and deserves further monitoring [20].

Geographic mapping revealed that most CML cases were concentrated in the Absheron economic region, particularly Baku and Sungayit. This is unsurprising given population density and proximity to advanced hematology centers. However, it is also notable that Absheron is an area with substantial industrial activity and documented air pollution [21]. Airborne pollutants, including benzene and particulate matter, have previously been associated with leukemogenesis [22, 23]. The observed geographic clustering is therefore consistent with the possibility of environmental or population-related influences on disease distribution. Nevertheless, this study was observational and descriptive in design and cannot establish a causal relationship between environmental exposures and CML occurrence. The higher case concentration in Absheron may also reflect population density, referral patterns, or healthcare accessibility. Future prospective studies incorporating quantitative environmental exposure assessment and individual-level risk factor data are needed to clarify potential associations.

Seasonal diagnostic patterns were also observed, with a higher proportion of diagnoses in summer and a lower rate in winter. This pattern should be interpreted with caution, as CML is a chronic myeloproliferative disorder with an insidious onset, making true biological seasonality unlikely. The observed distribution more plausibly reflects seasonal differences in healthcare utilization, infection-related laboratory testing, or healthcare-seeking behavior, which may lead to incidental detection of hematologic abnormalities [24]. Therefore, the

seasonal variation likely represents differences in diagnostic timing rather than underlying disease biology. This should be considered a limitation of the present study, and larger prospective investigations incorporating detailed clinical and healthcare utilization data will be needed to clarify these findings.

An association between ABO blood group distribution and CML was observed, with a higher frequency of blood group A among patients compared with controls. However, this finding should be interpreted cautiously. As this was an observational, registry-based analysis, the association cannot be considered causal or definitive. Potential confounding factors, population structure, or referral patterns may have influenced the observed distribution. Therefore, the blood group association should be regarded as preliminary and hypothesis-generating, requiring independent validation in larger population-based cohorts.

Age distribution showed that most patients were diagnosed between 40 and 69 years, peaking in the 50–59 decade, which is consistent with global CML epidemiology [25]. The repeated finding of female predominance across several age brackets deserves closer study, as hormonal, environmental, or occupational exposures could all contribute.

The mutation findings in this study are generally consistent with international experience, with T315I and F359C/V emerging as the most frequent variants. However, these results should be interpreted with caution, as mutation testing was performed in a subset of 115 patients, representing those with treatment resistance or suboptimal response. This limited sample may not fully capture the true population distribution of ABL kinase-domain variants in Azerbaijan. Expanded molecular screening and longitudinal surveillance will be required to define mutation epidemiology more comprehensively.

In addition, BCR-ABL1 transcript subtype information (e.g., p190, p210, e13a2, e14a2) was not consistently available in the registry and was therefore not included in the analysis. This limits detailed baseline prognostic assessment and evaluation of treatment selection strategies. Future registry updates should incorporate systematic transcript-type recording to enhance prognostic modeling.

Treatment response to first-line imatinib was encouraging, with nearly 80% of patients achieving major molecular response by one year, consistent with international data [26]. Nevertheless, about 15% of patients showed suboptimal or failed responses, underlining the necessity of early molecular monitoring and the availability of second- and third-generation TKIs [27]. Mutation testing revealed a range of BCR-ABL kinase domain mutations among resistant cases, with T315I being the most common, similar to international experience [28]. Expanding mutation testing facilities and second-line treatment options will be critical for optimal disease control.

Lastly, survival analyses confirmed the enormous benefit of TKIs, with 5-year survival above 80% compared to a pre-TKI median survival of less than four years. These results highlight the importance of sustained access to these therapies to continue improving outcomes for Azerbaijani patients with CML [27, 29].

Detailed subgroup survival analyses from this national cohort, including sex-based comparisons, have been reported separately to provide more focused prognostic evaluations.

In summary, this study lays the foundation for understanding CML epidemiology in Azerbaijan. Ongoing efforts should prioritize strengthening registry data, expanding molecular testing, addressing possible environmental risk factors, and ensuring equitable access to care across both urban and rural areas.

Limitations

This study has several limitations to consider. Its retrospective design may introduce information bias and limit the completeness of clinical records, particularly from the earlier years of the observation period. Molecular analyses for BCR-ABL kinase domain mutations were conducted only in a subset of patients with imatinib resistance, potentially underestimating the overall mutation prevalence. Although geographic clustering was observed in industrial regions, this study did not directly collect detailed environmental exposure data, limiting causal conclusions about pollution and CML. Seasonal diagnosis patterns could also be influenced by healthcare utilization rather than true seasonal disease variation.

However, as the National Hematology and Blood Transfusion Center is the only hematology reference center in Azerbaijan, this dataset is likely to represent nearly the entire population of CML patients in the country, which strengthens the generalizability of these findings. Future prospective, multicenter collaboration could further validate and enrich these results.

Conclusion

This comprehensive epidemiological study provides the first nationwide description of chronic myeloid leukemia in Azerbaijan, leveraging data from the country's sole hematology reference center. The findings reveal unique gender patterns, with a slight female predominance, as well as an increasing incidence and prevalence trend over the study period. Geographic clustering of cases in the Absheron region and seasonal variations in diagnosis highlight the importance of further investigations into possible environmental and healthcare utilization factors.

Treatment responses to first-line imatinib were comparable to international standards, although approximately 15% of patients showed suboptimal or failed responses, emphasizing the need for continuous molecular monitoring and access to second- and third-generation TKIs. The notable survival benefit associated with TKI therapy underscores the value of sustaining investments in modern hematology infrastructure.

Finally, this large single-center dataset, which effectively reflects the CML population nationwide, provides a robust basis for health planning and public policy. Establishing a comprehensive national leukemia registry could further validate these findings and support policy planning. Future work should focus on exploring environmental risk factors, expanding regional diagnostic capabilities, and strengthening support for long-term disease monitoring and equitable care across Azerbaijan. This study provides a robust foundation for health system planning and public health initiatives.

Author Contributions: Conceptualization, A.S. and C.A.; methodology, A.S., C.A. and A.H.; validation, A.S. and Z.A.; formal analysis, A.S. and A.H.; investigation, A.S., C.A. and Z.A.; resources, C.A.; data curation, A.S. and A.H.; writing – original draft preparation, A.S.; writing – review and editing, A.S., C.A., A.H. and Z.A.; visualization, A.S.; supervision, C.A.; project administration, A.S.; funding acquisition, Not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: The authors have no conflicts of interest.

Acknowledgments: The authors would like to thank the staff of the National Hematology and Blood Transfusion Center for their invaluable assistance in data collection and patient care. We also express our gratitude to the patients and their families, whose participation made this study possible.

Funding: None.

Data availability statement: All raw data underlying the findings of this study can be obtained from the corresponding author upon reasonable request.

Artificial Intelligence (AI) Disclosure Statement: AI-Unassisted Work.

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