Arab American University
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Department of Health Sciences
Master Program in Immunohematology

Unveiling Current Trends in Clinical Features and Assessing Induction Outcomes in Chronic Myeloid Leukemia (CML): A Multicenter Retrospective Analysis in Palestine

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Thesis Approval

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Palestine, 7/ 2025

Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is substantially my own work and has not been submitted for any other degree at the Arab American University or any other institution.

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Dedication

To the soul of my beloved father, though you are no longer with us, your prayers, sacrifices, and love continue to guide me. May Allah have mercy on you and grant you the highest place in Paradise.

To my dearest mother, The source of endless love and support. Your presence is a blessing, and your unwavering belief in me gave me the strength to keep going. I owe this achievement to you after Allah.

To my dear brother, always by my side with quiet strength and support.

To my precious sister, my companion in life, my safe haven, and to her three daughters—The little lights of our home, whose innocent smiles brightened my days.

To my mentors and teachers, whose guidance and wisdom have shaped both my journey and this work.

To the patients and individuals affected by chronic myeloid leukemia—your courage inspires the pursuit of knowledge and better outcomes in the field.

I dedicate this work to all of you, with deep love and gratitude that words can never fully express.

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Abstract

Background: Chronic Myeloid Leukemia (CML) is a hematologic malignancy characterized by the BCR-ABL1 fusion gene, resulting from the Philadelphia chromosome translocation. While treatment with tyrosine kinase inhibitors (TKIs) has significantly improved outcomes globally, limited data are available regarding the clinical characteristics and treatment responses of CML patients in Palestine.

Objective: This study aimed to evaluate the clinical features, induction treatment outcomes, and prognostic factors affecting response among Palestinian patients diagnosed with CML.

Methods: A retrospective multicenter study was conducted on 85 CML patients treated between 2018 and 2023 at An-Najah National University Hospital and Watani Hospital in Nablus. Clinical, laboratory, and treatment-related data were extracted from electronic medical records. Treatment responses were assessed based on European LeukemiaNet (ELN) 2020 criteria. Statistical analysis was performed using SPSS version 21.

Results: The mean age of patients was 47.6 years, with a male-to-female ratio of 1.24:1. The most frequent presenting symptoms were fatigue and bone pain (51.8%), weight loss (41.2%), and splenomegaly (38.8%). The majority of patients (95.3%) were diagnosed during the chronic phase. A complete hematologic response (CHR) was achieved in 82.4% of cases, while major molecular response (MMR) was observed in 58.8%. Clinical features such as fever, weight loss, and splenomegaly were significantly associated with poorer treatment response ($p < 0.05$), whereas age, gender, and baseline hematological parameters showed no significant impact.

Conclusion: CML in Palestine is more commonly diagnosed in middle-aged males and typically during the chronic phase. Most patients demonstrate favorable hematologic and molecular responses to first-line TKI therapy. However, certain clinical signs at diagnosis—namely fever, weight loss, and splenomegaly—are associated with suboptimal response, highlighting the importance of early detection and individualized treatment strategies.

Keywords: Chronic Myeloid Leukemia, Palestine, Tyrosine Kinase Inhibitors, Hematologic Response, Molecular Response.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Definitions of Abbreviations

Abbreviations	Title
MPDs	myeloproliferative disorders
MPNs	myeloproliferative neoplasms
ET	essential thrombocythemia
PV	polycythemia vera
PMF	primary myelofibrosis
CML	chronic myelogenous leukemia
WHO	World Health Organization's
JAK2	Janus kinase 2
V617F	Valine-to-Phenylalanine substitution at codon 617 (JAK2 V617F mutation)
MPL	Myeloproliferative Leukemia Virus Oncogene
CALR	Calreticulin
BM	Bone marrow
LDH	Lactate Dehydrogenase
BCR	breakpoint cluster region
ABL1	Abelson murine leukemia
Ph	Philadelphia chromosome
t(9;22)	translocation between chromosomes 9 and 22
RAS	Rat Sarcoma Viral Oncogene Homolog
RAF	Rapidly Accelerated Fibrosarcoma Kinase
JUN	Jun Proto-Oncogene
MYC	Cellular myelocytomatosis oncogene
STAT	Signal Transducer and Activator of Transcription
M-bcr	major breakpoint cluster region
DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
CML-CP	Chronic Myeloid Leukemia – Chronic Phase
CML-AP	Chronic Myeloid Leukemia – Accelerated Phase
CML-BP	Chronic Myeloid Leukemia – Blast Phase
ELN	European Leukemia-Net
(CCA/Ph+)	Clonal chromosome abnormalities in Ph+ cells

FISH	fluorescence in situ hybridization
CBC	Compleat blood count
µL	Microliter
WBCs	white blood cells
RT-PCR	Reverse Transcription Polymerase Chain Reaction
QPCR	Quantitative Polymerase Chain Reaction
mRNA	Messenger Ribonucleic Acid
RQ-PCR	Real-Time Quantitative Polymerase Chain Reaction
TKI	Tyrosine Kinasw Inhibitor
ASCT	Allogeneic stem cell transplantation
(CCR)	complete cytogenetic response
T315I mutation	Threonine-to-Isoleucine substitution at position 315 of ABL1
ATP	adenosine triphosphate binding
CHR	complete hematologic response
EMR	early molecular responses
DMR	Deep molecular response
MCyR	Major cytogenetic response
PCyR	Partial cytogenetic response
BMT	bone marrow transplantation
IFN	interferon
TLC	Total Leukocyte Count
NNUH	Najah national university hospital
HU	Hydroxyurea
SPSS	social sciences software
Sd	Standard Deviation
IRB	Institutional Review Boards
HB	hemoglobin
PLT	platelet count
IQR	Interquartile Range
P value	Probability value
AML	acute myeloid leukemia
ALL	acute lymphoblastic leukemia

Chapter One: Introduction

1.1 Introduction to leukemia

Leukemia is a type of cancer that originates in the bone marrow—the soft tissue inside bones responsible for blood cell production. It is characterized by the abnormal proliferation of blood cells, most commonly white blood cells (leukocytes). This uncontrolled growth can crowd out normal blood cells, leading to complications such as anemia, increased susceptibility to infections, and bleeding disorders. Leukemia is classified based on the type of affected blood cell—myeloid or lymphoid—and the rate of disease progression—acute or chronic (1). Growth factors, transcription factors, and the bone marrow environment all influence the hematopoietic process. A diverse range of diseases referred to as myeloproliferative neoplasms have been brought on by the abnormal expansion of one or more types of terminal myeloid cell types in the peripheral circulation (2).

1.1.1 Introduction to myeloproliferative disorders

Myeloproliferative disorders (MPDs), more recently termed myeloproliferative neoplasms (MPNs), are a group of diseases characterized by the excessive production of blood cells by the bone marrow. These conditions can impact platelets, white blood cells, and red blood cells, which can result in a number of health issues. Comprehending MPNs is essential for accurately identifying and treating these ailments (3).

In order to characterize erythroleukemia, essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML), William Dameshek established the term "myeloproliferative disorders (MPDs)" in 1951 (4).

According to the current World Health Organization (WHO) classification, myeloproliferative neoplasms (MPNs) are divided into four primary subgroups: (i) Chronic Myeloid Leukemia; (ii) classical Philadelphia-negative MPNs (Polycythemia Vera; Essential Thrombocythemia; Primary Myelofibrosis); (iii) non-classical Philadelphia-negative MPNs (Chronic Neutrophilic Leukemia; Chronic Eosinophilic Leukemia); and (iv) MPNs, unclassifiable (MPN-U)(5).

1.1.2 The pathophysiological understanding:

MPNs are caused by mutations in hematopoietic stem cells. Patients with the JAK2 V617F mutation are much more likely to have PV, ET, or PMF (primary myelofibrosis) than healthy

individuals. The JAK2 V617F mutation is the most frequently observed mutation associated with these conditions. These disorders are also linked to further mutations, including those in the MPL and CALR genes. Due to these genetic alterations, signaling pathways that control the creation of blood cells are abnormally activated, which results in the excessive proliferation of one or more blood cell types (6, 7).

1.1.3 Clinical manifestation of myeloproliferative disorders:

Clinically, myeloproliferative disorders (MPDs) may present with a wide spectrum of manifestations, ranging from asymptomatic cases to complications such as bleeding, thrombosis, and progression to acute leukemia (8).

Depending on the particular disease and the organs impacted by aberrant blood cell production, many personality disorders have different clinical presentations. Common symptoms of various MPN subtypes include fatigue, itching, nocturnal sweats, bone pain, fever, and weight loss. However, these might vary in frequency and severity (9).

1.1.4 Diagnostic of myeloproliferative disorders:

The diagnosis of myeloproliferative neoplasms (MPNs) typically involves a combination of clinical evaluation, blood tests, bone marrow biopsy, and genetic profiling. Key diagnostic criteria include elevated blood cell counts, the presence of specific genetic mutations (such as JAK2, CALR, or MPL), and bone marrow histopathology showing hypercellularity or fibrosis. Additionally, it is essential to rule out other potential causes of elevated blood cell counts (10).

According to WHO guidelines, the diagnosis of myeloproliferative neoplasms (MPNs) is based on a combination of clinical, morphological, and molecular criteria (see Table 1.1). While a bone marrow examination is not always mandatory, it remains a valuable diagnostic tool—particularly in cases of polycythemia vera (PV)—despite ongoing debate over the subjectivity and reproducibility of histopathological assessment (11).

Table 1.1: The World Health Organization's diagnostic criteria of myeloproliferative neoplasms (MPNs) incorporate a combination of clinical features, bone marrow morphology, and the genetic markers (Szybinski & Meyer, 2021).

	PV	ET	Myelofibrosis	
Major criteria			Prefibrotic/Early	Overt/Fibrotic
Blood (m/f)	Hemoglobin >165 g/L/ 160 g/L or Hematocrit >49%/48% or Red cell mass >25% above normal	Platelet count >450 109/L	No specific requirement (cytoses or cytopenias possible)	No specific requirement (cytoses or cytopenias possible)
Marrow	Age-adjusted hypercellularity Trilineage growth (panmyelosis) including erythroid, granulocytic and megakaryocytic proliferation Pleomorphic, mature megakaryocytes	Proliferation of megakaryocytic lineage: increased, enlarged, megakaryocytes, hyperlobulated nuclei No increase in granulo/ erythropoiesis Rarely increase in reticulin fibers (grade 1)	Megakaryocytic proliferation/atypia a No reticulin fibrosis greater than grade 1 Increased age-adjusted cellularity Granulocytic proliferation, often decreased erythropoiesis	Megakaryocytic proliferation and atypia Reticulin and/or collagen fibrosis of grade 2 or 3
Exclusion	No specific exclusions	Not PV, PMF, other myeloid neoplasm	Not CML, PV, ET, MDS, other myeloid neoplasms	
Geneticsa	JAK2 V617F or exon 12 mutation	JAK2, CALR, or MPL mutation	JAK2, CALR, MPL mutation or Another clonal markerb or absence of reactive BM fibrosis	
Minor criteria				

Additional	Subnormal serum erythropoietin	Presence of a clonal marker or Absence of evidence of reactive cause	Anemia not owing to comorbidity Leukocytosis 11 109/L Palpable splenomegaly LDH above reference	Anemia not owing to comorbidity Leukocytosis 11 109/L Palpable splenomegaly LDH above reference Leukoerythroblastosis
Required	All 3	All 4 major	All 3 major +>1	All 3 major +>1 minor

	major criteria or First 2 major 1 minor criterion	criteria or First 3 major 1 minor criterion	minor criterion	criterion

1.1.5 The handling and therapy of myeloproliferative disorders

Treatment plans for patients with myeloproliferative neoplasms (MPNs) are individualized based on the patient's clinical needs and the specific characteristics of their disease. Typical methods include:

- Phlebotomy: Individuals with PV may have a decrease in the mass of red blood cells.
- Drugs: Medication such as ruxolitinib, hydroxyurea, and antiplatelet therapy: PV and ET patients are commonly given low-dose aspirin.
- Bone marrow transplants: Patients who are younger and have more serious conditions or who do not react to previous therapies may be candidates for this procedure (12).

The goals of management are to reduce bleeding and thrombotic hazards, relieve symptoms, and stop the condition from becoming worse. Phlebotomy, cytoreductive therapy, and targeted molecular therapies are examples of therapeutic methods. More research is being conducted to investigate new therapeutic approaches (13, 14).

1.2 Study problem

To the best of our knowledge, no studies have been conducted in Palestine to evaluate treatment outcomes and prognostic factors in patients with chronic myeloid leukemia (CML). This study represents the first effort to assess therapeutic responses and identify prognostic markers that influence overall survival and the clinical course of CML patients over a defined period.

1.3 Significance of the Study

This study will be the first in Palestine to identify specific prognostic factors that significantly influence the clinical course and survival outcomes of patients with chronic myeloid leukemia (CML). By analyzing various therapeutic approaches, the research aims to determine which treatments are associated with the highest response rates, longest progression-free survival, and most favorable overall survival. Furthermore, long-term data

analysis may reveal trends in CML management, including changes in treatment strategies over time and their corresponding impact on patient outcomes.

1.4 Aim of the Study

The aims of this study are to evaluate and document the clinical characteristics and prognostic factors of chronic myeloid leukemia (CML) patients in Palestine. In addition, the study aims to generate valuable insights that can enhance CML management, improve patient outcomes, and guide future clinical practices and healthcare strategies in the region.

1.5 Specific objectives of the study

1- Identify current clinical features: We intend to recognize the usual clinical manifestations of chronic myeloid leukemia (CML) in the Palestinian population, taking into account the first laboratory findings, symptoms upon diagnosis, and the distribution of disease stages.

2- Analyze induction outcomes: We aim to assess if the first (induction) treatment plans, particularly those including tyrosine kinase inhibitors (TKIs), are helpful in achieving the desired hematologic, cytogenetic, and molecular responses for Palestinian patients with CML.

3- To assess patient- and disease-related variables that may influence induction outcomes, and to compare the observed patterns with those reported in previous literature.

4- Compare with global statistics: We aspire to place the Palestinian experience in the perspective of the global CML management environment. Our goal is additionally to identify any particular regional trends or issues, and to compare the findings with global statistics.

1.6 Study hypothesis

We hypothesized there are notable differences between the clinical features and treatment outcomes of CML patients in Palestine and those reported in international studies, reflecting regional variations in disease presentation and healthcare delivery.

Additionally, we hypothesized there exists a correlation between the clinical features such as age, gender, signs and symptoms and hematological parameters at diagnosis and the treatment outcomes of CML patients in Palestine.

Chapter Two: Literature Review

2.1. Introduction to Chronic Myeloid Leukemia

Undoubtedly, uncontrolled myeloid cell production in the bone marrow characterizes chronic myeloid leukemia (CML), which is a type of blood cancer. It is often associated with the Philadelphia chromosome and is translocated as [t(9;22)(q34;q11)]. CML is considered one of the myeloproliferative neoplasms. This form of translocation leads to the formation of BCR-ABL1 fusion gene (15, 16).

Enhanced peripheral blood myleoid, erythroid, and platelet counts, as well as enhanced bone marrow myeloid proliferative activity, are indicators of CML, a clonal neoplastic disease of hematopoietic progenitor cells. Moreover, most patients exhibit thrombocytosis supporting the transformation of pluripotent hematopoietic stem cells (17).

1.2 Epidemiology and Etiology of Chronic Myeloid Leukemia

15% of adult instances of leukemia are CML, with an estimated yearly incidence rate of one to two cases per 100,000 persons. When they present, patients range in age from 45 to 55 on average. Twelve to thirty percent of patients are sixty years of age or older; however the condition affects people of all ages, including young children (18).

Based on the records of An-Najah National University Hospital and Watani Hospital in Nablus, approximately 150–160 patients were diagnosed and have received treatment for CML between 2018 and 2023. Given that these two hospitals are among the main referral centers in the northern West Bank, this number likely represents a significant proportion of CML cases in the region. When extrapolated to the national population of approximately 5.4 million (as of 2023), the estimated annual incidence rate of CML in Palestine would be around 0.9 to 1 case per 100,000 population, which is consistent with global prevalence rates of CML.

The etiological evidence is still lacking. Exposure to benzene and some other chemicals, as well as acute high-dose ionizing radiation, can cause CML (19).
According to a study of published data, males who work in agricultural or farming environments and are exposed to pesticides are more likely than the general population to acquire many forms of leukemia, including CML (20).

2.3 Pathogenesis of Chronic Myeloid Leukemia

The Philadelphia chromosome (Ph) associated with the t(9; 22) translocation is mainly located in the causative factors of chronic myeloid leukemia (CML), CML is associated with the bands q34 and q11 of chromosomes 9 and 22 which are referred to as t(9;22)(q34;q11) in clinical cytogenetic. Figure (1.1) illustrates this translocation produces the BCR-ABL1 fusion gene which is the defining molecular feature of CML (21).

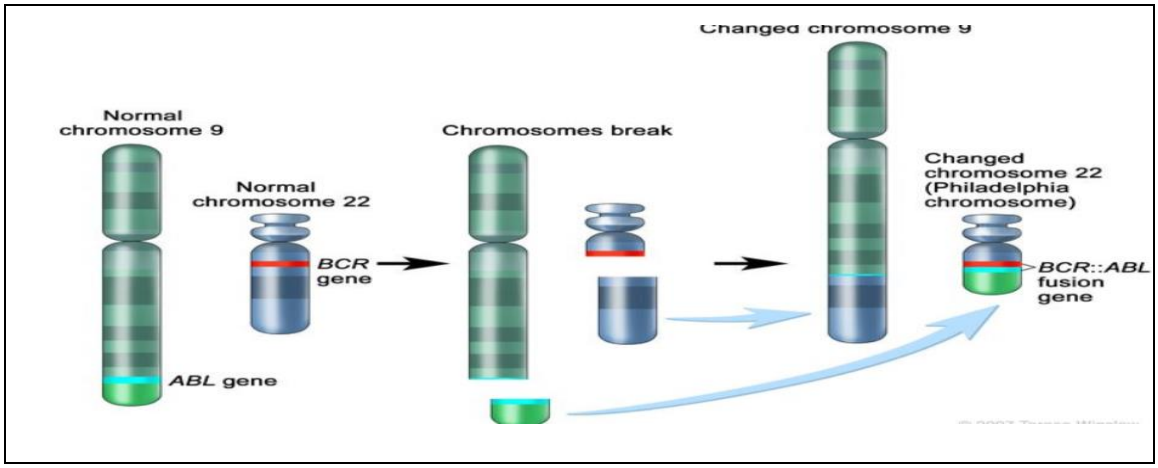

Figure 2.1: Chronic myeloid leukemia pathogenesis (Board, 2002).

The fusion of the Abelson murine leukemia (ABL1) gene found on chromosome 9 and the breakpoint cluster region (BCR) gene situated on chromosome 22 results in the formation of BCR-ABL1 oncoprotein and associated chronic myeloid leukemia (CML). This oncoprotein exerts control over cellular proliferation together with cell cycle progression by downstream pathways that involve RAS, RAF, JUN kinase, alongside MYC and STAT due to its constant tyrosine kinase activity. By creating a cytokine-independent cell cycle and generating defective apoptotic signals following the withdrawal of cytokines, these pathways promote leukemogenesis (22).

BCR-ABL1 activation triggers dysregulated signaling pathways, affecting cellular adhesion, preventing apoptosis, and encouraging cell proliferation. This leads to myeloid progenitor cell growth in bone marrow, thus causing CML. This myeloproliferative phenotype with mature and immature myeloid cells in peripheral circulation can result in secondary genetic abnormalities and genomic instability, contributing to the progression of the illness, resistance to treatment, and the development of more severe types of CML, such as blast crises (23, 24).

The ABL1 gene encodes for a tyrosine kinase which has a role in maintaining and regulating cellular processes such as DNA repair, integrin signaling, proliferation of cells, and cell cycle control. Similarly, the BCR/ABL1 fusion gene in CML creates a chimeric protein that remains perpetually active and causes changes in the downstream signaling pathways (25).

Within CML, BCR and ABL translocate to chromosomes 22 and 9 respectively. Due to the presence of several breakpoints in a given region, multiple fusion transcripts may form. For the BCR gene, the most common site of breakpoint is within the M-bcr (major breakpoint cluster region) between exons e12 and e16; previously known as b1-b5. One of the common locations of breakpoints in the ABL gene is in exon a2 (26). This creates fusion transcripts e13a2(b2a2) and e14a2 which code for the 210-kDa protein P210BCR-ABL (b3a2).

The other less common translocations are e1a2, e19a2, e2a2, e1a3, e6a2, e13a3(b2a3), and e14a3(b3a3). Due to alternative splicing, these code for proteins of varying molecular weights. For example, e1a2 codes for a 190-kDa protein, P190BCR-ABL, and e19a transcripts are normally expressed in CML. Indeed, the coexistence with e1a2 transcripts is possible. It is rare, nevertheless, for CML to express solely e1a2 transcripts—a condition known as P190BCR-ABL CML (figure1.2) (27).

BCR-ABL1 fusion can occur in AML and ALL, but its significance in these conditions is still being studied. Different types of BCR-ABL1 fusions and breakpoints occur in CML. For instance, the p190BCR-ABL1 variant e1a2 (one of the lesser-known variants) may constitute 1-2 percent of cases and encodes a 190 kDa hybrid protein. There is also p230 BCR-ABL1 which is another one of these variants (28).

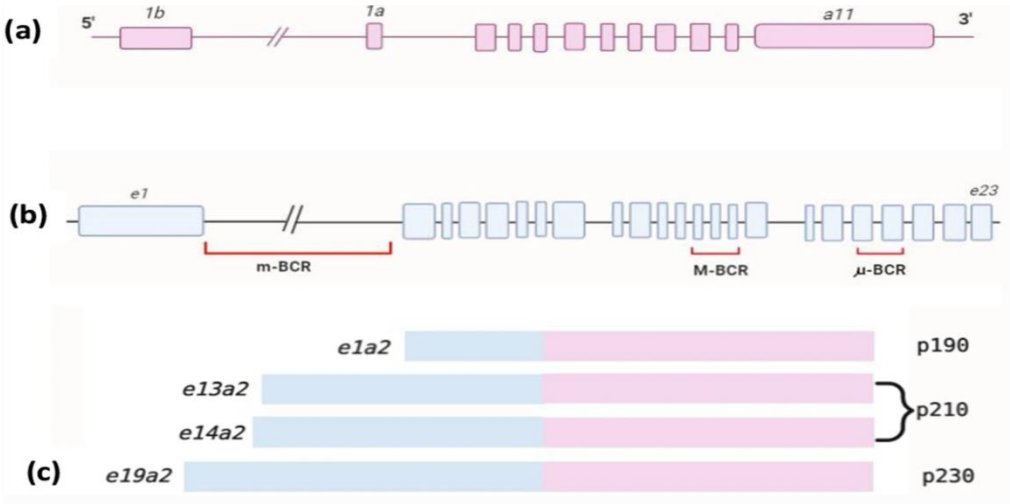

Figure 2.2: The ABL1 gene (a) and the BCR gene (b) breaking sites result in the recombinant RNA transcripts e1a2, e13a2, e14a2, and e19a2 (c). (Benchikh et al., 2022)

2.4 Staging and Classification of CML by Phases:

Three stages of CML are distinguished by distinct morphological and clinical characteristics:

1- Chronological Phase (CML-CP): This is the first stage, which usually lasts for a few years. Myeloid cells in CML-CP are differentiated, only ten percent of blast cells can be seen in the bone marrow. Patients at this stage tend to respond well to treatment and have a gradual clinical course (29).

Most patients receive their diagnosis during this phase, which can last several years and is typically indolent. Patients may show minimal symptoms such as splenomegaly, weariness, and weight loss, or they may show no symptoms at all. Many patients get long-term remission with the right care, especially when using tyrosine kinase inhibitors (TKIs) (30).

2- Accelerated Phase (CML-AP): CML-CP can develop into CML-AP if treatment is not received. During this stage, the bone marrow contains 10–19% more blast cells due to the cells' rapid multiplication. The response to treatment deteriorates and there may be observable chromosomal abnormalities other than the Philadelphia chromosome (31).

As the illness progresses, additional symptoms and abnormal test results are seen. Weight loss, splenomegaly, and increased weariness are possible symptoms. Controlling the disease gets harder, and there is a greater chance that it may advance to the explosion phase. It could be necessary to escalate treatment (32).

3-Blastic Phase (CML-BP): Acute leukemia-like CML-BP is a possible progression of CML-AP. Chronic Myeloid Leukemia Blast Phase is a situation whereby the bone marrow blasts surpass 20%, or up to 30% depending on some factors, and can be either myeloid or lymphoid in characteristics. In this stage, the patient responds to therapy quite poorly (33).

This phase symbolizes the transition to a condition resembling acute leukemia. Severe symptoms include organ invasion by leukemic cells, bleeding, and infections. The median survival is drastically lowered, and the prognosis is often bad. It could be necessary to undergo allogeneic stem cell transplantation and intensive chemotherapy (34).

Quantitative morphological criteria have been used to create the staging and categorization of the various phases of CML; the WHO and ELN have proven useful in this regard. Different categorization methods employ different criteria for blast cell percentages, and determining

the illness phase is the first step in developing a treatment strategy as shown in table 2. For example, the ELN sets the criteria at 30%, although the WHO classifies CML-BP as having ≥20% blast cells (35, 36).

Table 2.1: Definitions of CML phases depend on recommendations of European Leukemia-Net (ELN) and World Health Organization (WHO) (Baccarani et al., 2013)

Accelerated phase	**Definition**
ELN criteria	Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% Basophils in blood ≥20% Persistent thrombocytopenia (<100 × 109/L) unrelated to therapy Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment
WHO criteria	Blasts in blood or marrow 10-19% Basophils in blood ≥20% Persistent thrombocytopenia (<100 × 109/L) unrelated to therapy CCA/Ph+ on treatment Thrombocytosis (>1000 × 109/L) unresponsive to therapy Increasing spleen size and increasing white blood cell count unresponsive to therapy
Blast phase	
ELN criteria	Blasts in blood or marrow ≥30% Extramedullary blast proliferation, apart from spleen
The diagnosis of CML WHO criteria	Blasts in blood or marrow ≥20% Extramedullary blast proliferation, apart from spleen Large foci or clusters of blasts in the bone marrow biopsy

2.5 Signs and symptoms of chronic myelogenous leukemia

Chronic myeloid leukemia (CML) destroys healthy red, white and platelet forming cells in the bone marrow by crowding bone marrow with CML cells. At first, the patients may show no symptoms of CML and may only find out they have the illness after a routine medical check-up or an ordinary blood test. Weakness, exhaustion, dyspnea, fever, bone pain, weight

loss, and nocturnal sweats are among the symptoms. Because of an enlarged spleen, CML frequently causes discomfort and unexplained weight loss (37).

Hemorrhages in the retina, ulcers in the upper gastrointestinal tract, gout in the joints, bleeding, and thrombosis are a few of the less serious side effects of CP. This often exceeds 100 times ten to the power of nine per liter; yet, leukaemic cells have the rare ability to produce leukostasis. Bell's palsy or ptosis may result from leukemic infiltration of the facial nerve. Leukostasis can also cause priapism, dyspnea, somnolence, and neurological impairments that manifest as aphasia, confusion, and lethargy in the case of cerebral leukostasis (38).

Among the symptoms of CML-CP are malaise, exhaustion, splenomegaly, and weight loss. Although CML-CP is the diagnosis for the majority of patients, some may have advanced stages. While most patients develop via CML-AP, others go from CML-CP to CML-BP without exhibiting CML-AP symptoms. Patients with CML-BP have symptoms similar to acute leukemia as their condition progresses, such as fever, infections, bleeding, and constitutional problems (22).

2.6 Diagnosis of chronic myeloid leukemia:

Most patients with chronic myeloid leukemia (CML) do not show any symptoms at the time of diagnosis. One of the earliest indicators that can be seen during a routine checkup or blood investigation for other diseases is the increase in the level of white blood cells.

The diagnosis of Chronic Myeloid Leukemia (CML) is straightforward in the presence of persistent unexplained leukocytosis (or less commonly, thrombocytosis). The Ph chromosomal
abnormality t(9;22)(q34;q11) translocation is identified by standard cytogenetic analyses. Molecular techniques and FISH are applied to identify the associated BCR-ABL1 molecular aberrations (39).

A number of laboratory procedures are needed to diagnose CML, with the goal of determining the genetic abnormalities unique to the illness. These techniques concentrate on identifying the distinctive genetic markers.

Screening with complete blood count (CBC):

The initial screening approach for chronic myeloid leukemia (CML) is routine blood work such as a complete blood count (CBC) with differential and other specific analyses. Potential CML may be indicated by elevated leukocyte counts, which are frequently accompanied with absolute basophilia and monocytosis (40).

It was found by Hochlaus and colleagues that 90% of patients have monocytosis, which is quite uncommon in CBC, blast <2%, leftshift and typical myelocyte bulge, leukocytosis, and absolute basophilia. Megakaryocytes come in a variety of sizes and forms; if their morphology is proven, it may be verified by looking for BCR-ABL1 transcripts, the Philadelphia chromosome, or 22q in peripheral blood or bone marrow cells (41).

Peripheral smear test:

Using Peripheral blood films, an essential diagnostic tool, shows certain morphological and compositional changes in blood cells that correlate with these stages. The typical results on the peripheral blood film at every phase of chronic myeloid leukemia are summarized below (42).

The initial stable phase of the condition, known as the chronic phase, is when most cases of diagnosis occur. Since the disease's symptoms might be extremely mild or nonexistent at this point, diagnosing the condition is typically difficult. The following are a few of the symptoms: anemia, granulocytosis, basophilia, eosinophilia, and leukocytosis. Leukocytosis is defined by a sharp increase in the white blood cell (WBC) count, which often exceeds 100,000 cells/μL. Granulocytosis is characterized by a high concentration of both immature and mature granulocytes, although anemia can vary from mild to severe. The platelet count might be decreased, increased, or within the normal range (Figure 1. 3) (43, 44).

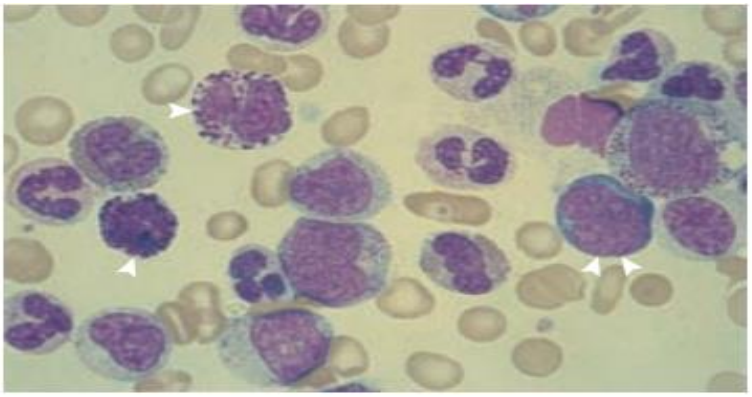

Figure 2.3: Patient with chronic myeloid leukemia has a lot of mature granulocytes in their peripheral blood film, including two basophils (arrow); the blast cell can be observed (double arrow) (Goldman, 2005).

During the accelerated phase of the illness, symptoms develop and blood count management becomes increasingly challenging. A higher proportion of immature cells, such as myeloblasts, are often present (10–19% of WBCs), which indicates a shift toward the blast phase. More than 20% of differential counts are basophilia. Thrombocytopenia or thrombocytosis can cause a platelet count to drop or rise, which is indicative of a destabilized hematopoiesis. There is a more noticeable anemia along with potential poikilocytosis and anisocytosis (Figure 1.4) (45, 46).

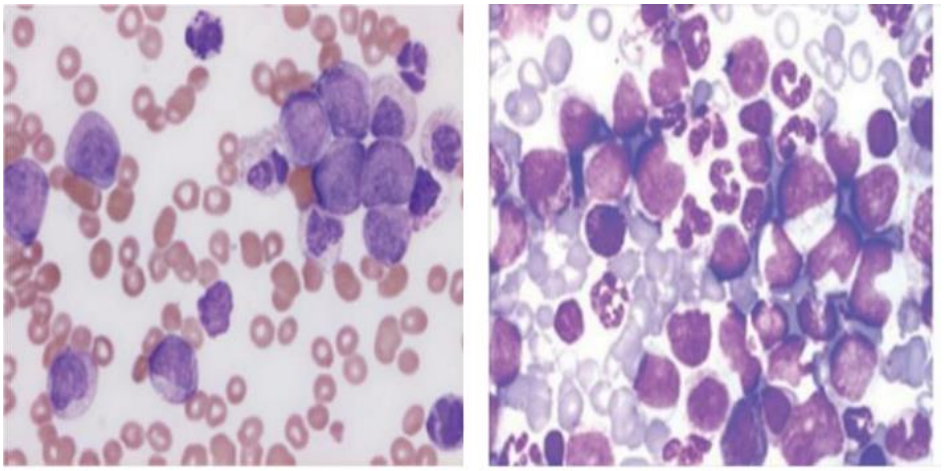

Figure 2.4: A. CML (accelerated phase) peripheral blood smear: displaying thrombocytopenia, myeloblasts, and basophils. B. Accelerated phase of CML: megakaryocytes and myeloid cells with enormous blasts were seen in the bone marrow aspirate smear. (Al-Bayati et al

The most aggressive phase of CML is the blast phase. In this stage, immature blast cells proliferate rapidly and comprise more than 20% of the white blood cells either in the bloodstream or the bone marrow. They resemble the large cells of acute leukemia and have a high nuclear-cytoplasmic ratio. Red blood cell shape varies significantly in cases of severe anemia. The hallmarks of thrombocytopenia are a low platelet count and noticeable morphological abnormalities. Blasts obscure other immature cells, which include myelocytes, metamyelocytes, and basophils. These cells can still be seen (Figure 1.5) (45).

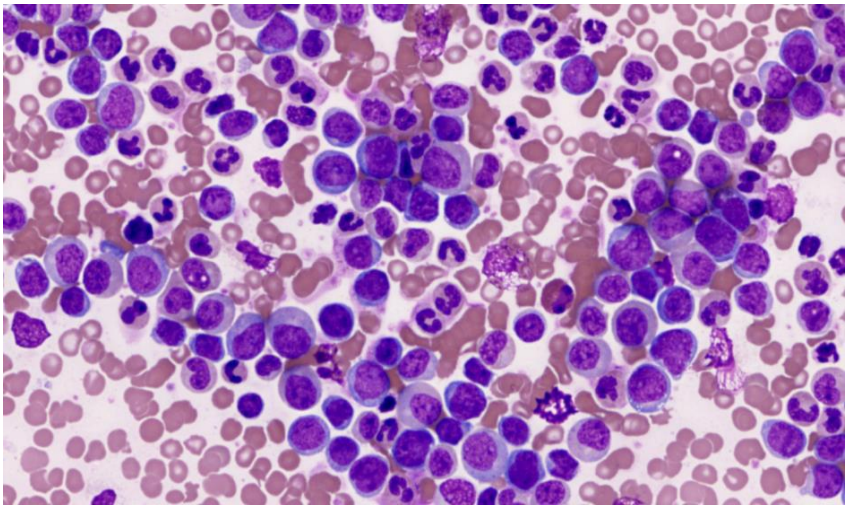

Figure 2.5: A patient suffering from the blast phase of chronic myeloid leukemia (CML-BP) had undergone a blood film procedure. the background abundance of mature neutrophils and myelocytes, including eosinophilic myelocytes, and the numerous myeloblasts (compared

Examining the bone marrow

Assessing the bone marrow through aspiration and biopsy is crucial towards evaluating the progression of the disease and confirming the diagnosis of chronic myeloid leukemia. Significant results are noted with either the Ph chromosome or the BCR-ABL1 transcripts detected in the marrow cells, in addition to the granulocytic overpopulation coupled with hypercellularity (29).

One characteristic of the hypercellular bone marrow is the growth of the myeloid cell line (such as neutrophils, eosinophils, and basophils) and its progenitor cells. Megakaryocytes are noticeable and could even grow in number (see the figure below (Figure 1.6)). With the reticulin stain, mild fibrosis is frequently observed. (47)

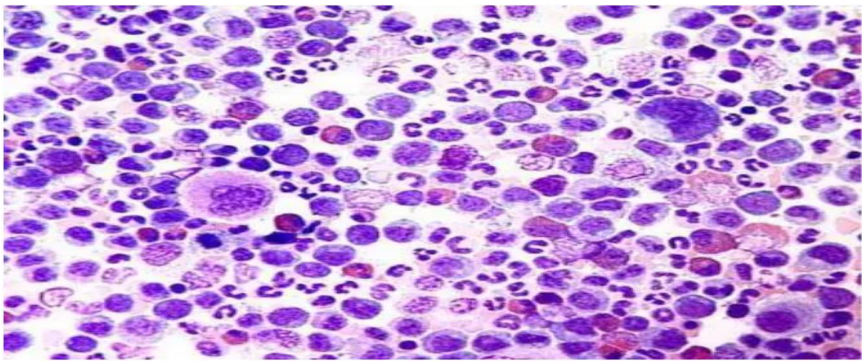

Figure 2.6: Chronic myelogenous leukemia. A 400X magnification of a bone marrow film clearly shows the prevalence of granulopoiesis. Megakaryocytes and eosinophils are more prevalent.

Confirmation of Diagnosis: The definitive criteria for the diagnosis of CML includes the Ph chromosomal deviations t(9;22)(q34;q11) and BCR-ABL1 fusion gene. For such verification, cytogenetic analysis, fluorescence in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (RT-PCR) are the standard methods used.(48).

A verified diagnosis of CML can be determined by looking for the Philadelphia chromosome, 22q, or BCR-ABL1 transcripts in peripheral blood or bone marrow cells. In 5% of instances, the BCR-ABL1 fusion is verified by fluorescence in situ hybridization (FISH) or RT-PCR; however, in 18% of cases, the Ph chromosome is lacking.(45)

Fluorescence in situ hybridization (FISH)

Fluorescence in situ hybridization (FISH) uses fluorescently tagged probes to hybridize with either the interphase nuclei or the metaphase chromosomes; the hybridized probe is then identified using fluorochromes. This approach is fairly sensitive and enables speedy identification of mistake repeats in both structure and number (49). In this method, a single probe that targets the ABL1 gene as well as probes for a portion of the BCR gene may be utilized to identify the rearrangements inside the M and m BCR sections. Using two probes, 5′ and 3′ ABL1 and two probes, 5′ and 3′ BCR, increases the specificity of FISH (dual-colourFISH). Nonetheless, if the third ASS gene probe is used in close proximity to the ABL1 gene, a triple signal may result.

When certain FISH probes are used, strong signals are produced and several targets can be seen at once; these signals are then seen under a fluorescent microscope (figure 1.7) (50).

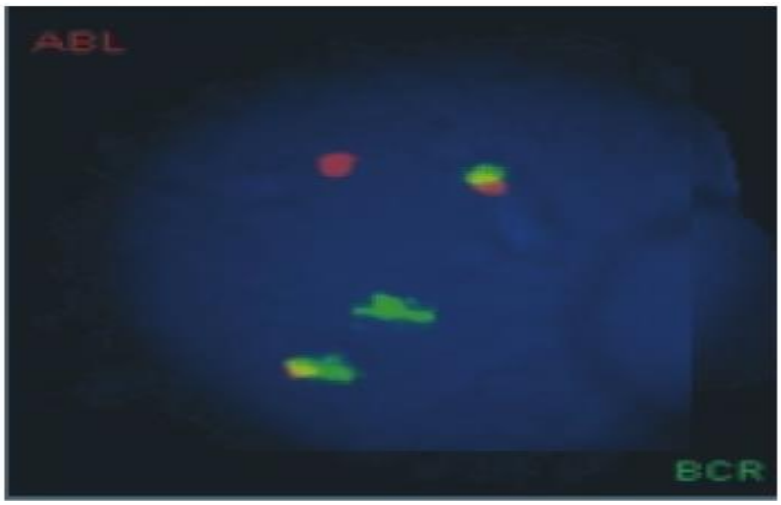

Figure 2.7: Dual color FISH of chronic phase CML reveals two fusion signals (red, green, and yellow fused signals), one normal BCR signal on chromosome 22 (single green signal), and one normal ABL1 signal on chromosome 9 (single red signal). two from chromosomes 9

Colocalization of large genomic probes that are fully selective for the BCR and ABL genes is required for the FISH investigation. This brief research reveals that when samples of blood and bone marrow are analyzed simultaneously, FISH analysis yields excellent concordancy. This is due to the fact that false positive rates in FISH examinations utilizing various probes might vary from 1 to 10% (51).

PCR (Polymerase Chain Reaction) at the mRNA Level

RT-PCR is used to find very low levels of residual illness in CML patients. It can be either quantitative PCR (ABL) or qualitative PCR (QPCR), and it is helpful in establishing CML. However, low-quality RNA, unsuccessful reactions, or contamination might result in false-positive and false-negative readings. The findings that are achieved can also be influenced by prior lab and sample handling experience. It also demonstrates that concurrent investigation of QPCR produces good concordance (52).

RQ-PCR is the most used molecular technique for measuring BCR-ABL mRNA in CML patients to evaluate their response to therapy. It is still true that over 95% of CML patients exhibit the BCR-ABL fusion gene; as a result, RQ-PCR is a stable, high-throughput technique that can precisely gauge the degree of therapeutic response and also signals the emergence of treatment resistance (53).

Molecular monitoring

Advances in molecular biology methods, particularly in the field of real-time quantitative RT-PCR, have shown to be highly beneficial for the detection of minimum residual sickness and the monitoring of medication response in CML patients. The assessment of BCR-ABL1 mRNA levels in the bloodstream yields important insights into treatment effectiveness and possible medication resistance (54). Table 1.3 lists the laboratory techniques used for diagnosis and tracking therapy response.

Table 2.2: Laboratory techniques used to monitor CML patients (Tohami et al., 2012).

Method	Target	Time to use	Advantages	Disadvantages
Karyotyping	Metaphase chromosomes	At diagnosis and in case of advanced disease	Available in most laboratories	Low sensitivity (1-5%) BM aspiration only
Qualitative	RNA sequence	Diagnosis	Monitoring the	Not sensitive for

OCR for BCR ABL1	of BCR-ABL		specific breakpoint of BCR-ABL1	BCRABL1 monitoring during treatment
Fish	DNA-specific markers	Every 3 months *	Rapid (1-2days) More sensitive than metaph.karyotyping (0.1-3%)	Dose not detect other clonal events
Qualitative OCR for BCR ABL1	RNA breakpoint of specific BCR ABL transcript	Every 3 months *	Very sensitive (0.001-0.0001%)	Requires standardization is labor-intensive
Mutation screening of ABL1 kinase domain	RNA sequencing of ABL kinas domain	Suspected	In case of mutation: overcome resistance with more potene TKI therapy	Depends on the specific assay for mutation detection

2.7 Treatment of CML

In the past, spleen x-rays and traditional medications like Hydroxyurea and Busulfan were used to treat CML. While the disease did not stop or noticeably slow its development to a more advanced condition, this therapy did enhance the quality of life in the early and middle phases of the chronic phase of the illness (55).

Before starting TKI therapy, hydroxyurea, a cytoreductive drug, is used to manage elevated white blood cell counts in CML patients. Despite hydroxyurea's effectiveness as a symptom management medication in the early stages of the disease, it does not provide a cure.(56).

In the days before TKIs, interferon-alpha was the go-to medication for CML. It is still used in some situations even though it is less effective than TKIs, especially for individuals who cannot tolerate TKIs or pregnant women. Interferon-alpha stimulates the immune system to target leukemic cells, which in certain cases can result in long-lasting remissions (57).

A revolutionary treatment for cancer, human recombinant interferon-alfa, produced full cytogenetic remission in 15%–30% of patients, increasing patient longevity compared to standard chemotherapy (58).

Allogeneic stem cell transplantation, or ASCT, is currently the sole treatment for CML. It is usually saved for individuals in advanced stages of the illness or those who do not respond to TKI treatment. The leukemic cells can be eliminated using ASCT, which replaces the patient's bone marrow with healthy donor cells. Because of its risks, including as graft-

versus-host disease and treatment-related mortality, TKI therapy is only appropriate for patients who are not good candidates for ASCT (59).

The treatment of CML, which involved almost half of eligible patients receiving allogeneic stem cell transplantation (alloSCT), enhanced quality of life throughout the chronic phase, which represents the first notable development in the management of CML (60).

About 15 years ago, toward the close of the 20th century, a class of small compounds targeting tyrosine kinases (TK) swiftly supplanted all of these therapies by being able to elicit a substantial molecular remission in the majority of patients (61).

Imatinib was the first oral TKI approved for the treatment of CML in May 2001. Subsequently, first-line therapy with TKIs from the second and third generations (such as dasatinib and nilotinib) was approved.(62)

The cornerstone of CML therapy is tyrosine kinase inhibitors (TKIs). The constitutively active tyrosine kinase known as the BCR-ABL1 fusion protein, which is in charge of the uncontrolled proliferation of leukemic cells, is the target of these drugs. The first TKI, imatinib, revolutionized in CML therapy by increasing complete cytogenetic response (CCR) rates and long-term survival. Following the introduction of imatinib, second-generation TKIs such as dasatinib and nilotinib provided deeper, faster molecular responses in addition to more potent inhibition of the BCR-ABL1 protein. Third-generation TKIs, such as ponatinib, are effective in treating CML patients with the T315I mutation, which is resistant to earlier TKIs.(63, 64).

After imatinib was the first oral TKI authorized for the treatment of CML, two and three-generation TKIs, dasatinib and nilotinib, were also approved. The extraordinary improvements in patient outcomes that these TKIs have brought about have resulted in a considerable rise in overall survival. CML used to have a poor 5-year survival rate, but currently most patients receiving TKI therapy have an overall survival rate and a long-term progression-free survival rate (62).

Imatinib

Imatinib is a derivative of 2-phenylaminopyrimidine that was initially developed as a general inhibitor of tyrosine kinase (TKI). It was able to block the dysregulated enzymatic activity of the Bcr-Abl oncoprotein by chemically competing with ATP for the Abl protein's ATP-binding site, or P-loop. When it was originally administered in 1998 to patients who were thought to be resistant to interferon-alpha, early outcomes have shown that it might restore Ph-negative, or likely normal, hemopoiesis (65).

The mechanism of signal transduction inhibition mediated by imatinib.

Imatinib binds to the adenosine triphosphate binding (ATP) site of Abl, preventing the protein from becoming phosphorylated by its substrate and keeping it inactive. By inhibiting the BCR-Abl tyrosine kinase, the oncogenic signal is stopped from entering the nucleus and, as a result, the malignant transformation is not allowed to occur. As seen in figure 1.8, the unphosphorylated Bcr-Abl tyrosine kinase remains dormant, which stops the oncogenic signal from reaching the nucleus (66).

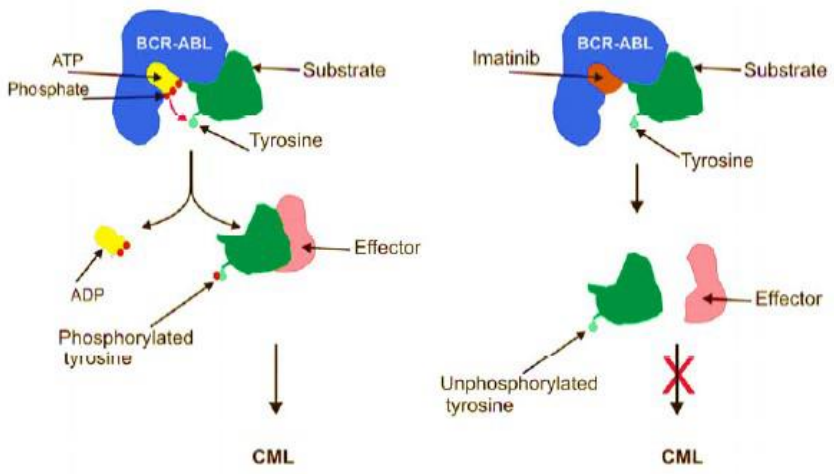

Figure 2.8: The mechanism of signal transduction inhibition mediated by imatinib. Imatinib contributes to the kinase's inhibitory effects on BCR-ABL by stabilizing the kinase's inactive non-ATP binding conformation and occupying the ATP binding pocket of the BCR-A

Tyrosine kinase inhibitors (TKIs), such as imatinib (400 mg daily) are often begun on treatment for adult patients with chronic myeloid leukemia (CML) in the chronic phase. Sixty percent of these patients will be in complete cytogenetic response (CCyR) five years after beginning imatinib, and a sizable fraction will have achieved a profound molecular response (67). The study compares the side effects and cost of TKI therapy with allogeneic stem cell transplantation for juvenile CML in the chronic phase. For people with intolerance or resistance, or those going through a fast or explosive crisis, it suggests stem cell transplantation. Nonetheless, TKI therapy alone needs to be the first course of treatment (68). Blast crisis, or BC, is a major therapy challenge for chronic myeloid leukemia (CML). It is caused by continuous BCR-ABL activation, which destroys DNA and reduces its ability to repair itself. Tyrosine kinase inhibitor therapy has increased survival, although long-term survivors undergo transplantation. Tyrosine kinase inhibitor medication, either with or

without chemotherapy, should be administered to patients in order to induce a second chronic phase and facilitate allogeneic stem cell transplantation (69, 70).

Options for treating leukemia include raising dosages, moving to a different TKI, setting to the interferon or chemotherapy, or, in the case of younger patients with compatible tissue types, considering stem cell transplantation. The ideal medication may be determined by genetic modifications, and for people who cannot take TKIs, chemotherapy may be an option (71).

2.8 Response to the treatment of chronic myeloid leukemia

The first stage of response to treatment for Chronic Myeloid Leukemia (CML) is known as the hematologic response, or the recovery of blood counts to normal. During the first three months of treatment, tyrosine kinase inhibitor therapy frequently produces a complete hematologic response (CHR) (TKIs). A patient with chronic-phase CML often has a favorable prognosis if they attain a CHR (72).

The next phase, referred to as the cytogenetic reaction, is the reduction or elimination of bone marrow cells that carry the Philadelphia chromosome. Complete (0% Ph+ cells) and partial (1-35% Ph+ cells) responses are the two categories. A complete cytogenetic response (CCR) obtained in less than a year is associated with notably improved outcomes over an extended period of time (73).

Effectiveness of treatment in CML depends on the molecular response, particularly when using tyrosine kinase inhibitors such as dasatinib, nilotinib, or imatinib. A major molecular response (MMR), which denotes longer-term survival and a lower likelihood of disease progression, is frequently a crucial objective (30).

Better long-term results are associated with early molecular responses (EMR) during the first three to six months of treatment. Real-time PCR monitoring is essential for modifying treatment methods, as a loss of EMR may signal resistance or relapse (29).

Monitoring the response to treatment is crucial for managing CML, with a higher response extending disease control duration, as shown in table 1.4.

Table 2.3: Response types and definitions (Deininger et al., 2020)

Hematologic response	• Blood counts are normal • No immature cells, such as myelocytes, promyelocytes, and blasts in blood • No signs and symptoms of disease (spleen is normal size)
Cytogenetic (Philadelphia chromosome or Ph) response	• Complete cytogenetic response (CCyR): No Philadelphia chromosomes (Ph-) • Major cytogenetic response (MCyR): Ph+ are between 0% and 35% • Partial cytogenetic response (PCyR): Ph+ are between 1% and 35% • Minor cytogenetic response: Ph+ are between 36% and 65%
Molecular (BCR::ABL1) response	• Early molecular response (EMR): BCR::ABL1 (IS) is 10% or less at 3 and 6 months • Major molecular response (MMR): BCR::ABL1 (IS) is 0.1% or less • Deep molecular response (DMR): BCR::ABL1 (IS) is 0.01% or less (MR4.0) or BCR::ABL1 (IS) is 0.0032% or less (MR4.5)
Relapse	• Any sign of loss of response

2.9 Literature Review

One of the hallmarks of Chronic Myeloid Leukemia (CML) is the Philadelphia chromosome, which is the product of the t(9;22)(q34;q11) translocation. The genetic defect causes the BCR-ABL1 fusion gene to arise, which in turn results in an aberrant tyrosine kinase that causes leukemia to develop (74). Three phases are often seen in the progression of chronic myelogenous leukemia: blast crisis, accelerated, and chronic (48).

Tyrokinase kinase inhibitors (TKIs) have revolutionized the field of CML therapy. This implies that for many individuals, CML is now a chronic illness that can be lived with and managed rather than a fatal one (63). Tyrosine kinase inhibitors (TKIs) have revolutionized the field of CML therapy. This implies that for many individuals, CML is now a chronic illness that can be lived with and managed rather than a fatal illness.

The lack of comprehensive data from Palestine necessitates focused research to understand the unique aspects of CML in this population. This gap in knowledge has driven the need for

a multicenter retrospective analysis to assess treatment outcomes and prognostic factors in Palestinian patients with CML.

In the Middle East, CML has not received much attention, and information from Palestine is especially hard to come by. Regional research, however, indicates that CML patients' clinical traits and treatment results in the Middle East could not be the same as those seen in Western populations.

In a Saudi Arabian study, the research team included younger patients with a mean age of 43.3± 18.1 years and a comparable frequency in both genders. There was an equal distribution of genders. Among the symptoms were fatigue and bone discomfort; hepato-splenomegaly was the most common clinical sign, followed by epistaxis and weight loss (75).

According to Iraqi research, the average age of CML patients was lower than previously thought, and female patients fared better in terms of survival. Older people and children were worst. The majority of patients had symptoms when they were first diagnosed, however immunomodulatory treatment had positive results (76).

According to research conducted in Pakistan, the myeloproliferative condition CML, which has a male-to-female ratio of 2:1 and a peak incidence between the ages of 21 and 50, accounts for 80% of all myeloproliferative disorders. The predominant clinical characteristics in 92% and 47% of patients, respectively, were anemia and severe splenomegaly (77).

It was found in the Trakya study that 95 patients (93.1%) were in the chronic phase and 6 patients (5.9%) were in the accelerated phase. Just 17 patients (16.7%) were unable to elicit at least a significant molecular reaction, whereas 83 patients (81.4%) were successful in doing so (78).

Patients with chronic phase illnesses did not differ in their therapy responses depending on socioeconomic background, sex, or age, according to retrospective research conducted at South Egypt Cancer Institute and Assiut University Hospital. On the other hand, a greater percentage of individuals with chronic phase illnesses or limited vigorous exercise attained both CHR and CCyR. Additionally, a strong inverse relationship between TLC and CyR, Hb, and both HR and CyR was discovered by the study. For three months, every patient received care and evaluations. As first-line treatment, hydroxyurea was given to 50.6% of patients, imatinib to 37.2%, and other treatments to 12.2%. The study emphasizes how crucial it is to

comprehend how patients' hematologic markers and treatment results relate to one another (79).

As far as the studies show, 2.2% of patients suffering from chronic myeloid leukemia (CML) were observed to be in the accelerated phase while 0.9% were in the blastic phase with the overwhelming majority of 96.8% in the chronic phase. Out of these patients, 46.6% were treated with imatinib, 16.3% had a bone marrow transplant (BMT), and 82.2% were treated with interferon (IFN).The research offers comprehensive information on CML patients' utilization of medications and procedures (80).

Those suffering from late-chronic-phase CML and who had not responded to earlier interferon alfa therapies were treated with 400 mg of oral imatinib daily. Their cytogenetic and hematologic responses were both assessed. With imatinib treatment, a high rate of responses were achieved (81).

A registry was created to capture the specific characteristics and epidemiology of chronic myeloid leukemia (CML). For 39 months, it documented all cases of CML BCR-ABL positive in a cohort of 92.5 million people from 20 European countries. Of the 2904 CML patients, 94.3% were diagnosed in the chronic phase and the median age was 56 years. The raw incidence increased with age, starting at 0.69 in Poland and peaking at 1.39 in Italy (82).

90% of patients with CML reported experiencing exhaustion and stomach pain, according to research conducted at a Saudi Arabian tertiary hospital. With 55.5% falling into the intermediate-risk Sokal score range, the chronic phase was common. With 42.5% receiving first-generation TKIs and 52.5% receiving second-generation TKIs, first-generation TKIs were the most often used first-line therapy. Three months later, 77.2% of patients had a significant molecular response, and 96.2% of patients had a full hematological response (83).

Chapter Three: Methodology

3.1 Study design

This retrospective multicenter cohort study was designed to collect and analyze medical records of patients diagnosed with Chronic Myeloid Leukemia (CML) at two major referral hospitals in Nablus, Palestine: Watani Government Hospital and An-Najah National University Hospital. The study focused on patients treated between January 2018 and December 2023. The data collection period began in 2018 as this was when electronic medical record systems (EMR) were fully implemented in both hospitals, ensuring accurate and comprehensive data retrieval.

3.2 Study area and setting

This multicenter retrospective study was conducted at two major referral centers in Nablus, Palestine: An-Najah National University Hospital and Watani Hospital.

An-Najah National University (NNUH): An average of 800 inpatient admissions are handled by NNUH's busy oncology department each year. It provides specialist care and treatment for a range of hematologic malignancies, including Chronic Myeloid Leukemia (CML), and has been the primary referral facility for adult leukemia patients from the West Bank and Gaza since January 2014.

Watani Government Hospital: A major medical center in Nablus, the Watani Government Hospital offers a variety of medical treatments, including thorough cancer treatment. It is a significant referral facility that provides cancer patients with diagnostic and treatment services, with an emphasis on Chronic Myeloid Leukemia (CML) management.

This study included An-Najah National University Hospital and Watani Hospital as the primary centers for CML management in Palestine. An-Najah Hospital serves as a major referral center not only for the West Bank but also for Gaza, due to its advanced hematological and molecular diagnostic capabilities. Meanwhile, Watani Hospital primarily covers the northern West Bank population and receives a large number of CML cases annually. The only other major center treating CML patients is Augusta Victoria Hospital (Al-Mutla') in Jerusalem, which serves the southern West Bank. However, due to the geographical, logistical, and political challenges—particularly the restricted access to Jerusalem for patients and researchers from the West Bank and Gaza—the inclusion of

Augusta Victoria Hospital was not feasible. Consequently, only An-Najah and Watani hospitals were selected. These two institutions together manage the majority of CML cases in Palestine, and thus the study sample is considered representative of the national CML population in terms of geographic coverage, diagnostic approach, and treatment outcomes.

3.3 Sampling Methods and Data Collection Tool.

A selective sampling approach was used based on the Hospital Information System (HIS) databases of both hospitals. Medical records of patients diagnosed with CML between 2018 and 2023 were identified using HIS query functions. Relevant data were extracted and exported into Excel spreadsheets for further filtering and cleaning to ensure inclusion criteria were met and to exclude duplicate or incomplete records. This method enabled efficient retrieval of accurate and comprehensive clinical and laboratory data for retrospective analysis. The comprehensive dataset for this study encompasses sociodemographic variables such as age and gender, and clinical symptoms and signs, including fatigue, bone pain, weight loss, fever splenomegaly and hepatomegaly. Hematology tests, including the total and differential complete blood count (CBC), blood film, and bone marrow results. Hematological parameters such as, hemoglobin levels, platelet counts, and initial white blood cell (WBC) counts are scrutinized to determine the disease phase (chronic, accelerated, or blast phase); establishing baseline parameters for the study. The treatment protocol, like hydroxy-urea and TKIs; including first-generation (e.g., imatinib), second-generation (e.g., dasatinib, nilotinib), and third-generation (e.g., ponatinib) inhibitors and evaluated the effectiveness of different TKIs in achieving complete hematologic response (CHR) and major molecular response (MMR).

3.4 Diagnostic criteria

The diagnostic process for Chronic Myeloid Leukemia (CML) in both An-Najah National University Hospital and Watani Government Hospital followed internationally recognized guidelines, particularly those established by the World Health Organization (WHO) and the European LeukemiaNet (ELN). Diagnosis was based on a combination of clinical presentation, hematological parameters, cytogenetic findings, and molecular confirmation.

3.4.1 Initial Clinical Evaluation

Patients typically presented with symptoms such as fatigue, unintentional weight loss, bone pain, or splenomegaly. At the time of diagnosis, all patients underwent a thorough physical examination to assess for hepatomegaly and splenomegaly. These findings were routinely confirmed using abdominal ultrasound imaging.

3.4.2 Hematological Investigations

The initial laboratory workup included:

- Complete Blood Count (CBC) with differential to detect leukocytosis, anemia, thrombocytosis, or thrombocytopenia
- Peripheral blood smear to assess for immature granulocytes, blasts, and basophils
- Bone marrow aspiration and biopsy for morphological analysis and blast cell quantification

These investigations were performed at the respective hospital where the patient was treated. However, in many cases—particularly for patients at Watani Hospital—bone marrow biopsies and advanced laboratory investigations were referred to An-Najah Hospital, which serves as a regional reference laboratory for molecular and cytogenetic testing.

3.4.3 Cytogenetic and Molecular Confirmation

Cytogenetic analysis was carried out using Fluorescence In Situ Hybridization (FISH) to detect the Philadelphia chromosome [t(9;22)(q34;q11)], the hallmark of CML. In parallel, molecular testing was performed using Reverse Transcription Polymerase Chain Reaction (RT-PCR). mRNA was extracted from peripheral blood or bone marrow samples and converted into complementary DNA (cDNA) to quantify BCR-ABL1 transcript levels. This molecular confirmation was essential for establishing the diagnosis and later used for treatment response monitoring.

3.4.4 Classification of CML Phase

Following diagnosis, each patient was classified into one of three disease phases—chronic phase, accelerated phase, or blast crisis—based on WHO criteria:

- Chronic Phase (CP):
  <10% blasts in peripheral blood or bone marrow, basophils <20%, mild or no symptoms, and no additional cytogenetic abnormalities
- Accelerated Phase (AP):

10–19% blasts in blood or marrow, or ≥20% basophils, persistent thrombocytopenia or thrombocytosis unresponsive to treatment, or clonal evolution

- Blast Crisis (BC):
  ≥20% blasts in blood or marrow, extramedullary blast proliferation, or presentation consistent with acute leukemia(84)

This staging was essential for guiding the treatment strategy and assessing the prognosis of each patient. Diagnostic staging information was extracted directly from the patient files, which included both physician assessments and laboratory data.

3.5 Treatment Strategy and TKI Therapy Sequencing

Initially, patients presenting with severe leukocytosis or symptomatic hyperviscosity were started on hydroxyurea (HU) at doses ranging from 1 to 4 g/day to rapidly reduce white blood cell counts. Once hematologic stability was achieved, HU was discontinued and Patients were initially started on first-line tyrosine kinase inhibitor (TKI) therapy with imatinib (400 mg once daily. The selection of imatinib as the initial treatment aligned with international guidelines for CML management. If patients experienced significant adverse effects, failed to achieve an adequate hematologic or molecular response, or if their clinical condition worsened during treatment, they were promptly switched to second-generation TKIs such as nilotinib (300 mg twice daily) or dasatinib (100 mg once daily). The choice of second-generation TKI was individualized based on patient comorbidities and risk profiles. Throughout treatment, patients were closely monitored for response and toxicity, with therapy adjustments made accordingly to optimize outcomes.

In the event of drug toxicity, treatment was typically withheld for 1 to 2 weeks, after which therapy was resumed with a dose adjustment and close monitoring for recurrence of adverse effects.

Although treatment strategies were broadly aligned between both hospitals, slight protocol variations existed. In most cases, hydroxyurea or imatinib served as the first-line or bridging therapy until patient-specific decisions were made regarding the most appropriate TKI based on clinical evolution and diagnostic findings(83).

Evaluation of Treatment Response

The National Comprehensive Cancer Network and the European Leukemia Network provide the most often used guidelines for the diagnosis and management of CML patients in normal practice. (78).

The effectiveness of different tyrosine kinase inhibitors (TKIs) in treating CML was evaluated by monitoring the achievement of Complete Hematologic Response (CHR) and Major Molecular Response (MMR) within defined time frames, as per European LeukemiaNet (ELN) 2020 recommendations.

Complete Hematologic Response (CHR)

CHR was assessed within the first 3 month**s** of initiating TKI therapy. It was defined as:

- Normalization of white blood cell (WBC) count
- Platelet counts within the normal range
- Absence of immature granulocytes (e.g., promyelocytes, myelocytes, blasts) in the peripheral blood
- Resolution of clinical symptoms such as fatigue and weight loss
- Disappearance of palpable splenomegaly

Routine complete blood count (CBC) tests were used to monitor blood parameters, typically conducted every 2–4 weeks during the first three months. The CHR was considered achieved if all criteria were met on two consecutive visits (40).

Major Molecular Response (MMR)

MMR was evaluated at the 12-month mark using quantitative reverse transcription polymerase chain reaction (RT-qPCR) to measure BCR-ABL1 transcript levels in peripheral blood samples, standardized to the International Scale (IS). MMR was defined as:

- MMR-BCR-ABL1 $\leq$ 0.1% (IS).
- Partial response- BCR-ABL1> 0.1-1 %(IS).
- Failure- BCR-ABL1 >1 (IS).(85)

Samples for molecular monitoring were collected at baseline, 3, 6, and 12 months post-TKI initiation, and analyzed in the molecular diagnostics lab at An-Najah Hospital. Patients who achieved MMR were considered to have a favorable prognosis and were maintained on the current treatment regimen. In contrast, failure to achieve MMR at 12 months prompted

further evaluation for resistance or poor adherence and potential change in therapeutic approach. (86).

3.6 Study population

The study population consisted of patients diagnosed with chronic myeloid leukemia (CML) who were treated at An-Najah National University Hospital and Watani Hospital, the two primary hematology referral centers in Nablus, Palestine, between January 2018 and December 2023.

Initially, 120 patients diagnosed with chronic myeloid leukemia (CML) between 2018 and 2023 were identified through hospital records. Following the application of the predefined inclusion and exclusion criteria, a total of 85 eligible patients were enrolled in the study, 20 patients were managed primarily at An-Najah Hospital, while the remaining 65 patients received treatment at Watani Hospital. Notably, key diagnostic and follow-up tests—such as blood films, bone marrow examinations, and BCR-ABL molecular assessments—for many patients at Watani Hospital were conducted at An-Najah Hospital due to resource limitations.

The study period was restricted to post-2018 cases, as this marked the full implementation of the Hospital Information System (HIS) in both institutions, enabling consistent electronic documentation and data retrieval.

3.7 Inclusion Criteria

Individuals must have received a diagnosis of Chronic Myeloid Leukemia (CML) between 2018 and 2023, supported by cytogenetic, molecular, or hematologic evidence, such as the presence of the BCR-ABL1 fusion gene or the Philadelphia chromosome. Patients must have been treated at Watani Hospital in Nablus or Al Najah National University Hospital.

The analysis only included patients with complete medical records; including clinical history, demographic data, laboratory results (such as bone marrow testing and complete blood counts), and recorded therapy responses. In order to evaluate therapy responses, including hematologic and molecular outcomes, patients must have had at least three months of follow-up at the two hospitals.

3.8 Exclusion Criteria

The research excluded patients whose medical records were missing important information, including demographics, clinical history, laboratory results (e.g., complete blood count, blood film, bone marrow assays), or information regarding the type and duration of treatment received.

Also, the study excluded patients who had less than three months of follow-up data, since this length of time was required to properly evaluate therapy responses, especially hematologic and cytogenetic results. Patients who were misidentified as having CML or who had other hematologic malignancies were not included.

To guarantee the uniformity in the assessment of treatment responses, patients who did not get conventional CML treatments—such as hydroxyurea or (imatinib)—or who did not adhere to recommended treatment regimens were not included in the analysis.

3.9 Statistical Analysis

All collected data were entered into the Statistical Package for the Social Sciences (SPSS), version 21, for processing and analysis. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess the normality of data distribution. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Comparisons between groups were conducted based on different clinical and laboratory variables. Statistical significance was set at $p \leq 0.05$. Depending on the type and distribution of data, appropriate statistical tests were applied, including the t-test, Chi-square test, One-Way ANOVA, Mann–Whitney U test, and Kruskal–Wallis test.

3.10 Ethical Considerations

The researcher ensured that all ethical considerations, necessary for conducting the research, were adhered to, and the needed approval from the Institutional Review Boards (IRB) of Arab American University- Palestine and the clinical research center of NNUH and official permission was secured from the Palestinian Ministry of Health to access and utilize patient medical records at Watani Hospital; meeting held on 15/02/2024 under the number: R-2024/A/31/N, see appendix A, B and C.

Chapter Four: Results

Overall, the results section presents the findings derived from data collected on 85 patients diagnosed and treated for chronic myeloid leukemia (CML) at two hospitals between 2018 and 2023.

The Demographic and clinical features of the study sample

Table 5 presents a summary of the demographic characteristics of study patients with chronic myeloid leukemia (CML) A total of 85 patients were included in the study. This included 47 patients that were male (55.3%) and 38 patients that were female (44.7%). The current study had a male to female ratio of 1.24:1. As noted, there is a small male preponderance in the study sample.

The average age in the sample was 47.6 years (SD = 15.5), minimum was 18 years while the maximum age was 83. Age as a factor was normally distributed as confirmed by Shapiro-Wilk test age was a normally distributed variable ($p > 0.05$). To better illustrate the age distribution, patients were categorized into four age groups: 17.6% were aged 18–29 years, 29.4% were 30–44 years, 32.9% were 45–59 years, and 20.0% were 60 years and above.

Table 4.1: Demographic Characteristics of the Study Population.

Variable	N	Frequency (%)	Mean (SD) / Median (IQR)	Min	Max
Age (years)	85		47.6 (15.5) / 48 (18–83)	18	83
Age groups					
• 18–29	15	17.6%			
• 30–44	25	29.4%			
• 45–59	28	32.9%			
• ≥60	17	20.0%			
Gender	85				
• Male	47	55.3%			
• Female	38	44.7%			

From the total of 85 patients, the most frequently reported clinical manifestations were fatigue and bone pain, observed in 44 patients (51.8%), followed closely by asymptomatic presentation in 43 patients (50.6%). Weight loss was reported in 35 patients (41.2%), and splenomegaly was identified in 33 patients (38.8%). Less common symptoms included fever, affecting 20 patients (23.5%), and hepatomegaly, which was found in only 10 patients (11.8%) (table 6).

Table 4.2: Distribution of Clinical features of CML Patients at Diagnosis

Sign / Symptom	**N (%)**
Fatigue and bone pain	44 (51.8%)
No symptoms (asymptomatic)	43 (50.6%)
Weight loss	35 (41.2%)
Splenomegaly	33 (38.8%)
Fever	20 (23.5%)
Hepatomegaly	10 (11.8%)

The illness phase at initial presentation depicted in Figure 9 Under the patient population of 85 patient diagnosed 81 (95.3%) were in chronic phase, 3 (3.5%) in accelerated phase and 01(1.2%) in the blastic phase. Most patients were diagnosed in the chronic phase, as expected with typical disease progression patterns.

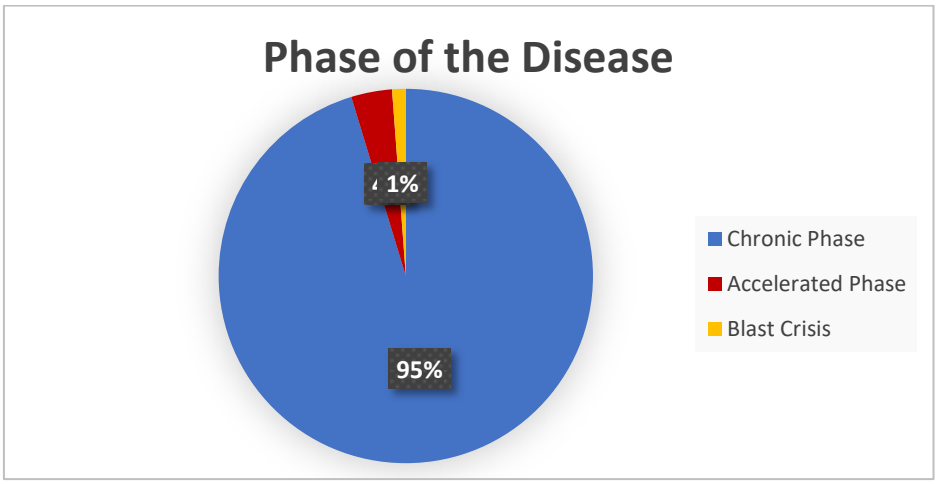

Figure 4.1: Distribution of Disease Phases Among CML Patients

As shown in Table 7, the mean hemoglobin (Hb) level at the onset of the disease was 10.8 ± 2.01 g/dL, indicating a generally reduced hemoglobin concentration among patients. However, the white blood cell (WBC) and platelet (PLT) counts were not normally distributed, as assessed by the Shapiro–Wilk test. Consequently, their values were expressed as medians and interquartile ranges (IQR) to more accurately reflect the central tendency. The median WBC count was 90 × 10^9/L (IQR: 62.8–155.5 × 10^9/L), and the median PLT count was 266 × 10^9/L (IQR: 183–455 × 10^9/L).

Table 4.3: Descriptive Statistics of Hematological Parameters in CML Patients

Parameter	Mean ± SD	Median (IQR)	Min – Max
HB (g/dL)	10.8 ± 2.01	10.8 (9.7-12)	6-16
WBC (×10^9/L)		90 (62.8-155.5)	25-508
PLT (×10^9/L)		266 (183-455)	47-1555

The treatment and response of studied population

Table 8 captures the different treatments given to the studied population. Hydroxyurea was given to 74 patients (87.1%) as an initial or adjunctive therapy. Every patient (100%, n = 85) was treated with a first generation TKI, with all of them receiving Imatinib. Due to resistance or intolerance to first line therapy, 9 patients (10.6%) were started on second line TKIs.

Table 4.4: Treatment of the Studied Population

Treatment Modality	Frequency (N)	Percentage (%)
Hydroxyurea	74	87.1%
First-Generation TKI Imatinib	85	100%
Second-Generation TKI Dasatinib Nilotinib Bosutinib	9	10.6%

Molecular and hematological changes were used to evaluate the therapy response and summarized in table 9. In contrast to a variety of molecular and hematological responses, the majority of patients appeared to respond favorably to therapy.

As regards the study population, molecular response was consistent. MMR was noted in 50 patients (58.8%) which indicated considerable treatment response, while PMR was seen in 20 patients (23.5%) which indicates moderate response. On the other hand, 15 patients (17.6%) with no observed molecular response understandably indicates resistance or insufficient treatment potency.

Addressing the blood test results, the patient's group with some sort of response was: Complete Hematological Response (CHR) in 70 patients out of 85 or 82.4% which indicates effective disease control in a majority. On the flip side, 15 patients or 17.6% did not respond with some sort of hematological response which means the treatment did not work or disease activity is ongoing. This clearly marks a divergence in response to treatment and some other approach needs to be taken with those who do not respond

Table 4.5: The hematological and molecular response to the treatment.

Response Type	Frequency (N)	Percentage (%)
Major Molecular Response (MMR)	50	58.8
Partial Molecular Response (PMR)	20	23.5
Failure to Achieve Response	15	17.6
Complete Hematological Response (CHR)	70	82.4
No Hematological Response	15	17.6

As far as the chronic phase is concerned, most patients, precisely 77 (90.62%), did not undergo transformation of the disease. Nonetheless, 2 patients (2.4%) did progress to the accelerated phase, while 3 patients (3.5%) transformed to acute myeloid leukemia (AML), and 2 (2.4%) transformed to acute lymphoblastic leukemia (ALL). Also, 1 patient (1.2%) developed myelofibrosis. The patients who transformed into AML or myelofibrosis had significantly lower molecular and hematological responses compared to the patients who remained in the chronic phase, suggesting a more advanced disease course (Figure 10).

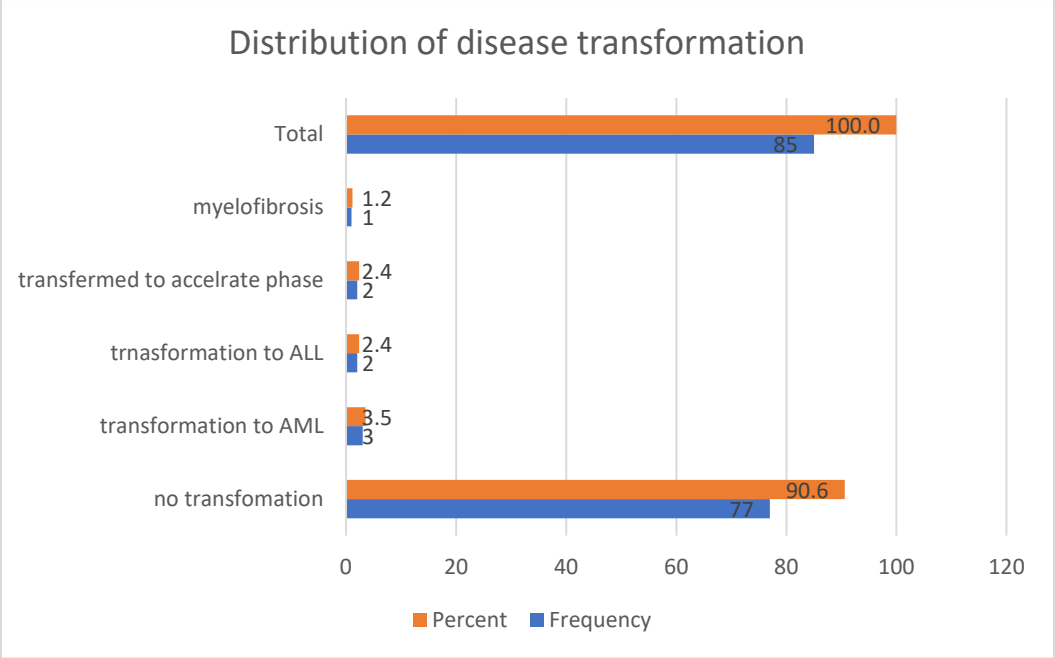

Figure 4.2: Illustrates the distribution of disease transformation among CML patients.

The Survival Status of Chronic Myeloid Leukemia (CML) Patients

the survival status of CML patients, we categorized patients as Alive or Deceased in table 10.

Table 4.6: The survival status of cml patient

Survival Status	Frequency (N)	Percentage (%)
Alive	81	95.3%
Deceased	4	4.7%

Survival status was assessed over a one-year period following diagnosis.The majority of patients 81 (95.3%) were alive, while 4 (4.7%) had deceased. This indicates a high survival rate among CML patients in our study.

The association between gender and treatment response

A Chi-Square test was conducted to evaluate the association between gender and response among 85 patients with CML. The results summarized in Table 11 revealed no statistically significant association between gender and response

Table 4.7: The association between gender and treatment response.

Response Type	Male (n, %)	Female (n, %)	p-value
Molecular Response			0.413
Major Molecular Response (MMR)	32 (68.1%)	22 (57.9%)	
Partial Molecular Response (PMR)	9 (19.1%)	7 (18.4%)	
Failure to Achieve Response	6 (12.8%)	9 (23.7%)	
Hematological Response			0.305
Complete Hematological Response (CHR)	40 (85.1%)	30 (78.9%)	
No Hematological Response	7 (14.9%)	8 (21.1%)	

The molecular reaction and gender did not significantly correlate (p = 0.413). Specifically, the proportion of patients achieving Major Molecular Response (MMR) was 68.1% in males and 57.9% in females. Furthermore, PMR was noted in 19.1% of males and 18.4% of females. No molecular response was recorded in 12.8% of males and 23.7% of females.

For the case of CHR vs No CHR, analysis did not demonstrate a meaningful association with gender in p = 0.305. Among those achieving Complete Hematological Response (CHR), males were 85.1% and females were 78.9%

Association between age and treatment response.

Since age is normally distributed, an appropriate statistical test for comparing age across different response groups is one-way ANOVA (for three groups: MMR, PMR, Failure) or an independent t-test (for two groups: CHR vs. No CHR). The results are present in table 12.

Table 4.8: The association between age and treatment response

Response Type	N	Mean Age (Years)	Std. Deviation	p-value
Molecular Response				0.061
MMR	50	45.74	14.11	
PMR	20	54.95	15.99	
Failure	15	44.27	17.48	
Hematological Response				0.996
CHR	70	47.64	14.77	
No CHR	15	47.67	19.37	

Abbreviations: CHR = Complete Hematologic Response; MMR = Major Molecular Response; PMR = Partial Molecular Response.

Patients with major molecular response (MMR) had an average age of 45.74 ± 14.11 years and those with partial molecular response (PMR) had an even greater average age of 54.95 ± 15.99 years. Patients who experienced failure had an average age of 44.27 ± 17.48 years. The averages of these values give the total average of the study population which was 47.65 ± 15.55 years. In regard to age and the molecular response achieved, there was no statistically significant difference (p = 0.061) although it can be noticed that the PMR cohort was older than the MMR and failure groups. Still, post-hoc analysis did not indicate significant differences.

Patients with complete hematological response (CHR) had an average age of 47.64 years (SD = 14.77) while the average of those who did not achieve it was 47.67 years (SD = 19.37).

There was no statistically significant difference between the two groups.

The t-test showed no statistically significant difference in age between the two groups p = (0.996).

The association between clinical signs and symptoms and the treatment response

A chi-square test was used to investigate the relationship between the symptoms of patients suffering from chronic myeloid leukemia (CML) and complete hematologic response (CHR) in CML patients table 13. Patients who reported weariness and bone pain had a CHR of 45.7%, whereas those who did not reported these symptoms had a CHR of 80.0%. The

statistically significant difference (p = 0.016) suggests that bone pain and tiredness may have a negative correlation with hematologic response.

While 73.3% of patients who did not reach CHR had lost weight, 34.4% of patients who reported losing weight had done so. The statistical significance of this difference (p = 0.05) raises the possibility of an inverse link between treatment response and weight reduction.

Compared to 60.0% of patients who did not reach CHR, only 15.7% of those who did so have a fever. Given that this correlation was extremely significant (p = 0.000), fever at diagnosis may be a poor predictor of CHR.

Splenomegaly was present in 30.0% of patients who achieved CHR and in 80.0% of those who did not. The association was statistically significant (p = 0.000), supporting a strong negative correlation between splenomegaly and hematologic response.

Hepatomegaly was more common among patients who did not achieve CHR (26.7%) than those who did (8.6%); however, the difference did not reach statistical significance (p = 0.07).

Patients who reported no clinical symptoms were more likely to achieve CHR (55.7%) than those who did not (26.7%), with the difference being statistically significant (p = 0.041). This suggests that asymptomatic presentation may be associated with a more favorable hematologic outcome.

Table 4.9: The association between clinical signs and symptoms and complete hematologic response (CHR)

Symptoms	Yes/NO	CHR Achieved (N) %	No CHR (N) %	p-value
Fatigue and	**Yes**	32 (45.7%)	12 (80.0%)	0.016
Bone Pain	**NO**	38(54.3%)	3(20.0%)	
Weight Loss	**Yes**	24 (34.4%)	11(73%)	0.05
	NO	46(65.7%)	4(26.7%)	
Fever	**Yes**	11(15.7%)	9(60%)	0.000
	NO	59(84.3%)	6(40%)	
Splenomegaly	**Yes**	21(30.0%)	12(80%)	0.000
	NO	49(70%)	3(20%)	
Hepatomegaly	**Yes**	6(8.6%)	4(26.7%)	0.07
	NO	64(91.4%)	11(73.3%)	
No Symptoms	**Yes**	39(55.7%)	4(26.7%)	0.041
	NO	31 (44.3%)	11 (73.3%)	

Abbreviations: CHR = Complete Hematologic Response

Molecular response (MMR, PMR, and Failure) was analyzed in relation to symptoms. In table 14 significant associations were found for fatigue and bone pain (p = 0.006), weight loss (p = 0.007), fever (p = 0.000), splenomegaly (p = 0.000), and absence of symptoms (p = 0.031). However, hepatomegaly (p = 0.21) was not significantly associated with molecular response.

Table 4.10: The association between clinical signs and symptoms and Molecular response.

Symptoms	**Yes/No**	**MMR N (%)**	**PMR N (%)**	**Failure N (%)**	**p-value**
Fatigue and Bone Pain	Yes	21(38.9%)	11(68.8%)	12(80%)	0.006
	No	33(61.1%)	5(31.3%)	3(20%)	
Weight Loss	Yes	16(29.6%)	8(50%)	11(73.3%)	0.007
	No	38(70.4%)	8(50%)	14(26.7%)	
Fever	Yes	6(30%)	5(25%)	9(45%)	0.000
	No	48(73.8%)	11(16.9%)	6(9.2%)	
Splenomegaly	Yes	12(22.2%)	9(56.3%)	12(80%)	0.000
	No	42(77.8%)	7(43.8%)	3(20%)	
Hepatomegaly	Yes	4(40%)	3(30%)	3(30%)	0.21
	No	50(66.7%)	13(17.3%)	12(16%)	
No Symptoms	Yes	33(61.1%)	6(37.5%)	4 (26.7%)	0.031
	No	21(38.9%)	10(62.5%)	11(73.3%)	

Abbreviations: MMR = Major Molecular Response **,** PMR = Partial Molecular Response.

This study explored the connection between baseline clinical symptoms and molecular response outcomes in individuals diagnosed with chronic myeloid leukemia (CML). Major Molecular Response (MMR), Partial Molecular Response (PMR), and therapy failure were the three categories used to describe molecular response. The statistical significance of these correlations was evaluated using chi-square tests, with a p-value of less than 0.05.

Fatigue and bone pain and molecular response were shown to be significantly correlated (p = 0.006). In contrast to 68.8% in the PMR group and 80.0% in the treatment failure group, 38.9% of patients who reached MMR reported feeling tired and having bone discomfort. This

gradient shows that the symptom load is larger in individuals with worse molecular responses.

Additionally, there was a substantial correlation between molecular response and weight loss ($p = 0.007$). It was observed in 29.6% of MMR patients, rising to 50.0% in PMR and 73.3% in the failure group. This suggests a strong correlation between worse molecular results and the intensity of symptoms.

There was a significantly significant correlation ($p < 0.001$) between molecular reaction and fever at presentation. Fever was experienced by just 30.0% of MMR patients, compared to 45.0% of the treatment failure group. This lends credence to the idea that fever and other systemic symptoms might be signs of a more severe or advanced disease phenotype.

Splenomegaly was seen in 80.0% of patients who did not respond to therapy, 22.2% of the MMR group, and 56.3% of PMR. It was substantially more common in patients with inadequate molecular responses ($p < 0.001$). This implies that splenomegaly might be a clinical sign of advanced illness or resistance to therapy.

On the other hand, hepatomegaly was seen in 40.0% of MMR patients, 30.0% of PMR, and 30.0% of failed cases; it was not significantly correlated with molecular response ($p = 0.21$). This lack of correlation suggests that hepatomegaly has no diagnostic or prognostic value in predicting molecular outcomes in CML.

Remarkably, improved molecular response outcomes were substantially correlated with the lack of clinical symptoms upon diagnosis ($p = 0.031$). In contrast to just 37.5% of PMR and 26.7% of failed patients, 61.1% of asymptomatic patients attained MMR, underscoring the predictive significance of baseline symptom load.

According to this study, there is a substantial correlation between inferior molecular response in CML patients with certain baseline symptoms, specifically weariness and bone pain, weight loss, fever, and splenomegaly. On the other hand, a more positive molecular response can be predicted by the lack of symptoms upon diagnosis.

The association between hematological parameter with treatment response.

Hematological parameters (WBC, HB, and PLT) were analyzed with treatment response, as shown in Table 15. The results noted within this analysis comparatively evaluated these parameters within response groups such as Complete Hematologic Response (CHR) versus

No CHR and Molecular Response (MMR, PMR, and Failure). Within CHR patients the median WBC count was 87.6 (IQR = 99.00) while the non-CHSR patients had 95.0 (IQR = 115.0). This was however, statistically insignificant (p = 0.064). This indicates the difference might need to be ignored as the difference could be random noise in the data.

When comparing WBC counts across different levels of treatment response, patients who achieved Major Molecular Response (MMR) had the lowest median WBC count at 82.5 × 10^9/L (IQR: 91.75), followed by those with Partial Molecular Response (PMR) at 90.7 × 10^9/L (IQR: 138.75), and those with treatment failure at 109.0 × 10^9/L (IQR: 115.0). Although this trend suggests that higher WBC counts at admission may be associated with poorer molecular response, the association did not reach statistical significance (p = 0.061).

Table 4.11: The association between hematological with treatment response.

Variable	**CHR (n=70) Median (IQR)**	**No CHR (n=15) Median (IQR)**	**p-value**	**MMR (n=50) Median (IQR)**	**PMR (n=20) Median (IQR)**	**Failure (n=15) Median (IQR)**	**p-value**
WBC	87.6 (99.00)	95.0 (115.0)	0.064	82.5 (91.75)	90.7 (138.75)	109.0 (115.0)	0.061
PLT	269.5 (265.50)	250.0 (249.00)	0.657	274.0 (268.50)	190.7 (301.50)	250.0 (249.0)	0.157
Variable	**CHR (n=70) Mean ± SD**	**No CHR (n=15) Mean ± SD**	**p-value**	**MMR (n=50) Mean ± SD**	**PMR (n=20) Mean ± SD**	**Failure (n=15) Mean ± SD**	**p-value**
HB	10.86 ± 2.12	10.71 ± 1.49	0.802	11.03 ± 2.17	10.41 ± 1.98	10.73 ± 1.48	0.496

Abbreviations: CHR = Complete Hematologic Response; MMR = Major Molecular Response; PMR = Partial Molecular Response; WBC = White Blood Cell count; PLT = Platelet count; HB = Hemoglobin.

The median PLT count for patients who achieved complete hematologic response (CHR) was slightly higher than those who did not achieve CHR (269.5, IQR = 265.50; 250.0, IQR = 249.00). Nevertheless, this failed to achieve statistical significance (p = 0.657), suggesting that admission PLT levels do not reliably predict a hematologic response.

Among the molecular response categories, MMR group had the highest median PLT (274.0, IQR = 268.50), followed by treatment failure (250.0, IQR = 249.00) and PMR had the lowest value (190.7, IQR = 301.50). This difference in PLT in some of these response groups did not

reach statistical significance (p = 0.157), It implies that the degree of molecular reaction is not significantly affected by PLT at admission.

The mean values of HB were 10.86 ± 2.12 in individuals with CHR and 10.71 ± 1.49 in those without CHR. Since there is no discernible difference (p-value of 0.802), it is assumed that admission hemoglobin levels do not signify a hematologic reaction.

Also, examining molecular response groups, it was noted that Patients with MMR showed the highest mean HB level (11.03 ± 2.17), followed by Failure (10.73 ± 1.48) and the lowest in PMR (10.41 ± 1.98). No significant differences between the groups were found using the ANOVA test (p = 0.496), indicating that HB levels upon admission are not strongly related to attaining molecular response.

The association between age categories and one-year survival status

The table 16 presents the relationship between patients' age categories and their one-year survival status following a diagnosis of Chronic Myeloid Leukemia (CML). Patients were divided into four age groups: 18–29, 30–44, 45–59, and ≥60 years.

The results show that younger age groups had higher survival rates. In both the 18–29 and 30–44 age groups, 100% of patients were still alive after one year. In contrast, the survival rate decreased to 97.0% in the 45–59 group and dropped further to 85.0% in patients aged 60 and above.

Statistical analysis using the Pearson Chi-Square test indicated no significant association between age category and one-year survival ($p = 0.089$).

Table 4.12: the relationship between patients' age categories and their one-year survival status.

Age Category (Years)	Still Alive (n)	Deceased (n)	Total (n)	% Alive	% Deceased
18–29	12	0	12	100.0%	0.0%
30–44	20	0	20	100.0%	0.0%
45–59	32	1	33	97.0%	3.0%
≥60	17	3	20	85.0%	15.0%
Total	81	4	85	95.3%	4.7%

Pearson Chi-square test: χ^2 (3) = 6.513, p = 0.089

The association between disease transformation type and one-year survival status.

A statistically significant association was observed between transformation type and one-year survival status (p = 0.000). in table 19 the vast majority of survivors (96.1%) had no disease transformation, whereas the only patient who transformed to myelofibrosis died within one year. No deaths were observed among patients who transformed to AML, ALL, or the accelerated phase during the study period. These findings suggest that disease transformation, especially to myelofibrosis, may be associated with poorer short-term survival outcomes, though the small number of cases in transformation subgroups warrants cautious interpretation.

Table 4.13: Association between transformation type and one-year survival status among CML patients (n=85).

Type of Transformation	**Survivors**	**Deceased**	**Total**
No transformation	74 (96.1%)	3 (3.9%)	77 (90.6%)
Transformed to AML	3 (100%)	0 (0%)	3 (3.5%)
Transformed to ALL	2 (100%)	0 (0%)	2 (2.4%)
Transformed to Accelerated Phase	2 (100%)	0 (0%)	2 (2.4%)
Myelofibrosis	0 (0%)	1 (100%)	1 (1.2%)
Total	81 (95.3%)	4 (4.7%)	85 (100%)

P-value (Pearson Chi-square test): 0.000

Chapter Five: Discussion

In the present study, we analyzed the clinical presentation and demographic characteristics of 85 Palestinian patients diagnosed with chronic myeloid leukemia (CML). The male-to-female ratio was 1.24:1, indicating a slight male predominance. This finding aligns with previous research from the region. For example, a study conducted in Lebanon reported a significantly higher male-to-female ratio of 3:1, while data from Turkey also demonstrated a higher prevalence among males (78, 87). Although the underlying cause of this gender disparity remains unclear, previous literature has suggested possible roles for genetic, environmental, or hormonal factors. In the context of Palestine, this male predominance may be further explained by occupational and environmental exposures more common among men, such as agricultural work, exposure to radiation, and frequent contact with chemical substances. These factors are considered important contributors that may increase the risk of developing the disease.

The patients' ages ranged from 18 to 83 years, with a mean age of 47.6 years (SD = 15.5). These results are consistent with findings from neighboring countries. A Saudi Arabian study reported a mean age of 41.6 years with a similar slight male predominance (83), while an Egyptian study identified a median age of 42 years, ranging from 16 to 80 years (79) . In India, the median age was reported to be between 32 and 42 years, also with a notable male predominance (88). These regional similarities may reflect shared genetic backgrounds, environmental exposures, or differences in healthcare access and early detection.

Conversely, the United States and Germany, being high-income countries, have a higher median age of diagnosis which occurs between 55 60 years(71, 89). This variation may be influenced by differences in genetic susceptibility across populations, which can affect both the age of disease onset and its progression. Therefore, the observed disparity in the age of CML diagnosis between high-income and low- to middle-income countries is likely driven, at least in part, by population-specific genetic predispositions.

In the current study, the most commonly reported clinical symptoms among patients with chronic myeloid leukemia (CML) in Palestine were bone pain and fatigue (51.8%), weight loss (41.2%), and fever (23.5%). These findings are generally consistent with symptom patterns reported in other regional studies, though some variation exists. For instance, a study from Pakistan reported fatigue in 59% of CML patients, weight loss in 43%, and fever in 28%, closely aligning with our observations(89). Similarly, Patnaik et al. in India documented

fatigue in 55%, weight loss in 38%, and fever in 26% of cases (90). These overlapping results suggest that constitutional symptoms such as fatigue and weight loss are prominent initial presentations of CML across diverse populations.

In our cohort, splenomegaly was observed in 38.8% of patients, which is significantly lower than Indian studies where the prevalence was greater than 60% (90). This difference could indicate a lower diagnostic odyssey in the Indian population, possibly because of the Indian Health care system not having adequate diagnostic facilities or lesser health awareness as compared to our population, which then led to diagnosis after the development of notable splenic enlargement. Hepatomegaly was present in 11.8% of patients, a figure generally in line with the literature.

Over half of the patients in our study (50.6%) being asymptomatic at the time of diagnosis is notable. Italians also reported that about 48% of their patients were diagnosed during routine check-ups (91). In my study, the high rate of asymptomatic detection highlights the likely influence of opportunistic screening and emphasizes the value of routine blood tests in the earlier detection of CML, which may enhance prognosis and treatment response.

Delayed diagnosis of chronic myeloid leukemia (CML), resulting in presentation during advanced phases, can significantly affect prognosis and treatment efficacy. Patients diagnosed in the accelerated or blast phase typically exhibit poorer responses to tyrosine kinase inhibitors (TKIs) and have reduced overall survival rates compared to those diagnosed during the chronic phase (92).

In our cohort, the vast majority of patients (95.3%) were diagnosed in the chronic phase, while 3.5% were in the accelerated phase, and only 1.2% presented in the blast phase. This distribution is consistent with the classical clinical course of CML, in which the majority of cases are identified in the chronic phase—often incidentally through routine hematologic testing.

Our findings are in agreement with those reported in other countries. For example, a study from Trakya documented a similar distribution, with 93.1% of patients in the chronic phase, 5.9% in the accelerated phase, and 1% in the blast phase (78).Likewise, a study from Southern Nigeria reported that 93.3% of cases were diagnosed in the chronic phase, and 6.7% in advanced stages(93).In high-income countries such as the United States, the proportion of chronic-phase diagnoses is even higher—often exceeding 95%—attributed to improved healthcare infrastructure, regular health screenings, and greater public health awareness(71).

The pronounced accessibility to diagnostic aids and heightened provider-level awareness in Palestine may explain the high chronic-phase diagnosis percentage (95.3%) in our study. This is a positive trend since an early-stage diagnosis is linked to better clinical outcomes and long-term survival during TKI therapy. Nevertheless, the existence of a small percentage of advanced-phase cases points to the need for ongoing public education, as well as devising efficient public referral systems to circumvent delays in diagnosis that can hinder the effectiveness of treatment.

The hematological findings in this study align with the well-established diagnostic profile of chronic myeloid leukemia (CML). At the time of diagnosis, the mean hemoglobin (Hb) level was 10.8 ± 2.01 g/dL, indicating that mild to moderate anemia is a prevalent feature in CML patients. This anemia is likely attributable to bone marrow infiltration by leukemic cells, resulting in impaired erythropoiesis. Comparable results have been reported in other regions; for example, a study from Pakistan found a mean hemoglobin level of 10.4 ± 2.2 g/dL, supporting the notion that anemia represents a consistent and cross-regional hallmark of CML (94).

Regarding leukocyte and platelet counts, the median white blood cell (WBC) count in our cohort was 90 × 10^9/L (IQR: 62.8–155.5 × 10^9/L), and the median platelet (PLT) count was 266 × 10^9/L (IQR: 183–455 × 10^9/L). These values are characteristic of CML, in which marked leukocytosis and variable thrombocytosis are common at presentation. Similar findings have been documented in international studies. For instance, Indian research reported a median WBC count of 110 × 10^9/L and a median PLT count of 300 × 10^9/L .(90), while a Nigerian study recorded values of 122 × 10^9/L and 280 × 10^9/L, respectively (95) . These parallel patterns reflect the biological consistency of CML manifestations across diverse ethnic and geographic populations.

Overall, the hematological parameters observed in our Palestinian cohort are consistent with the known pathophysiology of CML and reinforce the role of complete blood count (CBC) as an essential, low-cost, and widely available tool in the initial evaluation and staging of the disease. The combination of moderate anemia, pronounced leukocytosis, and fluctuating platelet levels should prompt clinicians to consider CML in differential diagnoses, particularly in asymptomatic individuals undergoing routine blood testing.

In this study, hydroxyurea was administered to 74 patients (87.1%) as an initial cytoreductive agent to control leukocytosis prior to initiating definitive treatment with tyrosine kinase

inhibitors (TKIs). This approach remains prevalent in many resource-limited settings due to hydroxyurea's affordability, rapid onset of action, and established efficacy in initial disease stabilization (96, 97). Its widespread use in developing countries reflects practical considerations where immediate access to TKIs or molecular diagnostics may be limited.

Based on the worldwide protocols of managing newly diagnosed chronic-phase CML, every patient in the cohort received first-line treatment with imatinib, a first-generation TKI which is considered the global benchmark now Imatinib has changed the outlook of CML from being a deadly cancer to a controllable chronic disease and its availability in developing countries has been aided greatly by international access programs(98).

Despite this, the use of second-generation TKIs dasatinib and nilotinib was needed in 9 patients (10.6%) due to imatinib resistance or intolerance. This figure is comparable to findings from other Pakistan and Trakya studies where 8–15% of patients required treatment alteration due to inadequate response or adverse effects In comparison, higher income countries tend to have a higher later use of second-generation TKIs, whether as first-line or shortly after molecular failure, due to more availability of sophisticated diagnostic tools and comprehensive health insurance(99). These results illustrate the necessity of having a balanced approach between clinical effectiveness and accessibility within the treatment approach for CML, especially in low-resourced healthcare systems. In the clinical setting in Palestine, the decision to initiate second-generation tyrosine kinase inhibitors (TKIs) is primarily guided by standardized response assessments, particularly hematologic and molecular response evaluations. A switch to second-generation TKIs is typically considered when patients exhibit treatment failure, loss of response, suboptimal molecular responses, or disease progression while on first-line therapy. These criteria align with international guidelines and ensure that therapeutic adjustments are based on measurable disease dynamics and individual patient response profiles.

The timing of response assessments in CML treatment follows internationally established guidelines, such as those issued by the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN). A complete hematologic response (CHR) is typically assessed within the first 3 months of treatment, as it reflects the initial control of the disease's clinical manifestations—such as normalization of blood counts and resolution of symptoms like splenomegaly. Hematologic response is expected to occur rapidly after the

initiation of tyrosine kinase inhibitors (TKIs) and is therefore used as an early indicator of treatment effectiveness.

In contrast, molecular response (MR) is assessed using quantitative PCR to detect BCR-ABL1 transcript levels and reflects a much deeper level of disease control at the molecular level. Because it takes longer for BCR-ABL1 levels to decline to measurable thresholds (such as MMR or DMR), the molecular response is generally evaluated at 12 months, although early molecular milestones (at 3 and 6 months) are also recommended to predict long-term outcomes. A major molecular response (MMR) by 12 months is considered a critical goal in therapy, and failure to achieve it may warrant treatment modification.

In the present research, 50 patients (58.8%) attained Major Molecular Response (MMR) which indicates a satisfactory treatment response for most of the group. Molar responses were classified into two categories. In PMR, 20 patients (23.5%) and 15 patients (17.6%) did not achieve any molecular response. All of these results are consistent with other local and global findings. For instance, an Indian study reported an MMR rate of approximately 46.7% after one year of imatinib therapy (100), and similar outcomes were noted in Nigeria, where 55% of patients achieved MMR after 12–18 months of treatment.(95)

Our cohort's non-responder rate of 17.6% could be due to factors such as primary resistance to TKIs (tyrosine kinase inhibitors), poor compliance to the prescribed therapy, or infrequent molecular monitoring resulting in infrequent dose modification. In developed countries with routine real-time PCR testing, treatment failures are identified and addressed more promptly by employing strategies like switching to second-generation TKIs.(40).

Focusing on hematological outcomes, we find that Complete Hematological Response (CHR) was attained in 70 patients (82.4%), which falls in line with the expectations for patients in the chronic phase of CML. This finding is indeed corroborated by studies conducted in Pakistan and Saudi Arabia which reported CHR rates between 75% and 96%, even in setting devoid of advanced molecular diagnostic tools (83, 94). On the other hand, the 17.6% of patients in our study who did not achieve CHR represent a clinically significant subset that requires deeper investigation. In those situations, sustained disease activity could indicate resistance due to insufficient compliance, presence of advanced disease at the time of diagnosis, or delayed diagnosis. These findings strongly suggest that comprehensive follow-up care and patient education to improve adherence, along with advanced molecular

diagnostic infrastructure to improve monitoring and long-term outcomes, are essential in the management of CML, especially in under-resourced healthcare systems.

During the period of this study, several factors were identified that may have contributed to the lack of treatment response among patients with chronic myeloid leukemia (CML) in Palestine. One major factor is the limited health awareness among patients regarding the symptoms of the disease, which led to delays in diagnosis and, consequently, delays in initiating treatment—an issue that can significantly affect therapeutic outcomes. Furthermore, treatment interruption was observed in some cases, either due to the patient's personal decision to stop therapy after experiencing temporary improvement, or because of inconsistent availability of medications in some healthcare centers. In addition, access to hospitals posed a serious challenge, especially for patients in the Gaza Strip, where logistical and political barriers often prevent patients from receiving regular follow-up and continuous care. Another critical factor is the presence of certain genetic mutations, such as the T315I mutation, which confer resistance to tyrosine kinase inhibitors (TKIs). These mutations limit the effectiveness of standard therapy and necessitate the use of more advanced and often less accessible or more costly second- or third-generation TKIs.

The majority of patients in our cohort (77 out of 85; 90.6%) remained in the chronic phase throughout the follow-up period, with no evidence of disease transformation. However, a minority experienced disease progression: two patients (2.4%) advanced to the accelerated phase, while five patients (5.9%) underwent transformation to acute leukemia—three to acute myeloid leukemia (AML) and two to acute lymphoblastic leukemia (ALL). Additionally, one patient (1.2%) developed secondary myelofibrosis, a known but rare progression associated with poor prognosis in chronic myeloid leukemia (101).

These changes were strongly linked with worse clinical outcomes. Individuals who developed AML, ALL, or myelofibrosis exhibited markedly lower molecular and hematological response rates, indicating more advanced disease biology, possibly due to resistance to TKI therapy or inadequate adherence to treatment. Myelofibrosis, in particular, has been associated with greater treatment futility and decreased survival in CML patients, probably because of marrow failure with fibrosis-related osteosclerosis and clonal evolution (102).

Our results are consistent with global figures. For example, the long-term follow-up of the IRIS trial showed that with frontline imatinib therapy, nearly 7% of patients progressed to the accelerated or blast phase within the first five years of treatment(73). Likewise, an Egyptian

study reported transformation rates of about 8%, particularly in patients with low adherence to treatment and infrequent molecular monitoring (79). It is remarkable that the relatively low transformation rate in our cohort of 9.4% may suggest the advantage of early diagnosis and consistent TKI treatment, along with possibly enhanced educational and follow-up support from the treating physicians. This highlights the need for frequent molecular assessments and timely proactive changes to the treatment strategy to avert disease progression while maintaining the valuable long-term outcomes.

The transformation rate of chronic myeloid leukemia (CML) in Palestine was found to be 9.4%, which is considered relatively high compared to some international studies. Several contributing factors may explain this observation. First, delayed diagnosis remains a major challenge, often due to limited public awareness regarding the symptoms of CML, leading to late presentation and initiation of treatment. Second, treatment discontinuation is common, either due to patient-related factors such as non-adherence or systemic issues like interruptions in drug supply.

In particular, patients from Gaza face significant barriers in accessing specialized treatment centers, resulting in poor follow-up and delayed response assessments. Additionally, a lack of consistent molecular monitoring and limited access to advanced diagnostic tools may contribute to the under-detection of treatment failure or the emergence of resistant mutations, which ultimately increase the risk of disease progression and transformation.

These findings highlight the urgent need to improve early detection strategies, ensure uninterrupted access to tyrosine kinase inhibitors (TKIs), and establish routine molecular response monitoring to reduce the risk of transformation and improve patient outcomes.

At the point of data collection, just 4 patients (4.7%) had died, while the overwhelming majority (81 out of 85; 95.3%) alive, suggesting a remarkably high total survival rate of chronic myeloid leukemia (CML) patients in Palestine. This positive survival statistic might be due to several reasons such as earlier diagnosis, strict compliance to first line TKI therapy—especially with imatinib—and the availability of routine hematological and molecular evaluations.

These results are consistent with global benchmarks. The IRIS trial, for instance, is a landmark study which showed that patients who received imatinib during the chronic phase of CML had an overall survival rate of about 85% after 8 years(73). More recent studies conducted in countries like Turkey and Brazil showed that patients with a good molecular

response and treatment adherence had 5–10-year survival rates of 90% to 96% (103, 104). The 95.3% survival rate in our cohort indicates that even with limited resources, Palestinian CML patients can achieve high-income country comparable outcomes when treatment guidelines are followed and there is proper access to TKIs. These findings highlight the importance of national healthcare programs in conjunction with international collaborations that provide essential drugs and molecular tests.

In this research, male participants showed greater frequencies of both Major Molecular Response (MMR) and Partial Molecular Response (PMR) in comparison to female participants. Nonetheless, the discrepancy lacked statistical significance, indicating that sex is not an isolated determinant of the clinical outcome in response to tyrosine kinase inhibitors (TKIs) therapy in chronic myeloid leukemia (CML).

Research published earlier aligns well with this study. For example, an Egyptian study found no significant association of gender with molecular response rates in CML patients receiving treatment with Imatinib(79). In addition, an Iraqi study also found that gender did not play a significant role in determining the molecular response, although male patients seemed to achieve somewhat better outcomes, likely due to earlier diagnosis or better treatment adherence(105).

Examination of the hematological response did not show any statistically significant differences by gender. While males comprised a slightly greater proportion of patients achieving complete hematologic response (CHR) with 58.6% males and 41.4% females, this association did not reach significance. These findings are consistent with a Pakistani cohort where gender did not notably impact hematologic outcomes (94). Overall, these findings highlight the more meaningful prognostic factors like disease phase at diagnosis, compliance to treatment, and molecular assessment as opposed to demographic characteristics such as gender in evaluating response to treatment in CML.

In our cohort, the assessment of treatment outcome differences relative to age showed no significant association of molecular and hematological responses with age. Those achieving Major Molecular Response (MMR) had an average age of 45.74 years, while patients with Partial Molecular Response (PMR) had an average age of 54.95 years which is older, but not significantly so. In parallel, the average age of patients who attained Complete Hematological Response (CHR) was comparable to those who did not achieve this level of response,

strengthening the notion that age was not a major factor impacting the probability of attaining hematologic remission.

These findings are consistent with multiple other studies around the world that report limited influence of age as a factor in treatment response for CML. For example, a German study found that although younger patients seemed to achieve molecular milestones sooner, age did not independently affect long-term outcomes or survival in patients treated with TKIs(106). Also, a study from Turkey found no significant relationship between age and achieving either MMR or CHR in CML patients treated with Imatinib(103). The lack of correlation between age and treatment response may partly result from the mechanism of action of TKIs which bluntly inhibit the BCR-ABL1 oncoprotein's functions, acting independently of a patient's age(107). Also, this strengthens the clinical recommendation that age is not a reason to modify treatment plans; adjustments should be made based on the disease phase, risk score, other health conditions, and therapy adherence (29). Still, the somewhat older average age of patients with PMR or those who have treated failed means those patients may need more detailed examination in larger prospective studies regarding the possible impact of aging on pharmacokinetics, comorbidity burden, or drug metabolism and adherence.

This study examined the association of baseline clinical symptoms with complete hematologic response (CHR) achievement in patients suffering from chronic myeloid leukemia (CML). This study along with some others also shows that these specific symptoms do indeed have some prognostic value as fever, splenomegaly, fatigue, bone pain, and even weight loss are shown to have significant correlation with of the metabolic outcomes.

Within our group, asymptomatic patients had a significantly higher rate of achieving Complete Hematologic Remission (CHR), 55.7%, versus symptomatic patients, who had a rate of 26.7% ($p = 0.041$). The symptomatic patients with fatigue and bone pain manifested lower remission rates of 45.7% compared to those without these symptoms, who had a much better rate of 80.0% ($p = 0.016$). Furthermore, weight loss was negatively associated with CHR: only 34.4% of those with CHR reported weight loss, while 73.3% of those without CHR had experienced it ($p = 0.050$). Fever as a factor was the most strongly associated, as it was noted that only 15.7% of febrile patients achieved CHR while 60.0% of afebrile patients ($p <0.001$) did. In addition, splenomegaly was noted in 80.0% of non-responders and only 30.0% of responders ($p <0.001$), which supports a strong association with poor hematologic

outcomes. Hepatomegaly and elevated WBC counts appeared more often in non-responders; however, these associations were not significant ($p = 0.070$ and $p = 0.240$, respectively)

Similar patterns have been observed in regional and international studies. Saudi Arabian research found splenomegaly, fatigue, and fever as common symptoms with splenomegaly being most associated to the disease burden and poor treatment results (108). An Indian study also noted fever and abdominal discomfort as common associations with elevated leukocyte counts and sluggish hematologic recovery (109). Ethiopians studies also reported fatigue, weight loss, and splenomegaly which were often linked with suboptimal hematologic responses (110). On a broader level, the United Kingdom and the United States data also incorporated the notion that greater symptom burden, particularly in advanced stages, correlates with low CHR rates. Systemic symptoms such as fatigue, weight loss, and organomegaly are believed to indicate more aggressive disease biology along with delayed hematologic recovery (111).

These emphasize the importance of symptom evaluation during diagnosis. Patients who are asymptomatic are more likely to have better outcomes, which might be attributed to earlier detection of the disease and lower overall burden of disease. On the other hand, systemic symptoms might suggest either an underdiagnosed condition or a more advanced stage of the disease, both of which may reduce the chances of achieving CHR.

The correlation between baseline clinical signs and symptoms with molecular response in patients with CML was analyzed with special attention to the epidemiology of Major Molecular Response (MMR), Partial Molecular Response (PMR), and whether treatment was successful or not in relation to patient symptoms.

Fatigue and bone pain were statistically significant on molecular outcomes ($p = 0.006$). Notably, only 38.9% of patients who attained MMR surveyed reported these symptoms compared to 68.8% in the PMR cohort and 80.0% in the treatment failure cohort. This is suggestive that greater symptom burden is associated with reduced likelihood of achieving optimal molecular response.

Weight loss also showed strong association on molecular response ($p = 0.007$), being present in only 29.6% of MMR patients but increasing to 73.3% among those who failed. This reinforces the systemic symptoms hypothesis in relation to more advanced, aggressive disease biology.

In the same way, fever at diagnosis was linked to the molecular outcomes significantly ($p < 0.001$), seen in 30% of MMR patients but rising to 45 % in those who did not respond to treatment. This suggests febrile symptoms may indicate more aggressive disease or greater leukemic burden.

Splenomegaly was markedly more frequent among non-responders, with therapy failing in 80.0% of patients with splenomegaly compared to only 22.2% of those achieving MMR ($p < 0.001$). This further strengthens its usefulness as a clinical marker of disease severity and a possible sign of resistance to TKI therapy.

On the other hand, hepatomegaly did not exhibit a significant association with molecular response ($p = 0.21$), thus having little value as a predictive factor. Furthermore, leukocytosis, although present in 64.6% of MMR patients, did not significantly correlate with molecular response ($p = 0.60$), suggesting that white blood cell count does not independently forecast therapeutic results.

Absence of symptoms at diagnosis, on the other hand, emerged as a favorable prognostic factor. As described, asymptomatic patients achieved MMR at much higher rates of 61.1% relative to those in PMR (37.5%) and failure (26.7%) groups ($p = 0.031$), illustrating the strong prognostic importance of symptom-free presentation

These findings align with broader regional studies. In a Turkish cohort, patients with systemic features like fever and weight loss were more likely to have inadequate molecular response, whereas asymptomatic individuals responded more favorably to TKIs (96). An Indian study similarly noted that splenomegaly along with constitutional symptoms predicted an incomplete or delayed molecular response(112). An Indian study similarly noted that splenomegaly along with constitutional symptoms predicted an incomplete or delayed molecular response(113). On a global scale, European cohort studies reinforce the concept that the symptom burden not only reflects the underlying disease biology but also correlates with the molecular response; screened patients, who were mostly asymptomatic, demonstrated significantly higher rates of MMR and enhanced progression-free survival compared to symptom-driven diagnosed patients(25, 28).

The explanation for these findings could be that the presence of clinical symptoms during diagnosis usually indicates greater disease progression and a more advanced stage of the illness. Symptoms which are systemic manifest as fatigue, weight loss, fever, and splenomegaly, and they are usually seen with increased hematopoiesis, inflammation, or

greater infiltration of the marrow which can adversely affect how well the treatment works. In addition, patients who are symptomatic with these clinical features may have longer diagnostic odysseys, which may adversely impact the likelihood of responding to treatment with tyrosine kinase inhibitors (TKIs). It has been noted that asymptomatic patients who are diagnosed are often through routine screening have been noted to achieve better molecular responses and overall longer lasting positive outcomes than symptomatic patients(114, 115). Therefore, symptom burden at diagnosis may serve as a valuable clinical predictor of therapeutic response and disease aggressiveness.

In our research, we found out that patients who met complete hematologic response (CHR) criteria had a lower median white blood cell (WBC) count at diagnosis (87.6 $\times 10^9$/L) compared to patients who did not achieve CHR (95.0 $\times 10^9$/L). It should be noted that this difference, while observable, was not statistically significant ($p = 0.064$). The same pattern was observed in the evaluation of molecular response groups; those who attained major molecular response (MMR) showed the lowest median WBC count (82.5 $\times 10^9$/L), followed by post-molecular responders (PMR) (90.7 $\times 10^9$/L), and those categorized as treatment failure (109.0 $\times 10^9$/L), demonstrating a trend approaching significance ($p = 0.061$).

These findings are consistent with Qin et al., who showed that newly diagnosed patients in the chronic phase of CML with WBC counts less than or equal to 150 $\times 10^9$/L at presentation had much better chances of achieving deep molecular remission (MR4.5) compared to patients with WBC counts exceeding 150 $\times 10^9$/L(116).

Similarly, a study conducted in Tanzania found that patients with higher mean WBC counts at diagnosis (277.6 ± 142.7 $\times 10^9$/L) were less likely to achieve optimal molecular responses compared to those with lower WBC counts (230.2 ± 110.7 $\times 10^9$/L).(117)

In contrast, a study from Pakistan found that although baseline WBC counts were correlated with EMR in univariate analysis, multivariate analysis identified only spleen size at diagnosis as a significant predictor of EMR. These findings indicate that while WBC count is significant, other clinical parameters can also independently influence prediction of treatment response(118).

In summary, the noted pattern of decreased median WBC counts in patients with more favorable treatment responses (hematologic and molecular) indicates that leukocyte burden may impact outcomes in CML. Elevated WBC counts at diagnosis may indicate a more advanced disease stage which is less responsive to TKIs(119). While our study did not

achieve statistically significant results, these conclusions are in alignment with prior findings and highlight the importance of more extensive, prospective research to confirm these relationships and enhance predictive frameworks for treatment response.

In our cohort, CHR patients had a median PLT count that was slightly elevated relative to non-CHR patients (269.5 $\times 10^9$/L versus 250.0 $\times 10^9$/L), but this difference lacked significance ($p = 0.657$). Likewise, within the molecular response subgroups, the highest median PLT count was in the MMR group (274.0 $\times 10^9$/L), then followed by treatment failure (250.0 $\times 10^9$/L) and PMR (190.7 $\times 10^9$/L), again without any significant differences ($p = 0.157$).

These results reinforce the findings of earlier works that although PLT counts in CML may be elevated due to greater megakaryocyte activity, they do not reliably anticipate the result of treatment. Akay et al. noted, for example, that the imatinib therapy did not markedly alter the abnormal PLT function during CML, inferring that PLT counts and functions do not appear to directly depend on the therapeutic intervention(120).

Looking at the HB values, we observed no significant differences for CHR and non-CHR patients (10.86 ± 2.12 g/dL vs 10.71 ± 1.49 g/dL; $p = 0.802$). Furthermore, among the molecular response groups, the MMR subgroup had the highest HB values (11.03 ± 2.17 g/dL) followed by those who had treatment failure (10.73 ± 1.48 g/dL) and PMR (10.41 ± 1.98 g/dL), with no significant differences ($p = 0.496$).

These outcomes align with research assessing anemia in patients with CML receiving long-term imatinib treatment, which reported that anemia persisted in a significant proportion of patients despite treatment, and that baseline HB levels were not predictive of treatment response (121).

Our study looked into the relationship between certain hematological parameters at the time of diagnosis, namely, platelet (PLT) counts and hemoglobin (HB) levels, and the outcomes of therapy in patients with chronic myeloid leukemia (CML). There were no statistically significant changes in PLT or HB levels in patients who attained complete hematologic response (CHR) or major molecular response (MMR) compared to those who did not. These results indicate that PLT and HB levels at diagnosis do not seem to be strong predictors for the response to treatment in CML.

The present study revealed a trend suggesting that younger patients with Chronic Myeloid Leukemia (CML) had higher one-year survival rates compared to older age groups, although

the association was not statistically significant (p = 0.089). Specifically, patients aged 18–29 and 30–44 years had a 100% survival rate, while survival declined to 97.0% among those aged 45–59, and further dropped to 85.0% in patients aged ≥60 years.

This age-related survival pattern is consistent with findings from Bower et al. (2013), who analyzed SEER data and reported a significant decline in survival with increasing age. The five-year survival rate was 82% among patients aged 15–39 years but dropped to 54% for those aged 65–69 years, indicating that age is a crucial prognostic factor in CML outcomes (122).

However, a UK-based study by Smith et al. (2016) suggested that socioeconomic disparities and access to treatment may explain part of the age-related survival gap. When patients had equal access to tyrosine kinase inhibitors (TKIs), the impact of age on survival was significantly reduced, suggesting that non-biological factors also play a critical role.(123).

This trend aligns with existing literature suggesting that advanced age is associated with poorer outcomes in CML, possibly due to comorbidities, reduced tolerance to tyrosine kinase inhibitors (TKIs), or delayed diagnosis. However, the lack of statistical significance in this study may be attributed to the small number of deaths (n=4) and limited sample size, which may have reduced the power to detect meaningful associations.

A statistically significant association was found between disease transformation and one-year survival status (p = 0.000), with the highest survival observed in patients without transformation (96.1%). Only one patient—who developed myelofibrosis—died within one year, while no deaths occurred among those who transformed to AML, ALL, or the accelerated phase during the study period.

These findings are partially aligned with previous studies. For instance, a study by Jain et al. reported that transformation to advanced phases, particularly blast crisis and myelofibrosis, significantly reduced overall survival among CML patients(124). Similarly, the study by Hehlmann et al. emphasized that progression to accelerated or blast phase strongly correlates with poor prognosis and limited response to tyrosine kinase inhibitors (TKIs).(125)

However, in our study, no deaths were reported in patients with transformation to AML, ALL, or accelerated phase. This contrasts with the aforementioned literature and may be explained by several contextual factors. Firstly, the number of transformation cases in this cohort was very limited, making statistical interpretation challenging. Secondly, some patients may have

died or been lost to follow-up after the first year, potentially underestimating mortality associated with these transformation types. Additionally, early detection of transformation and prompt switching to second-generation TKIs in Palestine may have contributed to temporarily preserving short-term survival in these cases.

From my perspective, the particularly high mortality in the patient with myelofibrosis may reflect the limited treatment options and poor response to TKIs in fibrotic transformation. Moreover, inadequate monitoring, delayed molecular testing, and limited access to bone marrow transplant in low-resource settings may further worsen outcomes in this group.

5.1 Conclusion

This study presents a comprehensive overview of the clinical, demographic, hematologic, and therapeutic characteristics of chronic myeloid leukemia (CML) patients in Palestine, offering valuable insight into the local disease profile and treatment landscape. The findings demonstrate a younger age of onset and a male predominance, with most patients diagnosed in the chronic phase. Hematologic and molecular features aligned closely with international patterns, and the high rates of Complete Hematologic Response (CHR), Major Molecular Response (MMR), and overall survival (95.3%) reflect the effectiveness and accessibility of first-generation tyrosine kinase inhibitors (TKIs), particularly imatinib.

Despite these favorable outcomes, several challenges persist. A substantial proportion of patients with advanced clinical symptoms—including fatigue, bone pain, fever, weight loss, and splenomegaly—exhibited suboptimal hematologic and molecular responses, underscoring the prognostic significance of clinical presentation at diagnosis. Conversely, asymptomatic cases were consistently associated with better treatment outcomes, reinforcing the value of early detection and routine screening. Importantly, while leukocytosis at diagnosis was inversely correlated with treatment success, hemoglobin and platelet counts showed limited predictive value. Age and gender did not demonstrate significant associations with response rates, although older age and disease transformation were linked to non-significant trends of reduced survival, indicating the need for more tailored age- and stage-specific management strategies.

Barriers such as delayed diagnosis, treatment interruptions, and limited access to molecular monitoring and second-line TKIs—especially in Gaza—were identified as key obstacles to optimal care. These findings highlight the urgent need for enhanced public health education,

uninterrupted access to TKIs, and routine molecular surveillance. Strengthening the national healthcare infrastructure and fostering international collaboration are crucial steps toward improving long-term outcomes for CML patients in Palestine and reducing disparities between resource-limited and high-income settings. Ultimately, these efforts are essential to ensure that CML continues to evolve into a manageable chronic condition for all affected

5.2 Limitations

It is important to recognize that the study has limitations. Because the sample was taken from only two hospitals in Nablus, Palestine, may limit the statistical power to detect subtle associations and decrease the applicability of the results to larger groups. The sample size was relatively small, as many patients had to be excluded due to missing or incomplete clinical and laboratory data in their medical records.

The lack of cytogenetic response assessment is a significant limitation because these tests are essential to evaluating the cytogenetic response. This represents a significant gap, as cytogenetic response is a key parameter in the diagnosis, monitoring, and prognostication of chronic myeloid leukemia (CML). Also, essential baseline data were missing which, in combination with the Sokal and EUTOS scores, hinders the ability to classify patients according to their risk profile.

Lastly, the evaluation of treatment outcomes was done three months post treatment. This time frame is too short to evaluate long-term adherence to therapy, relapse rates, resistance mechanisms, and recurrence.

5.3 Recommendations

Future research should strive to use bigger sample sizes and integrate data from several hospitals in various parts of Palestine in order to increase statistical power and the generalizability of findings. In order to enable comprehensive treatment response monitoring in accordance with international CML management guidelines, efforts should be made to establish access to cytogenetic analysis, including conventional karyotyping and fluorescence in situ hybridization (FISH). Strengthening diagnostic capacity is also crucial. Moreover, future research should focus on collecting comprehensive baseline data to allow for risk stratification using established scoring systems such as the Sokal, Hasford, and EUTOS

scores, which are crucial for guiding personalized treatment decisions and estimating prognosis.

Extended follow-up periods are recommended to assess the durability of treatment responses, monitor major molecular remission (MMR), identify TKI resistance, and detect relapse. Additionally, studies should incorporate evaluations of medication adherence, quality of life, and treatment-related adverse events to provide a more holistic understanding of therapeutic outcomes. Investigating genetic mutations, particularly ABL1 kinase domain mutations, is also vital to elucidate mechanisms of resistance and optimize therapeutic strategies. Lastly, future analyses should account for key confounding variables, including comorbidities, socioeconomic status, and treatment adherence, which may significantly influence patient outcomes.

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Appendices

Appendix A: Institutional Review Boards (IRP) of Arab American University.

Arab American University
Institutional Review Board - Ramallah

الجامعة العربية الأمريكية
مجلس اخلاقيات البحث العلمي – رام الله

IRB Approval Letter

Study Title: "Unveiling Current Trends in Clinical Features and Assessing Induction Outcomes in Chronic Myeloid Leukemia (CML): A Multicentre Retrospective Analysis in Palestine"

Submitted by: Bashar Rawhi Ibrahim Abu Hoos

Date received:	15th 2024	February
Date reviewed:	15 th 2024	February
Date approved:	15th 2024	February

Your Study titled "Unveiling Current Trends in Clinical Features and Assessing Induction Outcomes in Chronic Myeloid Leukemia (CML): A Multicentre Retrospective Analysis in Palestine" with the code number "R-2024/A/31/N" was reviewed by the Arab American University Institutional Review Board - Ramallah and it was approved on the 15th of February 2024.

Sajed Ghawadra, PhD

IRB-R Chairman

Arab American University of Palestine

الجامعة العربية الأمريكية - فلسطين
مجلس اخلاقيات البحث العلمي - رام الله
IRB-R
ARAB AMERICAN UNIVERSITY-PALESTINE
INSTITUTIONAL REVIEW BOARD - RAMALLAH

General Conditions:

1. Valid for 6 months from the date of approval.
2. It is important to inform the IRB-R with any modification of the approved study protocol.
3. The Bord appreciates a copy of the research when accomplished.

Tel: 02-294-1999 E-Email: IRB-R@aaup.edu Website: www.aaup.edu

Appendix B: Institutional Review Boards (IRP) from Palestinian Ministry of Health.

State of Palestine
Ministry of Health
Education in Health and Scientific Research Unit

دولة فلسطين
وزارة الصحة
وحدة التعليم الصحي
والبحث العلمي

الرقم: ٢٠٢٤/٤١٥/٢٢٦
التاريخ: ٢٠٢٤/٣/١٤

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عطوفة الوكيل المساعد لشؤون المستشفيات والطوارئ المحترم،،،

الاخت ق. أ. مدير عام الادارة العامة لتكنولوجيا المعلومات المحترمة،،،

تحية واحترام،،،

الموضـــوع: تسهيل مهمة بحث

بشار روحي ابراهيم ابو الهوس – برنامج ماجستير برنامج علم الدم والمناعة / الجامعة العربية الامريكية، وباشراف د. صبا شنك في عمل بحث بعنوان:

Unveiling Current Trends in Clinical Features and Assessing Induction Outcomes in Myeloid Leukemia (CML): A Multicenter Retrospective Analysis in Palestine

خلال السماح بجمع معلومات عن مراجعة ملفات المرضى، وذلك في – **المستشفى الوطني**

ان يتم الالتزام باساليب واخلاقيات البحث العلمي، وعد التعرض للمعلومات التعريفية للمرضى .
على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة الوزارة على نتائج البحث.

مع الاحترام،،،

د. عبدالله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي

نسخة عميد الدراسات العليا المحترمة –الجامعة العربية الامريكية

Telfax.:09-2333901 scientificresearch.dep@gmail.com 09-2333901

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Appendix C: Institutional Review Boards (IRP) from clinical research center of NNUH

مركز البحث العلمي السريري
Clinical Research Centre

Approval date: 2024-03-27
Ref: CRC_2024_0255

Subject: Approval to conduct a research project at An-Najah National

University Hospital

Dear Mr. bashar abu hoos,

I am writing this letter to grant you permission to conduct your research project titled "Unveiling Current Trends in Clinical Features and Assessing Induction Outcomes in Chronic Myeloid Leukemia (CML): A Multicenter Retrospective Analysis in Palestine"". I hope your study will provide new insights and contribute the advancement of knowledge and evidence. Furthermore, I would like to emphasize the importance of adhering to the ethical guidelines set forth by the hospital throughout the research process.

On behalf of An-Najah National University Hospital, I extend my best wishes and support for your research endeavors. Sincerely,
Sa'ed H. Zyoud, Ph.D.
Clinical Toxicology
Director of Clinical Research Center
CC:
Chief Medical Officer
Chief Nursing Officer
Note: this approval letter is not valid unless signed and stamped by the CRC and the Chief Medical Officer of An-Najah National University Hospital

الكشف عن الاتجاهات الحالية في السمات السريريةوتقييم نتائج العلاج في سرطان الدم النخاعي المزمن: تحليل بأثر رجعي متعدد المراكز في فلسطين.

بشار روحي ابو الهوس

د. صبا شنك

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ملخص

الخلفية:

ابيضاض الدم النقوي المزمن (CML) هو أحد أنواع سرطانات الدم، يتميز بوجود طفرة جينية تُعرف بجين الاندماج BCR–ABL1 الناتج عن انتقال صبغي يُعرف بـ "صبغي فيلادلفيا". على الرغم من التقدم الكبير عالميًا في علاج هذا المرض باستخدام مثبطات التيروزين كيناز(TKIs) ، إلا أن هناك نقصًا واضحًا في البيانات المتعلقة بالسمات السريرية والاستجابة العلاجية لدى المرضى الفلسطينيين المصابين بالمرض.

الهدف:

هدفت هذه الدراسة إلى تحليل السمات السريرية، واستجابات العلاج التحريضي، والعوامل التنبؤية المرتبطة بنتائج العلاج لدى مرضى CML في فلسطين.

المنهجية:

أُجريت دراسة استعادية متعددة المراكز على 85 مريضًا تم تشخيصهم بـ CML وتلقوا العلاج ما بين عامي 2018 و2023 في مستشفى النجاح الوطني الجامعي ومستشفى الوطني في مدينة نابلس. تم جمع البيانات السريرية والمخبرية والعلاجية من السجلات الطبية الإلكترونية. تم تقييم الاستجابة للعلاج استنادًا إلى معايير الشبكة الأوروبية لسرطانات الدم(ELN 2020) ، باستخدام برنامج SPSS الإصدار 21 للتحليل الإحصائي.

النتائج:

بلغ متوسط عمر المرضى 47.6 عامًا، وكانت نسبة الذكور إلى الإناث 1.24:1. أكثر الأعراض شيوعًا عند التشخيص كانت التعب وآلام العظام (51.8%)، فقدان الوزن (41.2%) وتضخم الطحال (38.8%). تم تشخيص معظم المرضى (95.3%) خلال المرحلة المزمنة للمرض. أظهر 82.4% من المرضى استجابة دموية كاملة(CHR) ، بينما حقق 58.8% استجابة جزيئية كبيرة .(MMR) وُجدت علاقة معنوية بين الأعراض مثل الحمى، فقدان الوزن، وتضخم الطحال وبين ضعف الاستجابة للعلاج

($p < 0.05$)، في حين لم يكن للعمر أو الجنس أو المؤشرات الدموية الأساسية تأثير معنوي على الاستجابة

الاستنتاج:

يتسم مرض CML في فلسطين بكونه يُشخّص في سنٍ مبكر نسبيًا، مع انتشار أكبر بين الذكور، وغالبًا ما يتم اكتشافه خلال المرحلة المزمنة. معظم المرضى يستجيبون جيدًا للعلاج بمثبطات التيروزين كيناز. إلا أن وجود أعراض مثل الحمى، فقدان الوزن، وتضخم الطحال عند التشخيص، يرتبط بسوء الاستجابة، مما يؤكد أهمية الكشف المبكر ووضع خطط علاجية مخصصة لكل مريض.

الكلمات المفتاحية : اللوكيميا النقوية المزمنة، فلسطين، مثبطات التيروزين كيناز، الاستجابة الدموية، الاستجابة الجزيئية.