Arab American University
Faculty of Graduate Studies
Department of Health Sciences
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Molecular and Cytogenetic Abnormalities in Acute Myeloid Leukemia Patients, a Retrospective, Single-Center Study from the West Bank, Palestine.

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Thesis Approval

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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

This thesis is dedicated to my parents, my wonderful wife Eman Amer, and my daughter "Taleen", who have been a constant source of inspiration for me. This endeavor would not have been feasible without their love and support.

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Abstract

Background: Acute myeloid leukaemia (AML) is a blood cancer characterized by the uncontrolled growth of myeloid progenitor cells. The outlook and treatment strategies for AML patients depend heavily on specific molecular and cytogenetic alterations. These genetic profiles help determine cancer categorization, difficult assessment and treatment options, and outcomes for people with AML.

Aims: In a retrospective study, we aimed to determine the molecular and cytogenetic profiles in acute myeloid leukemia patients during the last 7 years at An-Najah National University Hospital.

Method: Electronic medical records of adult and pediatric acute myeloid leukemia patients were reviewed from the period of 2018 to 2024 at the oncology department of An-Najah National University Hospital, Nablus, Palestine. Data were analyzed using IBM Statistical Package for Social Science (SPSS) for Windows v.21

Results: A total of 170 patients with AML were included in the study. The age range of patients in our study was 1–79 years old, with a median age of 36 years. 41.2% of the patients showed clonal cytogenetic anomalies, with 58.8% of the patients having normal karyotypes. The most frequently found structural anomaly was t(15;17), while the most frequently and only seen numerical abnormality was monosomy 7. 59.4% of patients fell into the intermediate-risk group according to cytogenetic risk classification. Regarding molecular findings among the patients, 10.6% harbored FLT3-ITD mutations, 4.1% had FLT3-TKD mutations, and 10.6% carried NPM1 mutations.

Conclusion: The study highlights that the intermediate-risk category was most common, with normal karyotypes being the most frequent. t(15;17), t(8;21), and inv(16) were the most frequent structural abnormalities; Older patients tended to show intermediate cytogenetic features. Platelet counts varied significantly across cytogenetic groups, indicating a prognostic marker. Cytogenetic and molecular patterns in our area displayed similarities and differences when analyzed against other populations.

Keywords: Acute Myeloid Leukemia, Karyotyping, Cytogenetics, Palestine

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List of Definitions of Abbreviations

Abbreviations	Title
ALL	Acute Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
APL	Acute Promyelocytic Leukemia
BM	Bone Marrow
CBC	Complete Blood Count
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
DIC	Disseminated Intravascular Coagulation
DNA	Deoxyribonucleic Acid
del	Deletion
ELN	European Leukemia Net
FAB	French-American-British
FLT3	Fms-like tyrosine kinase 3
FLT3-ITD	Internal Tandem Duplication
FLT3-TKD	Tyrosine Kinase Domain
inv	Inversion
FC	Flow Cytometry
FISH	Fluorescence In Situ Hybridization

HSCs	Hematopoietic Stem Cells
HSCT	Hematopoietic Stem Cell Transplantation
IHC	Immunohistochemistry
HB	Hemoglobin
inv	Inversion
MDS	Myelodysplastic Syndromes
MOH	Ministry of Health
MPO	Myeloperoxidase
MRD	Minimal Residual Disease
NPM1	Nucleophosmin 1
NNUH	An-Najah National University Hospital
Ml	Microliter
PCR	Polymerase Chain Reaction
PLT	Platelet count
RBC	Red Blood Cell
T	Translocation
WBC	White Blood Cell
SD	Standard Deviation
SNPs	Single Nucleotide Polymorphisms
WHO	World Health Organization https://dndi.org/viewpoints/2021/who-2030-ntds-roadmap-how-science-and-partnerships-can-support-fight-end-neglected-diseases/

Chapter One: Introduction

1.1 Background

Leukemia is a heterogeneous group of hematological malignancies characterized by the clonal proliferation of immature hematopoietic cells in the bone marrow and peripheral blood. This disease has several types, including a group of blood cancers known as Acute Myeloid Leukemia (AML), which is considered one of the most aggressive forms. Clones proliferate in an unregulated manner and fail to differentiate into fully mature, functional cells. AML is the primary cancer in adults, but it can also be found in children. AML appears in 80% of the cases of acute leukemia in adults and is a source of significant challenge in clinical practice due to fast progression and the lack of a same therapeutic effect on all (Short, Rytting, & Cortes, 2018). The pathogenesis of acute myeloid leukemia (AML) is complex, involving a constellation of genetic and cytogenetic aberrations that disrupt normal hematopoiesis. The majority of the AML-related genetic alterations are caused by chromosomal translocations, deletions, and inversions that also become the major diagnostic and prognostic parameters. Specific chromosomal translocations, including t(8;21), inv(16), and t(15;17), represent critical genetic alterations in acute myeloid leukemia (AML) and are integral to risk stratification models and subtype classification. On the other hand, unfavorable karyotypes detected as loss of chromosome 7 or complex abnormalities correlate with poor outcomes (Lagunas-Rangel, Chávez-Valencia, Gómez-Guijosa, & Cortes-Penagos, 2017). Recently, AML classification and prognostication have been further fueled by molecular genetic profiling. Mutations in FLT3, NPM1, CEBPA, and IDH1/2 genes present evidence of being determinants of disease biology, treatment response, and survival. FLT3-ITD mutations are associated with a high relapse rate and poor prognosis, whereas NPM1 mutations may indicate a favorable prognosis, particularly in the absence of FLT3-ITD (Khwaja et al., 2016). The 2016 and 2022 updates to the WHO classification of AML, along with the ELN guidelines, emphasize the critical role of cytogenetic and molecular features in defining AML subgroups. These classifications are essential for guiding treatment decisions and selecting patients for targeted therapies. Consequently, a comprehensive understanding of the cytogenetic and molecular landscape of AML is vital for accurate diagnosis, risk stratification, and the advancement of precision medicine in leukemia care.(Attardi et al., 2023).

1.2 Statement of the Problem

Acute myeloid leukemia (AML) is a highly diverse hematological malignancy distinguished by various cytogenetic and molecular irregularities that significantly influence the progression of the disease and the effectiveness of treatments. Despite extensive global research on AML, there is limited knowledge regarding the prevalence and clinical implications of these cytogenetic and molecular irregularities among AML patients in the West Bank, Palestine. In light of this gap, the current study aims to explore the range of molecular and cytogenetic abnormalities in AML patients receiving treatment at a tertiary referral center in Palestine.

1.3 Significance of the Study

To the best of our knowledge, this is the first study in Palestine to comprehensively examine both molecular and cytogenetic abnormalities in patients with acute myeloid leukemia.

A thorough understanding of the diverse molecular and cytogenetic abnormalities in AML patients enables accurate analysis and robust risk assessment. This knowledge serves as a valuable resource for clinicians in developing personalized treatment strategies tailored to each patient's genetic profile, thereby enhancing therapeutic outcomes and avoiding unnecessary interventions. By identifying the predominant cytogenetic and molecular abnormalities, this study will aid in resource allocation and healthcare planning for AML patients in the West Bank. Insights into the genetic landscape of AML will also guide the procurement of diagnostic tools, targeted therapies, and essential supportive care services, thereby optimizing patient management in the region. Furthermore, characterizing the molecular and cytogenetic abnormalities in AML patients can help in detecting subgroups most likely to benefit from novel targeted therapies or experimental interventions. This information can also guide the design and execution of clinical trials that evaluate emerging treatment modalities, thereby expanding therapeutic options for AML patients in the region.

1.4 Aim and Objectives

1.4.1 Aims: This study aims to identify and characterize the spectrum of cytogenetic abnormalities—such as translocations, deletions, and duplications—in patients with acute myeloid leukemia (AML) treated at An-Najah National University Hospital's hematology-oncology center over the past seven years. Additionally, it seeks to investigate the prevalence of common molecular mutations associated with AML, including FLT3 and NPM1. The findings will be compared with international data to contextualize the genetic profile of AML patients in Palestine within the global landscape.

1.4.2 Objectives:

1. To assess the frequency and categories of cytogenetic anomalies in AML patients, including both normal and abnormal karyotypes.
2. To evaluate the prevalence of molecular mutations, including FLT3-ITD, FLT3-TKD, and NPM1.
3. To assess the association between cytogenetic risk groups and demographic and clinical data, such as age, gender, white blood cell count, hemoglobin levels, platelet count, and absolute neutrophil count.
4. To assess the correlation between age, gender, and FAB subtypes.
5. To categorize AML cases based on cytogenetic risk categories following the latest WHO and ELN guidelines.

1.5 Study hypotheses

Hypothesis I

H0: There is no association between age, gender, and cytogenetic findings in AML patients.

H1: There is an association between age, gender, and cytogenetic findings in AML patients.

Hypothesis II

H0: There is no correlation between hematological findings and cytogenetic findings in AML patients.

H1: There is a correlation between hematological findings and cytogenetic findings in AML patients.

1.6 Conceptual Definitions

1. **Anemic manifestations: -** are the clinical signs and symptoms of anemia, a disorder characterized by a decrease in hemoglobin or RBCs, resulting in insufficient oxygen delivery to tissues. Some symptoms are fatigue, weakness, malaise, dyspnea, and pallor or yellowish discoloration of the skin and dizziness
2. **Cytogenetic risk stratification**: - is an approach that allows for prognostication and therapeutic decisions by grouping individuals depending on their chromosomal abnormalities. This aids in identifying patients who have different characteristics of the disease, such as having more aggressive disease evolution or a higher likelihood of relapsing. Indeed, it helps guide treatment decisions.

Chapter Two: Literature Review

2.1 Leukemia

Leukemia is a hematological malignancy caused by neoplastic growth of myeloid or lymphoid cells. The name is composed of 'leuk/o', which literally means "white" and refers to the neoplastic proliferation of white blood cells. In leukemia, leukocytosis is persistent and gradually increases without any apparent explanation (Bain, 2017). Bone marrow stem cells are either pluripotent or primitive stem cells. This means that they have the potential to mutate and promote the development of leukemia. They are characterized by an abnormal production of leukemic cells and a reduction in the production of normal red and white blood cells and platelets. The presence of these mutated cells and the disturbed hematopoiesis mechanism could lead to the leukemic cells spreading into the peripheral blood and spreading to certain tissues such as the spleen, kidneys, lymph nodes and possibly the central nervous system. Leukemic cells exhibit unusual morphological, cytogenetic and immunophenotypic features that help determine the respective leukemia category (Bain, 2017).

Leukemia ranks as the fifteenth frequently occurring malignancy globally where 437,033 fresh instances of leukemia are identified in 2.4 percent of all freshly diagnosed malignancies annually (Tebbi, 2021). Half of all the leukemia cases are found in chronic lymphocytic leukemia (CLL), 20 percent in CML and another 20 percent in AML (Bray et al., 2018). The Palestinian Health Information Centre in 2018 introduces leukemia as the fourth most prevalent malignancy in Palestine constituting 6.7 % and an average rate of 7.9 per 100,000 citizens (WHO, 2019).

The world average survival rate after 5-year treatment stands at 20 percent of all combined cases of leukemia. In developed countries there is an estimate of 31 percent survival after 5 years and in developing countries there is also an estimate of 15 percent. This is because in the developing countries, there is a shortage of access to high-tech treatments. In 2018, the World Health Organization estimates that there have been 309 006 deaths (3.2 percent) due to all types of leukemia (Bray et al., 2018).

2.2 Classification of leukemia

The European Association for Hematopathology has collaborated with the WHO to publish a new classification system of the hematopoietic and lymphoid neoplasms. Their proposed classification of hematopoietic and lymphoid neoplasms gives consideration to characteristics of the disease in terms of immunophenotype, genetics, epigenetics, and clinical manifestations

along with the morphological characteristics. Recently, the WHO has embraced the REAL classification of Lymphoid neoplasms as Revised European-American Lymphoma.

WHO classification of myeloid neoplasms incorporates many of the French-American-British (FAB) and Cooperative Group and the Polycythemia Vera Study Group classifications of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) and of chronic myeloproliferative neoplasms (CMPNs), respectively (Ahmed, Yigit, Isik, & Alpkocak, 2019).

2.3 Acute myeloid leukemia

AML is a kind of leukemia disease impacting the haemopoietic stem cells and characterized with clonal advancement of the inappropriately myeloid cells (Short et al., 2018). Some of the impacts of this exertion of inappropriate myeloid cells are the maturity of immature progenitor cells, the myeloblasts, as they appear in the bone marrow and the circulation. Red blood cells, platelets and white blood cells are common myeloid progenitor cells (Khwaja et al., 2016).

More than 30 years ago, genomic aberration was found and used to create the foundation of acute myeloid leukemia pathophysiology as well as cytogenetic abnormality. The abnormalities in cytogenetics have become the formed prognostic and diagnostic marker. In the past 15 years, there has been a growth of knowledge in molecular heterogeneity in relation to AML as a result of the improved microarray and next-generation sequencing-based "-omics" technologies (Bullinger, Döhner, & Döhner, 2017). Acute leukaemia mostly occurs in AML, which is the most prevalent in adults and is 3-4 times more prevalent among adults as compared to ALL (Khwaja et al., 2016).

2.4 Physiopathology of AML

AML occurs when hematopoietic precursors undergo clonal transformation as a result of chromosomal rearrangements and numerous gene alterations (Jeffrey E. Rubnitz, Gibson, & Smith, 2010). These changes promote growth and survival while preventing hematopoietic differentiation (Kelly & Gilliland, 2002). This approach is in line with the two-hit model of Gilliland, who claimed in 2001 that AML is caused by a combination of two types of mutations: Class I mutations, which promote proliferation and survival, and Class II mutations, which affect cell differentiation and death. However, recent studies using improved sequencing technology have identified mutations that do not fit into these categories and mostly cause epigenetic changes and therefore cannot yet be categorised in the model (S.-J. Chen, Shen, & Chen, 2013; Kelly & Gilliland, 2002; Takahashi, 2011).

Some of the most significant factors of AML include exposure to high-dose radiations, chronic exposure to benzene (> 40 ppm-years), chronic tobacco smoking and exposure to some disparities of chemotherapies (especially alkylating agents, and topoisomerase II inhibitors). All these exogenous factors lead to DNA damage, mostly using oxidation mechanisms (Hiraku & Kawanishi, 1996; Iliakis, Wang, Guan, & Wang, 2003; Pfeifer et al., 2002). Disease is another risk of obesity which is a concern of the body. There are no known specific links between obesity and AML, although they include hyperinsulinemia, insulin resistance, elevated levels of leptin, reduced levels of adiponectin and shorter telomeres that have been observed in affected patients (Estey et al., 1997; Lichtman, 2010). Conversely, secondary AML may arise when other clonal diseases in hematopoietic stem cells (HSCs) advance rendering them genetically unstable and attaining new mutations (Lagunas-Rangel et al., 2017).

This type of blood cell overproduction is used to distinguish the most significant ones: myeloproliferative neoplasms (MPN), which are characterized by overproduction of one or more types of blood cells, and myelodysplastic syndromes (MDS) with its maturation issues related to ineffective hematopoietic processes (Abbas, Aster, Cotran, Kumar, & Robbins, 2015). MPNs are often triggered by tyrosine kinase mutations, leading to continuous activation without ligands or alterations in downstream signaling, and are categorized as class I mutations. MDS, in contrast, is characterized by irregularities in crucial transcription factors necessary for normal hematopoietic differentiation and apoptotic regulators, akin to class II mutations (Kelly & Gilliland, 2002). Both conditions experience an initial impact, making them susceptible to AML formation upon acquiring a second mutation. Additionally, some inherited disorders, including deficiencies in DNA repair (e.g., Fanconi anemia), genetic tendencies for secondary mutations (e.g., familial platelet syndrome), flaws in tumor suppressors (e.g., dyskeratosis congenita), and unidentified mechanisms (e.g., ataxia-pancytopenia), elevate the risk of AML (Lichtman & Williams, 2006).

2.5 Classification of AML

The two currently most widely used AML classification systems are the WHO classification system, which is the more modern approach, and the Franco-American-British classification system, which is the most commonly used method.

2.5.1 The French-American-British (FAB) classification of AML

The FAB classification system for acute leukemia was introduced in the 1970s and was based on

a morphological assessment of lymphoblasts and myeloblasts using cytochemical staining techniques (Arber et al., 2017).

Table 2.1 indicates that the existence of immature leukocytes is a defining characteristic of AML subtypes M0 to M5.In contrast, AML subtypes M6 and M7 are limited to immature progenitor cells that develop into red blood cells and platelets, respectively ((ACS), 2018).

Table 2.1: FAB classification of AML

M0	Undifferentiated AML
M1	AML with minimal maturation
M2	AML with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M4a	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Pure erythroid leukemia
M7	Acute megakaryoblast leukemia

2.5.2 The World Health Organization (WHO) classification of AML

Hematologists and pathologists now rely on immunophenotyping, the identification of chromosomal abnormalities, and genetic anomalies observed in patients to achieve a more accurate classification of leukemia. These disorders can be linked to oncogenes, tumor suppressor genes, and various other genes that regulate essential processes such as cell division, maturation, and apoptosis (H, 1974).

The 2017 fourth revised edition of the WHO classification categorizes acute myeloid leukemia (AML) into six distinct groups: (1) AML characterized by recurrent genetic abnormalities, (2) AML linked to myelodysplasia-related changes (MRC), (3) therapy-related myeloid neoplasms (t-MN), (4) AML not otherwise specified (NOS), (5) myeloid sarcomas, and (6) myeloid proliferations associated with Down syndrome (DS) (refer to Table 2.2) (Hwang, 2020).

Table 2.2: Classification of myeloid neoplasms and acute leukemia by the World Health Organization (WHO)

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22q22.1); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3
AML with t(6;9)(p23;q34.1); DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutation of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified (NOS)
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

2.6 Clinical presentation of AML

The symptoms associated with Acute Myeloid Leukemia (AML) primarily stem from pancytopenia and the increase of blast cells, with the key leukemia symptoms illustrated in Figure 2.1. Significant indicators of leukemia, including splenomegaly and hepatomegaly, result from the infiltration of leukemic blasts into normal organs. Organomegaly is observed in nearly 50% of individuals diagnosed with AML. Fever is a prevalent symptom, often appearing as the first sign in 15-20% of cases. Weight loss is relatively rare. Skin infiltration may occur due to the involvement of extramedullary sites, such as the gums. Clinical manifestations affecting the central nervous system (CNS) have been noted in 20% of AML patients, with identifiable leukemic blast cells present in the cerebrospinal fluid. Symptoms related to the CNS may include persistent headaches, changes in mental status, visual disturbances, excessive drowsiness, neurological deficits, as well as symptoms resulting from CNS bleeding and spinal cord compression. Nonetheless, some patients may exhibit asymptomatic CNS involvement (Tamamyan et al., 2017).

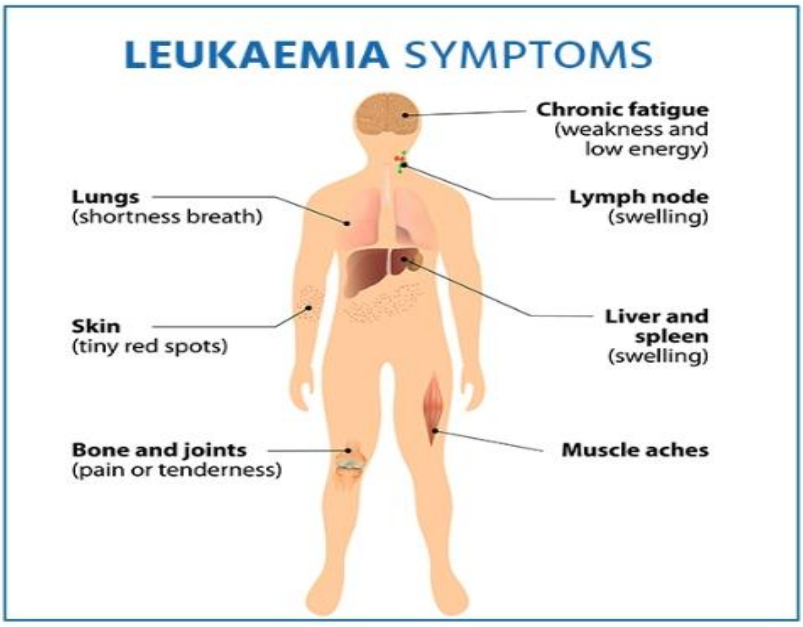

Figure 2.1: Symptoms of leukemia

https://www.medicoverhospitals.in/diseases/leukaemia/

2.7 Laboratory evaluation

2.7.1 Blood findings

In a patient diagnosed with acute myeloid leukemia (AML), a complete blood count (CBC) reveals alterations in the levels of red blood cells (RBC), white blood cells (WBC), and platelets. It is common to observe thrombocytopenia and anemia, while the white blood cell count may vary, appearing elevated, within normal limits, or decreased(Khwaja et al., 2016).

Blood film: Several datasets containing microscopic blood counts have been utilized for the diagnosis of leukemia (Ahmed et al., 2019). The presence of over 20% myeloblasts in a thin blood sample can confirm a diagnosis of acute myeloid leukemia (AML); however, a lower percentage does not exclude the possibility of this diagnosis (Khwaja et al., 2016). Figure 2.2 illustrates the various blood counts associated with the French-American-British (FAB) classification of acute myeloblastic leukemia.

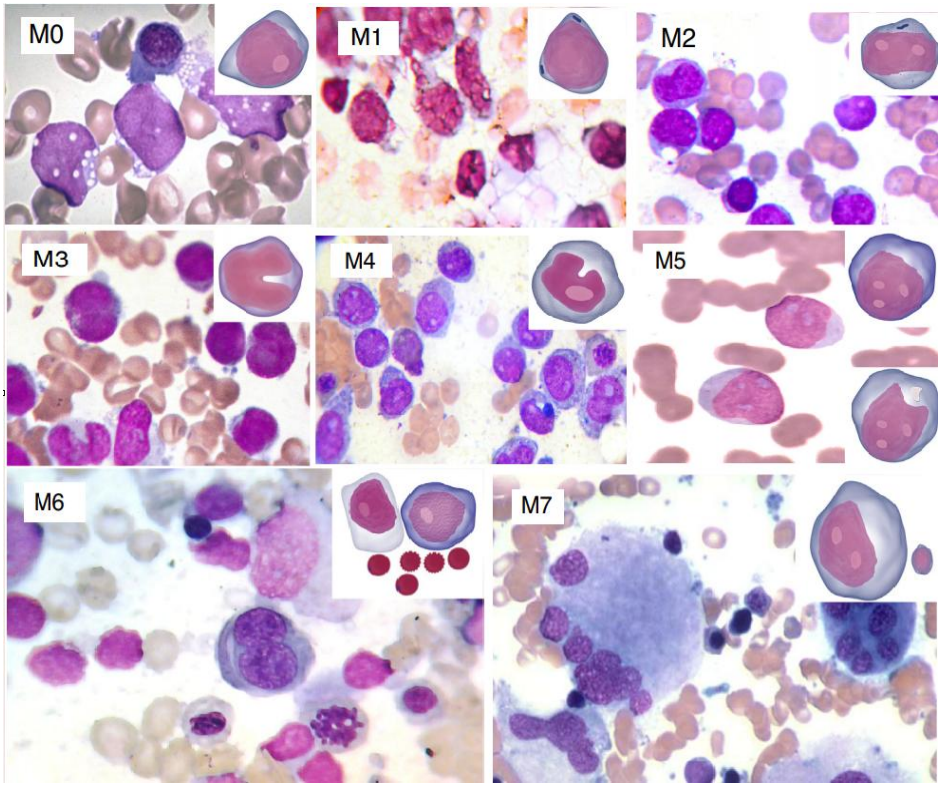

Figure 2.2: The different blood images for French-American-British (FAB) classification of acute myeloblastic leukemia (Ladines-Castro et al., 2016).

2.7.2 Bone marrow aspiration

A bone marrow smear is a crucial procedure for enabling molecular and cytogenetic assessments. Under low magnification, one can observe an increase of 10 to 20 times in infiltrated bone marrow containing myeloblasts. Additionally, Auer rods—red, needle-like structures located in the cytoplasm of myeloblasts—are also present in myelodysplastic syndromes (MDS). Other neoplastic cells can be identified based on their distinct morphologies, which include abnormal promyelocytes, neoplastic monoblasts, promonocytes, and atypical megakaryoblasts. The expression of myeloperoxidase (MPO) is used to differentiate between leukemic and normal myeloblasts, as leukemic myeloblasts generally show positive MPO enzyme expression. Furthermore, the monocytic lineage can be differentiated from lymphoid and other myeloid lineages by the presence of α-naphthyl acetate esterase, which is characteristic of monocytes (Khwaja et al., 2016).

2.7.3 Immunophenotyping by Flow Cytometric Analysis

The process of immunophenotyping via flow cytometric analysis serves as an essential tool for the diagnosis and classification of acute myeloid leukemia (AML). It facilitates the detection of blast cells, the assignment of their lineage, and the immunophenotypic profiling that differentiates abnormal blast populations from healthy progenitor cells.

A fundamental strategy for identifying blasts involves the combination of CD45 expression with side scatter (SSC) gating, which is based on the expression levels of both CD45 and SSC across various hematopoietic lineages. This technique allows for the accurate identification of mature lymphocytes, monocytes, developing granulocytes, myeloid progenitor cells, and lymphoid progenitor cells (X. Chen & Cherian, 2017). Figure 2.3 summarizes the cell markers involved in each stage of AML.

Possible FC weaknesses in gating analysis, cell lysis, and preservation of cells may result in a wrong count for blasts. FC may also be ineffective when the aspirate yield is low due to marrow fibrosis and requires IHC staining.

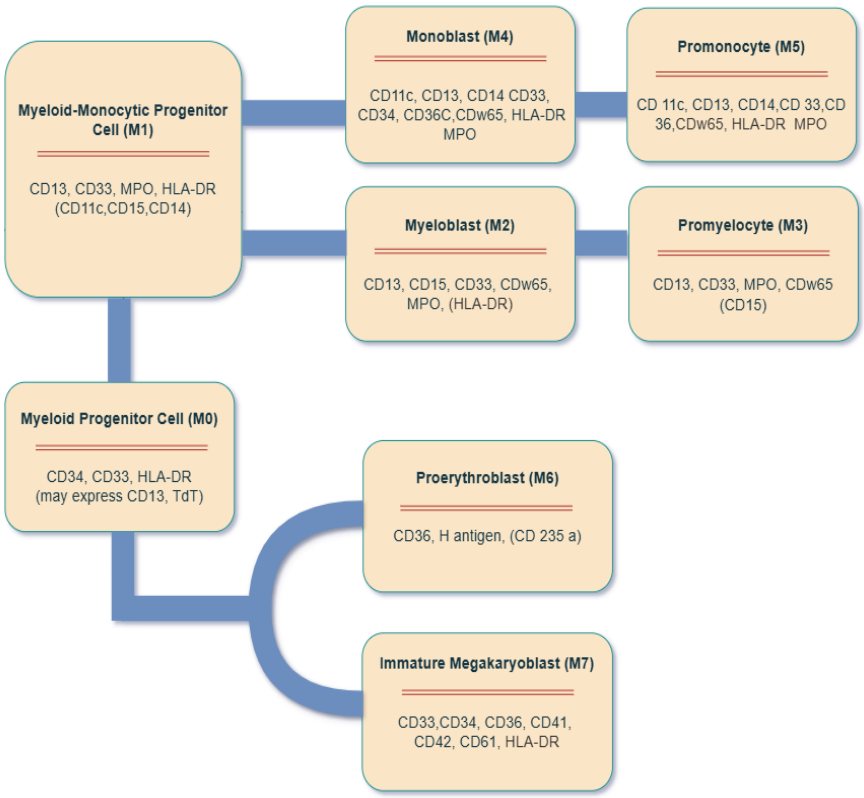

Figure 2.3: Illustrative diagram of myeloid development that includes the related acute leukemia types and the cell markers associated with each phase (Plesa et al., 2006).

2.7.4 Immunohistochemistry (IHC)

IHC investigations, typically conducted on bone marrow biopsy samples, serve as either a supplementary or alternative method for immunophenotyping and assessing the count of blast cells, particularly when bone marrow aspirates are either unavailable or deemed inadequate. CD34 is the most frequently utilized IHC stain for identifying myeloblasts and quantifying blasts. Certain subtypes of acute myeloid leukemia (AML) may present with CD34-negative blasts; in instances of significant fibrosis, IHC stains targeting different markers can be employed to assess blast counts. In these scenarios, the relative proportions of various cell lineages can be evaluated using an IHC panel that encompasses CD117, CD33, CD71, MPO, CD61, and CD34. Furthermore, IHC testing for specific proteins can act as an auxiliary method to detect underlying mutations. For instance, research has indicated that leukemic cells harboring NPM1 mutations exhibit an abnormal pattern of cytoplasmic expression of NPM1 (Narayanan & Weinberg, 2020).

2.7.5 Genetic finding

2.7.5.1 Chromosomal abnormalities

The early evidences of genetic nature of acute myeloid leukemia (AML) were observed in cytogenetic research, which demonstrated different cytogenetic aberrations, such as translocations, deletions, insertion, inversions, monosomes, trisomies, polyploidy, and other defects. According to the World Health Organization (WHO) classification, the presence of one or more cytogenetic abnormalities is frequently observed in AML patients (considering the overall risk to prognosis), that is, around 55 percent of the patient body (Plesa et al., 2006).

The cytogenetic data in the literature allow to sort AML patients into three groups of favorable, moderate, and unfavorable prognosis. As a rule, t(8;21)(q22;q22) [RUNX1/RUNX1T1], inv(16)(p13q22) [CBFB/MYH11], and t(15;17) (q24;q21) [PML/RARA] constitute particularly favorable prognosis because they are characterized by high rates of treatment response and complete remissions. Conversely, an intermediate prognosis is observed in patients who have t(9;11)(p22;q23) [MLLT3/MLL] change. The cytogenetically abnormal individuals, such as t(6;9)(p23;q34) [DEK/NUP214], inv(3)(q21q26) [RPN1/EVI1], and t(1;22)(p13;q13) [RBM15/MKL1], are subject to classification as a poor prognosis because the treatment may not yield sufficient responses to the aggressive nature of the disease. The above-mentioned cytogenetic changes all lead to the creation of fusion genes thus producing abnormal proteins with altered functional properties (Narayanan & Weinberg, 2020).

Recurrent cytogenetic abnormalities

1.The t(8;21) (q22;q22.1); RUNX1-RUNX1T1

The alteration t(8;21)(q22;q22.1), known as RUNX1-RUNX1T1, may define a specific subset of the disease, exhibiting unique clinical and biological characteristics. This translocation involves the fusion of the AML1 gene located on chromosome 21 with the ETO gene on chromosome 8. It is also referred to as the RUNX1T1 gene, which encodes the CBFA2T1 protein. The t(8;21) anomaly is found in approximately 5-10% of all acute myeloid leukemia (AML) cases and in 10-22% of AML cases classified as M2 according to the previous FAB classification system. This translocation results in the formation of two fusion genes: AML1-ETO and ETO-AML1; however, only the AML1-ETO transcript, produced from the derived chromosome 8, can be detected through RT-PCR. Patients with the t(8;21) alteration generally represent one of the more favorable categories, as their prognosis following intensive chemotherapy is often more

positive than that of many other AML patients. The occurrence of t(8;21) diminishes with advancing age, being more prevalent in younger individuals and rare in those over 60 years. This translocation is observed in about 10-20% of children diagnosed with AML (Bendari et al., 2020; Reikvam, Hatfield, Kittang, Hovland, & Bruserud, 2011).

2.The inv(16) (p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11

Approximately 5-7% of individuals diagnosed with acute myeloid leukemia (AML) present with the genetic alterations inv(16)(p13;q22) or t(16;16)(p13;q22). At a molecular level, these alterations lead to the fusion of the MYH11 gene, which encodes for the myosin heavy chain 11 found on chromosome 16p13, with the gene for the β-subunit of the nuclear binding factor, CBFB, located on chromosome 16q22. This fusion results in the formation of the CBFB-MYH11 gene. The variability in genomic breakpoints accounts for the inconsistencies observed in research, as well as the identification of multiple variants of the CBFB-MYH11 fusion transcript of varying sizes. More than 85% of these fusions are categorized as type A, while types D and E each represent about 5-10%. This particular cytogenetic grouping is typically associated with high complete remission rates and a relatively positive prognosis (Schwind et al., 2013). Phenotypically, the inv(16) or t(16;16)(p13;q22) alteration is associated with AML that displays myelomonocytic characteristics and eosinophilia (Bendari et al., 2020).

3.The t(15;17)(q24;q21); PML-RARA

t(15;17)(q24;q21) is a defining genetic alteration associated with acute promyelocytic leukemia (APL, classified as FAB subtype M3). RARA, which encodes for the nuclear retinoic acid receptor α, interacts with specific gene response elements related to retinoic acid within the nucleus, thereby activating the promoters of these genes. The fusion of RARA with the PML (Promyelocytic leukemia protein) gene—known for its role as a transcription factor and tumor suppressor, as well as its involvement in cell cycle regulation and apoptosis—leads to the creation of the PML/RARA fusion gene. Typically, the RARA protein forms dimers with the retinoid X receptor and acts as a transcriptional repressor by associating with the nuclear corepressor complex histone deacetylase, which facilitates nucleosome compaction and silencing of promoters. Upon binding to a ligand, particularly a retinoic acid receptor, RARA undergoes a conformational shift that markedly enhances the expression of genes essential for the maturation of promyelocytes (Puccetti & Ruthardt, 2004; Swerdlow et al., 2016b; Wintrobe, 2009).

PML/RARA similarly inhibits the target promoters within the signaling pathway, akin to RARA

when it is not bound to its ligand. However, unlike the wild type, it necessitates a higher concentration of ligand to counteract the repression due to its more robust interaction with the corepressor complex and specific methyltransferases, including DNMT1 and DNMT3A. Furthermore, PML/RARA significantly impacts apoptosis by negatively influencing the function of regular PML and its regulatory effect on p53. This leads to apoptotic anomalies that promote oncogene activation and contribute to genomic instability. The majority of patients with acute promyelocytic leukemia (APL) respond positively to trans-retinoic acid (ATRA) therapy, which enhances DNA transcription and facilitates cellular maturation (E. De Braekeleer, Douet-Guilbert, & De Braekeleer, 2014).

4.The t(5;11)(q35;q12)

The chromosomal translocation t(5;11)(q35;q12) can lead to the fusion of the NUP98 gene located on chromosome 11 with the NSD1 gene on chromosome 5. This fusion may play a role in leukemogenesis, the process through which normal hematopoietic cells evolve into malignant leukemic cells, ultimately resulting in leukemia. While the effects may differ among individuals, evidence suggests that this particular chromosomal alteration is linked to a worse prognosis compared to other genetic changes. This association affects its potential to induce the transformation of healthy blood cells into cancerous leukemic cells, as indicated by various focused studies on patients diagnosed with AML who exhibit this specific genetic anomaly (Manabe et al., 2018).

5.The t(10;11)(p12;q23)

Chromosomal translocation t(10;11)(p12;q23) refers to the genetic rearrangement occurring between chromosome 10 at the p12 locus and chromosome 11 at the q23 locus. This specific translocation leads to the fusion of the MLL gene on chromosome 11 with the AF10 gene on chromosome 10. The resulting fusion protein from MLL and AF10 disrupts normal gene regulation, which plays a role in the development of leukemia. This abnormal protein has been identified to activate certain pathways that promote unchecked cell growth and survival, thereby facilitating the onset of leukemia. The outlook for patients with MLL-AF10 rearrangements can differ, but it is generally observed that MLL rearrangements correlate with a more aggressive form of the disease and poorer outcomes in comparison to leukemias lacking such rearrangements (Ksiazek et al., 2020).

6.The t(11;19)(q23;p13)

The chromosomal translocation t(11;19)(q23;p13) involves a rearrangement of genes located on chromosome 11 at band q23 and chromosome 19 at band p13. This alteration results in the fusion of the MLL gene (Mixed Lineage Leukemia) on chromosome 11 with the ENL gene (Eleven-Nineteen Leukemia) on chromosome 19. The resulting fusion gene, which combines elements of both MLL and ENL, is linked to specific types of leukemia. The t(11;19) fusion creates a chimeric protein that disrupts typical gene regulation, contributing to the process of leukemogenesis. This fusion protein generally enhances pathways that promote the proliferation and survival of leukemic cells. The prognosis for patients with MLL-ENL rearrangements can vary significantly; however, MLL rearrangements are generally correlated with a more aggressive disease trajectory and an increased likelihood of relapse compared to leukemias that do not exhibit such rearrangements (Jeffrey E Rubnitz et al., 1996).

7.The t(6;11)(q27;q23)

The chromosomal translocation t(6;11)(q27;q23) involves the swapping of genetic material between chromosome 6 at band q27 and chromosome 11. This genetic alteration leads to the formation of a fusion gene that merges the AF6 gene, also referred to as MLLT4, located on chromosome 6, with the MLL (Mixed Lineage Leukemia) gene found on chromosome 11. The resulting fusion gene, known as MLL-AF6, is associated with the molecular mechanisms that contribute to certain types of leukemia. The combination of MLL and AF6 produces an unusual fusion protein that inhibits critical genes related to the development of leukemia. This inhibition may activate specific pathways that promote the survival and growth of leukemic cells. Patients with MLL-AF6 gene rearrangements generally face a poor prognosis. In comparison to individuals without this genetic modification, those with MLL gene rearrangements tend to have a greater likelihood of experiencing a more aggressive disease form and a higher rate of relapse (Kundu, Kowarz, & Marschalek, 2021).

8.The t(6;9) (p23;q34)

t(6;9) represents a rare and recurring cytogenetic anomaly observed in 0.7–1.8% of acute myeloid leukemia (AML) cases. This balanced translocation, designated as t(6;9)(p23;q34) and marked by the presence of the DEK/NUP214 fusion gene, is linked to leukemias that may or may not exhibit monocytic characteristics. Additionally, it is frequently associated with basophilia and multilayer dysplasia. Predominantly, this translocation is found in AML with

maturation (FAB subtype M2) and AML with myelomonocytic features (FAB subtype M4), although it can also manifest in other phenotypic variations. The DEK/NUP214 fusion gene produces a nucleoporin protein that functions as an unconventional transcription factor, disrupting nuclear transport by inhibiting soluble transport factors. Furthermore, FLT3 mutations are also found to be associated with this translocation (Swerdlow et al., 2016b).

9. The t(9;11) (p22;q23); MLL-MLLT3

Acute myeloid leukemia characterized by the translocation t(9;11) occurs in 3–5% of AML instances. This specific chromosomal rearrangement, t(9;11)(p22;q23), impacts the MLL and MLLT3 genes and is frequently linked to leukemias exhibiting monocytic characteristics, such as acute monocytic leukemia (FAB subtype M4) and acute myelomonocytic leukemia (FAB subtype M5). The MLLT3-MLL fusion gene represents the most prevalent alteration in AML involving the MLL gene, although there are other infrequent rearrangements. The MLL gene encodes a histone methyltransferase that works with various protein complexes to regulate transcription through chromatin modification. It serves as a positive regulator of HOX gene expression and transcription factors essential for the development of different organs, including the hematopoietic system. Rearrangements within MLL employ diverse mechanisms to promote leukemogenic expression. Notably, the MLLT3-MLL fusion lacks the SET domain of MLL, which is crucial for H3K4 methylation. In contrast, the MLLT3 region contains transcriptional regulatory domains and is linked to DOT1L, another histone methyltransferase that methylates lysine 79 in histone 3 (H3K79), and MENIN1, a transcription factor associated with multiple promoters. This combination enhances the transcription of HOX genes, stimulates cell proliferation, and partially restores the cell's self-renewal capabilities (Krivtsov & Armstrong, 2007; Marschalek, 2011).

10. The inv(3) (q21q26.2) or t(3;3)(q21;q26.2)

The inv(3)(q21q26) alteration impacts the EVI1 gene, which functions as a transcription factor exhibiting a specific expression pattern in haematopoietic stem cells (HSCs) and plays a crucial role in self-renewal. EVI1 influences the expression of other transcription factors, including GATA2, PBX1, and PLM. It can induce epigenetic changes that silence certain genes by interacting with histone deacetylases and chromatin-modifying enzymes, while also activating genes related to acetyltransferases. The protein RPN1 promotes the expression of EVI1. Consequently, the fusion gene results in enhanced cell proliferation and hinders differentiation,

leading to leukaemic transformation. Beyond acute promyelocytic leukaemia (APL), this alteration can present in various morphological forms, with the most prevalent being AML without maturation (FAB subtype M1), AML myelomonocytic (M4), and AML megakaryoblastic (FAB subtype M7) (M. De Braekeleer et al., 2015; Swerdlow et al., 2016b).

11. The t(1;22) (p13;q13)

The t(1;22) (p13;q13) translocation results in the creation of the fusion gene RBM15/MKL1. This genetic fusion brings together the DNA-binding motif of MKL1 and the RNA-binding motif of RBM15, playing a role in chromatin remodeling. As a result, this hybrid gene influences chromatin modification and differentiation linked to HOX genes while simultaneously interfering with extracellular signaling pathways. This genetic alteration is primarily associated with acute myeloid leukemia (AML) that includes a megakaryocytic component, specifically the FAB subtype M7 (Rørvik, Torkildsen, Bruserud, & Tvedt, 2024; Swerdlow et al., 2016b).

12. Monosomy 7 or − 7/del(7q)

Monosomy 7, or − 7/del(7q) is a cytogenetic abnormality wherein there's a loss of one replica of chromosome 7, such that cells endure the handiest one single replica as opposed to a pair. Monosomy 7 is often related to AML, in particular pediatric AML and secondary AML related to previous myelodysplastic syndromes or drug/radiation publicity. Generally, monosomy 7 is a terrible diagnosis. It is associated with a higher chance of progressing illnesses, resistance to remedy, and decreased common survival costs. Symptoms of the problems associated with monosomy 7 can also encompass fatigue, anemia, infections, smooth bruising or bleeding, and plenty of different signs that relate to bone marrow failure (Pezeshki, Podder, Kamel, & Corey, 2017).

2.7.5.2 Recurrent mutations

The diagnosis, prognosis, as well as the classification of AML, relies on citing the genetic abnormalities. Since an evident reference point and the biochemical elucidation of causality on AML are unclear, approximately 45 percent of patients are found to be of normal karyotype, which land them in a middle group of clinical prognosis.

Genetic mutations with AML have commonly been related to disturbances in multiple processes such as epigenetic processes (DNMT3A, TET 2, IDH1, and IDH2), disturbances of differentiation and apoptosis in blood and bone marrow cells (CEBPA, RUNX1 and NPM1), and cell division and survival (FLT3 and KIT) (Narayanan & Weinberg, 2020).

The WHO made significant revised in the classification of myeloid neoplasms in 2008. Among these modifications, NPM1 and CEBPA mutations were included into the list of unique diseases that are patients with AML and frequent genetic aberrations. The FLT3 mutations are not considered as its own disease because of the fact that it is related to too many different diseases but they cannot be underestimated. FLT3 mutations are present in the patients with a normal karyotype as well as in those containing chromosomal abnormalities; which may drastically affect the leukemia prognosis (Swerdlow et al., 2016a).

The Nucleolar Protein Nucleophosmin 1 (NPM1)

NPM1 was initially identified as a phosphoprotein that apoptotically modulated very well in the granular region of the nucleolus. NPM shuttles between the nucleus and the cytoplasm; although its expression is generally localized to nucleoli. It participates in the different cellular activities in the cytoplasm concerning the pre-ribosomes traffic and synthesis of ribosomes (Falini, Nicoletti, Bolli, et al., 2007). It reacts to multiple cues such as UV radiation and low oxygen, contributes to maintenance of genomic stability through the condition of cellular ploidy, and help in DNA repair processes and controls chromatin condensation and decondensation process which is governed by regulation of DNA transcription occurrence. NPM 1 also inhibits aggregation of proteins in the nucleolus and is regulator of the activity and stability of important tumor suppressor proteins, such as p53 and ARF. NPM1 reflects a histone chaperone, which allows the assembly of the histones, building-up of the nucleosomes as well as acetate-dependent transcription (Falini et al., 2005).

NPM1 gene mutations are mostly heterozygous and can only be found in exon 12 although in rare cases the mutation may be found in exon 11 and exon 9. Even though more than 50 genetic variants have been found, 95 percent of them are caused by mutations in the nucleotide position 960 with the nucleotide duplication GTCT at the positions 956-959 (A variant) being the most common. Virtually all mutations, irrespective of their nature, lead to the change in protein C terminus such as an insertion of a leucine-rich nuclear export domain and the removal of 2 aromatic residues at 288 and 290 which are essential in nucleolar localization. As such, one of the possibilities that occur in mutation of NPM1 is the excessive expression of the protein within the cytoplasm of the AML-positive leukemic cells (NPM1c+) (Falini et al., 2009; Falini, Nicoletti, Martelli, & Mecucci, 2007; Verhaak et al., 2005).

Acute myeloid leukemia (AML) is one of the most common hereditary conditions that is caused

by NPM1 gene mutation which occurs in about 25-35 percent of patients. It is especially high in patients with cytogenetically normal AML (CN-AML), in whom the mutations are found in 45-64 percent of patients. The mutations of the NPM1 tend to be permanent as a rule; they are not eliminated except in the event of a transformation of a normal into an abnormal karyotype. Moreover, those suffering with AML, but with NPM1 mutation tend to respond well to treatment, with increased survival rate within five years. NPM1 mutation is well correlated with the presence of FLT3-ITD alterations whereas MLL mutations are not usually observed with NPM1 mutations. Moreover, NPM1 mutation is associated with acute myelogenous leukemia myelomonocytic (FAB subtype M4) and acute myelogenous leukemia monocytic (FAB subtype M5) (Falini, Nicoletti, Bolli, et al., 2007).

Fms-Like Tyrosine Kinase 3 (FLT3)

FLT3 is a kind of tyrosine kinase; that acts as the receptome to the FLT3 ligand. First identified in 1991, the FLT3 gene is mainly found in the hematopoietic stem cells and is of great significance in several major biological activities like proliferation, differentiation and apoptosis. In the normal case, the FLT3 is in monomeric form on the cell membrane and is activated in a manner that is inhibitory (Saultz & Garzon, 2016). The most common mutation related to FLT3 is the internal tandem duplication (ITD) in the juxtamembrane area, being between exons 14 and 15; there is variation in the length, and positioning in various patients. The mechanism thought to allow dimerization brought on by the conformational change induced by the FLT3-ITD is by abolishing the steric hindrance to dimerization that would normally occur prior to ligand stimulation. This change presenting many sites in the tyrosine kinase domains, autophosphorylation happens. FLT3-ITD has mainly been associated with the high numbers of blast cells, increased risk of relapse, lower survival chances. Roughly one-fourth of the acute leukemia of myeloid origin (AML) cases are sensitive to FLT3-ITD mutations (Grimwade, Ivey, & Huntly, 2016). This mutation is highly found not only in the patients with a normal karyotype but also with particular chromosomal translocations, including t(15;17) [PML-RARA] and t(6;9) [DEK-NUP214]. There is also the possibility of mutations at NPM1 and DNMT3a that is linked to FLT3-ITD. Compared to the wild-type FLT3 protein the FLT3-ITD strongly activates the signaling pathway of STAT5. The activation improves Cyclin D1, c-MYC, and p21 expression which plays a vital role in cellular proliferation. Besides, FLT3-ITD was shown to significantly suppress protein levels of both CEBPA and Pu.1 proteins which play an important role in the differentiation of hematopoietic cells

implying that they play a role in the inhibition of such a process (Kayser et al., 2009).

The second mutation, most frequent in FLT3, is a missense mutation of exon 20 that lies at activation loop of the tyrosine kinase domain (TKD), also called the A-loop. The mutation is mostly a transitional one namely aspartate to tyrosine which is at position 835 (D835Y) and has occurrence through substitution of only one nucleotide (GAT to TAT). This aspartate is part of DFG motif, which is a combination of Aspartate-Phenylalanine-Glycine in the A-loop, which is vital to exclude successful binding of ATP. This residue can be in either active open conformation or autoinhibited closed state. The modifications which occur here are mutations leading to structural changes in the protein disturbing the energy balance. Therefore, the autoinhibited closed conformation can no longer be attained, and the autoinhibitory interaction is thus broken and results in sustained activation. Several other variants affecting nucleotides have also been documented at this codon besides in the surrounding areas such as deletion and insertions. Approximately 7 percent of instances of acute myeloid leukemia (AML) have the FLT3-TKD mutations (Griffith et al., 2004; Meshinchi & Appelbaum, 2009; Stirewalt & Radich, 2003).

2.8 Treatment

Acute myeloid leukemia (AML) should also be managed immediately after its diagnosis. However, newly available research shows that the time between the moment of diagnosis and the start of the treatment is not a negative factor.Moreover, the presence of zero known residual leukemic cells, known as MRD, minimal residual disease, allows a specific approach towards a patient with AML. Treatments of AML rely on general wellbeing of the patient. Although it may bring a remission in most patients, there are still high chances of relapse with the induction therapy. This probability will be related to aspects like the age of the patient and the amount of minimal residual disease (MRD) and cytogenetics features of the leukemia as well as the molecular features. Hematopoietic stem cell transplant is considered as the best post-remission procedure that can reduce the prospects of the recurrence of the ailment especially on patients that have been found to be at a high risk of an extremely high risk of recurrence. Further, the treatment protocol also involves medicines that would help in mitigating the symptoms and problems related to the disease as well as antifungal, antibiotics and platelet transfusion which would help to reduce chances of infections and bleeding in patients diagnosed with acute myeloid leukemia (AML) (Khwaja et al., 2016).

2.9 Literature Review and previous studies

Molecular mutations and cytogenetic abnormalities are notable prognostic factors in acute myeloid leukemia (AML) and help predict the disease prognosis by stratifying the risk. Cytogenetic abnormalities that are associated with good prognosis include specific patterns (inv(16), t(8;21), t(15;17)) and others (complex karyotypes or monosomy 5 or 7) that have unfavorable prognosis. Moreover, mutations in other genes, such as FLT3, NPM1, and IDH1/2, are also associated with prognosis, with certain ones, in particular, NPM1 mutations being more favorable, whereas others, e.g., FLT3-ITD mutations, indicating the increased risk or treatment resistance. The aim of this literature review is to trace the latest and recent past research findings about cytogenetic and molecular abnormalities of AML and also what caused it to develop and spread.

Cytogenetic and molecular data also influence the choice of AML therapy in the sense of determining its intensity and the choice of type of therapy. Routine induction chemotherapy may be of use to the patients with favorable-risk cytogenetics, but patients with the adverse-risk cytogenetics may need something alternative, or even more comprehensive treatment, which can be allogeneic stem cell transplantation. Moreover, with the targeted medications, including FLT-3 inhibitors or hypomethylating agents, the treatment is tailor-made to the molecular characteristics of the sickness and has led to the greater effectiveness of the treatment options available and the outcomes of the treated patients.

Also, targeted medicine will be important in the determination of minimal residual disease (MRD) in the AML patients after treatment. The persistence of low level cytogenetic abnormalities or molecular mutations following therapy may indicate an increased risk of a disease recurrence and possibly require further treatment, whether in an 'upfront cured' population (consolidation therapy) or prophylaxis (therapy to prevent a recurrence). Besides, in defining minimal residual disease (MRD) in the treated AML patients, targeted medicine will also be significant. The endpoint of the low level cytogenetic abnormalities or molecular mutations that persist after treatment may raise the possibility of a disease recurrence and may need additional therapy, either in the so-called upfront cured population (consolidation therapy) or prophylaxis (therapy to prevent a recurrence). The information obtained about the key biological mechanisms of acute myeloid leukemia (AML) through cytogenetic and molecular studies include leukemogenesis, clonal evolution, and treatment resistance. Disclosure of

uniform cytogenetic aberrations and molecular mutations defines key signaling pathways and cellular regulations that were gone haywire in AML. This knowledge opens up the route towards the development of specific treatments and realization of precision medicine strategies (Falini, Nicoletti, Martelli, et al., 2007).

According to a number of international research, cytogenetic abnormalities in Acute Myeloid Leukemia (AML) patients occurred. A substantial piece of work by Mohamed G. Elnaggar, a group of researchers who were dealing with 120 adult AML patients in Southern Egypt, concluded that the mean age of a participant was 36.5 years old with 18 and 86 year old extreme ends. These results revealed a relatively minor male bias, as males in the sample were 53.3 percent and the females 46.7 percent, which created a male-female proportion of 1.14. Fifty-six point seven percent of the participants were found to have normal karyotypes with 43.3 percent portraying clonal cytogenetic abnormalities. The structural counterpart was t(15;17) that was the most frequently identified as far as the numerical anomaly is regarded, the most widespread one was +8. The most common FAB subtype was the AML with monocytic differentiation (M4 and M5) with 51.7% and AML-M2 (23.3%) came second. Regarding cytogenetic risk stratifications, most of the patients were categorized as intermediate risk as 65 percent (Elnaggar, Mosad, Makboul, & Shafik, 2022).

The latest study conducted by Abdulaziz I. Alrajeh and others in Saudi Arabia during 2012-2014 enrols 100 patients with acute myeloid leukemia (AML), with the median age of 29 years. About 98 of these were precisely karyotyped with the results showing that 64 percent of them exhibited different abnormalities. The results produced by the 100 AML-FISH panel and molecular tests were significantly high with the abnormalities being detected in 50 percent and 45 percent of the cases respectively. Traditional and molecular cytogenetic assessments identified various genetic changes, e.g. trisomy 8 (15%), t(8;21) at 12% and trisomy 21 (8%), inv(16) at 7%, t(15;17) 6%, 11q rearrangements 6% and inv(3) at 2%. Moreover, mutation analysis has also demonstrated cases of nucleophosmin 1 (12%), FMS-like tyrosine kinase-3-internal tandem duplication (9%), IDH2 (7%), IDH1 (6%), WT1 (5%), DNMT3A (4%), CEBPA (4%) and c-KIT (3%) (Alrajeh, Abalkhail, & Khalil, 2017).

One more study conducted by Oum Kaltoum Ait Boujmia and coauthors is aimed at exploring the group of 927 individuals who were diagnosed in the Moroccan adult population with Acute Myeloid Leukemia (AML) during the seven-year research period. The ratio of these patients was

such that 466 (50.3%) were male, and 461 (49.7%) female. The participants were aged between 46 with the majority of them, 83.2 percent between 18 and 60 years old. The FAB M2 subtype turned out to be the most common one with 27 percent of the cases, followed by the M1 with 24.8 percent. Cytogenetic measurements also showed that many patients with normal karyotype. The most frequently observed balanced translocations in this group were t(8;21) but the highest proportion belonged to the intermediate cytogenetic category with 65.4 percent of the cases (Lamchahab, Hda, & Quessar, 2021).

Magdalena Sierra al. have performed a research in which 1,271 consecutive patients with acute myeloid leukemia (AML) who were diagnosed in 3 geographic regions in Spain: the North, Centre and South between 1995 and 2002. Of these patients, 624 were males and 505 were females representing 55 and 45 percent respectively. The patients were of varied age and the youngest was of one month, and the oldest was of 94 years, and the median age was 61 years. The abnormal karyotype was presented in around two-thirds of the cases. Numerical abnormalities had been the sole cytogenetic change in approximately one sixth of the patients, whereas structural abnormalities occurred in approximately one third of the patients, and combined numerical and structural abnormalities occurred in more than a fifth of the patients. Anomalous distribution of t(15;17) translocations prevailed in the southern Spain (21.6%) than in the central (17%) and northern (12.6%) areas of Spain. Conversely, the south Spanish patients experienced lesser incidences of t(8;21) translocations as compared to the central (1.6%) and the north (3.6%) regions. The prevalence of the trisomy 8 was similar in the southern (14%) and central (10%) areas, but reduced in the north area. Also, the incidence of other chromosomes aberrations including inv(16) and 11q23 shifting were reported to be analogous in all the three regions (Sierra et al., 2006).

The study performed by John C. Byrd and colleagues included 1,213 adults who were diagnosed with acute myeloid leukemia during the last four years. This was done so as to determine cytogenetic abnormalities which influence the complete remission rate, the 5 years cumulative incidence of relapse and overall 5 years survival because they can be reproducible. The induction therapy was same to all the patients, and the median of surviving patients follow-up was 8.3 years. The non-prioritized cytogenetic factors analysis showed that t(8;21) and inv(16)/t(16;16) were associated with a vastly superior prognosis as opposed to individuals having normal karyotype. Nevertheless, an independent prognostic significance of an array of

abnormalities could not be identified because of the relations to complex karyotypes. Patients having t(8;21), inv(16)/t(16;16), or t(9;11) were not influenced by complex karyotypes or secondary changes. The patients who showed up with complex karyotypes, however, showed results that were significantly worse than the cytogenetically normal ones. The division of patients into three categories of risks according to certain cytogenetic characteristics and complexity of karyotype were as follows: Favorable: 88 percent completion of remission, 54 percent cumulative occurrence of recurrence, and 55 percent survival. Intermediate: Incomplete remission rate of 67 percent, cumulative relapse incidence of 67 percent and overall survival of 24 percent .Adverse: Incomplete remission rate of 32 percent, cumulative relapse incidence of 92 percent and overall survival of 5 percent (Byrd et al., 2002).

Gmidene et al. conducted a study that entailed 631 successive patients diagnosed with acute myeloid leukemia (AML) by using standard cytogenetic-based diagnosis. In 397 subjects, they found abnormal karyotype, which is 62.9 percent of the sample. The most common Abnormalities were t(15;17) and t(8;21) which were observed in 83 (13.2) and 78 (12.4) of patients respectively. More uncommon were complex karyotypes, actually less prolific, {minus 5/del(5q), -7/del(7q) only 14 (2.2%), 19 (3%) respectively (Gmidène et al., 2012).

In a cytogenetic study of ethnic Omanis with de novo acute myeloid leukemia (AML), Udayakumar AM and colleagues report the observation of 63 cases of ethnic Omani men and women who had de novo acute myeloid leukemia (AML) of the type de novo acute myeloid leukemia (AML). Of the participants, 45 of them were adults and 18 children whose ages were 16 years and below. There were 41 males to 22 females, with a mean age of diagnosis at 25 years. The morphological classification followed the French-American-British (FAB) / WHO classification. Among the 63 patients, 39 (62 percent in general; 44 percent in adults and 18 percent in children) show chromosomal abnormalities. Also 20 patients (32%) had one anomaly of karyotype. It is also worth noting that the prevalence of chromosomal alteration was increased among those with the FAB-M2 subtype where 15 out of 22 patients (68%) had it hence the most frequently observed subtype (at 22 out of 63 cases (35%)) (Udayakumar et al., 2007).

RN Sanderson et al. (2006), gave demographic and karyotypic information on patients of acute myeloid leukemia (AML) who were sampled at two regional leukemia registries in Scotland and the Northern Region of England. The overall population-based study had included 1,709 patients, 1,235 in Northern England and 474 in Scotland, and were aged 16 or above. Those

cytogenetic abnormalities most frequently identified were revealed on chromosomes 5 and/or 7, which disturbed 17 per cent of patient cohort. Patients with particular conjunctions of alternations affecting chromosomes 5 and 7, e.g. -5, del(5q), -5/-7, del(5q)/-7 were much older ($P<0.01$, ANOVA). The only karyotype which has been found to be a favorable one among the older generation is the t(8;21) (Sanderson et al., 2006).

Ja Min Byun et al. examined the clinical records of 2,806 patients with acute myeloid leukemia (AML) that was identified in 11 tertiary teaching hospitals in Korea during the period between January 2007 and December 2011. The t(15;17) translocation was yielded a percentage of almost equally, that is 8.6 (235/2717), and the most frequently-occurring recurrent chromosomal alteration was the t(8;21) translocation present in 8.8 (238/2717). Among the most common abnormalities detected in de novo AML was the presence of t(15;17) isolation, with an identified consecutive 229 cases or 10.7 percent. M2 turned out to be the most common of FAB subtypes as it comprised 32.2%. Also, specific misrepeating cytogenetic aberrations were related to the FAB subtypes, whereas FLT3 internal tandem duplication defects were present in a comparatively low extent (15%) (Byun et al., 2016a).

Chapter Three: Methodology

3.1 Study design

The study design of this research is quantitative descriptive retrospective study.

This retrospective study was conducted in the Hematology-Oncology Department at An-Najah National University Hospital, located in Nablus, Palestine.

3.2 Study sample

The study population consists of 170 patients diagnosed with acute myeloid leukemia (AML) who were admitted to the Hematology-Oncology Department at An-Najah National University Hospital (NNUH) between February 2018 and December 2024.

3.3 Inclusion and exclusion criteria

3.3.1 Inclusion criteria

Patients must have a clear diagnosis of AML according to traditional criteria, which encompass morphological evaluations from both bone marrow and peripheral blood smears, immunophenotyping, and cytochemical staining. Patients must be admitted to the following single center, placed in the West Bank, Palestine, for diagnostic and therapeutic interventions of AML, to permit uniformity in clinical control and data collection.

It should provide detailed clinical information on the medical records of eligible patients, including demographic data: patients' age, sex, disease characteristics such as white blood cell count and FAB classification, signs, and symptoms; results of cytogenetic and molecular testing, including karyotype of mutation profiling. This information on the subjects under study is essential.

3.3.2 Exclusion criteria

- All patients with myelodysplastic syndrome (MDS), secondary or therapy-related AML.
- Patients with AML who have missing data in their files.

3.4 Morphologic evaluation

By using electronic data files, the patients are classified using the French-American-British system, which divides them into various morphological categories from M0 to M7

3.5 Flow cytometric immunophenotyping

Flow cytometric immunophenotyping data was collected from the patient’s medical files.

3.6 Molecular and Cytogenetic Analysis

This data was collected from the patient's medical files at diagnosis.

3.7 Data entry and statistical analysis

The data collected by using the Hospital Information System (HIS) of the An-Najah hospital, putting it on an Excel sheet. The data entry process was performed by assigning a serial number to a record on each patient, coding of the variables, and analyzing the data was done using Statistical Package for the Social Sciences (SPSS) version 21. Descriptive statistics were performed on all variables. Continuous variables will be represented as means ± SD, while categorical variables will be shown as frequencies and percentages. For variables that do not follow a normal distribution, medians will be utilized. The chi-square test was applied to assess the significance of relationships between categorical variables. The One-Way ANOVA test, along with Tukey Post-Hoc analysis, will be employed to examine differences in means between categories. Results were deemed significant with p-values of ≤ 0.05.

3.8 Ethical considerations

All ethical requirements for conducting this research were strictly observed. The necessary approvals were obtained from the Institutional Review Board (IRB) of Arab American University (Approval Ref: R-2024/A/43/N; see Appendix A) and the Clinical Research Center of An-Najah National University Hospital (Approval Ref: CRC_2024_0288; see Appendix B).

Chapter Four: Result

4.1 Features, morphology, and immunophenotypic profile of AML patients

A total of 170 patients diagnosed with acute myeloid leukemia (AML) were enrolled in this study. The median age of the patients with AML was 36 years. When stratified by gender, 97 patients (57.1%) were male and 73 (42.9%) were female, yielding a male-to-female ratio of 1.31:1. The median count at presentation for WBC, HB, PLTs, and ANC was 18.43 ×103/uL, 9.02 mg/dl, 35.25×103/ul, and 1.93×103/ul, respectively (Table 4.1).

In terms of morphological classification, the most common subtype observed was AML with maturation (AML-M2), representing 32.9% of cases, followed by acute promyelocytic leukemia (AML-M3), which accounted for 21.2% of patients (Table 4.1). The distribution of AML subtypes according to the FAB classification is illustrated in Figure 4.1.

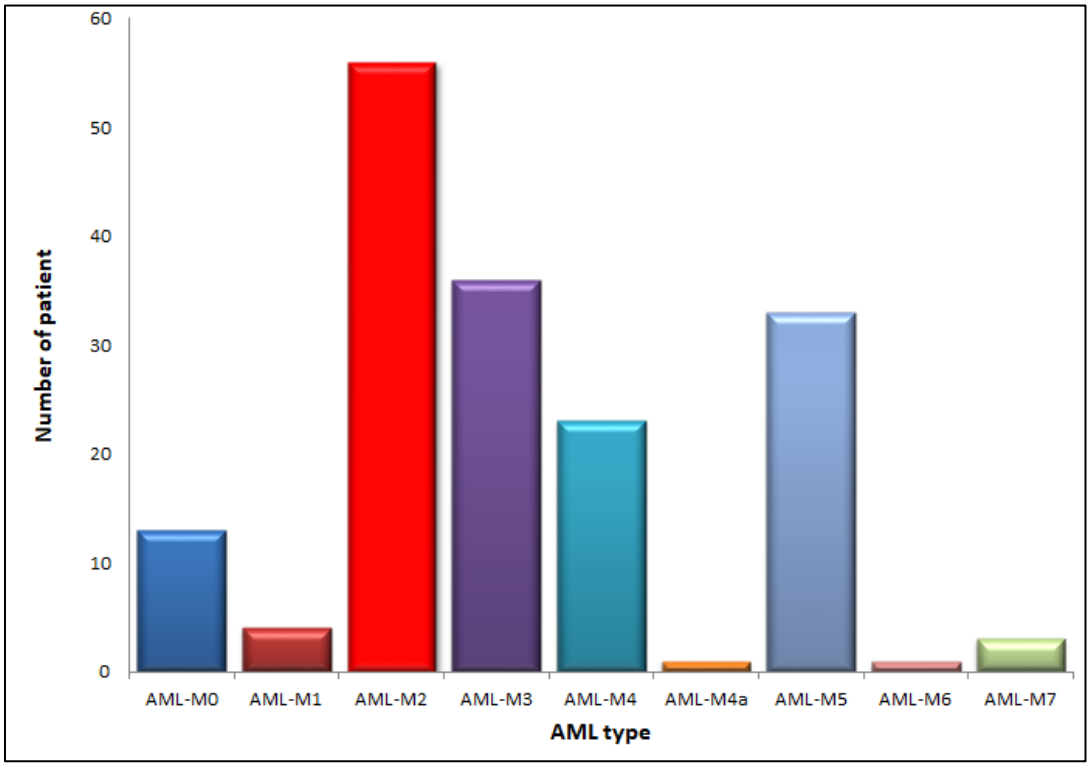

Figure 4.1: The distribution of FAB classification for AML

Table 4.1: Demographic, hematologic, and FAB subtype characteristics of AML patients

Total number of patients: 170 patients		
1. Age group:		
Mean ±SD	36.95 ±20.085	
Median age (range)	36 years (1 – 79 years)	
2. Gender:		
Male	97	57.1%
Female	73	42.9%
Male: female ratio	1.33:1	
3. Hematological data: at presentation		
Median WBC	18.43×10^3/Ul	
Median HB	9.02 mg/dl	
Median PLT	35.25×10^3/Ul	
Median ANC	1.93×10^3/Ul	
4. FAB subtypes		
AML-M0	13	7.6 %
AML-M1	4	2.4 %
AML-M2	56	32.9 %
AML-M3	36	21.2 %
AML-M4	23	13.5 %
AML-M4a	1	0.6 %
AML-M5	33	19.4 %
AML-M6	1	0.6 %
AML-M7	3	1.8 %

FAB: French, American British, WBC: White blood cell; AML: Acute myeloid leukemia

Regarding the clinical presentation, the most common symptom among our AML patients was anemic manifestations, observed in 82 patients (48.2%), followed by easy bruising or bleeding in 28 patients (16.5%). A summary of the clinical presentations is provided in Table 4.2.

Table 4.2: Clinical presentation of AML patients

Clinical Symptom	**Number of patients**	**Percentage (%)**	**Clinical Description**
Fever	20	11.8%	Common sign of infection due to neutropenia or leukemic fever.
Anemic manifestations	82	48.2%	Fatigue, pallor, dyspnea—due to reduced red cell production.
Bruising or bleeding easily	28	16.5%	Thrombocytopenia leading to petechiae or mucosal bleeding.
Cough/Sore throat	5	2.9%	Possible respiratory infection due to immunosuppression.
Lymph node enlargement	7	4.1%	Occasional in monocytic AML subtypes or extramedullary disease.
Pelvic Mass	1	0.6%	Rare; possible chloroma (myeloid sarcoma) manifestation.
Body or bone pain	13	7.6%	Bone marrow expansion or leukemic infiltration.
Oral ulcer	1	0.6%	Often due to neutropenia or leukemic cell invasion.
Gum swelling or bleeding	8	4.7%	Common in monocytic leukemia (M4/M5).
Organomegaly	2	1.2%	Hepatosplenomegaly due to leukemic infiltration.
Lower Limb Swelling	3	1.8%	Possible venous obstruction or leukemic infiltration.

Table 4.3 indicates that evaluating the specified age groups (<20, 20–39, 40–59, ≥60 years) revealed a statistically significant relationship between age brackets and FAB subtype ($p = 0.039$). Patients younger than 20 years showed a greater proportion of M1 and M2 subtypes, and the 20–39 age group appeared to retain this trend, but with a higher proportion of M4 and M5 subtypes. The 40–59 age group appeared to have a more balanced distribution of subtypes, and patients greater than or equal to 60 years appeared to group into a limited number of FAB subtypes with relatively less M4 and M5.

Table 4.3: Distribution of FAB subtypes across age groups in AML patients

Age groups	FAB subtypes									
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M4 Eo**	**M0**	**Total**
<20 Years	0 (0.0%)	19 (48.7%)	5 (12.8%)	5 (12.8%)	7 (17.9%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	39 (22.9%)
20–39 Years	2 (3.8%)	16 (30.2%)	13 (24.5%)	11 (20.8%)	7 (13.2%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	2 (3.8%)	53 (31.2%)
40–59 Years	2 (3.8%)	13 (25.0%)	16 (30.8%)	6 (11.5%)	10 (19.2%)	0 (0.0%)	1 (1.9%)	0 (0.0%)	4 (7.7%)	52 (30.6%)
≥60 Years	0 (0.0%)	8 (30.8%)	2 (7.7%)	1 (3.8%)	9 (34.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)	26 (15.3%)
Total	4 (2.4%)	56 (32.9%)	36 (21.2%)	23 (13.5%)	33 (19.4%)	1 (0.6%)	3 (1.8%)	1 (0.6%)	13 (7.6%)	170 (100%)

4.2 Cytogenetic profile of AML patients

The normal karyotype was revealed among 100 patients, and 70 patients (41.2%) had the cytogenetics abnormalities. The predominant structural abnormality was t(15;17)(q24;q21) which occurred in 34 patients (20 percent) followed by t (8;21) (q22;q22) in 15 patients (8.8 percent), inv (16)/t (16; 16)(p13;q22) in 12 patients (7.1 percent) as well as t(v;11q23) in 2 patients (1.2 percent). The only among the numerical abnormalities was monosomy 7 (-7/del(7q)), observed in 1 of the patients (0.6 percent). Table 5 demonstrates cytogenetic results Cytogenetic results in Table 4.4

Cytogenetics in FAB subtypes differed significantly. The M3 abnormality, t(15;17) was the most common one and it was mainly related to the M3 subtype which has a well-known association with acute promyelocytic leukemia. Translocation t(8;21) and inv(16) were placed mainly on M2 and M4 respectively as expected due to the associated favorable-risk AML. In all subtypes, normal karyotypes were seen and most often in M2 and M5. The rare adverse-risk abnormalities; t(6;11) and t(v;11q23), were present in Monocytic subtype (M5) and were found to be predominantly associated with poor outcome (Table 4.4).

Table 4.4: Cytogenetic findings distribution across FAB subtypes

Cytogenetic findings	**FAB subtypes**								
	M0	**M1**	**M2**	**M3**	**M4**	**M4a**	**M5**	**M6**	**M7**
Normal karyotype	13	4	37	2	15	0	26	1	2
t(15;17)(q24;q21)	-	-	-	34	-	-	-	-	-
inv(16)/t(16;16)(p13;q22)	-	-	1	-	8	1	2	-	-
t(8;21)(q22;q22)	-	-	15	-	-	-	-	-	-
t(v;11q23)	-	-	1	-	-	-	2		
t(6;11)(q27;q23)	-	-	-	-	-	-	2	-	-
t(5;11)(q35;q12)	-	-	1	-	-	-	-	-	-
t(10;11)(p12;q23)	-	-	1	-	-	-	-	-	-
t(11;19)(q23;p13)	-	-	-	-	-	-	1	-	-
t(9;11)(p22;q23)	-	-	1	-	-	-	-	-	-
-7/del(7q)	-	-	-	-	-	-	-	-	1

t: Translocation; inv: Inversion; del: Deletion; FAB: French American British

Concerning the assessment of cytogenetic risk, patients were categorized according to the European LeukemiaNet (ELN) risk classification system. Among the cohort, 61 patients (35.9%) were identified as having a favorable risk profile, while 101 patients (59.4%) were classified as intermediate risk, and 8 patients (4.7%) were identified as having an adverse risk. Cytogenetic evaluations indicated that a significant portion of acute myeloid leukemia (AML) patients (59.4%) fell into the intermediate-risk group, largely due to the presence of a normal karyotype. Around 36% exhibited cytogenetic features indicative of favorable risk, with the t(15;17) translocation being the most prevalent in cases of acute promyelocytic leukemia, followed by t(8;21) and inv(16). Conversely, only 4.7% of the patients presented with adverse-risk

cytogenetic characteristics, including 11q23 rearrangements and monosomy 7/del(7q), both of which are linked to a poor prognosis. This distribution highlights the critical role of cytogenetic testing in the risk stratification of AML, informing treatment intensity and transplantation decisions (Table 4.5).

Table 4.5: Cytogenetic risk stratification of AML patients

Risk category	**Number**	**Percent (%)**
Favorable risk	**61**	**35.9**
t(8;21)(q22;q22)	15	8.8
inv(16)/t(16;16)(p13;q22)	12	7.1
t(15;17)(q24;q21)	34	20
Intermediate risk	**101**	**59.4**
Normal karyotype	100	58.8
t(9;11)(p22;q23)	1	0.6
Adverse risk	**8**	**4.7**
t(v;11q23)	2	1.2
t(5;11)(q35;q12)	1	0.6
t(10;11)(p12;q23)	1	0.6
t(11;19)(q23;p13)	1	0.6
t(6;11)(q27;q23)	2	1.2
− 7/del(7q)	1	0.6

t: Translocation; inv: Inversion; del: Deletion

Table 4.6 indicates a statistically significant association between age group and cytogenetic risk group ($p = 0.028$). This suggests that older patients tend to have different cytogenetic risk profiles compared to younger patients. Patients aged > 18 had a higher proportion of intermediate risk cytogenetics compared to younger age groups. Younger patients (≤18 years) were more likely to have favorable-risk abnormalities compared to older age groups. By using One-Way ANOVA, there is a statistically significant difference in mean age across cytogenetic risk groups ($p < 0.001$). Patients in the intermediate group had the highest mean age. Patients with favorable cytogenetics were significantly younger on average. The mean age in the intermediate group (41.7 years), followed by the adverse group (33.4 years), and lowest in the

favorable group (29.6 years). All the cytogenetic risk groups equally affected males and females, and no significant association was observed between the different cytogenetic risk groups and genders (p=0.098). ANOVA results showed a significant difference in platelet counts across cytogenetic risk groups (p = 0.006), with intermediate-risk patients having significantly higher platelet counts than those in the favorable group. No significant differences were found for WBC, hemoglobin, or ANC.

Table 4.6: Patient baseline characteristics across various AML cytogenetic risk categories

Variables		**Cytogenetic Risk Groups**			**p-value**
		Favorable risk group n=61 (35.9%)	Intermediate risk group n=102(59.4%)	Adverse risk group n=8 (4.7%)	
Age	≤ 18Years	20 (51.3%)	16 (41%)	3 (7.7%)	0.028
	> 18 Years	41 (31.3%)	85 (64.9%)	5 (3.8%)	
Gender	Male	39(40.2%)	56(57.7%)	2(2.1%)	0.098
	Female	22(30.1%)	45(61.6%)	6(8.3%)	
Hematological parameters	Median WBC	16.41	25.62	17.43	0.092
	Median HB	8.85	9.18	9.60	0.090
	Median PLT	23.80	47	59.05	0.006
	Median ANC	1.95	1.86	1.26	0.469

4.3 Molecular profile of AML patients

Among the 170 AML patients, 64 (37.7%) were tested for the NPM1 mutation and 68 (40%) for FLT3 mutations. NPM1 mutations were detected in 7 of 64 cases (10.6%), with a median age of 47 years (range: 9–83 years); all NPM1-positive patients had normal karyotypes. FLT3-ITD mutations were identified in 7 of 68 cases (10.6%), also with a median age of 47 years (range: 9–72 years), and all were associated with normal karyotypes. In contrast, FLT3-TKD mutations

were detected in 3 of 68 cases (4.1%), with a median age of 25 years (range: 2–61 years). Unlike FLT3-ITD, the majority of FLT3-TKD–positive cases (71.4%) had abnormal karyotypes, while 28.6% showed normal karyotypes (Table 4.7).

Table 4.7: Molecular Mutation Profile in AML Patients (n = 170)

Mutation Type	**Mutated (n, %)**	**Wild Type (n, %)**	**Not Performed (n, %)**
FLT3-ITD	18 (10.6%)	50 (29.4%)	102 (60.0%)
FLT3-TKD	7 (4.1%)	61 (35.9%)	102 (60.0%)
NPM1	18 (10.6%)	46 (27.1%)	106 (62.4%)

Chapter Five: Discussion

5.1 Discussion

Acute myeloid anemia is a type of hematological malignancy, the character of which is the myeloid blasts. In spite of the fact that morphological analysis of bone marrow aspirates and biopsies is a pillar of the AML diagnosis, cytogenetic abnormalities and acquired genetic mutations characterizing a patient may be the key to the prognosis and thus treatment strategy (Debnath & Nath, 2024; C. C. Kumar, 2011).

In our studies the mean age of patients with AML was 36 years (range 1-71 years). In accordance with findings of many other works, we arrive at conclusions that AML patients are likely to be diagnosed at somewhat younger age (Abuhelwa, Al Shaer, Taha, Ayoub, & Amer, 2017; Alrajeh et al., 2017; Elnaggar et al., 2022; Lamchahab et al., 2021). Conversely, the intermediary age of presentation of AML in Western World countries entailed among 61 to 71 years, and it occurs above than the median age found in our study. Such observations have been reported in complex economies such as the United States, the United Kingdom and Spain (Dores, Devesa, Curtis, Linet, & Morton, 2012; Gangatharan et al., 2013; Shallis, Wang, Davidoff, Ma, & Zeidan, 2019; Sierra et al., 2006; Smith, Howell, Patmore, Jack, & Roman, 2011). The AML patients detected in our study at younger age than the patients of Western origin can be explained by differences in demographic, ethnic and environmental and genetic backgrounds (Darbinyan et al., 2017). Such factors might play an important role in developing earlier age AML. Age remains a major prognostic factor in AML and regional disparities should be researched further especially with regard to age-based strategies in treatment which will be more advanced in future (Patel, Ma, Mitchell, & Rhoads, 2015).

Based on what we found, it seems the expression of FAB subtypes in AML changes with age. Younger patients often have the M1/M2 morphology, which in some studies is seen as more favorable in terms of cytogenetics and response to treatment, while older patients are more likely to have the prognostically poor and chemotherapy-resistant subtypes. This supports the previously published studies demonstrating that the biological features of AML, such as morphology, cytogenetic profile, and molecular mutations, are age-dependent (Döhner et al., 2017; Juliusson et al., 2009). These patterns are essential to improve the modification of risk stratification and personalize treatment approaches (Grimwade et al., 2010).

Our study indicated that 57.1% of the participants were male, indicating a predominance and

resulting in a male-to-female ratio of 1.33. This finding aligns with existing literature that also notes a greater incidence of leukemia in males (Abuhelwa et al., 2017; Alrajeh et al., 2017; Dores et al., 2012; Gangatharan et al., 2013; Lamchahab et al., 2021; Sierra et al., 2006). Scientists have proposed several theories regarding the higher incidence of blood cancers in men. One possibility is that men's responses to cancer-causing agents differ from those of women. Additionally, hormonal factors may influence the process of blood cell formation. Furthermore, men might have increased exposure to certain occupational hazards. Collectively, these factors could explain why hematologic malignancies are more prevalent in men globally compared to women (A. Kumar, Rathee, Vashist, Neelkamal, & Gupta, 2016; Kusum et al., 2008).

The FAB subtype with the highest (32.9 %) incidence of AML was AML with maturation (AML-M2), followed by Acute promyelocytic leukemia AML-M3 with 21.2%. Among the different subtypes of FAB, Acute Myeloid Leukemia with maturation (AML-M2) was found out as the most common, resulting in 32.9 percent of the cases. The next was Acute Promyelocytic Leukemia (AML-M3) and it also equalled 21.2 per cent. Since M2 is the most commonly observed FAB subtype, it is notable that only a small proportion of M2 cases exhibit translocations, such as t(8;21). For the most part, over 60% of M2 cases are cytogenetically normal. This unique combination of high prevalence and moderate cytogenetic abnormality contributes to M2 having the highest number of normal karyotypes in smear-based FAB classification (W. Chen, Yang, & Chen, 2021; Klaus et al., 2004; Thao et al., 2023).

Our results coincide with those of M Lamchahab et al. and AM Udayakumar et al., who in their studies described the most prevalent subtype as AML-M2 (Lamchahab et al., 2021; Udayakumar et al., 2007). Ja Min Byun and the others based in Korea identified that AML-M2 was the dominant appearance subtype with the AML-M7 subtype being the minimum prevalence among the subtypes of AML (Byun et al., 2016a). Conversely, there have been a lot of studies suggesting that the commonest subtype is always the acute myeloid leukemia, which have monocytic differentiation, namely M4 and M5 (Elnaggar et al., 2022; Mertelsmann et al., 1980; van der Reijden et al., 1983). According to Chang et al. and Khoubila et al. the most common subtype in the research groups was AML-M1 (Chang, Shamsi, & Waryah, 2016; Khoubila et al., 2019). The differences will arise that can be described to be as a result of genetics, ethnicity, and environmental factors. Thus, it is rather important to apply both the FAB and WHO classification models, as well as the information on chromosomes and molecules to have a clear picture of the

types of AML (Kakepoto, Adil, Khurshid, Bumey, & Zaki, 2002).

In the current study, abnormal karyotypes were detected in 41.2% of patients with acute myeloid leukemia (AML), aligning with previously documented rates that fall between 40% and 60% in earlier research (Cheng et al., 2009; Takeuchi, Ohshima, & Amaki, 1981). We found that a normal karyotype was the most common cytogenetic result, occurring in 58.8% of our patients. Comparable results have also been documented in research carried out in Arab, Western, and Asian nations (Alrajeh et al., 2017; Byrd et al., 2002; Cheng et al., 2009; Elnaggar et al., 2022; Gmidène et al., 2012; Lamchahab et al., 2021; Sanderson et al., 2006; Udayakumar et al., 2007). Although AML with maturation (AML-M2) is the most frequently reported subtype according to the French-American-British (FAB) classification, it predominantly includes patients with a normal karyotype, as shown in Table 4.4. Cases of AML with a normal karyotype are classified as having an intermediate risk. This category exhibits considerable heterogeneity in terms of treatment responses and rates of recurrence. Various genetic alterations, such as NPM1 and FLT3 mutations, along with other gene mutations, play a significant role in influencing these cases. Therefore, molecular studies must be integrated into clinical practice alongside cytogenetic testing to ensure accurate categorization of patients into risk groups, ultimately enhancing treatment outcomes.

Regarding the classification of the acute myeloid leukemia (AML) cases we studied according to prognostic groups, the distribution was as follows: 35.9% were classified as favorable, 59.4% as intermediate, and 4.7% as adverse. In a study conducted in Egypt by MG Elnaggar et al., the reported distribution was 24.2% for favorable risk, 65% for intermediate risk, and 10.8% for adverse risk (Elnaggar et al., 2022), which aligns closely with our findings. Conversely, a study in Morocco indicated a higher percentage of individuals in the high-risk category, at 17.6% (Lamchahab et al., 2021). This discrepancy may be attributable to variations in the methods used for identifying and diagnosing the disease.

The most commonly observed cytogenetic structural anomaly was t(15;17)(q24;q21), detected in 20% of patients. This prevalence significantly exceeds the rates typically observed in Western countries, where it occurs in 8% of the British population and 14.5% of the Spanish population, as noted in studies by Sanderson et al. and Sierra et al., respectively (Sanderson et al., 2006; Sierra et al., 2006), However, this finding aligns with results from research conducted in Egypt by Elnaggar et al. and in Tunisia by Gmidene et al.(Gmidène et al., 2012). This specific

translocation indicates that the patient has acute promyelocytic leukemia (APL), a particular form of leukemia characterized by a unique clinical progression. Patients diagnosed with APL often respond favorably to treatments involving ATRA and arsenic trioxide. Given the high incidence of APL in this context, it is crucial to promptly verify the PML-RARA fusion at a molecular level. This early confirmation enables healthcare providers to initiate treatment swiftly, thereby reducing the risk of early mortality associated with blood clotting complications. (See appendix C).

The occurrence of t(8;21)(q22;q22) was found to be 8.8%. Similar findings were reported by J. M. Byun et al. and Byrd et al., who noted incidences of 8.8% and 8.7%, respectively (Byrd et al., 2002; Lamchahab et al., 2021). Conversely, other investigations indicated a greater prevalence of t(8;21) among patients. For instance, a study conducted in Oman identified t(8;21) in 11% of participants (Udayakumar et al., 2007). Furthermore, studies focusing on Saudi and Tunisian cohorts reported t(8;21) in 12% and 12.4% of patients, respectively (Alrajeh et al., 2017; Gmidène et al., 2012). Additionally, a study from India documented t(8;21) in 20.8% of patients (Udupa et al., 2020) (See appendix C).

Inv(16)/t(16;16)(p13;q22) was identified in 7.1% of the patients in our study, aligning with the observations made by Al Rajeh et al. in Saudi Arabia and Byrd et al. in Egypt, where the prevalence of inv(16) was reported at 7% and 7.4%, respectively (Alrajeh et al., 2017; Elnaggar et al., 2022). In contrast, lower frequencies of inv(16) were noted in research conducted in the United Kingdom(Sanderson et al., 2006), Spain (Sierra et al., 2006), Tunisia (Gmidène et al., 2012), and Morocco (Lamchahab et al., 2021), However, an Indian study reported a higher incidence, with 21.3% of patients exhibiting inv(16) (Udupa et al., 2020) (See appendix C).

The differences and similarities observed in the incidence of t(15;17), t(8;21), and inv(16) across multiple studies is a combination of the following: 1) Differences of the genetic makeup in a population (Reikvam et al., 2011; Sierra et al., 2006); 2) Exposures to the environment, such as benzene or other carcinogens, as well as lifestyle choices like smoking, have been linked in one way or the other to the development of AML (Zhou et al., 2024); 3) The use of diagnostic tools and their performance in the different institutions; 4) Differences in the design of the studies, including their sample size, the criteria for the selection of the patients, and the duration of the study; 5) Changes in the age distribution of patients (Baul et al., 2022; Lin et al., 2008).

Together, t(8;21), inv(16), and t(15;17) are considered "favorable" by the WHO, meaning people

with these changes tend to respond better to regular chemotherapy.

Looking at numerical aberrations, we saw monosomy 7 (-7/del(7q)) in just 0.6% of patients. This is usually linked to a worse outcome and often happens in secondary or therapy-related AML. Methodological limits, sample size concerns, biological population variability, and the clinical composition of the study fully explain the low frequency of monosomy 7 (Baranger, Baruchel, Leverger, Schaison, & Berger, 1990; Olson, Dickerson, Nakano, & Wlodarski, 2021; Pezeshki et al., 2017).

Regarding the genetic finding, we found mutations in FLT3-ITD, FLT3-TKD, and NPM1 in 10.6%, 4.1%, and 10.6% of cases, respectively. These numbers are lower than what's been seen in Europe (Thiede et al., 2002), the U.S. (Loghavi et al., 2014), and some parts of Asia (Elyamany et al., 2014; Ghosh et al., 2012; Suzuki et al., 2005), but they match what's been reported in some regions of China (Su et al., 2014) (See table 5.1). The lower rates in our study are probably because we didn't test a lot of patients (only 40-38% had the FLT3 and NPM1 tests), which makes it harder to get a clear picture. For a variety of structural, laboratory, and clinical reasons, more than 60% of the our AML patients did not get FLT3-ITD and NPM1 tests. Low-resource environments, which are prevalent in many lower-middle-income nations, frequently lack the PCR/NGS platforms and skilled personnel required for molecular diagnostics. When resources are limited or patient referrals are unavailable, many medical centers deprioritize molecular testing and instead depend exclusively on cytogenetics (Falini & Dillon, 2024; Kennedy & Smith, 2020)

Even with this limited data, it's clear we need to improve our ability to do these tests. Interestingly, if the NPM1 mutation is present and the FLT3 gene is normal, it's often a good prognosis. On the other hand, FLT3-ITD, particularly with high allelic burden, is a strong indicator of relapse and a worse outcome.

Table 5.1: Mutation frequencies in AML patients

Mutation	**County or region**	**Number**	**Frequency**	**Author**
FLT3-ITD	Our region	68	10.6%	
	Germany	979	20.4%	(Thiede et al., 2002)
	UK	854	27.0%	(Kottaridis et

				al., 2001)
	Japan	257	22.6%	(Suzuki et al., 2005)
	India	207	19.4%	(Ghosh et al., 2012)
	Saudi	97	14.4%	(Elyamany et al., 2014)
	Southwest China	605	10.2%	(Su et al., 2014)
	Northeast China	312	14.0%	
FLT3-TKD	Our region	68	4.1%	
	Germany	979	7.7%	(Thiede et al., 2002)
	UK	1107	11.0%	(Mead et al., 2007)
	Japan	429	7.0%	(Yamamoto et al., 2001)
	India	207	9.0%	(Ghosh et al., 2012)
	Saudi	97	4.1%	(Elyamany et al., 2014)
NPM-1	Our region	64	10.6%	
	Germany	1485	27.5%	(Thiede et al., 2006)
	Japan	257	22.6%	(Suzuki et al., 2005)
	USA	178	30.9%	(Loghavi et al., 2014)
	India	207	28.4%	(Ghosh et al., 2012)
	South Africa	160	7.5%	(Marshall et al., 2014)

A significant association exists between age categories and cytogenetic risk groups ($p = 0.028$), indicating that older patients exhibit distinct cytogenetic characteristics when compared to their younger counterparts. Specifically, individuals aged above 18 years are more frequently assigned to the intermediate risk categories, whereas those aged 18 years and below are predominantly found in the favorable cytogenetic group. Additionally, there is a statistically significant difference in the average ages across the cytogenetic risk categories ($p < 0.001$). The intermediate risk group shows the highest mean age at 41.7 years, followed by the adverse risk group at 33.4 years, and the favorable group with an average age of 29.6 years. This data suggests that poorer cytogenetic profiles are associated with advancing age.

We observed no significant association between gender and cytogenetic risk ($p = 0.098$), indicating that chromosomal abnormalities occur similarly in both males and females. Additionally, when examining the correlation between gender and FAB subtype, we observe no significant association between them ($p = 0.894$). In contrast, there was a notable difference in platelet counts among the various risk groups ($p = 0.006$), with patients classified as intermediate-risk displaying higher platelet levels than those in the favorable-risk category. Notably, elevated platelet counts at the time of diagnosis were linked to poorer treatment outcomes, characterized by reduced complete remission rates following induction chemotherapy and shorter relapse-free survival, when compared to patients with lower platelet counts (Zhang et al., 2023). Additionally, we found no significant variations in white blood cell count, hemoglobin levels, or absolute neutrophil count across the different risk groups. This observation is consistent with findings from other research, indicating that cytogenetic risk may not always be mirrored in baseline hematologic parameters.

The present study has significant limitations. Missing laboratory or genetic data for some patients potentially impacted the statistical analysis. Since this study's data were derived from one institution, the generalizability could be limited. Patient demographics, treatment paradigms, and diagnostic tools may differ across institutions and regions. The genetic mutation data were confined to select key markers (FLT3, NPM1), excluding other mutations that are crucial for prognostic alterations in AML (TP53, ASXL1, IDH1/2), which limits the thoroughness of the genetic analysis. In addition, whilst the study population was large enough to detect significant associations, only a small number of subjects carried out the FLT3, NPM1 mutation test. Finally, there were no records on survival and treatment outcomes for patients in this study. Therefore,

this would mean that the direct prognostic value of the cytogenetic and hematologic associations found could not be measured.

5.2 Conclusion

In conclusion, a cytogenetic examination of 170 patients with acute myeloid leukemia (AML) revealed that the intermediate-risk karyotype was the most common, with the normal karyotype being the most frequently observed. The most prevalent structural abnormalities included t(15;17), t(8;21), and inv(16), whereas monosomy 7 was identified as the most common numerical aberration. A significant relationship was observed between age and cytogenetic risk group, indicating that older patients were more likely to exhibit intermediate cytogenetic features. Additionally, notable differences in platelet counts were found among the various cytogenetic risk groups, implying their potential role as a prognostic factor. However, no significant associations were identified between cytogenetic risk and gender, nor between other hematological parameters and cytogenetic classification. The cytogenetic characteristics of AML patients in our area show both interesting similarities and marked differences when compared to AML patient groups from Arab, Asian, and Western nations.

5.3 Recommendations

To deepen the comprehension of the molecular features of AML within the Palestinian demographic, we propose that upcoming research should encompass further gene mutations, including CEBPA, DNMT3A, IDH1/2, and TP53. To enhance statistical power and broaden the applicability of results, subsequent studies should engage larger patient cohorts and foster collaborations with multiple medical institutions throughout Palestine. Additionally, it is essential to develop and maintain local resources for advanced diagnostic methods, such as next-generation sequencing (NGS) and optical genome mapping, to guarantee precise hematological care in Palestine.

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Appendices

Appendix A: IRB Approval Letter

Arab American University
Institutional Review Board - Ramallah

الجامعة العربية الأمريكية
مجلس اخلاقيات البحث العلمي – رام الله

IRB Approval Letter

Study Title: "Molecular and Cytogenetic Abnormalities in Acute Myeloid Leukemia Patients, A Retrospective, Single-Center Study From the West Bank, Palestine".

Submitted by: Hazem Za'eim Fahed Sawalhi

Date received: 29th February 2024

Date reviewed: 21th March 2024

Date approved: 21th March 2024

Your Study titled **"Molecular and Cytogenetic Abnormalities in Acute Myeloid Leukemia Patients, A Retrospective, Single-Center Study From the West Bank, Palestine"** with the code number **"R-2024/A/43/N"** was reviewed by the Arab American University Institutional Review Board - Ramallah and it was approved on the 21th of March 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 year 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.

Appendix B: Clinical research center approval

مركز البحث العلمي السريري
Clinical Research Centre

CLINICAL RESEARCH CENT

Approval date: 2024-04-15
Ref: CRC_2024_0288

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

Dear Mr. Hazem Sawalhi,

I am writing this letter to grant you permission to conduct your research project titled "Molecular and cytogenetic abnormalities in Acute Myeloid Leukemia patients, a retrospective, single-center study from the West Bank, 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

الإدارة الطبية
Medical Management

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

Appendix C: Comparison of the cytogenetics in AML patients between our research and other studies globally

Cytogenetic finding	Frequency (%)												
	Our study	Western population			Middle east population						Asian population		
		USA 2002 (Byrd et al., 2002)	UK 2006 (Sanderson et al., 2006)	Spain 2006 (Sierra et al., 2006)	Tunisia 2012 (Gmidène et al., 2012)	KSA 2017 (Alrajeh et al., 2017)	Omani 2007 (Udayakumar et al., 2007)	Egypt 2021 (Elnaggar et al., 2022)	Morocco 2021 (Lamchahab et al., 2021)	Korea 2016 (Byun et al., 2016b)	China 2009 (Cheng et al., 2009)	India 2020 (Udupa et al., 2020)
Median age	36	52	-	61	37	29	25	36.5	46	-	-	39
Normal karyotype	58.8%	48%	45%	36%	37.1%	36%	38%	56.7%	44%	41.4%	42%	34.7%
Most frequent abnormalities:												
t(8;21)(q22;q22)	8.8%	8.7%	4%	2.7%	12.4%	12%	11%	7.5%	8.4%	8.8%	8%	20.8%
inv(16) /t(16;16)(p13;q22)	7.1%	7.9%	2%	2.7%	3.8%	7%	3%	7.5%	4.7%	3.6%	-	21.3%
t(v;11q23)	1.2%	4.5%	2%	3.3%	3.5%	6%	2%	7.5%	1%	2.1%	1%	3.4%
t(15;17)(q24;q21)	20%	-	8%	14.8%	13.2%	6%	10%	9.2%	3.9%	8.6%	14%	8.6%
Complex karyotype	-	2.5%	15%	-	-	-	8%	7.4%	12%	-	6%	2.3%
-7/del(7q)	0.6%	7.8%	5%	8.6%	3.0%	-	5%	2.9%	2.7%	5.8%	1%	1.1%

التشوهات الجزيئية والوراثية الخلوية لدى مرضى سرطان الدم النخاعي الحاد، دراسة استيعادية احادية المركز من الضفة الغربية، فلسطين

حازم زعيم فهد صوالحي

د. صبا شنك

د. كمال ضميدي

د. أدهم ابو طه

ملخص

الخلفية:

سرطان الدم النقوي الحاد (AML) هو سرطان دم يتميز بنمو غير منضبط للخلايا السلفية النقوية. يعاني مرضى ابيضاض الدم النقوي الحاد (AML) بشكل كبير من تغيرات جزيئية وخلوية وراثية محددة، مما يؤثر سلبًا على توقعاتهم واستراتيجيات علاجهم. تساعد هذه الملامح الجينية في تحديد نوع السرطان، وصعوبة التقييم، وخيارات العلاج ونتائجه لمرضى ابيضاض الدم النقوي الحاد.

الأهداف:

في دراسة استعادية، كان الهدف تحديد السمات الجزيئية والخلوية الوراثية لدى مرضى سرطان الدم النخاعي الحاد خلال السنوات السبع الماضية في مستشفى النجاح الوطني الجامعي. الطريقة: تمت مراجعة السجلات الطبية الإلكترونية لمرضى سرطان الدم النخاعي الحاد من البالغين والأطفال، للفترة من 2018 إلى 2024، في قسم الأورام بمستشفى النجاح الوطني الجامعي، نابلس، فلسطين. حُللت البيانات باستخدام برنامج IBM Statistical Package for Social Science (SPSS) لنظام ويندوز، الإصدار 21.

النتائج:

شملت الدراسة 170 مريضًا مصابًا بسرطان الدم النقوي الحاد (AML). تراوحت أعمار المرضى في دراستنا بين سنة و79 عامًا، بمتوسط عمر 36 عامًا. أظهر 41.2% من المرضى شذوذات خلوية وراثية مستنسخة، بينما كان لدى 58.8% منهم أنماط كروموسومية طبيعية. كان الشذوذ الهيكلي الأكثر شيوعًا هو t (15؛ 17)، بينما كان الشذوذ العددي الأكثر شيوعًا والوحيد هو أحادي الصبغي 7. وقع 59.4% من المرضى في فئة الخطر المتوسط وفقًا لتصنيف الخطر الخلوي الوراثي. وفيما يتعلق بالنتائج الجزيئية بين المرضى، حمل 10.6% طفرات FLT3-ITD، و4.1% طفرات FLT3-TKD، و10.6% طفرات NPM1.

الخلاصة:

تُسلّط الدراسة الضوء على أن فئة الخطورة المتوسطة كانت الأكثر شيوعًا، حيث كانت النمط النووي الطبيعي هو الأكثر شيوعًا. كانت التشوهات الهيكلية t(15;17)، وt(8;21) ، وinv(16) هي الأكثر شيوعًا؛ يميل المرضى الأكبر سنًا إلى إظهار سمات خلوية وراثية متوسطة. تفاوتت أعداد الصفائح الدموية بشكل ملحوظ بين المجموعات الخلوية الوراثية، مما يشير إلى علامة تشخيصية. أظهرت الأنماط الخلوية الوراثية والجزيئية في منطقتنا أوجه تشابه واختلاف عند تحليلها مقارنةً بمجموعات سكانية أخرى.

الكلمات المفتاحية: ابيضاض الدم النخاعي الحاد، تحديد النمط النووي، علم الوراثة الخلوية، فلسطين