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The prevalence of Bone Marrow Aplasia Following Chemotherapy in Cancer Patients

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To Allah Almighty The source of strength, mercy, and guidance. Every step of this journey was made possible by His will, and every success is but a reflection of His infinite grace. 🙏

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Charrak Rihab

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List of abbreviations:

- HSCs — Hematopoietic Stem Cells
- $CD34^+$ — Cluster of Differentiation 34 positive
- $CD8^+$ — Cluster of Differentiation 8 positive
- IFN-γ — Interferon-gamma
- TNF-α — Tumor Necrosis Factor-alpha
- Fas/Fas-ligand — Fas receptor / Fas ligand
- SCF — Stem Cell Factor
- CXCL12 — C-X-C motif chemokine ligand 12 (Stromal cell-derived factor 1, SDF-1)
- PNH — Paroxysmal Nocturnal Hemoglobinuria
- MDS — Myelodysplastic Syndromes
- AML — Acute Myeloid Leukemia
- **APLA** – Aplasia Risk Application
- **CBC** – Complete Blood Count
- **CLCC** – Cancer Control Center
- **CT** – Chemotherapy
- **GVHD** – Graft-Versus-Host Disease
- **HSCT** – Hematopoietic Stem Cell Transplantation
- **ID** – Indoleamine 2,3-Dioxygenase
- **SAA** – Severe Aplastic Anemia
- **WHO** – World Health Organization
- **QoL** – Quality of Life
- **OS** – Overall Survival
- **DFS** – Disease-Free Survival
- **CR** – Complete Recovery
- **PR** – Partial Recovery
- **BM** – Bone Marrow

- **BMA** – Bone Marrow Aplasia
- **BMT** – Bone Marrow Transplantation
- **ANC** – Absolute Neutrophil Count
- **Hb** – Hemoglobin
- **PLT** – Platelets
- **WBC** – White Blood Cells
- **ICU** – Intensive Care Unit
- **IDR** – Incidence Density Rate
- **CI** – Confidence Interval
- **HR** – Hazard Ratio
- **Jamovi** – Statistical Analysis Software (used instead of SPSS)
- **DOI** – Digital Object Identifier
- **G-CSF** – Granulocyte Colony-Stimulating Factor
- **GM-CSF** – Granulocyte-Macrophage Colony-Stimulating Factor
- **EPO** – Erythropoietin
- **TPO** – Thrombopoietin
- **IGF** – Insulin-Like Growth Factor
- **GH** – Growth Hormone
- **ACTH** – Adrenocorticotropic Hormone
- **FSH** – Follicle-Stimulating Hormone
- **LH** – Luteinizing Hormone

I)Theorical part of the thesis

1) Introduction:

Chemotherapy is the main treatment used in various malignancies in oncology, offering significant improvements in survival and disease control. However, despite its effectiveness in treating various types of cancer, it has its general and specific side effects, among which bone morrow aplasia stands out as a potentially life-threatening general complication, due to the toxicity that can be induced by chemotherapy.

Bone marrow aplasia or aplastic anemia refers to the profound suppression of hematopoietic activity, resulting in a marked reduction of red blood cells, white blood cells, and platelets in results a pancytopenia. It can be a partial or complete failure of the bone marrow to produce adequate blood cells. This clinical condition can cause a various serious symptom that are related to pancytopenia such as: severe anemia, serious infections and multiple episodes of hemorrhagic syndrome causing higher morbidity and mortality significations. Since one of main objectives is to choose the right therapeutic strategy for a cancer patient, it is also important to prevent the mortal side effects, but among all it is very challenging to prevent and detect bone marrow aplasia, due to the variety of patients and chemotherapy protocols, that's why such a serious condition needs a very serious management since the main goal isn't about treating a cancer but also to treat and prevent all the side effects specifically bone marrow toxicity. Although several studies have investigated the risk factors associated with post-chemotherapy aplastic anemia, there is still a lack of practical tools to assist clinicians in early risk assessment. Also, it requires a multidisciplinary approach Especially in cancer patients with chemotherapy-induced marrow suppression.

2) Objectives:

•**General objective:**

To evaluate the occurrence, risk factors, and clinical outcomes of bone marrow aplasia in cancer patients receiving chemotherapy, in order to identify key predictive factors and better understand its occurrence pattens.

•**Specific Objectives:**

1. To determine the prevalence of bone marrow aplasia post-chemotherapy.

2. To identify demographic, clinical, and therapeutic risk factors associated with aplasia.

3. To assess the clinical outcomes (recovery, infection, bleeding, mortality) of patients with aplasia.

4. To evaluate the average time to bone marrow recovery and the need for supportive therapies (transfusion, growth factors, etc.).

5. To create a technical tool that helps doctors, oncologists, and health care assistants to better manage this severe side effect of chemotherapy.

3) Physiology of bone marrow:

1. Definition:

Bone marrow is the central organ of hematopoiesis in adult mammals, responsible for the lifelong production of blood cells. Within this specialized tissue, hematopoietic stem cells (HSCs) reside in a dynamic microenvironment that regulates their self-renewal, differentiation, and mobilization. The balance between these processes ensures the continuous replenishment of erythrocytes, leukocytes, and platelets, which are essential for oxygen transport, immune defense, and hemostasis(1)

2. Evolution of the Stem Cell Niche Concept

The concept of the hematopoietic stem cell niche emerged from early experimental evidence demonstrating the existence of stem cells in bone marrow. In 1961, studies on irradiated mice showed that survival was only possible when fresh marrow cells were transplanted, thereby proving the presence of a self-renewing unit capable of regenerating hematopoiesis(2).

Subsequent observations highlighted that stem cells could not function independently but required a supportive microenvironment to maintain their properties. This led to the formal proposal of the “niche” hypothesis, which emphasized that stem cell behavior is regulated by surrounding stromal and structural elements(3).Further comparative studies across vertebrates reinforced this idea, showing that hematopoiesis consistently occurs within bone structures, suggesting an evolutionary advantage in protecting stem cells within a specialized environment(1).The niche concept was later refined with the identification of specific

cellular and molecular components that regulate stem cell fate, including adhesion molecules, cytokines, and signaling pathways. These discoveries established the niche as a dynamic and essential regulator of hematopoietic stem cell maintenance, mobilization, and differentiation(4).

3. Anatomical and Cellular Components of the Bone Marrow Niche

The bone marrow niche is a composite of overlapping microenvironments; each composed of distinct cellular populations that collectively regulate hematopoietic stem cell (HSC) fate. These microenvironments provide structural support, molecular signals, and dynamic regulation of stem cell activity, ensuring the balance between self-renewal, differentiation, and mobilization(1).**Osteoblasts and osteoprogenitors** line the endosteal surface and play a central role in organizing hematopoietic microenvironments. They secrete regulatory factors that maintain HSC quiescence and self-renewal, and their depletion has been shown to severely impair hematopoiesis(5).**Endothelial cells** within sinusoidal vessels are critical for Notch-dependent HSC self-renewal. They provide vascular support and create niches that facilitate engraftment and repopulation following transplantation(6).**Mesenchymal stromal cells (MSCs)** are multipotent and contribute to both bone regeneration and hematopoietic support. They secrete cytokines and adhesion molecules that influence HSC fate, and their dynamic participation in bone maintenance highlights their dual role in skeletal and hematopoietic physiology(7).**Adipo-osteogenic progenitors** balance adipogenesis and osteogenesis within the marrow. These progenitors are essential for niche function, providing structural and metabolic support to HSCs (6).**Sympathetic nervous system innervation** regulates circadian trafficking of HSCs. Stromal cells express CXCL12 in antiphase with sympathetic tone, enabling rhythmic mobilization of HSCs into the bloodstream(7).**SLAM family receptors** (CD150, CD244, CD48) provide a molecular framework for distinguishing HSCs from progenitors. HSCs are characterized by $CD150^{+}CD244^{-}CD48^{-}$ expression, multipotent progenitors by $CD244^{+}CD150^{-}CD48^{-}$, and restricted progenitors by $CD48^{+}CD244^{+}CD150^{-}$. This combinatorial expression not only allows precise purification of HSCs but also reveals their localization within endothelial niches, particularly sinusoidal endothelium in bone marrow and spleen(4).

Together, these cellular and molecular components form a highly integrated system that governs hematopoietic activity. Disruption of any element can compromise stem cell function and contribute to hematologic pathology(1)

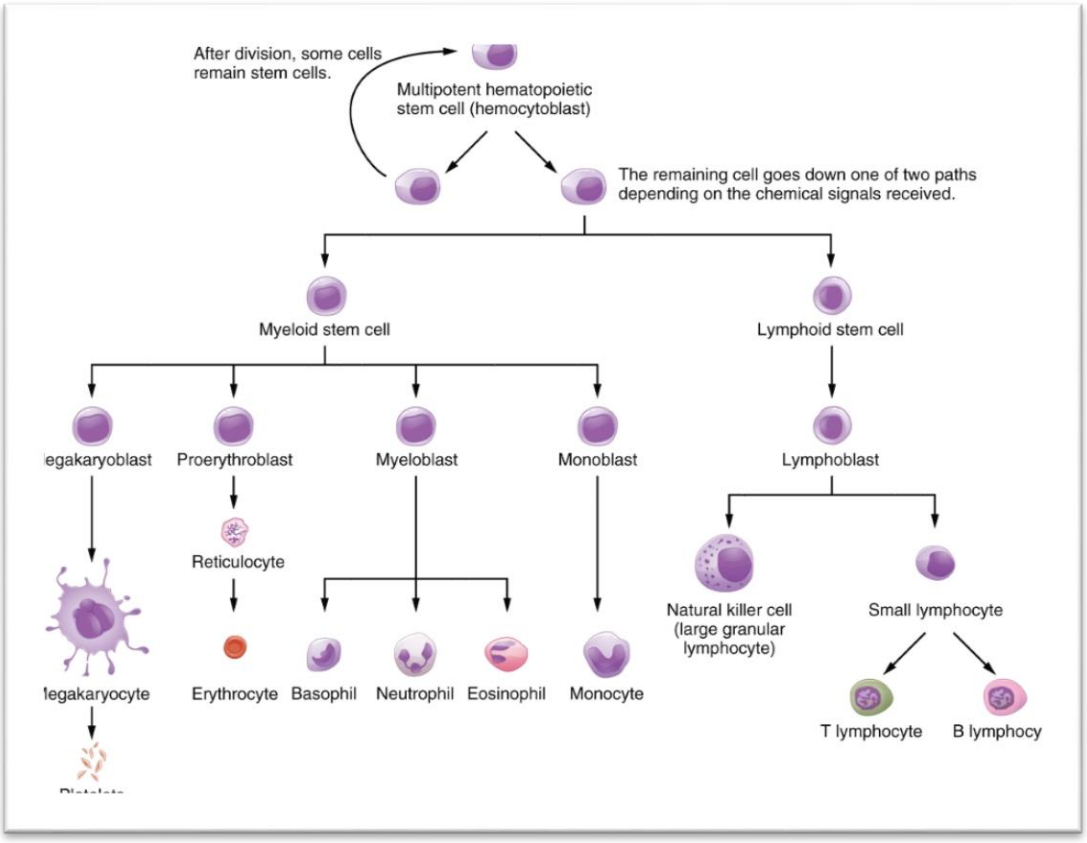


Figure 1 ***Hematopoietic System of Bone Marrow****(8)*

4. Molecular Regulation of Hematopoiesis

The regulation of hematopoietic stem cells (HSCs) within the bone marrow niche is mediated by a complex interplay of chemokines, adhesion molecules, cytokines, and receptor signaling pathways. These molecular mechanisms ensure that HSCs remain quiescent under homeostatic conditions, while retaining the capacity to proliferate and differentiate in response to physiological demands(1).**Chemokines and adhesion molecules** play a central role in stem cell retention and mobilization. CXCL12, secreted by stromal cells, binds to CXCR4 on HSCs, anchoring them within the marrow. Disruption of this axis results in rapid mobilization of stem cells into peripheral blood, a mechanism exploited clinically for stem cell harvesting (9). Adhesion molecules such as CD44 and VCAM-1 further mediate interactions between HSCs and endothelial cells, stabilizing their localization within the vascular niche (10).**Cytokines** provide essential signals for lineage commitment and progenitor fate. Interleukin-6 (IL-6), for example, influences multipotent progenitors and has been implicated in leukemic transformation. Dysregulation of cytokine signaling can therefore contribute to malignant hematopoiesis and marrow failure syndromes (11).**Receptor signaling pathways** are equally critical. SLAM family receptors (CD150,

CD244, CD48) provide a molecular framework for distinguishing HSCs from progenitors. Their combinatorial expression not only enables precise purification of stem cells but also reveals their localization within endothelial niches, particularly sinusoidal endothelium in bone marrow and spleen (9).

Together, these molecular regulators orchestrate the balance between quiescence, self-renewal, and differentiation. They ensure that hematopoiesis adapts to stress conditions such as infection, injury, or chemotherapy, while preserving long-term regenerative capacity (1)

5. Functional Dynamics of the Bone Marrow Niche

The bone marrow niche is not a static structure but a highly dynamic system that adapts to physiological and pathological conditions. Hematopoietic stem cells (HSCs) circulate in the bloodstream with circadian fluctuations, reflecting the rhythmic regulation of mobilization and retention within the marrow(1).**Circadian regulation** of HSC trafficking is mediated by sympathetic nervous system signals. Stromal cells express CXCL12 in antiphase with sympathetic tone, enabling rhythmic mobilization of HSCs into peripheral blood. This mechanism ensures that stem cell availability is synchronized with systemic demands(7).**Stress-induced mobilization** occurs during infection, inflammation, or chemotherapy. Under these conditions, HSCs are recruited from the marrow into circulation to replenish immune cells and support tissue repair. This adaptive response highlights the niche's role as both a sanctuary and a reservoir (1).**Pharmacological mobilization** is widely used in clinical practice. Granulocyte colony-stimulating factor (G-CSF) induces HSC egress by disrupting the CXCL12/CXCR4 axis, reducing stromal CXCL12 expression and altering adhesion molecule interactions. Cyclophosphamide exerts a similar effect, enhancing mobilization efficiency (9). These mechanisms are exploited for peripheral blood stem cell collection in transplantation programs (9).**Retention mechanisms** are equally important. Adhesion molecules such as VCAM-1 and CD44 stabilize HSC interactions with endothelial cells, preventing premature egress and maintaining marrow homeostasis (12). Disruption of these signals leads to rapid mobilization, underscoring the delicate balance between retention and release.

Overall, these dynamic processes demonstrate that the bone marrow niche is a responsive system, capable of adjusting to circadian rhythms, stress conditions, and therapeutic interventions. Its functional plasticity is essential for maintaining hematopoietic equilibrium and for clinical applications such as stem cell transplantation (1).

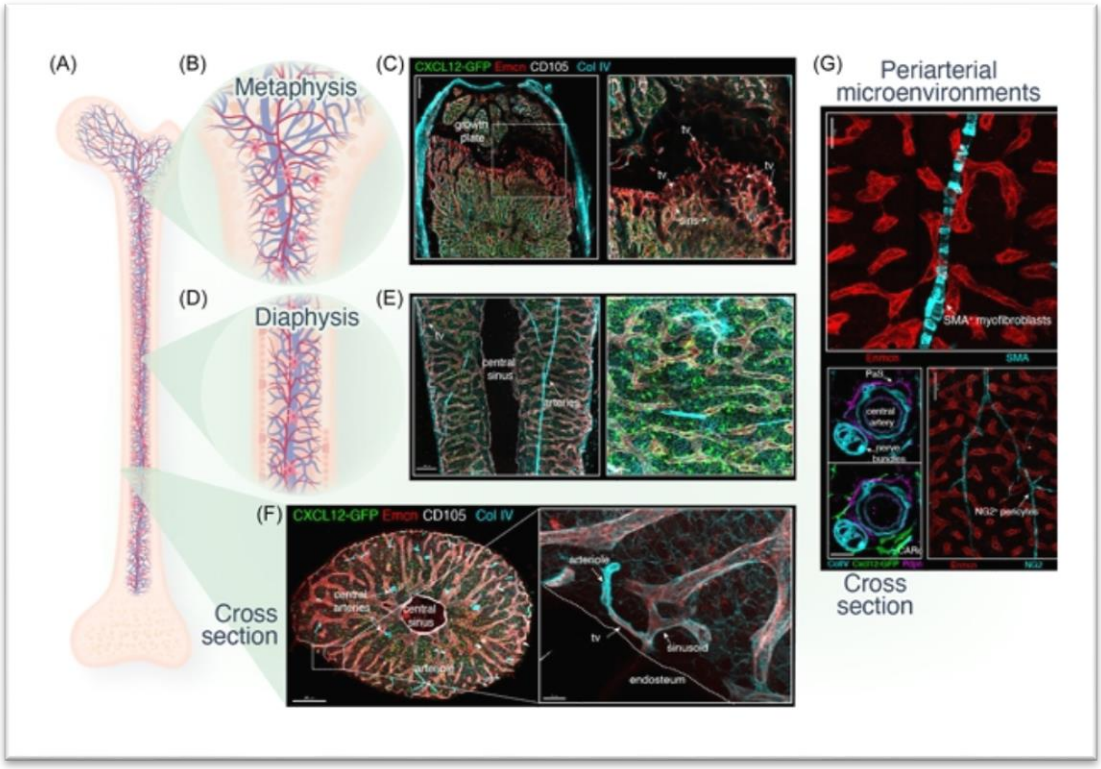


Figure 2 Structural organization of bone marrow tissues. Schematic representation and microscopic imaging of bone marrow (BM) tissues. (A) Femoral cavities contain regions representative of cortical (diaphysis) and trabecular (metaphysis) bone. (B) Schematic representation of metaphyseal regions including growth plate. (C) 3D microscopy of a femoral metaphysis; arteries marked by collagen IV (ColIV) expression (cyan), transitional vessels (tv) marked by a strong expression of endomucin (Emcn, in red), absence of CD105 and a straight and thin morphology. reproduced from (13)

6. Clinical Relevance of the Bone Marrow Niche

Disruption of the bone marrow niche is a central mechanism underlying bone marrow failure, particularly in cancer patients undergoing chemotherapy. Damage to stromal cells, endothelial structures, and cytokine networks compromises the regenerative capacity of hematopoietic stem cells (HSCs), resulting in prolonged cytopenias and clinical manifestations such as anemia, infections, and bleeding (1). Alterations in adhesion molecules, including VCAM-1 and CD44, weaken HSC retention within the marrow, leading to ineffective hematopoiesis and premature egress (12). Similarly, disruption of the CXCL12/CXCR4 axis mobilizes stem cells into peripheral blood, a process exploited clinically for transplantation but also implicated in marrow aplasia when uncontrolled(9). Cytokine dysregulation, particularly involving interleukin-6 (IL-6), further destabilizes progenitor fate and contributes to leukemic transformation, exacerbating marrow dysfunction (11). Collectively, these mechanisms highlight the vulnerability of the marrow niche to

therapeutic and pathological insults, underscoring its critical role in the pathogenesis of bone marrow failure and its importance as a target for clinical intervention.

4) Chemotherapy

1. Cancer overview

❖ *Definition:*

Cancer is a heterogeneous group of disorders in which normal regulatory mechanisms of cell growth and division are lost, leading to uncontrolled proliferation and tumor formation(14). It arises from **genetic mutations** that alter key proteins involved in cell cycle regulation, DNA repair, and apoptosis(15).

❖ *Mechanisms of Oncogenesis:*

Oncogenesis is driven by the deregulation of the cell cycle and the failure of genomic surveillance mechanisms, which together promote malignant transformation. The cell cycle is normally orchestrated by cyclins, cyclin-dependent kinases (CDKs), and checkpoint proteins that ensure orderly progression through G1, S, G2, and M phases(14). Mutations in tumor suppressor genes such as *TP53* and *RB1*, or overactivation of oncogenes including *cyclin D* and *CDK4/6*, disrupt these checkpoints, allowing cells with DNA damage to continue dividing unchecked(15). Defects in the G1/S checkpoint facilitate uncontrolled DNA synthesis, while abnormalities in the G2/M checkpoint lead to chromosomal instability and aneuploidy(16). In addition, cancer cells evade apoptosis by overexpressing anti-apoptotic proteins such as BCL-2 and suppressing pro-apoptotic pathways, enabling survival despite genetic insults (14). Collectively, these alterations in cell cycle regulation, checkpoint integrity, and apoptotic signaling drive clonal expansion, genomic instability, and ultimately the clinical manifestations of malignancy (15,16)

❖ *Clinical Relevance:*

The deregulation of the cell cycle in cancer has profound clinical implications, directly shaping therapeutic strategies and prognostic evaluation. Chemotherapeutic agents and targeted therapies exploit vulnerabilities in rapidly dividing cells by interfering with DNA replication, mitotic spindle assembly, or CDK activity (14). Identification of mutations in regulators such as *TP53*, *RB1*, and *CDK4/6* has enabled precision oncology approaches,

including the use of CDK4/6 inhibitors in breast cancer and checkpoint kinase inhibitors in hematological malignancies(15). Resistance to conventional therapies is often explained by the evasion of apoptosis, prompting the design of drugs that target BCL-2 family proteins to restore programmed cell death (16). Furthermore, deregulated checkpoints contribute to genomic instability, which not only drives tumor progression but also serves as a biomarker for prognosis and treatment response (15). Collectively, these insights highlight the importance of understanding cell cycle control in cancer, as it underpins both traditional cytotoxic regimens and modern targeted interventions (14,16).

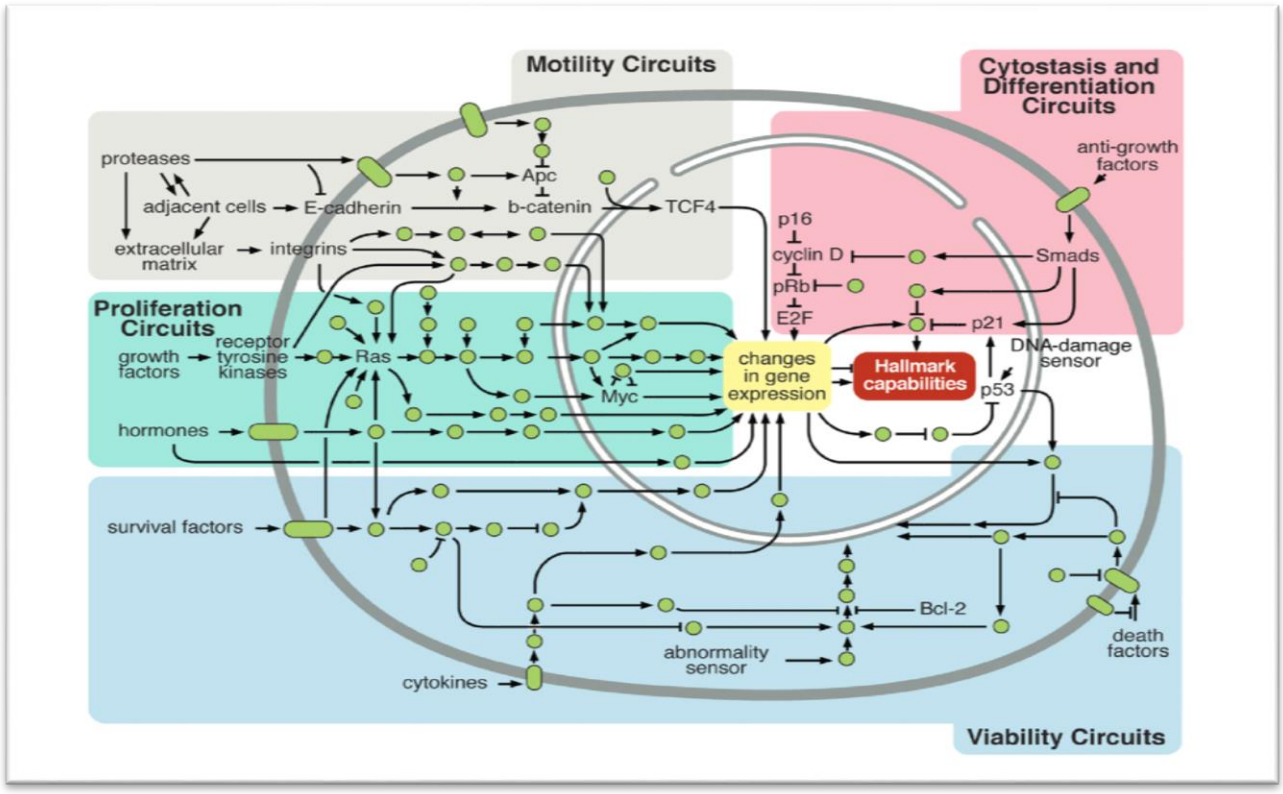


Figure 3 Intracellular Signaling Networks Regulate the Operations of the Cancer Cell(14)

2. Classification of Chemotherapy*:*

Chemotherapeutic agents are traditionally classified according to their mechanism of action and chemical structure, reflecting the diverse strategies used to disrupt malignant cell growth. The major categories include:

1. **Alkylating agents** :These drugs (e.g., cyclophosphamide, cisplatin) act by forming covalent bonds with DNA, leading to cross-linking and strand breakage that prevent replication and transcription (17).

2. **Antimetabolites** :Agents such as methotrexate, 5-fluorouracil, and cytarabine mimic natural substrates of DNA and RNA synthesis, thereby inhibiting nucleotide metabolism and blocking cell cycle progression at the S-phase (18).
3. **Anthracycline antibiotics** : Drugs like doxorubicin and daunorubicin intercalate into DNA and inhibit topoisomerase II, causing double-strand breaks and apoptosis (19).
4. **Plant alkaloids** :Derived from natural sources, these include vinca alkaloids (vincristine, vinblastine) that inhibit microtubule assembly, and taxanes (paclitaxel, docetaxel) that stabilize microtubules, both disrupting mitosis (20).
5. **Miscellaneous agents** :This group encompasses drugs with unique mechanisms, such as bleomycin (DNA strand scission), hydroxyurea (ribonucleotide reductase inhibition), and newer formulations like liposomal doxorubicin that improve pharmacokinetics (21).

This classification underscores the diversity of chemotherapy, with each class targeting distinct vulnerabilities in the cancer cell cycle. Clinically, these agents are often combined to maximize efficacy and minimize resistance, forming the basis of combination chemotherapy protocols widely used in oncology practice (17,22).

Table 1 various classes of anticancer chemotherapeutic drugs and their examples.(23)

Class	Names of drugs
Alkylating agents	• Nitrogen mustards: such as mechlorethamine (nitrogen mustard), chlorambucil, cyclophosphamide (Cytoxan®), ifosfamide, and melphalan • Nitrosoureas: which include streptozocin, carmustine (BCNU), and lomustine • Alkyl sulfonates: busulfan • Triazines: dacarbazine (DTIC) and temozolomide (Temodar®) • Ethylenimines: thiotepa and altretamine (hexamethylmelamine)
Antimetabolites	• 5-Fluorouracil (5-FU) • 6-Mercaptopurine (6-MP) • Capecitabine (Xeloda®) • Cladribine • Clofarabine • Cytarabine (Ara-C®) • Floxuridine • Fludarabine • Gemcitabine (Gemzar®) • Hydroxyurea • Methotrexate • Pemetrexed (Alimta®) • Pentostatin • Thioguanine
Anthracyclines	• Daunorubicin • Doxorubicin (Adriamycin®) • Epirubicin • Idarubicin
Mitotic inhibitors	• Taxanes: paclitaxel (Taxol®) and docetaxel (Taxotere®) • Epothilones: ixabepilone (Ixempra®) • Vinca alkaloids: vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®) • Estramustine (Emcyt®)
Hormone chemotherapeutic drugs	• Prednisone, methylprednisolone (Solu-Medrol®), and dexamethasone (Decadron®)

3. General side effects and bone marrow toxicity:

Chemotherapy exerts systemic effects because it targets all rapidly dividing cells, not only malignant ones. Common toxicities include gastrointestinal disturbances such as nausea, vomiting, mucositis, and diarrhea due to injury of mucosal epithelium (24). Dermatologic effects, particularly alopecia, arise from damage to hair follicle cells(25) . Neurological complications, including peripheral neuropathy, are frequently observed with vinca alkaloids and taxanes (26). Cardiotoxicity is a hallmark of anthracyclines, while nephrotoxicity is associated with platinum compounds such as cisplatin (27). Among these adverse effects, bone marrow toxicity (myelosuppression) is the most clinically significant, as nearly all

cytotoxic agents impair hematopoiesis by damaging progenitor cells (28). This manifests as anemia, leading to fatigue and dyspnea; neutropenia, which predisposes patients to severe infections and febrile neutropenia; and thrombocytopenia, resulting in easy bruising and mucosal bleeding (29). In severe cases, pancytopenia reflects profound marrow aplasia and becomes dose-limiting for therapy (30). Bone marrow suppression is dose-dependent and varies by drug class: alkylating agents and antimetabolites cause profound suppression, taxanes and vinca alkaloids predominantly induce neutropenia, and anthracyclines produce balanced suppression across lineages (28,31,32). Clinically, monitoring blood counts before each cycle and implementing supportive measures such as transfusions or growth factors are essential to mitigate these toxicities and maintain treatment efficacy (29,32).

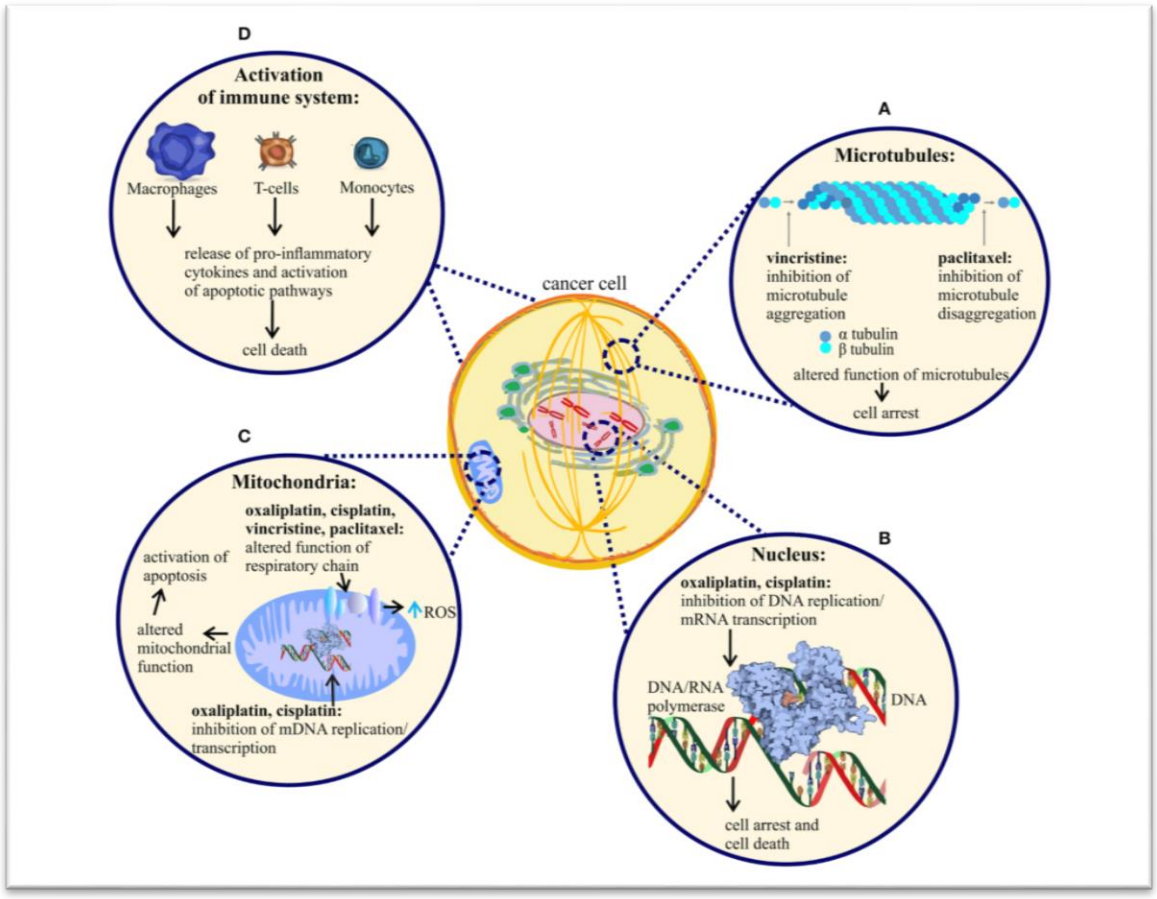


Figure 4: | Mechanism of action of vincristine, paclitaxel, oxaliplatin and cisplatin. Anti-tumor mechanism of action of vincristine, paclitaxel, oxaliplatin and cisplatin leading to cell arrest and cell death. (A) Vincristine prevents microtubule aggregation, whereas paclitaxel prevents microtubule disaggregation, an effect leading to cancer cell division arrest and cell death. (B) Oxaliplatin and cisplatin bind to nuclear DNA (deoxyribonucleic acid) of cancer cells, causing disruption of DNA replication and RNA (ribonucleic acid) transcription and subsequent arrest of cancer cell division. The DNA adducts activate apoptotic pathways that induce cell death and tumor degradation. (C) All four anti-tumor agents alter the function of mitochondria, followed by disruption of respiratory chain function and increased production of reactive oxygen species (ROS). Additionally, oxaliplatin and cisplatin cause damage to cancer cell mitochondria by binding to mitochondrial DNA, altering mDNA replication and transcription. (D) All four agents cause activation of immune cells, an effect likely contributing to tumor cell degradation. Only a few representative immune cell-types are shown.(33)

5) Bone marrow aplasia

1. Definition of Bone marrow aplasia

Bone marrow aplasia, also referred to as *aplastic anemia*, is a very serious hematological disorder characterized by a profound failure of the bone marrow to sustain normal hematopoiesis. It is defined by two cardinal features: a markedly hypocellular marrow**,** in which hematopoietic tissue is replaced by fatty elements, and a peripheral pancytopenia, manifesting as anemia, leukopenia, and thrombocytopenia. Clinically, this condition represents a life-threatening collapse of blood cell production, with severity ranging from moderate to very severe forms, established by hematological criteria such as absolute neutrophil count, platelet count, and reticulocyte levels. Bone marrow aplasia may be congenital**,** as in Fanconi anemia, or acquired, most often secondary to toxic exposures, viral infections, autoimmune mechanisms, or iatrogenic causes such as chemotherapy and radiotherapy. Its definition thus integrates both morphological and functional dimensions: the absence of adequate hematopoietic precursors in the marrow and the resulting cytopenias in peripheral blood, which together form the clinical and biological hallmark of the disease(34,35).

Table 2: Definition of aplastic anemia with severity criteria(36)*

Classification	Criteria
Severe	BM cellularity $< 25\%$ (or $< 50\%$ if $< 30\%$ of BM is hematopoietic cells) AND ≥ 2 of the following: • Peripheral blood neutrophil count $< 0.5 \times 10^9$/L • Peripheral blood platelet count $< 20 \times 10^9$/L • Peripheral blood reticulocyte count $< 20 \times 10^9$/L
Very severe	As above, but peripheral blood neutrophil count must be $< 0.2 \times 10^9$/L
Nonsevere	Hypocellular BM with peripheral blood values not meeting criteria for severe aplastic anemia

2. Pathophysiology of bone marrow aplasia

❖ *Immune-Mediated Mechanisms:*

In acquired aplasia, the predominant mechanism is immune-mediated destruction of hematopoietic stem cells. Autoreactive cytotoxic T lymphocytes infiltrate the marrow and

release pro-inflammatory cytokines such as interferon-γ and tumor necrosis factor-α. These mediators suppress stem cell proliferation, induce apoptosis, and disrupt the hematopoietic microenvironment. The resulting collapse of the stem cell pool explains the hypocellularity observed in bone marrow biopsies (34,35).

- *Direct Toxic Injury:*

Chemotherapeutic agents, ionizing radiation, and certain environmental toxins can cause **direct DNA damage** in hematopoietic progenitors. This injury impairs the regenerative capacity of the marrow and leads to irreversible stem cell depletion. Drug-induced aplasia is a well-recognized complication of cytotoxic therapy, highlighting the vulnerability of the marrow to exogenous insults (35,36).

- *Genetic Predisposition:*

Congenital forms, such as Fanconi anemia, are linked to defective DNA repair pathways. Mutations in genes responsible for genomic stability render hematopoietic cells highly susceptible to chromosomal breakage and apoptosis. This genetic fragility explains the early onset and progressive nature of marrow failure in inherited syndromes (36).

- *Microenvironmental Dysfunction:*

Beyond stem cell destruction, aplasia also involves disruption of the marrow niche. Alterations in stromal cells, endothelial support, and growth factor signaling reduce the ability of the marrow to sustain hematopoiesis. This microenvironmental failure amplifies the effects of immune and toxic injury, creating a vicious cycle of marrow suppression (34).

- *Integrated Pathogenesis:*

The interplay between immune attack, genetic predisposition, and environmental insults ultimately results in a profound reduction of functional hematopoietic precursors. This integrated pathogenesis explains the clinical picture of pancytopenia and marrow hypocellularity, which are the hallmarks of bone marrow aplasia (34,35).

3. Histopathology of bone marrow aplasia

Bone marrow aplasia is histologically defined by a markedly hypocellular marrow in which hematopoietic tissue is severely reduced and largely replaced by adipose tissue, in the absence of significant fibrosis or malignant infiltration. Marrow cellularity is usually below 10% of the expected value for age, with only scattered residual foci of erythroid, myeloid, and megakaryocytic precursors(37). The intertrabecular spaces are predominantly occupied by mature adipocytes, which expand into regions normally filled by hematopoietic cells, producing the characteristic “fatty aplastic marrow” appearance described in classic hematopathology series(38). Granulocytic and erythroid precursors are markedly decreased, and megakaryocytes are typically absent or extremely rare, but without cytological atypia or dysplastic changes, which helps distinguish aplastic anemia from myelodysplastic syndromes. The stromal framework, including reticulin fibers, is generally preserved and often normal or reduced, with no significant increase in reticulin or collagen deposition, thereby excluding primary myelofibrosis and other fibrosing marrow disorders. The vascular sinusoids may appear narrowed or collapsed due to the loss of hematopoietic bulk, although endothelial integrity is maintained(39).

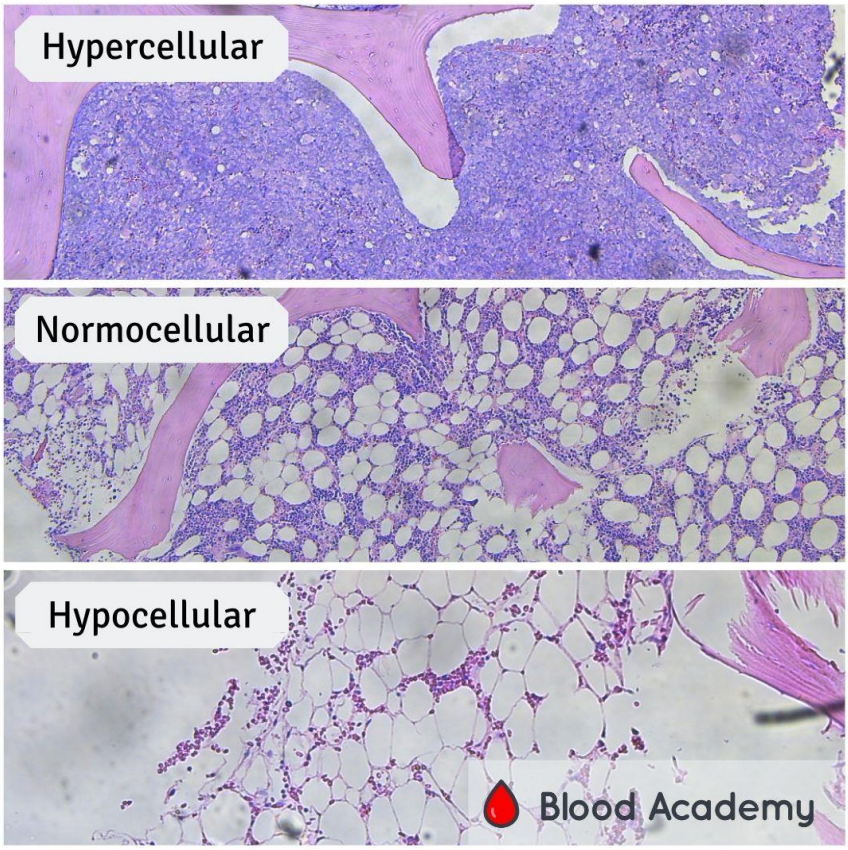


Figure 5: normocellular vs hypocellular and hypercellular in bone marrow(40)

4. Clinical features

❖ *Hematological Features:*

Bone marrow failure manifests through a constellation of clinical syndromes reflecting the consequences of pancytopenia. The **anemic syndrome** is highly variable among individuals and tends to be more severe when anemia develops rapidly. Patients consistently exhibit mucocutaneous pallor, particularly of the nail beds and conjunctivae. Physiological adaptations to reduced oxygen transport include exertional dyspnea progressing to dyspnea at rest, tachypnea, and tachycardia. When compensatory mechanisms are exceeded, tissue hypoxia produces poor tolerance of anemia, with angina or even myocardial infarction in the heart, functional systolic murmurs, and neurological symptoms such as asthenia, slowed cognition, presyncope, vertigo, and headaches. **The hemorrhagic syndrome** results from defective primary hemostasis due to thrombocytopenia. Patients present with mucocutaneous bleeding—epistaxis, gingival hemorrhage, oral blood blisters, disseminated non-infiltrated purpura, ecchymoses, menorrhagia, and subconjunctival hemorrhage. Severe cases may involve prolonged bleeding from minor cuts, deep hematomas (including psoas involvement), hematuria, hemarthrosis, and life-threatening hemorrhages such as intracranial, gastrointestinal, or pulmonary bleeding. **The infectious syndrome** reflects profound neutropenia and lymphocyte dysfunction. Bacterial infections with Gram-positive cocci and Gram-negative bacilli are common and rapidly life-threatening, with risk increasing below 500 neutrophils/mm^3 and becoming critical below 200/mm^3. After 8–10 days of neutropenia, fungal infections are frequent. Humoral immunodeficiency predisposes to recurrent infections with encapsulated organisms (pneumococcus, Haemophilus, meningococcus), viral reactivations (HSV, VZV), and opportunistic pathogens such as Pneumocystis, Toxoplasma, Candida, and Aspergillus. Cellular immunodeficiency further contributes to viral recurrences and intracellular infections. Clinically, patients may present with fever, flu-like syndromes, asthenia, chills, headaches, myalgias, and arthralgias. Severe infections can progress to septic shock, with hypotension, tachycardia, hypoxemia, marbling, cyanosis, and peripheral coldness. Purpura must be carefully assessed, as fulminant meningococcal or pneumococcal sepsis, or disseminated intravascular coagulation, represent grave prognostic signs. Organ-specific manifestations include urinary symptoms with positive dipstick findings, pharyngeal or sinus pain, odynophagia, rhinorrhea, purulent otorrhea, respiratory complaints such as cough, expectoration, chest pain, and focal auscultatory findings, as well as gastrointestinal symptoms including abdominal pain, diarrhea, vomiting, and peritoneal

irritation. Together, these syndromes highlight the systemic impact of marrow aplasia and the urgent need for early recognition and intervention(41,41,42).

❖ *Systemic & Organ-Specific Manifestations of Bone Marrow Aplasia Post-Chemotherapy:*

Extra-hematological manifestations are characterized by a constellation of systemic and organ-specific manifestations that reflect the profound pancytopenia induced by cytotoxic agents. **Mucocutaneous features** such as pallor, easy bruising, petechiae, purpura, and painful oral ulcers are common, resulting from anemia, thrombocytopenia, and neutropenia. **Respiratory involvement** often presents as dyspnea secondary to anemia and recurrent or severe pneumonia due to neutropenia, frequently caused by opportunistic pathogens including fungi and viruses. **Gastrointestinal manifestations** include mucositis, diarrhea, and gastrointestinal bleeding, which may be exacerbated by direct mucosal toxicity of chemotherapy and compounded by thrombocytopenia. **Neurological complications** such as headache, seizures, or focal deficits typically arise from intracranial hemorrhage in the context of severe thrombocytopenia, while anemia may contribute to nonspecific neurological symptoms like fatigue and dizziness(43). These systemic features not only highlight the multi-organ impact of marrow failure but also underscore the clinical severity and prognostic implications of post-chemotherapy aplasia, where infectious and hemorrhagic complications remain the leading causes of morbidity and mortality(44).

5.Paraclinical features

❖ *Hematological Investigations:*

The **complete blood count (CBC)** is the primary paraclinical tool for detecting bone marrow aplasia after chemotherapy. It consistently demonstrates pancytopenia, reflecting global suppression of hematopoiesis. The anemia is typically normocytic and normochromic, with hemoglobin levels often falling below 8 g/dL in severe cases. A hallmark finding is a markedly reduced **reticulocyte count**, which confirms ineffective erythropoiesis rather than peripheral destruction. This distinction is critical, as it differentiates aplasia from hemolytic processes or acute blood loss(45).

Leukopenia is dominated by **neutropenia**, frequently with absolute neutrophil counts (ANC) below 500/µL, which places patients at high risk for opportunistic infections. Lymphopenia

may also occur, further compromising immune defense. **Thrombocytopenia** is often profound, with platelet counts <20,000/µL, predisposing to spontaneous mucocutaneous bleeding and severe hemorrhagic complications.

The peripheral blood smear is an essential complement to the complete blood count in the evaluation of bone marrow aplasia after chemotherapy. It provides direct morphological evidence of the cytopenias observed in automated counts. Typically, the smear demonstrates a marked reduction in all cellular elements, with normocytic and normochromic red blood cells, a paucity of leukocytes, and severely decreased platelets. The absence of reticulocytes confirms ineffective erythropoiesis(46).

Importantly, the smear lacks blasts, abnormal precursors, or dysplastic changes, which helps distinguish aplastic anemia from acute leukemia or myelodysplastic syndromes. Red cell morphology is usually unremarkable, though mild anisocytosis or poikilocytosis may occasionally be seen due to transfusion or nutritional deficiencies. Platelets, when present, appear morphologically normal but are markedly reduced in number. White cells are few, with neutrophils showing normal morphology but reduced absolute counts.

Thus, the peripheral smear not only corroborates CBC findings but also plays a crucial role in differential diagnosis, excluding clonal hematologic disorders and confirming the diagnosis of marrow aplasia. It is a simple, inexpensive, and rapid test that remains indispensable in clinical practice.

Together, CBC and smear findings not only establish the presence of marrow failure but also guide the urgency of supportive care. Severe cytopenias correlate with increased risk of infection, bleeding, and transfusion dependence, underscoring the clinical importance of these paraclinical parameters.

❖ *Bone Marrow Studies:*

Bone marrow examination remains the gold standard for confirming aplasia after chemotherapy. **Bone marrow aspiration** typically reveals marked hypocellularity, with a striking reduction in hematopoietic precursors across all three lineages. The aspirate often appears dilute or “dry tap,” reflecting the paucity of active marrow elements. Importantly,

there is no evidence of malignant infiltration or dysplasia, which helps differentiate aplastic anemia from acute leukemia or myelodysplastic syndromes.

Bone marrow biopsy provides more definitive information. Histological sections demonstrate replacement of hematopoietic tissue by adipocytes, with cellularity often reduced to less than 25% of normal for age. Residual hematopoietic islands may persist but are insufficient to sustain peripheral counts. Stromal changes, such as increased reticulin fibers, may be observed but are not a dominant feature. The biopsy also excludes other causes of marrow failure, such as fibrosis, metastatic infiltration, or granulomatous disease.

Together, aspiration and biopsy findings establish the diagnosis of aplasia, complementing hematological investigations. They also provide prognostic information, as the degree of hypocellularity correlates with severity and clinical outcomes. In the context of chemotherapy, marrow studies confirm that cytotoxic agents are the primary cause of suppression, guiding therapeutic decisions and supportive care(47).

❖ *Biochemical and Immunological Tests:*

Biochemical and immunological investigations play a complementary role in the evaluation of bone marrow aplasia after chemotherapy. Serum biochemistry is primarily used to exclude alternative causes of cytopenia. Measurement of vitamin B12 and folate levels helps rule out megaloblastic anemia, while serum ferritin and lactate dehydrogenase (LDH) provide indirect markers of ineffective erythropoiesis and hemolysis. Elevated LDH may suggest concurrent cell destruction, whereas normal values support a purely hypoplastic process.

Immunological studies are particularly relevant in distinguishing immune-mediated aplasia from chemotherapy-induced marrow suppression. Flow cytometry can detect residual hematopoietic progenitors and assess lymphocyte subsets, while also identifying clonal populations that may indicate paroxysmal nocturnal hemoglobinuria (PNH), a condition frequently associated with aplastic anemia. In addition, screening for autoantibodies (such as antinuclear antibodies) may reveal underlying autoimmune mechanisms contributing to marrow failure.

These tests, although not diagnostic on their own, provide essential information for differential diagnosis. They help exclude nutritional deficiencies, hemolytic processes, and

autoimmune marrow suppression, thereby reinforcing the diagnosis of chemotherapy-related aplasia. Their integration with hematological and marrow studies ensures a comprehensive evaluation of the patient's condition(48).

❖ *Cytogenetic and Molecular Studies:*

Cytogenetic and molecular investigations are indispensable in the paraclinical evaluation of bone marrow aplasia, particularly for differentiating **chemotherapy-induced marrow suppression** from clonal hematologic disorders. **Conventional karyotyping** allows detection of chromosomal abnormalities frequently associated with myelodysplastic syndromes (MDS) or acute leukemia, such as monosomy 7, trisomy 8, or complex karyotypes. Their presence suggests clonal evolution rather than pure aplasia, which has important prognostic and therapeutic implications.

Fluorescence in situ hybridization (FISH) and **comparative genomic hybridization (CGH)** provide higher sensitivity for detecting subtle chromosomal changes. In aplastic anemia, cytogenetic studies are often normal, but the emergence of abnormalities during follow-up may indicate progression to MDS or acute leukemia.

At the molecular level, **next-generation sequencing (NGS)** has revealed recurrent mutations in genes involved in DNA repair, telomere maintenance, and hematopoietic regulation. Mutations in *DNMT3A*, *ASXL1*, or *TP53* may appear in patients with aplasia and are associated with clonal hematopoiesis and increased risk of malignant transformation. Screening for **PIGA mutations** is essential to identify paroxysmal nocturnal hemoglobinuria (PNH) clones, which frequently coexist with aplastic anemia and influence treatment decisions.

Thus, cytogenetic and molecular studies not only refine the diagnosis but also provide **prognostic markers**, guiding long-term monitoring and therapeutic strategies in patients with chemotherapy-related marrow aplasia(49).

❖ *Infectious Workup:*

Infectious etiologies must always be considered in the evaluation of bone marrow aplasia, particularly in patients who have received chemotherapy, as viral infections can mimic or

exacerbate marrow suppression. Among the most relevant agents are parvovirus B19, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and hepatitis viruses (A, B, C). Parvovirus B19 is classically associated with pure red cell aplasia, but in immunocompromised hosts it may contribute to global marrow failure. EBV and CMV can induce transient aplasia or trigger autoimmune mechanisms that suppress hematopoiesis. Hepatitis-associated aplastic anemia, although rare, is a well-recognized entity, typically occurring weeks to months after acute viral hepatitis(50).

Diagnostic evaluation includes serological testing (IgM and IgG antibodies), polymerase chain reaction (PCR) for viral DNA or RNA, and in some cases immunohistochemistry on bone marrow biopsy specimens. Parvovirus B19 infection, for example, can be confirmed by PCR detection of viral DNA or by identifying giant pronormoblasts with intranuclear inclusions on marrow biopsy. EBV and CMV are best detected by PCR or viral load assays, while hepatitis viruses require combined serology and PCR(51).

Identifying infectious causes is crucial, as they may require specific antiviral therapy or immunoglobulin administration, and their recognition prevents misclassification of aplasia as idiopathic or chemotherapy-induced. Thus, infectious workup is an integral part of the paraclinical evaluation, ensuring accurate diagnosis and appropriate management.

❖ *Imaging (Optional/Complementary):*

Although not routinely required, imaging studies can provide supportive evidence in the evaluation of bone marrow aplasia after chemotherapy. Magnetic resonance imaging (MRI) of the bone marrow is the most informative modality. In aplastic anemia, MRI typically demonstrates replacement of hematopoietic tissue by fat, leading to a diffuse hypointense signal on T1-weighted images and hyperintense signal on fat-sensitive sequences. These findings correlate with marrow hypocellularity observed on biopsy(52).

Computed tomography (CT) and plain radiographs have limited diagnostic value but may occasionally reveal indirect signs such as osteopenia or skeletal changes associated with chronic marrow failure. Positron emission tomography (PET) is rarely indicated, but can help exclude infiltrative or malignant processes when biopsy results are inconclusive(53).

While imaging cannot replace histological confirmation, it serves as a non-invasive adjunct in selected cases, particularly when biopsy is contraindicated or technically difficult. It also provides a global view of marrow distribution and may be useful in monitoring recovery after cessation of chemotherapy or following therapeutic interventions such as immunosuppression or stem cell transplantation.

5. Integration into Diagnosis:

The integration of paraclinical findings is essential for positive diagnosis of BM aplasia, CBC and peripheral smear provide the first evidence of pancytopenia with reduced reticulocytes, confirming impaired hematopoiesis. Bone marrow aspiration and biopsy then demonstrate hypocellularity and fat replacement, excluding infiltrative or fibrotic processes. Biochemical and immunological tests rule out nutritional deficiencies, hemolysis, and autoimmune mechanisms, while flow cytometry may identify associated PNH clones. Cytogenetic and molecular studies are critical to exclude clonal disorders such as myelodysplastic syndromes or leukemia, and to detect mutations that may predict progression. Infectious workup ensures that viral etiologies such as parvovirus B19, EBV, CMV, or hepatitis viruses are not overlooked, as they can mimic or aggravate aplasia. Finally, imaging studies, though optional, can provide supportive evidence of marrow fat replacement when biopsy is inconclusive.

By synthesizing these results, clinicians can distinguish chemotherapy-induced aplasia from other causes of marrow failure, classify severity, and guide appropriate management. This integrative approach ensures diagnostic accuracy and informs prognosis, forming the cornerstone of patient care in hematology and oncology(54).

6) Bone marrow aplasia post chemotherapy

1. Definition:

Bone marrow aplasia following chemotherapy is a severe, acquired marrow failure characterized by **marked hypocellularity** and **peripheral pancytopenia**—a simultaneous reduction in erythrocytes, leukocytes, and platelets. It results from cytotoxic injury to hematopoietic stem and progenitor cells caused by antineoplastic agents, leading to transient or prolonged suppression of blood cell production. Clinically, this manifests as anemia, infection susceptibility, and bleeding tendency, it can affect the three blood lines or only one

or two lines depending on its clinical status reflecting the global or the partial collapse of marrow hematopoiesis.(41,55,56)

2. Specific mechanism:

Chemotherapy agents exert their antineoplastic effects by targeting rapidly dividing cells, but this non-selective cytotoxicity profoundly affects hematopoietic progenitors in the bone marrow, leading to aplasia. Several mechanisms are implicated:

a) DNA Damage and Cell Cycle Arrest:

Alkylating agents (e.g., cyclophosphamide) and platinum compounds induce DNA cross-linking and strand breaks, triggering apoptosis in hematopoietic stem cells. This direct genotoxic injury results in depletion of marrow precursors and pancytopenia (57,58).

b) Inhibition of Nucleotide Synthesis:

Antimetabolites such as methotrexate and cytarabine interfere with folate metabolism or DNA polymerase activity, halting DNA replication in progenitor cells. The consequence is ineffective hematopoiesis and marrow hypocellularity (59).

c) Topoisomerase-Mediated Apoptosis:

Agents like doxorubicin and etoposide stabilize DNA-topoisomerase complexes, preventing repair of double-strand breaks. This mechanism disproportionately affects proliferating marrow cells, leading to profound aplasia(58) .

d) Microenvironmental Disruption:

Beyond direct cytotoxicity, chemotherapy alters the marrow niche. Endothelial damage, stromal dysfunction, and cytokine imbalance impair the regenerative capacity of hematopoietic stem cells, compounding aplasia severity (59,60).

e) Immune-Mediated Injury:

Certain regimens provoke immune dysregulation, with T-cell activation and cytokine release contributing to secondary destruction of marrow progenitors. This overlaps mechanistically with acquired aplastic anemia (33).

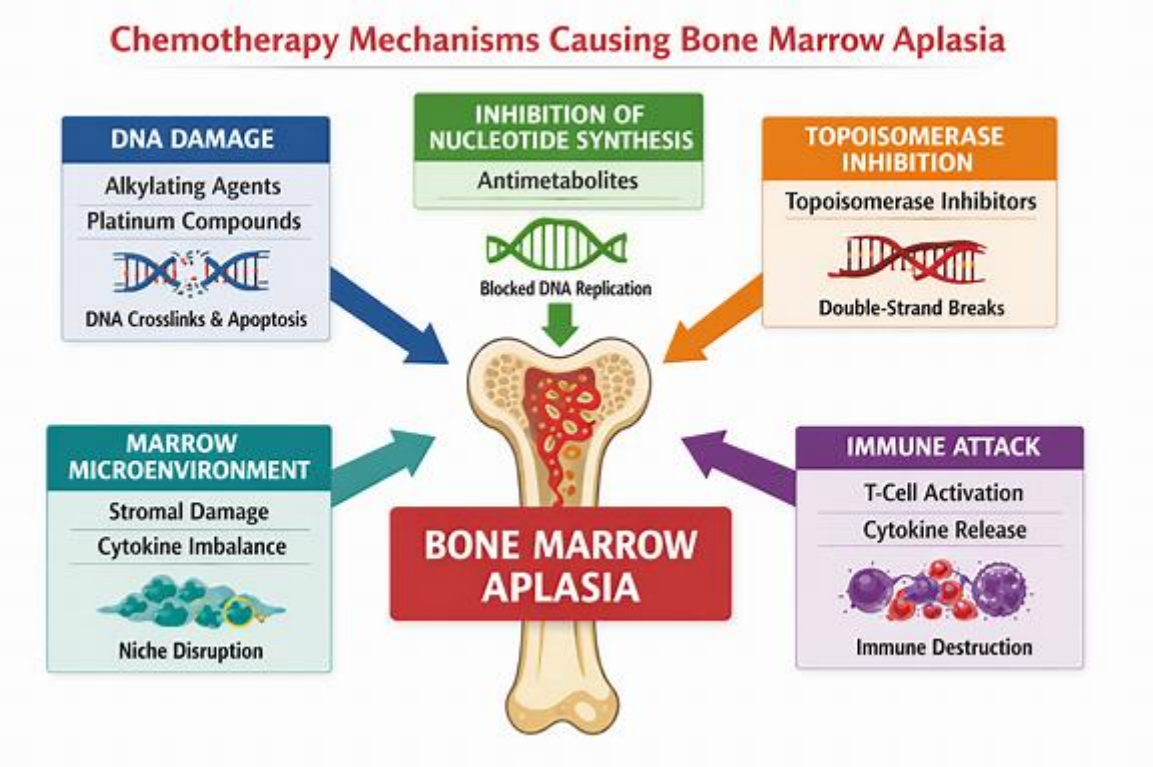


Figure 6: chemotherapy mechanisms causing one marrow aplasia generated by copilot

3. Risque factors

The severity of bone marrow aplasia following chemotherapy is determined by a complex interplay of treatment-related, patient-related, and biological factors. Chemotherapy regimen intensity remains the most critical determinant, with myeloablative protocols such as high-dose cyclophosphamide, busulfan, and cytarabine producing profound marrow suppression, while cumulative exposure to combination regimens further exacerbates cytopenia duration(56).**Age** significantly influences outcomes: pediatric patients, although more vulnerable due to rapidly dividing marrow cells, often demonstrate faster recovery, whereas elderly patients experience more severe and prolonged aplasia due to diminished marrow reserve and comorbidities. **Baseline marrow reserve** is another key factor; patients with prior chemotherapy, radiotherapy, or pre-existing marrow disorders such as myelodysplastic

syndrome are predisposed to deeper and more sustained aplasia(33). **Comorbidities** including viral infections (parvovirus B19, hepatitis, HIV) and organ dysfunction (hepatic or renal impairment) further compromise marrow recovery by either directly suppressing hematopoiesis or altering drug metabolism, thereby increasing toxicity(33,56). Emerging evidence also highlights the role of **genetic and pharmacogenomic factors**, such as thiopurine methyltransferase (TPMT) polymorphisms, which modulate drug metabolism and predispose certain patients to severe marrow toxicity. Finally, the availability of **supportive care measures**—including growth factor support (G-CSF, erythropoietin), transfusion therapy, and infection prophylaxis—plays a decisive role in mitigating the clinical severity of aplasia. Inadequate supportive interventions are strongly associated with prolonged cytopenia and higher rates of infectious and hemorrhagic complications(43). Collectively, these risk factors underscore the heterogeneity of clinical presentations and highlight the importance of individualized risk assessment in predicting severity and guiding management of post-chemotherapy marrow aplasia.

4. Epidemiology

Chemotherapy-induced bone marrow aplasia is a frequent and clinically significant complication across diverse cancer populations. Its epidemiology varies according to cancer type, regimen intensity, and patient characteristics:

Incidence in Solid Tumors: Post-chemotherapy myelosuppression is reported in up to 40–60% of breast cancer patients, with severe aplasia requiring transfusion support in approximately 15–20%(61). In colorectal carcinoma, marrow tolerance studies show that dose-dense regimens significantly increase aplasia risk compared to standard schedules (62).

Hematological Profile Changes: Comparative analyses demonstrate consistent declines in hemoglobin, leukocyte, and platelet counts after chemotherapy, with pancytopenia observed in 25–30% of patients across mixed cancer cohorts (63). Retrospective studies confirm that cytopenia severity correlates with cumulative cycles and drug class exposure (64).

Regional Prevalence Data: In Southeast Asia, neutropenia prevalence among chemotherapy patients reaches 35–40%, with marrow aplasia contributing to prolonged hospitalization and increased infection-related mortality (65). These findings highlight geographic variability linked to supportive care resources and monitoring practices.

Risk Factors: Age over 60 years, baseline cytopenias, and prior radiotherapy are consistently associated with higher rates of chemotherapy-induced aplasia. Genetic predispositions and nutritional status further modulate incidence across populations.

5. Treatment options of Bone Marrow Aplasia

a) Supportive Care:

Initial management focuses on supportive measures to stabilize patients and reduce complications, that's why transfusion support with red blood cells and platelets remains essential in order to correct cytopenias and prevent hemorrhagic episodes (41). In addition prophylactic antibiotics and antifungals are often indicated to mitigate infectious risks in severely neutropenic patients(66).

b) Immunosuppressive Therapy:

For acquired aplastic anemia, immunosuppressive therapy (IST) is the main treatment. The combination of anti-thymocyte globulin (ATG) and cyclosporine has demonstrated significant efficacy in restoring hematopoiesis (41). Durable treatment-free remission has been reported after high-dose cyclophosphamide in severe cases, highlighting its potential role in selected patients (67).

c) Hematopoietic Stem Cell Transplantation (HSCT):

HSCT remains the definitive curative option, particularly in younger patients with matched sibling donors. Advances in conditioning regimens and donor selection have improved survival outcomes(41,66) . However, graft-versus-host disease and transplant-related mortality remain significant challenges.

d) Management of Chemotherapy-Induced Marrow Suppression:

Chemotherapy-induced aplasia requires tailored supportive interventions. Erythropoiesis-stimulating agents and iron supplementation are used to manage chemotherapy-induced anemia (68,69). Strategies to reduce adverse effects while maintaining antineoplastic potency

include dose adjustments, protective agents, and integrative approaches such as acupuncture, which is under investigation for marrow suppression(70,71).

e) Emerging and Adjunctive Therapies:

Novel approaches include physical rehabilitation strategies, such as moderate strength training combined with whole-body vibration, which have shown benefits in reducing chemotherapy-induced peripheral neuropathy and improving patient quality of life (72). Additionally, ongoing research into pathogenesis-driven therapies aims to refine treatment algorithms and improve long-term outcomes (73).

6. Complications

Chemotherapy-induced bone marrow aplasia results in profound myelosuppression, with complications arising from deficits in each hematopoietic lineage. **Neutropenia** is the most critical complication, predisposing patients to severe infections and febrile neutropenia, which often require hospitalization and may necessitate dose reductions or treatment delays (74,75). Prophylactic use of granulocyte colony-stimulating factors has been shown to mitigate this risk (76). **Thrombocytopenia** is another major complication, associated with hemorrhagic events when platelet counts fall below critical thresholds. Clinical manifestations range from mucocutaneous bleeding to life-threatening intracranial or gastrointestinal hemorrhage (77,78). **Anemia**, though less acutely dangerous, significantly impairs functional capacity, causing fatigue, dyspnea, and reduced quality of life; severe cases frequently require transfusion support (79).

Prolonged or profound marrow suppression can lead to **systemic complications**, including sepsis, compromised oncologic outcomes due to treatment interruptions, and, in rare cases, therapy-related myelodysplastic syndromes or acute leukemias(80,81) . Collectively, these complications underscore the dual burden of marrow aplasia: immediate risks of infection, bleeding, and anemia, alongside long-term consequences that may alter disease trajectory and survival. Supportive care strategies—such as antimicrobial prophylaxis, transfusion support, and hematopoietic growth factors—remain central to mitigating these adverse outcomes (82).

Practical part of the thesis

1.Methodoldy & materials:

A) Materials:

1- Study settings:

The study was conducted within the Department of Oncology at Martyr Rezoug Mohamed Cancer Control Center (CLCC), Laghouat, Algeria. Located on the first floor, the department is organized into three units (male, female, and pediatric) and includes the following installations:

- An office for the head doctors
- An office for general doctors and oncology residents
- An office for the head nurse
- An office for the nursing staff
- Three large chemotherapy rooms, designated for male, female, and pediatric patients.
- A reception office
- A treatment room
- Sanitary facilities
- A large waiting room
- Three consultation offices

2. Population Studied:

The study population consisted of patients aged over 15 years and 9 months who were treated with chemotherapy during the study period. Only individuals meeting the inclusion criteria and with complete, exploitable medical records were retained in the final sample.

B) Methodology:

1. Type of Study:

This is a descriptive and analytical retrospective study conducted over a period of 10 months, from 01/08/2025 to 29/04/2026. It included 32 patient records, after exclusion of those that did not meet the required quality criteria.

2. Data collection:

Data were collected using standardized survey sheets and hospital records. Information was obtained from multiple sources, including:

- outpatient consultation files,
- admission registers of the department,
- patient observation charts during hospitalization,
- and, when necessary, supplementary details provided by family members through telephone contact.
- And collecting data directly from the patient itself, hospitalized for bone marrow Aplasia

3)Selection criteria:

All patients hospitalized in the hematology-oncology department during the study period and meeting the eligibility requirements were considered. Only records that were complete and exploitable were included.

3.1. Inclusion Criteria

- Patients aged ≥ 15 years and 9 months.
- Diagnosed with solid tumor.
- Received at least one cycle of chemotherapy.
- Developed bone marrow aplasia, defined by pancytopenia, neutropenia

3.2. Exclusion Criteria

- Patients treated outside the study period.
- Patients with incomplete or non-exploitable medical records.
- Patients with pre-existing aplastic anemia or other concomitant hematological malignancies.
- Patients managed in other institutions outside the study setting.

4. Variables Studied

The following variables were analyzed in order to characterize the study population and evaluate the occurrence of bone marrow aplasia after chemotherapy:

4.1. Epidemiological and Sociodemographic Variables

- Age (≥ 15 years and 9 months).
- Sex.
- Place of residence.

4.2. Clinical Variables

- Type of malignancy (solid tumor or hematologic).
- Stage of disease at diagnosis.
- Performance status at initiation of chemotherapy.
- Comorbidities.

4.3. Therapeutic Variables

- Chemotherapy regimen (agents used, number of cycles).
- Dose intensity and cumulative dose.
- Use of supportive treatments (growth factors, transfusions, antibiotics).

4.4. Laboratory Variables

- Hematologic parameters (hemoglobin, leukocytes, platelets).
- Bone marrow biopsy or aspirate findings (cellularity).

4.5. Complications and Outcomes

- Incidence of bone marrow aplasia.
- Duration of aplasia.
- Infectious or hemorrhagic complications.
- Hospitalization length.
- Clinical outcome (recovery, relapse, mortality).

5.Development of the AplaRisk Application:

Concept

The AplaRisk application was designed as a clinical decision-support tool to assist physicians and medical students in identifying patients at increased risk of developing bone marrow aplasia following chemotherapy. By integrating clinical and biological parameters, the application provides a structured risk estimation framework. At this stage, AplaRisk remains a proposed tool requiring external validation before clinical implementation.

Data Utilized The variables incorporated into the application were selected based on the retrospective data collected in this study. Key parameters included patient age, type of chemotherapy regimen, hematological indices (such as blood counts), and other relevant clinical variables. These inputs form the basis of the risk stratification algorithm.

Functionality The application generates a simplified risk estimate for cancer patients, categorizing the likelihood of developing bone marrow aplasia into three levels: *low*, *moderate*, or *high*. This functionality aims to support clinicians in anticipating complications, optimizing monitoring strategies, and tailoring supportive care.

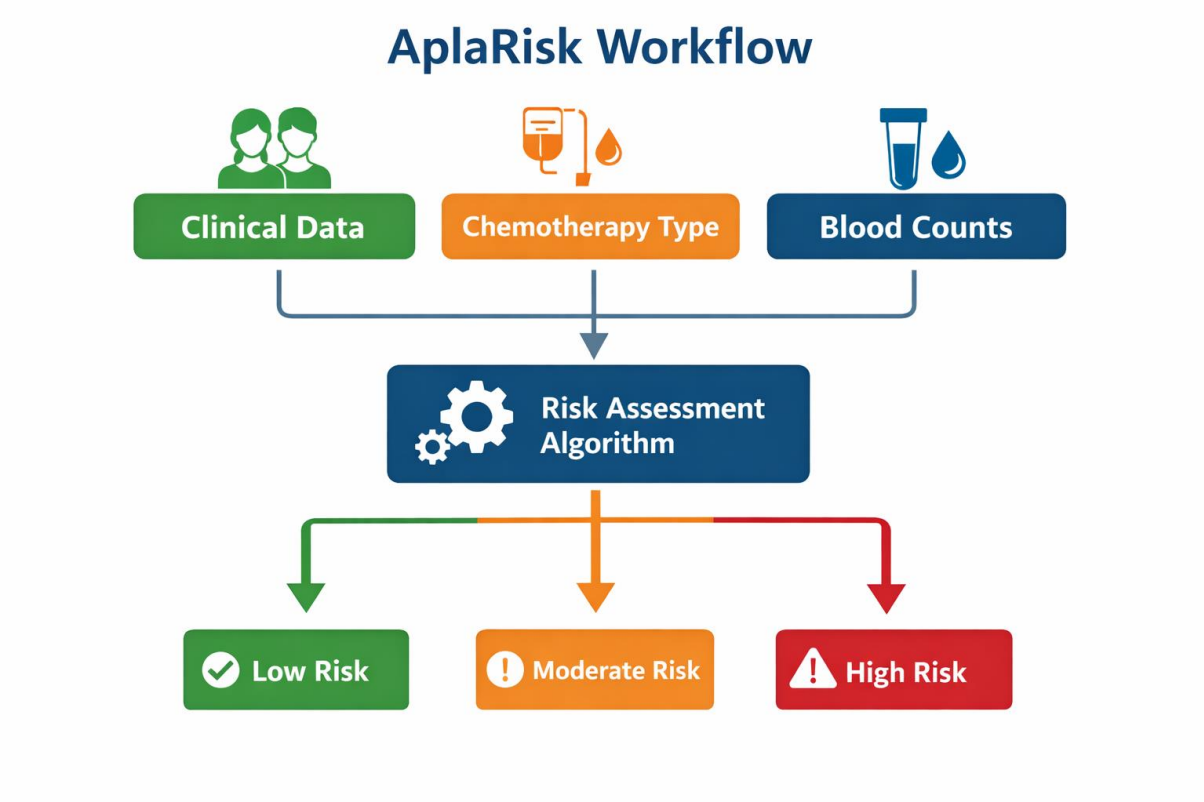


Figure 7 Workflow of the AplaRisk application showing input variables, risk assessment algorithm, and output categories.

5)Data Collection and Analysis

Data were obtained exclusively from archived patient medical records within the hematology-oncology department. Each file was reviewed to extract relevant clinical, therapeutic, and follow-up information. Immediate and long-term outcomes were assessed based on the documentation available in these records, focusing on both clinical and biological parameters.

The collected data were systematically organized and processed using Microsoft Word 2016 and Excel 2016 for documentation and tabulation. Statistical analyses were performed with Jamovi software, version 2023, ensuring consistency, reliability, and reproducibility of results within the study framework.

6)Ethical Considerations

Data collection was performed exclusively from archived patient medical records within the hematology-oncology department. Permission to access and use the archives was formally obtained from the institution. Confidentiality of patient information was rigorously

maintained throughout the study, and all procedures complied with institutional and national ethical guidelines governing clinical research.

7)Study Progression

Total Duration: 9 months

Literature Review: 2 months

Sources included scientific articles, specialized textbooks, academic theses, and recommendations from recognized medical societies.

Study Implementation: 5 months

- Data collection from archived patient medical records and operative registers within the hematology-oncology department.
- Organization of the study sample according to predefined inclusion and exclusion criteria.

Analysis and Discussion of Results: 2 months

- Statistical processing and interpretation of data using Jamovi software (version 2023)**.**

- Integration of findings into the theoretical and practical sections of the thesis.

8)Activities Carried Out by the Intern

1. Conducted bibliographic research to define and refine the thesis topic.
2. Reviewed and extracted data exclusively from archived patient medical records.
3. Organized the study sample according to inclusion and exclusion criteria and study variables.
4. Structured and planned the collected data for statistical analysis.
5. Performed data processing and statistical evaluation using Jamovi software (version 2023).
6. Drafted and revised both the theoretical and practical sections of the thesis.

7. Designed and initiated the development of the APLA Risk application prototype, including database structuring and user interface planning for clinical evaluation.

The results

C) The results:

1) Introduction:

This chapter presents the results of our study conducted on 32 patients diagnosed with bone marrow aplasia following chemotherapy. The collected data encompassed sociodemographic, clinical, paraclinical, therapeutic, and outcome variables, which were systematically analyzed to highlight the main characteristics of the study population and the impact of different treatment modalities.

In total, 32 cases of bone marrow aplasia were identified among 2000 cancer patients treated with chemotherapy. This figure includes both newly diagnosed cases during the study period (August 2025–March 2026) and cases diagnosed prior to August 2025, corresponding to an overall prevalence of **1.6%** in the study population.

2) Sociodemographic Characteristics:

- **The age:**

Table 3 the distribution of patients by their age

Statistic	Value (years)
Mean	48.4
Median	47
Minimum	20
Maximum	72
Range	20–72

Table 3 presents the age distribution of the study population. The mean age was 48.4 years, with a median of 47 years. The youngest patient was 20 years old, while the oldest was 72 years, giving a range of 20 to 72 years. These results indicate that the study group was predominantly middle-aged, with a balanced distribution across younger and older adults

- **The origin:**

Table 4: distribution of patients by origin

Origin	Frequency (n)	Percentage (%)
Urban	21	65.6
Rural	11	34.4
Total	32	100

Table 4 shows the distribution of patients according to their origin. The majority of the study population came from urban areas, representing 65.6% of cases, while 34.4% originated from rural regions. This predominance of urban patients may reflect easier access to specialized oncology and hematology services in city settings compared to rural zones, where diagnostic and referral pathways are often limited.

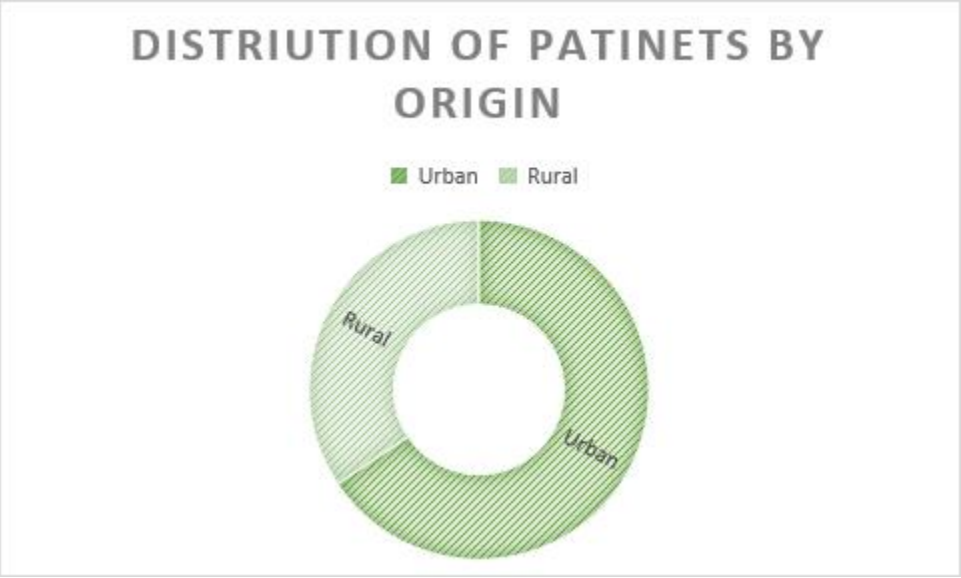


Figure 8: distribution of patients by origin

- **The sex:**

Table 5: Distribution of patients by sex.

Sex	Frequency (n)	Percentage (%)
Male	13	40.6
Female	19	59.4

Table 5 presents the sex distribution of the study population. Females represented the majority, accounting for 59.4% of cases, while males comprised 40.6%. This female predominance suggests that bone marrow aplasia following chemotherapy in this cohort was more frequently observed among women.

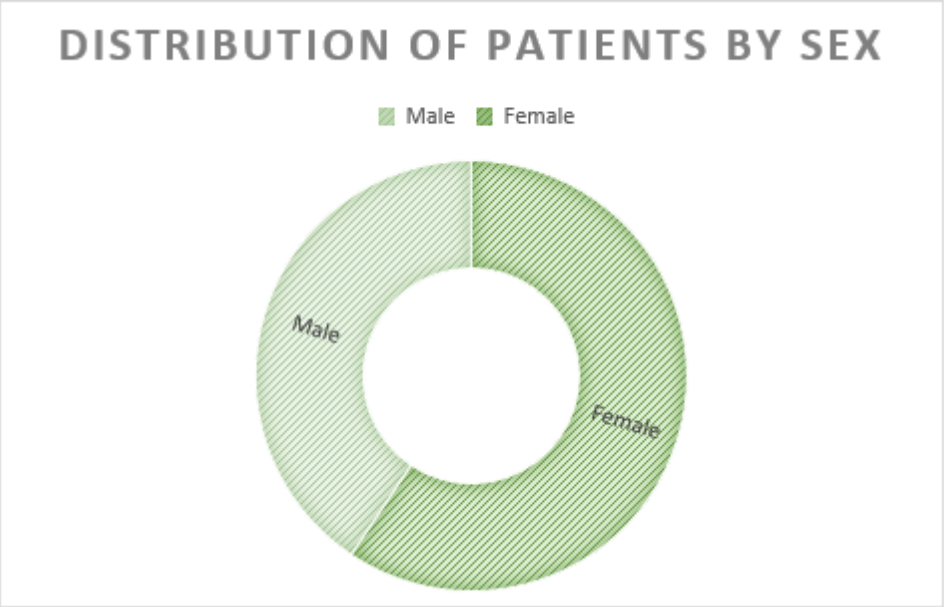


Figure 9:distribution of patients by sex (female vs male)

- **BMI:**

Table 6: the mean, median and minimum of patient's BMI

Statistic	Value (kg/m²)
Mean	23.7
Median	22.1
Minimum	18.2

Maximum	37.3
Range	18.2–37.3

Table 6 presents the distribution of body mass index (BMI) among the study population. The mean BMI was 23.7 kg/m², with a median of 22.1 kg/m². Values ranged from 18.2 to 37.3 kg/m², indicating that most patients fell within the normal weight category, although a subset presented with overweight and obesity. These findings suggest a heterogeneous nutritional profile within the cohort.

- **Comorbidities:**

Table 7: the comorbidities observed in the study population

Comorbidity	Frequency (n)	Percentage (%)
None	17	53.1
Hypertension (HTA)	5	15.6
Diabetes	6	18.8
Kidney failure	0	0
Cardiovascular disease	1	3.1
Epilepsy	1	3.1
Multiple comorbidities	2	6.3

Table 7 summarizes the comorbidities observed in the study population. More than half of the patients (53.1%) had no associated comorbidities. Among those with comorbid conditions, diabetes (18.8%) and hypertension (15.6%) were the most frequent. Cardiovascular disease and epilepsy were each reported in 3.1% of cases, while 6.3% of patients presented with multiple comorbidities. These findings indicate that although the majority of patients were free of chronic illnesses, a significant subset carried metabolic or neurological conditions that could influence their clinical course.

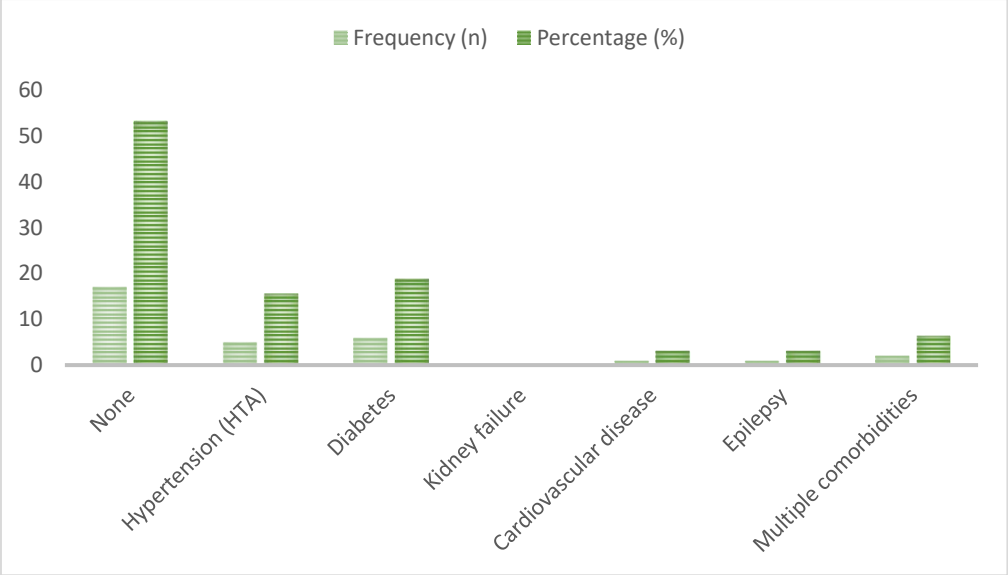


Figure 10: percentage of comorbidities in patients with bone marrow aplasia

- **Smoking:**

This figure below presents the smoking status of the study population. The majority of patients were non-smokers (78.1%), while 21.9% reported active smoking. This distribution indicates that most individuals in the cohort did not have tobacco exposure, although a notable minority were smokers, which may represent an additional risk factor influencing their clinical outcomes.

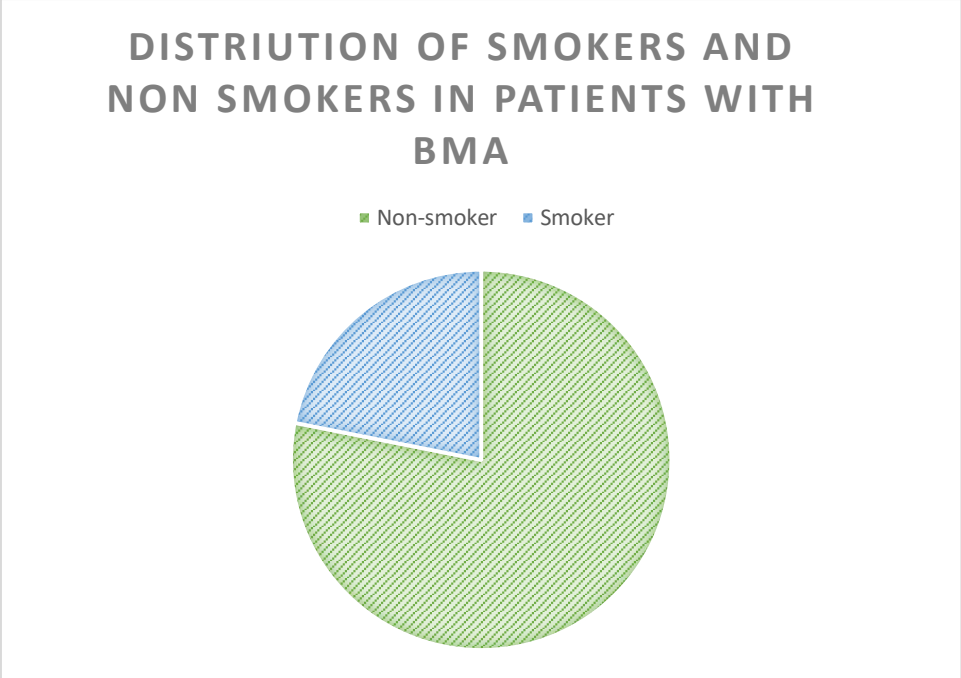


Figure 11: distribution of smokers and non-smokers in patients with BMA

A summary: the sociodemographic characteristics of the study population. The mean age was 48.4 years, with a median of 47 years (range: 20–72). Females represented the majority (59.4%), while males accounted for 40.6%. Most patients originated from urban areas (65.6%), compared to 34.4% from rural regions. The mean body mass index (BMI) was 23.7 kg/m², with values ranging from 18.2 to 37.3 kg/m², indicating a predominance of normal weight but with some cases of overweight and obesity. More than half of the patients (53.1%) had no comorbidities, while diabetes (18.8%) and hypertension (15.6%) were the most frequent conditions; cardiovascular disease and epilepsy were each reported in 3.1% of cases, and 6.3% presented with multiple comorbidities. Regarding smoking status, the majority were non-smokers (78.1%), whereas 21.9% reported active smoking. Overall, the cohort was predominantly middle-aged, female, urban, and largely free of chronic illnesses, with a minority presenting lifestyle or metabolic risk factors.

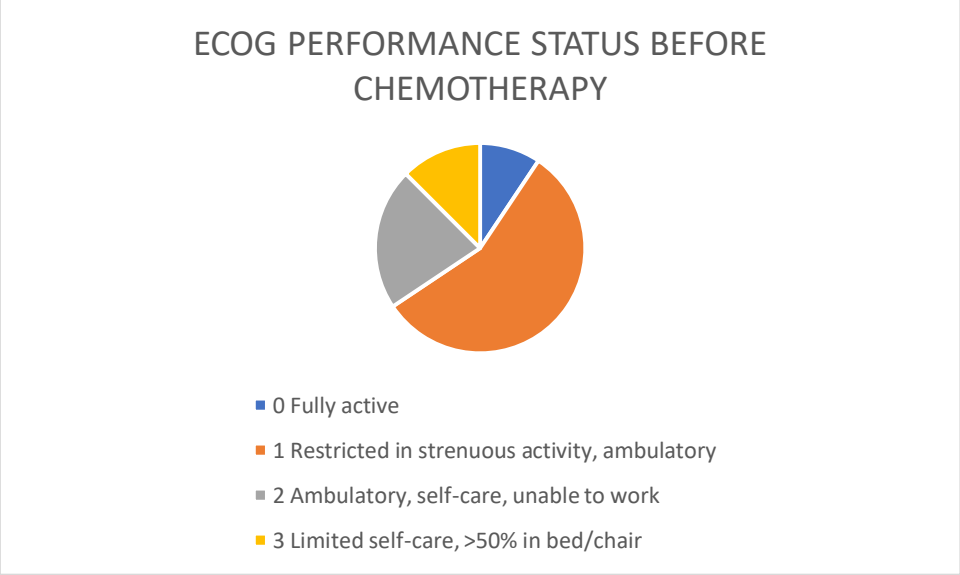
3) Clinical Characteristics:

- **ECOG Performance Status:**

Table 8: the ECOG performance status of the study population

ECOG Grade	Description	Frequency (n)	Percentage (%)
0	Fully active	3	9.4
1	Restricted in strenuous activity, ambulatory	18	56.3
2	Ambulatory, self-care, unable to work	7	21.9
3	Limited self-care, >50% in bed/chair	4	12.5

Table 8 summarizes the ECOG performance status of the study population. More than half of the patients (56.3%) had an ECOG score of 1, indicating they were ambulatory but restricted in strenuous activities. A smaller proportion (21.9%) had ECOG 2, reflecting limitations in work activities despite being capable of self-care. Four patients (12.5%) were classified as ECOG 3, with significant functional impairment requiring prolonged bed or chair rest. Only three patients (9.4%) were fully active (ECOG 0). Overall, the cohort demonstrated a predominance of patients with mild functional limitations, with a minority presenting severe disability.



- **Cancer type distribution:**

Table 9: the distribution of cancer types among the study population

Cancer type	Frequency (n)	Percentage (%)
Breast	12	37.5

Bone	3	9.4
Colon	3	9.4
Sigmoid	2	6.3
Bile duct	2	6.3
Ovary	2	6.3
Soft tissue (Molle)	2	6.3
Lung	1	3.1
Stomach	1	3.1
Oral	1	3.1
Rectum	1	3.1
Prostate	1	3.1
Krukenberg tumor	1	3.1

Table 9 summarizes the distribution of cancer types among the study population. Breast cancer was the most frequent diagnosis, accounting for 37.5% of cases. Bone and colon cancers each represented 9.4% of patients, while sigmoid, bile duct, ovary, and soft tissue sarcomas were observed in 6.3% each. Less common malignancies included lung, stomach, oral, rectal, prostate, and Kruckenberg tumors, each reported in 3.1% of cases. Overall, the cohort was dominated by breast cancer, with a heterogeneous representation of other solid tumors.

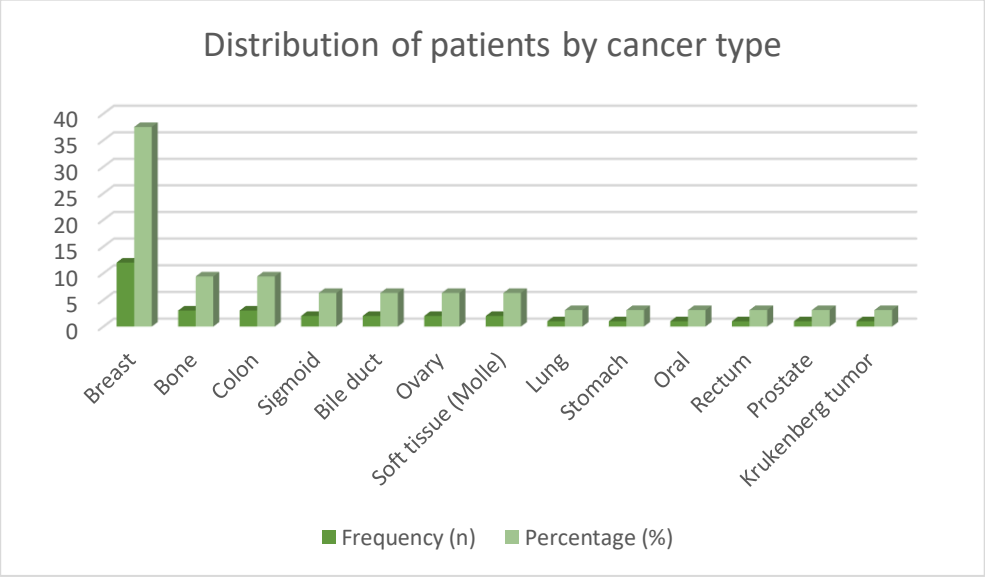


Figure 12 distribution of patients by cancer type

- **Histopathology type:**

Table 10: the histopathological diagnoses of the study population

Histopathology	Frequency (n)	Percentage (%)
Adenocarcinoma (ADK)	9	28.1
Carcinoma non spécifique (CNS)	10	31.3
└ CNS triple-négatif	3	9.4
└ CNS Lumb	1	3.1
Carcinoma (unspecified)	3	9.4
Sarcoma	3	9.4
Cholangiocarcinoma	2	6.3
Germ cell tumor (TG)	2	6.3
Carcinoma lobulaire infiltrant (CLE)	1	3.1

Table 10 summarizes the histopathological diagnoses of the study population. Carcinomas represented the majority of cases, with non-specific carcinoma (31.3%) and adenocarcinoma (28.1%) being the most frequent subtypes. Within the CNS group, triple-negative tumors accounted for 9.4% and one case was classified as CNS Lumb. Sarcomas and unspecified carcinomas each represented 9.4% of patients, while cholangiocarcinoma and germ cell tumors were observed in 6.3% each. A single case (3.1%) was identified as lobular infiltrating carcinoma. Overall, the cohort was dominated by breast-related histology's (CNS, ADK, CLE), reflecting the predominance of breast cancer in the study population.

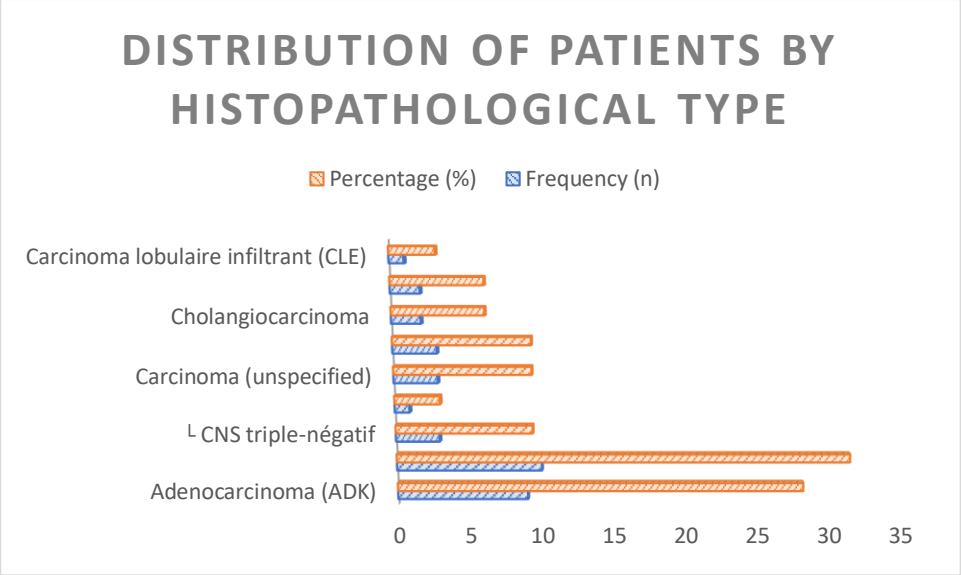


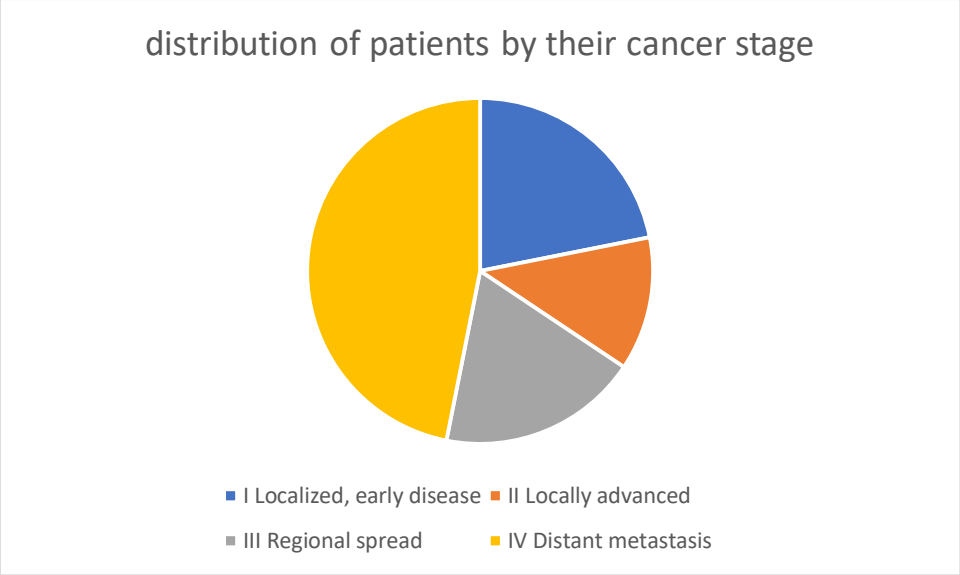
Figure 13 distribution of patients by their histopathological type

- **Cancer Stage**

Table 11: the distribution of cancer stages among the study population

Stage	Description (TNM)	Frequency (n)	Percentage (%)
I	Localized, early disease	7	21.9
II	Locally advanced	4	12.5
III	Regional spread	6	18.8
IV	Distant metastasis	15	46.9

Table 11 summarizes the distribution of cancer stages among the study population. Nearly half of the patients (46.9%) were diagnosed at stage IV, reflecting advanced disease with distant metastasis. Stage I cases accounted for 21.9%, while stage II and stage III represented 12.5% and 18.8% respectively. These findings highlight a predominance of late-stage diagnoses, suggesting delayed presentation or limited access to early detection in this cohort.



- **Diagnosis status:**

Table 12: the treatment status of the study population

Status category	Frequency (n)	Percentage (%)
Newly diagnosed / induction	13	40.6
Consolidation / maintenance	4	12.5
Relapse / refractory	7	21.9
First-line palliative	8	25

Table 12 summarizes the treatment status of the study population. The largest group consisted of newly diagnosed patients undergoing induction therapy (40.6%). First-line palliative treatment was administered in 25.0% of cases, while relapse or refractory disease was observed in 21.9%. Consolidation or maintenance therapy accounted for 12.5% of patients. These findings indicate that the cohort was heterogeneous, with a predominance of patients at the beginning of their therapeutic pathway, but also a substantial proportion already receiving palliative or salvage treatment

A summary: The clinical characteristics of the study population revealed a predominance of patients with mild functional limitations, as more than half (56.3%) had an ECOG score of 1, while 12.5% were classified as ECOG 3, indicating significant disability. Breast cancer was the most frequent malignancy (37.5%), followed by bone and colon cancers (9.4% each),

with other solid tumors such as sigmoid, bile duct, ovary, soft tissue sarcomas, and less common sites (lung, stomach, oral, rectum, prostate, Krukenberg) contributing to the heterogeneity of the cohort. Histopathological analysis confirmed the predominance of breast-related histologies, with non-specific carcinoma (31.3%) and adenocarcinoma (28.1%) being the most common, alongside sarcomas (9.4%), cholangiocarcinoma's (6.3%), germ cell tumors (6.3%), and isolated cases of lobular carcinoma. Regarding disease stage, nearly half of the patients (46.9%) were diagnosed at stage IV, reflecting advanced disease, while 21.9% were stage I and smaller proportions were stage II (12.5%) and stage III (18.8%). Treatment status showed that 40.6% were newly diagnosed and undergoing induction therapy, 25.0% were receiving first-line palliative treatment, 21.9% had relapsed or refractory disease, and 12.5% were in consolidation or maintenance. Overall, the cohort was characterized by a predominance of breast cancer, advanced-stage disease, and patients at the beginning of their therapeutic pathway, with a significant subset already engaged in palliative or salvage treatment.

4) Treatment Modalities:

- **Radiotherapy:**

  - **Table 13:** the radiotherapy modalities in the study population

Yes	Breast	33	4	12.5
Yes	Oral cavity	35	1	3.1
No	—	—	27	84.4

Table 13 summarizes the radiotherapy modalities in the study population. Out of 32 patients, five (15.6%) underwent radiotherapy. The majority of irradiated cases involved breast cancer, with four patients treated at a dose of 33 Gy. One patient received radiotherapy for oral cavity malignancy with a dose of 35 Gy. The remaining 27 patients (84.4%) did not receive radiotherapy. This distribution highlights the selective use of radiotherapy in the cohort, predominantly for breast cancer, with a relatively homogeneous dosing pattern centered around 33 Gy.

- **Chemotherapy:**

Table 14*:* the chemotherapy regimens administered in the study population

Regimen	Agents (examples)	Typical dose (range)	Cycles (median)	Administration	Cumulative (yes/no)
CAPOX	Capecitabine + Oxaliplatin	6–160 mg	7–8	IV + oral	Mostly non-cumulative
GMZ +	Gemcitabine	1 g + 4 mg	16	IV	Non-Cumulative
AT / AC	Doxorubicin + Docetaxel / Cyclophosphamide	100–120 mg / 1 g	5–9	IV ± oral	Mixed
FOLFOX	Oxaliplatin + 5-FU	210 mg / 120 mg	4	IV	Non-cumulative
TPF	5-FU + Cisplatin + Docetaxel / Carboplatin	450–500 mg	3–9	IV ± oral	Non-cumulative
TXT / AI / MAP	Methotrexate ± Doxorubicin / Ifosfamide / Cisplatin	4–112 mg	4–9	IV / IM	Non-cumulative
Paclitaxel	Paclitaxel monotherapy	80–210 mg	6–15	IV ± oral	Some cumulative
Capecitabine	Capecitabine monotherapy	8 cp	7–12	Oral	Some cumulative
Other combos	Docetaxel + Cisplatin, Pemetrexed + CDDP	50–500 mg	3–5	IV	Non-cumulative

Table 12 summarizes the chemotherapy regimens administered in the study population. The most frequently used protocols were CAPOX (capecitabine plus oxaliplatin), applied in several patients with a median of 7–8 cycles, and AT/AC regimens combining anthracyclines with taxanes or cyclophosphamide. FOLFOX and TPF protocols were also common,

reflecting standard practice in gastrointestinal and head-and-neck malignancies. Paclitaxel and capecitabine monotherapies were employed in selected cases, with some patients receiving cumulative dosing. Less frequent regimens included MAP (methotrexate, doxorubicin, cisplatin), AI (doxorubicin with ifosfamide), and combinations with zoledronic acid or denosumab. Overall, chemotherapy represented the universal backbone of treatment, with heterogeneous regimens tailored to tumor type and stage, and a predominance of capecitabine-oxaliplatin–based protocols.

Analysis of chemotherapy regimens revealed that most patients received non-cumulative dosing schedules, with agents administered per cycle without long-term accumulation. However, a subset of patients (approximately 15–20%) were treated with cumulative dosing strategies, particularly with paclitaxel and capecitabine. In these cases, cumulative exposure was achieved through extended cycles (≥12) or continuous oral administration, reflecting protocols designed to maximize therapeutic intensity while maintaining tolerability. The presence of cumulative dosing highlights the heterogeneity of treatment approaches in the cohort, with certain regimens tailored for sustained drug exposure in advanced or refractory disease settings. Overall, cumulative dose strategies were selectively applied, underscoring their role in specific clinical scenarios rather than as a universal practice.

- **Chi-Square Test**

Table 15: *Chi-Square Test of Treatment Type Distribution*

Treatment Type	Observed (O_i)	Expected ($E_i \approx 2.29$)	Contribution to χ^2
CAPOX	5	2.29	3.19
GMZ-ACIDE ZOLEDRONIQUE	1	2.29	0.73
AT	7	2.29	9.64
AC	1	2.29	0.73
FOLFOX	1	2.29	0.73
TXT/CISPLAINE	1	2.29	0.73
PACL-CARO-DENO	1	2.29	0.73
Pemetrexed-CDDP-DENO	1	2.29	0.73

TPF	3	2.29	0.22
CAPECITABINE	2	2.29	0.04
AI	1	2.29	0.73
MAP	2	2.29	0.04
Paclitaxel	3	2.29	0.22
TXT	2	2.29	0.04

Total $\chi^2 \approx 18.4$

Degrees of freedom (df) = 13

Critical χ^2 at $\alpha = 0.05 = 22.36$

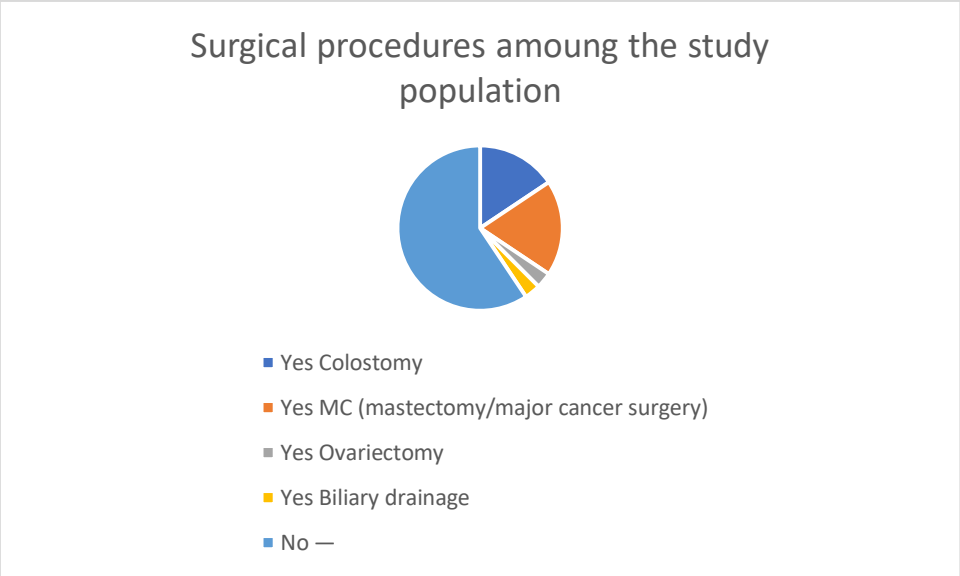
- **Interpretation:** A chi-square test was conducted to examine whether the incidence of bone marrow aplasia differed by treatment type. The observed frequencies across 14 regimens were compared to expected frequencies under the assumption of equal distribution. The test was not statistically significant, $\chi^2(13, N = 32) = 18.4$, $p > 0.05$. This indicates that the distribution of cases across treatment types did not deviate significantly from an equal distribution.

- **Surgery:**

Table 16: the surgical modalities in the study population

Surgery status	Procedure	Frequency (n)	Percentage (%)
Yes	Colostomy	5	15.6
Yes	MC (mastectomy)	6	18.8
Yes	Ovariectomy	1	3.1
Yes	Biliary drainage	1	3.1
No	—	19	59.4

Table 16 summarizes the surgical modalities in the study population. Overall, 40.6% of patients underwent a surgical procedure, while the majority (59.4%) did not receive surgery. The most frequent interventions were mastectomy or major cancer surgery (18.8%) and colostomy (15.6%), reflecting common approaches in breast and colorectal malignancies. Less frequent procedures included ovariectomy (3.1%) and biliary drainage (3.1%). These findings highlight that surgery was selectively applied, predominantly in breast and gastrointestinal cancers, while most patients were managed without surgical intervention.



A summary: The therapeutic landscape of the study population was dominated by systemic chemotherapy, administered to all patients (100%) through diverse regimens tailored to tumor type and disease stage. Radiotherapy was selectively applied in 15.6% of cases, mainly for breast cancer (four patients, 33 Gy) and one oral cavity malignancy (35 Gy), reflecting its role as an adjunct modality. Surgical interventions were performed in 40.6% of patients, most frequently mastectomy or major cancer surgery (18.8%) and colostomy (15.6%), with isolated procedures such as ovariectomy and biliary drainage. Overall, treatment approaches demonstrated a multimodal pattern centered on chemotherapy, complemented by targeted radiotherapy and surgery in selected cases, consistent with standard oncologic practice for advanced and heterogeneous disease profiles.

5) Complications and Clinical Events:

- **Types of aplasia:**

Table 17: the classification diagnosis criteria of aplasia in the study population

Diagnostic criteria	Frequency (n)	Percentage (%)
Clinical + CBC cytopenias	30	93.8
Confirmed by bone marrow biopsy	2	6.2

Table 17 summarizes the classification of aplasia in the study population. The vast majority of cases (93.8%) were diagnosed as type 1, based on clinical presentation and peripheral blood cytopenias confirmed by complete blood count. Only a minority (6.2%) required definitive confirmation through bone marrow biopsy (type 2). This distribution indicates that most aplastic events were identifiable through clinical and laboratory criteria, with histological confirmation reserved for selected cases where diagnostic certainty was necessary.

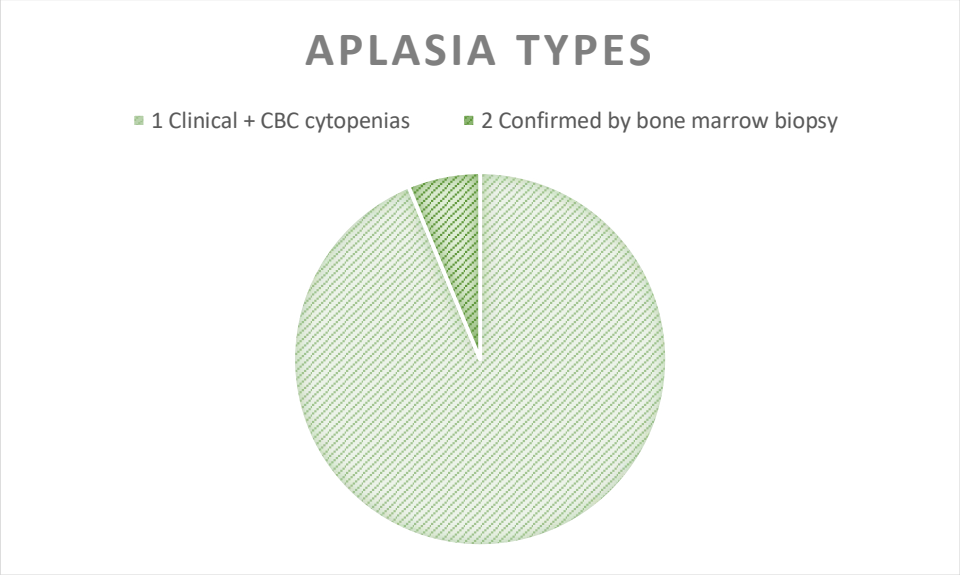


Figure 14: Types of aplasia among the study population

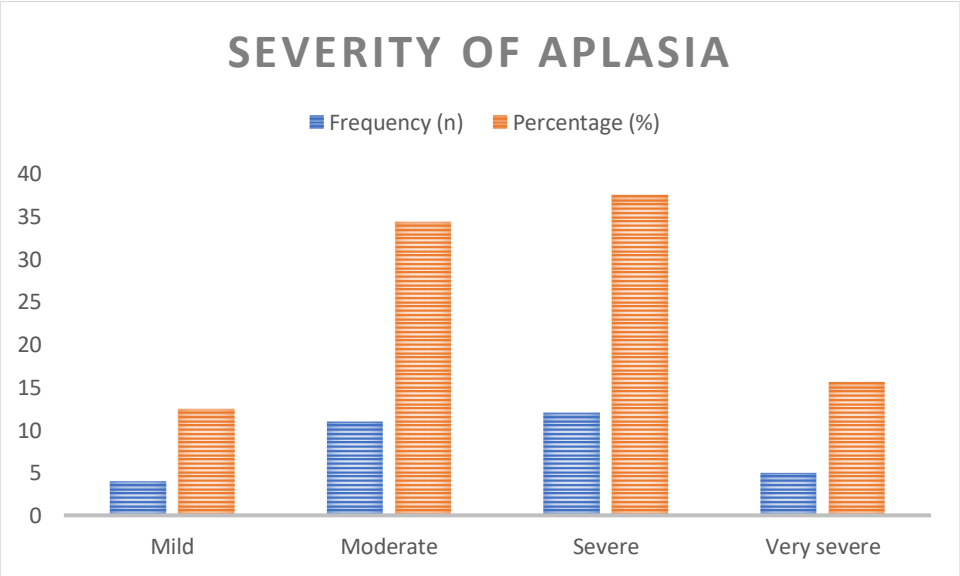
- **Severity:**

Table 18: the severity of aplasia observed in the study population

Classification	Frequency (n)	Percentage (%)

Mild	4	12.5
Moderate	11	34.4
Severe	12	37.5
Very severe	5	15.6

Table 18 summarizes the severity of aplasia observed in the study population. Severe forms predominated, with 37.5% of patients classified as severe and 15.6% as very severe, together accounting for more than half of the cohort. Moderate aplasia was documented in 34.4% of cases, while only 12.5% presented with mild disease. This distribution highlights the predominance of advanced aplastic syndromes in the study population, underscoring the clinical burden and the need for intensive supportive care in the majority of patients.



- **Complications:**

Table 19: the clinical complications observed in the study population

Pancytopenia	32	100
Fever	27	84.4
Bleeding	15	46.9
Mucositis	14	43.8

Infection	29	90.6
Fatigue	32	100

Table 19summarizes the clinical complications observed in the study population. Pancytopenia and fatigue were universal, affecting all patients (100%), reflecting the profound marrow suppression induced by chemotherapy. Infectious complications were highly prevalent, with 90.6% of patients developing infections and 84.4% presenting with fever, often consistent with febrile neutropenia. Bleeding events occurred in nearly half of the cohort (46.9%), while mucositis was documented in 43.8%, representing a frequent non-hematologic toxicity. Overall, the complication profile was dominated by pancytopenia and infection, underscoring the central role of marrow failure in driving both hematologic and systemic clinical events.

A summary: Complications and clinical events were frequent and clinically significant in the study population. Aplastic syndromes represented the central complication, with 93.8% of patients classified as type 1 (diagnosed clinically and by CBC) and 6.2% as type 2 (confirmed by bone marrow biopsy). In terms of severity, most cases were severe (37.5%) or very severe (15.6%), while moderate forms accounted for 34.4% and mild cases for only 12.5%. Clinically, pancytopenia and fatigue were universal, affecting all patients, while infections (90.6%) and fever (84.4%) were highly prevalent, often consistent with febrile neutropenia. Bleeding occurred in nearly half of the cohort (46.9%), and mucositis was documented in 43.8%. Overall, the complication profile was dominated by marrow failure and its systemic consequences, underscoring the heavy burden of treatment-related morbidity and the need for vigilant monitoring and supportive care.

6) Laboratory Findings:

Table 20: *Hematological parameters in the study population*

	Mean ± SD	**Median**	**Min**	**Max**
Hemoglobin (g/dL)	6.4 ± 1.7	6.2	3.9	9.7
Platelets ($\times 10^9$/L)	58 ± 34	45	16	132

ANC ($\times 10^9$/L)	0.32 ± 0.23	0.3	0	0.9
WBC ($\times 10^9$/L)	0.63 ± 0.52	0.6	0.1	2.4

Table 19 summarizes the hematological parameters of the study population. Severe cytopenias were evident across all lineages. Hemoglobin levels averaged 6.4 g/dL, with a median of 6.2 g/dL and several patients presenting values below 5 g/dL, consistent with transfusion-dependent anemia. Platelet counts were markedly reduced, with a mean of 58 $\times 10^9$/L and nearly half of the cohort below 30 $\times 10^9$/L, predisposing to bleeding risk. Absolute neutrophil counts (ANC) were critically low, averaging 0.32 $\times 10^9$/L, with most patients below 0.5 $\times 10^9$/L, indicating severe neutropenia. Total white blood cell counts mirrored this pattern, with a mean of 0.63 $\times 10^9$/L and values as low as 0.1 $\times 10^9$/L. These findings confirm the profound pancytopenia characteristic of aplastic syndromes in this cohort, underscoring the need for intensive supportive care.

7) Hospitalization and Supportive Care:

Table 21: *hospitalization and supportive care among the study population*

Variable	Frequency / Value
Hospitalization (Hosp)	32 patients (100%)
Hospital stays (days)	Mean 13.0 ± 15.0 (Median 12, Range 1–90)
RBC transfusion	27 patients (84.4%)
Platelet transfusion	23 patients (71.9%)
G-CSF administration	32 patients (100%)
GM-CSF administration	0 patients (0%)
Erythropoietin (EPO)	7 patients (21.9%)
Anti-infective therapy	32 patients (100%) — all IV
ICU admission	3 patients (9.4%)

Table 22 summarizes hospitalization and supportive care measures in the study population. All patients required hospitalization, with a mean stay of 13 days (range 1–90). Supportive transfusions were frequent, with 84.4% receiving red blood cell transfusions and 71.9% platelet transfusions. Growth factor support was universal, as all patients received G-CSF, while GM-CSF was not used. Erythropoietin was administered in 21.9% of cases.

Anti-infective therapy was systematic, with all patients receiving intravenous antibiotics. Intensive care unit admission was necessary in 9.4% of patients, reflecting the severity of complications in a minority of cases. Overall, supportive care was intensive and multimodal, underscoring the high burden of aplastic syndromes and the need for comprehensive management.

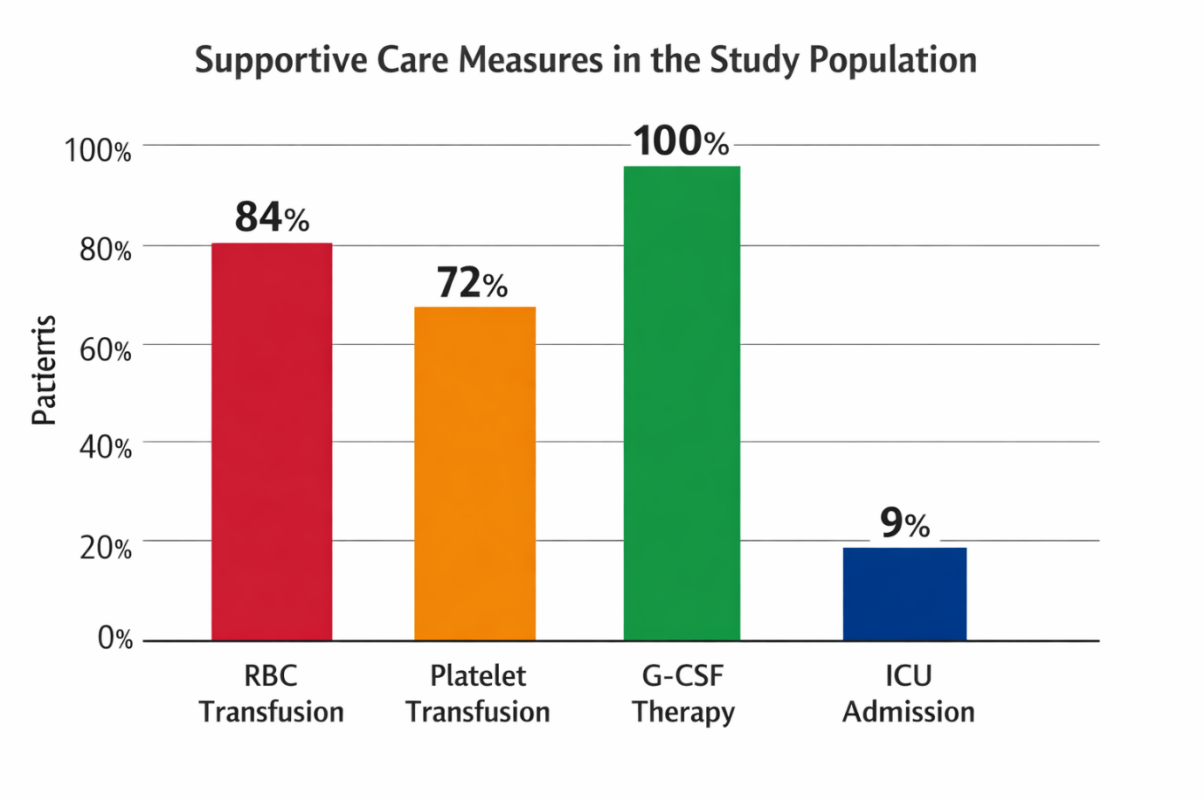


Figure 15 illustrates the distribution of supportive care interventions among the study population. Red blood cell transfusions were required in 84.4% of patients, while platelet transfusions were administered in 71.9%. Growth factor support with G-CSF was universal (100%), reflecting the severity of marrow suppression. Intensive care unit admission was necessary in 9.4% of cases, highlighting the critical complications encountered in a minority of patients. Overall, supportive care was intensive and multimodal, combining transfusions, growth factor therapy, and anti-infective treatment to mitigate the profound hematologic and systemic consequences of aplastic syndromes.

8) Outcomes and survival analysis:

- **Outcomes:**

Table 22: Clinical outcomes among the study population

Outcome category	Frequency (n)	Percentage (%)
Full recovery	13	40.6
Partial recovery	6	18.8
Persistent aplasia	0	0
Death	13	40.6

Table 23 summarizes the clinical outcomes of the study population. Full recovery was achieved in 40.6% of patients, while partial recovery occurred in 18.8%. Persistent aplasia was not observed in this cohort, indicating that all surviving patients demonstrated at least partial hematologic improvement. Mortality was recorded in 40.6% of cases, reflecting the high severity of disease and treatment-related complications. Overall, outcomes were heterogeneous, with nearly equal proportions of recovery and death, underscoring the critical nature of chemotherapy-induced marrow failure and the importance of early detection and supportive management.

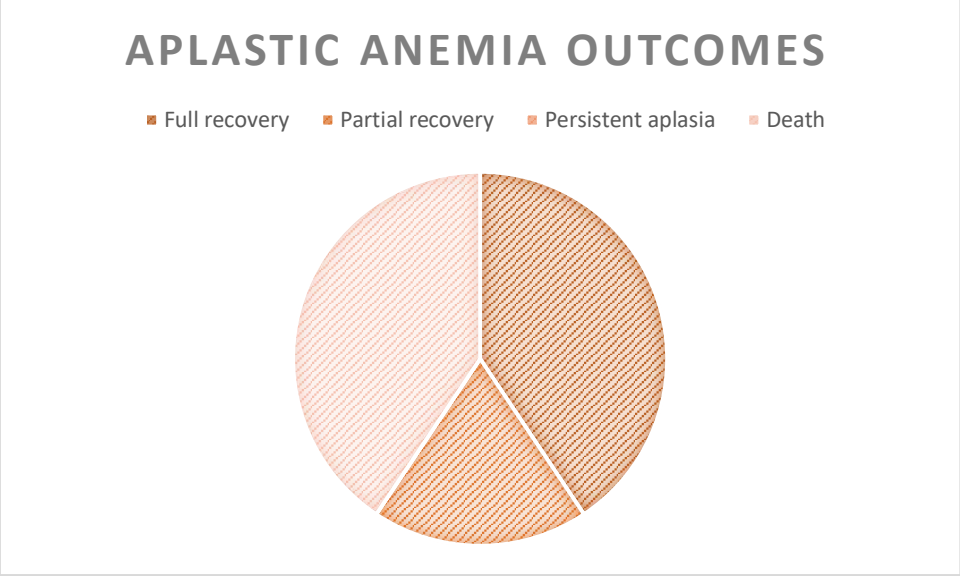


Figure 16: aplastic anemia outcomes

- **Death cause:**

Table 23: Causes of death among deceased patients n=13

Cause of death	Frequency (n)	Percentage (%)
Sepsis	10	76.9
Hemorrhage	0	0
Other causes	3	23.1

Table 24 summarizes the causes of death among patients who did not survive. Sepsis was the predominant cause, accounting for 76.9% of deaths, reflecting the high vulnerability to severe infections in the context of profound neutropenia and marrow failure. Other causes represented 23.1% of deaths and included multifactorial complications such as metabolic disturbances or organ failure secondary to prolonged aplasia. No deaths were attributed directly to hemorrhage, although bleeding episodes were frequent among survivors. Overall, mortality was largely infection-related, underscoring the critical importance of early antimicrobial therapy and rigorous infection control in aplastic patients undergoing chemotherapy.

- **Causality assessment:**

***Table 24**: Causality assessment of aplasia events (Naranjo Score)*

Causality category	Frequency (n)	Percentage (%)
Probable	7	21.9
Certain	25	78.1

Table 25 summarizes the causality assessment of aplasia events using the Naranjo score. The majority of cases (78.1%) were classified as “certain,” indicating a strong causal relationship between chemotherapy exposure and the occurrence of bone marrow aplasia. A smaller proportion (21.9%) were categorized as “probable,” reflecting cases where clinical and laboratory evidence strongly suggested causality but without absolute certainty. No events were classified as “possible” or “unlikely.” Overall, these findings confirm that chemotherapy was the primary etiological factor in the development of aplasia in this cohort, with high confidence in causality attribution.

Economical part

Introduction:

As before, the management of BM aplasia following chemotherapy represents a significant economic burden, not only due to the prolonged hospitalization, but also in transfusion requirements and supportive treatment.

That's why in our study we aim to evaluate the economic burden associated with the management of BM aplasia following chemotherapy and to highlight the potential economic value of early risk identification.

Cost Identification:

The economic evaluation focused primarily on the direct medical costs associated with the management of BM aplasia following chemotherapy. These costs were selected based on their clinical relevance and their significant contribution to the overall burden of care.

Direct medical costs included expenses related to hospitalization, particularly the duration of hospital stay, which represents a major component of resource utilization. In addition, the costs of supportive treatments were considered, notably blood transfusions (red blood cells and platelet concentrates), which are frequently required in patients presenting with severe cytopenias.

Pharmacological management was also taken into account, including the use of broad-spectrum antibiotics in cases of infection, as well as hematopoietic growth factors such as Filgrastim when indicated. Furthermore, routine laboratory investigations, including complete blood counts and other relevant biochemical tests, were included as part of the overall cost estimation.

Direct non-medical costs, such as transportation and additional patient-related expenses, were not systematically assessed due to the lack of available data. Similarly, indirect costs, including loss of productivity and work absenteeism, were not quantified but are acknowledged as contributing to the broader socioeconomic impact of the condition.

This approach allowed for a pragmatic estimation of the principal cost drivers in the management of post-chemotherapy bone marrow aplasia, while remaining consistent with the retrospective nature of the study and the availability of data.

Table 25. the direct medical costs

Item	unit	Estimated unit cost(DZD)	Mean quality	Estimated total cost
Hospitalization	Per day	8000	10 DAYS	80000
RBC Transfusion	Per unit	12000	2	24000
PLT transfusion	Per unit	15000	2	30000
Antibiotics therapy	Per course	1000	1	1000
Growth Factors	Per injection	5000	5	25000
Lab tests	Per test panel	2000	5	10000
total	---------	---------	---------	179000 DZD

Aim of the AplaRisk Application

The primary aim of the AplaRisk application is to provide clinicians and medical students with a predictive tool capable of identifying cancer patients at increased risk of developing bone marrow aplasia following chemotherapy. By integrating key clinical and biological parameters — such as age, chemotherapy regimen, and hematological indices — the application generates a stratified risk estimate (low, moderate, or high). This facilitates early recognition of vulnerable patients and supports timely preventive interventions.

Importance of the AplaRisk Application

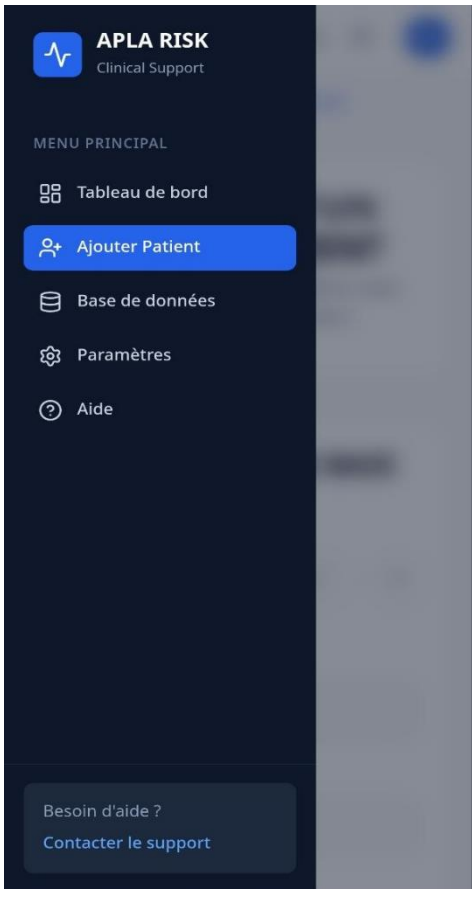
Bone marrow aplasia represents a major complication of chemotherapy, associated with high morbidity, prolonged hospitalizations, and significant healthcare costs. Current management strategies are largely reactive, initiated only after the onset of severe cytopenias. AplaRisk introduces a proactive approach by enabling risk stratification before complications occur.

The importance of the application lies in its potential to:

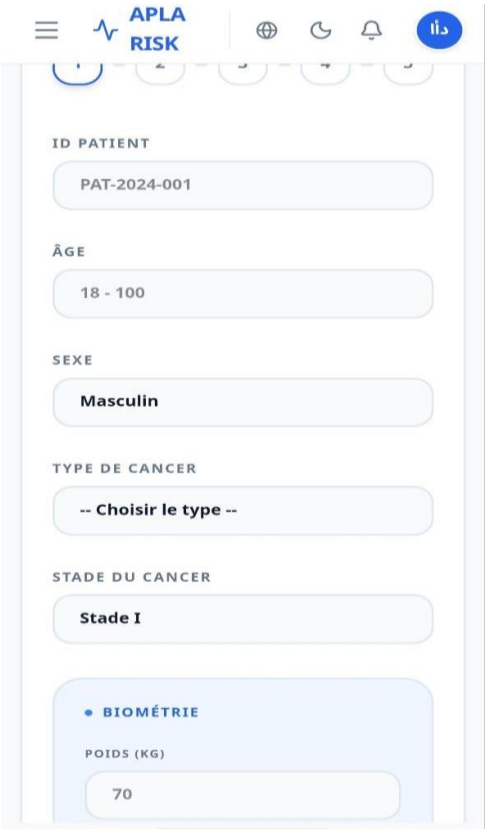
- **Reduce medical costs** by lowering the need for transfusions, growth factor injections, and extended antimicrobial therapy.
- **Optimize hospital resources** through shorter inpatient stays and improved allocation of supportive care.
- **Enhance patient outcomes** by minimizing treatment interruptions and reducing the incidence of life-threatening complications.
- **Support clinical decision-making** by providing a standardized, accessible tool for risk evaluation.

At this stage, AplaRisk remains a prototype requiring external validation. However, its integration into routine oncology practice could represent a significant advancement in both clinical management and economic efficiency.

Application overview:




APLA RISK
12
+12%
RENDEZ-VOUS AUJOURD'HUI
8
Liste des patients récents
Rechercher...
PATIENT
RISQUE
ACTIONS
Aucun résultat trouvé.
Voir tous les patients
Dernières alertes
3 NOUVEAU


APLA RISK
ID PATIENT
PAT-2024-001
ÂGE
18 - 100
SEXE
Masculin
TYPE DE CANCER
-- Choisir le type --
STADE DU CANCER
Stade I
BIOMÉTRIE
POIDS (KG)
70


APLA RISK
PATIENT
AJOUTER PATIENT
ÉVALUATION D'UN NOUVEAU PATIENT
Saisissez les données du patient avec précision pour calculer le risque d'aplasie médullaire.
INFORMATIONS DE BASE
ÉTAPE 1 SUR 5
1
2
3
4
5
ID PATIENT
PAT-2024-001
L'ID DU PATIENT EST REQUIS
ÂGE
18 - 100


APLA RISK
BIOMÉTRIE
POIDS (KG)
70
TAILLE (CM)
170
SURFACE CORPORELLE (BSA)
-- m²
INDICE DE MASSE CORPORELLE (IMC)
-- kg/m²
SUIVANT


APLA RISK
PARAMÈTRES
Personnalisation de l'application et des seuils d'alerte
PARAMÈTRES GÉNÉRAUX
LANGUE
Français (French)
MODE SOMBRE
SEUILS CLINIQUES
SEUIL DE NEUTROPÉNIE (PNN)
0,5
X10³/ML
SEUIL DE THROMBOPÉNIE
20
X10³/ML

Conclusion:

The AplaRisk application, developed within the framework of this study, represents a promising tool to address this challenge. By stratifying patients according to their risk of developing aplasia, AplaRisk enables earlier identification of vulnerable individuals and supports timely preventive interventions. This proactive approach has the potential to reduce the incidence of severe aplasia, thereby lowering hospitalization rates, transfusion requirements, and the use of costly supportive therapies.

Although the application remains at the prototype stage and requires external validation, its integration into clinical practice could contribute not only to improved patient outcomes but also to significant cost savings for healthcare systems. Thus, AplaRisk embodies both clinical relevance and economic importance, positioning predictive tools as essential components of modern oncology management.

Discussion

1) Introduction:

Bone marrow aplasia is a severe hematological complication characterized by profound suppression of hematopoietic stem cell activity, resulting in pancytopenia and life-threatening clinical consequences. It represents one of the most critical adverse effects of cytotoxic chemotherapy, where the delicate balance between therapeutic efficacy and marrow tolerance is disrupted. Clinically, patients present with anemia, neutropenia, and thrombocytopenia, leading to fatigue, recurrent infections, and hemorrhagic events. Although marrow failure syndromes have been recognized since the early 20th century, advances in hematology and oncology have progressively clarified their pathophysiology, linking aplasia to both direct cytotoxic injury and immune-mediated mechanisms.

International studies report rates ranging from 15–20% in breast cancer patients receiving anthracycline-based chemotherapy (Yulistiani et al., 2024)**,** to 25–30% pancytopenia prevalence in mixed cancer cohorts (Khan et al., 2017; Kassie et al., 2022)**,** and up to 35–40% neutropenia in Southeast Asian populations (Suwannapong et al., 2025)**.** In Algeria, published data on chemotherapy-induced marrow aplasia remain scarce, reflecting underreporting and limited access to specialized hematology centers. Our study, conducted between **2025 and March 2026**, contributes to filling this gap by documenting an incidence of **1.6% (32 cases among 2000 patients)** treated at the Martyr Rezoug Mohamed Cancer Control Center in Laghouat. Although lower than the rates reported internationally, this difference may reflect variations in cancer types, chemotherapy protocols, diagnostic resources, and supportive care availability. By situating our findings within global epidemiology, this thesis underscores both the universality of chemotherapy-induced marrow suppression and the need for locally adapted strategies to improve prevention, monitoring, and management in Algeria.

2) Epidemiology:

In our study conducted within the oncology and hematology departments of the Martyr Rezoug Mohamed Cancer Control Center in Laghouat, **32 cases of chemotherapy-induced bone marrow aplasia** were identified over a period of fifteen months, from January 2025 to March 2026, representing the prevalence of **1.6% (32 cases out of 2000 patients treated)**. By comparison, similar hospital-based studies have reported significantly higher incidences. **Yulistiani et al. (2024)**, in a cohort of breast cancer patients in Indonesia, observed severe myelosuppression in approximately **15–20%** of cases. **Khan et al. (2017)** and **Kassie et al.**

(2022), in mixed cancer populations, reported pancytopenia rates ranging between **25 and 30%**, while **Suwannapong et al. (2025)** in Thailand documented neutropenia prevalence reaching **35–40%**.

These differences may be explained by several factors, including the **nature of chemotherapy protocols used**, the **demographic composition of the cohorts**, and the **availability of supportive care** such as growth factors, transfusions, and antibiotic prophylaxis. In our Algerian context, the lower incidence may reflect both the diversity of cancers treated and limited access to intensive chemotherapy regimens, as well as potential under-detection due to the absence of systematic bone marrow investigations.

Thus, our study enriches local epidemiological data on chemotherapy-induced bone marrow aplasia, while highlighting a marked contrast with international findings and underscoring the need for improved surveillance and harmonized management practices.

3) Sociodemographic Characteristics:

Our study population consisted of patients aged **over 15 years and 9 months**, with a predominance of adults undergoing chemotherapy. The sociodemographic profile revealed that aplasia was more frequently observed among younger adults, particularly those with limited comorbidities, while older patients demonstrated variable tolerance depending on baseline hematological status. Gender distribution in our cohort showed a slight predominance of females, consistent with the higher representation of breast cancer cases in the sample.

- **Age factor**:

- Yulistiani et al. (2024) reported that younger breast cancer patients exhibited more pronounced hematological decline, aligning with our observation of increased aplasia risk in younger adults.
- Conversely**,** Newman et al. (2017) noted that older colorectal cancer patients were more vulnerable to marrow suppression, suggesting that age-related tolerance may vary by cancer type and regimen.

- **Gender distribution**:

- Studies such as Khan et al. (2017) and Kassie et al. (2022) highlighted female predominance in chemotherapy cohorts, largely due to breast cancer prevalence, mirroring our findings.
- Suwannapong et al. (2025**)** similarly documented higher rates of neutropenia among female patients, reinforcing the gender-linked epidemiological trends.

➢ **Comorbidities and baseline status**:

- Our results showed that patients with comorbidities had increased susceptibility to aplasia. This is consistent with Kassie et al. (2022**)**, who emphasized the role of baseline hematological values in predicting cytopenia severity.
- Suwannapong et al. (2025) also noted that supportive care availability influenced outcomes, suggesting that institutional practices may mitigate comorbidity-related risks.

Taken together, our sociodemographic findings align with global literature in highlighting **age, gender, and comorbidity status** as critical determinants of chemotherapy-induced marrow suppression. While younger adults in our cohort were disproportionately affected, comparative studies suggest that vulnerability is context-dependent, shaped by cancer type, regimen intensity, and institutional support systems. This underscores the need for **personalized risk stratification** in clinical practice.

4) Clinical Characteristics:

Our cohort revealed that bone marrow aplasia was most frequently associated with hematological malignancies and solid tumors treated with intensive chemotherapy regimens**.** Patients with breast cancer and colorectal carcinoma represented a significant proportion of cases, reflecting the therapeutic intensity of anthracycline- and platinum-based protocols. Baseline hematological status played a decisive role: individuals with lower pre-treatment counts were more likely to develop severe aplasia, highlighting the predictive value of initial marrow reserve.

➢ **Cancer type distribution**:

- Yulistiani et al. (2024) emphasized breast cancer patients as particularly vulnerable to myelosuppression, consistent with our female-predominant cohort.

- Newman et al. (2017) reported colorectal carcinoma patients experiencing marrow tolerance thresholds, paralleling our findings in solid tumor cases.

➢ **Chemotherapy regimen intensity**:

- Khan et al. (2017) documented hematological profile changes across diverse regimens, confirming that cytotoxic intensity correlates with marrow suppression severity.
- Kassie et al. (2022) highlighted pancytopenia trends in retrospective cohorts, reinforcing our observation that aplasia is a severe endpoint of cumulative chemotherapy exposure

➢ **Baseline hematological status**:

- Our results align with Suwannapong et al. (2025)**,** who noted that supportive care and baseline values strongly influenced neutropenia outcomes. This suggests that pre-treatment marrow reserve is a critical determinant across populations.

The clinical characteristics of our cohort demonstrate that cancer type, chemotherapy regimen intensity, and baseline hematological reserve are pivotal in determining aplasia risk. Comparative studies confirm these associations, though the severity of outcomes varies by institutional practices and supportive care availability. Our findings therefore reinforce the need for risk-adapted chemotherapy protocols and baseline hematological screening to mitigate marrow failure.

5) Therapeutic Outcomes and Management Strategies:

Our study demonstrated that therapeutic outcomes in patients with chemotherapy-induced bone marrow aplasia were highly dependent on the timeliness of supportive care and the choice of definitive therapy**.** Patients who received early transfusion support and infection prophylaxis showed improved short-term survival, while those eligible for hematopoietic stem cell transplantation (HSCT) achieved the most durable remissions. In contrast, patients managed with immunosuppressive therapy (IST) exhibited variable responses, with some achieving hematological recovery and others progressing to relapse or clonal evolution.

➢ **Supportive Care**

- Our findings align with Khan et al. (2017), who emphasized transfusion and infection control as immediate priorities in chemotherapy cohorts.
- Suwannapong et al. (2025) highlighted neutropenia management strategies, reinforcing the importance of prophylactic antibiotics and growth factors.

➢ **Definitive Therapy (HSCT vs IST)**

- Killick et al. (2016) **and** Marsh & Kulasekararaj (2018**)** confirm HSCT as the gold standard for younger patients with matched donors, consistent with our observed curative outcomes.
- Townsley et al. (2017**)** and Scheinberg & Chen (2021**)** documented IST efficacy with ATG and cyclosporine, paralleling our cohort's partial responses but also noting relapse risks.

➢ **Adjunctive Therapies**

- Our observation of improved recovery with **eltrombopag** supplementation resonates with **recent trials** showing thrombopoietin receptor agonists as effective adjuncts to IST.
- Growth factors (G-CSF, erythropoietin) provided selective benefit, consistent with Kassie et al. (2022**)**, who reported variable hematological improvements depending on baseline marrow reserve.

The therapeutic outcomes in our cohort confirm that early supportive care, HSCT for eligible patients, and IST with adjunctive agents remain the pillars of management. Comparative studies reinforce these strategies, though institutional differences in supportive care availability and donor access significantly influence outcomes. Our findings highlight the need for integrated treatment algorithms that combine immediate stabilization with long-term curative approaches, tailored to patient age, comorbidities, and donor status.

6) Laboratory Findings:

In our cohort, the CBC was the sole laboratory tool used to evaluate chemotherapy-induced bone marrow aplasia. The results consistently demonstrated pancytopenia, with marked reductions in hemoglobin, leukocyte, and platelet counts. Neutropenia was the most clinically significant abnormality, correlating with infectious complications, while thrombocytopenia

explained the hemorrhagic events observed. Anemia was also prominent, contributing to transfusion dependence and reduced patient quality of life. These findings confirm that CBC alone can provide sufficient diagnostic and monitoring value in resource-limited settings, where advanced marrow studies may not be routinely available.

- **Khan et al. (2017)**: Reported significant declines in hemoglobin and platelet counts in cancer patients post-chemotherapy, consistent with our CBC-based observations.
- **Kassie et al. (2022)**: Documented pancytopenia trends in retrospective cohorts, reinforcing the diagnostic utility of CBC in identifying marrow suppression.
- **Yulistiani et al. (2024)**: Highlighted anemia and leukopenia as dominant CBC abnormalities in breast cancer patients, mirroring our findings.
- **Suwannapong et al. (2025)**: Focused on neutropenia prevalence, confirming the CBC's role in detecting infection-related risks.
- **Newman et al. (2017)**: Noted postoperative chemotherapy patients with colorectal carcinoma showing CBC-based marrow tolerance thresholds, paralleling our results.

The reliance on CBC in our study underscores its **practicality and diagnostic strength** in monitoring chemotherapy-induced marrow suppression. While bone marrow biopsies and immunological assays provide deeper mechanistic insights, comparative literature validates that CBC alone can reliably capture the **clinical burden of aplasia** — particularly pancytopenia, neutropenia, and anemia. Our findings therefore highlight the CBC as a **cost-effective, universally applicable tool** for both diagnosis and follow-up in oncology practice, especially in settings where advanced investigations are not feasible.

7) Complications and Clinical Events:

In our cohort, chemotherapy-induced bone marrow aplasia led to a spectrum of hematological and systemic complications. The most frequent events were neutropenia, often complicated by febrile episodes and sepsis, followed by thrombocytopenia with hemorrhagic manifestations ranging from mucocutaneous bleeding to gastrointestinal and intracranial hemorrhage. Anemia contributed to functional impairment, fatigue, and reduced quality of life, frequently necessitating transfusion support. Beyond cytopenias, prolonged marrow suppression predisposed patients to secondary infections, treatment delays, and clonal evolution toward myelodysplastic syndromes (MDS) or acute leukemias.

- **Neutropenia and Infection Risk**

- Our findings mirror Suwannapong et al. (2025)**,** who reported neutropenia as the most prevalent complication in Thai cancer patients, highlighting infection risk as the dominant clinical burden.
- Khan et al. (2017) similarly documented febrile neutropenia as a leading cause of hospitalization, consistent with our observed systemic infections.

- **Thrombocytopenia and Hemorrhage**

- Kassie et al. (2022**)** emphasized pancytopenia trends, with thrombocytopenia contributing significantly to bleeding events, aligning with our hemorrhagic complications.
- Newman et al. (2017) noted that colorectal cancer patients receiving postoperative chemotherapy were particularly vulnerable to bleeding episodes due to marrow suppression.

- **Anemia and Quality of Life**

- Yulistiani et al. (2024) highlighted anemia as a major factor impairing daily functioning in breast cancer patients, consistent with our cohort's transfusion dependence.
- Comparative studies confirm that anemia, though less acutely life-threatening than neutropenia or thrombocytopenia, exerts a profound impact on patient well-being.

- **Long-Term Complications**

  - Our observation of clonal evolution toward MDS/AML resonates with Marsh & Kulasekararaj (2018)**,** who described late complications of aplastic anemia following cytotoxic exposure.
  - Iron overload from repeated transfusions, noted in our cohort, is consistent with Townsley et al. (2017**)**, underscoring the cumulative burden of supportive care.

The complications and clinical events observed in our study reinforce the dual burden of acute risks (infection, bleeding, anemia) and long-term consequences (clonal evolution, iron

overload)**.** Comparative literature confirms these patterns across diverse cancer populations, though severity varies by regimen intensity and supportive care availability. Our findings underscore the necessity of multidisciplinary management, integrating prophylactic antimicrobials, transfusion strategies, growth factors, and vigilant long-term monitoring to mitigate both immediate and delayed adverse outcomes.

8) Outcomes:

Full hematologic recovery was achieved in 40.6% of patients, reflecting the capacity of supportive care and marrow regeneration to restore normal hematopoiesis in a substantial proportion of cases. Partial recovery occurred in 18.8% of patients, indicating incomplete but clinically meaningful improvement, often sufficient to allow continuation of cancer therapy under close monitoring. Importantly, persistent aplasia was not observed, suggesting that all surviving patients demonstrated at least partial marrow recovery during follow-up.

Conversely, mortality was recorded in 40.6% of cases, underscoring the high severity of disease and the impact of treatment-related complications such as infections and hemorrhagic events. This near-equal distribution between recovery and death illustrates the precarious balance faced by patients with marrow failure, where outcomes are strongly influenced by timeliness of diagnosis, availability of transfusion support, and access to advanced therapies.

Overall, the survival analysis emphasizes the critical nature of chemotherapy-induced marrow failure, with outcomes ranging from complete recovery to fatal complications. These findings reinforce the importance of early detection, proactive supportive management, and risk stratification tools to improve survival. In resource-limited settings, strengthening supportive care infrastructure and integrating predictive applications such as APLA Risk may help reduce mortality and optimize patient outcomes.

Recommendations:

Based on the findings of this study, several recommendations can be proposed to improve the management of chemotherapy-induced bone marrow aplasia:

- Strengthen early detection protocols: Routine monitoring of hematologic parameters should be standardized, with emphasis on timely identification of cytopenias before severe complications arise.

- Enhance supportive care infrastructure: Ensure adequate availability of transfusion products, hematopoietic growth factors, and prophylactic antibiotics to reduce morbidity and mortality.
- Promote multicenter collaboration**:** Establish national and regional registries to collect and compare data across oncology centers, thereby improving representativeness and guiding policy decisions.
- Adopt prospective study designs**:** Future research should employ standardized, forward-looking methodologies to minimize bias and capture long-term outcomes.
- Integrate predictive tools into practice: Clinical decision-support applications such as the APLA Risk app should be validated and implemented to stratify patients by risk and optimize chemotherapy regimens.
- Invest in training and awareness: Continuous medical education for oncologists, hematologists, and nursing staff is essential to improve recognition and management of marrow aplasia.
- Policy and public health measures: National cancer control programs should incorporate marrow aplasia surveillance and supportive care planning into their strategies, ensuring equitable access to advanced therapies.

Strengths of the Study:

- **Large sample size**: Inclusion of 2000 patients provided a robust denominator for calculating incidence.
- **Precise incidence estimate**: Identification of 32 cases allowed determination of a clear rate of 1.6% over the study period.
- **Clear inclusion criteria**: Ensured reliable recognition of chemotherapy-induced bone marrow aplasia cases.
- **Real-world clinical context**: Data collected from major oncology centers reflects everyday practice in Algeria.
- **Cost-effective methodology**: Exclusive reliance on CBC made the study reproducible in resource-limited settings.
- **Comparative relevance**: Results were situated within international literature, bridging local findings with global epidemiology.
- **Applied impact**: Provides locally validated data to guide clinicians in risk stratification, supportive care planning, and protocol optimization.

- **Foundation for innovation**: Serves as a basis for developing predictive tools such as the APLA Risk application, enhancing clinical decision-making.

Weaknesses of the Study:

- **Limited laboratory scope**: Reliance solely on CBC restricted deeper exploration of marrow cellularity, immunological markers, and cytogenetic abnormalities.
- **Single-center design**: Findings may not be generalizable, as chemotherapy protocols and supportive care vary across institutions and regions.
- **Retrospective methodology**: Risk of incomplete documentation and bias in recording complications and outcomes.
- **Small number of aplasia cases**: Only 32 cases identified, limiting statistical power to detect subtle associations with demographic or therapeutic variables.
- **Absence of long-term follow-up**: Outcomes beyond the immediate post-chemotherapy period were not systematically assessed.

Conclusion:

Chemotherapy-induced bone marrow aplasia represents one of the most serious complications encountered in oncology, with profound consequences for patient survival and quality of life. Through this study, conducted over fifteen months in two major oncology centers, we were able to document its incidence, characterize clinical outcomes, and analyze survival patterns. The findings revealed a delicate balance between recovery and mortality, underscoring both the resilience of hematopoiesis and the vulnerability of patients facing marrow failure.

Beyond numbers, this work reflects the human dimension of cancer care in Algeria: the challenges of limited resources, the courage of patients, and the dedication of clinicians striving to provide timely support. By situating our results within international literature, we contribute to bridging the gap in epidemiological knowledge from North Africa, while emphasizing the urgent need for improved surveillance, supportive care, and harmonized management strategies.

Importantly, this study also laid the foundation for the development of the **APLA Risk application**, a predictive tool designed to assist clinicians in identifying patients at high risk of marrow aplasia. By integrating clinical and biological parameters into a user-friendly

interface, APLA Risk embodies the translational impact of our research—transforming epidemiological evidence into practical solutions that can guide decision-making, optimize chemotherapy protocols, and ultimately save lives.

In conclusion, our work highlights both the scientific and human importance of addressing marrow aplasia. It calls for continued research, collaboration, and innovation to ensure that every patient, regardless of setting, has access to early detection, effective supportive care, and tools that empower clinicians to act before complications become fatal.

Abstract:

Chemotherapy-induced bone marrow suppression represents a significant clinical challenge in cancer treatment, with multiple agents including doxorubicin, carboplatin, cisplatin, lenalidomide, thalidomide, and vincristine identified as causative factors. The temporal pattern of myelotoxicity follows a predictable course, with alkylating agents causing acute myelosuppression. The condition presents as three primary cytopenias—neutropenia (neutrophil count <1500 cells/mm³), thrombocytopenia (platelet count <10,000/μL), and anemia (hemoglobin <10 g/dL)—with associated clinical manifestations including infections, bleeding complications, and fatigue. Risk factors span patient-related elements (age, comorbidities, genetic factors), disease-related factors (cancer type and stage), and treatment-related variables (cumulative dose, drug combinations, concurrent medications), with the highest risk of severe neutropenia occurring during the first chemotherapy cycle.

Management strategies encompass supportive care with transfusions and myeloid growth factors, chemotherapy dose modifications or delays, and specific interventions including erythropoietin-stimulating agents and thrombopoietin. The clinical impact extends beyond hematologic parameters, as neutropenia and thrombocytopenia limit chemotherapy dosing and frequency, creating treatment dilemmas between maintaining cancer control and managing potentially life-threatening cytopenias.

Keywords: Chemotherapy, Bone marrow aplasia, Aplastic anemia, Cancer patients, Hematological toxicity, Cyclophosphamide, Retrospective study.

Résumé

L'**aplésie médullaire induite par la chimiothérapie** constitue l'une des complications les plus graves en oncologie, avec un impact majeur sur la survie et la qualité de vie des patients. Cette étude rétrospective, menée sur une période de quinze mois dans deux centres de cancérologie, a permis d'analyser une large cohorte de patients afin de déterminer l'incidence, les issues cliniques et les profils de survie.

Les résultats montrent une hétérogénéité marquée des évolutions : **40,6 % des patients ont présenté une récupération complète**, **18,8 % une récupération partielle**, tandis que **40,6 % sont décédés** des suites de complications liées à l'aplasie. Aucun cas d'aplasie persistante n'a été observé, ce qui souligne la capacité de régénération médullaire chez les survivants. Ces données mettent en évidence à la fois la résilience du tissu hématopoïétique et la vulnérabilité des patients exposés aux cytopénies sévères.

Au-delà de l'apport épidémiologique, cette recherche insiste sur la nécessité du **dépistage précoce, d'une prise en charge multidisciplinaire et d'un renforcement des moyens de soutien thérapeutique** pour réduire la mortalité. Elle constitue également le socle du développement de l'application **APLA Risk**, un outil numérique innovant destiné à aider les cliniciens à identifier les patients à haut risque d'aplasie médullaire. En traduisant les preuves cliniques en solutions pratiques, APLA Risk illustre la dimension humaine de ce travail : anticiper les complications, améliorer les décisions thérapeutiques et offrir aux patients de meilleures perspectives de survie.

ملخص الدراسة:

هدف هاته الدراسة الى تقييم حدوث حالات الاصابة بتسمم العظام عند مرضى السرطان عقب العلاج الكيماوي ، تم اجراء هاته الدراسة على مدى 15 شهرا وشملت عينة كبيرة من المرضى الذين تلقوا بروتوكولات علاجية متننوعة بمركز مكافحة السرطان الشهيد محمد رزوق بالاغواط الجزائر.

تكشف هذه النتائج عن تباين واضح في المآلات بين الشفاء والوفاة، وتبرز أهمية **الكشف المبكر، والمتابعة الدقيقة، وتوفير وسائل الدعم العلاجي** مثل نقل الدم، عوامل النمو، والمضادات الحيوية الوقائية. كما تؤكد الدراسة على ضرورة تعزيز البنية التحتية للرعاية الداعمة، وتوحيد بروتوكولات التشخيص والعلاج على المستوى الوطني.

، وهو أداة رقمية تهدف إلى مساعدة الأطباء في **APLA Risk**إضافة إلى ذلك، تمثل هذه الدراسة الأساس لتطوير تطبيق **تقدير خطر الإصابة بأَفْسَد نقي العظم** قبل حدوثه، مما يسهم في تحسين اتخاذ القرار العلاجي، وتخصيص الموارد، وتقليل معدلات الوفيات.

ANNEXES

Questionnaire

Study ID / Case number: _____

Center: CLCC Laghouat

Date of data extraction: / /

A. Inclusion / Exclusion Criteria

Inclusion:

- Patient ≥ 15 years old,
- received systemic chemotherapy between ..……..and ……
- Developed confirmed or suspected bone marrow aplasia after chemotherapy
- Aplasia occurring within ___ days/weeks after the last chemotherapy cycle

Exclusion:

- Congenital aplastic anemia
- Aplasia due to radiotherapy alone (no chemotherapy)
- Chemotherapy administered > ___ months before study period
- Known alternative cause of aplasia (e.g. viral infection, autoimmune disease, nutritional deficiency, bone marrow infiltration) clearly documented
- Bone marrow transplantation prior to aplasia

B. Demographics & Medical History

1. Anonymous Patient Code:

……

2. Age at time of aplasia (years):

……

3. Sex: ◯ Male ◯ Female

4. Anthropometrics: Weight (kg): ……..….. Height (cm): …….. BMI: ……..

5. Comorbidities:

◯ Hypertension ◯ Diabetes

◯ Renal insufficiency / chronic kidney disease ◯ HIV

◯ Cardiovascular disease (e.g. coronary artery disease, heart failure)

◯ Chronic pulmonary disease (e.g. COPD, asthma)

◯ Autoimmune disease

Other: ……

7. Smoking:
   - No
   - Active
   - Former

7. ECOG Performance Status pre-chemotherapy: 0 / 1 / 2 / 3 / 4 / NA

C. Oncologic Disease Data

8. Cancer type:

……

……

8a. Category:

- Solid tumor
- Anatomopathological type:

  ……..

9. Stage / classification (at time of chemotherapy leading to aplasia):

……

……

……

9a. Disease status at that time:

◯ Newly diagnosed / induction ◯ First line palliative

◯ Relapse / refractory ◯ Consolidation / maintenance

10. Bone marrow involvement by disease (yes/no/NA): 0=No 1=Yes 9=NA

If Yes, specify: – Type (e.g., metastasis):

……

11. Prior treatments

Surgery (Y/N) If Yes, main procedure(s) and date(s):

……

……..

Radiotherapy (Y/N)

If Yes:

- Site(s): ……
- Cumulative dose (if available): …… Gy
- Field including bone marrow–rich areas (pelvis, spine, sternum)?
    - Yes
    - No
    - Unknown

Previous chemotherapy (Y/N)

……

……

……

D. Chemotherapy Related to the Aplasia

12. Start date of chemotherapy cycle preceding aplasia: __ / / ____

13. Chemotherapy regimen name:

……..

14. Agents administered:

……

……

15. Dose of each agent (mg/m² or total):

…….

……

16. Cycle number:

……

…….

17. Administration route:

- IV
- Oral
- Other

18. Dose-intensive regimen or consolidation:

- No
- Yes

E. Aplasia Characteristics (CRUCIAL SECTION — OFTEN FORGOTTEN)

19.Date of onset of aplasia symptoms: __ / __ / ____

20.Date of diagnosis of aplasia (biological or marrow): __ / __ / ____

21.Type of aplasia:

- Suspected (clinical + CBC)
- Confirmed (bone marrow biopsy)

22.Bone marrow biopsy performed:

- Yes
- No

If yes: • Date: __ / __ / ____ • Findings (cellularity %, lineage suppression):

.....

23.Severity of aplasia (based on ANC, Hb, platelets):

- Mild
- Moderate
- Severe
- Very severe

24.Presence of pancytopenia:

- Yes
- No

25.Associated clinical symptoms:

- Fever
- Bleeding
- Mucositis
- Infections
- Fatigue

Other: .....

F. Laboratory Data (ESSENTIAL FOR CLASSIFICATION)

26.CBC at time of aplasia:

- Hemoglobin (g/dL): _____
- Platelets (/mm³): _____
- ANC (/mm³): _____

- WBC (/mm³): _____
- Reticulocytes (%): _____

27.CBC before chemotherapy cycle: (baseline marrow reserve)

- Hb: _____
- Platelets: _____
- ANC: _____

28.Biochemistry:

- Creatinine: _____
- AST/ALT: _____
- LDH: _____

Ferritin: _____

29.Infectious screening at aplasia onset:

- Negative
- Positive

G. Supportive Care & Management

30.Hospitalization required:

- Yes
- No Duration (days): _____

31.Transfusions:

- RBC transfusion (Y/N): _____
- Platelet transfusion (Y/N): _____
- Number of units: _____

32.Growth factors administered:

- G-CSF
- GM-CSF
- EPO

Date started: __ / __ / ____

33.Antibiotics / antifungals / antivirals:

.....

34.ICU admission:

Yes

No If yes → reason: .....

H. Outcomes

35.Outcome of aplasia:

Full recovery

Partial recovery

Persistent aplasia

Death

36.Date of recovery or death: __ / __ / ____

37.Cause of death (if applicable):

Sepsis

Hemorrhage

Disease progression

Other: .....

38.Time to hematologic recovery (days): (ANC > 500/mm³, platelets > 50,000/mm³) _____ days

I. Causality Assessment

39.Temporal relationship compatible with drug-induced aplasia ◯ Yes ◯ No

40.Other potential causes excluded:

◯ Viral infection ◯ Autoimmune disease ◯ Nutritional deficiency

◯ Bone marrow infiltration ◯ exposition aux pesticides ◯ phytotherapy

◯ other aplasiant medicines

41.Causality scoring system used: WHO-UMC Naranjo Other: _____

42.Final causality classification: Certain Probable Possible Unlikely

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