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Review Article

# A Review of Leukemia in Children

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**Abstract**: Leukemia is the most common cancer in children, accounting for approximately one-third of all pediatric cancers. This disease affects the blood-forming tissues, with leukemic cells first growing in the bone marrow, then entering the peripheral blood, and possibly spreading to various organs, including the skin. Acute leukemia's clinical symptoms stem from the frequently rapid onset of bone marrow failure. The clinical presentation typically includes high fever, gastrointestinal and pulmonary symptoms, severe and worsening anorexia, muscle and joint pain, and bleeding. This review explores the incidence and general epidemiology of childhood leukemia, including risk-increasing syndromes; recognizes the clinical presentation and interpretation of blood counts; examines potential oncologic emergencies; describes prognostic factors and the importance of minimal residual disease in precursor B-lymphoblastic leukemia; highlights supportive care in treating acute myelogenous leukemia; and addresses long-term complications of modern childhood leukemia treatments. This narrative review discusses the evidence suggesting an in utero origin of childhood acute leukemia, focusing on acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). It highlights the significant diagnostic presence of these acute leukemias among hematologic cancers, the investigations into prenatal leukemogenesis, and the literature on prenatal risk factors during gestation.

**Key words:** Acute Myeloid Leukemia, Lymphoblastic Leukemia, Pulmonary Symptoms, Childhood Acute Leukemia.

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## 1. INTRODUCTION

Leukemia is the most prevalent cancer among children, responsible for about one-third of all pediatric malignancies [1]. This disease impacts the hematological system, with leukemic cells initially proliferating in the bone marrow before appearing in the peripheral blood and potentially spreading to various organs, including skin [2]. The morphological, immunophenotypical, and cytogenetic properties of the neoplastic cells, as well as the biological activity of the disease, differentiate acute from chronic lymphocytic, or myeloid, forms of leukemia [3]. The French-American-British (FAB) Cooperative Group has classified acute leukemia into distinct categories to aid in understanding [4]. Whereas acute myeloid leukemia (AML) is categorized by subtypes M0–M7, acute lymphocytic leukemia (ALL) is categorized by subtypes L1–L3 [5]. Leukemia cutis (LC), a specific skin manifestation, is characterized by leukemic infiltrates detectable through histological studies [6]. Advances in immunohistochemistry and molecular genetic techniques have improved the identification of leukemic cells, even in non-specific skin changes associated with leukemia and other skin conditions, such as herpes simplex lesions, psoriasis vulgaris, and various epidermal neoplasms [7]. Early symptoms of childhood leukemia often include pallor, weakness, swollen cervical glands, skin hemorrhages, cough, difficulty breathing, joint pains, mouth sores, abdominal pain, and neurological symptoms [8]. Physical examinations often reveal small, palpable cervical lymph nodes [9]. Children may experience muscle pain, particularly in the legs, and exhibit rheumatism-like nodules. Initial blood tests might show moderate leukopenia with a normal differential count, potentially leading to a misdiagnosis of rheumatic fever until more definitive symptoms, such as significant gland enlargement and a marked increase in leukocytes, confirm acute leukemia [10]. Fever and persistent pain are common indicators of acute leukemia [11]. Long-term survivors of childhood acute lymphoblastic leukemia (ALL) often face increased risks of mortality and morbidity, especially those who underwent radiation therapy or experienced a relapse. The Childhood Cancer Survivor Study (CCSS) has extensively reported on these outcomes, although earlier research sometimes combined ALL cases with other pediatric malignancies [12].

### *1.1 Clinical Symptoms*

The rapid onset of symptoms due to bone marrow insufficiency distinguishes acute leukemia from other forms of the disease [13]. Patients typically present with a sudden high fever, along with gastrointestinal and pulmonary issues, severe hunger, muscle and joint pain, and bleeding tendencies [14]. Chronic lymphocytic leukemia (CLL), a type of chronic leukemia, is often incidentally detected during routine blood tests or abdominal ultrasounds that reveal an enlarged spleen (splenomegaly) [15]. Dermatological symptoms associated with leukemia can be categorized into nonspecific changes in the skin and specific alterations based on clinical and histological criteria [16]. Nonspecific skin changes may arise due to abnormal hematopoiesis or manifest as part of cutaneous paraneoplastic disorders associated with leukemia [17]. Opportunistic infections, such as herpes zoster, furunculosis, and fungal abscesses, often result from insufficient production of certain types of white blood cells (granulocytes) [18]. Thrombocytopenia, a condition characterized by low platelet counts, can lead to hemorrhagic skin conditions such as thrombocytopenic purpura [19]. Cutaneous paraneoplastic disorders may also present with skin changes resembling insect bites, such as pyoderma gangrenosum and sweet syndrome [20]. These dermatological and hematological manifestations are crucial for diagnosing and distinguishing between different types of leukemia stressing the importance of thorough clinical evaluation [21]. Moreover, these skin changes can serve as early indicators of leukemia, prompting timely medical intervention. The complex relationship between leukemia and skin health emphasizes the need for healthcare providers to remain vigilant in identifying and managing these symptoms [22]. By understanding the wide range of clinical signs associated with leukemia, medical professionals can improve patient outcomes through early detection and targeted treatment strategies [23]. Parents often notice pallor and weakness as initial symptoms of childhood leukemia. Other commonly observed symptoms include swollen cervical glands (9 cases), skin hemorrhages (7 cases), cough and difficulty breathing (5 cases), joint pain (5 cases), mouth sores (2 cases), abdominal pain (2 cases), and neurological symptoms [24]. Despite the absence of visible limb swelling, there is widespread muscular discomfort when slight pressure is applied. Physical examination often reveals palpable lymph nodes in the anterior and posterior neck. Children may wake up crying due to muscle discomfort, particularly in their legs, resembling symptoms of rheumatism, with nodules in the neck and a small lump near the base of the right thumb's metacarpal bone [25]. Although electrocardiograms typically show normal heart function, a subtle systolic murmur may develop at the heart's apex. Early blood tests may not detect anemia but can reveal mild leukopenia (4,000 to 6,000 leukocytes) with a normal differential count, even in the presence of fever and persistent pain [26]. In certain cases, a diagnosis of rheumatic fever may be considered until additional symptoms such as skin and mucous membrane hemorrhaging, significant enlargement of cervical glands, and a marked increase in leukocyte count (up to 20,000) suggest acute leukemia [27]. Unfortunately, this progression can be rapid, as evidenced by cases where patients passed away within a week of diagnosis [28].

### *1.2 Long-Term Complications*

Survivors of childhood acute lymphoblastic leukemia (ALL) often face significantly higher rates of mortality and morbidity compared to the general population, focussing the necessity of ongoing medical vigilance and support [29]. ALL primarily targets immature lymphocytes, a type of white blood cell crucial to the immune system, and is predominantly diagnosed in children [30]. Despite high survival rates due to advancements in treatment, long-term survivors are at increased risk for a multitude of chronic health issues [31]. These complications can include endocrine disorders, neurocognitive deficits, and musculoskeletal problems, which can severely impact the quality of life [32]. Furthermore, the aggressive treatments required to combat ALL, such as chemotherapy and radiation, can predispose survivors to subsequent malignancies, such as secondary cancers [33]. Cardiovascular complications are also a significant concern, with treatments potentially leading to cardiomyopathy, heart failure, and other cardiovascular diseases later in life [34]. The psychosocial impact on survivors is profound as well, with many facing challenges such as anxiety, depression, and difficulties in social integration [35]. Therefore, understanding the comprehensive, long-term health implications of ALL and its treatments is crucial for effectively managing pediatric patients [36]. Implementing a multidisciplinary approach that includes regular monitoring, preventive care, and tailored interventions can help mitigate these risks and

improve the overall health and well-being of childhood ALL survivors [37]. This holistic strategy is essential in ensuring healthy, fulfilling lives long after their initial diagnosis and treatment. Enhanced survivorship care plans, incorporating routine screenings, lifestyle modifications, and mental health support, are vital components in addressing the unique needs of this population and fostering their long-term health and resilience [38].

### *1.3 Supportive Care in Acute Myelogenous Leukemia*

Historically, acute myeloid leukemia (AML) treatment has primarily commenced in hospital settings, following guidelines established prior to 1996 [39]. However, recent studies suggest that outpatient care following chemotherapy may be both practical and safe, despite its unconventional association with this treatment modality [40]. In a specific trial, forty percent of patients were selected to receive outpatient management, facilitated by their proximity to the clinic where they received daily medical care [41]. A critical prognostic indicator in acute lymphoblastic leukemia (ALL) is the detection of minimal residual disease (MRD) post-treatment, assessed through techniques such as flow cytometry and polymerase chain reaction (PCR) [42]. Each method offers unique advantages; PCR, for instance, is highly sensitive but technically demanding, whereas flow cytometry is cost-effective and efficient [43]. Both are valuable for risk stratification, alongside considerations of age, white blood cell count, and cytogenetic features to comprehensively evaluate outcomes [44]. Children with leukemia and high circulating leukemic blast cell counts face increased risks of early morbidity and mortality, often due to metabolic complications or leukostasis in cerebral or pulmonary vasculature [45]. Hyperleukocytosis, defined by leukocyte counts exceeding 100,000/mL, varies in incidence depending on leukemia subtype [46]. Tumor lysis syndrome, a severe consequence of leukemia treatment, involves rapid release of cellular contents into the bloodstream following tumor cell destruction, leading to metabolic disturbances like hyperuricemia, hypocalcemia, and renal failure [47]. Managing leukemia in children requires a thorough understanding of disease risks and tailored treatment strategies, including addressing complications such as anemia, which affects a significant portion of ALL patients at diagnosis [48]. Evaluations conducted between January 1996 and July 1998 sought to assess the safety and feasibility of early outpatient supportive therapy for AML patients undergoing induction chemotherapy [49]. Discussions on outpatient care for granulocytopenic AML patients have highlighted the potential benefits of selective outpatient treatment, supported by reports of safe and practical approaches in high-risk populations undergoing chemotherapy [50]. Future studies aim to validate models for outpatient supportive care and identify predictive factors for successful hospital discharge [51].

### *1.4 Prognostic Factors and Minimal Residual Disease*

Numerous studies have shown that the presence of minimal residual disease (MRD) after treatment for acute lymphoblastic leukemia (ALL) is a significant predictor of patient prognosis [52]. Flow cytometry detects MRD by identifying leukemic cells based on unique antigen profiles distinct from normal bone marrow cells [53]. PCR amplification of clonotypic immunoglobulin or T-cell receptor gene rearrangements can also be used for MRD detection, requiring custom clone-specific reagents to achieve sufficient sensitivity [54]. Despite flow cytometry being less standardized compared to molecular methods, it offers faster, more cost-effective results and is informative for a larger proportion of patients. Flow-based MRD assessment holds promise for promptly identifying high-risk patients, enabling timely treatment adjustments like intensified therapy [55]. Although direct comparisons generally show agreement between PCR and flow cytometry methods, individual patient classification may differ [56]. Both PCR and flow cytometry effectively contribute to risk stratification in clinical practice [57]. Despite MRD's well-established prognostic importance in ALL, research studies are often limited in scale. Other established prognostic factors such as age, white blood cell count, cytogenetic characteristics, and conventional response assessments must be considered alongside MRD in evaluating outcomes in childhood ALL [58]. Further exploration is needed to understand the interactions between MRD and other prognostic factors. MRD's prognostic relevance persists even after accounting for common risk factors, suggesting its independent predictive value [59]. However, uncertainties remain about whether complex interactions exist between MRD and other factors or if MRD alone is sufficient for outcome prediction. For example, previous research has shown differences in the frequency of positive MRD results at the end of induction therapy between the two most prevalent [60].

### *1.5 Hyperleukocytosis*

An important risk factor contributing to early morbidity and mortality is a high concentration of circulating leukemic blast cells, potentially resulting from leukostasis or rapid cell breakdown in brain or pulmonary capillaries [61]. Hyperleukocytosis, defined as a leukocyte count (WBC) exceeding 100,000/mL$^3$, is observed in 5% to 20% of confirmed cases of juvenile leukemia, with acute lymphoblastic leukemia (ALL) being more common. Hyperleukocytosis becomes clinically significant when WBC counts exceed 200,000/mL$^3$ in cases of acute myeloid leukemia (AML), ALL, and chronic myeloid leukemia (CML). Myeloid leukemias frequently lead to tumor lysis syndrome, also referred to as stroke in cases of ALL. Leukocytes have the potential to proliferate and form white thrombi in smaller veins, obstructing blood flow to the brain and lungs. Increased oxygen demand not only enhances bleeding, but also damages arterial walls [62]. Blood viscosity, influenced by factors such as packed erythrocyte and leukocyte counts, fluid viscosity, and cell deformability, correlates with higher morbidity risk. Arterial obstruction is more likely with the presence of myeloblasts and monoblasts, as they are larger and less flexible compared to granulocytes and lymphoblasts [63]. Hyperleukocytosis predominantly affects intracerebral and pulmonary circulations, presenting symptoms like altered mental status, headache, seizures, papilledema, and retinal venous swelling, though asymptomatic cases exist. Respiratory distress, hypoxemia, and right ventricular failure are potential outcomes of pulmonary leukostasis, observed variably on chest radiographs [64]. Additional complications may include dactylitis, priapism, and renal failure, with mortality risk heightened, particularly when WBC exceeds 300,000/mL$^3$ in monocytic AML subtypes. Cytocrit levels above 30% and rising WBC count are also risk factors. Management strategies for hyperleukocytosis lack controlled investigations but typically involve hydration, alkalinization, and allopurinol to reduce metabolic burden. Platelet transfusions aim to maintain counts above 20,000/mL$^3$ to prevent cerebral hemorrhage. Coagulopathy in AML cases may require vitamin K and fresh frozen plasma, while PRBC transfusions are cautiously managed to avoid excessive blood

viscosity (Hb ≤ 10 g/dL). Diuretics are avoided until WBC counts normalize [65]. Exchange transfusions and leukapheresis effectively lower WBC counts and metabolic load, reducing counts by approximately 48% to 66%. Although not studied extensively for CNS or pulmonary bleeding reduction, leukapheresis reportedly decreases tumor lysis syndrome occurrence in ALL cases. Complications include rapid leukocyte count rise, intravascular access challenges, and anticoagulation needs. Upon stabilization, prompt antileukemic therapy is recommended [66].

### *1.6 Tumor Lysis Syndrome (TLS)*

Leukemia can lead to a serious complication known as tumor lysis syndrome, characterized by the rapid proliferation of abnormal white blood cells. TLS is not only a common consequence, but also a critical concern in leukemia management [67]. This type of cancer affects both bone marrow and blood, triggering TLS when a large number of cancer cells die suddenly, either spontaneously or due to treatment, releasing their contents into the bloodstream [68]. This rapid release overwhelms the body's metabolic and excretory systems, causing significant challenges in managing cellular waste [69]. The sudden release of cellular components leads to elevated levels of potassium, phosphate, and uric acid, contributing to conditions such as acute kidney injury, hyperkalemia, hyperphosphatemia, and hypocalcemia, all of which pose serious risks, especially to kidney function [70]. Hyperkalemia, for instance, involves dangerously high potassium levels, exacerbating health complications [71]. The rapid breakdown of leukemic cells during TLS can result in severe issues such as cardiac arrhythmias, seizures, and renal failure, necessitating urgent medical attention [72]. Effective management of TLS in leukemia involves proactive strategies aimed at alleviating symptoms and preventing its occurrence [73]. These strategies include hydration, medications to lower uric acid levels, and regular monitoring of electrolytes to prevent complications [74]. Implementing these interventions is criticall for improving outcomes and reducing the risks associated with TLS in leukemia patients [75]. Tumor cells rapidly degrade due to tumor cell death, releasing nucleic acids, potassium, and phosphates into the bloodstream [76]. Hypocalcemia, hyperuricemia, and renal failure are a few of the potential side effects. Some of the conditions that may make primary metabolic problems worse include acute kidney precipitation of calcium and urate, tumor invasion of renal tissue, obstructive uropathy, and dehydration. Tumor lysis syndrome (TLS) patients receiving acute treatment run the danger of multi-organ failure and, in the worst case, death [77]. Particularly in lymphomas like Burkitt's lymphoma and T-cell acute lymphoblastic lymphoma, which are intimately linked to significant tumor burdens but also highly responsive to chemotherapy, and symptoms of TLS frequently appear before or within five days of the start of cytotoxic treatment [78]. Certain characteristics increase the likelihood of developing TLS, including poor urine output , elevated pre-treatment and serum uric acid and lactate dehydrogenase levels [79]. Renal failure risk is increased by renal parenchymal tumor infiltration and obstruction of the ureter or veins due to tumor compression, further complicating the prognosis. TLS-associated renal failure occurs due to impaired kidney clearance of uric acid, phosphorus, and potassium, which are released from shattered tumor nuclei containing intracellular purines. Uric acid solubility in physiological pH conditions (pH 3.6 to 7.2) prevents crystallization in the kidneys' collecting ducts, but acidic environments can promote crystallization, exacerbating obstructive nephropathy [80]. Lactic acidosis may occur due to leukocyte-associated tissue perfusion deficiencies, further complicating renal function. Three examples of purine precursors that influence blood vessel tone include adenosine, adenosine triphosphate, and adenosine diphosphate. Because of the possibility of preglomerular vasoconstriction and postglomerular vasodilation, excessive angiotensin II levels raise the risk of renal failure and decrease filtration [81]. Patients may experience non-specific symptoms including fatigue, nausea, or vomiting [82]. However, these symptoms may not always be indicative of TLS. Most of the time, renal failure does not show up as a clearly defined clinical condition [83].

### *1.7 Anemia*

Leukemia's impact on the bone marrow, where blood cells are produced, often leads to an association with anemia [84]. Leukemia is a type of cancer affecting both the bone marrow and blood, characterized by uncontrolled growth of abnormal white blood cells [85]. These malignant cells disrupt normal blood cell production by displacing healthy cells responsible for synthesizing blood. This disruption can result in anemia, a condition marked by insufficient red blood cells or hemoglobin. Symptoms of anemia include weakness, fatigue, and pale skin [86]. Insufficient red blood cells impair the body's ability to effectively transport oxygen, worsening the patient's overall health. The development of anemia in individuals with leukemia directly stems from the cancer's interference with normal blood cell formation, highlighting the critical need for treatments that address both the cancer itself and its hematologic consequences.Several factors contribute to the development of anemia, including chronic inflammation, hemorrhage-induced blood loss, inadequate response to erythropoietin, and most commonly, reduced production due to malignant infiltration of the bone marrow [87]. Emergency situations due to anemia are rare. Children can often tolerate hemoglobin levels between 2 and 3 g/dL without symptoms due to a gradual decline in production over time. Red blood cell volume can be restored through packed red blood cell transfusions. In cases of significant anemia (hemoglobin levels < 2–3 g/dL) resulting from decreased production, preventing congestive heart failure (CHF) may involve administering small volumes (3-5 mL/kg over 3-4 hours) of PRBCs [88]. Supplemental oxygen may increase tissue oxygen delivery. Blood banks can preserve PRBC units for patients requiring repeat transfusions within three days by initially using only a portion of a unit. Patients experiencing CHF symptoms or hyperleukocytosis may require double-volume exchange transfusions for rapid erythron replenishment [89]. Conversely, for severe anemia due to acute bleeding, PRBC transfusions are typically calculated at 10 mL/kg to increase hemoglobin levels by three grams per deciliter [90]. In cases of acute blood loss and cancer, transfusions of 15-20 mL/kg or more may be necessary to achieve the same increase in hemoglobin, as hemoglobin levels are measured in grams per deciliter [91]. Anemia frequently accompanies leukemia and is often considered an unavoidable complication of the disease. Over the past two decades, numerous laboratories have extensively studied the intricate processes responsible for anemia development in various forms of leukemia. Initially, it was widely believed that leukemia's infiltration of the bone marrow uniformly reduced red blood cell production. Recent advances in radioisotopic techniques have greatly enhanced our understanding of red blood cell dynamics in vivo. Early histological studies by Jaffe challenged the notion that leukemic infiltration universally

suppresses red cell production [92]. In some cases, despite active leukemic proliferation in the bone marrow, red cell components were found to be normal or even increased. While some individuals exhibit dense leukemic infiltration and reduced erythroid cells, physical displacement of erythroid cells alone does not comprehensively explain the pathophysiology of anemia in most cases. Anemia in leukemia patients can stem from various mechanisms, such as decreased erythropoiesis alongside normal or heightened red cell destruction, or normal to enhanced erythropoiesis coupled with significant red cell destruction. In certain instances, anemia may result from bone marrow hypoplasia and decreased red cell synthesis. Patients with chronic leukemia and severe anemia, who nonetheless have prolonged survival potential, often benefit from transfusion therapy to maintain quality of life. Regular transfusions administered at appropriate intervals help sustain functional capacity without necessarily aiming for a hematocrit above 25%. This approach minimizes excessive blood use and reduces the risk of acute transfusion reactions. In managing such cases, it is preferable to administer one to two units of blood regularly rather than waiting until severe anemia necessitates large-volume transfusions over a short period. This proactive approach ensures better patient outcomes and mitigates complications associated with acute blood loss.

### *1.8 Clinical Presentation and Diagnosis*

Children initially presenting with leukemia often exhibit nonspecific symptoms such as pallor, fatigue, and recurrent infections, which are indicative of underlying conditions [93]. Recent advancements in medical imaging and molecular diagnostics have stressed the critical importance of early and precise diagnosis in clinical practice [94]. Despite these advancements, conventional methods like complete blood counts and bone marrow examinations remain pivotal, although newer techniques have enhanced the detection of minimal residual disease[95]. The clinical presentation of various types of leukemia often includes distinctive features. Infants with acute lymphoblastic leukemia, diagnosed before the age of one, typically present with markedly elevated white blood cell counts. T-cell ALL should be suspected in young males presenting with high WBC counts and an anterior mediastinal mass, often associated with respiratory distress exacerbated in the supine position, warranting urgent airway management [96]. Chronic myelogenous leukemia patients frequently present with severe splenomegaly alongside elevated WBC or platelet counts. Acute promyelocytic leukemia, a rare subtype of acute myelogenous leukemia (AML), is often associated with bleeding, central nervous system hemorrhage, and disseminated intravascular coagulation (DIC) at diagnosis, highlighting critical early intervention needs [97]. Extramedullary collections termed "chloromas" can manifest throughout the body in association with leukemic blasts, commonly observed in soft tissues and the central nervous system, particularly in AML with monocytic differentiation. Children with trisomy 21 and AML may initially present with isolated thrombocytopenia following transient myeloproliferative disease [98]. In pediatric practice, interpreting complete blood counts (CBC) and differential counts is crucial for evaluating bone marrow function. CBC provides essential insights into platelet, neutrophil, and red blood cell production, crucial for diagnosing cytopenias and distinguishing between leukemia and other conditions such as viral suppression or drug-induced cytopenia [99]. Definitive diagnosis of leukemia often necessitates bone marrow aspirate and peripheral blood examination for blast quantification. Morphologic analysis under a microscope aids in distinguishing leukemic blasts, while flow cytometry utilizes immunophenotypic markers to differentiate between ALL and AML. Specific immunophenotypic profiles are instrumental in diagnosing leukemia subtypes accurately. Chronic myelogenous leukemia (CML) diagnosis often relies on morphological analysis, identifying characteristic features like the proliferation of normal hematopoietic progenitors in peripheral blood. Lumbar puncture is standard to rule out central nervous system involvement, especially if neurological symptoms are present at diagnosis, mandating magnetic resonance imaging for further evaluation. A thorough testicular examination is imperative for all male leukemia patients during initial assessment. The time interval between the initial symptoms of leukemia and its diagnosis can vary unpredictably. Research findings indicate that between 55% and 77% of patients eventually develop leukemia cutis (LC) subsequent to their initial leukemia diagnosis [100]. LC can manifest in diverse ways, including concurrent skin and systemic involvement, which occurs in approximately 23% to 38% of cases [101]. These lesions can present as single or multiple clinical manifestations, often resembling an exanthematous rash that may be localized to specific areas or spread throughout the body. In rare instances, widespread cutaneous lesions may suggest acute leukemia [102]. The distribution pattern of lesions—whether solitary, scattered, or clustered—helps in classifying the type of leukemia, whether acute or chronic [103]. The growth characteristics of different types of cutaneous leukemia can vary; acute forms typically progress rapidly, sometimes in bursts, while chronic forms generally progress more gradually and consistently, with exceptions such as chloromas and gingival hyperplasia [104]. Despite the varied clinical presentations, specific lesions do not serve as definitive indicators of the type of leukemia. Common nodular manifestations of LC include papules, nodules, and larger tumors. Papules are typically soft and dome-shaped, occasionally reaching the size of a pea [105]. The coloration of nodular lesions can range from yellowish to brown, crimson, or purple, with occasional reports of lesions displaying a bluish tint [106].

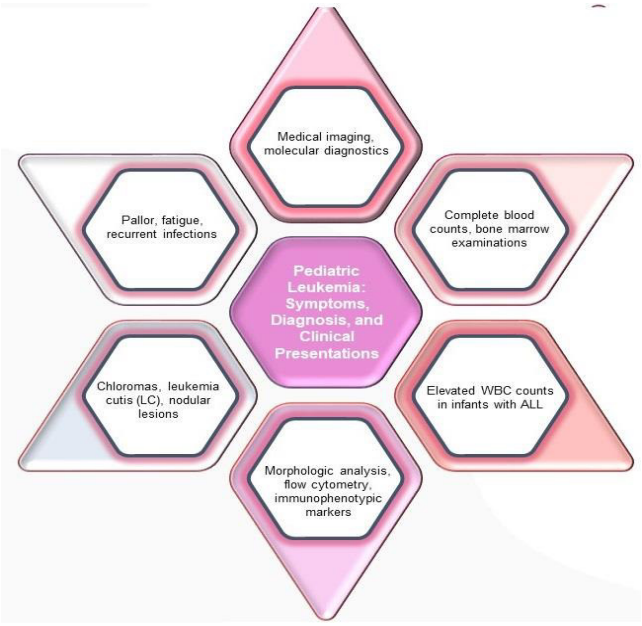


**Fig 1: Overview of Leukemia in Children: Symptoms, Diagnosis, and Clinical Manifestations**

### *1.9 Treatment Advances*

Recent research has predominantly focused on advancing risk stratification and treatment strategies in leukemia. The prognostic role of minimal residual disease (MRD) has now been firmly established to guide chemotherapy intensity and the use of targeted therapies. Novel agents, including monoclonal antibodies and tyrosine kinase inhibitors, have demonstrated potential to improve outcomes in high-risk patients. Each case of precursor B-lymphoblastic leukemia/lymphoma (B-ALL) exhibits distinct immunophenotypic abnormalities compared to normal maturing B-cell precursors (hematogones). The persistence of these anomalies during and after therapy stresses their importance in MRD monitoring. Monitoring MRD using flow cytometry (FC) relies on the premise that leukemic cells maintain these aberrant immunophenotypes. Understanding the stability of these leukemia-associated immunophenotypes over time is critical for effective follow-up assessments. Several studies have identified immunophenotypic changes such as CD10, HLA-DR, TdT, CD20 loss, and acquisition or loss of myeloid antigens. However, comprehensive investigations comparing these anomalies between B-ALL and hematogones' typical immunophenotype are lacking. A thorough comparison of lymphoblast and hematogone immunophenotypes throughout diagnosis could broaden the spectrum of detectable immunophenotypic abnormalities, potentially enhancing MRD detection capabilities.

## 2. CONCLUSION

Childhood leukemia, particularly acute lymphoblastic leukemia (ALL), poses significant challenges due to the demanding nature of its treatment. Breakthroughs in chemotherapy, risk evaluation, and innovative medications have notably increased survival rates, which is a positive outcome. However, survivors often deal with ongoing health issues such as secondary cancers, heart diseases, and hormonal disorders, which affect their quality of life. A vital advancement in treatment is the detection of minimal residual disease (MRD), which allows for more accurate treatment adjustments and better results. Despite these advancements, survivors continue to face health challenges, requiring a holistic, multidisciplinary approach to their care. This approach includes customized interventions, preventive measures, and continuous monitoring. Future research should concentrate on creating strategies to lessen the long-term risks of treatment and understanding how MRD interacts with other prognostic factors. Improving care practices and expanding our knowledge base is crucial to enhance the health and well-being of childhood leukemia survivors.

## 3. AUTHORS CONTRIBUTION STATEMENT

Sanjeev Kumar Jha was responsible for the conceptualization, methodology, and supervision of the project, as well as the original draft writing. Amit Kumar Choudhary contributed to data curation and formal analysis and participated in writing the review and editing the manuscript. Akriti Yadav was involved in investigation and resource gathering and contributed to the visualization of the data. Somenath Ghosh took charge of validation and project administration and also contributed to the review and editing of the manuscript.

## 4. CONFLICT OF INTEREST

Conflict of interest declared none.

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