

PROSPECTIVE STUDY OF CLINICAL PRESENTATION, DIAGNOSTIC PROCESS, TREATMENT AND INDUCTION OUTCOME; ONE YEAR EXPERIENCE IN PAEDIATRIC ACUTE MYELOID LEUKEMIA (AML).

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ABSTRACT

Background: Leukemias constitute one third of all paediatric cancers with myeloid neoplasms constituting about 20% of childhood leukemias.

Objectives: To study the clinical features of pediatric Acute Myeloid Leukemia (AML) at presentation and to evaluate impact of these features on outcome.

Methods: It is a Cross-Sectional study conducted at The Children's Hospital, Lahore from January 2022 to December 2023. The participants included 103 cases of AML diagnosed on bone marrow biopsy and flowcytometry, selected through consecutive convenience sampling. Data was analyzed through SPSS version 20.

Results: Among 103 patients, ninety-three received treatment. The mean age of presentation was 6.9 ± 4.5 years and 72.1% were males. The common presenting feature was fever (92%) followed by pallor (64%). Majority of the patients (46%) had initial WBC count of 50,000-100,000/ μ L. The mean hemoglobin was 6g/dl and the mean platelet count was 14×10^9 /L. Signs and symptoms involving central nervous system were observed in five patients and all were found to have hyperleukocytosis at presentation. The most common FAB subtype was M2(36%) followed by M4(15.5%), M5(12%) and M7(6.8%). Induction mortality rate was 53% and most common cause of death was septic shock. Among rest of the patients, remission rate after first induction was 74%.

Conclusion: Pediatric AML presented with fever, cytopenias, and hyperleukocytosis, with FAB M2 being the most prevalent subtype. While a substantial proportion of patients achieved remission after initial induction, the considerable induction-related mortality, largely attributable to sepsis, emphasizes the need to enhance supportive management and infection prevention strategies to improve survival outcomes.

Keywords: Acute myeloid leukemia, pediatric malignancies, Hyperleukocytosis.

How to cite this article: Riaz S, Mushtaq W, Fatima J, Zafar H, Saqlain N, Ahmad S, Prospective Study Of Clinical Presentation, Diagnostic Process, Treatment And Induction Outcome; One Year Experience In Paediatric Acute Myeloid Leukemia (Aml). Pak Postgrad Med J 2026;37(3): 135-139

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Received: Mar 07, 2026; Revised: Sep 26, 2026

Accepted: Sep 27, 2026

DOI: <https://doi.org/10.51642/ppmj.v37i03.885>

INTRODUCTION

Acute myeloid leukemia (AML) accounts for approximately 20% of childhood leukemias but contributes disproportionately to leukemia-related mortality in the pediatric population.¹ In contrast to acute lymphoblastic leukemia, pediatric AML is characterized by marked biologic heterogeneity, with outcomes largely determined by cytogenetic and molecular features, early treatment response, and the intensity of supportive care.² Current classifications recognize distinct pediatric AML subtypes, including de novo AML, acute promyelocytic leukemia,

and myeloid leukemia associated with Down syndrome, each with unique clinical behaviour and therapeutic implications.³ Over the past two decades, incorporation of cytogenetic and molecular risk stratification into treatment algorithms has substantially improved outcomes in pediatric AML. Favorable-risk abnormalities such as t(8;21), inv(16)/t(16;16), and t(15;17) are associated with high remission rates and durable survival, whereas adverse cytogenetics, secondary AML, and failure to achieve early remission predict poor outcomes in the absence of hematopoietic stem cell transplantation.⁴ As a result, long-term survival for pediatric AML now exceeds 60% in high-income settings.⁵

Despite these advances, data from low- and middle-income countries remain limited, and outcomes reported from high-resource settings may not be directly applicable. Differences in disease presentation, burden of infection, treatment intensity, and access to advanced diagnostics and transplantation may significantly modify the impact of established prognostic factors.^{6,7} In Pakistan, comprehensive institutional data on pediatric AML are scarce, and historically, access to curative therapy has been restricted.

Our centre has implemented contemporary, protocol-based therapy for newly diagnosed pediatric AML. In this study, we describe the clinical characteristics of pediatric AML in our cohort and analyse their association with treatment outcomes. Our objective is to study the presenting clinical features and haematological parameters in newly diagnosed pediatric AML patients and to evaluate the relevance of these factors in treatment outcome in a resource-limited setting and to generate locally applicable evidence to inform risk-adapted management strategies

METHODS

This cross-sectional study was conducted in the Departments of Pediatric Hematology/Oncology and Pathology, The Children's Hospital, Lahore after obtaining permission from Institutional Review Board (Letter No. 2019-12-CHICH, dated 19/02/2019) from January 2022 to December 2023. It included all newly diagnosed cases of AML, from 1-16 years of age after obtaining informed consent from the parents/guardians. For diagnosis, CBC, peripheral blood smear, and/or bone marrow biopsy were done. Flowcytometry, was performed on bone marrow aspirate or peripheral blood samples based on initial WBC and blast counts. AML was further classified Denovo AML, APML and AML with Down Syndrome and others (FAB classification) based on clinical findings, morphology and flowcytometry results. CSF was sent for cytospin to further identify CNS disease.

Treatment was planned according to COG protocols. Patients with Denovo AML were treated on AAML 0531, APML on AAML 0631 and AML with Down syndrome on AAML1531. Induction response was defined as less than 5% blasts in bone marrow aspirate and trephine at the end of two cycles of induction, based on MRD (minimal residual disease) assessment through morphology and flowcytometry.

Data was collected on a pre-formed proforma, including demographic and clinical presentations, complications, treatment regimen and induction outcome. Mean and standard deviation were calculated for age and HB, Platelets and WBCs count. Frequency and percentage were computed for gender, AML subtypes. Statistical analysis was done using IBM SPSS version 20.

RESULTS

During our study period, a total of 524 patients were diagnosed with acute leukemias. Out of these registered patients, 421(80.3%) patients had acute lymphoblastic leukemia and 103(19.6%) patients were diagnosed as AML. Parents/guardians of 10(9.7%) patients refused treatment and left against medical advice while 93(90%) patients received treatment.

The mean age of presentation was 6.9 ± 4.5 years with 72.1% were males and 27.9% were females. The most common presenting feature was fever in 92% followed by pallor (64%) and bleeding (32%). Extramedullary presentations (6.7%) included orbital involvement in three patients (2.9%), presenting with proptosis or visual impairment. Two (1.9%) patients developed spinal masses resulting in cord compression. Additionally, two patients (1.9%) with bulky cervical masses exhibited hyperleukocytosis and subsequently developed tumor lysis syndrome (TLS), reflecting high tumor burden at presentation. CNS involvement at diagnosis was documented in two patients. (Fig. 1)

Initial WBC of $>100,000/\mu\text{l}$ was seen in 12% of patients, $50,000-100,000/\mu\text{l}$ in 46% of patients, $10,000-50,000/\mu\text{l}$ in 25% of patients, $>10,000/\mu\text{l}$ in 16% of patients. The mean hemoglobin was 6g/dl and the mean platelet count was 14×10^9 . (Table 1) Signs and symptoms involving central nervous system were observed and seen in five patients and all of these were found to have hyperleukocytosis at presentations.

Fig 1: Clinical presentation of pediatric patients with AML

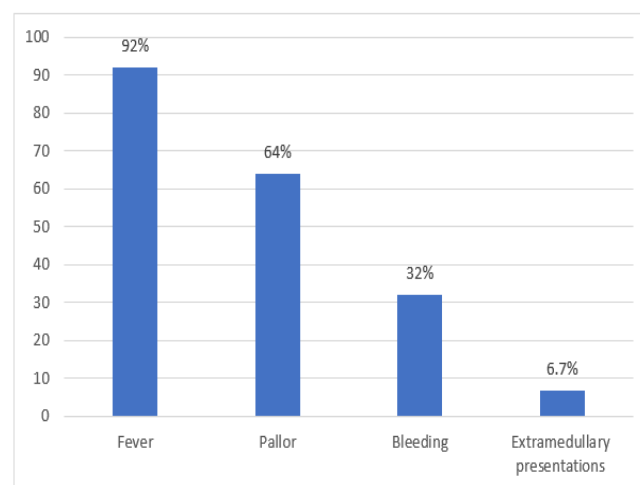


Table 1: Baseline White Blood Cells (WBCs) Count in Paediatric AML Patients

WBCs COUNT/ μ l	NUMBER	%
>100,000	13	12
50,000-100,000	47	46
10,000-50,000	26	25
<10,000	17	16

Sixty-two patients were diagnosed on flow cytometry using bone marrow aspirate while 38% were diagnosed using peripheral blood sample. The most common FAB subtype was M2(36%). Further breakdown revealed M0 (n=0/103, M1 (n= 13/103), M3-APML (n= 4/103), M4 (n= 16/103), M5 (n= 12/103), M6 (n= 2/103) and M7 (n= 7/103). Of them, two patients had associated Downs syndrome and one patient had Fanconi's anemia. (Fig. 2) Induction mortality rate was 53% (57 patients) and most common cause of death was septic shock. Among rest of the 36patients, remission rate after first induction was 74% (26patients).

Pediatric AML Subtypes

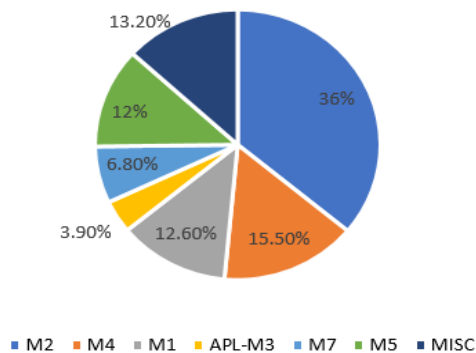


Fig. 2: Distribution of AML according to morphological features (FAB classification)

DISCUSSION

Acute myeloid leukemia represents a biologically diverse and clinically aggressive subtype of acute leukemia, accounting for approximately 15–20% of childhood leukemias. The reported global incidence ranges from 5 to 7.7 cases per million children annually under 15 years of age.^{1,8} Although substantial advances in risk stratification, molecular diagnostics, and supportive care have improved survival rates in high-income countries (HICs), outcomes in low- and middle-income countries (LMICs) remain comparatively inferior.^{5,9} Comprehensive epidemiologic and outcome data from Pakistan are limited, and most available reports are retrospective or single-institution experiences.

In the present study, AML comprised 19.6% of all diagnosed acute leukemias. This proportion is higher than the 9% frequency reported by Zaki et al. in their decade-long institutional audit from Pakistan¹⁰ but closely

approximates the 20% incidence described in multicenter data from the Children's Oncology Group (COG).² The discrepancy between local reports may reflect differences in diagnostic infrastructure, referral bias, evolving classification systems, and improved access to immunophenotyping. The integration of flow cytometry into routine diagnostic workup at our center likely enhanced accurate disease classification, thereby reducing misclassification of ambiguous cases.

The clinical manifestations observed in our cohort are consistent with the classical presentation of pediatric AML. These findings align with previously published data from Pakistan and other countries.^{11,12} Fever in AML patients may result from infection secondary to neutropenia or from cytokine release associated with leukemic proliferation. Severe anemia and thrombocytopenia at presentation, as observed in our patients, indicate substantial bone marrow replacement by blasts.

Hyperleukocytosis is a recognized adverse prognostic factor in AML and is associated with complications such as leukostasis, tumor lysis syndrome (TLS), and early mortality.⁷ In our study, a subset of patients presented with markedly elevated WBC counts, and those with central nervous system (CNS) symptoms were found to have hyperleukocytosis. Ayremlou et al. demonstrated that increasing age, fever at presentation, and elevated WBC counts were significantly associated with mortality in acute leukemia patients.¹³ Our findings support these observations, as infection and leukocytosis were prominent among patients with poorer outcomes. Recent data emphasize that early mortality in pediatric AML is frequently linked to infection-related complications rather than chemotherapy resistance alone.^{14,15} This highlights the critical importance of robust supportive care and timely antimicrobial therapy.

Extramedullary involvement in AML, commonly termed myeloid sarcoma, remains a distinctive clinical entity. Reported incidence in children varies from 5.7% to as high as 40%, depending on study population and diagnostic approach.^{16,17} In our cohort, 6.7% of patients exhibited extramedullary disease in form of orbital involvement, spinal and bulky cervical masses who developed TLS. All had concomitant bone marrow involvement, indicating systemic leukemia rather than isolated myeloid sarcoma. Orbital myeloid sarcoma is well described in pediatric AML and may precede or accompany systemic disease.¹⁸ Spinal masses in AML underscores the importance of early imaging when neurological deficits are present. While extramedullary disease has variably been associated with both favorable and adverse cytogenetic profiles, current evidence suggests that prognosis is largely determined by underlying molecular risk factors rather than anatomical site alone.¹⁹

Down syndrome-associated AML represents a biologically distinct subtype characterized by unique molecular alterations, particularly GATA1 mutations.²⁰ Two patients

with Down syndrome in our cohort achieved complete remission following induction therapy. This observation is consistent with international data demonstrating enhanced chemosensitivity and improved survival outcomes in myeloid leukemia of Down syndrome (ML-DS) when treated with risk-adapted regimens.²¹ Recognition of this subtype is essential, as treatment intensity may be modified to reduce toxicity without compromising efficacy.

CNS involvement at diagnosis was documented in two patients, both classified as FAB M2. CNS disease occurs in approximately 10% of pediatric AML cases and has been associated with hyperleukocytosis and certain morphological subtypes.²² Early detection through cerebrospinal fluid cytopspin examination and appropriate intrathecal therapy is critical to prevent neurological morbidity. Resource limitations may hinder routine CNS evaluation in some settings, potentially affecting disease control.

Regarding morphological distribution, FAB subtype M2 was the most common, followed by M4. Similar patterns have been reported in Pakistani studies by Ghafoor et al. and Bashasha et al.^{11,12} However, Fadoo et al. observed M4 as the predominant subtype.²³ Variability in subtype distribution may reflect geographic, genetic, and methodological differences. Historically, M2 morphology has frequently been associated with favorable cytogenetics such as t(8;21), which correlates with improved overall survival and disease-free survival (DFS). Contemporary molecular profiling further refines prognostication by incorporating FLT3-ITD, NPM1, and CEBPA mutations into risk stratification models.^{3,4}

The induction mortality rate observed in our study remains a significant concern and mirrors early experiences from other LMIC centers. Song YT et al. documented progressive improvement in AML survival over two decades, with survival rates increasing from less than 10% before 1990 to over 50% after implementation of standardized protocols and enhanced supportive care.²⁴ Similar trends have been reported globally, emphasizing that improved infection control, antimicrobial availability, and pediatric intensive care access substantially reduce early deaths.¹⁵ Although intensive chemotherapy protocols have increased survival rates to nearly 70% in several developing nations, infection continues to be a leading cause of treatment-related mortality. Strengthening supportive care infrastructure, implementing standardized febrile neutropenia guidelines, and ensuring early sepsis management are therefore essential to improving outcomes in our setting.

CONCLUSION

In summary, pediatric AML in our population demonstrates clinical and morphological characteristics comparable to international data. However, early mortality, primarily infection-related, remains disproportionately high. Establishing multicenter

national registries, integrating cytogenetic and molecular diagnostics, and prioritizing supportive care optimization are pivotal steps towards improved survival rates. Continued institutional experience, protocol refinement, and collaborative research will be critical to improving long-term survival outcomes for children with AML in Pakistan.

LIMITATIONS

This study has certain limitations. As it was conducted at a single tertiary care center, the results may not be representative of the broader pediatric AML population in other settings. In addition, detailed cytogenetic and molecular analyses were not available for all patients, which restricted comprehensive risk stratification. Furthermore, the study evaluated early induction outcomes only, and long-term follow-up data regarding survival, relapse, and event-free survival were not assessed.

ETHICAL APPROVAL

Ethical approval of article was granted by the Institutional Review Board of the Children's Hospital and Institute of Child Health, Lahore, vide reference No. 2019-12. Dated 19 Feb, 2019

AUTHOR'S CONTRIBUTIONS

SR: Conceived the idea, designed, analysis, final revision of the manuscript.

WM: Data analysis, literature review, manuscript writing

JF: Data collection, data analysis, literature review.

HZ: Specimen collection, data collection & analysis.

NS: Data analysis, Literature review, Manuscript writing

SA: Data collection, data analysis.

All Authors: Approval of the final version of the manuscript to be published

CONFLICT OF INTEREST

Authors declare no conflict of interest.

FUNDING SOURCE: None

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