



MIXED PHENOTYPIC ACUTE LEUKEMIA: REAL-WORLD INSIGHTS FROM A RETROSPECTIVE STUDY AT A TERTIARY CARE INSTITUTE

Oncology

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ABSTRACT

Mixed phenotypic acute leukemia (MPAL) is a rare and aggressive hematologic malignancy that can occur across all age groups. It is characterized by the expression of markers from more than one lineage, resulting in diagnostic and therapeutic challenges. Given the limited data on its features and outcomes, we conducted a retrospective analysis of 29 consecutive adult patients (≥ 18 years) diagnosed with MPAL by flow cytometry at our institution between January 2020 and December 2024. The study aimed to evaluate the clinicopathological profile, cytogenetic and molecular characteristics, and their relation to outcomes in these patients. Among the 29 patients, 15 (51.7%) were male and 14 (48.3%) were female, with a median age of 37 years. The T/myeloid subtype was the most frequent (15 cases), followed by B/myeloid and B/T subtypes (7 cases each). Cytogenetic analysis revealed normal karyotypes in 14 cases, while t(9;22) was the most common abnormality, seen in 3 patients. Other abnormalities occurred in single cases, and 4 cases had no yield. Molecular testing identified BCR-ABL and FLT3-ITD mutations in one patient each; 11 patients were negative for molecular abnormalities, and testing was not performed in 16 cases. Most patients received the modified BFM 95 protocol, an ALL-based regimen, while two received BFM with a tyrosine kinase inhibitor (TKI). Other treatments included a hypomethylating agent (1 case), TKI with steroids (1 case), or steroids alone (2 cases). The presence of D8 blasts in the peripheral smear was significantly associated with poor end-of-induction bone marrow response ($p < 0.001$). End-of-induction bone marrow remission status showed a significant correlation with survival ($p < 0.001$). After a median follow-up of 4.37 months, both the median overall and progression-free survival were 17.85 months (range, 11.3–70.8 months). MPAL remains a heterogeneous leukemia with poor outcomes, underscoring the need for comprehensive diagnostic evaluation and individualized treatment strategies.

KEYWORDS

Mixed-phenotype acute leukemias, Cytogenetics, flow cytometry.

INTRODUCTION

MPAL is an uncommon subtype of acute leukemia, once termed biphenotypic or bilineage leukemia, which features blasts with overlapping myeloid and lymphoid markers, reflecting dual-lineage differentiation with incidence of less than 3%¹.

While MPAL can present at any age, it is diagnosed more often in adults. The condition has a characteristic bimodal age distribution, with peaks at around 19 and after 60 years of age. It also shows a slight male predominance²⁻⁴.

Determining the prevalence of mixed phenotype acute leukemia (MPAL) has been challenging, largely because its definition and diagnostic approach have changed over time¹.

The WHO 2022 classification updated MPAL criteria by eliminating the scoring system and focusing on strict lineage-defining markers. B-lineage requires strong CD19 with CD79a, cytoplasmic CD22, or CD10; weaker CD19 must be supported by two additional B-cell markers. Myeloid lineage is defined by MPO positivity or monocytic differentiation, while T-lineage requires cytoplasmic or surface CD3. MPAL is subclassified into BCR:ABL1-positive, KMT2A-rearranged, B/myeloid NOS, T/myeloid NOS, and rare B/T types. Leukemias with recurrent genetic abnormalities (e.g., t(8;21), inv(16), t(15;17)), CML blast crisis, or therapy-related AML are excluded, regardless of marker expression³.

Although updated diagnostic criteria have improved clarity, there are still no standardized treatment protocols for MPAL, making outcome assessment across studies challenging⁵.

MPAL is associated with a particularly unfavorable prognosis as the disease is inherently complex, exhibiting a wide range of clinical, immunophenotypic, cytogenetic, and molecular genetic variations⁶.

To the best of our knowledge, no study has comprehensively assessed the end-of-induction response and Day 8 prednisone response in conjunction with the clinical profile in adult patients with MPAL.

This study sought to identify individuals diagnosed with MPAL at a tertiary care hospital according to the WHO criteria and to analyze their clinical manifestations, hematological data, immunophenotypic characteristics and also the treatment outcomes.

METHODS

This was a retrospective single-center study conducted in a tertiary care hospital in South India. A comprehensive review of the medical records of all patients who presented with acute leukemia to our institute between January 2020 and December 2024 was undertaken and MPAL diagnosed on the basis of bone marrow and/or peripheral blood smear. Flowcytometry was included in the study.

Flowcytometry

Flow cytometric immunophenotyping was done in all cases either on bone marrow or peripheral blood. Immunophenotyping results were corroborated for lineage determination of the blasts and diagnosis of a mixed lineage AL was made based on the WHO 2022 criteria of lineage assignment.

Cytogenetics

Bone marrow samples were subjected to conventional karyotyping after 24–48 hours of culture in tissue culture medium, following standard procedures. A complex karyotype was defined as the presence of three or more clonal structural chromosomal abnormalities. Out of 29 MPAL patients, 13 underwent molecular testing for diagnosis and risk stratification. Samples were obtained from bone marrow (preferred) or peripheral blood, based on blast availability. RNA and DNA were extracted using standard protocols, followed by RT-PCR to detect fusion transcripts (BCR-ABL1, KMT2A rearrangements, ETV6-RUNX1, TCF3-PBX1). qPCR was used for MRD assessment

when applicable. Targeted NGS using a myeloid-lymphoid panel identified mutations in key leukemia-associated genes (e.g., TP53, IKZF1, NOTCH1, FLT3, RAS, DNMT3A, JAK family).

Statistical Analysis

Good prednisolone response (GPR) was defined as an absolute blast count of <1 x 10⁹/L on Day 8 of treatment. Poor prednisolone response (PPR) was defined as an absolute blast count of >1 x 10⁹/L on Day 8 of treatment⁸. Complete remission (CR) was defined as an EOI marrow with <5% blasts, normal blood counts and no evidence of extramedullary disease⁹.

Statistical analysis was performed using SPSS for Windows version 17 (SPSS Inc., Chicago, IL, USA). All continuous variables were assessed for normal distribution and equality of variances and then subjected to Mann Whitney U test. All categorical variables were subjected to Pearson Chi-square test or Fischer's exact test to assess significant variability. Kaplan Meier test was used for survival analysis.

RESULTS

A total of 29 consecutive patients, aged ≥18 years, were included in the study.

Patient Characteristics

Table 1: Age Distribution

	Number of patients	Percentage
19 to 30 years	10	34.5
31 to 40 years	6	20.7
41 to 50 years	7	24.1
51 to 60 years	6	20.7
Total	29	100.0

The mean age of patients was 38.07 years (SD = 13.6), while the median age was 37.0 years (IQR: 25.0–50.0).

Table 2: Sex Category

	Number of patients	Percentage
Male	15	51.7
Female	14	48.3
Total	29	100.0

There was nearly equal distribution between males and females.

Table 3: Blood Components

	Mean (SD)	Median (IQR)	Min-Max
Hemoglobin	7.29 (1.28)	7.2 (6.6-8.3)	4.8-9.9
Platelets	35551.72 (3582.3)	27000 (15000-44000)	4000-188000
Total Count	23700.69 (3172.54)	10080 (2350-31800)	800-127000

The mean hemoglobin level was low at 7.29 g/dL (median: 7.2 g/dL; range: 4.8–9.9 g/dL). Platelet counts varied widely, with a mean of 35,552/μL and a median of 27,000/μL. Total leukocyte counts also showed considerable variation, with a mean of 23,701/μL and a median of 10,080/μL.

Table 4: Diagnosis

	Number of patients	Percentage
B/Myeloid	7	24.1
T/Myeloid	15	51.7
T/B Leukaemia	7	24.1
Total	29	100.0

T/Myeloid leukemia was the most common diagnosis, followed by B/Myeloid and T/B leukemia (each 24.1%).

Table 5: Complaints

	Number of patients	Percentage
Conjunctival bleed with Fever	3	10.3
Dyspnea	2	6.9
Fever	10	34.5
Fever with Anemia	2	6.9
Fever with Cough	2	6.9
Fever with Fatigue	1	3.4
Fever with LOA	4	13.8
Fever with Paralysis	2	6.9

Fever with TLS	2	6.9
Haemoptysis	1	3.4
Total	29	100.0

Fever was the most common symptom, followed by fever with loss of appetite (LOA) and conjunctival bleed. Other symptoms like anemia, cough, and fatigue were less common.

Table 6: Cytogenetics

	Number of patients	Percentage
46 XX	7	24.1
46 XY	7	24.1
46 XY 9:22	2	6.9
46 XY T (3:9:22)	1	3.4
46 XY, T (8:22)	1	3.4
47 XY, T (8:22), +19	1	3.4
47XX, +22 with inversion 16, FLT3 ITD positive	1	3.4
47 XX TRISOMY 8	1	3.4
47XY, del7, +mar	1	3.4
Complex Karyotype	1	3.4
Del 3,6,9,11,10	1	3.4
Hypo + Tetra	1	3.4
No Yield	4	13.7
Total	29	100.0

The most common cytogenetic findings were normal female (46 XX) and male (46 XY) karyotypes, while various chromosomal abnormalities and complex karyotypes were found in smaller percentages.

Table 7: Treatment Received

	Number of patients	Percentage
BFM 95	23	79.3
BFM 95+TKI	2	6.9
HMA	1	3.4
Received only TKI	1	3.4
Received steroids	2	6.8
Total	29	100.0

Most common treatment received was BFM 95 protocol. 6.8% of patients were given steroids.

Treatment Response

Table 8: Day 8 Blasts In Peripheral Smear

	Number of patients	Percentage
Present	9	31.0
Absent	14	48.3
Not Available	6	20.7
Total	29	100.0

On day 8, blasts were present in the peripheral smear of 31% of patients, absent in 48.3%, and data was not available for 20.7% of the cases.

Table 9: Remission

	Number of patients	Percentage
BM in Remission	11	37.9
BM not in Remission	4	13.8
Reassessment Not Done	14	48.3
Total	29	100.0

Out of the 29 patients, 37.9% achieved bone marrow remission, 13.8% did not achieve remission, and reassessment was not done in 48.3% of the cases.

Table 10: Association Between Day 8 Blasts and Bone Marrow Remission

D8 blasts	Patients in remission	Not in Remission	Reassessment Not Done	p
+	0 (0)	3 (75)	6 (42.9)	<0.001
-	11 (100)	0 (0)	3 (21.4)	
NA	0 (0)	1 (25)	5 (35.7)	
Total	11 (100)	4 (100)	14 (100)	

The table shows a significant association between Day 8 peripheral smear blasts and end-of-induction bone marrow remission. Among patients with D8 blasts (n=9), 3 (75%) did not achieve remission and 6 (42.9%) had no reassessment. In contrast, all patients without D8

blasts (n=11) achieved remission ($p < 0.001$).

Table 11: Comparison Of Median Months Of Survival Between BM In Remission And BM Not In Remission Patients – Mann Whitney U Test

	Mean (SD) (months)	Median (IQR) (months)	P value
BM in Remission	27.9 (17.1)	16.7 (15.7-23.0)	<0.001
BM not in Remission	5.6 (2.6)	4.7 (4.3-5.1)	

	Mean (SD) (months)	Median (IQR) (months)	Min-Max
Overall Follow up	13.49 (19.7)	4.37 (0.6-16.43)	0.03-70.8
Overall survival	30.36 (22.76)	17.85 (15.62 -53.44)	11.3-70.8
Progression free survival	27.62 (21.04)	17.85 (15.4-42.58)	11.3-70.8

Patients in bone marrow (BM) remission had significantly longer median survival (16.7 months; IQR 15.7–23.0) compared to those not in remission (4.7 months; IQR 4.3–5.1) ($p < 0.001$). The average follow-up was 13.5 months, with median overall and progression-free survival around 17.8 months, highlighting improved outcomes with remission.

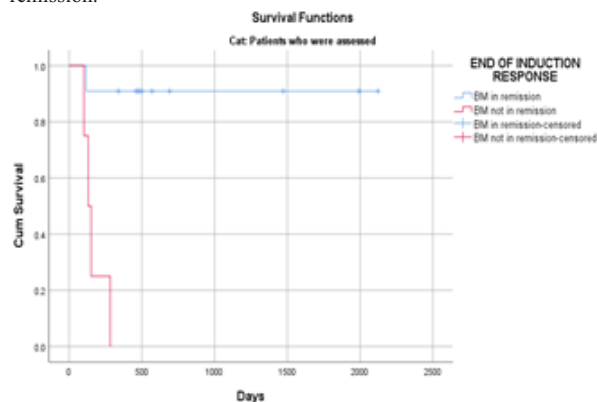


Figure 1: Kaplan Meier survival curve

The Kaplan Meier survival curve shows that patients achieving bone marrow remission at end-of-induction had significantly better long-term survival, with many living beyond 2400 days. In contrast, non-responders showed a sharp decline within 400 days, underscoring remission as a key predictor of overall survival.

DISCUSSION

MPAL shows bland blasts and requires immunophenotypic or molecular confirmation. Overlap with other leukemias and evolving definitions hinder accurate prevalence estimates¹.

Flow cytometry is the key diagnostic tool, enabling detection of multiple lineage-specific antigens on blasts. With advances in multicolor flow cytometry, accurate identification of mixed phenotypes has improved. The 2022 WHO classification provides strict criteria to differentiate true MPAL from leukemias with aberrant antigen expression³. In our study, most MPAL cases were diagnosed using flow cytometry.

MPAL generally demonstrates a bimodal age distribution, with incidence peaks in late adolescents (~19 years) and older adults (≥60 years)^{2,4}. In our retrospective analysis, most cases were clustered within the adolescent and young adult age range, indicating a tendency toward a younger patient population in our cohort. The slight male predominance observed in our cohort was consistent with previously reported trends^{2,4}.

In our 29 MPAL cases, T/Myeloid was the most common immunophenotype (51.7%), followed by B/Myeloid and T/B (each 24.1%), similar to Rubnitz et al.⁷, who reported 57% of T/Myeloid cases. However, most studies, including Pawar et al.⁸ and Matutes et al.⁴, found B/Myeloid to be the most frequent subtype, highlighting the variability of MPAL immunophenotypes across different groups.

MPAL lacks a defining chromosomal abnormality, reflecting its diverse cytogenetic landscape. In the study by Yan et al.⁹, complex karyotypes were the most common abnormality (23.9%) in adult

MPAL patients, followed by t(9;22)(q34;q11) (15.2%), monosomy 7 (7.6%), and polysomy 21 (7.6%). In contrast, our study showed a higher frequency of normal karyotypes (48.2%) and lower incidences of t(9;22) (6.9%) and complex karyotypes (3.4%), with other structural abnormalities also being limited (3.4%). These findings suggest a lower cytogenetic complexity in our cohort.

In the study by Matutes et al.⁴, cytogenetic abnormalities in MPAL cases included t(9;22)/Philadelphia chromosome in 20%, 11q23/MLL rearrangements in 8%, complex karyotypes in 32%, aberrant karyotypes in 27%, and normal karyotypes in only 13%.

In our cohort, fever was the most common presenting symptom (86.2%), either alone or with loss of appetite, conjunctival bleed, anemia, cough, paralysis, or tumor lysis syndrome. Similarly, Sethy et al.¹⁰ reported fever in 87.5% of cases, followed by weakness (70.8%), bleeding and weight loss (54.2% each), and bone pain (37.5%). While both studies identify fever as the predominant symptom, differences in accompanying features may reflect variation in disease burden.

In terms of clinical presentation, pallor was observed in 72.4% of our patients, which was lower than the 95.8% reported by Sethy et al.¹⁰. Splenomegaly was seen in 37.9% of our cohort, whereas hepatosplenomegaly was noted in 66.6% of cases in their study. Lymphadenopathy was also less frequent in our patients (17.2% vs. 45.8%). Interestingly, bleeding manifestations were unique to our cohort (10.3%), while Sethy et al.¹⁰ reported additional features such as sternal tenderness (45.8%), gum hypertrophy (37.5%), and easy bruisability (33.5%), which were not observed in our series.

Baseline hematological parameters in our study showed more severe cytopenias than those reported by Sharma et al.¹¹. Mean hemoglobin (7.29 g/dL) and platelet count (35,551/μL) were markedly lower than in their cohort (8.22 g/dL and 148,400/μL), indicating more pronounced anemia and thrombocytopenia. The mean WBC count was slightly higher (23,700/μL vs. 21,540/μL), with frequent leukocytosis, possibly reflecting a more aggressive disease course or delayed presentation.

BCR-ABL and FLT3-ITD mutations were each detected in 3.44% of cases, 37.9% tested negative, and 55.2% were not tested. A key limitation was the lack of NGS in most cases, with only PCR-based testing used, limiting mutation detection.

MPAL is a rare hematologic malignancy, often managed using ALL-based protocols. In this cohort, 79.3% received a modified BFM 95 regimen; dasatinib was added for Philadelphia chromosome-positive cases. This approach aligns with current evidence supporting ALL-directed therapy in MPAL [12,13,14]. Smaller subsets received hypomethylating agents (3.4%), TKI monotherapy (3.4%), or steroids alone (6.8%).

One patient in our cohort, treated with an AML protocol, was found to have inv(16) on cytogenetics, classifying it as AML with recurrent genetic abnormalities under WHO 2022. However, the initial diagnosis was MPAL based on flow cytometry, and treatment was initiated accordingly. Although this case does not meet current WHO MPAL criteria, it was included to reflect real-world diagnostic practice, where early decisions are often guided by immunophenotypic findings prior to cytogenetic confirmation.

No studies have directly compared the toxicity of ALL-like versus AML-like regimens in adult MPAL or evaluated Day 8 blast clearance and post-induction remission as prognostic indicators in this setting.

On Day 8 in peripheral smear, 48.3% of patients in our adult cohort showed no blasts, indicating an early favorable response, while 31.0% had persistent blasts and 20.7% had missing data. In comparison, Seetharam et al. (pediatric cohort) reported a good prednisolone response in 76.1% of patients. The higher early response in their study may be due to younger age and differences in disease biology¹⁵.

Post-induction bone marrow remission was achieved in only 37.9% of patients in our adult cohort, compared to 90.5% in the pediatric study by Seetharam et al.¹⁵. This stark contrast may reflect differences in age group, disease biology, treatment tolerance, and protocol adherence. Additionally, nearly half of our patients lacked reassessment data (48.3%), possibly due to early mortality or loss to follow-up, limiting

outcome interpretation.

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In our cohort, bone marrow remission was linked to longer median survival (16.7 vs. 4.7 months; $p < 0.001$), highlighting its prognostic value. However, this did not reflect in overall survival rates, likely due to early deaths and limited follow-up. Similarly, Bhella et al. reported a 71% remission rate and 13-month median survival, reinforcing the survival benefit of early remission in adult MPAL¹⁶⁻¹⁷.

Substantial evidence supports the survival benefit of allogeneic stem cell transplantation (allo-SCT) after complete remission in Philadelphia chromosome-positive ALL¹⁸⁻¹⁹; however, none of our patients underwent transplant due to financial and resource limitations.

CONCLUSION

MPAL represents a rare and clinically challenging leukemia with limited available data on its presentation, biology, and outcomes. This study adds to the growing body of evidence in this understudied field. In low-resource settings, early response markers such as Day 8 prednisolone response and end-of-induction remission may offer practical guidance for treatment decisions. The limitations of our study include its retrospective design, the relatively small sample size, and the lack of comprehensive molecular assessment in all patients. Ongoing prospective research is crucial to establish uniform treatment protocols and identify key predictors of prognosis.

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