

Infection Prevalence in Adolescents and Adults With Acute Myeloid Leukemia Treated in an Indian Tertiary Care Center

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PURPOSE Infections remain a major challenge in the treatment of acute myeloid leukemia (AML). Induction-related mortality reported in the literature is approximately < 5% in clinical trials. However, the real-world scenario is different, especially in developing countries, given the high incidence of multidrug-resistant (MDR) organisms, high incidence of fungal pneumonia at baseline, and significant delay before initiation of chemotherapy. We aimed to look at contemporary infections and infection-related mortality and analyze the patterns of infections.

MATERIALS AND METHODS This retrospective study was conducted at a large tertiary care oncology center in India. Patients with newly diagnosed AML who were older than age 15 years, considered fit for intensive therapy, and treated in the general wards of the adult hematolymphoid unit from March 1, 2014, until December 31, 2015, were included.

RESULTS One hundred twenty-one patients were treated during the study period. The most common presenting complaint was fever (85%). The focus of infection at presentation was found in 63% of patients, with respiratory infection being the most common (47%). MDR organisms were isolated in 55% of patients during induction from various foci. *Klebsiella pneumoniae* was the most common blood culture isolate (42.9%). Fungal pneumonia was diagnosed in 55% of patients during induction despite antifungal prophylaxis. Treatment-related mortality was 10.7% in all phases, with an induction mortality rate of 7.4%. Complete remission was attained in 69% of patients. Of all patients who received induction chemotherapy, 74% completed all three consolidation cycles. The 121 patients were followed up for a median period of 53 months. Four-year event-free survival was 35.8%, and 4-year overall survival was 41.5%.

CONCLUSION Infections and infection-related mortality are major challenges during AML induction. Gram-negative MDR and fungal infections are particularly common in our region.

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INTRODUCTION

The challenges in the management of acute myeloid leukemia (AML) are treatment-related mortality as a result of infections and bleeding and relapsed disease. Infections during therapy are associated with mortality, morbidity, and increased health care expenditure and can compromise the dose intensity of chemotherapy. The induction mortality reported in the literature is < 5% in clinical trials.¹⁻³ However, induction-related mortality reported from tertiary care centers in India ranges from 4.4%-24.7%.⁴⁻⁸ The higher mortality rate is a result of factors such as presence of infections at presentation, multidrug-resistant (MDR) organisms infection during induction, invasive fungal infections at baseline,⁸ and significant delay before diagnosis and initiation of chemotherapy. A study from India reported infections

in 46% of patients at baseline.⁸ Another retrospective study from southern India showed a 4-week gap from onset of symptoms to first presentation to hospital.⁴ To improve outcomes, it is important to understand the pattern of infections to devise an appropriate strategy. Herein, we present the pattern of infections and infection-related mortality in patients with AML from a high-volume tertiary care center in India.

MATERIALS AND METHODS

Study Design

This is a retrospective study of patients with newly diagnosed AML who were older than age 15 years, received intensive therapy, and were treated in the general wards from March 1, 2014, until December 31, 2015. This study was approved by the institutional review board vide letter IEC/0319/3209/001. Patients

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

We analyzed the patterns of infection and infection-related mortality in patients with acute myeloid leukemia (AML) from a region with a high incidence of drug resistance and fungal infections.

Knowledge Generated

A clinically evident focus at presentation was found in 63% of patients, with a respiratory focus being most common. Multidrug-resistant organisms were isolated in 55% of patients during induction from various sources, with *Klebsiella pneumoniae* being the most common blood culture isolate. Treatment-related mortality was 10.7% and induction mortality was 7.4%, predominantly as a result of infections.

Relevance

Drug-resistant infections are a major challenge in the management of AML in our setting. They result in greater morbidity, higher antimicrobial usage, and slightly higher mortality compared with rates reported in the literature.

with antecedent hematologic disorder, acute promyelocytic leukemia, and therapy-related AML were excluded as a result of variable management and outcomes.

There are six beds in the general ward for AML induction. Patients get waitlisted for admission from the leukemia clinic. Priority is given to good-risk patients and then according to age. These wards do not have high-efficiency particulate air filters. The patients' beds are placed in a hall with adequate spacing. Chemotherapy is delivered through a peripherally inserted central catheter (PICC). The patients are managed as inpatients until recovery of blood counts. Granulocyte colony-stimulating factor injections were not routinely used after induction chemotherapy. All patients who did not have evidence of fungal pneumonia at baseline received posaconazole as antifungal prophylaxis. As departmental policy, routine antibiotic prophylaxis was not given with the 7+3 induction regimen. Cotrimoxazole and acyclovir prophylaxis was given if a cladribine-based regimen was used.⁹

All patients were treated with standard intensive therapy with 7+3-based (cytarabine plus daunorubicin or idarubicin) induction¹ or 7+5+3 (cytarabine plus cladribine plus daunorubicin) induction.¹⁰ Cladribine was used in patients with high-risk features such as adverse cytogenetics on a case-by-case basis at the physician's discretion. The deciding factors included logistics, funds, and general condition to tolerate 4 weeks of neutropenia.

All episodes of fever⁹ were evaluated with detailed history and physical examination directed at finding the focus of infection, radiologic investigations if required, and cultures. Cultures were taken from the PICC line and peripheral blood at the onset of fever, escalation of antimicrobials, and/or deterioration of general condition of patients attributed to infection. Cultures were also taken from other sites (eg, urine, stool) whenever clinically indicated. All episodes of fever, unexplained tachycardia, hypotension, infectious diarrhea, and soft tissue infections (eg, furuncle,

skin abscess, inflammation at site of PICC line insertion, and/or perianal tenderness) were considered infections.

The choice of initial antibiotics and subsequent change or total duration of antibiotics were consistent with the Infectious Diseases Society of America guidelines.⁹ The only difference was the use of cefoperazone-sulbactam and amikacin as the preferred first-line agents based on our hospital antibiogram and the higher incidence of drug-resistant gram-negative infections.

Objectives

The primary objective was to evaluate the pattern and frequency of infections and infection-related outcomes. The secondary objectives were to estimate the treatment-related mortality, response to chemotherapy (as defined per the Cancer and Leukemia Group B working group criteria¹¹), antimicrobial usage, event-free survival (EFS), and overall survival (OS). Exploratory objectives were to correlate the risk of death with time to initiation of therapy, multidrug-resistant infections, and fungal pneumonia.

EFS and OS were calculated. EFS was calculated from the date of diagnosis to the date of treatment failure, relapse, or death.¹¹ OS was calculated from the date of diagnosis to last follow-up, death as a result of any cause, or probable death as a result of advanced disease.¹¹

Methods

The details of the patients were retrieved from case files and electronic medical records. Baseline details such as demographic characteristics, presenting symptoms, clinical findings, Eastern Cooperative Oncology Group performance status, presence of comorbidities, infectious foci at presentation (detected in baseline workup and symptom-directed evaluation), and laboratory parameters were recorded. AML disease-related characteristics such as cytogenetics (fluorescence in situ hybridization and conventional karyotyping) and molecular abnormalities were recorded. As per the cytogenetics results, patients were divided into favorable-, intermediate-, and poor-risk

TABLE 1. Demographic and Clinical Characteristics at Baseline

Characteristic	No. of Patients (%)
Sex	
Males	76 (63)
Females	45 (37)
Age, years (median, 30 years)	
< 30 (AYA)	59 (48)
30-50	57 (47)
> 50	5 (4)
Comorbidities ^a	
None	100 (83)
At least one	18 (15)
Not known	3 (2)
Presenting complaints	
Fever ^b	103 (85)
Fatigue/weakness	62 (51)
Bleeding manifestations	22 (18)
Cervical lymphadenopathy	2 (2)
Gum swelling	2 (2)
Generalized lymphadenopathy	1 (1)
Paraparesis	2 (2)
Duration of illness before presenting to hospital, months	
Range	0.13-16 ^c
Median	1
ECOG performance status at baseline	
0-1	81 (67)
2-4	40 (33)
Infectious focus at presentation	
None	44 (37)
Respiratory	57 (47)
Skin and soft tissue	24 (20)
Perianal	4 (3)
Oral	3 (2)
GI tract	2 (2)
Multiple foci	12 (10)
Cytogenetic risk at presentation	
Favorable risk	59 (49)
Intermediate risk	44 (36)
Poor risk	15 (12)
Unknown	3 (2)
Induction regimen	
7+3 (cytarabine plus daunorubicin or idarubicin)	104 (86)
Daunorubicin, cladribine, and cytarabine	17 (14)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: AYA, adolescent and young adult; ECOG, Eastern Cooperative Oncology Group.

^aComorbidities defined as hypertension, diabetes, heart disease, or hypothyroidism, as per standard criteria.

^bFever is defined as a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ (101°F) or a temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F) sustained over a 1-hour period.⁹

^cOne patient in the data set had a duration of illness of 12 months, and another had a duration of illness of 16 months. One patient presented with a history of swelling over the left shoulder and fever, and the other patient presented with generalized weakness, off and on fever, and pain in right hip (extramedullary presentation).

groups.¹² The interval from diagnosis to the initiation of induction chemotherapy and the type of chemotherapy administered during induction and consolidation were recorded. The type of infections, infection-related outcomes, need for ICU admission, ventilator support, and PICC line removal as a result of infection were recorded. The response to induction and subsequent postremission therapy was recorded. Minimal residual disease (MRD) was assessed using bone marrow aspirate multicolor flow cytometry with the residual blasts cutoff being $< 0.1\%$.¹³ The disease status at last follow-up was noted.

Analysis

Descriptive statistics were used to summarize the data, including medians and standard deviations. Survival was presented using Kaplan-Meier analysis. Correlation between survival and factors such as MDR infections, fungal pneumonia, and time to initiation of therapy was estimated using multivariable analysis. SPSS v25 (SPSS, Chicago, IL) was used for statistical analysis.

RESULTS

One hundred twenty-one patients with AML were treated during the study period. The median time from registration to start of induction chemotherapy was 21 days (range, 1-75 days). The baseline characteristics are listed in Table 1. For this study, individuals between the age of 15 and 30 years were considered adolescents and young adults.¹⁴ Seventy-seven patients had a focus of infection (63%), with respiratory infections being the most common site (47%). The 7+3 regimen was the most common induction strategy. Consolidation therapy consisted of high-dose cytarabine (HIDAC) as a 3-hour infusion every 12 hours on days 1, 3, and 5. The cause for attrition in each phase is given in Figure 1.

Infections During Induction

All patients developed infections at some point in their treatment course. Most of the infections (90%) were observed during the induction phase. Organisms were isolated from blood, stool, sputum, perianal swabs, wound swabs, and pus cultures, which were sent from clinical infectious foci (Table 2).

During induction, gram-positive cocci (GPCs) were isolated from different sites in 25 patients (20%), with the most common being enterococci (12% of patients; Table 3). Gram-negative bacilli (GNBs) were observed in 91 patients (75%), with *Escherichia coli* being the most common isolate seen (35.4% of patients).

Twenty-seven patients (22%) had blood culture positivity during induction. GNBs were more common (20 patients; 16%), followed by GPCs (six patients; 5%). Mixed infection with GNBs and GPCs was seen in one patient, and one patient had a *Candida* infection. Nineteen patients (16%) had an isolate from the PICC, of whom six patients were successfully treated with antibiotic lock, whereas 13

patients required removal. Only seven PICCs that were removed grew a pathogen from tip culture. The median number of days for clearance of blood cultures was 5 days (range, 2-11 days).

Sixty-seven patients (55%) had MDR organisms in the isolates. Thirty-four patients (28%) had extended-spectrum β -lactamase (ESBL)-producing organisms, 14 patients (12%) had carbapenamase-producing organisms, four patients (3%) had methicillin-resistant *Staphylococcus aureus*, two patients (2%) had vancomycin-resistant *Enterococcus*, and one patient had colistin-resistant *Klebsiella*.

The MDR organisms were isolated from different foci of infection (Table 2), with *Klebsiella pneumoniae* being the most common among blood culture isolates (42.9%). *E coli* was most common among stool culture isolates (47.1%), and *Pseudomonas* was the most common in the wound swabs (63.6%). The numbers of patients with MDR infections in different phases of therapy (after start of induction and during consolidation cycles) are listed in Table 3. Neutropenic patients with prolonged or breakthrough fever were suspected of having fungal pneumonia. Patients with fungal pneumonia were categorized as having proven, probable, or possible invasive fungal disease.¹⁵ In total, 67 patients (55%) were suspected of having fungal pneumonia during induction. Among these patients, seven patients (5%) had probable fungal pneumonia, and the rest had possible fungal infection.

During the course of induction, 19 patients received acyclovir for clinical suspicion of herpes infection. Six patients were tested for cytomegalovirus infection based on clinical suspicion; however, none were positive. One patient had scabies during induction.

Induction Complications

Five patients (4%) required intensive care unit (ICU) admission, with a median ICU stay of 3 days. Six patients required inotropic support during their course of induction. The induction mortality rate was 7.4%, with all patients dying from severe sepsis and three patients having a life-threatening infection prohibiting further therapy.

Infections During Consolidation

Patients developed infections in all phases of consolidation therapy, with predominantly GNBs, as illustrated in Figure 2. In total, 17 patients (14%) developed probable fungal pneumonia during the consolidation phase. In two patients, the third HIDAC course was omitted, and the patients proceeded directly to follow-up in view of their complicated course.

Only two patients could proceed to an allogeneic stem-cell transplantation (ASCT) as consolidation therapy. One patient subsequently developed corticosteroid-refractory graft-versus-host disease after transplantation and died, and the other patients experienced relapse and died.

Antimicrobial Use

As per departmental policy, cefoperazone-sulbactam and amikacin were used as the first-line antibiotics for febrile neutropenia. Most patients (104 of 121 patients) required stronger antibiotics (carbapenems, colistin, tigecycline, teicoplanin, or vancomycin) for control of infections, with most antibiotics requiring courses of > 10 days. Details of antimicrobial type and duration are listed in Table 4. The mean durations of antimicrobial use during induction are listed in Appendix Table A1.

Efficacy Outcomes

Complete remission was attained in 84 patients (69%). Of 66 patients in whom MRD was assessed, 30 patients (45%) attained MRD-negative status. The median follow-up time was 53 months. Of the 108 patients who achieved remission, 55 patients experienced relapse. The mean time to relapse was 10.7 months (standard deviation, 7.9 months). Thirty-three patients were lost to follow-up. The patient survival statistics and relapses are presented in Figure 3.

Of the 121 patients, 75 patients (62%) experienced an event (treatment failure, relapse, or death), leading to a 4-year EFS rate of 35.8% (95% CI, 28% to 46%) and median EFS time of 19 months. Nine patients did not survive

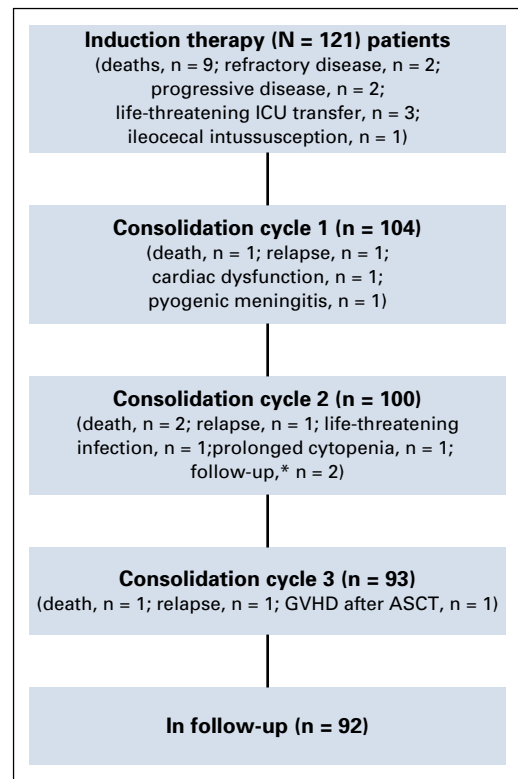


FIG 1. Causes for attrition. (*) Two patients were unfit for further therapy and went on to follow-up after cycle 2 consolidation. ASCT, allogeneic stem-cell transplantation; GVHD, graft-versus-host disease; ICU, intensive care unit.

TABLE 2. Percentage of Cultures Isolating MDR Organisms During Induction

Culture During Induction	Total (N = 121)	No. of Cultures (%)							
		<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas</i>	Enterococci/VRE	Streptococci	<i>Acinetobacter</i>	<i>Staphylococcus aureus</i>	Multiple Organisms
PICC/blood ^a	120	4 (11.4)	15 (42.9)	8 (22.9)	8 (22.9)	1 (2.9)	6 (17.1)	5 (14.3)	6
Sputum	59	1 (7.1)	7 (50)	5 (35.7)	2 (14.3)	2 (14.3)	3 (21.4)	2 (14.3)	6
Stool	90	16 (47.1)	6 (17.6)	1 (2.9)	11 (32.4)	1 (2.9)	3 (8.8)	1 (2.9)	9
Wound swab ^b	14	0 (0)	6 (54.5)	7 (63.6)	0 (0)	1 (9.1)	1 (9.1)	3 (27.3)	3
Perianal	4	0 (0)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1

Abbreviations: MDR, multidrug resistant; PICC, peripherally inserted central catheter; VRE, vancomycin-resistant *Enterococcus*.

^aIncludes both PICC line infection and blood-borne infection.

^bIncludes cellulitis, hidradenitis, furuncle, abscess, otitis externa, soft tissue infections, tonsillitis, and thrombophlebitis.

induction, and remission status could not be assessed. Twenty-nine patients died, of whom 21 died as a result of disease relapse and eight died in remission. The 4-year OS rate was estimated to be 41.5% (95% CI, 39.4% to 59%).

Multivariable Analysis

Patients with complete remission with MRD negativity had a better EFS. No statistically significant correlation could be made between disease risk status, time to induction, incidence of MDR infections, or incidence of fungal infections and EFS. Completion of treatment was found to have a statistically significant influence on EFS ($P < .001$), with a median EFS time of 30 months and 4-year EFS of 42.4% (95% CI, 33% to 54.4%; Appendix Fig A1) in patients who completed treatment. The analysis of EFS and OS is provided in Table 5.

TABLE 3. Patients With MDR Isolates in Different Phases of Therapy

MDR Organisms Isolated	No. of Patients (%)			
	Induction	HIDAC Cycle 1	HIDAC Cycle 2	HIDAC Cycle 3
Total No. of patients	121	104	100	93
<i>Escherichia coli</i>	43 (35)	4 (4)	3 (3)	2 (2)
<i>Klebsiella pneumoniae</i>	20 (17)	5 (5)	4 (4)	2 (2)
<i>Pseudomonas</i>	13 (11)	3 (3)	1 (1)	3 (3)
Enterococci	15 ^a (12)	0	0	1 ^b (1)
Streptococci	4 (3)	0	0	0
<i>Acinetobacter</i>	6 (5)	0	1 (1)	0
<i>Staphylococcus aureus</i>	6 ^c (5)	1 (1)	1 ^d (1)	1 ^d (1)
Others (rare organisms)	6 (5)	1 (1)		

Abbreviations: HIDAC, high-dose cytarabine; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

^aTen patients had VRE.

^bVRE.

^cFour patients had MRSA.

^dMRSA.

DISCUSSION

The key findings from our study include a higher incidence of infections at baseline, a higher incidence of drug-resistant infections and fungal infections, and consequently a higher use of antimicrobials than reported in the literature. The study population is different from that reported in other studies but is reflective of patients with AML in our region in terms of the younger age, male predominance, and greater prevalence of patients with good-risk disease.

This study included patients age 15 to 57 years. The median age of our cohort was 30 years, with only 4% of patients older than 50 years. This reflects the younger age of our AML population. Collective data reported on 3,848 patients from a multicenter consortium in India showed a median age of 40 years, with only 14% of patients > 60 years old.¹⁶ This could reflect the fact that our population comprises a younger population and a possible referral bias as a result of elderly patients not seeking medical care. Only one third of the patient were female, reflecting the overall sex disparity in seeking care in our region. Half of our cohort had good-risk disease, unlike other studies where < 20% of patients have good-risk disease.¹⁷ This could be a result of the long time to treatment initiation (Fig 4). Good-risk patients are more likely to survive the waiting period. This could also reflect the preferential support given to good-risk patients by the

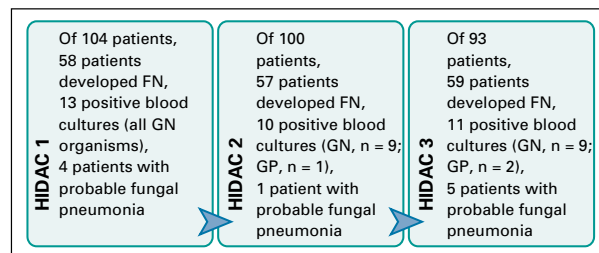
**FIG 2.** Infections during consolidation. FN, febrile neutropenia; GN, gram-negative; GP, gram-positive; HIDAC, high-dose cytarabine.

TABLE 4. Antibiotic, Antifungal, and Antiviral Use in Different Phases of Therapy

Treatment	No. of Patients			
	Induction	HIDAC Cycle 1	HIDAC Cycle 2	HIDAC Cycle 3
Total No. of patients who received treatment	121	104	100	93
Carbapenem	99	14	19	22
Colistin	41	0	4	2
Tigecycline	23	1	1	1
Linezolid	15	1	0	1
Teicoplanin	48	8	21	10
Vancomycin	3	1	0	0
Clindamycin	33	7	7	9
Amphotericin B	19	1	0	0
Caspofungin	68	3	3	3
Voriconazole	17	0	0	0
Acyclovir	19	1	0	0
Ganciclovir	6	0	0	0

Abbreviation: HIDAC, high-dose cytarabine.

nongovernmental funding agencies. This is a problem because there is no universal health care system or insurance in our region and patients rely on support from external agencies.

An important reason for the higher incidence of infections at baseline (63%) is the significant delay in presentation and treatment initiation. In the current study, patients received induction chemotherapy an average of 3 weeks after the registration date (Appendix Fig A1). This is similar to reports from other centers in India. The mean duration from onset of symptoms to initiation of treatment in a study by Philip et al⁴ was 4 weeks. Nair et al⁸ described a delay in initiation of 12 weeks in patients with infection compared with 6 weeks in those without infection. Kumar et al¹⁸

reported that 72% of patients had a focus of infection at presentation, and Nair et al⁸ reported that 46% of patients had baseline infections.

In the current study, blood cultures were positive in only 22% of patients. This is similar to the Polish Adult Leukemia Group (PALG) study, with 26% blood culture positivity,³ but low compared with the study by the Children’s Oncology Group, which showed 56% blood culture positivity in induction,¹⁹ and a study from the Indian subcontinent, which demonstrated 51% blood culture positivity.¹⁸ Gram-negative organisms were more frequent and distributed along the treatment phases similar to other studies in the country.^{6,20,21} Gram-positive organisms were seen in 25 patients during induction, but only in three patients in

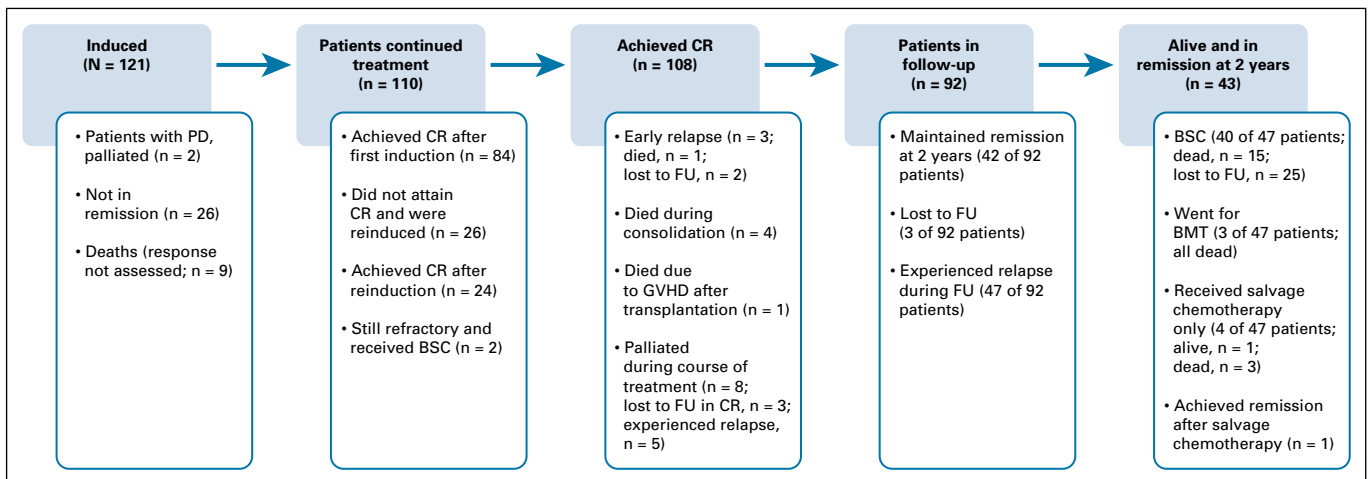


FIG 3. Patient survival statistics and chronology of relapse. BMT, bone marrow transplantation; BSC, best supportive care; CR, complete remission; FU, follow-up; GVHD, graft-versus-host disease; PD, progressive disease.

TABLE 5. Analysis of EFS and OS

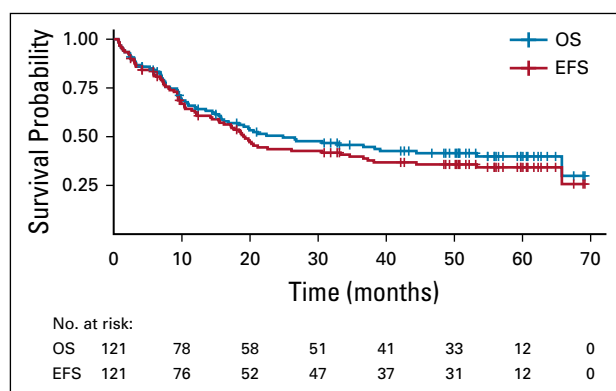
Survival	No. of Patients	Median (months)	95% CI (months)	4-Year Rate (%)	95% CI (%)
EFS	121	19	15 to 35	35.8	28 to 46
OS	121	25	16 to NR	41.5	33 to 52

Abbreviations: EFS, event-free survival; NR, not reached; OS, overall survival.

subsequent HIDAC cycles. This is different from the clinical trial data from the AML-BFM2004, PALG, and Children's Oncology Group trials reported in the Western literature, which showed predominantly gram-positive infections.^{3,19,22} The probable explanation for this is a lack of fluoroquinolone prophylaxis and low threshold for escalation to broad-spectrum antibiotics in the current study. In addition, as reported by Murali et al,²¹ increased gut colonization with MDR GNB (as high as 50% in surveillance cultures) could possibly explain the increased number of patients with GNB sepsis after the gut barrier is compromised after anthracycline-based chemotherapy.

MDR organisms were found in the isolates of 55.3% of the patients. ESBL production was the most frequent resistance mechanism, with *E coli* being the most common organism overall (35.54% of isolates). The most common isolate in blood cultures was *Klebsiella* (42.9%). This was similar to the study by Gupta et al,⁶ which demonstrated 81% ESBL isolates, with *Pseudomonas* (37%) and *Klebsiella* (23%) being the most common organisms. With uniform antibiotic guidelines, all patients had microbiologic negativity by the end of treatment. Mean duration of antibiotic therapy was 16 days in the study by Nair et al.⁸ In the current study, all patients required antibiotics for a mean duration of 10 days during the course of treatment.

We report a high incidence of fungal infections possibly as a result of ongoing construction activity and the weather.²³ In the current study, 67 patients (55%) developed fungal pneumonia during induction (seven patients had probable fungal pneumonia during induction). This is in contrast to the AML-BFM2004 trial by Bochennek et al,²² who reported a 3% incidence of fungal infections. In contrast, the

**FIG 4.** Overall survival (OS) and event-free survival (EFS) curves.

PALG study by Lech-Maranda et al³ reported a 20% rate of proven fungal infections, and Sung et al¹⁹ reported a fungal pneumonia rate of 14% to 21% distributed over all phases of treatment. Because of the limited number of patients in this study, correlation could not be made between fungal infection and OS and response rate, but other larger studies have shown that fungal infections definitely affect survival.²⁴

The complete remission rate of 69% in this study is comparable to that of similar studies at centers across India at other tertiary centers (65%-70%).^{7,17} Among the 121 patients who started induction therapy, 90 patients completed therapy (three cycles of consolidation), for a treatment completion rate of 74%. The advantages of a younger cohort and overrepresentation of good-risk disease were offset by the low transplantation rates, with just three patients undergoing ASCT. Hence, the EFS in our study must be interpreted in that context (Table 6 and Appendix Fig A2).

Thirteen patients (10.7%) experienced treatment-related mortality in all phases, with induction mortality experienced by nine patients (7.4%). This is in concordance with Western literature.^{2,3,22} Similar studies from the Indian subcontinent have reported relatively higher induction mortality rates, with Pandian et al²⁰ reporting a rate of 15.6% (Malabar Cancer Center), Philip et al⁴ reporting a rate of 24.7% (Christian Medical College Vellore), Kumar et al¹⁸ reporting a rate of 15.6% (Women's Indian Association Cancer Institute, Chennai), and Bahl et al⁷ reporting a rate of 17.1% (All India Institute of Medical Sciences Delhi). Collective data from 10 tertiary care cancer centers in India reported an induction mortality rate of 18%.¹⁶

The strengths of this study are that the patterns of infection and infection-related outcomes are from a homogenous cohort. These data will be useful for other centers in our region. Because of the decent follow-up period, we are able to understand the efficacy outcomes in a low-transplantation setting. It is reassuring that despite the higher rates of infection and antibiotic use, the mortality is low.

The limitation of this study is its retrospective design. The outcomes of patients who experienced deterioration while waiting for induction is not known.

The focus in our setting should be to shorten the time to treatment initiation and look at strategies such as outpatient therapy with a 7+3 regimen in selected patients or other agents while awaiting admission. The other area to be addressed is the optimal use of antimicrobial prophylaxis and antimicrobial stewardship. We need to look at non-transplantation strategies to improve outcomes.

In conclusion, AML treatment in our setting is complicated by drug-resistant gram-negative infections and fungal infections. This leads to increases in morbidity, antimicrobial use, and use of health care resources.

TABLE 6. Comparison of Outcomes of Similar Studies

Study	Patient Age (years)	No. of Patients	Risk Strata (%)	Treatment Arm	Comparator Arm	CR Rate (%)	Induction Mortality	Transplantation Rate (%)	Outcomes
PALG ³	16-60	309	Not done	DAC for 7 days	DA for 7 days	84	13% v 9%	—	—
ECOG ¹	17-60	657	FR, 13.6 IR1, 41.1 IR2, 26.6 AR, 18.7	D ₄₅ for 3 days + C ₁₀₀ for 7 days	D ₉₀ for 3 days + C ₁₀₀ for 7 days	FR, 81.3 IR, 58.7 AR, 51.4	D ₄₅ , 4.5% D ₉₀ , 5.5%	50.3	OS, 20.7 v 34.3 months
JALSG ²⁵	< 65	1,064	D arm: FR, 22 IR, 65 AR, 8	D ₅₀ for 3 days + C ₁₀₀ for 7 days	I ₁₂ + C ₁₀₀ for 7 days	D arm: FR, 91 IR, 79 AR, 51	Early death < 60 days: 2.1% v 4.7%	12	5-year OS with D + HIDAC, 58%
Bahl et al ⁷	8-60	480	FR, 21.6 IR, 69.3 AR, 9.1	D ₄₅₋₉₀ for 3 days + C ₁₀₀ for 7 days	—	FR, 84.8 IR, 67.9 AR, 54.2	18.7%	14	5-year OS, 35.5%
Kumar et al ¹⁸	1-74	404	FR, 29.6 IR, 48.7 AR, 21.7	D ₆₀ for 3 days + C ₁₀₀ for 7 days	—	—	15.6%	—	—
Philip et al ⁴	Any	109	FR, 11.8 IR, 70 AR, 18.2	D ₆₀ for 3 days + C ₂₀₀ for 7 days	—	—	24.7%	22	1-year OS: < 15 years, 70% 15-60 years, 55.6% > 60 years, 42.4%
Pandian et al ²⁰	> 14	96	FR, 19 IR, 64 AR, 17	D ₆₀ for 3 days + C ₁₀₀ for 7 days	—	74	15.6%	—	3-year OS, 39%
Our study	> 15	121	FR, 49 IR, 36 AR, 12	D ₆₀ for 3 days or I ₁₂ for 3 days + C ₁₀₀ for 7 days	—	FR, 79 IR, 61 AR, 73	7.4%	2	4-year OS, 48.2% 4-year EFS, 35.9%

NOTE. Subscript dose in mg/m² is followed by number of days (eg. D₆₀ for 3 days).

Abbreviations: AR, adverse risk; C, cytarabine; D, daunomycin; DA, daunorubicin and Ara-C; DAC, daunorubicin, Ara-C, and cladribine; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FR, favorable risk; HIDAC, high-dose cytarabine; I, idarubicin; IR, intermediate risk; JALSG, Japan Adult Leukemia Study Group; OS, overall survival; PALG, Polish Adult Leukemia Group.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

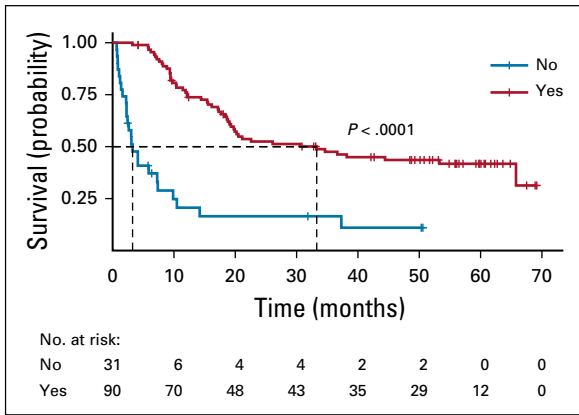


FIG A1. Event-free survival curve according to treatment completion.

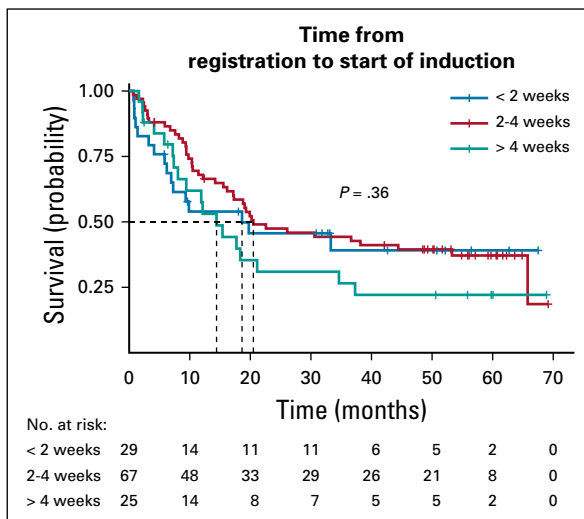


FIG A2. Event-free survival according to risk strata.

TABLE A1. Mean Duration of Antimicrobial Usage During Induction

Antibiotic	Mean Duration (days; SD)
Carbapenem	13 (5.9)
Colistin	9 (4.7)
Tigecycline	9 (5.3)
Linezolid	7 (3.5)
Teicoplanin	9 (4.3)
Vancomycin	10 (1.7)
Clindamycin	9 (5.3)
Amphotericin B	12 (4.9)
Caspofungin	12 (6.3)
Voriconazole	11 (7.5)

NOTE. All mean durations are provided as approximate.
Abbreviation: SD, standard deviation.