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Research article

Spectrum of infections in different regimens of post-induction chemotherapy in acute myeloid leukemia (*de-novo*): A comparative retrospective study☆

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ABSTRACT

Background: Patients diagnosed with acute myeloid leukemia (AML) face a heightened susceptibility to infections, which significantly elevates their risk of mortality and disability. The intensity of the chemotherapy treatment and its specific focus on inhibiting myeloid cell divisions render patients especially vulnerable, particularly during the early stages of chemotherapy. This vulnerability is compounded by the occurrence of repeated episodes of prolonged neutropenia, leaving patients highly susceptible to infections. The compromised immune systems of these individuals make them more susceptible to infections, which adversely affect their physical health and overall well-being. Consequently, our study aimed to investigate the range of infections experienced by patients with newly diagnosed AML undergoing different induction chemotherapy.

Methods: This was a comparative retrospective study, conducted at a tertiary hospital providing comprehensive cancer care in North India. All newly diagnosed patients with AML, who received induction chemotherapy from January 1, 2012 to November 1, 2022, were identified from the hospital database and included in this study.

Results: Four hundred and twenty AML patients treated with either high-intensity or low-intensity induction chemotherapy was observed in this study. It was found that patients who received high-intensity treatment had a higher rate of clinically and microbiologically documented infections, fever without a known cause, and more cases of febrile neutropenia than those who got low-intensity treatment. These differences between the two groups were particularly evident on day 14 ($p = 0.0002$) and persisted through day 28 ($p = 0.005$).

Conclusions: These findings underscore the effectiveness and downside of high-intensity induction chemotherapy regimens, as evidenced by the higher incidence of infections observed. Further investigation through prospective clinical studies is warranted to better evaluate and validate the efficacy of this approach.

☆ Clinical Trial Registration Link: https://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=64437&EncHid=&userName=.

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1. Introduction

Acute myeloid leukemia (AML) is one of the most common hematological malignancies, with 20,380 (1.0 %) estimated new cases and 11,310 (1.9 %) deaths in 2023 worldwide [1,2]. AML chemotherapy includes induction along with post-remission treatment. Induction chemotherapy aims to attain remission completely, without any demonstrable remaining illness if possible. Regardless of the induction chemotherapy regimen used, research has discovered that patients who reach complete remission may have a higher chance of survival [3,4]. The preference for the first induction chemotherapy is determined by the clinical status of the patient by evaluating their co-morbidities, functional ability, priorities, and stage of cancer by assessing the molecular characteristics and prognostic risk categories. In AML, the most commonly utilized induction treatments include cytotoxic regimens or hypomethylating drugs, both of which may or may not be targeted [3].

The core component of therapeutic interventions has not altered in the past five decades for AML patients. Hematological cancers, such as AML, are often treated with high-intensity induction chemotherapy (HIIC). To achieve full elimination of cancerous cells for complete remission, a robust collection of chemotherapy medications is administered in elevated dosages. Several medicines are usually administered at once or in a specific order during HIIC. These medicines are chosen for their capacity to interfere with the proliferation of rapidly proliferating cancer cells. Anthracyclines such as idarubicin or daunorubicin, cytarabine (Ara-C), and etoposide, along with some others, are part of this chemotherapeutic treatment [4]. High-intensity chemotherapeutic regimens and hematopoietic stem cell transplants (HSCT) are presumed to be the most efficacious and possibly curable therapeutic strategies for individuals suffering from AML [3,5,6]. The percentage of complete remission after receiving HIIC lies between 39 and 65% [5]. Patients acquiring complete remission and not undergoing consolidating therapies have an increased risk of mortality [5–7].

However, a large number of individuals are first diagnosed with AML at a median age of 68–70 and have substantial co-morbidities that generally preclude them from benefiting from these treatments [3,5]. Even though present treatment options enable around 90 % of cancer patients to survive the condition, several individuals die due to relapse of disease or infectious and non-infectious disorders [7]. The likelihood of morbidity and mortality is raised by the occurrence of infections in AML patients, as they are more susceptible to induction chemotherapy. This could occur due to the intensity of regimens used in chemotherapy and the emphasis on divisions of myeloid cells, leading to recurrent events of prolonged neutropenia and a poorer quality of life. Although improved treatment outcomes exist, existing studies addressing infections are limited because they were performed in a diverse population [8–11].

Exploring the incidence and features of infections such as bacterial, viral, parasitic, and fungal with their associated consequences in a specific population may provide insights into the underlying factors of sensitivity and response to infectious diseases by diverse pathogens. The complicated epidemiology of serious and often resistant microorganisms increases the usage of polypharmacy, and extensive anti-infective medications cause patients to suffer from the consequences of these diseases. Lately, hypomethylating drugs like Decitabine and Azacitidine are used to augment low-intensity induction chemotherapy [LIIC], to provide patients with a survival advantage [12–16]. In the setting of blood cancers like AML, LIIC is a therapeutic strategy used in medical treatment. It entails using chemotherapy regimens that are less strenuous and hazardous than those used for high-intensity induction. Chemotherapy medications and other drugs employed in LIIC are usually administered at lower dosages compared to those used in HIIC. In contrast to high-intensity therapies, low-intensity chemotherapy for induction aims to induce remission or control of the illness with fewer negative reactions and toxicity [17]. Among the elderly patients suffering from AML who are unable to tolerate intense treatment regimens, therapy with reduced intensity by Venetoclax, a BCL-2 inhibitor, along with a hypomethylating drug demonstrated reasonably high rates of complete remission as well as acceptable safety [18,19]. We hypothesize that chemotherapeutic regimens play an important role in the occurrence of infections, and through this study, we aim to determine which specific regimens are the likely cause of infections.

2. Methods

2.1. Study design

This was retrospective study conducted in a tertiary care hospital with cancer specialization in the capital of India. The study was approved by the Clinical Trial Registry of India with registration number CTRI/2022/10/046636 as any observational study is registered along with the approval of Institutional Review Board of the hospital-affiliated. At baseline, 420 patients with AML were divided into two cohorts, LIIC and HIIC. The data collected included 134 *de-novo* AML patients who were given LIIC and 286 *de-novo* patients administered with HIIC from the period of January 1, 2012, to November 1, 2022. The FAB (French, American, and British) and WHO (World Health Organization) criteria were used to classify AML. LIIC regimen consisted of i) low-dose cytarabine [10 mg/m^{2,} every 12 h on days 1–14); ii) Azacytidine [75 mg/m^2/day, on days 1–7] iii) Azacytidine with Venetoclax [75 mg/m^2/day, on days 1–7] and iv) Decitabine with or without Sorafenib [15–20mg/m2/day, on days 1–5]. The HIIC regimen consisted of i) Daunorubicin [60–90 mg/m^2/day for 3 days and Cytarabine (100–200 mg/m^2/day for 7 days] ii) Daunorubicin [60–90 mg/m^2/day for 3 days] and Cytarabine [100–200 mg/m^2/day for 5 days] iii) Daunorubicin [60–90 mg/m^2/day for 2 days and Cytarabine [100–200 mg/m^2/day for 5 days] iv) Daunorubicin [60–90 mg/m^2/day, Cytarabine [100–200 mg/m^2/day], and Venetoclax v) High-Dose Cytosine Arabinoside [3 g/m^2 every 12 h for 3 days] and Mitoxantrone [10–12 mg/m^2] (HAM) vi) High-dose cytarabine (HiDAC) [3 g/m^2] vii) Fludarabine, Ara-C, G-CSF, and Venetoclax. The baseline variables of the patients evaluated before induction chemotherapy were age, gender, country, and state of origin, date of diagnosis, cytogenetic classification, mutations, percentage of blasts, co-morbidities, BMI, complete blood count [CBC], white blood counts [WBC], kidney function tests [KFT], liver function tests [LFT], urine culture, High-

resolution computed tomography (HRCT) thorax/chest, infections and days delayed due to infection and its treatment.

Table 1 depicts the baseline in terms of their clinical features, demographics, and laboratory results. The patients were evenly divided between males and females in both cohorts [LIIC (Males: 61.19 %, Females: 38.80 %) and HIIC (Males: 60.13 %, Females: 39.86 %)].

2.2. Statistical analysis

The collected data was analyzed by SPSS software through Fisher's Exact test and the chi-square test. The baseline parameters such as mutations and the number of days febrile neutropenia existed before the start of chemotherapy along with results were assessed by Fisher's Exact test while other parameters were assessed by Chi-Square test with a 95 % confidence interval. A p-value less than 0.05 indicates that the difference between the groups is statistically significant. The infection-specific mortality rate of patients with AML at

Table 1
Baseline demographics of AML undergoing induction chemotherapy.

Baseline demographics:	LIIC (n = 134)	HIIC (n = 286)	p-value
Patients (n = 420)	134 (31.90)	286 (68.09)	0.837*
1. Male	82 (61.19)	172 (60.13)	
2. Female	52 (38.80)	114 (39.86)	
Age (years)			
1. <40	21 (15.67)	143 (50)	**<0.0001***
2.40-60	27 (20.14)	122 (42.65)	
3. >60	86 (64.17)	21 (7.3)	
Diagnosis (WHO Classification)			
1. AML with recurrent cytogenetic abnormality inv3	29 (21.64)	39 (13.63)	0.180*
2. AML with recurrent cytogenetic abnormality t9:11	9 (6.71)	23 (8.04)	0.631*
3. AML with recurrent cytogenetic abnormality t6:9	19 (14.17)	59 (20.62)	0.113*
4. AML with recurrent cytogenetic abnormality t8:21	24 (17.91)	52 (18.18)	0.946*
5. AML- MRC	3 (2.23)	14 (4.8)	0.289
6. AML- NOS Erythroid/Myeloid	17 (12.68)	26 (9.09)	0.257*
7. AML- NOS Monocytic	6 (4.47)	28 (9.7)	0.063*
8. AML- NOS Myelomonocytic	10 (7.4)	9 (3.1)	**0.047***
9. AML- NOS without maturation	8 (5.9)	7 (2.44)	0.070*
10. AML- NOS with minimal differentiation	11 (8.2)	13 (4.54)	0.132*
11. Unknown	13 (9.7)	17 (5.9)	0.163*
Cytogenetic risk stratification			
1. Low	36 (26.86)	95 (33.21)	0.190*
2. Intermediate	49 (36.56)	91 (31.81)	0.336*
3. High	27 (20.14)	67 (23.42)	0.453*
4. N/A	22 (16.41)	33 (11.53)	0.167*
Mutations			
CEBPA bZip gene	1 (0.7)	13 (4.5)	**0.044**†
BCL ABL1	0	3 (1.04)	0.554†
C-kit	1 (0.7)	1 (0.3)	0.537†
FLT3	14 (10.44)	40 (13.9)	0.313*
NPM1	18 (13.43)	45 (15.73)	0.538*
Co-morbidities			
1. Hypertension	18 (13.43)	20 (6.9)	**0.032***
2. Diabetes Mellitus	7 (5.2)	14 (4.8)	0.885*
3. Hypertension + Diabetes	21 (15.67)	12 (4.1)	**<0.0001***
4. Others	9 (6.7)	21 (7.3)	0.816*
5. No co-morbidities	79 (58.95)	219 (76.57)	**0.0002***
Baseline radiological Parameters			
HRCT Chest			
1. Normal	109 (81.34)	239 (83.56)	0.573*
2. Abnormal	25 (18.66)	47 (16.43)	
Serum Galactomannan			
1. Positive	9 (6.7)	21 (7.34)	**0.048***
2. Negative	5 (3.7)	31 (10.83)	
3. Not Available/Done	120 (89.55)	234 (81.81)	
Microbiologic culture analysis			
Urine Culture			
Positive	15 (11.19)	28 (9.7)	**0.024***
Negative	29 (21.64)	34 (11.88)	
Not Available/Done	90 (67.16)	224 (78.32)	
Febrile Neutropenia	3 (2.2)	7 (2.44)	1†

Abbreviations: AML: Acute myeloid leukemia, LIIC: Low intensity induction chemotherapy. HIIC: High intensity induction chemotherapy, n: number of patients, WHO: World Health Organization, MRC: Myelodysplasia-Related Changes, NOS: Not otherwise specified, N/A: not available, CEBPA: CCAAT/enhancer binding protein, alpha, C-kit: **receptor tyrosine kinase,** FLT3: Fms-like tyrosine kinase 3, NPM1: Nucleophosmin 1, HRCT: High-resolution computed tomography, †: Fisher Exact test, *: Chi square test.

Table 2
Percentage of infections in all patients.

Total number of patients = 420																
Time of assessment	**Baseline**				**Day 7**				**Day 14**				**Day 28**			
Incidence of Infections	**34.97 %**				**46.71 %**				**62.20 %**				**49.29 %**			
CDI	14.76 %				22.6 %				24.15 %				29.04 %			
MDI	85.23 %				77.38 %				75.84 %				70.95 %			
Type of infections in different regimens	**B**	**P**	**V**	**F**	**B**	**P**	**V**	**F**	**B**	**P**	**V**	**F**	**B**	**P**	**V**	**F**
Daunorubicin + Cytarabine [3 + 7] [n = 198]	47.16 %	3.77 %	11.32 %	37.73 %	64.70 %	3.77 %	4.41 %	22.05 %	56.81 %	7.95 %	13.63 %	21.59 %	66.07 %	1.78 %	8.9 %	23.21 %
Daunorubicin + Cytarabine [3 + 5] [n = 35]	58.33 %	0	0	38.46 %	89.65 %	3.44 %	0	6.89 %	76.66 %	3.33 %	6.66 %	13.33 %	54.14 %	4.1 %	16.66 %	16.66 %
Daunorubicin + Cytarabine [2 + 5] [n = 10]	66.66 %	0	50 %	50 %	100 %	16.66 %	0	0	50 %	25 %	25 %	0	50 %	0	0	100 %
Daunorubicin + Cytocristine [3 + 7] [n = 17]	50 %	0	16.66 %	33.33 %	55.55 %	22.22 %	11.11 %	11.11 %	73.33 %	13.33 %	0	13.33 %	75 %	8.33 %	0	16.66 %
Daunorubicin + Cytocristine [2 + 5] [n = 3]	50 %	0	0	50 %	0	0	0	0	100 %	0	0	0	100 %	0	0	0
Azacytidine [n = 38]	81.25 %	0	0	18.75 %	58.82 %	0	0	10 %	78.57 %	0	0	27.27 %	70 %	14.28 %	14.28 %	28.57 %
Azacytidine + Venetoclax [n = 37]	25 %	0	25 %	50 %	58.33 %	8.33 %	25 %	8.33 %	76.19 %	0	9.52 %	14.28 %	50 %	6.25 %	6.25 %	37.5 %
High dose cytarabine [n = 12]	100 %	0	0	0	80 %	0	0	20 %	100 %	0	0	0	60 %	0	0	40 %
Decitabine ± Sorafenib [n = 48]	83.33 %	0	0	16.66 %	58.33 %	0	0	41.66 %	90.9 %	0	0	9.09 %	77.77 %	0	0	22.22 %
Fludarabine + Ara-C + G-CSF + Venetoclax [n = 11]	25 %	0	75 %	0	25 %	0	50 %	25 %	71.42 %	0	28.57 %	0	100 %	0	0	0
High-Dose Cytosine Arabinoside + Mitoxantrone [n = 3]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: AML: Acute myeloid leukemia, CDI: Clinically documented infections, MDI: Microbiologically documented infections, B: Bacterial infections, P: Parasitic infections, V: Viral infections, F: Fungal infections, n: number of patients.

day 100 was conducted using the Kaplan-Meier method. Patient data, including survival times and censoring information, were collected from the study cohort. The analysis began by organizing the data into a survival curve, plotting the probability of survival against time. Patients who were still alive at day 100 were considered censored observations, as their survival times extended beyond this point.

3. Results

3.1. Description of patients and their demographic characteristics

According to the initial sample size, 134 (31.9 %) of the 420 patients had been identified as LIIC, whereas 286 (68.09 %) were designated as HIIC. Both the LIIC and HIIC had an almost equal number of male participants, with 61.19 %, while the HIIC had 60.13 %. Variations in age were found to be statistically significant. There were 15.67 % of patients under the age of 40, 20.14 % of patients between the ages of 40 and 60, and 64.17 % of patients above the age of 60 in the LIIC group.

The HIIC group, in comparison, had a substantially higher proportion of patients below the age of 40 (50 %), a significantly lower percentage between the ages of 40 and 60 (42.65 %), and just 7.3 % above the age of 60. The choice of treatment was because disease biology in younger patients may be associated with genetic mutations while certain comorbidities and health conditions present in patients above 60 years of age might increase their risk of adverse reactions to HIIC treatments. This approach aimed to minimize treatment-related morbidity and mortality by selecting individuals more likely to withstand the intensive regimen. The exclusion criteria were in line with established treatment guidelines, which routinely consider age, overall health, and performance status when recommending specific chemotherapy regimens to ensure clinical relevance and applicability. Ethical considerations also played a pivotal role, with a conscientious evaluation of potential risks and benefits, reflecting a commitment to patient safety and well-being.

Apart from certain groups, the diagnosis based on the WHO categorization showed little difference between the LIIC and HIIC groups. Among the AML subtypes, the LIIC group had a higher prevalence of NOS Myelomonocytic (7.4 % LIIC, 3.1 % HIIC) and NOS without maturation (5.9 % LIIC, 2.44 % HIIC). There were no statistically significant differences between LIIC and HIIC in the context of cytogenetic risk classification. The frequency of mutations in genes such as CEBPA, BCL ABL1, C-kit, FLT3, and NPM1 was also similar across the two groups. The LIIC group was shown to have a higher prevalence of hypertension and hypertension in combination with diabetes, whereas the HIIC group was found to have a lower prevalence of any co-morbidity. There was no significant difference in HRCT chest findings or serum galactomannan levels at baseline between the two groups. However, the LIIC group had a greater number of positive urine culture tests than the HIIC group did.

Table 3
Infections and events occurring in both groups.

Time of assessment	Baseline			DAY 7			DAY 14			DAY 28		
Assessments	LIIC (n = 134)	HIIC (n = 286)	P value	LIIC (n = 134)	HIIC (n = 286)	P value	LIIC (n = 134)	HIIC (n = 286)	P value	LIIC (n = 134)	HIIC (n = 286)	P value
CDI	6	11	0.760*	9	37	0.057*	11	34	0.256*	13	50	**0.037***
MDI	49	93	0.414*	34	125	**0.0003***	43	148	**0.0002***	32	108	**0.005***
Bacterial	31	48	0.121*	23	86	**0.005***	34	97	0.078*	18	72	**0.006***
Viral	3	7	1†	3	8	1†	2	15	0.108†	2	9	0.514†
Fungal	15	36	0.684*	7	21	0.417*	7	25	0.205*	10	22	0.934*
Parasitic	0	2	1†	1	10	0.186†	0	11	**0.020†**	2	3	0.656†
Site of Isolation of Microorganisms rowhead												
Bloodstream	22	29	0.066*	15	32	0.999*	19	37	0.727*	16	20	0.091*
Sputum	5	16	0.414*	4	19	0.167†	4	23	0.054†	7	12	0.637*
Urine	12	24	0.847*	7	31	0.062*	13	39	0.254*	6	19	0.382*
Swab (Throat)	9	15	0.545*	3	21	0.065†	5	28	**0.031***	2	32	**0.0004†**
ET secretion	0	8	0.059†	1	17	**0.017†**	2	21	**0.011†**	1	11	**0.114†**
Fever without source	2	7	0.725†	29	151	**<.0001***	59	212	**<.0001***	43	130	**0.009***
Clinically documented parameters rowhead												
Febrile neutropenia	x	x	x	84	224	**0.001***	112	219	0.101*	89	192	0.885*
Remission rate	Not assessed			Assessed			Assessed					
<5 % blasts	x	x	x	38	43	**0.001***	27	93	**0.009***	x	x	x
5–20 % blasts	x	x	x	42	61	**0.026***	51	69	**0.003***	x	x	x
>20 % blasts	x	x	x	44	106	0.399*	38	87	0.667*	x	x	x
Not done/Data not present	x	x	x	10	76	**0.0003***	18	37	0.888*	x	x	x
Overall mortality	X									7	18	0.666*

Abbreviations: CDI: Clinically Documented Infections, MDI: Microbiologically Documented Infections, LIIC: Low intensity induction chemotherapy. HIIC: High intensity induction chemotherapy, n: number of patients, ET: endotracheal, †: Fisher Exact test, *: Chi square test.

3.2. Description of all patients undergoing chemotherapy

Table 2 shows the percentage of infections and the types that were seen in different treatment plans at the start, on days 7, 14, and 28 of induction chemotherapy. A total of 11 regimens were observed during the 10-year and 2-month period of assessment. Inj. Daunorubicin + Inj. Cytarabine [3 + 7] along with Inj. Daunorubicin + Inj. Cytarabine [3 + 5] regimens had a relatively high incidence of infections across all time points, with the highest incidence on Day 14. Although the sample size of patients receiving HAM treatment was low, they did not observe any infections.

3.3. Description of infections, site of isolation, and clinically documented parameters in LIIC and HIIC

Table 3 depicts the findings obtained from the analysis of the data. The times of assessment at baseline, day 7, day 14, and day 28 were recorded. The diagnosis of clinical symptoms, signs, and physical examination findings served as evidence for clinically documented infections (CDI). Microbiologically documented infections (MDI) involve laboratory confirmation of the causative organism responsible for the infection. In this study, laboratory tests are conducted to identify the specific microorganisms (e.g., bacteria, viruses, fungi, and parasites) causing the infection. Also, the site of isolation, febrile neutropenia, remission rates, and overall survival were observed.

The p-values in the table indicate the statistical significance of the differences observed between the LIIC and HIIC groups at each time point. At baseline, there was no statistical significance since there were very few documented infections. The infections were observed to be statistically insignificant in HIIC vs. LIIC group for bacterial (48 vs. 31, $p = 0.121$), viral (7 vs. 3, $p = 1$), fungal (36 vs.15, $p = 0.684$), and parasitic (2 vs. 0, $p = 1$). Microorganisms were more commonly found in the bloodstream of the HIIC group (29 vs. 22), although this difference was not statistically significant ($p = 0.066$). Sputum, urine, throat swabs, and ET secretion showed no significant differences between the groups. Fever without a clear source was observed in 7 participants in the HIIC group and 2 in the LIIC group, with no significant difference ($p = 0.725$).

However, on day 7, the HIIC group had a significantly higher CDI rate (37 vs. 9, $p = 0.057$*) and MDI rate (125 vs. 34, $p = 0.0003$*) compared to the LIIC group. The HIIC group also had a significantly higher rate of bacterial infections (86 vs. 23, $p = 0.005$*) and a significantly lower rate of viral (8 vs. 3, $p = 1$), fungal (21 vs.7, $p = 0.417$), and parasitic (10 vs. 1, $p = 0.186$) infections compared to the LIIC group. The HIIC group had a slightly higher number of cases with microorganisms isolated from the bloodstream (32 vs. 15 in the LIIC group), but the difference was not statistically significant ($p = 0.999$). The HIIC group also had significantly higher rates of sputum, urine, and throat swab sites compared to the LIIC group but were not statistically significant, while a higher number of microorganisms was observed at ET secretion (17 vs. 1, $p = 0.017$). Additionally, fever without a source was considerably more common in the HIIC group ($p < 0.0001$). Cases of febrile neutropenia were higher in patients treated with HIIC (224 vs. 84, $p = 0.001$) as compared to LIIC.

On day 14, the differences between the groups became more pronounced. The HIIC group had significantly higher rates of CDI (34 vs. 11, $p = 0.256$), MDI (148 vs. 43, $p = 0.0002$), bacterial (97 vs. 34, $p = 0.078$), viral (15 vs. 2, $p = 0.108$), fungal (25 vs. 7, $p = 0.205$), and parasitic (11 vs. 0, $p = 0.020$) compared to the LIIC group. The HIIC group also had a significantly higher rate of microorganisms at sites such as throat swabs (28 vs. 5, $p = 0.031$), ET secretions (21 vs. 2, $p = 0.11$), bloodstream (37 vs. 19, $p = 0.727$), sputum (23 vs. 4, $p = 0.054$), urine (39 vs. 13, $p = 0.254$) compared to the LIIC group. Also, fever without a source occurred more in the HIIC group ($p < 0.0001$). Cases of febrile neutropenia were higher in HIIC (219 vs. 112, $p = 0.101$) as compared to LIIC but were statistically insignificant.

On day 28, the differences between the groups persisted. The HIIC group had significantly higher rates of CDI (50 vs. 13, $p = 0.037$), MDI (108 vs. 32, $p = 0.005$), bacterial (72 vs. 18, $p = 0.006$), viral (9 vs. 2, $p = 0.514$), fungal (22 vs. 10, $p = 0.934$), and parasitic (3 vs. 2, $p = 0.656$) compared to the LIIC group. The HIIC group also had a significantly higher rate of microorganisms at sites such as throat swabs (32 vs. 2, $p = 0.0004$), ET secretions (11 vs. 1, $p = 0.114$), bloodstream (20 vs. 16, $p = 0.091$), sputum (12 vs. 7, $p = 0.637$), and urine (19 vs. 6, $p = 0.382$) compared to the LIIC group. Also, fever without a source occurred more in the HIIC group (130 vs. 43, $p = 0.009$). Febrile neutropenia was higher in HIIC (192 vs. 89, $p = 0.885$) treated patients as compared to LIIC but was statistically insignificant.

A higher percentage of patients treated with HIIC had a remission rate of less than 5 % blasts on day 14 (43 vs. 38, $p = 0.001$) and 5–20 % blasts on day 14 (61 vs. 42, $p = 0.026$) compared to the LIIC group. The remission rate was assessed and was found to be significantly better in the HIIC group on days 7 and 14, with a lower percentage of blasts in both the 5–20 % and >20 % blast categories.

3.4. Description of bacterial infections in both groups

The number of infections caused by both Gram-positive and Gram-negative bacteria varied over time in the LIIC group, as observed in Fig. 1a. While Gram-negative infections were more prevalent at baseline, the number decreased by Day 7 and remained relatively stable thereafter. In contrast, the number of Gram-positive infections showed fluctuations, with an initial decrease by Day 7, followed by an increase on Day 14 and a subsequent decrease by Day 28. These findings suggest that bacterial infections, including both Gram-positive and Gram-negative types, are a common occurrence in patients undergoing LIIC. Close monitoring and appropriate management strategies should be implemented to effectively address and prevent these infections during treatment. On the other hand, the HIIC group experienced both Gram-positive and Gram-negative bacterial infections throughout the study period, as depicted in Fig. 1b. The baseline data indicates a higher occurrence of Gram-negative infections compared to Gram-positive infections. On Day 7, there

was a notable increase in both Gram-positive and Gram-negative infections compared to the baseline. Day 14 shows a higher occurrence of Gram-positive infections, surpassing the number of Gram-negative infections. By Day 28, the number of gram-positive infections had decreased compared to Day 14, while the number of gram-negative infections remained relatively consistent.

3.5. Infection-specific mortality rate

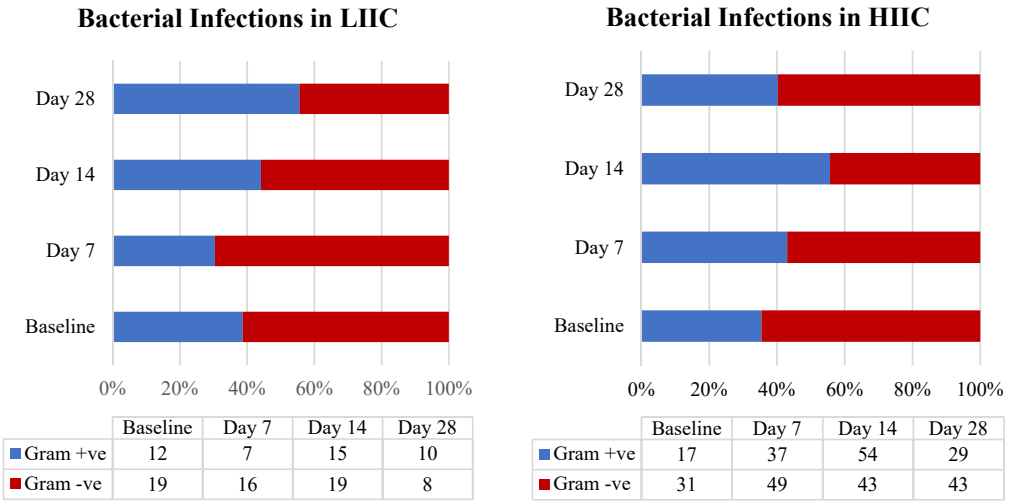
Tt was observed that the infection-specific mortality rate was slightly lower in the HIIC group compared to the LIIC group, although this difference was not statistically significant (18 deaths in HIIC vs. 7 deaths in LIIC, $p = 0.666$). These deaths were interpreted by reviewing the medical records, laboratory and diagnostic testing, and microbiological evidence from cultures. Fig. 2 provides the infection-specific mortality rate of AML patients in both groups at day 100. Most of the cases were due to sepsis (HIIC: 14; LIIC: 5), COVID-19 (HIIC: 2, LIIC: 1), pneumonia (HIIC: 2), and malaria (LIIC: 1).

4. Discussion

This study observed 420 people who were newly diagnosed with AML and found that the spectrum and frequency of LIIC and HIIC were very different. It was observed that mild to significant infections occurred after the first cycle of chemotherapy.

The administration of LIIC has been shown to significantly increase the chances of survival in people with AML who are either too old or have other health problems that prevent them from receiving high-dose therapies [1,5–10]. However, getting infections while taking LITR can be a problem, which could make the survival benefits of these drugs less effective [3,12,18–24]. LITR cycles have already acknowledged the presence of the underlying disease as a significant risk factor for infections [25,26]. Recently, a study observed the frequency of infections to be 8–17 % when compared with decitabine and azacytidine treatments by assessing 40 AML patients after 215 low-intensity treatments. The study observed that at least one infection occurred in 70 % of patients and caused serious complications in 20 % of them [25]. The members of the population with an elevated likelihood of contracting an infection were found. This category of individuals involves those whose neutropenia (low white blood cell count) is anticipated to last for a minimum of a week or those with more hazards like taking immunosuppressive drugs, getting a severe form of the illness that is causing it, becoming more mature, or getting other health problems already. Neutropenia frequently lasts longer than 7 days in acute myeloid leukemia (AML) patients using low-intensity treatment regimens. Additionally, the illness itself might have previously resulted in total or functional neutropenia in these individuals. They also frequently have other co-existing illnesses and are likely to be older. The usefulness of prophylactic antibiotics in the setting of AML and LITR has not been studied in a clinical investigation, notwithstanding suggestions made by AGIHO (German Society of Hematology and Medical Oncology). Current research on LITR treatment shows that regular prophylactic antibiotics are not given to these individuals [26–28].

The generally accepted induction treatment consisted of daunorubicin intravenously (IV) for three days as well as cytarabine at a dosage of 100–200 mg/m2 via IV by constantly administered infusion for a total of seven days (i.e., 3 + 7), even though there is no typical induction treatment for individuals with untreated AML who are appropriate for chemotherapy [29,30]. Sixty to eighty percent of younger people who get this course of therapy experience complete remission (CR), and the 5-year overall survival (OS) probability is around forty percent. About forty to sixty percent of elderly people who have reached at least sixty years of age or more can expect a complete recovery, but most of them experience a recurrence, and few among them are expected to survive for a period exceeding two



	Baseline	Day 7	Day 14	Day 28
Gram +ve	12	7	15	10
Gram -ve	19	16	19	8

	Baseline	Day 7	Day 14	Day 28
Gram +ve	17	37	54	29
Gram -ve	31	49	43	43

Fig. 1. a) Bacterial infections in LIIC b) Bacterial infections in HIIC.

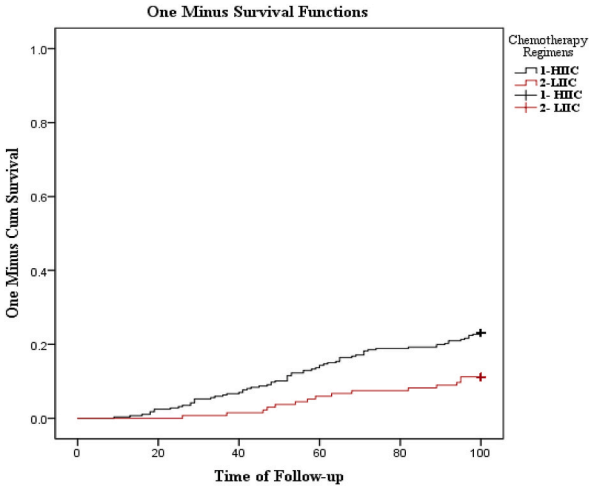


Fig. 2. Infection-specific mortality rate at day 100.

years [31–35]. Even though HIIC had a lot of different treatment plans, our study showed that patients who got the 3 + 7 and 3 + 5 induction regimens were more likely to get infections than patients who got other treatment plans. These results also correlate with previous studies conducted on the Polish population who were newly diagnosed with AML [36]. The observations held regarding the fact that the standard 7 + 3 regimen caused a higher frequency of infections post-induction.

It was found that all of the groups in this study had the same number and types of infections as those found in previous studies. This included AML patients who were starting induction treatment and complications like invasive fungal infections, neutropenic enterocolitis, pneumonia, and mucositis fever [37–40]. Similarly, it was observed that the cause of febrile neutropenia was related to bloodstream infections. The distribution of infections among neutropenic patients with cancer has changed noticeably during the last twenty years. The lower death rate in the HIIC group, on the other hand, suggested that the high-intensity chemotherapy regimen might help lower the risk of fatal infections. However, due to the lack of statistical significance, further investigation with a larger sample size may be required to draw definitive conclusions.

As this was a retrospective study, many limitations came to light. There are several unanswered questions regarding the choice of prophylactic use of medicines and the occurrence of infections. Our study had a limited sample size, and data was collected at a single center; therefore, not all chemotherapy regimens had enough sample sizes for complex analysis. Also, it is difficult to compare the exact outcome that would have occurred if the sample size was equivalent throughout all the regimens, as most patients were treated with 3 + 7. There were many clinically diagnosed infections for which the causative agent was unknown.

On the other hand, this is the first-ever study comparing HIIC and LIIC to observe the spectrum of infections occurring in various chemotherapy regimens. The study sheds light on the Indian population undergoing induction chemotherapy and observed which specific regimen caused more incidences of infections. The study provides significant results by providing evidence that HIIC increases the risk of infection complications in comparison to LIIC, which may suggest that instead of HIIC, patients can be treated with LIIC to obtain productive remission rates and reduce treatment-related complications.

5. Conclusion

In conclusion, this retrospective study aimed to investigate the spectrum of infections in Indian patients with *de-novo* acute myeloid leukemia undergoing different regimens of post-induction chemotherapy. The results indicate that infections are a significant concern in AML patients, particularly during the early phases of chemotherapy. High-intensity induction chemotherapy was associated with higher rates of clinically and microbiologically documented infections, fever without source, and increased febrile neutropenia compared to low-intensity induction chemotherapy. The data also revealed variations in the types of infections among different chemotherapy regimens. Some regimens showed higher susceptibility to specific types of infections, suggesting that tailored approaches may be necessary to optimize treatment outcomes and patient safety. Furthermore, age and cytogenetic risk stratification were found to be potential factors influencing infection rates. Patients aged over 60 years and those with certain cytogenetic abnormalities appeared to be at a higher risk of developing infections.

Ethics statement

The Institutional Review Board of Rajiv Gandhi Cancer Institute and Research Center approved the study with registration number RGCIRC/IRB-BHR/14/2022 with an approval number Res/SCM/49/2021/157. The Institutional Review Board also granted a waiver from consenting of participants.

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CRediT authorship contribution statement

Haya Majid: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Md Masoom:** Software, Methodology, Formal analysis. **Nitin Bansal:** Writing – review & editing, Methodology, Validation, Investigation, Formal analysis, Data curation, Visualization, Conceptualization. **Wasim Ahmad:** Writing – review & editing, Writing: original draft. **Mohd Faiyaz Khan:** Writing – review & editing, Writing – original draft. **Sadaf Farooqui:** Writing – review & editing, Writing – original draft. **Dinesh Bhurani:** Writing – review & editing, Investigation, Project administration, Supervision, Resources, Software, Methodology, Formal analysis, Visualization, Validation, Conceptualization. **Mohd Ashif Khan:** Writing – review & editing, Investigation, Project administration, Supervision, Resources, Software, Methodology, Formal analysis, Visualization, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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