Frequency of infections in patients with Acute Myeloid Leukemia receiving Cytarabine+ Daunorubicin (7+3) versus Azacitidine and Venetoclax during Induction Chemotherapy

Abstract

Introduction: Acute myeloid leukemia (AML) is a hematologic malignancy with high mortality rates due to infections, treatment-related toxicity, and multidrug-resistant (MDR) organisms, especially in resource-limited settings. Standard induction therapy includes a cytarabine–anthracycline (7+3) regimen for younger, fit patients and azacitidine–venetoclax (Aza/Ven) for elderly or younger patients with comorbidities unfit for intensive therapy. This study examined infection frequency, types, and outcomes in AML patients receiving these induction therapies at a tertiary hospital in Pakistan.

Materials and Methods: This observational study included AML patients over 18 years of age treated between January 2018 and December 2023. Patients receiving the 7+3 or Aza/Ven regimen were monitored for demographics, clinical status, infection patterns, organism types, antibiotic resistance, and induction outcomes. The data were analysed with SPSS 21, and Kaplan–Meier survival estimates, and Cox regression models were used to assess survival outcomes.

Results: Among 176 AML patients, 65.3% were treated with the 7+3 regimen, whereas 34.7% received Aza/Ven. Patients receiving 7+3 regime experienced significantly greater neutropenia, which correlated with a higher infection rate and increased incidence of infections ($p<0.001$). Among the 106 organisms identified on blood cultures, 22(12.5%) were multidrug resistant (MDR), of which carbapenem-resistant Enterobacteriaceae (CRE) constituted 14(63%) of MDR isolates, posing a serious therapeutic challenge. The induction-related mortality rate was 31.1% in the Aza/Ven group, which was notably higher than the 21.7% reported in the 7+3 group (p-value = 0.03). The Aza/Ven regimen was linked to a sixfold increased hazard of death ($p<0.001$) after adjusting for age and comorbidities, underscoring a strong association between the induction regimen and patient survival.

Conclusion: This study highlights the significant burden of infections and MDR organisms in AML treatment, especially in patients receiving the Aza/Ven regimen, which is commonly reserved for older and higher-risk patients. Infection prevention strategies, strict antibiotic stewardship, and tailored therapies are critical to improving outcomes. The findings advocate for continued research into optimizing induction

regimens to balance efficacy and infection-related risks, particularly in resource-limited settings where AML patients face unique treatment challenges.

Keywords: Hematological malignancy, Infections, Pakistan, Acute Myeloid Leukemia, Azacitidine, Venetoclax, Induction

Introduction

Acute myeloid leukemia (AML) is a haematological malignancy of the myeloid lineage. Owing to the deadly nature of this aggressive disease, the only curative therapy strategy is vigorous induction chemotherapy followed by allogenic stem cell transplantation in selected patients(1) . Standard induction chemotherapy for these patients consists of cytarabine combined with anthracycline for young fit patients, whereas hypomethylating agents in combination with venetoclax are used for elderly frail patients or young patients with multiple comorbidities and poor performance status at the time of presentation.

Acute myeloid leukemia care is complicated by treatment-related mortality caused by infections, haemorrhage, and resistant disease. Infections during treatment are linked to mortality, morbidity, and increased healthcare costs, and they can affect the optimal chemotherapy dose(2) . The introduction of a novel combination of azacitidine with venetoclax for the initial treatment of patients' ineligible for intensive chemotherapy has also been explored.

A key obstacle in treating acute myeloid leukemia (AML) continues to be infection. Given the high prevalence of multidrug resistant (MDR) organisms and the significant delay before the initiation of chemotherapy, this issue is of particular concern in developing countries (3).

To develop a suitable plan and improve outcomes, comprehending the pattern of infections is crucial. Here, we outline the trends of infections and infection-related mortality among AML patients treated at a tertiary care facility in Pakistan.

Objectives

To evaluate the frequency of infections and infection-related outcomes in patients receiving cytarabine and daunorubicin vs azacitidine and venetoclax during induction chemotherapy.

Materials and Methods:

In this observational prospective study, data was recorded on prefilled Pro Formas of all acute myeloid leukemias patients older than 18 years of age admitted to Aga

Khan University Hospital Karachi from January 2018 until December 2023. Approval was obtained from AKU's ethical review committee (ERC) (ERC #: 2024-9797-28491) before starting the study.

This information included the patients demographics, the disease initial characteristics and laboratory values, the induction course and any problems, the induction outcome, and the patients status as being in remission at the end. SPSS 21 was used to enter and analyse the collected data for results and descriptions.

Confidential files and computerized medical data were searched for patient information. Demographic information, presenting symptoms, clinical findings, Eastern Cooperative Oncology Group performance status, comorbidities present, infectious foci at presentation and laboratory parameters. We also documented the type of organism on culture, response to antimicrobials, deterioration of patients on antimicrobials and need for admission in special care and intensive care units. The amount of time between the diagnosis and the beginning of induction was also noted.

Inclusion criteria:

1.All patients above 18 years of age.

2.All patients diagnosed with Acute myeloid leukemia.

3. Relapsed Acute myeloid leukemia.

4.AML refractory to standard induction and salvage chemotherapy.

5.CML transformed in AML.

Exclusion criteria:

1.All leukemias other than acute myeloid leukemia.

2.Acute promyelocytic leukemia.

Therapeutics

All patients who were younger than 50 years of age and who did not have any significant comorbidities were treated with standard intensive therapy with 7+3-based induction (cytarabine from 100 mg/m2 from Days 1-7 along with daunorubicin from 60 mg/m2 from Days 1-3)(4), whereas patients older than 50 years of age or those younger than 50 years of age with multiple comorbidities or poor performance status received azacitidine in combination with venetoclax. Azacitidine was administered subcutaneously at a dose of 100 mg once daily for 7 days. Venetoclax was administered in combination with Voriconazole (a strong CYP3A4 inhibitor) during induction at a dose of 100 mg and was continued for 21 days. However, in the context of worsening cytopenia venetoclax was stopped earlier. Bone marrow biopsy to document remission was performed on day 28.

Supportive Care

Patients were admitted for AML induction in the hospital either through the emergency room or from the Hematology Outpatient Clinic. Patients remained admitted during the induction period until they were no longer dependent on blood product support and their neutropenia had resolved with no evidence of any ongoing infection.

Chemotherapy was administered with the help of a peripherally inserted central catheter (PICC). Patients receiving 7+3 induction chemotherapy were treated as inpatients until their blood counts improved. G-CSF was not administered before remission was documented on day 28 bone marrow biopsy.

All patients received voriconazole 200 mg PO BID as antifungal prophylaxis along with routine antibiotic and antiviral prophylaxis with ciprofloxacin 500 mg PO BID and acyclovir 200 mg PO BID respectively.

Blood products were transfused as needed. Platelets were transfused in cases of bleeding or when the platelet count decreased to < 10 x 10^9/L (< 20 x 10^9/L in febrile patients). Packed red cell concentrates were transfused when haemoglobin dropped to less than 8 g/dl.

A thorough history and physical examination aimed at identifying the focus of infection, radiologic studies where needed, and cultures were used to assess every episode of fever (5). Whenever an infection was suspected, cultures were taken from PICC line and peripheral blood in accordance with the institutional one hour sepsis bundle which comprises measuring lactate levels, obtaining blood cultures before antibiotic administration, administering broad-spectrum antibiotics, beginning rapid administration of crystalloid at a rate of 30 ml/kg if hypotensive or lactate > 4 mmol/L and applying vasopressors if hypotensive during and after fluid resuscitation to maintain a mean arterial pressure > 65 mmHg. When clinically necessary, cultures were also obtained from other locations (such as sputum, urine and stool). Beta D glucan and galactomannan was also sent from peripheral blood to investigate possible fungal infection. For patients with predominant chest symptoms with no other proven focus of infection who continued to be febrile, bronchoalveolar lavage was also performed. Every episode of infection was graded on the MEWS (modified early warning sign) score, and appropriate action was taken accordingly. Patients were usually escalated to broad-spectrum antibiotics usually meropenem. In cases of suspected or proven venous line infection vancomycin was added. The choice of subsequent change or total duration of antibiotic treatment was consistent with the hospital's Infectious Diseases Team policy. Amphotericin was added empirically if fever continued beyond 72 hours or if beta-D glucan/galactomannan revealed abnormal results.

Microbiological analysis:

All microbiological tests were performed at the Aga Khan University Hospital Laboratory. This laboratory is accredited with the College of American Pathologists (CAP). Cultures were performed according to American Society of Microbiology guidelines. Blood cultures were performed in BacT/Alert (BioMerieux). Bacteria were identified phenotypically using biochemical reaction and APIs. Yeasts were identified using Vitek 2 Yeast ID card (bioMerieux, France). Susceptibility testing was done by Kirby-Bauer disc diffusion method on Muller-Hinton agar (MHA) and VITEK 2 (BioMerieux). Susceptibilities were interpreted according to CLSI M100 latest edition according to respective year.

Operational definitions:

Induction: The first phase of treatment is induction therapy. The goal of induction therapy is to control the disease and achieve remission.

Complete remission: Bone marrow blasts < 5%, absence of extramedullary leukemia, absolute neutrophil count > 1.0 × 10^9/L, platelet count > 100 x10^9/L and independence of red cell or platelet transfusion.

Overall survival (OS): Defined as the time from randomization to death. Any patients lost to follow-up or still alive at the time of evaluation were censored.

Progression free survival (PFS): Defined as the time from randomization until the first evidence of disease progression or death.

Event-free survival (EFS): Time from randomization to an event that may include disease progression, discontinuation of treatment for any reason, or death.

Multi-drug-resistant organisms (MDRs): MDRs are defined as those organisms with acquired nonsusceptibility to at least one agent in three or more antimicrobial categories. (5)

Induction mortality: Defined as death occurring within 30 days of initiating treatment for AML.

Statistical analysis: Data was analysed in SPSS version (20.0). For continuous data independent sample t test was used and categorical data were analysed through Fisher's exact test. Kaplan–Meier survival curves were generated to assess patient overall survival (OS). The log-rank test was used to compare median survival times. Survival rates with their corresponding 95% CIs were reported. A Cox regression model was used to adjust the p-values and hazards for significant factors. A significance criterion of p-value ≤ .05 was used in the analysis.

Results:

A total of 176 patients with a confirmed diagnosis of acute myeloid leukemia were included in our study. **Table 1** shows a Descriptive summary of patient characteristics in both groups. Among these patients, 115 (65.3%) received cytarabine and daunorubicin (7+3 arm) for induction, whereas 61 (34.7%) underwent induction therapy with azacitidine and venetoclax (Aza/Ven arm). The mean age of patients in the 7+3 arm was 37.2 ± 13.0 years, whereas it was 58.5 ± 12.8 years in the Aza/Ven arm. Patients in the 7+3 arm were on average, younger than patients in the Aza/Ven arm, with a mean age difference of 21.4 [17.3–25.4] years, which was statistically significant with a p value less than 0.001. Overall, our cohort comprised predominantly males with 115 (65.3%) male patients. The duration of complete count recovery postinduction was 25.0 ± 9.0 days in the 7+3 arm, whereas it was 9.0 ± 7.0 days in the Aza/Ven arm. This difference of 15.8 [95% CI = 13.1–19.5] days was also statistically significant with a p value less than 0.001. Blood cultures were performed for 156 (88.6%) patients and were positive in 84 (53.8%). A statistically significant association was observed between the presence of growth on blood cultures and the type of regimen used in induction with a p value of 0.013. Urine cultures were performed for 149 (84.7%) patients with only 16 (10.7%) cases yielding growth of isolates. However, no association was detected between growth on urine cultures and the type of induction regimen with a p value of 1.000. **Table 2** shows organisms identified on blood cultures from patients in the two treatment arms. The most common organisms were Coagulase negative *Staphylococcus* species (CoNS) (n=32) followed by *E. coli* (n=16) and *Enterobacter* spp (n=14). **Figure 1** shows the resistance patterns in our patient population. A total of 22 multidrug-resistant (MDR) organisms were identified, accounting for 12.5% of the isolates. Among these, carbapenem-resistant Enterobacteriaceae (CRE) represented the majority, comprising 14 isolates (63% of MDR cases), followed by vancomycin-resistant enterococci (VRE), which accounted for 5 isolates (23% of MDR cases).

Survival outcomes for both induction arms are depicted in the Kaplan–Meier curves in **Figure 2**. Induction-related mortality occurred in 25 patients (21.7%) receiving the 7+3 regimen and in 19 patients (31.1%) receiving azacitidine and venetoclax. The difference in median overall survival between the two arms was statistically significant, as determined by the log-rank test ($p < 0.001$).

Table 3 describes the results of the multivariable Cox proportional hazard regression. The model included age, sex, type of induction regimen and blood culture results as covariates. This finding indicates that only regimen type significantly impacted the hazard of death in our patient population when adjusted for covariates. Patients who received Aza/Ven were 5.76 95% CI = 2.72–12.20 times more likely to die than patients who received 7+3. The growth of organisms on blood culture was not associated with a statistically significant increase in the hazard of death $p = 0.185$.

Discussion

This study provides a comprehensive analysis of infection frequency and associated outcomes in patients with acute myeloid leukemia (AML) receiving induction chemotherapy with either cytarabine + daunorubicin (7+3) or azacitidine + venetoclax (Aza/Ven). Our findings reveal a significant infection burden during induction chemotherapy, reflecting the challenges inherent in managing AML within a tertiary care setting in Pakistan.

In the current study, blood cultures were positive in 53.8% of patients. This is similar to studies reported in Indian subcontinent, which demonstrated 51% blood culture positivity(6) but higher when compared to similar studies conducted by Polish Adult Leukemia Group (PALG), with 26% blood culture positivity (2)

Among patients receiving the standard 7+3 chemotherapeutic regimen, 41 gram-positive organisms were isolated, with coagulase-negative Staphylococci being the most common. CoNS can also be colonizers therefore, determining the significance of culture positivity is crucial(7). On the gram-negative side, 42 organisms were isolated, with *Enterobacter* species being the predominant pathogen. For patients receiving Aza/Ven, 8 gram-positive and 9 gram-negative organisms were isolated, with CoNS and *E. coli* being the most frequently identified in each respective category. When both groups were combined, the total number of gram-positive and gram-negative organisms was nearly balanced, with 49 gram-positive and 51 gram-negative organisms.

Among the gram-positive organisms identified, coagulase-negative staphylococci (CoNS) were deemed pathogenic in only 16 cases (32.6%) based on specific criterias. These criterias included fever >100°F, septic appearance, systolic blood pressure <90 mmHg, and the presence of risk factors such as long-term intravascular catheterization or immunosuppression with central lines. These findings are consistent with Khan et al., who reported CoNS as pathogenic in 34.78% of cases(8). Similarly, Maranda et al. identified CoNS as the most frequently isolated gram-positive pathogen (28%) in a comparable cohort (2). These results highlight the importance of evaluating the clinical significance of CoNS in infection management for immunosuppressed patients.

Our results demonstrated a greater incidence of infections in patients treated with the 7+3 regimen than in those receiving Aza/Ven. This is likely due to the extended duration of neutropenia typically associated with the 7+3 regimen, which results in prolonged exposure to opportunistic pathogens. These findings align with those of previous studies, such as those of Osmani et al. who reported higher infection rates with gram-negative organisms in neutropenic patients undergoing intensive chemotherapy(9).

A significant finding of our study is the prevalence of multidrug-resistant (MDR) organisms, with 12.5% of isolates being MDR and carbapenem-resistant Enterobacteriaceae (CRE) accounting for 63% of these. This is slightly lower than the 17.3% incidence reported by Kumar et al. in India, likely reflecting regional differences in antimicrobial stewardship, healthcare infrastructure, and resistance patterns(6) . These findings underscore the importance of tailored infection control measures to address the challenges posed by MDR organisms in diverse healthcare settings.

The rise of MDR pathogens severely limits therapeutic options, complicates infection management, and is associated with increased mortality. This underscores the critical need for stringent infection control measures, enhanced antimicrobial stewardship, and judicious use of broad-spectrum antibiotics to prevent the spread of MDR organisms.

Survival analysis revealed notable differences between the two induction regimens. Patients receiving the Aza/Ven regimen experienced significantly lower overall survival than those receiving the 7+3 regimen did, with induction-related mortality rates of 31.1% versus 21.7%, respectively. Regional studies of Indian sub-continent, such as those by Rija et al.(10) and Philip et al (3), reported a higher induction-related mortality of 27.5% and 24.7% respectively in de novo AML patients treated with the 7+3 regimen. In contrast, induction mortality in other Indian institutes and Western centres, has significantly improved, with an induction related mortality of 15.6% reported by Pandian et al(11), Kumar et al reporting a rate of 15.6%(6) ,Bahl et al reporting a rate of 17.1%(12) and Polish Adult Leukemia Group (PALG) reporting an induction related mortality of 9%(2) . These variations underscore disparities in healthcare infrastructure, infection control, and supportive care between regions.

Our institute monitors induction-related mortality for patients receiving the standard 7+3 treatment, aiming for a benchmark of <17%. Annual mortality rates from 2018 to 2023 were 12%, 28%, 20%, 16%, 12%, and 12%, respectively. The notably higher rates in 2019 (28%) and 2020 (20%) coincided with the COVID-19 pandemic. While exact data on infection rates among patients is unavailable and not the topic of this discussion, the pandemic likely contributed significantly to the increased mortality due to the heightened vulnerability of immunosuppressed individuals to severe complications.

Cox regression analysis further demonstrated that the Aza/Ven regimen was associated with a nearly sixfold increase in the hazard of death. This finding is particularly concerning because Aza/Ven is typically reserved for older or frail patients, who are already at a greater risk of adverse outcomes. However, it is important to consider that selection bias may have contributed to the higher mortality rates observed with the Aza/Ven combination, as many patients in this cohort were of advanced age, had multiple comorbidities, or had previously received standard first-line chemotherapy but experienced relapse or refractory disease. Among this cohort 12(63%) patients who experienced induction related mortality were given Aza/Ven as first line therapy, whereas 7(36.8%) patients received Aza/Ven as second- or third-line therapy.

Our study emphasizes the importance of early and aggressive management of infections in AML patients, especially those undergoing intensive chemotherapy. The high prevalence of MDR organisms highlights the need for robust antimicrobial stewardship programs and innovative therapeutic approaches to address resistant infections. Furthermore, the poorer survival outcomes associated with the Aza/Ven regimen underscore the necessity of refining patient selection criteria and optimizing treatment protocols for elderly and frail AML patients.

While the presence of MDR infections is concerning, our findings suggest that the type of induction regimen is an even stronger predictor of mortality. Future research should focus on validating these results in larger, multicentre cohorts and exploring the potential benefits of incorporating targeted therapies and personalized medicine in AML management.

Overall, this study provides valuable insights into infection-related challenges in AML treatment and highlights critical areas for intervention to improve patient outcomes. Future studies should focus on validating these findings in larger, multicentre cohorts and exploring the potential benefits of incorporating targeted therapies and personalized medicine approaches in the management of AML.

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Figure and Table Legends:

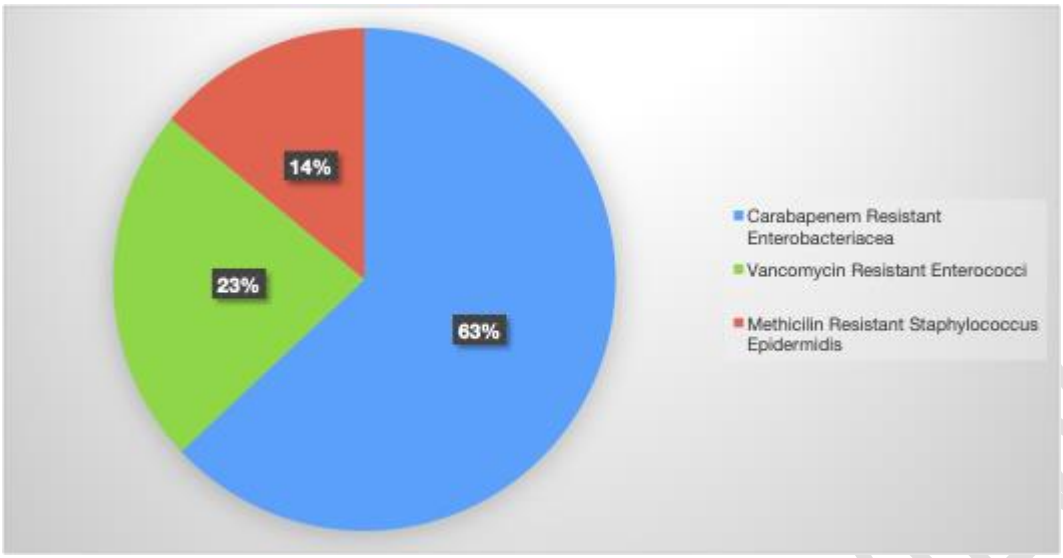

Figure 1: Resistance patterns in our patient population.

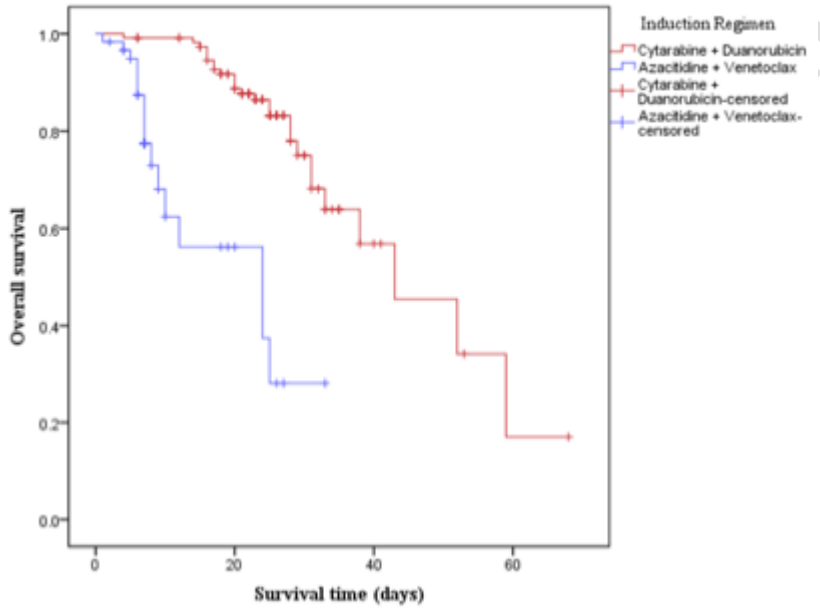

Figure 2: Kaplan–Meier Curve Survival outcomes for both induction arms.

Table 1: Descriptive summary of patient characteristics in both groups.

Table 2: Organisms identified on blood cultures from patients in the two treatment arms.

Table 3: Multivariable Cox proportional hazard regression model.

Table 1: Descriptive summary of patient characteristics among both groups

Variable	Cytarabine + Daunorubicin n (%)	Azacitidine + Venetoclax n (%)	Total n (%)
Gender			
Male	70 (60.9)	45 (73.8)	115 (65.3)
Female	45 (39.1)	16 (26.2)	61 (34.7)
Age			
< 50	86 (74.8)	9 (14.8)	95 (54.0)
50 – 60	23 (20.0)	19 (31.1)	42 (23.9)
> 60	6 (5.2)	33 (54.1)	39 (22.2)
			P<0.001
Count Recovery Post-Induction (days)	25.0 ± 9.0	9.0 ± 7.0	19.5 ± 11.4
Blood Culture			
Growth	67 (60.4)	17 (37.8)	84 (53.8)
No Growth	44 (39.6)	28 (62.2)	72 (46.2)
			P = 0.013
Death	25 (21.7)	19 (31.1)	44 (25.0)
Consolidation	82 (71.3)	33 (54.1)	115 (65.3)
Loss to follow	6 (5.2)	9 (14.8)	15 (8.5)
Palliative care	2 (1.7)	0 (0.0)	**2(1.7)**
			P = 0.03
Percentage resistant* isolates identified on BLCS	20 (29.8)	2 (11.8)	22 (12.5)

*Isolate was resistant to at least one antibiotic on sensitivity testing. These include MDR organisms.

Table2 : Organisms identified on blood cultures from patients among the two treatment arms.

Organisms identified on blood culture	Type of Organism	Cytarabine + Daunorubicin n (%)	Azacitidine + Venetoclax n (%)	Total n (%)
Staphylococcus (CN)	Gram-Positive	25 (28.1)	7 (41.2)	32 (30.18)
Enterococcus spp	Gram-Positive	8 (9.0)	-	8 (7.5)
Corynebacterium spp	Gram-Positive	6 (6.7)	1 (5.9)	7 (6.6)
Streptococcus spp	Gram-Positive	2 (2.2)	-	2 (1.88)
Enterobacter spp	Gram-Negative	12 (13.5)	2 (11.8)	14 (13.2)
Escherichia Coli	Gram-Negative	11 (12.4)	5 (29.4)	16 (15.09)
Acinetobacter spp	Gram-Negative	7 (7.9)	-	7 (6.6)
Pseudomonas spp	Gram-Negative	4 (4.5)	1 (5.9)	5 (4.7)
Klebsiella Pneumoniae	Gram-Negative	4 (4.5)	-	4 (3.7)
Proteus Mirabilis	Gram-Negative	-	1 (5.9)	1 (0.9)
Providencia spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Stenotrophomonas spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Bacteroides spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Aeromonas spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Candida spp	Yeast	6 (6.7)	-	6 (5.6)
Total Isolates identified		89 (84.0)	17 (16.0)	106

*Multiple isolates were identified in some patients; hence the number here does not represent the total number of patients with a given organism but rather the number of individual organisms identified on blood culture. CN – Coagulase Negative

Table 3: Multivariable Cox hazard model

Variable	Hazard Ratio	95% C.I	p value
Age	1.01	[0.99 – 1.04]	0.299
Gender Male Female	 2.025 Reference	 [0.92 – 4.45] -	 0.079

Regimen			
Azacitidine + Venetoclax	5.76	[2.72 – 12.20]	< **0.001**
Cytarabine + Daunorubicin	Reference	-	
Blood Culture			
No Growth	0.63	[0.32 – 1.21]	0.185
Growth	Reference	-	