Outcomes of patients with haematological malignancies and febrile neutropenia at the Universitas Academic Hospital multidisciplinary intensive care unit, Free State Province, South Africa

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Background. Mortality rates in patients with haematological malignancies who required intensive care unit (ICU) admission have in the past been high. More recently, however, improved outcomes for critically ill haematological patients have been reported.
Objective. To determine outcomes, average length of ICU stay, and factors associated with mortality in patients with haematological malignancies and neutropenic fever in the multidisciplinary ICU (MICU) at Universitas Academic Hospital (UAH), Bloemfontein, Free State Province, South Africa.
Methods. We conducted a retrospective review of medical and laboratory records of all patients admitted to the UAH MICU with haematological malignancies and febrile neutropenia between 2010 and 2019.
Results. A total of 182 patients with haematological malignancies were admitted to the MICU between 1 January 2010 and 31 December 2019, of whom 51 (28.0%) fulfilled the inclusion criteria for the study. The median age was 33 years, and 29 patients (56.9%) were female. Most patients had either acute myeloid leukaemia (*n*=22; 43.1%) or acute lymphocytic leukaemia (*n*=16; 31.4%), while B-cell lymphoma (*n*=12; 23.5%) and multiple myeloma (*n*=1; 2%) were less frequent. The median length of stay in the ICU was 3 days. ICU mortality was 76.5% and hospital mortality 82.4%. Factors associated with mortality included septic shock, vasoactive agent use and mechanical ventilation.
Conclusion. Patients with haematological malignancies and febrile neutropenia in the UAH MICU have high ICU and hospital mortality rates. More needs to be done with regard to timeous management of patients with haematological malignancies and septic shock in our setting to improve survival.
Keywords. Haematological malignancies, neutropenic fever, sepsis, intensive care unit.

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Study synopsis
This is the first study to report on ICU mortality of adult patients with haematological malignancies and neutropenic sepsis in a tertiary hospital ICU in the Free State. These patients had a high mortality rate.
What the study adds. Our study shows that septic shock, vasoactive agent use and mechanical ventilation were associated with increased ICU mortality.
Implications of the findings. Strict adherence to infection prevention and control measures in haematology wards is required. Early recognition and treatment of sepsis before it progresses to septic shock is important. ICUs must be designed so that isolation cubicles are readily available to prevent cross-infection of patients.

The World Health Organization estimated that there were ~1.28 million cases of haematological malignancy globally in 2020, with 710 000 deaths.[1] During the same year, an estimated 109 000 cases of haematological malignancies were diagnosed in South Africa (SA), and ~70 500 of these patients died.[1] Mortality rates in patients with haematological malignancies who required intensive care unit (ICU) admission have in the past been high.[2] More recently, however, improved outcomes for critically ill haematological patients have been published,[3] with hospital survival rates of up to 60.7% reported for a European cohort of patients.[4] It is not surprising that an increasing number of patients are referred and accepted for ICU admission.[5,6] In resource-limited settings such as SA, conditions are often very different from developed-world settings. Decisions on ICU admission invariably use triage and prioritisation models based on the improved incremental benefit that is highly influenced by prognostication and decision-making support systems.[7] Multiple-organ failure, the requirement for invasive mechanical ventilation or vasopressors, and Acute Physiology and Chronic Health Evaluation (APACHE II)

and Sequential Organ Failure Assessment (SOFA) scores have been found to be predictors of poor outcome in critically ill haematological patients.[8-11] However, it remains important that ICU admission policies reflect local data, that patients who are too ill to benefit are not inappropriately admitted for prolonged organ support, and that patients who may benefit are not inadvertently denied intensive care management.

At Universitas Academic Hospital (UAH), a tertiary hospital in Free State Province, SA, patients with underlying haematological malignancies undergoing chemotherapy are often referred for ICU admission after developing febrile neutropenia with septic shock and/or organ failure. Given the reported globally improved survival rates in patients with haematological malignancies, we aimed to determine the outcomes of patients with haematological malignancies with febrile neutropenia admitted to the UAH multidisciplinary ICU (MICU) between January 2010 and December 2019. The primary objective was to determine the mortality rate of the patients. Secondary objectives were to determine the median length of stay in the MICU, and identify prognostic variables that were associated with poor outcome.

Methods

Study design

This was a retrospective descriptive study. Ethics approval to conduct the study was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS) (ref. no. UFS-HSD2021/0186/2505).

Setting

UAH is a 636-bed hospital in Bloemfontein that serves as the referral hospital for the Free State. All patients with haematological malignancies in the Free State, Northern Cape Province and Lesotho are referred to the haematology division at UAH for management. Patients who develop neutropenic fever while undergoing chemotherapy for their underlying haematological malignancy are frequently referred to the UAH MICU for further management.

Study participants

Patients were included in the study if they were admitted to the UAH MICU with a diagnosis of neutropenic fever, had a concomitant diagnosis of an underlying haematological malignancy, and were admitted between 1 January 2010 and 31 December 2019. Patients with a haematological malignancy but for whom the primary reason for referral to the UAH MICU was not neutropenic fever were excluded.

Data collection

A data form was designed to capture information on age, sex, type of haematological malignancy, reason for ICU admission (ventilator support required, management of circulatory shock), severity of illness scores at the time of admission to the ICU (APACHE II and SOFA), HIV status (including absolute CD4 count and HIV viral load for HIV-positive patients, if available), ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2), white cell count, neutrophil count, platelet count, Glasgow Coma Scale (GCS) score (out of 15), total bilirubin level, serum creatinine level, lactate level, systolic blood pressure, any requirement for vasoactive agents at or prior to ICU admission, blood culture results (taken within 72 hours before or during the ICU stay), vasoactive agents (adrenaline, phenylephrine, noradrenaline, dobutamine) used at any time during the ICU stay, length of ICU stay (calculated from date of admission to date of discharge from the ICU), ICU survival and hospital survival.

Medical files of patients were reviewed. A pilot study with three patients was performed to test all aspects of the data form. No significant changes to the data form were required, and the results of the pilot study were included in the main study.

Bias

As this was a retrospective study of patient files, the medical records may have been incomplete, and information on all the data required to complete the data forms may not have been available. All patients in whom the primary outcome could be determined were included in the study. Patients were excluded from analysis pertaining to secondary outcomes if the information required to determine secondary outcomes was not available in the clinical files.

Bias could have been introduced in determining primary and secondary outcomes in this study by the lack of ICU bed availability in public sector hospitals, resulting in inability to accommodate all patients with haematological malignancies who developed neutropenic fever and were referred to the ICU. The number of patients who could not be accommodated due to limited ICU bed availability should, however, be small. We addressed this potential bias by increasing the duration of the study period to 10 years to include as many patients as possible in the study.

Another factor that could have resulted in bias in terms of the primary outcome is that treatment may have been withdrawn from patients when further treatment was deemed futile. This is, however, a universally accepted management strategy in patients with refractory organ failure in whom all other curative treatment options have been exhausted and whose likelihood of survival is deemed extremely poor.

Data analysis

Continuous variables were summarised by medians, minimum, maximum or percentiles. Categorical variables were summarised by frequencies and percentages. Differences between groups were evaluated using appropriate statistical tests (χ^2 test or Fisher's exact test) for unpaired data. The analysis was done by the Department of Biostatistics, Faculty of Health Sciences, UFS, using SAS version 9.4 (SAS, USA).

Results

A total of 182 patients with haematological malignancies were admitted to the MICU between 1 January 2010 and 31 December 2019, of whom 51 (28.0%) fulfilled the inclusion criteria. Baseline characteristics are shown in Table 1. The median (interquartile range) age was 33 (23 - 49) years, and most of the patients were female (*n*=29; 56.9%). Most patients were admitted with either acute myeloid leukaemia (*n*=22; 43.1%) or acute lymphocytic leukaemia (*n*=16; 31.4%), while B-cell lymphoma (*n*=12; 23.5%) and multiple myeloma (*n*=1; 2.0%) were less frequent. Most patients (*n*=41; 80.4%) had septic shock. The median APACHE II score for the study population was 23, while the median

Table 1. Baseline characteristics (*N*=51)

Variable	*n* (%)*
Age (years), median (IQR)	33 (23 - 49)
Sex	
Male	22 (43.1)
Female	29 (56.9)
Type of malignancy	
AML	22 (43.1)
ALL	16 (31.4)
B-cell lymphoma	12 (23.5)
Multiple myeloma	1 (2.0)
Reason for admission	
Septic shock	41 (80.4)
Sepsis	10 (19.6)
Vasoactive agents	
Yes	44 (86.3)
No	7 (13.7)
Types of vasoactive agents (*n*=43)†	
Phenylephrine	40 (93.0)
Adrenaline	18 (41.9)
Noradrenaline	5 (11.6)
Dobutamine	3 (7.0)
Number of vasoactive agents (*n*=43)	
1	22 (51.2)
2	19 (44.2)
3	2 (4.7)
Micro-organisms‡	
Escherichia coli	9 (20.0)
Coagulase-negative Staphylococcus	7 (15.6)
Klebsiella pneumoniae	6 (13.3)
Acinetobacter baumannii	6 13.3)
Enterococcus faecium	3 (6.7)
Enterobacter cloacae	1 (2.2)
Flavobacterium orizihabi	1 (2.2)
Methicillin-sensitive *Staphylococcus aureus*	1 (2.2)
Pseudomonas aeruginosa	1 (2.2)
Methicillin-resistant *Staphylococcus aureus*	1 (2.2)
No growth	9 (20.0)
Clinical and laboratory results, median (IQR)	
GCS score	15 (12 - 15)
Systolic blood pressure (mmHg) (*n*=50)	101 (93 - 113)
PaO_2/FiO_2 (*n*=44)	180 (141 - 258)
White cell count ($\times 10^9$/L)	0.15 (0.06 - 0.38)
Neutrophil count ($\times 10^9$/L)	0.03 (0.01 - 0.11)
Platelet count ($\times 10^9$/L)	15 (10 - 28)
Total bilirubin ($\times 10^9$/L)	20 (11 - 37)
Creatinine (µg/L)	111 (71 - 212)
Lactate (mmol/L) (*n*=32)	4.6 (1.9 - 8.1)
HIV-positive status (*n*=26)	13 (50.0)
Mechanical ventilation (*n*=50)	
Yes	35 (70.0)
No	15 (30.0)
Severity of illness scores, median (IQR)	
APACHE-II (*n*=48)	23 (19 - 29)
SOFA (*n*=46)	10 (7 - 13)
Outcomes	
Length of ICU stay (days), median (IQR)	3 (1 - 5)
ICU mortality	39 (76.5)
Hospital mortality (including ICU mortality)	42 (82.4)

IQR = interquartile range; AML = acute myelogenous leukaemia; ALL = acute lymphoblastic leukaemia; GCS = Glasgow Coma Scale; PaO2/FiO2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; APACHE-II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit.
*Except where otherwise indicated.
†Some patients received more than one vasoactive agent.
‡Five patients cultured 2 organisms each. There were 11 patients for whom culture results were not available.

SOFA score was 10. HIV status was under-reported, with results available for only 26 of the 51 patients. Of these patients, 13 (50.0%) were HIV positive. Vasoactive therapy was required by 44 patients (86.3%), but medical records for one patient only indicated use of inotropic support, and not which or how many agents. Phenylephrine was the most commonly provided vasopressor (*n*=40/43; 93.0%), followed by adrenaline (*n*=18/43; 41.9%), noradrenaline (*n*=5/43; 11.6%) and dobutamine (*n*=3/43; 7.0%). Blood specimens yielded positive culture results in 31 patients (60.8%) (9 patients had no growth, 5 cultured two organisms each, and there were 11 for whom culture results were not available). The most frequent organism cultured was *Escherichia coli* (*n*=9/45; 20.0%), followed by coagulase-negative *Staphylococcus* (*n*=7/45; 15.6%), *Acinetobacter baumanii* (*n*=6/45; 13.3%) and *Klebsiella pneumoniae* (*n*=6/45; 13.3%). No fungi were cultured. Mechanical ventilation was required by 35/50 patients (70.0%). The median length of stay in the ICU was 3 days. ICU mortality was 76.5%, while hospital mortality (including ICU mortality) was 82.4%.

ICU and hospital mortality are shown in Table 2. There were no statistically significant age or sex differences between survivors and non-survivors. There was also no statistically significant difference in mortality rates between the types of haematological malignancies in patients admitted to the ICU. The number of patients with septic shock requiring vasoactive agents or mechanical ventilation was statistically higher in the group who did not survive their ICU stay. Higher APACHE-II and SOFA scores were also associated with death. With regard to hospital survival data, there was a statistically significantly higher number of patients in the groups requiring more than one vasoactive agent and with high SOFA scores who did not survive. Table 3 shows odds ratios (ORs) for ICU mortality. The likelihood of death while in the ICU was increased in patients with septic shock (OR 4.9), as well as in those requiring vasoactive agents (OR 13.2) and mechanical ventilation (OR 8.6).

Discussion

As far as we are aware, this is the first outcomes study in patients with haematological malignancies and febrile neutropenia in a

Table 2. ICU and hospital survival data (*N*=51)

Variable	ICU survival data, *n* (%)†			Hospital survival data, *n* (%)†		
	Survivors (*n*=12; 23.6%)	Non-survivors (*n*=39; 76.4%)	*p*-value	Survivors (*n*=9; 17.6%)	Non-survivors (*n*=42; 82.4%)	*p*-value
Age (years), median (IQR)	27 (23.5 - 53.5)	33 (22 - 47)	0.9734	24 (23 - 30)	36 (24 - 50)	0.1192
Sex			0.2242			0.1499
Male (*n*=22)	7 (31.8)	15 (68.2)		6 (27.3)	16 (72.7)	
Female (*n*=29)	5 (17.2)	24 (82.8)		3 (10.3)	26 (89.7)	
Type of malignancy			1.00			1.00
AML (*n*=22)	5 (22.7)	17 (77.3)		4 (18.2)	18 (81.8)	
ALL (*n*=16)	4 (25.0)	12 (75.0)		3 (18.8)	13 (81.3)	
B-cell lymphoma (*n*=12)	3 (25.0)	9 (75.0)		2 (16.7)	10 (83.3)	
Multiple myeloma (*n*=1)	0	1 (100)		0	1 (100)	
Reason for admission			0.0422*			0.3534
Septic shock (*n*=41)	7 (17.1)	34 (82.9)		6 (14.6)	35 (85.4)	
Sepsis (*n*=10)	5 (50.0)	5 (50.0)		3 (30.0)	7 (70.0)	
Vasoactive agents			0.0054*			0.0947
Yes (*n*=44)	7 (15.9)	37 (84.1)		6 (13.6)	38 (86.4)	
No (*n*=7)	5 (71.4)	2 (28.6)		3 (42.9)	4 (57.1)	
Number of vasoactive agents‡			0.1459*			0.0458*
1 (*n*=22)	6 (27.3)	16 (72.7)		6 (27.3)	16 (72.7)	
2 (*n*=19)	1 (5.3)	18 (94.7)		0	19 (100)	
3 (*n*=2)	0	2 (100)		0	2 (100)	
Mechanical ventilation§			0.0031*			0.1056
Yes (*n*=35)	4 (11.4)	31 (88.6)		4 (11.4)	31 (88.6)	
No (*n*=15)	8 (53.3)	7 (46.7)		5 (33.3)	10 (66.7)	
Severity of illness scores, median (IQR)						
APACHE-II (*n*=48)	20 (16.5 - 22.5)	27 (20 - 30)	0.0207*	20 (18 - 22)	25 (20 - 30)	0.0551
SOFA (*n*=46)	7 (6 - 8)	11.5 (9 - 13.5)	0.0005*	7 (6 - 8)	11 (9 - 13)	0.0012*
Length of ICU stay (days), median (IQR)	6 (4 - 8)	2 (1 - 5)	0.0065*	-	-	-

ICU = intensive care unit; IQR = interquartile range; AML = acute myelogenous leukaemia; ALL = acute lymphoblastic leukaemia; APACHE-II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment.
*Statistically significant ($p<0.05$).
†Except where otherwise indicated.
‡Medical records for one patient indicated use of inotropic support, but not which or how many agents. This patient was therefore not included in this part of the analysis.
§There was no indication whether one patient was mechanically ventilated or not. This patient was therefore not included in this part of the analysis.

tertiary hospital ICU in Free State Province, SA. We found an ICU mortality rate of 76.5% and a hospital mortality rate of 82.4%. These results are in stark contrast to ICU and hospital mortality rates of 24.8% and 45.3%, respectively, found by Al-Zubaidi *et al.*[12] in a developed-world ICU, and the 38% and 46% reported in a recent systematic review.[13] The reasons for the high mortality in our ICU are probably delays in sepsis recognition with a disproportionally high number of patients with septic shock (80.4%) as opposed to sepsis only (19.6%),[14] and delays in administering appropriate antibiotic therapy in patients with septic shock.[15] ICU mortality in our study was significantly associated with septic shock and the requirement for vasoactive agents, as indicated by the ORs in Table 3.

Table 3. ORs for ICU mortality

Risk factors	OR (95% CI)
Septic shock v. sepsis only	4.9 (1.1 - 21.4)
Vasoactive agents required v. no vasoactive agents required	13.2 (2.1 - 82.2)
More than one vasoactive agent v. one vasoactive agent	7.5 (0.8 - 68.8)
Mechanical ventilation v. no mechanical ventilation	8.6 (2.1 - 37.0)

OR = odds ratio; ICU = intensive care unit; CI = confidence interval.

Mechanical ventilation was associated with an 8.6-fold increased ICU mortality in our study. Of the patients who were mechanically ventilated, 88.6% died in the ICU, as opposed to 46.7% who survived if mechanical ventilation was not required. In the study by Al-Zubaidi *et al.*,[12] mechanically ventilated patients also had higher ICU mortality of 53.5% and hospital mortality of 75% compared with non-ventilated patients The figures increased to ICU and hospital mortality of 59.3% and 90.6%, respectively, for patients who underwent allogeneic stem cell transplantation. Absence of respiratory failure requiring mechanical ventilation has been shown to be strongly associated with survival.[16]

Our study population consisted of young adults, with a median age of 33 years. The incidence of haematological malignancies other than Hodgkin's lymphoma, however, generally tends to increase with age up to 75 years.[17] Our patients' young age therefore probably reflects the ICU admission criteria, which prioritise younger patients. There

were no statistically significant differences in age between survivors and non-survivors.

Results on HIV status were only available for 26 of the 51 patients in our study, and there was a similar number of HIV-positive patients in the survivor and non-survivor groups. Viral load and CD4 counts were similarly not available. The influence of HIV status on mortality in the era of highly effective antiretroviral therapy is unclear, with some studies reporting worse outcomes and others equivalent outcomes.[18,19] In general, however, non-Hodgkin's lymphoma remains a common haematological malignancy in people with HIV, whereas the risk of leukaemia does not seem to be increased.[20] The risk of high-grade non-Hodgkin's lymphoma, especially Burkitt's lymphoma, is particularly high in HIV-positive patients compared with HIV-negative patients.[21]

APACHE-II and SOFA scores were higher in non-survivors than in survivors in our study. This finding is similar to those of other studies reporting on ICU outcomes of patients with haematological malignancies.[22,23] Although it is tempting to use illness severity scores, such as APACHE-II and SOFA, to assist with triage decisions on individual patients, much more work to improve the accuracy, validity and predictability of such scoring systems will have to be conducted before they can be used in clinical practice.[7]

Study limitations

There are several limitations to our study. Firstly, the study was retrospective and included patient medical records over a 10-year period. Incomplete medical notes or poor hospital archiving with lost files may have resulted in missing information. This aspect was addressed by combining data from hospital paper files and electronic hospital records to extract the required data.

Secondly, the historically poor survival rates of patients with haematological malignancies and septic shock could have biased the decision of the ICU consultant on call whether to admit these patients to the ICU.

Thirdly, several confounding factors could have influenced the outcomes of the patients. Improved management of haematological malignancies may have resulted in improved outcomes in general, with those developing neutropenic fever and septic shock representing a specific subgroup of patients with higher severity of illness and increased mortality in the ICU.

The study was conducted in a high HIV prevalence setting,[24] but the HIV reporting in the study was poor. This could be partially controlled by reviewing the prescription charts of the patients and assuming a positive or negative HIV status based on the presence or absence of antiretroviral agents on the prescription charts. However, this does not fully control for the lack of HIV data, which could potentially have influenced mortality rates in our study population.

ICU protocols and clinical management of patients in the ICU may have changed considerably over 10 years. This may have resulted in better outcomes in patients admitted to the ICU more recently. Alternatively, an increased prevalence of multidrug-resistant pathogens in the hospital and ICU environment may have resulted in a worse outcome in patients admitted to the ICU more recently. None of these variables could be definitively accounted for. Finally, the timeous management and institution of appropriate antibiotic therapy for septic shock at the time of recognition before transfer to the ICU could have influenced ICU and hospital survival rates.

Conclusion

Patients with haematological malignancies and febrile neutropenia in the UAH MICU in Free State Province have high ICU and hospital mortality rates. Mortality is associated with septic shock and vasoactive agent use, mechanical ventilation and high APACHE-II and SOFA scores. The study was conducted in a resource-limited setting with strict ICU admission criteria and may therefore not be generalisable to well-resourced healthcare settings. More needs to be done with regard to timeous management of patients with haematological malignancies and septic shock in our setting to improve ICU survival. Strict infection prevention and control measures should be implemented in all haematology wards. These measures need to be adhered to vigilantly. Tools such as early warning and quick SOFA scores can be used to recognise and implement treatment for sepsis early. Clinicians working in haematology wards should be trained to manage patients with sepsis and septic shock according to the Surviving Sepsis Campaign (SSC) guidelines. Timeous management of patients with haematological malignancies and neutropenic sepsis could result in improved ICU and hospital survival rates.

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