RESEARCH ARTICLE

Epidemiology, Clinical Characteristics, and Prognostic Factors in Critically Ill Patients with Hematolymphoid Malignancy

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Abstract

Objective: Despite advances in the field of oncology and intensive care, the outcomes of hematolymphoid malignancy (HLM) patients admitted to ICU are poor. This study was carried out to look at the demographic data, clinical features, and predictors of hospital mortality in these patients.

Materials and methods: We prospectively studied 101 adult critically ill patients with HLM admitted to the 14-bedded mixed medical surgical ICU of a tertiary care cancer center. Out of 101 patients, end-of-life care decisions were taken in 7 patients, who were excluded from the outcome analysis. Predictors of in-hospital mortality were evaluated using univariate and multivariate analysis.

Results: The ICU and in-hospital mortality recorded in our study were 48.9 and 54.3%, respectively. Neutropenia at ICU admission, Simplified Acute Physiology Score III (SAPS III) score, and mechanical ventilation (MV) within 24 hours of ICU admission were associated with in-hospital mortality on univariate analysis. On multivariate logistic regression analysis, neutropenia at ICU admission (OR 4.621; 95% CI, 1.2–17.357) and MV within 24 hours of ICU admission (OR 2.728; 95% CI, 1.077–6.912) were independent predictors of in-hospital mortality.

Conclusion: The HLM patients needing critical care have high acuity of illness, and acute respiratory failure is the commonest reason for ICU admission in these patients. In our study, the ICU survival was more than 50% and more than 45% patients were discharged alive from the hospital. We found a need for MV within 24 hours of ICU admission and presence of neutropenia at ICU admission to be independent predictors of hospital mortality in our study.

Keywords: Hematolymphoid malignancy, Mechanical ventilation, Multivariate analysis, Neutropenia, Predictors of hospital mortality, Sequential Organ Failure Assessment Score (SOFA), Simplified Acute Physiology Score III.

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Introduction

Cancer is one of the leading causes of death among developed countries, with 20% cases being hematolymphoid malignancies (HLMs).[1,2] Number of cancer patients in India is rising.[3] There has been an improvement in survival of patients with HLMs due to availability of newer chemotherapeutic agents and more aggressive protocols.[4,5] The ICU outcomes of these patients have improved due to changes in the management of these patients and also a change in the attitude of the intensivists toward admitting these patients to the ICU.[6–8] It is therefore likely that the number of ICU admissions will increase. These patients are admitted to the ICU for treatment of complications related to disease, treatment, or unrelated causes. The HLM patients have higher propensity to develop neutropenia and have an impaired immune system. They often present to the ICU with either acute respiratory failure, bleeding diathesis, and/or septic shock.[9]

In a large prospective, multicenter European study of all cancer patients admitted to general ICU, 15% patients had HLMs. Multiple studies in these patients have shown a high ICU mortality, ranging from 39.3 to 89.9%.[10,11] In India, unawareness, illiteracy,[12] and use of alternative medicine[13] may cause delayed presentation to the hospital. Poor nutrition due to low socioeconomic status and poor access to specialized care may compound the problem further. In a previous study from our institute, we found that the ICU costs were significantly higher for treating critically ill HLM patients.[14] In absence of data on prognosis of critically ill patients with HLM from our country, the economic impact of ICU care of these patients may also be a contributing factor to the apprehensions of hematologists and oncologists to transfer their patients to ICU. A recent, large,

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multicenter Indian point prevalence found that the incidence of HLM patients admitted to ICU was only 0.8% (vs 2.2%) as compared to data from the Western countries.[9,15] The poor representation of critically ill HLM patients in our scenario as compared to data from Western countries may be due to the perception among physicians and intensivists about poor ICU outcomes of these patients. There is scarcity of outcome data on critically ill patients with HLM from Southeast Asian region and, in particular, from India. We therefore analyzed our prospectively collected data to determine the prognostic factors and patient outcomes.

Patients and Methods

This prospective observational study was conducted after Institutional Ethics Committee (IEC) approval and waiver of a written informed consent, in our 14-bedded mixed medical surgical ICU, in a tertiary care cancer hospital from July 2014 to November 2015. All consecutive adult (>18 years) HLM patients having ICU stay of >24 hours admitted to the ICU were included. The ICU organization and type of patients in our tertiary care ICU have been previously described.[16] We excluded patients who had undergone hematopoietic stem cell transplant (HSCT) and those who did not have proven diagnosis of cancer.

Data Collection

Demographic, clinical, and laboratory variables over the first 24 hours of ICU admission were recorded. We also collected data about the type of malignancy, cancer status, cancer-directed treatment(s), ICU admission diagnosis, source and type of ICU admission, comorbidities, presence of neutropenia (absolute neutrophil count < 500 cells/mm^3), ICU interventions during first 24 hours of ICU admission (need of noninvasive or invasive mechanical ventilation (MV), vasopressors, renal replacement therapy), sequential organ failure assessment (SOFA) on day 1 of ICU admission and simplified acute physiology III (SAPS III) score on day 1 of ICU admission, ICU and hospital length of stay (LOS), and end-of-life decision (wherever applicable). The primary outcome studied was hospital mortality. We also analyzed the data for predictors of hospital outcome.

Statistical Analysis

The SPSS software version 21 (SPSS-21, IBM, Chicago, USA) for windows was used for statistical analysis. Data are presented as mean ± SD or median with the interquartile range (IQR), when indicated. Continuous variables were compared using the independent *t*-test. Categorical data were analyzed by either the Pearson's Chi-square or the Fisher's exact test. The binary logistic regression model was used to analyze the effect of multiple covariates on hospital mortality. A *p* value <0.05 was considered statistically significant.

Results

Patient Demographic and Clinical Characteristics

In the study period, 101 patients with HLM were admitted to the ICU. The demographics and clinical variables are shown in Tables 1 and 2. The most common reason for admission to ICU was acute respiratory failure. The most common ICU intervention used within first 24 hours of ICU admission was MV in any form. Many patients received multiple ICU interventions within first 24 hours of admission to ICU. End-of-life decisions were taken in only seven patients, of which six died in ICU and one died in the ward. These patients were excluded from the outcome analysis.

Table 1: Demographic and clinical characteristics of patients with HLM admitted to ICU

Variables	*Patients (n = 101)*
Age (years) mean ± SD	41.44 ± 15.676
Gender male *n* (%)	53 (52.5)
Neutropenia *n* (%)	47(46.5)
Cancer status *n* (%)	
Controlled/remission	17 (16.8)
Active—newly diagnosed	69 (68.3)
Active—recurrence/progression	15 (14.9)
Type of ICU admission *n* (%)	
Medical	98 (97)
Emergency surgical	3 (3)
Cancer-directed treatment *n* (%)	
No treatment	4 (4)
Chemotherapy only	97 (96)
Chemotherapy + radiotherapy	5 (5)
Source of admission *n* (%)	
Ward	51 (50.5)
Emergency room	35 (34.6)
Others	15 (14.8)
Cancer diagnosis *n* (%)	
ALL	19 (18.8)
AML	29 (28.7)
NHL	38 (37.6)
HL	6 (5.9)
CML	1 (1)
Plasma cell neoplasm	8 (7.9)
SAPS III score mean ± SD	65.87 ± 10.864
SOFA score ± SD	5.01 ± 2.791
Median ICU length of stay (IQR) days (*n* = 94)	4 (2–7.5)
Median hospital length of stay (IQR) days (*n* = 94)	10 (6–19)
End-of-life decisions (%)	7 (7)

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; CML, chronic myeloid leukemia; SAPS, simplified acute physiology score; IQR, interquartile range; SOFA, sequential organ failure assessment

Outcome Data

On univariate analysis, presence of neutropenia at ICU admission, SAPS III score on the day of ICU admission, and MV within 24 hours of ICU admission were found to be predictors of in-hospital mortality (Table 3). A multivariate logistic regression analysis was performed to ascertain the effects of SAPS III score, neutropenia, and need for MV on the likelihood of hospital mortality. On multivariate logistic regression analysis, neutropenia at ICU admission and institution of any form of MV within 24 hours of ICU admission were found to be independent predictors of in-hospital mortality (Table 4). ICU and in-hospital mortality recorded in our study were 48.9 and 54.3%, respectively.

Discussion

These data are one of the largest prospectively collected data of recent times from India on short-term outcome and its predictors,

Table 2: Reasons of ICU admission and ICU interventions required in first 24 hours

Variables	*Patients (n = 101)*
Reason for ICU admission *n* (%)	
Acute respiratory failure	37 (36.6)
Septic shock	30 (30)
Gastrointestinal	12 (12)
Neurological	6 (6)
Renal/metabolic	6 (6)
Cardiovascular	5 (5)
Postcardiac arrest	4 (4)
Others	1 (1)
ICU intervention within 24 hours *n* (%)	
Any MV (any NIV + upfront IMV)	84 (83.2)
Any IMV (upfront IMV + failed NIV)	64 (63.4)
Upfront IMV	43 (42.6)
Any NIV	41 (40.6)
Failed NIV	20 (19.8)
Vasopressor (V)	52 (51.5)
Dialysis (D)	3 (3)
Combination ICU therapies	
IMV + V	37 (36.6)
IMV + D	1 (1)

MV, mechanical ventilation; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; V, vasopressors; D, dialysis

in critically ill HLM patients. Neutropenia at ICU admission and MV within 24 hours of ICU admission were found to be independent predictors of hospital mortality. Our hospital mortality is higher than those reported by Azoulay et al., and Bird et al.[10,17] This probably reflects inclusion of patients with higher severity of illness, as can be seen with higher proportion of patients needing organ support therapy and more than one-third of the patients needing a combination of two therapies within 24 hours of ICU admission.

Multiple studies have shown that acute respiratory failure is one of the commonest reasons for ICU admission in critically ill HLM patients.[10,11,17–19] In such patients, either noninvasive or invasive MV is used. In our study MV was required in 83% patients. The mortality of patients requiring any form of MV was higher than those who did not need it (60.3% vs 25%, $p = 0.013$). Noninvasive ventilation (NIV) was initiated in 38 patients; however, of those started on NIV, 20 (52.6%) patients failed to improve and subsequently needed intubation and institution of invasive mechanical ventilation (IMV). A single-center retrospective study of 99 HLM patients of acute respiratory failure by Adda et al.[20] has reported a failure rate of NIV as 54%, and another multicentric observational study[21] performed in Italian ICUs evaluating 1,302 similar patients has reported the conversion rate of NIV to intubation and IMV as 46%. Another multicenter study from 58 Brazilian ICUs of 263 combined HLM and solid organ malignancy patients observed that 53% of patients failed to respond to the initial NIV trial and subsequently needed IMV.[22] Our rates of conversion of NIV to IMV were similar to these studies. We found that the mortality was higher among those who failed NIV, as compared to those who were intubated upfront and started on IMV (70% vs 57.5%). This finding was similar to a study by Gristina et al.,[21] which included 1,302 patients of HLM concluding higher mortality rates in those who failed initial NIV trial and required IMV as compared to those who underwent upfront IMV (77% vs 69%). Molina et al.[23] in their study evaluating impact of ventilatory management and NIV failure on outcome in hematology patients reported mortality of upfront IMV vs failed NIV as 72.2% vs 79.7%, respectively. They concluded, the risk factors associated with NIV success were age, congestive heart failure, and bacteremia. A study by Adda et al.[20] specifically looked into the predictors of failed NIV and found that the respiratory rate under NIV (32 breaths/minute vs 28 breaths/minute), longer delay between admission and NIV first use, need for vasopressors or renal replacement therapy, and acute respiratory distress syndrome (ARDS) are independent predictors of NIV failure on multivariate logistic regression. A separate study will be needed to ascertain the cause of this finding in our cohort; unfortunately, data on specific parameters of ventilation which could accurately define this were not recorded as it was not in scope of our study. Our findings of higher mortality in those who failed NIV trial vs those who were started upfront on IMV could be due to several reasons. First, the supposed benefits of NIV in improving outcome[21,23] of HLM patients might have led to overzealous attempt to use NIV as an initial therapy in absence of overt contraindications; second, we usually keep an absolute cut-off of respiratory rate as 35 breaths/minute in order to declare NIV failure, which might have led to delayed intubation; third, we did not characterize our patients based on acute respiratory failure of cardiac origin vs of noncardiac origin (ARDS), where, in former, NIV has proven benefit; and last, our unit strictly follows the protective lung ventilation protocol (tidal volume 6–8 mL/kg of predicted body weight), which is possible only when the patient is on IMV and deeply sedated. Our findings of lower mortality (57.5%) in the upfront IMV group as compared to other studies could be reflection of our adherence to the protective lung ventilation protocol. Several other studies of HLM patients needing IMV have reported high mortality but there is a large variation in outcomes, ranging from 60 to 95%.[10,11,17,19,24–26] We did not find upfront intubation and institution of IMV as an independent predictor of hospital mortality, a finding that has been reported in other studies.[10,11,17,19,24,26] In our study, need of any form of MV was found to be an independent predictor of hospital mortality. Only one other study has reported similar finding.[27]

Neutropenia was an independent predictor of mortality in our patients. This finding is similar to two old studies from Western ICUs and only one recent study from Mexico.[28–30] Most other studies did not find neutropenia as an independent predictor of mortality.[31,32] This probably reflects the importance of infrastructural aspects of caring for neutropenic patients. In our mixed medical-surgical ICU, we have only four isolation beds. Whether increasing the number of isolation beds and the number of nurses will translate into better outcomes will remain a speculation at best at present.

Apart from neutropenia and need for MV, no other factors predicted hospital mortality in our cohort. In other studies, need for vasopressors,[11,28,30] age,[33] acute respiratory failure,[10,33] SOFA,[19] and APACHE II[11,24,29,34] score have been shown to be independent predictors of mortality in ICU patients with HLM.

Our hospital outcomes are comparable to many other studies from across the world, with mortality ranging from 53 to 58%.[9,27,28,33] Barreto et al., in a cohort of HLM patients with similar SAPS III scores, however reported a comparable ICU mortality

Table 3: Univariate analysis of variables for hospital mortality

Variables	*Patients (n = 94)*	*Survivors (n = 43)*	*Nonsurvivors (n = 51)*	*p value*
Age (years) mean ± SD	41.53 ± 15.707	43.07 ± 16.589	40.24 ± 14.966	0.386
Gender male (%)	49 (52.13)	22 (44.89)	27 (55.10)	1.000
Cancer diagnosis				0.288
ALL	16 (17.02)	6 (37.5)	10 (62.5)	
AML	28 (29.79)	9 (32.14)	19 (67.86)	
NHL	36 (38.30)	20 (55.56)	16 (44.44)	
Plasma cell neoplasm	7 (7.45)	4 (57.14)	3 (42.86)	
HL	6 (6.38)	4 (66.67)	2 (33.33)	
CML	1 (1.06)	0 (0)	1 (100)	
Source of admission				0.537
Emergency room	32 (34)	17 (53.13)	15 (46.88)	
Other locations	15 (16)	7 (46.67)	8 (53.33)	
Ward	47 (50)	19 (40.43)	28 (59.57)	
Neutropenia (%)	43 (45.74)	14 (32.56)	29 (67.44)	0.023
Cancer status (%)				0.317
Controlled/remission	17 (18.09)	5 (29.41)	12 (70.59)	
Newly diagnosed	64 (68.09)	32 (50)	32 (50)	
Recurrence/progression	13 (13.83)	6 (46.15)	7 (53.85)	
MV within 24 hours (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
MV*	78 (82.98)	31 (39.74)	47 (60.26)	0.013
Any IMV[$]	60 (63.83)	23 (38.33)	37 (61.67)	0.084
Upfront IMV	40 (42.55)	17 (42.5)	23 (57.5)	0.677
Any NIV[#]	38 (40.43)	14 (36.84)	24 (63.16)	0.206
Failed NIV	20 (21.28)	6 (30)	14 (70)	0.134
Vasopressors within 24 hours (%)	49 (52.13)	18 (36.73)	31 (63.26)	0.097
Dialysis within 24 hours (%)	3 (3.19)	2 (66.67)	1 (33.33)	0.591
Mean SAPS III score ± SD	65.82 ± 10.829	62.86 ± 12.394	68.31 ± 8.673	0.018
Mean SOFA score ± SD	4.90 ± 2.744	4.44 ± 2.413	5.29 ± 2.962	0.134

SD, standard deviation; MV, mechanical ventilation; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; V: vasopressor, D: dialysis

*Patients who received any form of MV within first 24 hours in the form of only NIV, upfront IMV, or those who required IMV after failed NIV trial

[$]Patients who received any form of IMV within first 24 hours in the form of upfront IMV or those who required IMV after failed NIV trial

[#]Patients who received any form of NIV within first 24 hours that include both in whom NIV was successful or failed

Table 4: Variables predictive of in-hospital mortality on multivariate analysis

		95% confidence interval		
Variables	*Odds ratio*	*Lower*	*Upper*	*p value*
Neutropenia	2.728	1.077	6.912	0.034
MV within 24 hours of ICU admission	4.621	1.230	17.357	0.023

SAPS, simplified acute physiology score; MV, mechanical ventilation; ICU, intensive care unit

(47.8%) but much higher in-hospital mortality of 73.2%, than that seen in our patients.[35]

The ICU and hospital mortality in our study are also lower than another study from southeast Asian region that has reported ICU and hospital mortality as 55.9 and 62.5%.[36] However, exact comparison of all the studies is difficult—in view of heterogeneity in term of patient population, cancer types, usage of ICU therapies, different inclusion and exclusion criteria, type of ICU (specialized cancer vs noncancer), geographical variations of practice and patients, different patterns of data reporting, among other factors. End-of-life decision, with understanding that the patient will be offered only supportive care, was taken only in seven patients in our study. Since our study was not aimed at looking this aspect, it is difficult to say why only seven patients merited this.

The strength of our study is that the data have been collected prospectively and the study has been conducted in a specialized cancer hospital ICU of the southeast Asian region. However, there exist limitations to our study. First, as this study has been done in a specialized cancer ICU, the findings might not be applicable to general ICUs. Second, HSCT patients were not included in the study. Third, as the progression of the patient, events and the therapies initiated beyond 24 hours were not recorded in the study; these may also impact outcomes. Fourth, the number of cases, is small to look at the outcomes with respect to the type of cancer and the stage of the disease. Last, we did not record long-term outcomes and quality of life of critically ill cancer survivors.

Our outcomes are similar to those reported globally in terms of survival among critically ill patients with HLMs. This may be because this study was conducted in a tertiary cancer care center with good infrastructure and resources. Our findings suggest that

these patients should not be denied admission in Indian ICUs; rather, efforts should be directed toward optimization of care and resources to improve the outcome of these patients.

Conclusion

The HLM patients needing critical care have high acuity of illness, and acute respiratory failure is the commonest reason for ICU admission in these patients. In our study, ICU survival was more than 50% and more than 45% patients were discharged alive from the hospital. The need of MV within 24 hours of ICU admission and presence of neutropenia at ICU admission were independent predictors of hospital mortality in our study.

Authors' Contributions

Atul P Kulkarni, Jigeeshu V Divatia, and Suhail S Siddiqui conceived and designed the study. Suhail S Siddiqui, Natesh Prabu, Harish K Chaudhari, Amit M Narkhede, Satish V Sarode, and Ujwal Dhundi had substantial contribution to the acquisition of the data. Amit M Narkhede performed statistical analysis. Atul P Kulkarni, Jigeeshu V Divatia, and Suhail S Siddiqui drafted the article. All authors critically reviewed the article for important intellectual content and gave final approval of the version submitted for publication.

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