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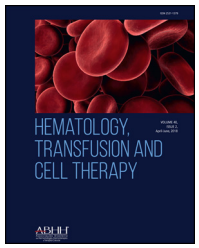

Original article

Predictors of mortality among patients with acute leukemias admitted to an intensive care unit specialized in patients with hematological disease at a Brazilian hospital

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ARTICLE INFO

Article history:
Received 19 February 2018
Accepted 7 January 2019
Available online 26 April 2019

Keywords:
Acute leukemia
Intensive care
Blood malignancies
Mortality
Sepsis

ABSTRACT

Introduction: Hematologists deal every day with high mortality rates of acute leukemia patients. Many times these patients need Intensive Care Unit (ICU) support and some general ICU teams believe that these patients have a much greater chance of dying than patients with other pathologies. In Brazil, data related to mortality rates and ICUs for acute leukemia patients are scarce.

Methods: Therefore, to assess mortality predictors in patients with acute leukemia admitted to a specialized hematological ICU, we evaluated demographics, supportive care, hospitalization time, disease status, admitting diagnosis, neutropenia, number of transfusions and Acute Physiology and Chronic Health Evaluation (APACHE)/Sepsis Related Organ Failure Assessment (SOFA) scores as possible factors associated with mortality. Data were extracted from the first admission records of 110 patients with acute leukemia admitted to the Hemocentro de Pernambuco (Hemope) ICU between 2006 and 2009.

Results: In this retrospective cohort study, 72/110 of the patients were men, and 64/110 were from the metropolitan area of Recife. The patients' age median was 43.5 years (±17.9); 67.3% had acute myeloid leukemia (AML) and 32.7% had acute lymphoid leukemia. The main admitting diagnosis in the ICU was sepsis (66.7%). The mean APACHE II score was 18.3. Of the total, 65 (59%) died, and the mortality rate was independently related to longer hospitalization ($p < 0.001$), the increase in the APACHE II score ($p < 0.038$) and having received hemodialysis ($p < 0.006$). Neutropenia, receiving multiple transfusions and using any kind of mechanical ventilation or vasoactive drug on admission were not relevant to mortality. Factors associated with higher mortality rates were: longer hospitalization, increase in the APACHE II score, and use of hemodialysis.

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https://doi.org/10.1016/j.htct.2019.01.004

Conclusion: With these data, to prevent organ lesions before admission to the ICU, a better strategy might be to reduce mortality for leukemia patients.

Introduction

Acute leukemias are disorders of hematopoietic stem cells, characterized by fast and uncontrolled proliferation of immature cells (blasts) in the bone marrow.[1] These very aggressive disorders suppress the production and normal function of bone marrow cells, causing immunosuppression. It requires urgent treatment, and the complete remission rate is high, approximately 60–75% for acute myeloid leukemia (AML).[2]

Apart from the bone marrow suppression promoted by leukemia, the use of chemotherapy (CT) drugs raises immunosuppression, resulting in frequent infectious complications, which in turn lead to organ dysfunction. Patients are often septic, with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and acute kidney failure (AKF). These conditions lead patients to require hospitalization in intensive care units (ICUs).[2,3]

The effervescence of successful anticancer therapies is linked to the better management of critically ill patients, which clamors for the rethinking of the role of intensive care, regarding indications, benefits and prognostic factors related to neoplasm patients in critical conditions. In the early 1990s, cancer survivors maintained a good quality of life and had no limitations to daily activities after admission to intensive care.[4] Despite high rates of mortality (45–87%), studies within this population of critically ill patients showed that intensive care was beneficial.[5–13] Thereafter, predictors of mortality among patients with cancer in the ICU started to be repeatedly evaluated.[3,6,13–17]

Currently, although there are many analyses on predictors of mortality among cancer patients in the ICU, reports of units specialized in exclusively treating patients with blood disease are insufficient.[18]

Thus, the aim of this study is to assess mortality risk factors among patients with acute leukemia admitted to a specialized hematological ICU.

Materials and methods

Patients and methods

This is a retrospective cohort study. All patients with acute leukemia over 16 years of age on their first admission to the ICU of the Hemocentro of Pernambuco (Hemope) Foundation Hospital between January 2006 and December 2009 had their medical records retrospectively evaluated in this study. During this period, there were 426 admissions, 137 with acute leukemia, and 110 patients met the inclusion criteria. This ICU is specialized in patients with blood disease. It is part of the Hemope Foundation Hospital, where there is a ward with 36 beds for treating acute leukemia (32), hemophilia (2) and sickle cell disease (2). This is a center of excellence in Pernambuco and neighboring states. The Research Ethics Committee approved this project under the CAEE number 11810213.5.0000.5195 2013.

The diagnosis of acute leukemia was established according to criteria of the World Health Organization (WHO), revised in 2008. The disease status was categorized as: aplasia, remission, progression or relapse. Aplasia was defined as the moment after CT when the hemoglobin (Hb) is lower than 10 g/dl, associated leukocyte count is lower than 1000 cells/mm^3 and platelets are lower than 100,000 cells/mm^3. Remission was defined as the status after CT when the patient has no active disease (<5% blasts in the bone marrow). Progression was defined as failure of therapy any time before admission or with refractory disease. Relapse was classified as a return of disease activity after a period of improvement (remission). Reasons for admission were those mentioned in the medical records and were categorized as respiratory failure of septic and nonseptic origins, acute renal failure (ARF), sepsis, sensory alterations, post-operative bleeding and shock.

The Acute Physiology and Chronic Health Evaluation (APACHE II) score was applied as a predictive mortality index within the first 24 h after admission. It is a severity classification system based upon 12 initial routine physiologic measurements (temperature, heart rate, mean arterial pressure, serum sodium, serum potassium, serum creatinine, oxygenation, hematocrit, blood cell count, Glasgow coma score), age and previous health status. An increasing score is closely related to subsequent in-hospital death.[17] To assess progression of organ failure, the Sepsis Related Organ Failure Assessment (SOFA) score was evaluated on days 1 and 3. This score has a descriptive function and individualizes the dysfunction of each organ daily.[19] The two scores are complementary and both of them were retrospectively calculated for this paper at http://www.globlarph.com/APACHEII.html and http://www.sfar.org/scores2/sofa2.html, respectively.[17,19]

Supportive care was categorized as the use of invasive or non-invasive mechanical ventilation (IMV/NIMV), vasoactive drugs (VAD) on admission, renal replacement therapy (RRT) and transfusion support. The IMV was defined as the use of an orotracheal tube at any time during the ICU stay, and the NIMV was considered every time that mechanical ventilatory support was necessary but an orotracheal tube was not; VAD was considered when the use of noradrenalin or dopamine was necessary, and; the use of any kind of hemodialysis, at least once and for any duration, defined RRT.

Statistical analysis

Core demographics, comorbidities, disease characteristics and factors associated with mortality in the ICU were evaluated using the STATA statistical software version 13.0 (StataCorp LP, College Station, TX, USA).

Results were presented in the frequency tables for qualitative variables. Descriptive statistics (mean, standard deviation, median and range) were used for continuous quantitative variables, according to the outcome in the ICU (death or survival). The outcome results were compared by nonparametric Mann–Whitney *U* tests.

For quantitative variables, measurements of central tendency and dispersion were made. In this study, considering the high mortality rate in that ICU (59%) on bivariate analysis, the prevalence rate (PR) and their 95% CIs were estimated to evaluate the correlation between the variables and death in the unit.[20,21] Variables independently associated with the mortality rate were analyzed with a multiple Cox regression (with robust variance) using variables that had *p*-values lower than 0.20 in univariate analysis. A chi-square test for linear trend was used for complete blood count (CBC) variables. Regarding non-quantitative variables, a nonparametric Mann–Whitney *U* test was used for comparison between patients who died and those who did not.

The modeling process started with the variable that had the lowest *p*-value during bivariate analysis, followed by the addition of all the others with *p*-values lower than 0.20, with just the variables with descriptive levels lower than 0.05 ($p < 0.05$) remaining for the final model. Finally, PRs were estimated for each variable in the final model with their respective confidence intervals.

Results

Sixty-five patients died during ICU hospitalization, totalling a 59.1% mortality rate. Table 1 shows demographic and clinical characteristics of the studied population, while Table 2 has hemogram data. Seventy-four out of 110 patients (67.3%) had AML, with French-American-British (FAB) subtypes classified as AML-M3 ($n = 17$, 23.0%), AML-M1 ($n = 16$, 21.6%) and AML-M2 ($n = 15$, 20.3%). The others (36/110) had acute lymphoid leukemia (ALL), 58.3% cases of B-cell (21/115) and 30.6% of the T-cell lineage (11/115).

The main admission diagnosis was acute respiratory failure (ARF) secondary to sepsis (39/110, 37.1%), followed by sepsis (37/110, 33.6%). The other causes of admission appear in Table 1. At that point, the main infection was pulmonary and 30% of the blood cultures were positive, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* being the most common agents detected.

The APACHE II scores were calculated for 85 admitted patients (77.3%), due to the lack of data in the other 25 medical records. The mean APACHE II score for these 85 patients was 18.3 (±6.4), ranging from 8 to 43, as shown in Figure 1. The SOFA score was calculated retrospectively, however, on the first day of admission, 63 patients could not have the SOFA calculated, a number that increased to 81 on the third day. Thus, the mean variation in SOFA in 27 patients was 2.7 (±3.5).

Table 1 – Characterization of patients with acute leukemia hospitalized in the ICU, according to social and demographic features, base pathology, reasons for admission, severity profile and organ dysfunction at the Hemope Foundation from 2006 to 2009.

	Number	%
Gender		
Male	72	65.5
Female	38	34.5
Age (years)		
Median (dp)	43.5 (17.9)	
City of residence		
Metropolitan area of Recife	46	41.8
Other municipalities	64	58.2
Blood condition		
AML	74	67.3
ALL	36	32.7
Leukemia status[a]		
Aplasia	40	40.4
Diagnosis	26	26.3
Progression	21	21.2
Relapse	10	10.1
Remission	2	2.0
Reasons for admission[b]		
Acute respiratory failure, septic	39	37.1
Acute respiratory failure, nonseptic	18	17.1
AKF	1	0.9
Sepsis	37	33.6
Sensory alteration	4	3.8
Bleeding	1	1.0
Oncologic emergencies	1	1.0
Post-operative	1	1.0
Ruptured spleen	3	2.9

Variables	Mean	Standard deviation
APACHE II[c]		
Mean (dp)	18.3	(6.4)
Time of hospitalization (days)[d]		
Median (dp)	19.1	(20.5)
SOFA D1[e]		
Mean (dp)	8.7	(3.6)
SOFA D3[f]		
Mean (dp)	11.1	(5.0)
ΔSOFA[g]		
Mean (dp)	2.7	(3.5)

Ignored data: (a) 11; (b) 5; (c) 25; (d) 1; (e) 63; (f) 81; (g) 83.

In regard to supportive care, 99/110 patients used mechanical ventilation (MV) of any kind, and only 21/110 needed RRT. The use of vasopressors on admission was not relevant. Among transfused patients, 52.7% received 1–5 units of leukocyte-poor packed red cells (LPPRC), and 51.8% received 1–5 platelet transfusions (Table 3).

After bivariate analysis, mortality among individuals who underwent hemodialysis was higher than those who did not ($p < 0.001$), and the use of MV might also be a factor associated with higher mortality rates ($p = 0.001$) in this scenario. We additionally found that patients who had a higher hemoglobin

Table 2 – Distribution of patients with acute leukemia admitted to the ICU and blood cell count data at admission and discharge at the Hemope Foundation from 2006 to 2009.

Variables	No.	%
Hemoglobin values at admission (g/dL)[a]		
<5	5	4.7
5–6.9	21	19.6
7–10	64	59.8
>10	17	15.9
Neutrophils values at admission (cells/mm³)[b]		
<500	50	64.9
500–999	3	3.9
1000–4999	13	16.9
5000–9999	4	5.2
10,000–30,000	6	7.8
30,001–99,999	1	1.3
≥100,000		
Hemoglobin values on discharge (g/dL)[c]		
<5	0	0.0
5–6.9	14	14.3
7–10	63	64.3
>10	21	21.4
Neutrophils values at admission (cells/mm³)[d]		
<500	38	57.6
500–999	2	3.0
1000–4999	16	24.2
5000–9999	3	4.5
10,000–30,000	7	10.6
30,001–99,999	0	0.0
≥100,000	0	0.0

Ignored data: (a) 3; (b) 33; (c) 12; (d) 44.

Table 3 – Distribution of patients with acute leukemia hospitalized in the ICU according to supportive therapies applied. Hemope Foundation, 2006 to 2009.

Variables	Number	%
Mechanical ventilation		
None	11	10.0
IMV	77	70.0
IMV or NIMV	22	20.0
Kidney support		
None	89	80.9
Yes	21	19.1
Leukocyte-poor packed red cells		
Did not use	25	22.7
1–5	58	52.7
6–10	11	10.0
>10	16	14.5
Platelet concentrate (transfusions)		
Did not use	19	17.3
1–5	57	51.8
6–10	11	10.0
>10	23	20.9

IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation.

value ($p = 0.039$) and more than 500 neutrophils/mm³ in the blood count ($p = 0.014$) at admission were less likely to die (Table 4).

The summary and comparison of the central tendency measurements of these variables among Hemope-ICU patients appear in Table 5. Variables independently associated with the mortality rate in this population were evaluated with a multiple Cox regression with robust variance. In this model, the following variables were included: having undergone RRT, used IMV, stayed longer in the ICU, presented higher APACHE II scores, presented higher Hb values on admission, had an increase in neutrophils on discharge, and had a higher number of platelet transfusions. The SOFA values were not analyzed due to the significant loss of information.

Among the sample of patients with acute leukemia in this study, the mortality in the Hemope ICU was independently associated with RRT [PR_{adj} 1.47 (1.12–1.94)], longer hospitalization [PR_{adj} 1.01 (1.00–1.01)] and higher APACHE II scores [PR_{adj} 1.02 (1.00–1.04)]. Mortality in this setting for patients who underwent RRT was 47% higher than among those who did not ($p = 0.006$), regardless of the ICU hospitalization time and the APACHE II score. Death risk also increased by 1% ($p = 0.001$) for each additional day at the unit, independently of the APACHE II score and of having RRT or not. In addition,

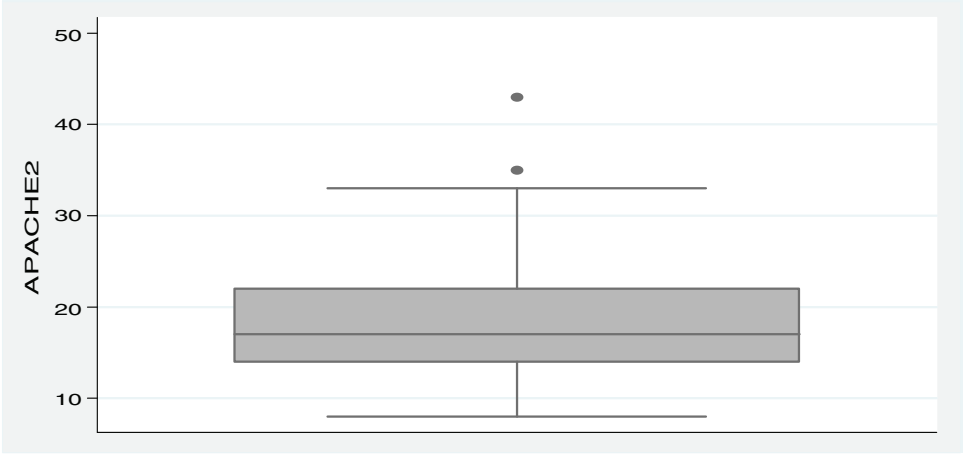

Figure 1 – APACHE II scores in patients with acute leukemia hospitalized in the ICU at the Hemope Foundation from 2006 to 2009.

Table 4 – Distribution of patients with acute leukemia hospitalized in the ICU, according to their characteristics and occurrence of death, at the Hemope Foundation from 2006 to 2009.

Variables	Total	Decease intra ICU number (%)	PR (CI 95%)	p
Gender				0.564
Male	72	44 (61.1)	1	
Female	38	21 (55.3)	0.90 (0.64–1.27)	
Blood condition				0.911
AML	74	44 (59.5)	1	
ALL	36	21 (58.3)	0.98 (0.70–1.37)	
Reason for admission				0.135
Acute respiratory failure, septic	39	25 (64.1)	1	
Acute respiratory failure, nonseptic	18	8 (44.4)	0.69 (0.39–1.23)	
AKF	7	6 (85.7)	1.34 (0.91–1.96)	
Sepsis	31	16 (51.6)	0.81 (0.53–1.22)	
Others	10	6 (60.0)	0.94 (0.53–1.64)	
Hemoglobin levels on admission (g/dL)				**0.039**[a]
>10	17	8 (47.1)	1	
7–10	64	36 (56.3)	1.19 (0.69–2.07)	
<7	26	20 (76.9)	1.63 (0.94–2.83)	
Neutrophil count on admission (cells/mm^3)				0.091
≥500	27	13 (48.2)	1	
<500	50	35 (70.0)	1.45 (0.94–2.24)	
Hemoglobin levels on discharge (g/dL)				0.292[a]
>10	21	11 (52.4)	1	
7–10	63	36 (57.1)	1.09 (0.69–1.73)	
<7	14	10 (71.4)	1.36 (0.80–2.31)	
Neutrophil count on discharge (cells/mm^3)				**0.014**
≥500	28	11 (39.3)	1	
<500	38	28 (73.7)	1.88 (1.14–3.10)	
IMV				**0.001**
None	33	1 (3.0)	1	
Yes	77	64 (83.1)	27.4 (3.9–191.2)	
Kidney support				**<0.001**
None	89	47 (52.8)	1	
Yes	21	18 (85.7)	1.62 (1.25–2.11)	
Leukocyte-poor packed red cells (IU)				0.634
Did not use	25	14 (56.0)	1	
≤10	69	40 (58.0)	1.04 (0.69–1.55)	
>10	16	11(68.8)	1.28 (0.76–1.99)	
Platelet concentrate (transfusions)				0.152
Did not use	19	9 (47.4)	1	
≤10	68	39 (57.4)	1.21 (0.72–2.03)	
>10	23	17 (73.9)	1.56 (0.91–2.66)	

PR: prevalence rate; IMV: invasive mechanical ventilation; LPPRC: leukocyte-poor packed red cells; PC: platelet concentrate. Bold values- the Values with p < 0,001 or tending to 0,001

[a] Chi-square test for linear trend.

the increase of one unit in the APACHE II score relates to a 2% increase in the mortality rate ($p = 0.038$), independently of having undergone RRT or not (Table 6).

Discussion

We analyzed 110 patients with acute leukemias during critical illness. This is a rarely found patient profile in general ICUs and there are few ICUs which are specialized in hematological diseases around the world. Therefore, describing this population and evaluating predictors of outcome are very important to improve knowledge, not only about their critical illness, but also about their prognosis during the stay in the ICU.

We found a high mortality rate in the studied population (59.1%), being RRT the most important risk factor. This mortality seems not to be different from those previously reported by Azoulay et al. and Abraham et al. in cancer patients in the ICU.[5,6] Twenty-nine percent of the patients were admitted with AKF and the mortality rate was 85% for those who needed hemodialysis. These data are similar to those formerly reported by Santos et al. Twelve percent to 49% of the AKF rate among cancer patients and a higher mortality were related to RRT (80%). Although these results are poor, they are in line

Table 5 – Descriptive statistics of quantitative variables of patients with acute leukemia, according to occurrence of death, at the Hemope Foundation from 2006 to 2009.

Variables	Death		p-Value
	No (n = 45)	Yes (n = 65)	
Age	45	65	0.292
APACHE2[a]	31	54	0.025
Duration of hospitalization (days)[b]	44	65	0.002
SOFA D1[c]	10	37	0.002
SOFA D3[d]	6	23	0.003
DeltaSOFA[e]	5	22	0.004

Ignored data (a) 25; (b) 11 (c) 63; (d) 81; (e) 83.

Table 6 – Estimation of the mortality prevalence ratio among patients with acute leukemia, with the multiple Cox regression model.

Variables	PR_{cr}	PR_{adj} (CI 95%)	p-Value
With kidney support	1.62	1.47 (1.12–1.94)	0.006
Time of hospitalization (days)	1.01	1.01 (1.00–1.01)	0.001
APACHE II	1.03	1.02 (1.00–1.04)	0.038

PR_{cr}: crude prevalence ratio; PR_{adj}: adjusted prevalence ratio.

with the outcomes found in non-cancer patients admitted to the ICU with AKF.[22,23]

Other important predictors of mortality were longer hospitalization time at the unit and increase in the APACHE II score. We did not find any description related to the length of hospitalization in other studies. And although the increase in the APACHE II score has been associated with a higher chance of death in the ICU, this index was not able to properly estimate mortality in this study because an average APACHE II score of 18 predicts a mortality rate of 20–30%, which is very far from the mortality rates in our study. Despite this disparity, similar data have already been described in publications by Hampshire and Jonge.[24,25]

Sepsis was the reason for admission for almost 70% in this study. Sepsis is a frequent condition among patients admitted to ICUs and also among patients with cancer. Its mortality rate is around 30–50%, not only for cancer patients, but also for the general population during critical illness. Therefore, despite having a high mortality rate in our study, it was not so different from the rate found among septic patients without cancer. Consequently, we must think about leukemic patients in this setting, as patients with a severe life-threatening disease, but with an almost 50–70% chance of surviving, when admitted to the ICU.[26–29]

There was also a tendency for lower mortality when there was a higher hemoglobin level on admission ($p = 0.039$) and when neutrophil levels were higher than 500 cells/mm^3 on discharge ($p = 0.014$). One can think that recovering from neutropenia may be a protecting factor against mortality in this scenario, but at this point, as also mentioned in former publications, studies with a greater number of patients are needed to confirm or refute this trend.[26]

Finally, the predictors of mortality found in our study are also in accordance with ICU studies related and not related to cancer patients. In this manner, it is important to note that to offer ICU support to leukemic patients is to give them a chance to survive after critical illness. Of course, multicenter prospective studies with a control population may be necessary to elucidate many other questions.

Conclusion

Our mortality rate was high, but not different from patients admitted to ICUs for sepsis without leukemias or other oncologic diseases. Predictors of higher mortality were: longer hospitalization, day-by-day increasing APACHE II scores and undergoing hemodialysis, which is also similar to the general population with critical illness.

All these data are important for public health because they call attention to the fact that factors associated with death in the leukemic population are not different from the reasons for death in the general population during critical illness. Therefore, it might be important to revisit admission policies in the ICU, and perhaps, to modify the ranking of priority related to leukemia patients, which may improve the outcomes after critical illnesses in this population.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We would like to thank Prof. Dr. Cesar de Almeida Neto of the Fundação Pró-Sangue, Hemocentro de São Paulo and Department of Medical Sciences at the College of Medicine, University of São Paulo, for his insightful comments, which improved our manuscript.

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