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Characteristics and outcomes of autologous hematopoietic stem cell transplant recipients admitted to intensive care units: A multicenter study

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ABSTRACT

Purpose: Studies of critically ill hematopoietic stem cell transplantation (HSCT) recipients have mainly been single-center and focused on allogenic HSCT recipients. We aimed to describe a cohort of autologous HSCT with an unplanned intensive care unit (ICU) admission.
Methods: This study is a retrospective cohort study of autologous HSCT performed as a treatment for a hematological malignancy, during their first unplanned ICU admission in 50 hospitals in Brazil. We assessed the hospital mortality and the association between mechanical ventilation, vasopressors, and renal replacement therapy and hospital mortality in autologous HSCT recipients, adjusted for potential confounders.
Results: We included 301 patients. Multiple myeloma was the most common malignancy driving to HSCT. ICU and hospital mortality were 22.9% and 37.5%, respectively. After adjustment for potential confounders, mechanical ventilation (OR = 9.10; CI 95%, 4.82–17.15) was associated with hospital mortality, but vasopressors (OR = 1.43; CI 95%, 0.77–2.64) and renal replacement therapy (OR = 1.30; CI 95%, 0.63–2.66) were not.
Conclusions: In this large cohort of critically ill autologous HSCT recipients, mechanical ventilation was the only organ support-therapy associated with increased mortality in autologous HSCT recipients.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is standard of care for many hematological malignancies [1]. HSCT recipients may develop life-threatening complications such as opportunistic infections and suffer from conditioning regime toxicity that may require intensive care unit (ICU) admission [2].

Although there is a vast literature on critical care of HSCT recipients, most studies have focused almost exclusively on allogenic HSCT recipients [3-5]. It is estimated that 5% of autologous HSCT recipients require ICU admission [6-9]. Very few studies addressed characteristics and outcomes of critically ill autologous HSCT recipients. These studies were

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single-center and comprised few patients [7,9]. Therefore, in a different manner from critically ill allogenic HSCT recipients, there is a gap on the impact of ICU life-sustaining measures on autologous HSCT patients' mortality.

Thus, we aimed to describe the characteristics and outcomes of autologous HSCT recipients with unplanned ICU admission in a Brazilian multicenter study. Additionally, we aimed to assess the association between organ support therapies and hospital mortality in autologous HSCT patients.

2. Methods

2.1. Study design and setting

This was a retrospective study on prospectively collected data from two databases. The first database is from Orchestra study [10]. From Orchestra, we included data from ICUs of 49 hospitals in several Brazilian cities which reported admitting HSCT recipients from January 2016 to December 2018. The second database is from A.C. Camargo Cancer, a cancer center in São Paulo, Brazil, which had data on ICU admission of HSCT recipients from January 2010 to December 2018. A.C. Camargo Cancer Center Local Ethics Committees (CAAE: 86761718.0.0000.5432) and the Brazilian National Ethics Committee (CAAE: 19687113.8.1001.5249) approved the study without the need for informed consent, since all data were fully anonymized before researchers could access them.

We followed the STROBE guidelines [11] and the guidance from editors of respiratory, critical care and sleep journals for reporting causal inference studies [12].

2.2. Patients

We included all patients aged 18 years or older who were admitted to the participant ICUs for medical and urgent surgical reasons during their first year after a HSCT performed as a treatment for a hematological malignancy during the study period. We included data only from patients' first ICU admission. We excluded patients admitted after elective surgeries, who receive a HSCT transplant due to conditions other than hematological malignancies, and patients with decisions to forgo life sustaining therapies. None of the included centers had a specific ICU admission policy for HSCT recipients.

2.3. Data collection

We retrieved patients' data from the Epimed Monitor System (Epimed Solutions, Rio de Janeiro, Brazil) [13] as in other analysis of the Orchestra study and from the local database from A.C. Camargo Cancer Center. Trained healthcare workers inserted all clinical data in both databases. All data were deidentified. We collected data on patients' sex and age, type of ICU admission (medical or urgent surgical), hematological malignancy (leukemia, lymphoma, multiple myeloma or other), performance status before hospital admission (evaluated by Eastern Cooperative Oncology Group [ECOG] categorized as absent/minor impairment, ie, ECOG 0 or 1, moderate impairment, ie, ECOG 2 or severe impairment, ie, ECOG 3 and 4) [14], comorbidities, Charlson Comorbidity Index (CCI), the Simplified Acute Physiology Score (SAPS 3) [15,16], the Sequential Organ Failure Assessment (SOFA) [17] at admission, use of organ support during ICU stay (vasopressors, noninvasive and invasive mechanical ventilation, and renal replacement therapy), ICU and hospital length of stay (LOS), ICU and hospital mortality.

2.4. Statistical analysis

We did not perform power calculation, instead we present all available data from the included patients, thus the sample size was pragmatic. All data are presented as frequencies (percentages) for categorical variables and as means (standard deviations) or medians (interquartile range – IQR) for continuous variables. We used chi-square test of independence for categorical variables and independent samples *t*-test test or Mann-Whitney test for continuous variables to compare patients who were alive or deceased at hospital discharge.

Our outcome of interest was hospital mortality. We assessed the association between organ support life-sustaining therapies during ICU stay (invasive mechanical ventilation, vasopressors, and renal replacement therapy) and hospital mortality. We built a direct acyclic graphic (DAG) to identify potential confounding variables to each of the three exposures. We included in the models only variables associated with the exposure (invasive mechanical ventilation, vasopressors, and renal replacement therapy) and the outcome (hospital mortality) (Fig. S1-S3). We assessed the association between organ support life-sustaining therapies during ICU stay and hospital mortality in a simple logistic regression (unadjusted model) and in a mixed effect logistic regression model, with ICU as a random-effect, and age, performance status, CCI, type of hematological malignancy and SOFA at admission as covariates (adjusted model). Odds ratio (OR) and 95% confidence intervals (CI 95%) were calculated for all variables. There were no missing data for all included variables in the models. We also generated survival curves using the Kaplan-Meier methodology. We censored patients at discharge or at 30 days. We used R version 4.1.1.1 for all analysis.

3. Results

A total of 369 autologous HSCT recipients were admitted to participating ICUs during the study period, of whom 68 were excluded from the analysis (Fig. S4).. We included 301 patients in the study. Multiple myeloma was the most common hematologic malignancy leading to autologous HSCT. Sepsis was the main reason for admission to ICU (Table 1).

Sixty-nine (22.9%) and 113 (37.5%) patients died at ICU and hospital, respectively. Deceased patients at hospital had higher SAPS 3 and SOFA scores at admission, and had longer ICU and hospital LOS (Table 1). Fig. 1 represents the 30-day patients' survival.

3.1. Use of organ support life-sustaining therapies

There were 145 (48.2%) patients who required at least one organ support life-sustaining therapy for 24 h or more during ICU stay. Vasopressors, mechanical ventilation, and renal replacement therapy were required by 107 (35.5%), 90 (29.9%) and 52 (17.3%) patients, respectively. Deceased patients at hospital needed the three-organ support life-sustaining therapies more frequently than patients who were alive at hospital discharge. Hospital mortality varied greatly according to which organ support therapies patients required, ranging from 13.5% for those who required only vasopressors to 75.8% for those who required mechanical ventilation and vasopressors combined. Patients who needed mechanical ventilation, but not vasopressors or renal replacement therapy had a hospital mortality of 73.9% (Fig. 2). The median duration of mechanical ventilation was 5.0 (IQR 1.0–9.75) days in survivors and 4.0 days (1.0–11.25) days in non-survivors ($p = 0.81$).

Mechanical ventilation (OR = 9.60; CI 95%, 5.51–17.22), vasopressors (OR = 2.33; CI 95%, 1.34–3.81) and renal replacement therapy (OR = 2.25; CI 95%, 1.23–4.14) were all associated with hospital mortality in the unadjusted analysis. However, when adjusted for the predefined potential confounders (Figs. S1-S3), mechanical ventilation (OR = 9.10; CI 95%, 4.82–17.15) was associated with hospital mortality, but vasopressors (OR = 1.43; CI 95%, 0.77–2.64) and renal replacement therapy (OR = 1.30; CI 95%, 0.63–2.66) were not.

4. Discussion

Our study describes a large population of critically ill autologous HSCT recipients who were admitted to ICU in several centers in Brazil.

Table 1
Patients' characteristics.

	All patients ($n = 301$)	Alive ($n = 188$)	Deceased ($n = 113$)	p
Age, mean (±SD)	55.6 (±13.0)	56.0 (±12)	55.0(±14)	0.53
Sex, n (%)				0.77
Male	179 (59.5)	113 (60.1)	66 (58.4)	
Female	122 (40.5)	75 (39.9)	47 (41.6)	
Charlson Comorbidity Index, mean (±SD)	3.1 (±1.8)	3.1 (±1.7)	3.1 (±1.8)	0.94
Hematological Tumor, n (%)				0.47
Multiple myeloma	167 (55.5)	106 (56.4)	61 (54.0)	
Lymphoma	102 (33.9)	63 (33.5)	39 (34.5)	
Leukemia	28 (9.3)	18 (9.6)	10 (8.8)	
Performance Status, n (%)				0.10
ECOG 0–1	217 (72.1)	143 (76.1)	74 (65.5)	
ECOG 2	62 (20.6)	35 (18.6)	27 (23.9)	
ECOG 3–4	20 (6.6)	9 (4.8)	11 (9.7)	
Type of admission, n (%)				0.26
Medical	294 (97.7)	182 (96.8)	112 (99.1)	
Urgent surgical	7 (2.3)	6 (3.2)	1 (0.9)	
Reason for admission, n (%)				0.13
Sepsis	143 (47.5)	83 (44.1)	60 (53.1)	
Cardiovascular	46 (15.3)	33 (17.6)	13 (11.5)	
Respiratory	33 (11.0)	15 (8.0)	18 (15.9)	
Neurological	21 (7.0)	14 (7.4)	7 (6.2)	
Metabolic disturbances	10 (3.3)	6 (3.2)	4 (3.5)	
SAPS 3, mean (±SD)	67.8 (16.3)	64.4 (±16)	73.3 (±15.5)	<0.01
SOFA, mean (±SD)	6.1 (4.2)	5.3 (±3)	7.5 (±5)	<0.01
Noninvasive ventilation, n (%)	72 (23.9)	36 (19.1)	36 (31.9)	<0.01
Invasive mechanical ventilation, n (%)	90 (29.9)	24 (12.8)	66 (58.4)	<0.01
Vasopressors, n (%)	107 (35.5)	53 (28.2)	54 (47.8)	<0.01
Renal replacement therapy, n (%)	52 (17.3)	24 (12.8)	28 (24.8)	<0.01
ICU LOS (days), mean (±SD)	5.7 (±7)	4.4 (±5)	7.8 (±8)	<0.01
Hospital LOS (days), mean (±SD)	29.3 (±36)	25.7 (±27)	46.2 (±35)	<0.01

AIDS: Acquired Immune Deficiency Syndrome. ECOG: Eastern Cooperative Oncology Group. ICU: Intensive Care Unit. LOS: Length of Stay. SAPS: Simplified Acute Physiology Score. SOFA: Sequential Organ Failure Assessment.

More than a third of all admitted patients died at hospital. Although all recorded ICU organ support life-sustaining therapies were associated with increased mortality in the unadjusted analysis, only invasive mechanical ventilation use remained associated with increased hospital mortality after adjustment for potential confounders.

Autologous and allogenic HSCT are different treatments, with different indications and patients' selection. Therefore, any study presenting outcomes of both types of HSCT recipients when admitted to ICU should be analyzed with caution [18]. Previous studies which included autologous and allogenic HSCT recipients admitted to ICU showed higher hospital mortality rates for allogenic HSCT recipients [19,20]. Few studies focused solely on critically ill autologous HSCT recipients. Trinkaus et al. included only 33 patients in a single-center study from 2001 to 2016 and observed a hospital mortality of 38% [9]. Kerhuel et al. studied 27 patients admitted to ICU after an autologous HSCT for the treatment of lymphomas and observed an ICU mortality of 18.5% [7]. In our

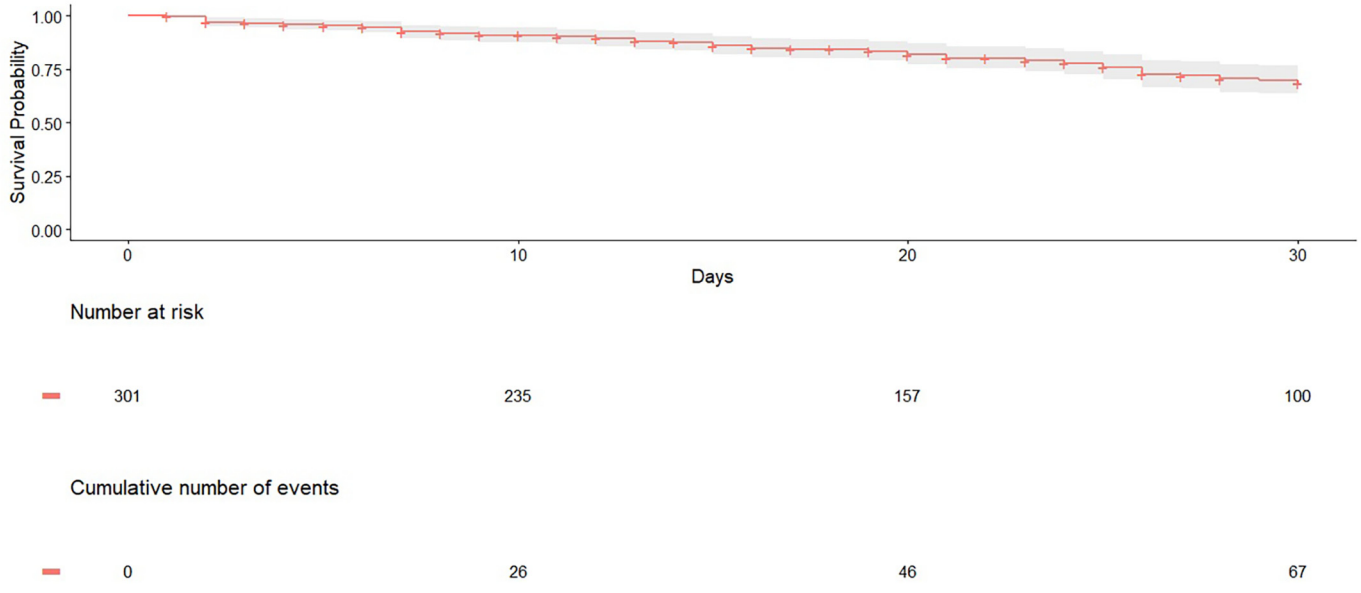

Fig. 1. 30-day survival of Hematopoietic Stem Cell Transplant recipients admitted to ICU.

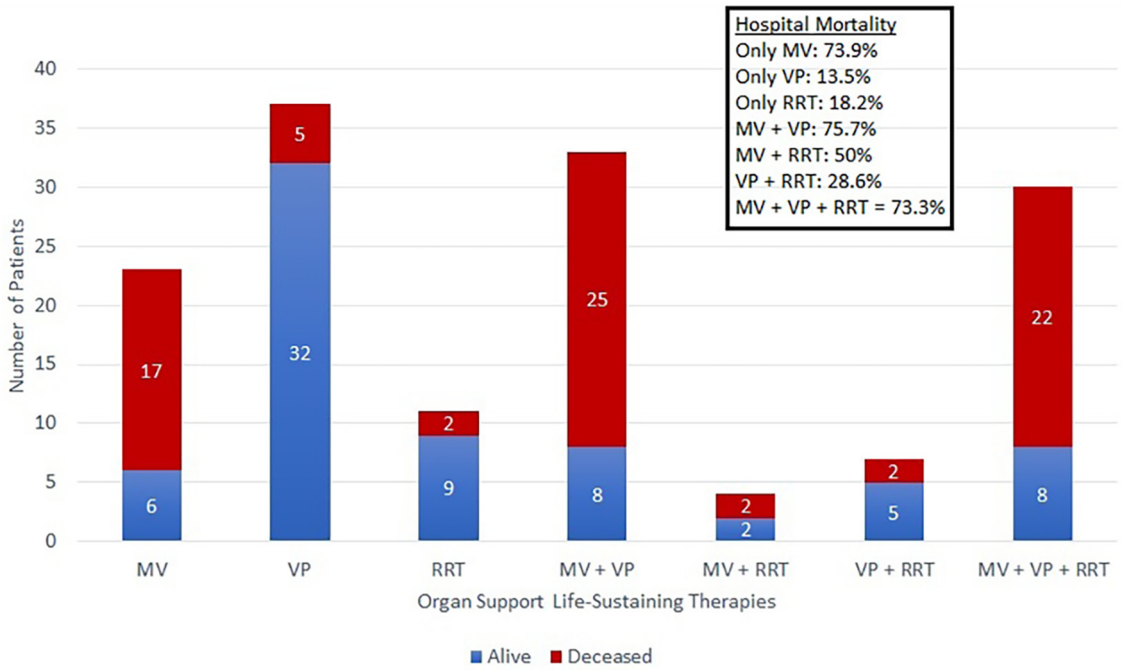

Fig. 2. Number of alive and deceased patients according to the use of each organ support life-sustaining therapy isolated or in combination.
MV: Mechanical ventilation. RRT: Renal replacement therapy. VP: Vasopressors.

multicenter study, we found similar mortality rates. These rates are similar to those of patients with hematological malignancies who were not submitted to HSCT but had an unplanned admission to ICU [21,22].

In the present study, patients who required invasive mechanical ventilation had a much higher hospital mortality than those who did not receive invasive mechanical ventilation (58.4 vs. 12.8%). An older single-center study had showed a hospital mortality of 74% for autologous HSCT recipients who received mechanical ventilation [23]. Once more, our results are similar to other studies of critically ill patients with hematologic malignancies [21]. We also demonstrated that invasive mechanical ventilation use was strongly associated with increased mortality in autologous HSCT recipients, even when adjusted for potential confounders (OR = 9.10; CI 95%, 4.82–17.15). A recent systematic review and meta-analysis of 18 studies which included 2342 allogenic HSCT recipients showed mechanical ventilation was strongly associated with ICU mortality (OR = 12.2; CI 95%, 6.2–23.7) [3]. Thus, although critically ill allogenic or autologous HSCT recipients have different outcomes, invasive mechanical ventilation use seems to impose similar risks for both types of HSCT recipients. Therefore, we believe it is of paramount importance that clinicians caring for HSCT patients are aware of the high mortality risk associated with acute respiratory failure eventually leading to mechanical ventilation.

On the other hand, unlike allogenic HSCT recipients [3], use of vasopressors and renal replacement therapy were not associated with hospital mortality in our study, after adjustment for confounders. This is in accordance with some [24] but not all [22] cohorts of critically ill patients with hematologic malignancies.

Our study presents one of the largest cohorts of autologous HSCT recipients. Although rates of ICU admission of autologous HSCT recipients is lower than that of allogenic HSCT recipients [4,7,9,25], this type of transplant is more commonly performed and understanding the prognostic factors when patients become critically ill is of paramount importance.

Our study also has several limitations. First, our data is based on two databases of ICU patients. Thus, we do not have specific data on the malignancies which led to the HSCT and neither on details of the HSCT, such as the conditioning regimen. Second, the study was performed in a single country and, therefore, specific cultural ICU admission policies and decisions on withholding or withdrawal of life-sustaining therapies may have impacted on the results. Nevertheless, the use of life support therapies during ICU stay and ICU and hospital mortality rates in our study were similar to other studies. Third, each database encompasses different time periods. However, only 13 included patients had an ICU admission before 2016. Probably, this is a small number to have any effect on our results.

In conclusion, in this large multicenter cohort of autologous HSCT recipients with unplanned ICU admissions, hospital mortality was of 37.5%, a percentage similar to critically ill patients with hematologic malignancies but who were not submitted to HSCT. Mechanical ventilation, but not vasopressors or renal replacement therapy was associated with increased hospital mortality. Thus, acute respiratory failure leading to mechanical ventilation should be considered when establishing care planning for these patients.

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CRediT authorship contribution statement

Antonio P. Nassar: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Project administration. **Letícia V.F. Archanjo:** Conceptualization, Data curation, Writing – original draft. **Otavio T. Ranzani:** Methodology, Formal analysis, Writing – review & editing. **Fernando G. Zampieri:** Data curation, Writing – review & editing. **Jorge I.F. Salluh:** Data curation, Writing – review & editing. **Genes F.R. Cavalcanti:** Data curation, Writing – review & editing. **Carlos E.N. Moreira:** Data curation, Writing – review & editing. **William N. Viana:** Data curation, Writing – review & editing. **Roberto Costa:** Data curation, Writing – review & editing. **Ulisses O. Melo:** Data curation, Writing – review & editing. **Christian N. Roderjan:** Data curation, Writing – review & editing. **Thiago D. Correa:** Data curation, Writing –

review & editing. **Samantha L.S. de Almeida:** Data curation, Writing – review & editing. **Luciano C.P. Azevedo:** Data curation, Writing – review & editing. **Marcelo O. Maia:** Data curation, Writing – review & editing. **Victor S. Cravo:** Data curation, Writing – review & editing. **Fernando A. Bozza:** Data curation, Writing – review & editing. **Pedro Caruso:** Methodology, Writing – review & editing, Supervision. **Márcio Soares:** onceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

MS is founder of Epimed Monitor®, an electronic healthcare system used to collect data and track ICU quality metrics. FGZ has received grants for investigator-initiated studies from Ionis Pharmaceuticals (USA), Bactiguard (Sweden) and Brazilian Ministry of Health, none related to the scope of this study.

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