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Low serum albumin levels prior to pediatric allogeneic HCT are associated with increased need for critical care interventions and increased 6-month mortality

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Abstract

Poor nutritional status in HCT patients is a negative prognostic factor. There are no pediatric studies evaluating albumin levels prior to HCT and need for critical care interventions. We hypothesized that pediatric patients with low albumin levels, routinely measured 30 days (±10 days) prior to allogeneic HCT, have a higher risk of critical care interventions in the post-transplant period. We performed a 5-year retrospective study of pediatric patients who underwent allogeneic HCT for any indication. Patients were categorized based on albumin level. Hypoalbuminemia was defined as <3.1 g/dL. A total of 73 patients were included, with a median age of 7.4 years (IQR 3.3, 13.2). Patients with hypoalbuminemia had higher needs for critical care interventions including non-invasive ventilation (44% vs 8%, *P*=.01), mechanical ventilation (67% vs 17%, *P*<.01), and vasoactive therapy (56% vs 16%, *P*=.01). Patients with hypoalbuminemia also had a higher 6-month mortality (56% vs 17%, *P*=.02). Our data demonstrate that children undergoing allogeneic HCT with hypoalbuminemia in the pretransplant period are more likely to require critical care interventions and have higher 6-month mortality. These findings identify an at-risk population in which nutritional improvements may be instituted prior to HCT in hopes of improving outcomes.

Keywords

critical care; nutritional status; pediatrics; stem cells; transplantation

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

1 | INTRODUCTION

Poor nutritional status prior to HCT is a negative overall prognostic factor.[1–3] Well-nourished patients have a shorter time to engraftment.[1] Patients are at risk for poor nutritional status both before and after HCT. Prior to transplantation, nearly all patients receive high-dose conditioning chemotherapy and/or systemic irradiation, both of which can lead to digestive tract malabsorption and nutritional deficiencies.[4] Post-transplant, patients receive prolonged courses of immunosuppressive medications that can affect the body's ability to absorb nutrients, due in part to mucositis.[5,6] In adults, malnutrition prior to HCT was associated with increased length of hospital stay and time to engraftment.[7,8] Proper nutritional status is crucial for improving quality of life and immune reconstitution, and reducing risk of infection.[4]

Although there are several studies describing overall nutritional status pre- and post-HCT, there are little data on pretransplant protein balance and outcomes. Most data on overall prognosis and protein balance are based on albumin levels and are derived from adult HCT patients. In adults, pretransplant hypoalbuminemia has been associated with increased mortality.[9,10] In studies evaluating pediatric HCT patients, investigators to date have looked at bone mineral densities, BMI, and vitamin D levels as markers of nutritional status.[1,11] A recent study of critically ill children found that hypoalbuminemia at admission to the PICU is associated with higher 60-day mortality and longer duration of mechanical ventilation.[12] Another study of critically ill children demonstrated hypoalbuminemia at PICU admission was associated with a greater frequency of organ failure compared to the normal albumin group.[13] The relationship between pre-HCT albumin levels and outcomes post-transplantation in pediatric HCT recipients has not been investigated.

The primary objective of our study was to determine whether there is an association between hypoalbuminemia in the pre-HCT period, routinely measured 30 days (±10 days) prior to transplant, and the need for critical care interventions. Additionally, we investigated an association with hypoalbuminemia and 6-month mortality. We hypothesized that pediatric patients with low albumin levels prior to undergoing allogeneic HCT have a higher need for critical care interventions in the post-transplant period and increased 6-month mortality.

2 | METHODS

A retrospective cohort study was conducted of pediatric patients who underwent allogeneic HCT for any indication between January 1, 2010, and December 31, 2014, at our institution. Institutional review board approval was obtained prior to start of the study.

2.1 | Patient population

Patients less than 25 years of age who had pre-HCT laboratory data at day negative 30 (±10 days) and underwent an allogeneic HCT for any indication were included in the study. At our institution, patients undergoing HCT routinely have pretransplant laboratory data drawn at day negative 30 (±10 days). All sources of HCT and donor types were included. Patients were excluded if they received an autologous HCT and/or if they had missing laboratory

data prior to transplant. In addition, all data from a patient's second transplant were excluded.

2.2 | Data collection

Data were taken from the electronic medical record and entered into our institution's Research Electronic Data Capture database.[14] The following demographic and transplant data were collected: age, gender, date of HCT (considered day 0), height and weight at day negative 30 (±10 days), indication for transplant, whether the patient had relapsed disease, donor source (bone marrow, cord blood, or peripheral blood stem cells), donor match, and whether or not the patient was related to the donor. We also collected data on whether or not the patient was diagnosed with hepatic VOD and/or GVHD in the post-transplant period.

Based on the CDC and Prevention nutrition surveillance guidelines, patients were defined as underweight at day negative 30 if they were less than the 5th percentile on their respective gender-specific growth charts.[15] Using the CDC recommendations, we used World Health Organization weight-for-length growth charts for infants and children aged 0–2 years of age, and CDC BMI-for-age growth charts for children aged 2 years and older.[16]

Nutritional data were collected at day negative 30 (±10 days). This included albumin (g/dL) and feeding regimen (ie, regular diet, feeding tube, parenteral nutrition). We defined feeding tube as the use of a nasogastric tube, nasojejunal tube, gastrostomy tube, jejunostomy tube, and/or a gastrojejunostomy tube.

Outcome data included critical care interventions and mortality. We defined critical care interventions a priori as the use of non-invasive ventilation (ie, CPAP or BiPAP), invasive mechanical ventilation requiring intubation, and use of vasoactive therapy. Mortality data were collected at 6 months post-transplant, overall mortality and cause of mortality.

2.3 | Statistical analysis

Bivariate analyses for comparing hypoalbuminemia and normal albumin groups were conducted for various demographic and clinical variables. Continuous variables are expressed as medians with IQR and were compared using Wilcoxon rank sum test. Categorical variables are expressed as absolute counts with percentages and were compared using Fisher's exact test or chi-squared analysis as appropriate. Due to the variability in the definitions of hypoalbuminemia in prior manuscripts, a sensitivity analysis was completed using single logistic regression to determine an ideal cut point for albumin levels at day negative 30. The optimal cut point for albumin levels was defined as 3.1 g/dL, and hypoalbuminemia was defined as <3.1 g/dL. We analyzed our outcome data using this cut point to evaluate for a statistically significant difference between the two groups. All patients were categorized into two groups: hypoalbuminemia or normal albumin level.

3 | RESULTS

During our study period, 73 patients met inclusion criteria for review. Demographics from the entire cohort, stratified by albumin status, are displayed in Table 1. Patients who were transplanted due to immunodeficiency were more likely to have hypoalbuminemia prior to

transplantation. Donor source was not different between the hypoalbuminemia group and those that had a normal albumin level. There was also no significant difference between albumin level pretrans-plant and method of nutritional delivery.

3.1 | Hypoalbuminemia and critical care interventions

Hypoalbuminemia prior to transplant was associated with an increase in critical care interventions in the post-transplant period (Table 2). These critical care interventions included non-invasive ventilation, mechanical ventilation, and vasoactive therapy.

3.2 | Hypoalbuminemia and post-transplant complications

There was no significant difference in the rate of VOD or GVHD between the normal albumin group and those with hypoalbuminemia. GVHD was diagnosed in 22% of patients with hypoalbuminemia vs 25% of patients with normal albumin levels (P=1.00). VOD was diagnosed in 22% of patients with hypoalbuminemia vs 16% of patients with normal albumin levels (P=.64).

3.3 | Hypoalbuminemia and mortality

There was a significant association between a low albumin level and 6-month mortality. Those in the hypoalbuminemia group had a higher mortality at 6 months post-HCT compared to the normal albumin group (56% vs 17%, P=.02). Overall survival was also significantly different, as those in the hypoalbuminemia group had increased overall mortality compared to the normal albumin group (63% vs 22%, P=.02). Cause of mortality was not different between the groups (Table 3).

4 | DISCUSSION

Our study showed that hypoalbuminemia in pediatric patients prior to allogeneic HCT is associated with increased need for critical care interventions and increased 6-month and overall mortality. This is an important finding because hypoalbuminemia may indicate poor nutritional status and negative protein balance in this patient population. Hypoalbuminemia may also be a marker of inflammation. Thus, low body mass in combination with chronic inflammation in our patients can be reasons for this hypoalbuminemia. Our results may help to identify a population of patients that are at risk for poor outcomes following HCT.

Pediatric patients may be at particularly high risk for poor nutritional status. This may be because children are more prone to nutritional deficiencies in the pretransplant period. This can be due to their diseases and related treatments, as well as increased nutritional requirements for growth and neurodevelopment.[17,18] Additionally, the developmental age of the child may make cooperation with a well-balanced diet or dietary supplementation difficult. Bicakli et al.[19] showed that the use of nasogastric tube feedings in pediatric patients who were in the process of undergoing a stem cell transplantation was successful in either maintaining or improving weight gain in those patients. Given our data showing an association between pretransplant hypoalbuminemia and poor clinical outcomes, clinicians could consider initiating supplemental enteral tube feedings if these children present with

hypoalbuminemia prior to transplantation. Optimizing nutritional status early on might be one way of improving albumin levels, which may help improve clinical outcomes.

Our mortality findings are similar to an adult study performed by Sivgin et al.[9] They found that albumin levels <3.2 g/dL prior to transplantation in leukemic adult patients were associated with poor survival in the post-transplant period. Prior to our study, there was no research examining the correlation between albumin levels and the need for critical care interventions in pediatric or adult HCT patients. However, it is known that need for critical care interventions in this population of patients is associated with high mortality rates.[20–22] Therefore, it is important to identify those at high risk for clinical deterioration, particularly when the risk factor could be modifiable. Our study adds to these findings by showing albumin levels as early as 30 days before HCT are associated with poor outcome. Identification of this risk factor at this time leaves ample time to attempt interventions with hopes of improving outcomes.

Our study found that patients requiring HCT for immunodeficiency were significantly more likely to have albumin levels <3.1 g/dL in the pretransplant period. It is possible that this is due to patients with immunodeficiencies already having low or abnormal immunoglobulin and protein levels at baseline, often from protein loss in the gut. We also found that patients in the hypoalbuminemia group were more likely to be younger than those in the normal albumin group. We attributed this difference to the muscle mass and ultimate difference in protein levels between these groups. These findings may also be related to the difference in dietary intake between a younger and older age group of children.

Our study is limited by the relatively small sample size along with a retrospective, single-center design. The small sample size prevented us from performing multivariate analysis to adjust for potentially confounding variables. Due to this, it is impossible to determine that hypoalbuminemia is associated with critical care interventions by itself, or whether there are potential confounders attributing to the association (ie, immunodeficiency, age, or match status). This question could be addressed using a larger sample size, which would necessitate larger center collaboration. In addition, hypoalbuminemia may be associated with a fluid overload state rather than a sign of nutritional status alone. However, this limitation is likely overcome by the vast majority of our patient population being at home, on regular diets, and with normal kidney function for age prior to transplantation. This indicates that our patients were unlikely to be fluid overloaded.

Given our findings, a natural next step is to start by determining whether improving nutritional status prior to HCT would lead to a decreased need for critical care interventions and ultimately help to improve overall survival. Hypoalbuminemia in the pretransplant period may act as an early signal for severity of illness in our population. It is known that serum albumin levels are influenced by numerous factors, including nutrition status and inflammatory status.[9] Studies have shown that when dietary protein intake is reduced, serum albumin concentrations will decrease.[23] A study looking at improvements in albumin levels with dietary changes among adult chronic hemodialysis patients found that there was a significant increase in albumin levels compared to control groups.[24] More research is needed

to further characterize the patient attributes and risks associated with albumin levels, and ultimately help identify patients that may benefit from interventions prior to HCT.

In conclusion, our study suggests that pretransplant hypoalbuminemia may function as a predictive marker for poor outcomes among pediatric allogeneic HCT recipients. Although the cause of hypoalbuminemia may be attributed to multiple factors, including poor nutrition and inflammation, it is important to study this relationship. Further studies are needed to evaluate whether improvements in nutritional status prior to HCT in this patient population will help improve both albumin levels and patient outcomes.

Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
BiPAP	bilevel positive airway pressure
BMI	body mass index
CDC	Centers for Disease Control
CPAP	continuous positive airway pressure
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplant
HLH	hemophagocytic lymphohistiocytosis
IQR	interquartile range
MDS	myelodysplastic syndrome
PICU	pediatric intensive care unit
TPN	total parenteral nutrition
VOD	veno-occlusive disease

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TABLE 1

Baseline characteristics for all patients stratified by albumin level at day negative 30 prior to HCT

	Entire cohort (n=73)	Hypoalbuminemia (n=9)	Normal albumin (n=64)	*P*
Gender (female), n (%)	30 (41)	4 (44)	26 (41)	1.00
Age (y), median (IQR)	7.4 (3.3, 13.2)	4.7 (0.8, 5.8)	8.1 (3.6, 14.9)	.05
Underweight at day negative 30, n (%)	6 (8)	1 (11)	5 (8)	.56
Diagnosis, n (%)				
AML	20 (27)	2 (22)	18 (28)	1.00
ALL	14 (19)	2 (22)	12 (19)	1.00
HLH	5 (7)	1 (11)	4 (6)	.49
Immunodeficiencies	7 (10)	3 (33)	4 (6)	.04
Lymphomas	3 (4)	0 (0)	3 (5)	1.00
Hemoglobinopathies	3 (4)	0 (0)	3 (5)	1.00
MDS	3 (4)	0 (0)	3 (5)	1.00
Bone marrow failure	10 (14)	0 (0)	10 (16)	.20
Others	8 (11)	1 (11)	7 (11)	1.00
Relapsed disease, n (%)	25 (34)	2 (22)	23 (36)	.71
Donor source, n (%)				.26
Bone marrow	39 (53)	3 (33)	36 (56)	
Cord blood	30 (41)	6 (67)	24 (38)	
Peripheral blood	4 (6)	0 (0)	4 (6)	
Matched, n (%)	47 (64)	3 (33)	44 (69)	.06
Related, n (%)	27 (37)	3 (33)	24 (38)	1.00
Feeding type at day negative 30, n (%)				
TPN	4 (6)	1 (11)	3 (5)	.42
Feeding tube	5 (7)	2 (22)	3 (5)	.11

Categorical variables are expressed as frequencies with (%) of the patient numbers in the respective column. Continuous variables are presented as median with IQR.

TABLE 2

Critical care outcomes associated with hypoalbuminemia at day negative 30

	Entire cohort (n=73)	Hypoalbuminemia (n=9)	Normal albumin (n=64)	*P*
Non-invasive ventilation, n (%)	9 (12)	4 (44)	5 (8)	.01
Mechanical ventilation, n (%)	17 (23)	6 (67)	11 (17)	<.01
Vasoactive medication, n (%)	15 (21)	5 (56)	10 (16)	.01

Categorical variables are expressed as frequencies with (%) of the patient numbers in the respective column.

TABLE 3

Cause of mortality for all patients stratified by albumin level at day negative 30 prior to HCT

	Entire cohort (n=16)	Hypoalbuminemia (n=5)	Normal albumin (n=11)	*P*
Pulmonary toxicity	3 (18)	2 (40)	1 (9)	.21
Disease progression	6 (38)	2 (40)	4 (37)	1.00
Infection	6 (38)	1 (20)	5 (45)	.59
Lymphoproliferative disorder	1 (6)	0 (0)	1 (9)	1.00

Categorical variables are expressed as frequencies with (%) of the patient numbers in the respective column.