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The impact of pretransplant malnutrition on allogeneic hematopoietic stem cell transplantation outcomes

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SUMMARY

Background: Malnutrition is a common finding in allogeneic hematopoietic stem cell transplantation (alloHSCT) patients, and there is some evidence that malnutrition might negatively affect the transplant outcomes.
Method: We performed a retrospective study with 148 patients aged 18–75 years, who underwent alloHSCT between 2011 and 2017. Patients were classified according to the body mass index (BMI) and the Subjective Global Assessment (SGA). The SGA was assessed on the day of hospitalization for the transplant, and classifies patients into three groups: A (well-nourished), B (moderately malnourished) and C (severely malnourished).
Results: The SGA classified 49 (33%) patients as well-nourished, 54 (37%) as moderately malnourished, and 45 (30%) as severely malnourished. SGA-C was also associated with severe acute graft versus host disease (aGVHD) with a cumulative incidence (CI) of 31% *vs.* a CI of 14% for combined well-nourished or moderately malnourished group (SGA-A or −B, P = 0.017). In multivariate analysis, SGA-C compared to SGA-A or −B, remained as an independent risk factor for aGVHD (hazard ratio - HR 1.68, 95% confidence interval - 95% CI 1.02–2.74), and nonrelapse mortality (NRM - HR 3.63, 95% CI 1.76–7.46), worse progression free survival (HR 2.12, 95% CI 1.25–3.60), and worse overall survival (HR 3.27, 95% CI 1.90–5.64).
Conclusion: Malnutrition increases the risk of aGVHD and NRM and has a negative impact on survival.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a potential curative treatment for several hematological diseases, whether benign or malignant [1]. The importance of this treatment has been increasing in recent years due to improved outcomes based on marked changes in the treatment regimen and supportive therapy [2].

Various factors can influence alloHSCT outcomes, such as diagnosis, disease status, conditioning regimen, stem cell source (peripheral blood, bone marrow or cord blood), donor (related or unrelated), prior treatment and age [3]. Regarding body weight at admission, both obesity and undernourishment have been considered risk factors for complications and increased relapse or nonrelapse mortality (NRM) in bone marrow transplant patients [4].

Many nutritional assessment indicators have been used, such as laboratory tests and anthropometric indexes [5]. However, these

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indicators have limitations [6]. To overcome these limitations, numerous nutrition screening tools have been developed for the purpose of screening and evaluating the nutritional status of patients and predicting clinical outcomes. The Subjective Global Assessment (SGA) [7] and Nutritional Risk Screening 2002 (NRS-2002) [8] have been commonly used in clinical practice [9,10]. Several studies applying these tools to patients in the alloHSCT setting have been published [11–14], but only a few analyzed the impact of malnutrition on the transplant outcomes [15–18].

This study aims to compare the nutritional status of adult patients submitted to alloHSCT at admission and to evaluate the impact of nutritional status on clinical outcomes.

2. Subjects and methods

This is a retrospective study based on clinical, nutritional and laboratory data of adult patients (18 years or older) who underwent alloHSCT between February 2011 and December 2017 in a bone marrow transplantation referral center in São Paulo, Brazil.

Data were collected from both electronic and paper charts and the local hematopoietic stem cell transplantation (HSCT) program database. The study was approved by the Research Ethics Committee of the referral center.

The nutritional status of each patient was evaluated by the body mass index (BMI), SGA questionnaire and NRS-2002. They were assessed on the day of the hospitalization for the transplant. BMI was calculated as the weight of the patient in kg divided by the square of the height of the patient in square meters and classified as proposed by the World Health Organization [19] for adults and the Pan-American Health Organization [20] for elderly patients.

The SGA is an assessment tool based on medical history and clinical examinations, mostly used to predict clinical outcome and to assess patients at high nutritional risk [7,10]. The SGA's main classification criterion is weight change in past 6 months and two weeks, dietary intake change (relative to normal), gastrointestinal symptoms (that persisted for >2 weeks), functional capacity, disease and its relation to nutritional requirements and a complete physical exam (fat loss, muscle loss and presence of edema) [7,10]. The SGA classifies patients in three groups: Well nourished, moderately (or suspected of being) malnourished and severely malnourished [10].

The NRS-2002 was designed to identify patients at increased nutritional risk expected to benefit from nutritional support, but it is also usually applied to assess patients' nutritional status [8]. The core components of this method include: severity of the impact of primary disease on nutritional status; recent changes of body weight (within the last 1–3 months); changes in dietary intake within the last one week; BMI; and the nutritional risk score plus 1 if the age $\geq$70 years. NRS score $\geq$3 is defined as being at nutritional risk [8,9].

All patients received nutritional support according to the institutional routine practice. At admission, the patients received routine hospital food and oral supplements on a daily basis. Those unable to meet the energy target by the oral route received either supplementary enteral feeding or parenteral nutrition, according to the presence of mucositis and the clinical condition. Oral, enteral and parenteral energy intake were monitored daily. After discharge, nutritional advice and oral supplements were provided to all patients.

Both the conditioning regimen, whether myeloablative (MAC) or reduced intensity (RIC), and graft-versus-host disease (GVHD) prophylaxis were performed following the institution's protocols. For acute GVHD (aGVHD), we considered cases with grades II – IV, while cases with grades III and IV were considered severe aGVHD [21]; we used the standard criteria for chronic GVHD (cGVHD) [22].

2.1. Statistical methods

For the patients' baseline characteristics and nutritional status, descriptive statistical analysis was reported by using percentages (categorical variables) and ranges and medians (continuous variables).

Probabilities of progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method and compared using the log-rank test. Cumulative incidence (CI) rates were calculated for aGVHD, cGVHD, (NRM) and relapse, with death being considered a competing event. Ninety-five percent confidence intervals (95% CI) were estimated using the Greenwood formula. Adjusted probabilities for outcomes after transplantation were estimated using the Cox proportional hazards method (PFS and OS) and Fine–Gray risk regression model (neutrophil engraftment, NRM, aGVHD, cGVHD and relapse). The association between nutritional status and HSCT outcome was investigated in the final multivariate models adjusting for the patient-, disease- and transplantation-related variables with impacts ($P < 0.05$) in the univariate analyses or those variables that had been reported to be clinically relevant. First-order interactions between nutritional status and each variable of interest were examined. The results are presented as relative risks of failure (adverse prognostic factors versus good prognostic factors), with 95% CI and 2-tailed P values. SPSS version 21.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses except for the CI analyses, which were performed using S-PLUS software (TIBCO Software Inc., Palo Alto, CA).

3. Results

3.1. Patient characteristics

A total of 148 patients were included in the study. The patients' baseline characteristics are listed in Table 1. Among the diagnosed lymphoproliferative diseases, 14 (9.5%) were non-Hodgkin's lymphoma (NHL), 10 (6.8%) were Hodgkin's lymphoma and 5 (3.4%) were chronic lymphocytic leukemia (CLL). Among the diagnosed nonmalignant diseases, 7 (4.7%) were aplastic anemia and 1 (0.7%) was sickle-cell anemia. Additionally, 4 patients (2.7%) had multiple myeloma and 1 (0.7%) had chronic myeloid leukemia. Nonmalignant disease and matched unrelated donor (MUD) transplants were *in vivo* T cell depleted, matched sibling donors (MSD) and haploidentical donors transplants were T cell replete.

The median follow-up time was 38 (8–84) months.

Before transplant, 68 (49%) patients were in first complete remission (CR), 20 (14%) were in second CR, 14 (10%) were in third CR, and 15 (11%) were in partial response (PR).

3.2. Patient nutritional status

The nutritional status of patients at hospital admission is presented in Table 2. According to the NRS-2002, all patients who underwent alloHSCT received at least a score of 3. After the screening, 77 (52%) patients reached a score $\geq$ 4. A total of 99 (67%) patients were considered malnourished by the SGA. The correlation between the NRS-2002 and SGA is shown in Table 3. The agreement between NRS >4 and SGA-B or –C classification was 84%, R = 0.63. There was no correlation between nutritional status and disease activity (SGA-C group, non-activity *vs.* activity: 28% *vs.* 40%, respectively, P = 0.20), and no correlation between nutritional status and the diagnosis of acute leukemia (SGA-C group, acute leukemia *vs.* other diseases: 35% *vs.* 24%, respectively, P = 0.23).

Table 1
Clinical features of 148 adults who received alloHSCT.

	Total
Number of patients	148
Age, years (range)	50 (18–75)
Male sex, n (%)	89 (60)
Diagnosis, n (%)	
Acute Myeloid Leukemia	51 (35)
Acute Lymphoblastic Leukemia	33 (22)
Lymphoproliferative (NHL, HL, CLL)	29 (20)
Myelodysplastic Syndrome	22 (15)
Nonmalignant (aplastic anemia/hemoglobinopathy)	8 (5)
Other malignant (multiple myeloma, CML)	5 (3)
Disease status at transplant (malignant diseases, n = 140), n (%)	
CR	102 (63)
PR	15 (11)
Relapse/refractory	23 (16)
Sex mismatch, no. (%)	
No	106 (72)
Yes	42 (28)
HCT-CI, no. (%)	
≤3	134 (90)
≥4	14 (10)
Donor, no. (%)	
Matched unrelated	57 (38)
Matched related	50 (34)
Haploidentical	41 (28)
Source, n (%)	
Peripheral blood	102 (69)
Bone marrow	33 (22)
Cord blood	13 (9)
Conditioning regimen, n (%)	
RIC	101 (68)
MAC	47 (32)
Conditioning regimen (RIC, n = 101), n (%)	
Cy + Flu + low-dose TBI	45 (45)
Bu + Flu	19 (19)
Other regimens − TBI	21 (20)
Other regimens + TBI	16 (16)
Conditioning regimen (MAC, n = 47), n (%)	
Bu + Flu ± other	24 (51)
TBI-based	17 (36)
Other regimens	6 (13)
GVHD prophylaxis, n (%)	
CsA + MMF	69 (47)
CsA + MMF + PTCy	41 (28)
CsA + MTX	33 (22)
Others	5 (3)
MEDIAN FOLLOW-UP, month, median (range) (living patients)	**39 (8–84)**

Abbreviations: NHL non-Hodgkin's lymphoma, HL Hodgkin's lymphoma, CLL chronic lymphocytic leukemia, CML chronic myeloid leukemia, Sex mismatch female to male donor/recipient, HCT-CI hematopoietic cell transplantation - specific comorbidity index, CR complete remission, PR partial response, RIC reduced intensity conditioning, MAC myeloablative conditioning, TBI total body irradiation, Cy cyclophosphamide, Flu fludarabine, Bu busulfan, CsA cyclosporine, MMF mofetil mycophenolate, MTX methotrexate, PTCy posttransplant cyclophosphamide.

3.3. Neutrophil engraftment, aGVHD and cGVHD

The univariate analyses of clinical and risk factors for alloHSCT outcomes are presented in Tables 4 and 5, respectively. The CI of neutrophil engraftment was 93% within 30 days and 97% within 60 days, with a median time of 16 days for engraftment (range 9–50 days). There was a significant difference in neutrophil engraftment according to stem cell source: CIs were 99%, 97% and 82% (P < 0.0001) in peripheral blood, bone marrow or cord blood recipients, respectively. Six patients (4%) did not reach neutrophilic engraftment: 2 due to engraftment failure, 2 due to autologous recovery, and 2 due to early deaths before engraftment.

At 120 days, the CI of aGVHD was 44%, and the CI of severe aGVHD was 20%. The aGVHD CI was higher in acute leukemia *vs.* other diseases (52% *vs.* 33%, respectively, P = 0.016) and in patients in the SGA-C group (SGA-C) *vs.* those in the SGA-A or -B group (58% *vs.* 38%, respectively, P = 0.016). SGA-C was also associated with severe aGVHD, with a CI of 31% *vs.* a CI of 14% for SGA-A or -B (P = 0.017). The NRS-2002 scores (CIs of 53% for NRS-2002 > 4 *vs.* 39% for NRS ≤4, P = 0.098) were not significantly associated with aGVHD.

In 3 years, the CI of cGVHD was 62%. None of the variables were significantly associated with an increased risk of cGVHD. There was only a trend toward higher risk if albumin <3.5 g/dL (CIs of 79% if albumin <3.5 g/dL *vs.* 58% if albumin ≥3.5 g/dL, P = 0.08) or patients met the SGA-C criteria (CIs of 71% in SGA-C *vs.* 58% in SGA-A or -B, P = 0.09).

Table 2
Nutritional status at admission of 148 adults who received alloHSCT.

Weight, kg, median (range)	71.4 (39.8–117.6)
BMI, kg/m^2, median (range)	25.2 (15.5–39.2)
BMI classification, n (%)	
Normal range	62 (43)
Overweight	42 (28)
Obese	23 (16)
Underweight	20 (13)
NRS-2002 (score), n (%)	
3	71 (48)
4	28 (19)
5	22 (15)
6	24 (16)
7	3 (2)
SGA classification, n (%)	
A- Well nourished	49 (33)
B- Moderately malnourished	54 (37)
C- Severely malnourished	45 (30)
Albumin, g/dl, median (range)	3.9 (2.1–4.9)
≥3.5 g/dL	118 (84)
<3.5 g/dL	23 (16)

Abbreviations: BMI body mass index, *NRS* nutritional risk screening, *SGA* subjective global assessment.

3.4. Relapse and nonrelapse mortality

Among 140 patients with malignant diseases, the CI of relapse was 28% at 3 years, with a median time to relapse of 4 months (range 1–46 months). In the univariate analysis, relapse was lower in patients in CR *vs.* not in CR, CIs of 15% *vs.* 62% (P < 0.0001), respectively. There was no impact of any of the analyzed parameters of nutritional status on the risk of relapse.

The CI of NRM was 31% at 3 years. Older age (≥60 years) was associated with a higher NRM (CIs of 60% *vs.* 22%, respectively, P = 0.001), although other comorbidities, as measured by the Hematopoietic cell transplantation - specific comorbidity index (HCT-CI) [23], had no impact on NRM. Patients at a higher nutritional risk also had a higher risk of NRM: obese/underweight *vs.* overweight/normal range (CIs of 51% *vs.* 23%, respectively, P = 0.03), BMI ≥30 kg/m^2 *vs.* BMI <30 kg/m^2 (CIs of 60% *vs.* 26%, respectively P = 0.03), NRS-2002 > 4 *vs.* NRS-2002 ≤ 4 (CIs of 46% *vs.* 24%, respectively, P = 0.009), and SGA-C *vs.* SGA-A or -B (CIs of 62% *vs.* 20%, respectively, P < 0.0001, Fig. 1).

3.5. Progression-free survival and overall survival

PFS and OS rates at 3 years were 47% and 52%, respectively. The OS rates were 60% *vs.* 28% for age <60 years *vs.* ≥60 years (P = 0.01), 55% *vs.* 39% for CR *vs.* not in CR (P = 0.048), 60% *vs.* 36% for NRS-2002 > 4 *vs.* NRS-2002 ≤ 4 (P = 0.002), and 66% *vs.* 22% for SGA-A or -B *vs.* SGA-C (P < 0.0001, Fig. 2), respectively.

The PFS rates (among patients with malignant disease, n = 140) were 56% *vs.* 20% for age <60 years *vs.* ≥ 60 years (P = 0.03), 54% *vs.* 29% for CR *vs.* not in CR (P < 0.0001), 54% *vs.* 34% for NRS-2002 > 4 *vs.* NRS-2002 ≤ 4 (P = 0.04), and 61% *vs.* 19% for SGA-A or -B *vs.* SGA-C (P < 0.0001, Fig. 3), respectively.

Table 3
Correlation between the Nutrition Risk Screening 2002 and Subjective Global Assessment of 148 adults who received alloHSCT.

		NRS-2002		Total
		≤4	>4	
SGA, n	A or B	89	14	103
	C	10	35	45
Total, n		99	49	148

Abbreviations: *NRS-2002* Nutrition Risk Screening 2002, *SGA* Subjective Global Assessment, *A* Well-nourished, *B* Moderately malnourished, *C* Severely malnourished.

3.6. Multivariate analysis

The multivariate analyses are shown in Table 6.

SGA-C remained significantly associated with the risk of increased rates of aGVHD (HR 1.81, 95% CI 1.11–2.94) and NRM (HR 3.63, 95% CI 1.76–7.48) and poorer PFS (HR 2.12, 95% CI 1.25–3.60) and OS (HR 3.27, 95% CI 1.90–5.64). In addition, obesity also remained a risk factor for NRM (HR 2.21, 95% CI 1.04–4.66) and poor OS (HR 1.94, 95% CI 1.08–3.49) .

Table 4
Univariate analysis of the effect of clinical risk factors on transplant outcomes in 148 adults who received alloHSCT.

	N	Neutrophil	NRM	aGVHD	Severe	cGVHD	Relapse	PFS	OS
		Engraftment 60 days (%)	(%)	(%)	aGVHD (%)	(%)	(%)	(%)	(%)
Total	148	97	31	44	20	62	28	47	52
Age. years									
<60	106	97	22	42	17	66	32	56	60
≥60	42	100	60	48	21	80	27	20	28
P value		0.8	**0.001**	0.69	0.54	0.1	0.68	**0.03**	**0.01**
Diagnosis									
Acute Leukemia	82	96	3	52	22	65	25	47	45
Other diseases	66	98	24	33	17	60	34	48	57
P value		0.43	0.23	**0.02**	0.36	0.34	0.27	0.83	0.28
Disease status									
CR	102	98	35	49	27	60	15	54	55
Not in CR	38	94	21	40	18	66	62	29	39
P value		0.67	0.31	0.29	0.21	0.8	**<0.0001**	**0.0001**	**0.048**
Donor									
MUD	57	92	37	44	23	62	29	42	48
MSD	50	100	27	40	14	66	36	44	49
Haploidentical	41	100	27	49	22	56	18	59	60
P value		0.14	0.56	0.53	0.45	0.54	0.3	0.22	0.55
Source									
Peripheral blood	102	99	33	43	20	68	34	41	46
Bone marrow	33	97	29	42	15	53	14	62	64
Cord blood	13	82	25	54	31	37	17	62	62
P value		**<0.0001**	0.97	0.5	0.41	0.15	0.12	0.21	0.46
Conditioning									
RIC	101	98	32	46	21	62	33	57	47
MAC	47	95	59	38	17	62	19	43	62
P value		0.55	0.83	0.32	0.63	0.99	0.12	0.16	0.09

Abbreviations: *NRM* nonrelapse mortality, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease, *PFS* progression-free survival, *OS* overall survival, *CR* complete remission, Not in CR includes patients in partial remission, relapse or refractory disease, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning. *Indicated in bold if P < 0.05.*

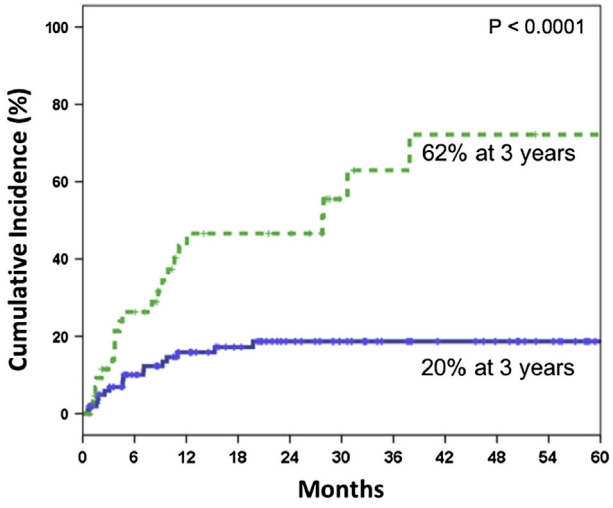

Fig. 1. Cumulative incidence of nonrelapse mortality (NRM) at 3 years according to patient SGA classification: SGA-A or -B 20% *vs.* SGA-C 62% (P < 0.001).

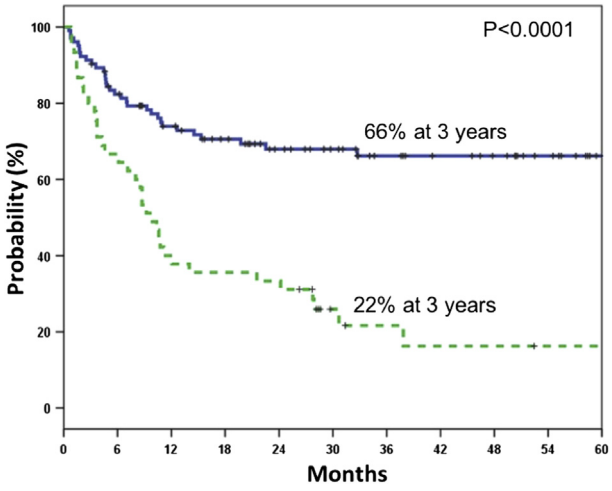

Fig. 2. Overall survival (OS) at 3 years according to patient SGA classification: SGA-A or -B 66% *vs.* SGA-C 22% (P < 0.001).

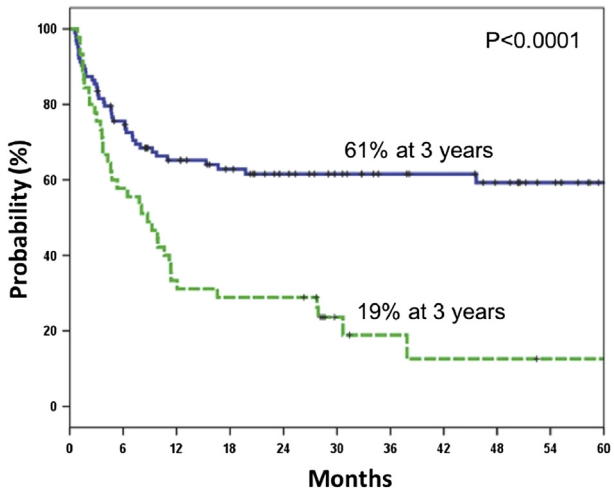

Fig. 3. Progression-free survival (PFS) at 3 years according to patient SGA classification: SGA-A or -B 61% *vs.* C- SGA 19% (P < 0.001).

4. Discussion

In this retrospective study, we showed that a higher nutritional risk as defined by an SGA score of C is associated with a higher NRM, higher risk of aGVHD and shorter PFS and OS. To the best of our knowledge, this was the largest study that analyzed the potential impact of malnutrition, using the SGA, on the clinical outcomes of allogeneic HSCT in adults.

Impaired nutritional status before alloHSCT is a common finding [17,18], which has been associated with unfavorable clinical outcome in previous studies of patients [4,24,25]. During transplant, there is a worsening in the nutritional status aaaaa[24–26], and more pronounced weight loss was also associated with an increased NRM risk and shorter OS [26,27]. This may be explained by the direct toxic effects of the conditioning regimen, lower nutritional intake, higher metabolic demands and nutrient malabsorption [28] or due to secondary complications such as infections, GVHD, relapse and hospitalization [29,30]. Other possible explanations include reduced physical activity [31] and catabolic effects on skeletal muscle induced by drugs such as cyclosporine [32] and corticosteroids [33]. Moreover, in non-small cell lung cancer patients, the incidence of chemotherapy-induced toxicity was shown to be higher in malnourished patients [34]. Malnutrition was also associated with grafting delay [18], higher incidence of aGVHD [15], prolonged hospitalization [35] and excessive medical costs [36].

To overcome these adverse outcomes, adequate nutritional support is a potentially important supportive measure. However, there is an ongoing controversy about its benefit. In a randomized trial, early nutritional support did not affect the outcomes in autologous HSCT [37], and a systematic review demonstrated that parenteral nutrition (PN) is an effective approach to increase

Table 5
Univariate analysis of the effect of nutritional risk factors on transplant outcomes in 148 adults who received alloHSCT.

	N	Neutrophil Engraftment 60 days (%)	NRM (%)	aGVHD (%)	Severe aGVHD (%)	cGVHD (%)	Relapse (%)	PFS (%)	OS (%)
Albumin (g/dl)									
≥3.5	118	97	28	47	20	58	28	49	54
<3.5	23	100	43	35	22	79	34	35	44
P value		0.45	0.39	0.26	0.91	0.08	0.65	0.39	0.27
BMI (kg/m^2)									
Obese	23	100	60	48	17	62	29	25	29
Overweight	44	100	25	43	20	69	42	40	49
Normal range	61	96	21	43	20	54	20	63	63
Underweight	20	90	32	45	20	65	24	40	43
P value		0.43	0.11	0.96	0.99	0.41	0.15	**0.009**	0.12
BMI (kg/m^2)									
Overweight/normal	105	98	23	43	20	60	29	53	58
Obese/Underweight	43	95	51	46	19	64	27	33	37
P value		0.92	**0.03**	0.59	0.93	0.37	0.92	0.19	0.07
BMI (kg/m^2)									
<30	125	97	26	48	19	62	29	51	56
≥30	23	100	60	43	17	62	28	25	29
P value		0.61	**0.03**	0.67	0.85	0.76	0.6	0.08	**0.03**
BMI (kg/m^2)									
≥18.5	137	98	30	54	19	62	29	55	51
<18.5	11	91	20	43	18	60	28	46	64
P value		0.55	0.48	0.4	0.91	0.99	0.98	0.64	0.51
NRS-2002									
3/4	99	97	24	39	16	62	24	54	60
>4	49	98	46	53	26	63	34	34	36
P value		0.86	**0.009**	0.098	0.14	0.49	0.66	**0.04**	**0.002**
SGA									
A	49	100	18	39	16	53	18	67	71
B	54	94	21	27	11	63	28	56	62
C	45	100	62	58	33	71	43	19	22
P value		0.21	**<0.0001**	0.05	**0.02**	0.2	0.17	**<0.0001**	**<0.0001**
SGA									
A/B	103	97	20	38	14	58	23	61	66
C	45	100	62	58	31	71	43	19	22
P value		0.63	**<0.0001**	**0.016**	**0.017**	0.09	0.12	**<0.0001**	**<0.0001**

Abbreviations: NRM nonrelapse mortality. aGVHD acute graft-versus-host disease. cGVHD chronic graft-versus-host disease. PFS progression-free survival. OS overall survival. CR complete remission. RIC reduced intensity conditioning. MAC myeloablative conditioning. NRS-2002 Nutrition Risk Screening 2002. SGA Subjective Global Assessment. A Well-nourished. B Moderately malnourished. C Severely malnourished. Indicated in bold if P < 0.05.

Table 6
Multivariate analysis of the effect of nutritional risk factors on transplant outcomes in 148 adults who received alloHSCT.

Outcome	HR	95% CI	P
NRM			
SGA-C	3.63	1.76–7.48	<0.0001
Obese	2.21	1.04–4.66	0.04
Age ≥60	1.22	0.58–2.55	0.60
HCT-CI	0.98	0.34–2.84	0.96
aGVHD			
SGA-C	1.81	1.11–2.94	0.02
Obese	1.16	0.61–2.22	0.65
Sex mismatch	0.89	0.52–1.53	0.66
cGVHD			
SGA-C	1.51	0.88–2.58	0.14
Albumin <3.5 g/dL	1.69	0.89–3.20	0.11
Sex mismatch	1.54	0.91–2.59	0.11
Relapse			
SGA-C	1.31	0.65–2.62	0.45
Active disease (not in CR)	4.73	2.38–9.43	<0.0001
PFS			
SGA-C	2.12	1.25–3.60	0.006
Active disease (not in CR)	1.91	1.17–3.10	0.009
Age ≥ 60	1.2	0.69–2.06	0.52
Obese	1.59	0.89–2.85	0.12
OS			
SGA-C	3.27	1.90–5.64	<0.0001
Age ≥ 60	1.06	0.60–1.86	0.86
Obese	1.94	1.08–3.49	0.03

Abbreviations: HR hazard ratio; 95% CI Ninety-five percent confidence interval; NRM nonrelapse mortality; PFS progression-free survival; OS overall survival; aGVHD acute graft-versus-host disease; cGVHD chronic graft-versus-host disease; BMI body mass index; SGA Subjective Global Assessment: A Well-nourished, B Moderately malnourished, C Severely malnourished; Sex mismatch female to male donor/recipient; HCT-CI hematopoietic cell transplantation - specific comorbidity index. Indicated in bold if $P < 0.05$.

patient weights [38]. Nevertheless, in other analyses, enteral nutrition had better outcomes than PN [39–42]. The conflicting findings and heterogeneity of peritransplant nutritional support approaches among different transplantation centers interfere with the analysis of these findings [43,44].

The role of BMI in predicting outcomes in the pretransplant context is controversial [24,25,45,46], and its isolated use is not an effective parameter for nutritional evaluation.

Prior studies of albumin levels in the context of HSCT have shown inconsistent effects on transplant outcomes. In a retrospective analysis, a pretransplant albumin concentration less than 3.5 g/dL was associated with higher TRM [47]. However, we did not find this association in our study.

The NRS-2002 was designed to assess the nutritional statuses of patients and to identify patients at increased nutritional risk expected to benefit from nutritional support [9]. The core components of this method include: the severity of the impact of primary disease on nutritional status, recent changes in body weight, changes in dietary intake, BMI, and age ≥70 years. Patients with a score ≥3 are considered at nutritional risk. In a prospective trial, the NRS-2002 presented modest specificity for predicting nutritional deficiencies [5]. In our study, NRS-2002 > 4 was associated with a worse prognosis, although the results are less consistent than those using the SGA.

The SGA main classification criteria are weight changes in the past 6 months and two weeks, dietary intake changes, gastrointestinal symptoms, functional capacity, diagnosis and physical examination [7,10]. In a prospective trial, the SGA showed high sensitivity for identifying malnourished patients [5]. However, in another prospective study, the SGA was not useful for predicting unfavorable outcomes [24]. In our series of studies, which included related and unrelated donors and different stem cell sources, patient classification in SGA-C group was associated with a worse prognosis compared to patient classification in a lower nutritional risk group. A recent retrospective study that only included patients who received HSCT from related donors also presented similar findings [16].

Moreover, obese patients who underwent alloHSCT had higher mortality [48] and adverse outcomes [49]. In our series of studies, in a multivariate analysis, we also observed higher NRM and worse survival in the group of obese patients.

There is no gold standard assessment tool to define nutritional status before HSCT because they all have low accuracy. In the nontransplant scenario, a systematic review [38] suggests that nutrition assessment tools can be used for screening, but their limitations should be acknowledged.

Compared to other recent similar investigations [16,24], our study had a higher frequency of malnourished patients according to the SGA (67%), possibly due to the fact that more of the patients in our series of patients had advanced diseases and were heavily pretreated. However, we observed a similar association of malnutrition (according to the BMI) on the risk of aGVHD [15] and also a similar impact of malnutrition (according to the SGA) on the risk of mortality [16].

Our study has several limitations including its retrospective, single-center design and a very heterogeneous population, especially in terms of conditioning regimens and GVHD prophylaxis.

In summary, we demonstrated that one-third of patients who undergo alloHSCT are severely malnourished at admission (SGA-C) and that malnutrition had an adverse impact on transplant clinical outcome (a higher risk of aGVHD and lower PFS and OS). Large prospective trials are needed to determine whether adequate pretransplant nutritional support might be able to avoid the adverse effects of malnutrition on the clinical outcomes of HSCT.

Authorship statement

E.Y.H., V.C.M and C.A.R. designed research, performed research, analyzed data, and wrote the paper; M.V.G. and C.A.R. performed statistical calculations; A.D.P., R.S.S., A.R.B.M.F, G.F., M.G.S., E.M.X., L.T., V.R., and Y.N. provided single institutional series of patients included in the study, performed critical review, and revised the manuscript. All authors drafted and approved the manuscript and agree with its submission.

Financial disclosure statement

The authors have nothing to disclose.

Declarations of interest

There are no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.05.005.

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