ORIGINAL ARTICLE

Correlation of nutrition-associated parameters with non-relapse mortality in allogeneic hematopoietic stem cell transplantation

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Abstract

Outcome of allogeneic stem cell transplantation (alloSCT) is hampered by substantial non-relapse mortality (NRM). Given its impact on organ function and immune response, the nutritional status has been suggested as relevant for NRM. We aimed to evaluate the association of NRM with nutritional status prior to alloSCT and in the post-SCT course. In a retrospective single-center study, we analyzed 128 alloSCTs. Besides standard characteristics, nutrition-associated parameters BMI, serum total protein, and serum albumin were recorded before conditioning and at various time points after alloSCT. Association with NRM was evaluated by univariate and multivariate survival analysis. The cohort comprised patients with a median BMI of 26 kg/m^2 (16.7–46.9 kg/m^2), median serum total protein of 59 g/l (41–77 g/l), and serum albumin of 36 g/l (22–46 g/l) before SCT. NRM at d_{+100} was 14.8% and at 1 year 26.6%. Prior to SCT, only serum albumin deficiency was associated with increased NRM ($p = .010$) in multivariate analysis. After SCT (d_{+30} and d_{+100}), all nutrition-associated parameters decreased ($p < .002$), but no association of deteriorating nutritional status with NRM was found. In multivariate analysis, serum albumin ($p = .03$) and severe albumin deficiency ($p = .02$) correlated with NRM at d_{+30} and d_{+100}, while BMI and serum total protein did not. In our study, albumin deficiency, particularly prior to alloSCT, shows a strong correlation with NRM. This finding may add to monitoring, risk evaluation, and counseling of patients and serve as a rational for interventions to improve the nutritional status in patients undergoing SCT.

Keywords Allogeneic stem cell transplantation · Nutrition-associated parameters · BMI · Albumin

Introduction

Allogeneic hematopoietic stem cell transplantation (alloSCT) represents a curative therapy for various malignant and non-malignant hematological diseases [1]. However, despite improvement, its success is still limited by its high toxicity. Around 20–32% of the patients die in consequence of non-relapse mortality (NRM) [2–4]. Predominant reasons are lethal infections, organ failure, and both acute and chronic graft-versus-host disease (GvHD) [5, 6]. Established risk factors for NRM include age [4, 7] and comorbidities [8] as well as conditioning intensity in older patients [9, 10]. The most common score used to assess the NRM risk is the HCT-CI score [11]. Despite the fact that alloSCT causes relevant metabolic changes [12] with an estimated increased basal metabolic rate of 130–150% [13] and that a deficient nutritional state is associated with worse outcome [14], the HCT-CI contains only one nutrition-related parameter which is obesity, i.e., a body mass index (BMI) of > 35 kg/

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m^2. However, there is conflicting evidence from different trials on the impact of obesity on alloSCT outcomes and NRM risk, and therefore the relevance of the BMI is still disputed [15–19].

Given its impact on organ function and immune response, a number of studies have explored nutrition-associated parameters in the setting of alloSCT; however, little data exist on their exact role in NRM [20] and no verified and easily accessible parameter for nutritional status monitoring specifically in the alloSCT setting has been established.

Possible parameters include weight as well as BMI or its categories based on WHO standards [21, 22]. Regarding an association of BMI prior to SCT with outcome conflicting results have been reported. Various studies show reduced survival for patients with obesity [15], while other studies did not support this finding [16–18]. There is agreement on a general reduction of BMI post-SCT [23–26], but data on the relevance of BMI change in the post-SCT course have only scarcely been analyzed.

Other parameters related to the nutritional status are serum total protein and serum albumin. For both association with outcome has been reported for different hemato-oncological entities, e.g., peripheral T-/NK-cell lymphomas [27]. A prognostic relevance for SCT has been suggested, but is disputed [28, 29].

A better understanding of nutrition particularly in the post-SCT course and its relevance for NRM may not only aid in assessing prognosis but also in designing interventions to improve outcome. The benefit of such interventions has been discussed, but data remain unclear [30, 31].

Given the sparse data particularly on the relevance of post-SCT nutritional status, we evaluated the association of nutritional status assessed by BMI, serum total protein, and albumin at different time points prior and after alloSCT with NRM-related outcome.

Patients and methods

Patients

A total of 126 adult patients (age ≥ 18 years) who received a first and second (two cases) alloSCT at our center between January 2005 and September 2013 were included. The two patients with a second alloSCT were 11 and 22 months disease-free before relapse leading to their second alloSCT. As this interval was considered sufficient to reconstitute nutritional status, both patients were included and total cohort size was 128 alloSCTs.

Patients received an alloSCT from either an unrelated or related donor. In the absence of an HLA-matched sibling, the search for an unrelated adult donor was conducted in collaboration with the German National Bone Marrow Donor Registry (Zentrales Knochenmarkspender-Register Deutschland, ZKRD).

Nutritional support during alloSCT was performed according to local standards (in-house standard operating procedure) following the recommendations of the European Society of Clinical Nutrition and Metabolism (ESPEN) and the German Society for Nutritional Medicine (DGEM). During neutropenia < 500/μl, a low germ and moist steam sterilized light-balanced diet was offered and patients were encouraged to maintain a sufficient oral food intake for as long as possible. On the basis of DGEM recommendations, indications for initiation of parenteral nutrition were inability to ingest food orally for > 3 days, enteral calorie intake of < 500 kcal per day for > 5 days, > 3 days in patients with severe malnutrition, or < 60% of daily requirement for > 10 days, therapy refractory emesis, diarrhea, ileus, gastroparesis or high-grade mucositis, prolonged inappetence, and prevention of catabolic metabolism.

Data collection and general SCT data

Data were collected retrospectively in our single-center study. Sources for data were inpatient and outpatient documentation. All patients had consented to treatment according to local standards. Data were handled pseudonymized during all stages of collection and analysis. Due to the pseudonymized analysis of retrospectively accrued data, no Institutional Review Board approval was deemed necessary. Patients consented to the collection and analysis of their data. Analyses were in line with the declaration of Helsinki.

Data were collected at the following time points: within 15 days prior to start of conditioning (preCond), the day of SCT ± 5 days (d_0) and post-SCT on day 30 ± 5 days (d_{+30}), day 100 ± 20 days (d_{+100}), day 180 ± 10 days (d_{+180}), and the last day of follow-up between day 110 and day 365 ± 10 days (d_{+365}). Conditioning intensity was classified according to established criteria [32]. Patients were censored in case of relapse or disease progression or if treatment for another malignancy was started. Death after SCT without preceding censorship was regarded as non-relapse mortality (NRM). Varying N for different parameters at different time points resulted from censorship, preceding NRM and missing data.

Analyzed nutrition-associated parameters

Patients' body weight and height were derived from patient records. BMI (kg/m^2) was calculated using body weight (in kg) divided by the square of the height (in m). For cross-sectional analyses, BMI was categorized according to WHO standards (BMI < 18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, ≥ 30.0 obesity). For analyses of longitudinal changes, an alteration in BMI of > 0.1 kg/m^2 was classified as increase or of ≤ 0.1 kg/m^2 as reduction. For

serum albumin, a value of < 35 g/l was considered deficient with the following subcategories emerging as relevant during the analysis: mild deficiency 32–34.9 g/l, moderate deficiency 28–31.9 g/l, severe deficiency < 28 g/l, whereas serum albumin level ≥ 35 g/l was defined as normal. Subgrouping was initially based on current guidelines suggesting albumin levels < 32 g/l as a marker for cachexia [33]. Further analysis revealed a particular worse outcome for patients with albumin < 28 g/l (Fig. 1), and thus the present subgroups were analyzed. Regarding serum total protein, a level < 60 g/l was regarded as deficiency.

Statistical analysis

All statistical analyses were conducted using software SPSS (version 25, IBM). Survival analysis was performed using the Kaplan–Meier method with log rank testing. Unifactorial associations of parameters with NRM were assessed using chi^2-test. T-test for dependent variables was used when comparing parameters at different time points. Multivariate analysis was performed by binary logistic regression model with stepwise backward likelihood inclusion for parameters showing an association in univariate analysis and relevant cofactors as stated. Results are shown as odds ratio (OR) with 95% confidence interval (CI). All reported p-values are explorative.

Results

Patient characteristics and nutritional data at pre-SCT

General patient characteristics are summarized in Table 1. Upon start of conditioning patients had a median weight of 77.4 kg (minimum 46 kg, maximum 157 kg; SD 18.9 kg) and a median BMI of 26 kg/m^2 (minimum 16.7 kg/m^2, maximum 46.9 kg/m^2, $SD \pm 5.2$ kg/m^2). The distribution of WHO-based BMI categories is shown in Table 1. Median serum total protein was 59 g/l (minimum 41 g/l, maximum 77 g/l; $SD \pm 7.1$ g/l) and median serum albumin was 36 g/l (minimum 22 g/l, maximum 46 g/l; $SD \pm 4.7$ g/l). This grouped patients according to normal or protein/albumin deficiency as shown in Table 1.

As shown in Table 1, NRM at d_{+100} was 14.8% and at 1 year (1y) 26.6%. The main cause of NRM was infection with sepsis, accounting for 84.2% of NRM at d_{+100} and 91.1% of NRM at 1y.

Association of pre-SCT nutritional status with post-SCT NRM

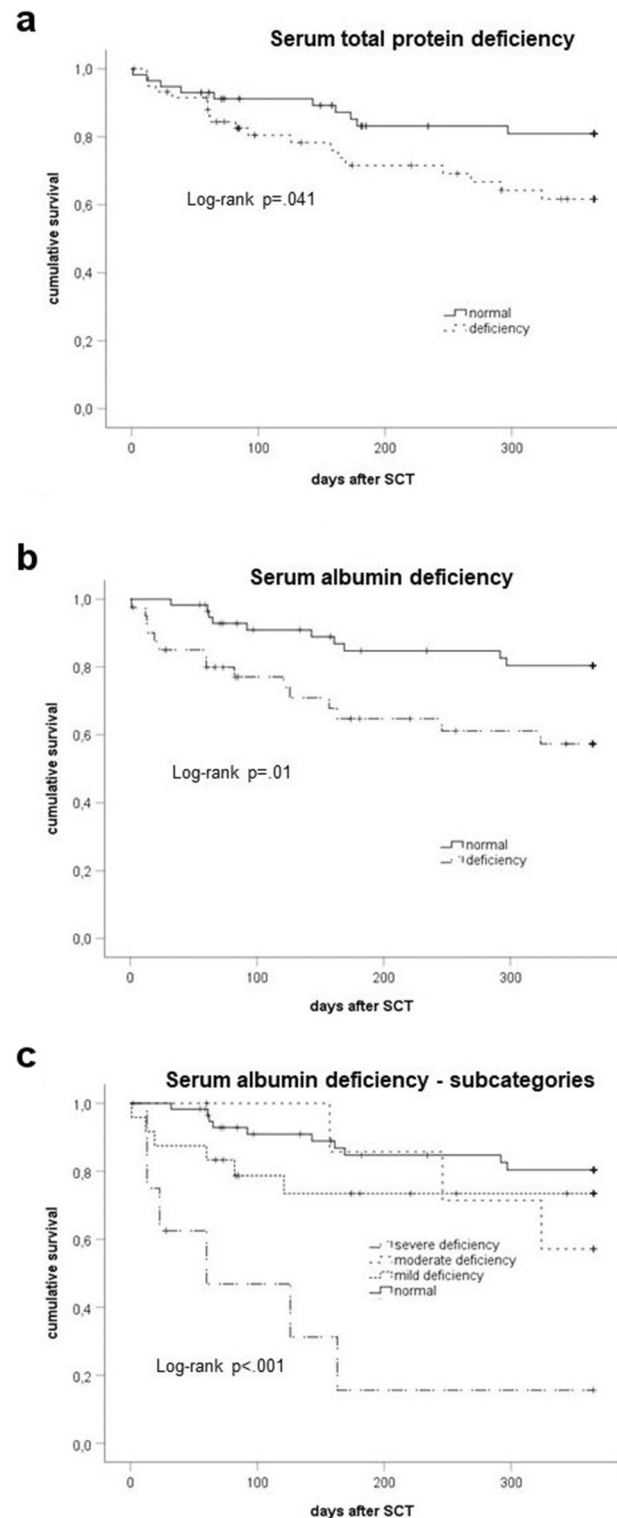Survival analysis did not reveal an association of pre-SCT BMI with NRM and showed an increased NRM

Fig. 1 Analysis of survival (Kaplan–Meier) according to nutrition-associated parameter levels and distribution prior to alloSCT. **a** Serum total protein deficiency, **b** serum albumin deficiency, **c** categories of serum albumin deficiency; log rank testing according to Kaplan–Meier method

Table 1 Patient characteristics pre-SCT ($N = 128$)

Characteristic	Specificity	Values
Gender, N (%)	Female	50 (39.1)
	Male	78 (60.9)
Age, years		median: 56.4, range: 18–72
Karnofsky index, %		median: 90%, range: 40–100%
Diagnosis, N (%)	AML	58 (45.3)
	Lymphoma	35 (27.3)
	Myeloma	19 (14.8)
	Other [1]	16 (12.5)
Disease status, N (%)	CR	56 (43.8)
	PR	34 (26.6)
	SD	28 (21.9)
	PD	8 (6.3)
	NA	2 (1.6)
Conditioning regimen, N (%)	MA	39 (30.5)
	RIC/NMA	89 (69.5)
Graft source, N (%)	Peripheral blood	124 (96.9)
	Bone marrow	4 (3.1)
Death, N (%)	Until d_{+100}	23 (18.0)
	Cumulative until 1y	53 (41.4)
Cause of death, N (%) (cumulative until d_{+100} / until 1y)	Relapse	4 (3.1) / 19 (14.8)
	NRM	19 (14.8) / 34 (26.6)
	Lethal sepsis as cause of NRM	16 (12.5) / 31 (24.2)
Pre-SCT BMI, N (%)	Obesity	22 (17.2)
	Overweight	55 (43.0)
	Normal weight	46 (35.9)
	Underweight	5 (3.9)
Pre-SCT total protein, N (%)	Normal	57 (44.5)
	Deficiency	60 (46.9)
	NA	11 (8.6)
Pre-SCT albumin, N (%)	Normal	58 (58.6)
	Mild deficiency	24 (24.2)
	Moderate deficiency	9 (7.0)
	Severe deficiency	8 (6.3)
	NA	29 (22.7)

[1]Includes acute lymphatic leukemia, chronic myelogenous leukemia, osteomyelofibrosis, aplastic anemia; *AML*, acute myeloid leukemia; *MA*, myeloablative; *MM*, multiple myeloma; *NA*, unknown; *NMA*, non-myeloablative; *NRM*, non-relapse mortality; *CR*, complete remission; *PD*, progressive disease; *PR*, partial remission; *RIC*, reduced intensity conditioning; *SCT*, stem cell transplantation; *SD*, stable disease

for patients with pre-SCT protein deficiency (Fig. 1a, log rank $p = 0.041$). Especially pre-SCT albumin deficiency was associated with worse NRM (Fig. 1b, log rank $p = 0.010$). Analysis for albumin deficiency subgroups revealed a particularly increased NRM for patients with pre-SCT severe albumin deficiency (Fig. 1c, log rank $p = 0.001$).

These results were confirmed by multivariate regression analysis for continuous levels of pre-SCT BMI, serum total protein, serum albumin and including covariates sex, age, and conditioning intensity. Only pre-SCT serum albumin but not BMI or serum total protein was independently associated with NRM as shown in Table 2 (stating the last step of the stepwise backward likelihood inclusion). Multivariate regression analysis stated a lower NRM with increasing pre-SCT serum albumin values (OR 0.82; 95%CI 0.73 to 0.92, $p = 0.001$). Furthermore, serum total protein deficiency and severe albumin deficiency were associated with clinically relevant increased NRM (OR 3.7; 95%CI 1.2–11.3 or OR 13.3; 95%CI 2.2–81.7) (Table 2).

Table 2 Results of multivariate analysis on association of nutrition-associated factors with NRM

Variable	p-value	OR [(Exp(B)]	95% CI
pre-SCT [a]			
Serum albumin	.001	.82	.73–.92
Protein deficiency	.02	3.72	1.23–11.29
Severe albumin deficiency	.005	13.28	2.16–81.72
d_{+30} [b]			
Serum albumin	.004	.80	.69–.93
Severe albumin deficiency	.005	6.30	1.75–22.71
d_{+100} [b]			
Serum albumin	.03	.90	.81–.99
Severe albumin deficiency	.02	15.00	1.63–138.16

[a]Covariates at pre-SCT: age, sex, disease leading to SCT, conditioning intensity (MAC vs. others) and linear (BMI, albumin, protein) or categorized (BMI 4 categories, protein deficiency, 4 categories albumin) nutrition-associated parameters

[b]Covariates at d_{+30} and d_{+100}: age, sex, conditioning intensity (MAC vs. others) and linear (BMI, albumin, protein) or categorized (BMI 4 categories, protein deficiency, 4 categories albumin) nutrition-associated parameters

Longitudinal alterations of nutrition-associated parameters in the post-SCT course

Average levels of all parameters—BMI, serum total protein and serum albumin—decreased post-SCT (Fig. 2a). Given the expected alterations in fluid status and metabolism during conditioning further analysis was performed for levels at d_{+30} and d_{+100} but not at d_0.

Compared to pre-SCT, on d_{+30} and d_{+100}, a decrease in mean BMI (27.1 vs. 25.6 kg/m^2 and 24,4 kg/m^2, $p < 0.0001$ for both), mean serum total protein (60.4 g/l vs. 53.9 g/l and 55.8 g/l, $p < 0.0001$ for both), and mean serum albumin (35.9 g/l vs. 30.5 g/l and 31.7 g/l, $p < 0.0001$ and $p = 0.001$ respectively) was observed (t-test for dependent variables).

This corresponded to a relevant change (non-parametric testing for dependent variables) in the proportion of BMI subgroups and in the number of patients with a deficiency of serum total protein and serum albumin (for all $p < 0.0001$) on d_{+30} compared to pre-SCT (Fig. 2b–d). For d_{+100}, a difference (non-parametric testing for dependent variables) was seen for the proportion of BMI subgroups ($p < 0.0001$) with a continuous increase of underweight
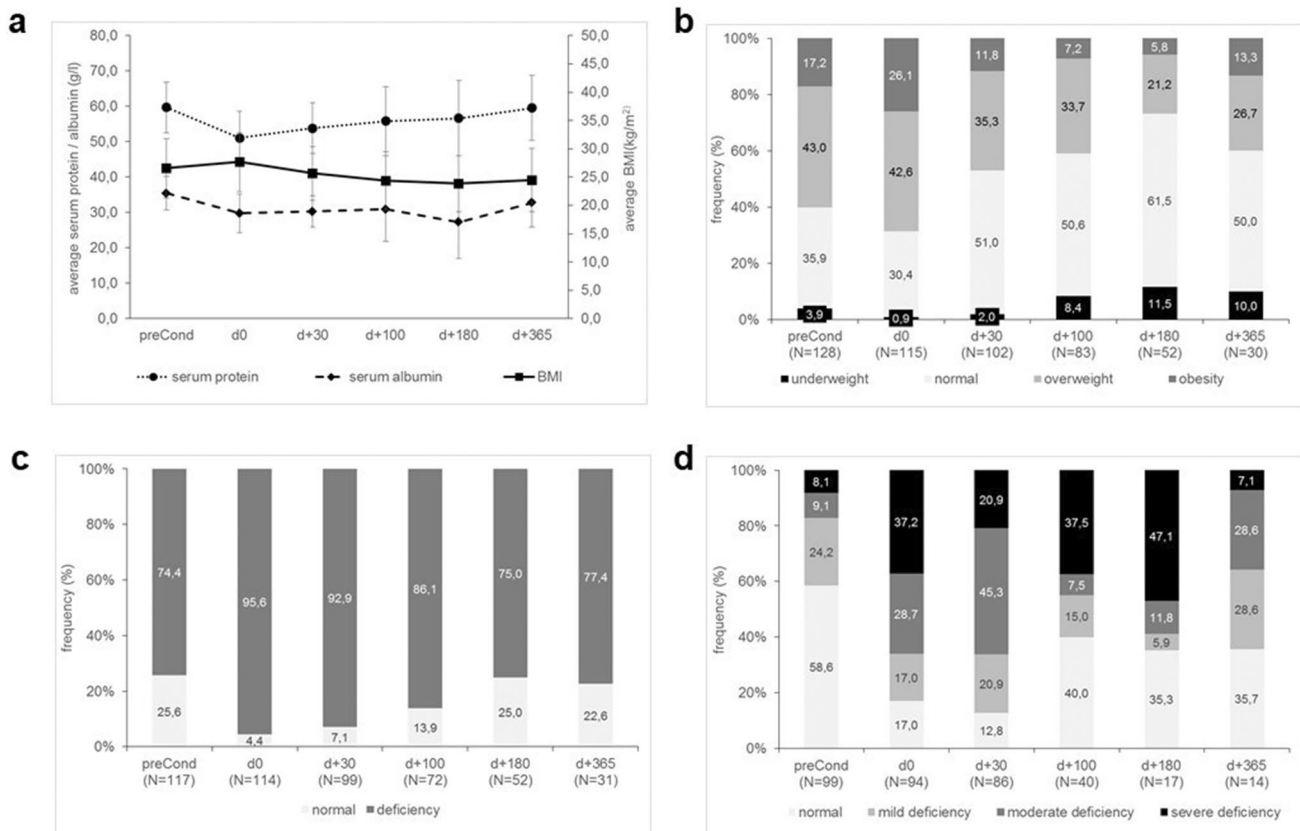
Fig. 2 Distribution of nutrition-associated parameters in the course from prior to SCT (preCond) until 1 year post-SCT. **a** Mean BMI (right Y-axis), serum total protein and serum albumin (left Y-axis), error bars represent standard deviation, **b** BMI categories, **c** categories of serum total protein deficiency, **d** categories of serum albumin deficiency

and decrease of obese patients as well as in the number of patients with deficient serum albumin ($p < 0.02$). However, no difference was seen for the number of patients with serum total protein deficiency ($p = 0.22$).

Association of NRM with longitudinal post-SCT alterations of nutrition-associated parameters

Given the evident changes in BMI status as well as in serum total protein and serum albumin on d_{+30} and d_{+100} (see Fig. 2), we analyzed whether the changes from pre-SCT status to d_{+30} and d_{+100} status correlated with NRM.

The occurrence of a decrease in serum total protein from pre-SCT to d_{+30} (log rank $p = 0.81$) and to d_{+100} (log rank $p = 0.06$) did not correlate with NRM (data not shown). Similarly, for serum albumin a decrease from pre-SCT to d_{+30} (log rank $p = 0.39$) and to d_{+100} (log rank $p = 0.24$) did not correlate with NRM-related survival (data not shown).

Interestingly, while a decrease in BMI from pre-SCT to d_{+30} did not correlate with NRM (log rank $p = 0.24$; data not shown), a decrease from pre-SCT to d_{+100} correlated with better NRM-related survival (log rank $p = 0.006$; Fig. 3), suggesting a better survival for patients with a decrease in BMI from pre-SCT to d_{+100} compared to patients with a stable or increasing BMI.

However, in multivariate regression analysis (binary logistic as well as Cox), BMI decrease from pre-SCT to d_{+100} showed no significant association ($p > 0.1$, data not shown) with NRM. Thus, it was not included in further multivariate analyses.
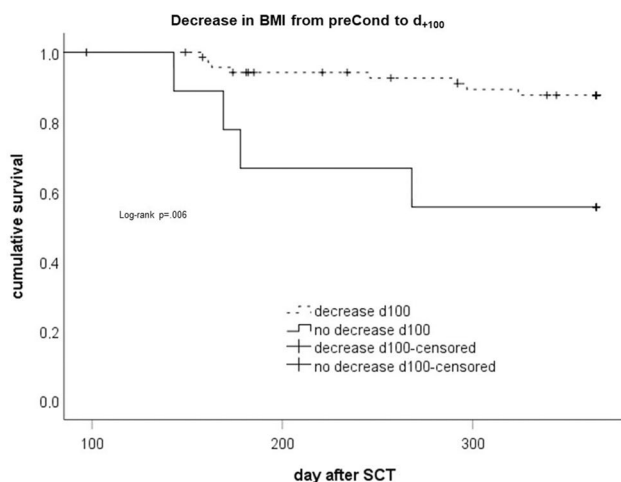

Fig. 3 Analysis of survival (Kaplan–Meier) according to occurrence of a decrease in BMI from prior to SCT to d_{+100}. Log rank testing according to Kaplan–Meier method

Association of post-SCT nutrition-associated parameters with NRM

Given the altered nutrition-associated parameters in the post-SCT course, we analyzed NRM-related survival according to nutritional status on d_{+30} and d_{+100}.

For d_{+30} status, according to the 4 BMI subgroups (log rank $p = 0.75$) as well as deficiency in serum total protein (log rank p = 0.11) and serum albumin (log rank p = 0.06) did not correlate with NRM (data not shown). However, severe serum albumin deficiency showed a strong correlation with very low NRM-related survival (log rank $p = 0.002$; Fig. 4a).

Similarly, for d_{+100}, BMI subgroups (log rank $p = 0.71$) showed no correlation with NRM. However, patients with low serum total protein (log rank $p = 0.04$, Fig. 4b), low serum albumin (log rank $p = 0.03$; Fig. 4c), and particularly severe albumin deficiency (log rank $p = 0.03$; Fig. 4d) at d_{+100} had a low NRM-related survival.

As shown in Table 2, multivariate regression analysis confirmed a significant impact of serum albumin levels and of severe albumin deficiency on d_{+30} and d_{+100} on NRM. In contrast, neither BMI and BMI categories nor serum total protein or deficiency in serum total protein were associated with NRM at these time points.

Discussion

Our present study belongs to the small number of studies analyzing nutrition-related data not only prior to alloSCT but also in the post-SCT course and in specific relation to NRM rather than overall survival (OS). In our single-center cohort, which comprised a typical distribution of donor, recipient, and transplant characteristics, we observed no association of BMI or its alterations in the post-SCT course with NRM. In contrast, serum albumin deficiency prior to SCT as well as at d_{+30} and d_{+100} post-SCT was consistently associated with NRM in multivariate analysis. While BMI, serum total protein, and serum albumin decreased in the post-SCT course, this decrease did not correlate with NRM.

Concerning the association between pre-SCT BMI and the outcome of allogeneic SCT, current data are inconsistent and comparability is hindered by different cut-offs of categorized BMI. Our finding of pre-SCT BMI being not associated with NRM is supported by other studies [16, 19], suggesting that neither underweight nor obesity prior to allogeneic SCT effect patients' outcome. Due to the rising prevalence of adiposity, many studies focused on the impact of obesity on safety and efficacy of allogeneic SCT. In a retrospective analysis of CIBMTR data, Navarro et al. reported a comparable outcome of AML patients with a BMI ≥ 30 kg/m², including OS [18]. These results were confirmed in
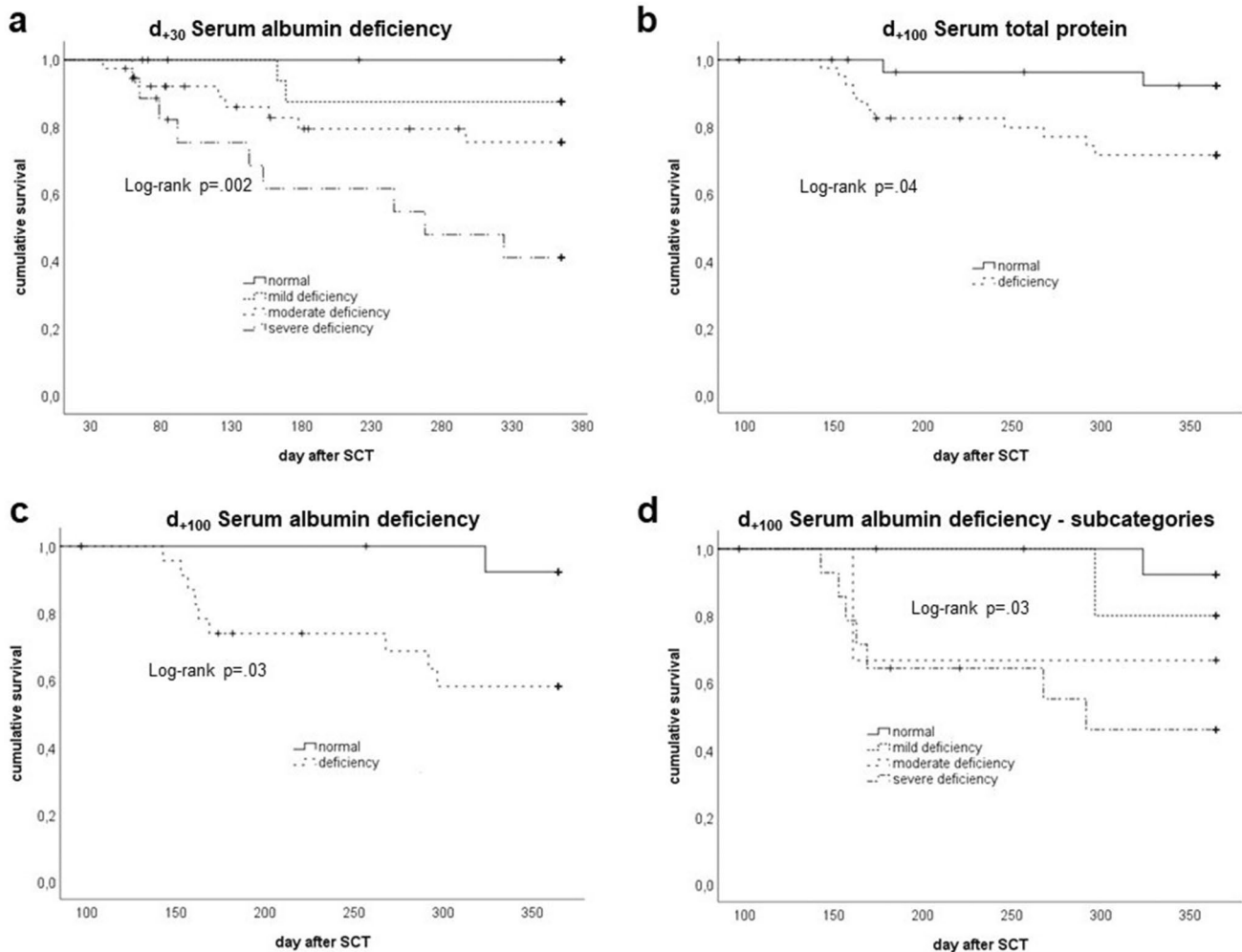
Fig. 4 Analysis of survival (Kaplan–Meier) according to nutrition-associated parameter levels at the time post-alloSCT. **a** serum albumin levels at d_{+30} post-SCT, **b** serum total protein deficiency at d_{+100}, **c** serum albumin deficiency at d_{+100}, **d** subcategories of serum albumin deficiency at d_{+100}; log rank testing according to Kaplan–Meier method

obese (BMI ≥ 30 kg/m^2) elderly patients (≥ 60 years) who underwent allogeneic SCT for myeloid malignancies and whose outcome including OS and progression-free survival were not affected by obesity [34].

Conversely, other authors reported an association of pre-SCT BMI with NRM-related survival [15, 17, 35, 36]. In a large cohort of 2503 adult patients, Doney et al. showed that both underweight (BMI ≤ 18.5 kg/m^2) and very obese (BMI ≥ 35.0 kg/m^2) patients had an increased NRM and underweight patients also had an elevated relapse and overall mortality rate [15]. In the retrospective analysis performed by Fuji et al. with registry data of 12,050 patients, NRM was significantly higher in the overweight and obese group (BMI ≥ 25.0 kg/m^2) compared with the normal BMI group, mainly due to an increased GvHD- and infection-related NRM. However, this did not translate into a decreased overall survival for this patient group due to an increased risk of relapse in patients with a BMI ≤ 18.5 kg/m^2 [35]. The study of Gleimer et al. showed the same association with a higher NRM in obese patients (BMI ≥ 30.0 kg/m^2), yet no difference in OS due to a lower incidence of relapse in the obese patient group. NRM was mainly caused by acute and chronic GvHD, but despite a trend towards a higher incidence of both acute and chronic GvHD in obese patients, no difference compared to normal weight patients was shown [36]. Given the limited size of our cohort, we did not include GvHD as an additional covariate in our analysis.

The data reporting a higher NRM for obese patients are reflected in the addition of obesity defined by a BMI > 35 kg/m^2 to the relevant comorbidities in the HCT-CI score, which is used for predicting transplant-related mortality risk prior to allogeneic SCT [11].

In a longitudinal analysis, we showed similar to other authors a relevant weight loss represented by a decrease

of BMI over the course of alloSCT. Due to the intensity of the treatment, this finding is expected and has been confirmed in other studies [25, 26, 37]. The retrospective study by Rieger et al. compared patients' weight at the time of hospital admission for alloSCT, discharge (median 41 days after alloSCT), and at the end of follow-up, which was 873 ± 361 days after transplant [37]. There was no difference between the medium BMI at these time points, providing a comparable cohort to our study with a medium follow-up of 1 year. Surprisingly, in our study, patients without a reduction in BMI after d_{+30} showed an increased NRM; however, this finding did not remain significant in multivariate analysis and may thus be related to other factors. For instance, other studies showed an association of GvHD with a BMI reduction [24, 26]. This was confirmed by Rieger et al., observing no meaningful difference in overall survival between patients with or without substantial weight loss. This data is contradicted by a study of Fuji et al., reporting a worse outcome (NRM and OS) of patients with a weight loss $\geq 10\%$ after alloSCT [38].

Overall, the effect of pre-SCT BMI and its course after SCT on the outcome of SCT remains unclear. Different institutional practices of chemotherapy dose modifications according to actual or adjusted body weight as well as internal guidelines on nutritional support further reduce the comparability of the data. In addition, BMI might not represent a suitable marker for describing the nutritional status of a patient, since it does not differentiate between excess body fat, muscle mass, or surplus water. Due to the retrospective design of our study, no further analyses of patients' body composition, e.g., by bioelectric impedance analysis, which allows an estimation of human body composition, especially body fat and muscle mass, were possible. Yet, since weight remains one of the few patient-related factors that can be influenced by reasonable interventions prior to SCT, further studies are needed to evaluate its impact.

One parameter that may represent the nutritional status of the patients more accurately is serum albumin. In our cohort, serum albumin pre-SCT as well as at 30 and 100 days after SCT was significantly associated with NRM and particularly a severe albumin deficiency (< 28 g/l) correlated strongly with a higher NRM risk. Various studies have shown that serum albumin levels both prior to SCT [39, 40] and in the post-SCT course [41, 42] correlate with outcome of SCT. Although different classifications and cut-offs for hypoalbuminemia limit the comparability of these studies, low serum albumin has been consistently associated to an increased NRM, and therefore the addition of this parameter to the HCT-CI score ("Augmented HCT-CI") has been suggested and retrospectively validated [43, 44]. A possible explanation for this observation is the higher susceptibility towards and worse outcome of complications after allogeneic SCT

in patients with hypalbuminemia, such as invasive fungal infections [45] and acute GvHD [46, 47].

Additionally, our present study for the first time to our knowledge shows that the further decrease of albumin levels in the post-SCT course is not relevant for NRM. We therefore reason that primarily albumin deficiency prior to SCT is a prognostic factor predicting increased NRM risk. This is relevant, as many other factors common in the SCT and post-SCT course influence albumin levels, e.g., hydration and sepsis [48, 49]. While low serum albumin levels are well-recognized markers of both nutritional status and liver function, it also serves as a surrogate parameter for chronic inflammation processes [50]. Among other laboratory indicators, lower albumin is associated with disease activity in patients with chronic GvHD [51]. In patients undergoing an allogeneic SCT, and therefore an intensive immunotherapeutic treatment characterized by extensive immune and inflammatory processes in the course of engraftment and further follow-up, this emphasizes the clinical relevance of pre-SCT albumin levels and underlines the difficulty of evaluating albumin levels during the course of the treatment.

In contrast to others [42], we have not found an association of serum total protein levels with NRM. In a multivariate analysis in a cohort of patients surviving 100 days after alloSCT, Wojnar et al. identified low serum total protein (< 60 g/l) on day $+ 100$ after allogeneic SCT as an independent risk factor for NRM. The authors suggested that low serum total protein may reflect most of the complications common about 3 months after SCT, including impaired liver function as part of both acute and chronic GvHD as well as infections, malabsorption, and low immunoglobulin levels, which may additionally contribute to an elevated risk of potentially lethal infections [42]. Additionally, in a retrospective analysis by Ferreira et al., a positive correlation between serum total protein level at discharge and survival time after alloSCT was shown; yet, the influence on NRM was not analyzed [52].

In our cohort, both low serum total protein pre-SCT and on d_{+100} after SCT were associated with increased NRM in univariate analysis. However, this correlation was not confirmed in multivariate analysis. These findings are supported by Dietrich et al., who showed that low serum total protein (< 70 g/l) is a strong predictor of relapse in patients undergoing allogeneic SCT for AML, but has no impact on NRM [28].

Overall, data on the impact of pre-SCT serum total protein on the outcome of SCT is very limited, possibly due to its limited ability in reflecting patients' nutritional status as it comprises many different serum proteins, including acute phase proteins and other short-lived proteins. In our cohort, only pre-SCT albumin, but not serum total protein was confirmed as a predictive marker of NRM in multivariate analysis. Yet, when assessing the nutritional status of

patients, nutrition-associated blood parameters are influenced by diverse (individual) factors and are subject to their own restrictions. In the setting of allogeneic SCT especially, edema needs to be considered for BMI evaluation and stress, infections, organ dysfunctions, and gastrointestinal symptoms for evaluation of blood parameters [25, 48, 49, 53]. Therefore, nutrition-associated parameters must always be interpreted in the clinical context of the individual patient.

In sum, it is apparent that nutritional parameters and status influence the outcome after allogeneic SCT. Since the nutritional status can be modified through nutritional support, the implementation of nutritional guidelines for patients during and after allogeneic SCT should be an essential component of clinical practice. In a survey among German, Swiss, and Austrian transplant centers, all centers stated that they had established nutritional guidelines for their patients undergoing alloSCT; yet, the clinical implementation of nutritional support was very heterogenous [54]. Therefore, more data are required to facilitate the development and implementation of evidence-based nutrition guidelines for patients undergoing alloSCT.

Our present single-center cohort study was limited by its retrospective design. Moreover, its heterogeneous cohort with a relatively small number of patients limited the interpretation of the results, especially in the subgroup analyses. Given our findings, larger studies and prospective trials are needed to confirm the adverse effects of pretransplant malnutrition and determine whether improving the nutritional status prior to alloSCT by an adequate pretransplant nutritional support would lead to an improved outcome.

Our findings of serum albumin deficiency both prior to SCT as well as post-SCT being associated with NRM after allogeneic SCT may not only add to the risk evaluation and counseling of patients but may also serve as a rational for early monitoring and interventions to improve the nutritional status in at-risk patients starting prior to SCT.

Declarations

References

1. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI et al (2015) Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for blood and marrow transplantation. Biol Blood Marrow Transplant 21(11):1863–1869. https://doi.org/10.1016/j.bbmt.2015.07.032

2. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M et al (2010) Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 363(22):2091–2101. https://doi.org/10.1056/NEJMoa1004383

3. McDonald GB, Sandmaier BM, Mielcarek M, Sorror M, Pergam SA, Cheng G-S et al (2020) Survival, nonrelapse mortality, and relapse-related mortality after allogeneic hematopoietic cell transplantation: comparing 2003–2007 versus 2013–2017 cohorts. Ann Intern Med. https://doi.org/10.7326/M19-2936

4. Carré M, Porcher R, Finke J, Ehninger G, Koster L, Beelen D et al (2019) Role of age and hematopoietic cell transplantation-specific comorbidity index in myelodysplastic patients undergoing an allotransplant: a retrospective study from the chronic malignancies Working Party of the European Group for blood and marrow transplantation. Biol Blood Marrow Transplant. https://doi.org/10.1016/j.bbmt.2019.10.015

5. Barrett AJ, Battiwalla M (2010) Relapse after allogeneic stem cell transplantation. Expert Rev Hematol 3(4):429–441. https://doi.org/10.1586/ehm.10.32

6. Tanaka Y, Kurosawa S, Tajima K, Tanaka T, Ito R, Inoue Y et al (2016) Analysis of non-relapse mortality and causes of death over 15 years following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 51(4):553–559. https://doi.org/10.1038/bmt.2015.330

7. Sorror ML, Storb RF, Sandmaier BM, Maziarz RT, Pulsipher MA, Maris MB et al (2014) Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. J Clin Oncol 32(29):3249–3256. https://doi.org/10.1200/JCO.2013.53.8157

8. ElSawy M, Storer BE, Pulsipher MA, Maziarz RT, Bhatia S, Maris MB et al (2015) Multi-centre validation of the prognostic value of the haematopoietic cell transplantation- specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. Br J Haematol 170(4):574–583. https://doi.org/10.1111/bjh.13476

9. Gilleece MH, Labopin M, Savani BN, Yakoub-Agha I, Socié G, Gedde-Dahl T et al (2020) Allogeneic haemopoietic transplantation for acute myeloid leukaemia in second complete remission: a registry report by the Acute Leukaemia Working Party of the EBMT. Leukemia 34(1):87–99. https://doi.org/10.1038/s41375-019-0527-4

10. McLornan D, Szydlo R, Koster L, Chalandon Y, Robin M, Wolschke C et al (2019) Myeloablative and reduced-intensity conditioned allogeneic hematopoietic stem cell transplantation in myelofibrosis: a retrospective study by the chronic malignancies Working Party of the European Society for blood and marrow transplantation. Biol Blood Marrow Transplant 25(11):2167–2171. https://doi.org/10.1016/j.bbmt.2019.06.034

11. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG et al (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106(8):2912–2919. https://doi.org/10.1182/blood-2005-05-2004

12. Martin-Salces M, de Paz R, Canales MA, Mesejo A, Hernandez-Navarro F (2008) Nutritional recommendations in hematopoietic stem cell transplantation. Nutrition 24(7–8):769–775. https://doi.org/10.1016/j.nut.2008.02.021

13. Zatarain L, Savani BN (2012) The role of nutrition and effects on the cytokine milieu in allogeneic hematopoietic stem cell transplantation. Cell Immunol 276(1–2):6–9. https://doi.org/10.1016/j.cellimm.2012.05.003

14. El-Ghammaz AMS, Ben Matoug R, Elzimaity M, Mostafa N (2017) Nutritional status of allogeneic hematopoietic stem cell transplantation recipients: influencing risk factors and impact on survival. Support Care Cancer 25(10):3085–3093. https://doi.org/10.1007/s00520-017-3716-6

15. Doney K, McMillen K, Buono L, Deeg HJ, Gooley T (2019) Impact of body mass index on outcomes of hematopoietic stem cell transplantation in adults. Biol Blood Marrow Transplant 25(3):613–620. https://doi.org/10.1016/j.bbmt.2018.10.006

16. Hadjibabaie M, Tabeefar H, Alimoghaddam K, Iravani M, Eslami K, Honarmand H et al (2012) The relationship between body mass index and outcomes in leukemic patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Transplant 26(1):149–155. https://doi.org/10.1111/j.1399-0012.2011.01445.x

17. Le Blanc K, Ringdén O, Remberger M (2003) A low body mass index is correlated with poor survival after allogeneic stem cell transplantation. Haematologica 88(9):1044–1052

18. Navarro WH, Agovi M-A, Logan BR, Ballen K, Bolwell BJ, Frangoul H et al (2010) Obesity does not preclude safe and effective myeloablative hematopoietic cell transplantation (HCT) for acute myelogenous leukemia (AML) in adults. Biol Blood Marrow Transplant 16(10):1442–1450. https://doi.org/10.1016/j.bbmt.2010.04.009

19. Aplenc R, Zhang M-J, Sung L, Zhu X, Ho VT, Cooke K et al (2014) Effect of body mass in children with hematologic malignancies undergoing allogeneic bone marrow transplantation. Blood 123(22):3504–3511. https://doi.org/10.1182/blood-2013-03-490334

20. Hirose EY, de Molla VC, Gonçalves MV, Pereira AD, Szor RS, da Fonseca ARBM et al (2019) The impact of pretransplant malnutrition on allogeneic hematopoietic stem cell transplantation outcomes. Clin Nutr ESPEN 33:213–219. https://doi.org/10.1016/j.clnesp.2019.05.005

21. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL (1972) Indices of relative weight and obesity. J Chronic Dis 25(6):329–343. https://doi.org/10.1016/0021-9681(72)90027-6

22. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1–253.

23. Iestra JA, Fibbe WE, Zwinderman AH, van Staveren WA, Kromhout D (2002) Body weight recovery, eating difficulties and compliance with dietary advice in the first year after stem cell transplantation: a prospective study. Bone Marrow Transplant 29(5):417–424. https://doi.org/10.1038/sj.bmt.1703375

24. Jacobsohn DA, Margolis J, Doherty J, Anders V, Vogelsang GB (2002) Weight loss and malnutrition in patients with chronic graft-versus-host disease. Bone Marrow Transplant 29(3):231–236. https://doi.org/10.1038/sj.bmt.1703352

25. Kyle UG, Chalandon Y, Miralbell R, Karsegard VL, Hans D, Trombetti A et al (2005) Longitudinal follow-up of body composition in hematopoietic stem cell transplant patients. Bone Marrow Transplant 35(12):1171–1177. https://doi.org/10.1038/sj.bmt.1704996

26. Urbain P, Birlinger J, Lambert C, Finke J, Bertz H, Biesalski H-K (2013) Longitudinal follow-up of nutritional status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 48(3):446–451. https://doi.org/10.1038/bmt.2012.158

27. Watanabe T, Kinoshita T, Itoh K, Yoshimura K, Ogura M, Kagami Y et al (2010) Pretreatment total serum protein is a significant prognostic factor for the outcome of patients with peripheral T/natural killer-cell lymphomas. Leuk Lymphoma 51(5):813–821. https://doi.org/10.3109/10428191003721359

28. Dietrich S, Radujkovic A, Stölzel F, Falk CS, Benner A, Schaich M et al (2015) Pretransplant metabolic distress predicts relapse of acute myeloid leukemia after allogeneic stem cell transplantation. Transplantation 99(5):1065–1071. https://doi.org/10.1097/TP.0000000000000471

29. Artz AS, Logan B, Zhu X, Akpek G, Bufarull RM, Gupta V et al (2016) The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes. Haematologica 101(11):1426–1433. https://doi.org/10.3324/haematol.2016.145847

30. Sommacal HM, Gazal CHA, Jochims AMK, Beghetto M, Paz A, Silla LMdR et al (2012) Clinical impact of systematic nutritional care in adults submitted to allogeneic hematopoietic stem cell transplantation. Rev Bras Hematol Hemoter 34(5):334–8. https://doi.org/10.5581/1516-8484.20120088

31. Skaarud KJ, Hjermstad MJ, Bye A, Veierød MB, Gudmundstuen AM, Lundin KEA et al (2018) Effects of individualized nutrition after allogeneic hematopoietic stem cell transplantation following myeloablative conditioning; a randomized controlled trial. Clin Nutr ESPEN 28:59–66. https://doi.org/10.1016/j.clnesp.2018.08.002

32. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V et al (2009) Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 15(12):1628–1633. https://doi.org/10.1016/j.bbmt.2009.07.004

33. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D et al (2008) Cachexia: a new definition. Clin Nutr 27(6):793–799. https://doi.org/10.1016/j.clnu.2008.06.013

34. Voshtina E, Szabo A, Hamadani M, Fenske TS, D'Souza A, Chhabra S et al (2019) Impact of obesity on clinical outcomes of

elderly patients undergoing allogeneic hematopoietic cell transplantation for myeloid malignancies. Biol Blood Marrow Transplant 25(1):e33–e38. https://doi.org/10.1016/j.bbmt.2018.08.031

35. Fuji S, Takano K, Mori T, Eto T, Taniguchi S, Ohashi K et al (2014) Impact of pretransplant body mass index on the clinical outcome after allogeneic hematopoietic SCT. Bone Marrow Transplant 49(12):1505–1512. https://doi.org/10.1038/bmt.2014.178

36. Gleimer M, Li Y, Chang L, Paczesny S, Hanauer DA, Frame DG et al (2015) Baseline body mass index among children and adults undergoing allogeneic hematopoietic cell transplantation: clinical characteristics and outcomes. Bone Marrow Transplant 50(3):402–410. https://doi.org/10.1038/bmt.2014.280

37. Rieger CT, Wischumerski I, Rust C, Fiegl M (2015) Weight loss and decrease of body mass index during allogeneic stem cell transplantation are common events with limited clinical impact. PLoS One 10(12):e0145445. https://doi.org/10.1371/journal.pone.0145445

38. Fuji S, Mori T, Khattry N, Cheng J, Do YR, Yakushijin K et al (2015) Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. Bone Marrow Transplant 50(1):100–105. https://doi.org/10.1038/bmt.2014.228

39. Sivgin S, Baldane S, Ozenmis T, Keklik M, Kaynar L, Kurnaz F et al (2013) The impact of pretransplant hypoalbuminemia on survival in patients with leukemia who underwent allogeneic hematopoietic stem cell transplantation (alloHSCT): a nutritional problem? Transplant Proc 45(9):3371–3374. https://doi.org/10.1016/j.transproceed.2013.02.144

40. Shouval R, de Jong CN, Fein J, Broers AEC, Danylesko I, Shimoni A et al (2018) Baseline renal function and albumin are powerful predictors for allogeneic transplantation-related mortality. Biol Blood Marrow Transplant 24(8):1685–1691. https://doi.org/10.1016/j.bbmt.2018.05.005

41. Kharfan-Dabaja MA, Chavez JC, Yu D, Zhu W, Fernandez-Vertiz EI, Perkins J et al (2011) Severe hypoalbuminemia at day 90 predicts worse nonrelapse mortality and overall survival after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant 17(3):384–393. https://doi.org/10.1016/j.bbmt.2010.07.011

42. Wojnar J, Giebel S, Holowiecka-Goral A, Markiewicz M, Wylezol I, Kopera M et al (2007) Prediction of nonrelapse mortality for patients surviving 100 days after allogeneic hematopoietic stem cell transplantation. Transplant Proc 39(10):3375–3379. https://doi.org/10.1016/j.transproceed.2007.03.111

43. Vaughn JE, Storer BE, Armand P, Raimondi R, Gibson C, Rambaldi A et al (2015) Design and validation of an augmented hematopoietic cell transplantation-comorbidity index comprising pretransplant ferritin, albumin, and platelet count for prediction of outcomes after allogeneic transplantation. Biol Blood Marrow Transplant 21(8):1418–1424. https://doi.org/10.1016/j.bbmt.2015.04.002

44. ElSawy M, Storer BE, Milano F, Sandmaier BM, Delaney C, Salit RB et al (2019) Prognostic performance of the augmented hematopoietic cell transplantation-specific comorbidity/age index in recipients of allogeneic hematopoietic stem cell transplantation from alternative graft sources. Biol Blood Marrow Transplant 25(5):1045–1052. https://doi.org/10.1016/j.bbmt.2018.11.030

45. Corzo-León DE, Satlin MJ, Soave R, Shore TB, Schuetz AN, Jacobs SE et al (2015) Epidemiology and outcomes of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens. Mycoses 58(6):325–336. https://doi.org/10.1111/myc.12318

46. Kharfan-Dabaja MA, Sheets K, Kumar A, Murthy HS, Nishihori T, Tsalatsanis A et al (2018) Hypoalbuminaemia segregates different prognostic subgroups within the refined standard risk acute graft-versus-host disease score. Br J Haematol 180(6):854–862. https://doi.org/10.1111/bjh.15105

47. Ayuk F, Bussmann L, Zabelina T, Veit R, Alchalby H, Wolschke C et al (2014) Serum albumin level predicts survival of patients with gastrointestinal acute graft-versus-host disease after allogeneic stem cell transplantation. Ann Hematol 93(5):855–861. https://doi.org/10.1007/s00277-013-1957-0

48. Arfons LM, Lazarus HM (2005) Total parenteral nutrition and hematopoietic stem cell transplantation: an expensive placebo? Bone Marrow Transplant 36(4):281–288. https://doi.org/10.1038/sj.bmt.1705039

49. Hess CT (2009) Monitoring laboratory values: protein and albumin. Adv Skin Wound Care 22(1):48. https://doi.org/10.1097/01.ASW.0000343728.99179.99

50. Soeters PB, Wolfe RR, Shenkin A (2019) Hypoalbuminemia: pathogenesis and clinical significance. JPEN J Parenter Enteral Nutr 43(2):181–193. https://doi.org/10.1002/jpen.1451

51. Grkovic L, Baird K, Steinberg SM, Williams KM, Pulanic D, Cowen EW et al (2012) Clinical laboratory markers of inflammation as determinants of chronic graft-versus-host disease activity and NIH global severity. Leukemia 26(4):633–643. https://doi.org/10.1038/leu.2011.254

52. Ferreira EE, Guerra DC, Baluz K, de Resende Furtado W, da Silva Bouzas LF (2014) Nutritional status of patients submitted to transplantation of allogeneic hematopoietic stem cells: a retrospective study. Rev Bras Hematol Hemoter 36(6):414–419. https://doi.org/10.1016/j.bjhh.2014.07.014

53. Stratton RJ, Green CJ, Elia M (2003) Disease-related malnutrition: an evidence-based approach to treatment. CABI, Wallingford

54. Toenges R, Greinix H, Lawitschka A, Halter J, Baumgartner A, Simon A et al (2021) Current practice in nutrition after allogeneic hematopoietic stem cell transplantation - results from a survey among hematopoietic stem cell transplant centers. Clin Nutr 40(4):1571–1577. https://doi.org/10.1016/j.clnu.2021.02.030