UNIVERSITE D'AIX-MARSEILLE

Ecole doctorale de Science de vie et de la santé

En co direction avec:

American University of Beirut Medical Center

Thèse présentée pour obtenir le grade universitaire de docteur

Discipline : Pathologie Humaine

Spécialité : Oncologie

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L'impact d'une intervention nutritionelle chez les receveurs de cellules souches hématopoïétiques: résultats d'un essai contrôlé randomisé

The Impact of Counseling on Nutritional Status among Hematopoietic Stem Cell Recipients: Results of a Randomized Controlled Trial

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Résumé

Contexte: Le conditionnement précédant la greffe de cellules souches hématopoïétiques (CSH) est associé avec des taux élevés de malnutrition à la sortie de l'hôpital et jusqu'à 100 jours après la greffe de CSH.

Objectif: Cette étude visait à évaluer l'impact d'une intervention nutritionnelle fournie à la sortie de l'hôpital sur l'état nutritionnel, 100 jours après la greffe de CSH.

Conception: Il s'agissait d'un essai contrôlé randomisé dans un centre unique. Les patients adultes recevant la greffe étaient admissibles à y participer. La collecte de données et l'intervention ont débuté à l'admission et à la sortie de l'hôpital, respectivement. Après la sorti de l'hôpital, les patients recrutés ont été randomisés dans un groupe témoin (GT) recevant des soins habituels et dans un groupe d'intervention (GI) recevant des conseils nutritionnels mensuels après la sortie de l'hôpital afin d'optimiser leur état nutritionnel et fonctionnel. Après la sortie de l'hôpital, des évaluations ont été effectuées aux jours 30, 60 et 100 après la greffe pour les deux groupes. Le résultat principal était le score de l'évaluation globale subjective générée par le patient (PGSGA) au jour 100 après la greffe. La malnutrition a également été évaluée par le score de malnutrition de la société américaine de nutrition parentérale et entérale / Académie de nutrition et diététique (AND-ASPEN). L'indice de masse de graisse a été évalué par analyse de bioimpédance. La force de la poignée a été comparée aux données normatives pour évaluer sa diminution. La qualité de vie a été évaluée à l'aide de l'outil d'évaluation fonctionnelle de la thérapie du cancer - greffe de cellules souches hématopoïétiques (FACT-BMT).

Résultats: 52 participants ont été randomisés (août 2016 jusqu'en août 2017) et 46 ont été analysés [65% d'hommes, 63% de greffes autologues, GI (n = 22), GT (n = 24)]. À l'admission à l'hôpital, le pourcentage de patients bien nourris selon le PGSGA était faible (45% GI vs. 50% GT, p = 0,79) et le pourcentage de patients ayant une force de la poignée faible était élevé (82% GI contre 67% GT, p = 0,24) dans les deux groupes. Cent jours après la greffe, le pourcentage de patients bien nourris n'était pas significativement différent entre les groupes selon l'outil de PGSGA (72% GI vs 43% GT, p = 0,063). Le pourcentage de patients bien nourris selon le scores AND-ASPEN s'est amélioré dans le GI (14% vs 50%, p = 0,02) et est resté le même dans le GT (50% vs 48%, p = 1) par rapport aux valeurs d'admission. Au jour 100 après la greffe, le GI avait un apport de protéine [médiane (grammes)]: 90 GI vs 80 GT, p = 0,037] et de calorie [[pourcentage médian par rapport aux besoins): 116 vs 85, p = 0,017] plus élevés. Comparé aux taux moyens à l'admission, le pourcentage de patients avec un indice de masse de graisse élevé a diminué chez le GI (71% contre 56%, p = 0,046) et non pas chez le GT (65% contre 62%, p = 0,56) 100 jours après la greffe. Il n'y avait pas de différence dans la force de la poignée entre les groupes. 100 jours après la greffe, le score FACT-BMT était meilleur chez le GI (117 GI contre 95 CG, p = 0,036).

Conclusion: cette étude a montré que la prévalence de la malnutrition est élevée chez les patients recevant une greffe de cellules souches hématopoïétiques même avant la greffe. Le conseil nutritionnel après la greffe de CSH a amerlioé le status nutritionel selon AND-ASPEN mais non pas selon le scores PGSGA. L'intervention a amélioré aussi l'apport en calorie et en protéine et la qualité de vie des patients 100 jours après la greffe.

Mots-clés: Greffe de cellules souches hématopoïétiques, conseil nutritionnel, qualité de vie, force de la poignée.

Abstract

Background: Conditioning preceding Hematopoietic Stem Cell Transplantation (HSCT) is associated with elevated rates of malnutrition at hospital discharge and up until 100 days post HSCT.

Objective: This study aimed to assess the impact of a nutrition intervention provided at hospital discharge on nutritional status 100 days post HSCT (defined as T4).

Design: This was a single center randomized controlled trial. Adult patients receiving HSCT were eligible to participate. Data collection and intervention were initiated at admission and hospital discharge, respectively. Around discharge from the hospital, recruited patients were randomized to a Control Group (CG) receiving usual care and to an Intervention Group (IG) receiving nutritional counseling on a monthly basis post discharge to optimize their nutritional and functional status. Post hospital discharge, assessments were done at days 30, 60 and 100 post HSCT for both groups. The primary outcome was the Patient Generated Subjective Global Assessment (PGSGA) scores at day 100 post HSCT (termed T4). Malnutrition was also assessed though the American Society for Parenteral and Enteral Nutrition/ Academy of Nutrition and Dietetics malnutrition score. Fat Mass Index (FMI) was assessed via bioimpedance analysis. Handgrip Strength (HGS) was compared to normative data to assess diminishment. Quality of Life (QoL) was assessed through the Functional Assessment for Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) tool.

Results: 52 participants were randomized (August 2016 until August 2017) and 46 were analyzed [65% males, 63% autologous HSCT, IG (n=22), CG (n=24)]. At hospital admission, the percent of patients who were well nourished as per PGSGA criteria was low (45% IG vs. 50% CG, p=0.79) and the percentage of patients with diminished HGS was high (82% IG vs. 67% CG, p=0.24) in both groups. At T4, the percent of well-nourished patients was not significantly different between groups when assessed via PGSGA (72% IG vs. 43% CG, p=0.063). Yet, the percent of well nourished patients as per AND-ASPEN scores at T4 improved in IG (14% vs 50%, p=0.02) and remained the same in CG (50% vs. 48%, p=1) compared to admission values. IG had higher protein intake [median (grams)]: 90 IG vs. 80 CG, p=0.037 and caloric intake (median percent compared to needs): 116 vs 85, p=0.017. Compared to admission, percentage of patients with high FMI decreased in the IG (71% vs. 56%, p=0.046) and not in CG (65% vs. 62%, p=0.56) at T4. There was no difference in HGS between groups. At T4, FACT-BMT score was better in IG (117 IG vs 95 CG, p=0.036).

Conclusion: This RCT showed that malnutrition is highly prevalent among HSCT patients even pre HSCT. Nutritional counseling post HSCT improved patients' caloric and protein intake, nutritional status as per AND-ASPEN criteria and QoL but did not significantly improve PGSGA scores.

Remerciements

Ecrire cette lettre de remerciement est un rêve qui devient réalité. Je commence par remercier mon père céleste pour la confiance qu'il m'a donné de prendre une route moins fréquentée, et pour m'avoir accompagné et encourager à travers tous les défis et obstacles.

Un proverbe africain dit: "Si vous voulez aller vite, partez seul. Si vous voulez aller loin, allez ensemble. "Je voudrais exprimer ma gratitude aux personnes qui m'ont aidé à aller loin:

* Les docteurs El-Cheikh et Blaise pour avoir cru à la valeur de notre projet et pour m'avoir fourni l'encouragement, le temps et le soutien nécessaires pour le mener à fin.

* Mes directeurs et collègues du service de nutrition clinique qui ont facilité et soutenu mon parcours de recherche.

* Le fondateur et les fournisseurs du programme de recherche Scholars in Health Research Program, un programme de recherche qui m'a fourni, ainsi que de nombreux autre chercheurs, des compétences de recherche requis pour réussir dans nos carrières de recherche.

* Les membres du jury de ma thèse qui ont consacré leur temps à réviser la thèse et à fournir des commentaires précieux.

* Les assistantes administratives de l'Unité Transversale de Thérapie Cellulaire à l'Institut Paoli Calmettes (Mme Mansuetto et Mlle Nasri) et du bureau des doctorants de la Faculté de Médecine (Mme Marouzé et Mme Douadi) pour le soutien fourni pour compléter toutes les étapes d'enregistrement et de candidature.

* Les patients qui ont participé à notre étude ainsi que les équipes soignantes du programme de transplantation de moelle osseuse, l'unité Bassil In et le programme de gestion bariatrique et métabolique au centre médical de l'université américaine de Beyrouth pour avoir facilité la collecte de données et les rendez-vous des patients.

* Batoul Manana pour son soutien à la collecte de données. Ce fut un plaisir de travailler avec une personne aussi passionnée.

Maman et Papa: je vous dédie cette thèse. Je suis très reconnaissante pour votre soutien et votre encouragement à persévérer et à continuer de grandir. Ce ne sont pas des traits que vous m'aviez appris à travers les mots, mais bien de la modélisation dans notre famille et dans votre travail. Les bénédictions pouvaient être aussi minuscules que la nourriture préparée et aussi grands que l'amour que vous m'avez donnés ainsi qu'à mes chers Ramy, Odile, Chadi, Jad et Mayssa.

Enfin, je remercie mes amis; votre présence dans ma vie rend définitivement la balade digne d'être vécue. Merci pour votre soutien, vos prières et surtout votre amour.
Ça n'aurait pas été amusant sans vous!

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Introduction

Malnutrition is a condition characterized by imbalances in energy, protein and micronutrient intake or absorption, weight changes, loss of lean body mass and functional impairment [1,2]. Historically, albumin was thought to be an indicator of malnutrition. Yet more recent literature showed that serum albumin, a positive acute phase reactant and is reflective of inflammatory status which often but not always accompanies malnutrition[3]. Indeed, malnutrition can be defined based on the presence and the nature of inflammation (acute vs. chronic). Starvation related malnutrition is commonly present in the setting of food insecurity and eating disorders. Chronic disease malnutrition can accompany inflammatory conditions that last 3 months or longer whereas acute or injury related malnutrition can be faced in the setting of acute states such as burns, major infections, etc. [3]. Malnutrition assessment is commonly done using the Patient Generated Subjective Global Assessment (PGSGA), a tool accepted by the Academy of Nutrition Dietetics (AND) as a reliable nutritional assessment method to be used among cancer patients[4]. The PGSGA categorical score defines the degree of malnutrition based on three categories (category A reflecting good nutritional status, category B revealing moderate malnutrition and category C indicating severe malnutrition) whereas the continuous score is a triaging tool with higher scores representing an increased risk of malnutrition, and scores 4 or above reflecting a need for a nutrition intervention[5]. Another malnutrition assessment tool recommended by AND and the American Society for Parenteral and Enteral Nutrition (ASPEN) is the AND-ASPEN tool that assesses malnutrition based on patients muscle and fat wasting, Hand

Grip Strength (HGS), edema, compromised caloric intake and weight loss [3]. Muscle and fat wasting and edema can be evaluated through body composition techniques as well as through nutrition focused physical assessment [6]. HGS, used to reflect muscle strength, is evaluated through handgrip dynamometry and is considered diminished when values are below gender, hand and population specific normative values[7]. Decreased caloric and energy intake are evaluated by comparing patients' individual requirements to their oral intake. Multiple techniques have been advised to evaluate individuals' macronutrient and micronutrient intake depending on the assessment goal [8].

Two conditions that are closely related to malnutrition are sarcopenia and cancer cachexia. Sarcopenia, a condition that was originally used to portray muscle wasting among elderly, is now used to describe diminished muscle mass, strength and performance status in all age categories[9]. It can result from a reduction in the signals from brain to muscle inducing movement, a decrease in protein synthesis, energy and/or protein intake to maintain muscle mass and strength[10]. The golden method to assess sarcopenia is through analysis of Computed Tomography (CT) when done at the level of the lumbar vertebrae 3 or 4. In this method, measured skeletal muscle mass is used to predict total muscle mass with levels below gender specific cut-off reflective of sarcopenia[11,12]. As CT imaging is associated with radiation exposure, CT derived body composition assessment is only recommended to be conducted when CT is done for disease evaluation. An alternative method to measure body composition is Bio Impedance Analysis (BIA). Body composition assessment in BIA is based on the body's conducive properties with the compartments with the higher water and lower fat content associated with decreased impedance[11]. With the assumption of constant hydration of 73%, fat free mass and fat mass are calculated, allowing for the diagnosis of sarcopenia[9] and obesity[13] respectively. Regression equations based on individuals'

height, gender, resistance to electric current and age allowed for the use of BIA to predict skeletal muscle mass [14]. Even though BIA can be affected by many factors including hydration, status, recent physical activity and dietary intake, it remains a safe, practical and cost effective method to measure body composition changes when CT is not available[11].

Cancer cachexia share common features with malnutrition and sarcopenia. Its defining feature is the eminent presence of systematic inflammation characterized with high levels of cytokines produced by the tumor and the host such as interleukin 1, interleukin 6 and tumor necrosis factor alpha which increase the host's metabolic rate, inhibit adipocyte and skeletal muscle masses differentiation, promote proteolysis and cause anorexia [15]. Tumor cells also affect macronutrient utilization and metabolism. Increased glucose needs are met through glycolysis, hepatic glycogenolysis and gluconeogenesis through the Cori Cycle and proteolysis [15,16]. Cancer cachexia has three stages: pre-cachexia, cachexia and refractory cachexia, classified based on weight loss, anorexia, insulin resistance and other metabolic and functional changes [16,17].

Hematopoietic Stem Cell Transplantation (HSCT) is a standard of care used in the treatment of many hematological diseases and malignancies and metabolic disorders[18]. HSCT involves the collection of stem cells from the peripheral blood or bone marrow of the patients themselves (autologous HSCT) or from matched donors (allogeneic HSCT). HSCT is preceded by the provision of chemotherapy sometimes accompanied with total body irradiation, and prophylactic antibiotic, antiviral and antifungal therapy. The goal of conditioning therapy is to reduce the tumor burden in neoplastic diseases, to allow for engraftment of infused cells and to reduce the risk of graft rejection in allogeneic HSCT [19]. Conditioning intensity is considered myeloablative when provided at a high dose to cause profound cytopenia and require stem cell infusion for recovery. Reduced intensity

conditioning does not cause cytopenia as profound as in myeloablative conditioning and is associated with lower toxicity [20]. Treatment intensity is based on disease type, stage, and progression, patients' age among other relevant factors[18]. Conditioning regimen accompanying HSCT is associated with Gastro Intestinal (GI) toxicity, pancreatic insufficiency, commonly compromising patients' food intake, nutritional status and functioning level [18,21]. Main GI symptoms experienced are oral mucositis, dry mouth, adynophagia, taste alterations, nausea and vomiting. Conditioning regimen also affects intestinal permeability, which has been described to start as early as 2 days post cytotoxic treatment, paving the way for other GI symptoms[22,23]. HSCT patients are often advised to limit their intake of raw fruits and vegetables and to follow a 'low microbial diet' that is supposed to reduce the risk of food borne illnesses. Even though, studies have shown no benefit of its use, many centers still advise it to their patients[24-26]. Additional factors limiting food intake among HSCT patients is the poor Quality of Life (QoL) that patients experience during and following transplantation[27-29].

Malnutrition, sarcopenia and cachexia are associated with worse QoL, response to treatment and survival in patients receiving chemotherapy [30-36]. In the setting of HSCT, malnutrition is associated with longer hospitalization, more febrile days and bacterial infection and lower survival [34,35,37]. Studies assessing malnutrition rates in HSCT showed that malnutrition rates were low at admission (ranging between 4-6%) then they spike up at hospital discharge (ranging between 35-60%), and then gradually decrease post discharge [21,38]. A prospective cohort study suggested that all patients at discharge and half the patients 100 days post HSCT required a nutrition intervention when assessed with the continuous PGSGA score [21]. Even though patients had improved QoL, physical activity level and lean body mass post HSCT, they did not regain their pre-HSCT levels 100 days post-transplantation[21]. Loss of lean body mass was correlated with low caloric

and protein intake in a study among umbilical cord HSCT patients [39] but not among allogeneic HSCT[40].

Recent studies showed that caregivers and physicians tended to misclassify nutritional status of cancer patients [41,42]. To prevent and manage malnutrition among cancer patients, the European Society for Parenteral and Enteral Nutrition (ESPEN) recommends screening all cancer patients irrespective of their Body Mass Index (BMI) and to incorporate measures of body composition, inflammatory markers and performance status in nutritional assessment [43]. Nutrition support has been recommended as part of a model for cancer cachexia prevention and rehabilitation[34]. Patients should be counseled with individualized meal plans to optimize their nutrient intake and to meet their dietary needs[43].

Nutrition interventions among cancer patients receiving chemotherapy reflected positive effects on nutritional status. Isenring et al. evaluated the effect of intensive nutrition counseling on nutritional and functional outcomes in cancer patients receiving radiotherapy to the GI or head and neck area[44]. At 12 weeks post randomization, patients in the intervention group had better PGSGA scores compared to those in the usual care group[44]. A follow up trial of colorectal patients showed that at a median follow up of 6.5 years, patients who received nutritional counseling had improved caloric and protein intake, QoL, survival, and reduced toxicity compared to those who did not receive counseling[45]. A systematic review assessing the efficacy of nutrition interventions in oncology patients revealed that nutrition counseling is effective in improving patients' protein and caloric intake and PGSGA scores. QoL was positively correlated with nutritional intake and status in 3 out of the 4 relevant RCT. However, not all RCT were effective in causing changes in weight, triceps and scapular muscle masses [46]. Survival was affected by nutritional status in one trial where depleted nutritional

status predicted worse survival and late toxicity [47]. No significant changes in survival rates were noted in other trials [46]. Among autologous (auto) HSCT patients HSCT, one pilot telephone based nutrition and physical activity intervention was performed at hospital discharge. This study showed that telephone based counseling had no significant impact on caloric and protein intake, nutritional status, body composition and QoL 100 days post HSCT[48]. To our knowledge, there are no RCT that evaluated the effect of nutritional counseling in a clinical setting post hospital discharge. In view of the impact of malnutrition on morbidity among HSCT patients, the study assessed the effect of nutritional counseling provided monthly at and post hospital discharge on the PGSGA score 100 days post HSCT.

Patients and Methods

Reporting of this study follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines [49] (Appendix 1).

Design

This study was a single center, open label RCT with a parallel design. Patients planned to be admitted to the Bone Marrow Transplantation (BMT) unit in the American University of Beirut Medical Center (AUBMC) were invited to participate in the study. All adult patients (≥16 years) admitted for HSCT in AUBMC and able to undergo body composition assessment were eligible to participate. Exclusion criteria included inability to present to > 1 follow up visit post discharge. Participants were briefed on the study by the BMT coordinator or case manager and those who agreed to participate were provided with a comprehensive informed consent by a member of the research team explaining the study goals, benefits and risks, the commitment involved, as well as the option to leave the study at any point without any impact on the treatment or care received. Data collection was initiated at hospital admission (T0) and continued at hospital discharge (T1). Follow up visits were conducted at days 30 (T2), 60 (T3) and 100 (T4) post HSCT in the private clinics of the Clinical Nutrition department. Day zero was defined as the day of the HSCT infusion.

Randomization

Around discharge time (T1), participants were randomized to an Intervention Group (IG) and to a Control Group (CG). In view of the sample size (described in "The Statistical

Considerations" section), and to avoid imbalances, randomization was based on permuted block sampling with 4 participants per block with an allocation ratio of 1:1. Sequence generation was performed via on online software: Sealed Envelope Ltd. 2016. The research assistant performed the sequence generation and informed the dietitians about the allocation. This study involved no blinding.

Intervention

Prior to hospital discharge, both groups were advised on food safety guidelines to reduce the risk of food borne illnesses [50]. CG patients did not receive nutritional counseling by the dietitian as outpatients. Information was collected on all variables without providing them with counseling. As for the IG patients, they were advised on a diet high in energy and protein and tailored to their anthropometrics and co morbidities at hospital discharge and were assessed and counseled at T2, T3 and T4. Oral nutrition supplements were prescribed if needed to meet patients' caloric and protein requirements of IG patients

On outpatient visits, patients' compliance was measured by comparing patients' caloric, protein and fluid intake to the recommended daily intake. Caloric and protein needs were calculated based on patients adjusted weight: 30-35 Calories and 1.5 grams protein per kg adjusted weight. Ideal weight was calculated using the Hamwi method. Adjusted weight was calculated using a fat free mass factor of 0.32 for obese females, 0.38 for obese males and 0.25 for all overweight patients.

If not contraindicated by the medical team, IG patients were encouraged by the dietitians to gradually increase their physical activity levels. Target physical activity goals for patients were in line with the physical activity recommendations for cancer survivors: 150 minutes of moderate intensity activity through-out the week and muscle-strengthening activities 2 or more days a week[51].

Assessment Tools

Unless indicated otherwise, patients' nutritional status, body composition and functional assessment were evaluated at all points for both groups (Figure 1). Below is a description of the assessment tools used.

Nutritional Status

Nutritional status was assessed using the PGSGA and the AND-ASPEN score.

The PGSGA comprises two sections:

- o Section 1 gathers information on the patient's body weight, food intake, symptoms affecting food intake and activities. This section is usually filled by the patient. In the absence of a validated Arabic PGSGA version, the research team has obtained permission from Ptglobal (authors of PGSGA) for the clinician to administer the first section of the PGSGA based on an oral script in Arabic, which was reviewed by 3 native Arabic speakers.
- o Section 2, filled by the clinician, assesses the patient's metabolic demand (presence, intensity and duration of fever and use and dosage of corticosteroids) and his/her muscle, fat and fluid statuses based on physical examination.

The AND-ASPEN tool was also used to diagnose malnutrition. Malnutrition was deemed present when at least 2 criteria of the following were present: significant weight loss, diminished caloric and protein intake, low hand grip strength and fat and/or muscle wasting (assessed through physical examination) [3].

Dietary Recall

24 hour recall is an assessment tool used to assess patients' food intake over 24 hours. Analysis of the 24 hour recall allows for the identification of eating patterns as

well as calculation of caloric and protein intake. In inpatient visits, recall assessed patients' intake of the previous day and focused on caloric and protein intake. At outpatient visits, recall focused on patients' typical intake since the last assessment point. Patients were asked to provide recalls on 2 weekdays and 1 weekend day. Macronutrient analysis was conducted on Nutritionist Pro®.

Body Composition

BIA is a noninvasive and safe technique to measure body composition parameters. Estimation of body composition parameters is done through the passage of an electric current through contact of the hands and feet with conductive surfaces allowing for quantification of resistance and reactance. Fat free mass is estimated at a constant hydration of 73%[11]. In this RCT, we used the Inbody 230®, a segmental and multi frequency (50 and 100 kHz) BIA machine for body composition assessment. To minimize variation, patients were asked to fast for 2 hours, and to urinate prior to BIA measurement. Output variables were total body water, fat mass, skeletal muscle mass and waist to hip ratio. Skeletal muscle mass was normalized to height to calculate Skeletal Muscle Index (SMI). Fat Mass Index (FMI) was calculated as FM normalized to height (m^2). FMI was derived from Kelly's categorization with fewer groups due to the small sample size [13].

- "Low" for FMI <3kg/m^2 and <5 kg/m^2 for males and females respectively
- "normal" for FMI in the ranges of 3.0-6.0 kg/m^2 and 5.0-9.0 kg/m^2 for males and females respectively
- "High" for FMI ≥6.1-9 kg/m^2 and 9.1-13.0 kg/m^2 for males and females respectively

Hand Grip Strength

HGS, a validated marker of functional status among cancer patients, complemented the patient's nutrition assessment [7]. Patients performed the HGS measurement using their dominant hand while sitting in chair or inpatient bed (when unable to sit in chair) with the shoulders adducted, neutrally rotated and elbow flexed at 90 degrees. Each patient was asked to complete a maximal contraction for 5 seconds. A standardized method for encouragement was used, asking the participants to apply maximal contraction for 5 seconds and then to relax. Measurement was repeated three times with a rest time of 10-20 seconds. The best of the three measurements was recorded for analysis. HGS was measured at inpatient and outpatient assessments (Figure 2). To determine if HGS measurements were diminished or not, they were compared with normative data reference that was deemed closest to our patient population [52].

Performance status

The Karnofsky performance scale was used for the assessment of functional performance of the patients at inpatient and outpatient assessments [53].

Quality of Life

Patients' QoL was assessed using the Functional Assessment of Cancer Therapy (FACT)-BMT questionnaire version 4 at days +2, +30, +60 and +100 post HSCT and at hospital discharge. FACT-BMT assesses patients' physical, functional, emotional and social well-being as well as other HSCT specific concerns. A validated Arabic version was self-administered by patients [54] (Figure 2).

Physical Activity

Physical activity was assessed using a questionnaire evaluating patients' habitual activity doing house chores as well as walking time at outpatient visits (Figure 2). The questionnaire that reflects patients' activity during the last 7 days was piloted on 5 adult

Lebanese individuals to ensure that questions can be well understood. Patients' activity was recorded in Metabolic Equivalent (METs)[55].

Outcomes

Study's primary outcome was the proportion of patients with a PGSGA categorical score≥4 assessed at T4. Secondary outcomes assessed were SMI, QoL, HGS and hospital readmissions assessed at T4.

Research Team

Study enrollment and data collection was performed by a research assistant and a data manager. Physicians were in charge of disease and medical evaluation. Two dietitians were in charge of nutritional assessment and counseling. To minimize inter-rater variability, dietitians conducted cross training on the study assessment tools prior to study initiation. Written protocols guided patient assessment and data collection processes.

Ethical Considerations

The study obtained approval from the Institutional Review Board at AUB. The control group was receiving the standard of care at AUBMC which does not involve nutritional intervention post discharge. Any participant found to be in need of nutrition intervention by the medical team was deemed to receive it regardless of the initial treatment allocation. Patients' allocation did not affect the medical treatment and conditioning received in the facility.

Statistical Considerations

Sample size calculation was based on a similar study assessing the effect of nutritional counseling on patients receiving radiotherapy [44]. Isenring et al. evaluated the

effect of an intensive nutrition counseling intervention on body weight, body composition, QoL and physical functioning of cancer patients. At 12 weeks, patients in the IG group had better PGSGA scores compared to those in the CG group (mean PGSGA= 4.8 vs. 8.4 respectively, p-value=0.02). The difference in the PGSGA scores between the intervention and control groups was around 43%.

Inspired from the above differences, we hypothesized that the nutrition intervention would reduce the proportion of patients requiring nutritional counseling (defined with a PGSGA score≥4) at T4 by 40%. Accordingly, and considering a power of 80%, an attrition rate of 30%, total sample size needed was 26 patients per arm.

Analysis was done based on 'intention to treat' analysis. Statistical significance was reported at the conventional level at $p < 0.05$. Measures of analyses were performed on IBM SPSS version 24 (SPSS Inc. Chicago, IL, USA). Due to the small size per group, the continuous variables were presented as medians and Inter Quartile Range (IQR) and non-parametric testing was used. Categorical variables were presented as counts and percentages. Patients' characteristics were compared by assignment group using Chi-square or Fisher Exact tests for categorical variables, and Mann Whitney test for continuous variables. Changes in the same variables were assessed using Friedman and Cochran tests for continuous and categorical variables, respectively. Analysis of QoL subscales was done using General Linear Models. Univariate logistic and linear regression (backward conditional) were used respectively to assess predictors of PGSGA, and of total QoL score at T4.

Results

Transplant and demographic characteristics

Consecutive eligible patients (n=68) were approached between August 2016 and August 2017 to assess their interest in joining the study. Patients who declined to participate had a median age of 46 years, with a low nutrition risk upon admission. Top reasons for not joining the study related to the burden of coming for additional appointments, travel reasons and lack of interest in the study. Figure 2 outlines the CONSORT diagram of the study by allocation group. 52 patients agreed to join and 46 patients were analyzed after drop out (n=22 in IG; n=24 in CG) (Figure 2). Post discharge, attendance of outpatient visits ranged between 68% and 95% with no significant differences between groups. One CG patient received nutrition intervention while hospitalized and was considered in the CG as per the intent to treat analysis.

There were no differences between any of the transplant characteristics (Table 1). All patients received HSCT from peripheral stem cell source. Lymphoma and auto HSCT were the most prevalent disease and HSCT type, respectively in both groups (Table 1). As for the demographic characteristics, 74% of patients had insurance coverage for their HSCT stay while the rest had to cover transplantation out of pocket; 20% had to quit their studies or work because of the HSCT, median days of absenteeism from work/college post HSCT was 76 days in the first 100 days post HSCT, 59% had a monthly salary less than 2000$ and the median cost of medication in the first 3 months post HSCT was 1,950$. Although not of statistically significance, IG patients tended to be older, married, unemployed and to have lower educational levels, higher salary ranges

and to be less absent from work or university pre HSCT compared to CG. The rest of the demographic characteristics were similar between allocation groups (Table 2).

Post discharge, medical characteristics were similar between groups. Chemotherapy administration was prevalent in both groups with a similar initiation time [median (days): 47 IG vs. 49 CG days post HSCT, p=0.40] (Table 3). Yet, CG patients had a higher steroid use from admission until 100 days post HSCT (median Prednisone equivalents: 75 mg IG vs. 100 mg CG, p=0.028).

Nutritional and functional assessment

As for patients' nutritional characteristics at T0, 49% of overall sample was well nourished as assessed via PGSGA and 76% had diminished HGS. All characteristics were comparable at T0 except for the fact that CG had more well-nourished patients as per AND-ASPEN criteria (WN$_{AND-ASPEN}$: 14% IG vs. 50% CG, p<0.01) (Table 4). Nutritional, functional and performance parameters worsened for all patients throughout the hospital stay, and allocation groups were comparable at hospital discharge (Table 4).

Post discharge, PGSGA categorical scores improved gradually in both groups (Figure 3). There was no difference in the number of patients needing nutrition intervention (PGSGA continuous score ≥4) at T4 (72% IG vs. 86% CG, p=0.38). Same group comparisons showed that compared to T0, IG had more well-nourished patients at T4 (WN$_{AND-ASPEN}$: 14% at T0 vs. 50% at T4, p=0.02). Yet, malnutrition scores were similar in CG at T4 compared to T0 (WN$_{AND-ASPEN}$: 50% T0 vs. 48% at T4, p=1) (Figure 3). When analyzed through multivariate regression (data not shown), the nutrition intervention was not a predictor of PGSGA score ≥4 (p>0.05). Yet, nutrition intervention predicted PGSGA categorical score at T4 (adjusted odds ratio for WN$_{PGSGA}$ =6.0; p value=0.028 after adjusting for relevant clinical predictors: age, transplantation type, conditioning intensity, corticotherapy and acute GvHD occurrence).

Zooming into the functional parameters, the percentages of patients with diminished HGS were not different post discharge between allocation groups (Table 5). Physical activity was better in IG at T2 (median weekly hours 7.5 hours IG vs. 2.4 hours CG, p=0.048) but was similar across groups thereafter. Karnofsky score and serum albumin were comparable between groups at all post discharge assessment points. FMI and SMI were not different between groups at T4 (Table 5). Paired group comparisons revealed that compared to T0, percentage of patients with high FMI decreased at T4 in the IG (71% at T0 vs. 56% at T4, p=0.046) and did not differ in CG (65% at T0 vs. 62% at T4, p=0.56) (Figure 4).

Subgroup analysis based on transplantation type showed that patients undergoing auto HSCT tended to be older [median age (years): 51 vs. 35, p=0.16]. Patients undergoing allo HSCT had a longer length of stay and more deterioration in nutritional status during hospitalization compared to their autologous peers (Table 6). Among IG, auto HSCT recipients benefited well from nutrition intervention (WN$_{PGSGA}$ increased from 36% at T0 to 75% at T4, p=0.014) compared to those undergoing allo HSCT who did not benefit from the intervention. Percentage of well-nourished patients decreased similarly in both transplantation types of CG (Table 6).

When assessing macronutrient intake, IG had improved caloric intake at all assessment points post discharge compared to CG (Figure 5). Protein intake was similar at T1 but improved post discharge in IG (90 grams IG vs. 80 grams CG at T4, p=0.037) (Figure 5). Fiber intake was very low in both groups at discharge. There was no difference between groups in fiber intake at T4. Paired assessment showed that fiber intake compared to needs improved in IG (49% at T0 vs. 77% at T4, p<0.01) but did not change in CG (71% at T0 vs. 70% at T4, p=0.85) (Figure 4). Figure 6 presents the contribution of each macronutrient to total caloric intake. There were no significant

differences between groups. Sugar intake was above 10% at all assessment points in both groups (Figure 6). Omega 6:3 ratio exceeded 9.8 at all assessment points with no differences between the groups.

Quality of Life Assessment

As for QoL, significant improvements were noted in PWB, BMT specific questions and the total FACT-BMT score for the whole cohort from D2 until T4. All of the QoL subscales except for the SWB improved gradually until T3 after which improvement slowed down. Focusing on differences between groups, there were no differences at D2 in any of the QoL subscales. At T4, Social Well being (SWB), Emotional Wellbeing (EMW) and total QoL score were better in IG compared to CG. Paired assessment of scores between D2 and T4 revealed that CG had worse EWB and improved BMT specific subscale and IG had significant improvement in Functional Wellbeing (FWB) and total QoL score (Table 7). It is worth noting that analysis of QoL subscales was done using General Linear Models entering clinically relevant variables such as age, HSCT type, HSCT-CI, nutritional status at admission and acute GvHD occurrence. As similar results and statistical significance were seen as in bivariate analysis (Table 7), results were not presented. Table 8 presents symptoms of clinical interest: nausea, fatigue, pain, sleep and sadness. All of these symptoms did not differ between allocation groups. Nausea worsened significantly in both groups from D2 until T4, with 78% of the cohort experiencing much/very much nausea at T4. Pain level fluctuated post transplantation and reached the highest level at T4 with 51% of patients still experiencing "much/very much" pain. Sadness level was highest at D2, decreased thereafter, yet started increasing after T3. The frequency of patients sleeping well improved significantly from D2 until T4 (Table 8). Subgroup analysis showed that type of transplantation did not affect total QoL scores. Older patients (>40 years) tended to have non-significantly better QoL (median of total QoL

score of 106 younger patients vs. 118 in older patients, p=0.34). Moreover, nutritional status assessed with the categorical PGSGA score at T4 correlated with the total QoL score at T4 (r_s=0.47, p<0.01). HGS did not correlate well with FWB, PWB and total QoL scores at T4. Univariate linear regression of total FACT-BMT score at T4 revealed that nutrition intervention was the only significant variable in the model (B= -15.9 p=0.037). Clinically relevant predictors such as age, transplantation type, HSCT-CI and PGSGA score at admission did not have significant odds ratio in predicting total FACT-BMT score at T4 at the univariate level. Hence, multivariate linear regression was not performed.

Discussion

This study is the first RCT to our knowledge to assess the effect of nutritional counseling at hospital discharge on nutritional and functional scores in both allo and auto HSCT patients. Even though the nutrition intervention did not improve PGSGA scores at T4, it improved caloric and protein intake, AND-ASPEN score and QoL at day 100 post HSCT.

Baseline nutritional status

This study contributes longitudinal data on the nutritional status of HSCT from a Middle Eastern medical center. Cohort studies assessing patients' malnutrition risk around HSCT showed that the majority of patients were well nourished at admission [21,34,37,38]. Using the same PGSGA tool, our study sample had a higher risk of malnutrition, with less than half of the sample being well nourished at admission. Clinical parameters such as age and underlying disease were similar to cohort studies assessing HSCT patients and could not explain the higher prevalence of malnutrition in our sample [21,34,37,38]. Not all studies included information on the number of previous chemotherapy lines received and the disease status at transplantation. Urbain et al. did assess disease status pre HSCT and even though more patients had advanced disease status, the rates of malnutrition were lower in their sample compared to ours [56]. Similar to malnutrition risk, HGS was at high risk in the study sample with high rates of diminished HGS at admission to start with. At admission, our study sample had a lower median HGS compared to Hung et al cohort [21], yet similar median HGS compared to Tanaka et al

cohort[57]. Future studies should reassess malnutrition risks in Middle Eastern centers to assess if higher malnutrition rates are truly higher than those of other treating centers.

Effect of counseling on nutritional status

Consistent with the literature, our patients' nutritional status worsened during hospital stay and gradually improved post HSCT [21,34,37,38]. At admission, IG had worse nutritional status when assessed via AND-ASPEN criteria. Post discharge, CG had a higher steroid intake. Even though the nutrition intervention was not able to significantly improve the proportion of patients' not needing intervention, it improved patients caloric and protein intake at T4. Patients not receiving nutritional counseling did not regain their pre HSCT nutritional status 100 days post HSCT. Yet, participants receiving nutrition counseling had better nutritional status at 100 days post HSCT compared to their pre HSCT status as measured by AND-ASPEN criteria.

Pair wise comparisons showed that IG had reduced rates of obesity from admission to day 100 post HSCT. Obesity among HSCT patients is a risk factor for non-relapse mortality [58]. A reduction in rates of obesity is hence a promising effect of nutritional counseling post HSCT. A recent study by our group (unpublished data) assessing body composition parameters through PET/CT analysis showed the ratio of visceral adiposity to SMI assessed pre HSCT, is a predictor of mortality among lymphoma patients undergoing HSCT. Assessment through PET/CT was not performed in this study as patients did not consistently have images available for body composition analysis at the study's assessment points. Future trials should consider assess the effect of interventions on the ratio of visceral adiposity to SMI when these parameters are available.

Patients undergoing allo HSCT had lower rates of malnutrition at admission yet more deterioration in their nutritional status compared to their peers undergoing auto HSCT.

Auto transplantation patients benefited more from the nutrition intervention. This might be explained by the fact that auto HSCT patients were older and had lower mortality rates. Moreover, auto patients had higher rates of diminished HGS and caloric intake as well as fluid retention at admission that responded well to the nutrition intervention. We know from the literature that compared to auto transplantation, allo HSCT is expected to worsen patients' nutritional status more as patients have a delayed engraftment, a longer hospitalization and risk GvHD which is associated with increased needs for corticosteroids and immunosuppression [56,59]. This study confirmed the impact of these risk factors on malnutrition rates post transplantation and revealed that auto HSCT patients were able to respond better to the nutrition intervention. Future trials should assess the effectiveness of intensified nutrition interventions among allo HSCT patients. Results of this RCT among auto HSCT patients are more promising than the telephone based RCT that showed no significant differences in caloric and protein intake and nutritional status when conducted in the same patient population[48]. The superiority in our intervention can be explained by the slightly larger sample size and the provision of counseling in a formal clinic setting compared to a telephone based assessment and intervention.

This study provides data on macronutrient intake of HSCT patients in the peri-transplantation phase. Fiber intake was very low at hospital discharge in both groups. This can be related to dietary restrictions advised to patients to reduce the risk of food borne illnesses [60]. Nutritional counseling was effective in improving fiber intake in IG compared to CG. Recent evidence revealed HSCT conditioning and the accompanying antibiotic therapy negatively affect gut microbiota; and dysbiosis was a risk factor for GVHD among patients receiving allogeneic HSCT [61,62]. In view of the importance of fiber intake in improving gut microbiota diversity and the lack of benefits of dietary

restrictions on the risk of bacterial infections, direction should be to liberalize the diet and to intensify counseling to boost fiber intake [25,26,63]. Omega 6:3 intake has also been postulated to affect gut microbiota with higher ratio associated with dysbiosis and low grade inflammation [64]. Indeed, omega 3 and 6 have opposing roles: the former being pro inflammatory and the latter being anti-inflammatory. As they compete for the same enzymes for their metabolism, their ratio in the human body regulates the inflammatory response. Nutrition intervention in this study focused on improving total caloric and protein intake rather than on reducing the omega 6:3 ratio. Both groups in this study had a similar intake of Omega 6:3 ratio that was ≥ 10:1 at all assessment points, thus surpassing recommendations for healthy individuals of 4:1. Yet intake of our patients does not exceed Omega 6:3 intake in western populations that ranges from 10:1 to 20:1[65,66]. When assessing the rest of nutrients, sugar intake was not significantly different between the groups. Recommendations on sugar intake vary depending on the organization -up to 10%[67] as per the WHO and up to 25% as per the Institute of Medicine (IOM) [68]. HSCT patients exceeded the WHO recommendations but did not exceed the IOM recommendations on sugar intake.

QoL: Effect of nutritional counseling and highlights from Lebanon

In cancer patients, the majority of studies assessing nutrition interventions showed positive effects on QoL [46]. Focusing on HSCT patients, a RCT optimizing patients' nutritional intake during hospital stay showed no changes in QoL subscales 3 months post HSCT [69]. To our knowledge, only one previous pilot study evaluated the effect of nutritional telephone and exercise counseling post hospital discharge among autologous HSCT patients. Results showed no significant improvements in global QoL and in the

QoL subscales. Our study showed that IG had improved EWB, SWB and global QoL and recovery of FWB. Positive findings experienced in this study are possibly due to the importance of live assessment and reinforcement compared to distant assessment over the phone. Moreover, the timing of the study is important. During hospital stay, patients are well monitored by the medical and nutrition teams as they are considered acutely ill. Hence, additional monitoring would not be impactful. Post hospital discharge, nutrition monitoring is not done except in severe malnutrition. Consideration for incorporation of nutrition evaluation and monitoring post HSCT should be made in view of the observed positive effect on nutritional intake and global QoL.

Few studies have assessed QoL of HSCT in the Middle East. One study assessing QoL of Jordanian survivors showed that physical and social functioning were the subscales most at risk in the sample [70]. Our study showed nutrition intervention is capable of recovering SWB and total QoL aspects at T4. Yet, nutrition counseling did not improve PWB and fatigue at T4. Systematic reviews on physical activity during and after HSCT reflected moderate improvement in cardio respiratory fitness and QoL and a reduction in fatigue [71,72]. Yet, a more recent RCT showed no effect of exercise post HSCT on physical fitness and fatigue. Authors related it to a dilution effect since a large proportion of control patients were exercising[73]. Our study showed that IG patients had improved physical activity at day 30 only post HSCT. This reflects that advice to increase physical activity can slightly improve patients' habitual physical activity. However, it is not as effective as interventions involving exercise sessions to increase actual physical activity performance. Hence, considerations for a combination of physical activity and nutrition interventions should be made for a substantial improvement in QoL subscales and fatigue.

Reduction in HGS reflecting low muscle strength has been correlated with sarcopenia and oxidative damage [74]. Our results showed that improvement rate decreased after T3 possible because many patients were started on chemotherapy around that time. Moreover, the nutrition intervention did not affect SMI and HGS rates and that HGS did not correlate with total QoL scores. The latter result was in line with Hung findings among auto HSCT patients who showed that change in HGS did not correlate with total QoL score and functional and physical well-being [21]. This might be explained by the fact that changes in HGS were not large enough to produce any change in FWB.

In Lebanon, HSCT has been offered to eligible patients since 1997 [75]. Compared to other studies assessing QoL in HSCT, patients had similar total QoL scores[76]. Patients reported high satisfaction with the support received from family, friends and partners and had high confidence in nurses. This reflects well the culture in the Middle East characterized by strong family and community ties; also observed in a study done among Jordanian HSCT patients [70]. The controversy of accessibility to care, an issue of concern worldwide and in Lebanon, is highlighted in the findings of this study[77]. Patients reported that cost of the treatment constituted a heavy burden on the patients and their families. Even though most patients had insurance coverage for the hospital stay of the HSCT, the majority of patients had to pay for medication administered post discharge which was substantial compared to the participants' median monthly salary. An additional burden that this study outlines is the effect of HSCT on employment and university enrolment with 20% of patients having to quit their career because of the transplantation effect on QoL and employed patients missing their career for a median of 76 days in the first 100 days post HSCT. These rates are in line with international findings that found higher unemployment rates among HSCT and cancer survivors compared to healthy peers and that only 50% of HSCT patients resume work 90 days

post HSCT[78-81]. Yet, unemployment is expected to be more burdensome in developing countries such as Lebanon, compared to developed countries, that lack disability pension plans to such patient populations [81].

Strengths and Limitations

The study strengths include its methodological design using validated nutritional, functional and QoL instruments as well as the randomization that was performed at the selection phase. Yet, the study sample size did not allow for stratification by transplantation type. There are differences between the two transplantation types in term of conditioning regimen and post transplantation complications such as GvHD and veno-oclusive disease. Studies stratified by transplantation type are expected to elude more comprehensive results on the differences across groups. Burden of coming to the hospital for additional visits affected the rates of follow up and drop out. Rates of drop out were lower than hypothesized (13% vs. 30% hypothesized). Yet, drop outs were higher in IG compared to CG (19% vs. 8%). This can be associated with the difficulty in agreeing on scheduling appointments for the IG with the dietitians compared to the research team dedicated for data collection. Threats to internal validity also included social desirability and recall bias as patients might intentionally or unintentionally miss to provide complete diet recalls. Moreover, assessment through DEXA measurements could have enhanced the quality of the results by providing data on visceral adiposity and SMI as we recognize that BIA measurements are affected by fluid imbalances which are common in our patient population. Moreover, the study follow up time was limited to the active study duration. Having a longer follow up time would have revealed if the positive effect of the intervention remains evident or dissolve with time. Exploring the study's external validity: data was collected on patients who refused to participate. They were found to be comparable to study participants. Threats to external validity included

the nature of this RCT, focusing on one medical center only. Multi-center RCT could be

useful to validate the study's results.

Conclusion

This study was the first to assess the effect of nutritional counseling post allogeneic and autologous HSCT on nutritional, functional and QoL indicators. Improvement in nutritional status was revealed among recipients of nutritional counseling but to a smaller extent than hypothesized. Sub group analysis patients revealed that autologous HSCT patients benefited from the intervention compared to their peers receiving allogeneic HSCT. Trends towards reduction in obesity and improvement in QoL were noticed among IG patients, yet sarcopenia and number of readmissions were not affected by the intervention. This study also presented the burden of HSCT experienced by patients in a developing Middle Eastern country relevant to accessibility of care and cost of medication compared to wages, and impact of transplantation on rates of drop out from university and professional careers. In view of the promising effect of this RCT, future interventions should validate the study findings on larger samples of autologous HSCT and assess the combined effect of physical activity and intensified nutritional counseling on allogeneic HSCT exploring the effects on gut microbiota, sarcopenia and QoL as well as nutritional status.

Trial Status

The RCT obtained approval from the Institutional Review Board at AUB in March 2016 (protocol identifier: IM.J-EC.01). This study is registered on the ClinicalTrials.gov database (Trial Identifier: NCT02791347). Recruitment started in August 2016 and was completed in November 2017.

Funding

This trial was awarded the Seed Grant research fund by the Faculty of Medicine in the American University of Beirut.

Tables

Table 1: Transplant Characteristics

Variable	Intervention (n=22)	Control (n=24)	p value
Gender, n (%)			
Male	15 (68)	15 (63)	0.69
Female	7 (32)	9 (38)	
Age (years), median (IQR)	52 (35-57)	39 (25-53)	0.15
HSCT –CI, n (%)			
≤1	20 (91)	22 (92)	0.92
≥2	2 (9)	2 (8)	
Primary Disease, n (%)			
Lymphoma	11 (50)	14 (58)	0.55
AML	5 (23)	7 (29)	
MM	5 (23)	3 (13)	
Ewing Sarcoma	1 (5)	0 (0)	
Disease Status pre HSCT, n (%)			
CR	17 (77)	16 (67)	0.32
RD	4 (18)	8 (33)	
PD / Relapse	1 (5)	0 (0)	
Type of HSCT, n (%)			
Autologous	14 (64)	15 (63)	0.94
Allogeneic	8 (36)	9 (38)	
Conditioning Autologous, n (%)			
BEAM	7 (50)	12 (80)	0.19
Melphalan ± Velcade	6 (43)	3 (20)	
Baltimore	1 (7)	0 (0)	
Conditioning Allogeneic, n (%)			
FB ATG	2 (22)	4 (44)	0.25
TBF ± ATG	3 (33)	5 (56)	
Sequential	2 (22)	0 (0)	
TCB	1 (13)	0 (0)	
TPN use in hospitalization,	11 (50)	11 (46)	0.78
LOS (days), median (IQR)	24 (18-26)	23 (20-28)	0.75

IQR: Inter Quartile Range, HSCT: Hematopoietic Stem Cell Transplantation, HSCT-CI: HSCT- Comorbidity Index, AML: Acute Myeloid Leukemia, MM: Multiple Myeloma, CR: Complete Remission, RD: Residual Disease, PD: Progressive Disease, FB: Fludarabine, BEAM: combination chemotherapy containing BCNU, etoposide, Ara-C, and Melphalan, ATG: Antithymocyte globulin, TBF: Thiotepa Busulfan Fludarabine, TCB: Thiotepa Cyclophosphamide Busulfan, TPN: Total Parenteral Nutrition, LOS: Length of Stay.

Table 2: Demographic characteristics

Variable	Intervention (n=22)	Control (n=24)	p value
Gender, n (%)			
Male	15 (68)	15 (63)	0.69
Female	7 (32)	9 (38)	
Age (years), median (IQR)	52 (35-57)	39 (25-	0.15
Marital Status, n (%)			
Single	5 (23)	10 (42)	0.16
Married	15 (68)	14 (58)	
Divorced	2 (9)	0 (0)	
Having children, n (%)	15 (68)	13 (54)	0.33
Number of children, median (IQR)	3 (2-4)	3 (2-4)	0.79
Education Level, n (%)			
Primary Education	6 (27)	2 (8)	0.29
Secondary Education	4 (18)	8 (33)	
University Degree	12 (54)	14 (58)	
Employment Status at admission, n (%)			
Unemployed	4 (18)	1 (4.2)	0.18
Quit work or studies recently	5 (23)	4 (17)	
Employed	13 (59)	19 (79)	
Salary range at admission*, n (%)			
Below 1000 $	3 (23)	8 (42)	0.30
1000-2000 $	2 (15)	6 (32)	
>2000 $	8 (62)	5 (26)	
Days off work/university pre HSCT admission, n (%)**	30 (20-83)	90 (40-180	0.13
Days off post HSCT*, n (%)**	57 (30-89)	90 (40-90	0.86

IQR: Inter Quartile Range, HSCT: Hematopoietic Stem Cell Transplantation

*among employed patients, ** in the 6 months pre HSCT, *** in the 3 months following HSCT.

Table 3: Patient characteristics post Transplantation

Variable	Intervention N=22	Control N=24	P value
Disease Status at 3 months post HSCT, n (%)			
CR	15 (75)	17 (81)	
RD	4 (20)	2 (10)	0.59
PD / Relapse	1 (5)	2 (10)	
Relapse, n (%)	2 (9)	3 (13)	0.71
Radiotherapy post HSCT, n (%)	2 (9)	0 (0)	0.13
Chemotherapy post HSCT, n (%)	14 (64)	11 (46)	0.23
Chemotherapy Cycles post SCT, n (%)			
1	3 (21)	3 (30)	0.44
≥2	11 (78)	7 (70)	
Day of chemotherapy initiation post HSCT, median (IQR)	47 (38-60)	49 (39-69)	0.40
Number of readmission median (IQR)	1 (0-6)	0 (0-3)	0.36
Duration of readmission (days), median (IQR)	5.5 (3-17)	6 (3-26)	0.97
aGvHD Incidence, n (%)	1 (5)	2 (8)	0.60
aGVHD Grade, n (%)			
I-II	1 (100)	0 (0)	0.22
III-IV	0 (0)	2 (50)	
aGvHD Site, n (%)			
Skin	1 (100)	0 (0)	
GI & skin	0 (0)	1 (50)	0.22
GI & liver	0 (0)	1 (50)	
cGvHD Incidence, n (%)	1 (100)	1 (100)	1
cGVHD Grade, n (%)			
Mild	0 (0)	0 (0)	
Moderate	1 (100)	0 (0)	0.16
Severe	0 (0)	1 (100)	
cGvHD Site, n (%)			
GI	1 (100)	0 (0)	0.37
Skin & liver	0 (0)	1 (100)	
Death at last follow up, n (%)	1 (4.8)	3 (13)	0.34

HSCT: Hematopoietic Stem Cell Transplantation, IQR: Inter Quartile Range, GvHD: Graft versus Host Disease, aGvHD: acute GVHD, cGvHD: chronic GvHD, CR: Complete Remission, RD: Residual Disease, PD: Progressive Disease.

Table 4: Nutritional and Functional Outcomes at hospital admission and discharge

ariable by assessment point	Intervention N=22	Control N=24	P value
Hospital admission			
PGSGA Category, n (%)			
Stage A	10 (45)	12 (50)	
Stage B	11 (50)	10 (42)	0.79
Stage C	1 (5)	2 (8)	
PGSGA Score, median (IQR)	12 (5-14)	13 (7-15)	0.73
Patients with PGSGA Score ≥ 4, n (%)	19 (86)	23 (96)	0.23
WN$_{AND/ASPEN}$, n (%)	3 (14)	12 (50)	<0.01
Percent caloric intake, median (IQR)	96 (73-121)	109 (81-129)	0.36
Protein intake (grams), median (IQR)	83 (54-106)	88 (68-109)	0.39
BMI (kg/m^2), median (IQR)	26.5 (21.2-30.7	27.2 (24.2-29.6	0.76
FMI Category, n (%)			
Fat Deficit	0 (0)	1 (4)	0.61
Normal FMI	6 (29)	7 (30)	
High FMI	15 (71)	15 (65)	0.65
SMI (cm^2/m^2), median (IQR)	10.2 (8.7-10.9)	10.6 (8.7-10.9)	
HGS (lb), median (IQR)	62 (49-86)	71 (51-99)	0.29
Diminished HGS, n (%)	18 (82)	16 (67)	0.24
Weekly physical activity Level (hours),	9.8 (4.4-21.3)	8.8 (1.7-15.7)	0.31
Serum albumin (gm/L), median (IQR)	41 (39-45)	43 (38-45)	0.96
Karnofsky Score, median (IQR)	80 (80-90)	80 (80-90)	0.58
Hospital discharge			
PGSGA Category, n (%)			
Stage A	0 (0)	0 (0)	0.71
Stage B	20 (91)	21 (88)	
Stage C	2 (9.1)	3 (13)	
PGSGA Score, median (IQR)	19 (15-26)	21 (18-25)	0.50
Patients with PGSGA Score ≥ 4, n (%)	22 (100)	24 (100)	1
WN$_{AND/ASPEN}$, n (%)	3 (14)	3 (12)	0.91
Percent caloric intake, median (IQR)	52 (39-72)	54 (33-67)	0.91
Protein intake (grams), median (IQR)	49 (22-62)	43 (28-64)	0.56
BMI (kg/m^2), median (IQR)	26 (21.4-30)	26.2 (23.5-29.1	1
Significant weight loss, n (%)	2 (9.1)	3 (13)	0.71
FMI Category, n (%)			
Fat Deficit	1 (5)	1 (5)	
Normal FMI	7 (32)	8 (38)	0.95
High FMI	14 (64)	12 (57)	
SMI (cm^2/m^2), median (IQR)	10 (8.7-10.9)	10.3 (8.6-10.8)	0.90
HGS (lb), median (IQR)	66 (49-79)	71 (51-95)	0.58

Diminished HGS, n (%)	18 (82)	18 (75)	0.58
Weekly physical activity level (hours), median (IQR)	0.21 (0-0.68)	0.42 (0-2)	0.40
Serum albumin (gm/L), median (IQR)	34 (31-37)	35 (32-38)	0.54
Karnofsky Score, median (IQR)	70 (70-80)	70 (70-80)	0.58

PGSGA: Patient Generated Subjective Global Assessment; IQR: Inter Quartile Range, WN$_{AND/ASPEN}$: Well-nourished as per AND-ASPEN criteria, AND: Academy of Nutrition and Dietetics, ASPEN: American Society for Parenteral and Enteral Nutrition, BMI: Body Mass Index, FMI: Fat Mass Index, SMI: Skeletal Muscle Index, FACT-BMT: Functional Assessment of Cancer Therapy- Bone Marrow Transplantation

Table 5: Nutritional and Functional Outcomes post transplantation

Variable by assessment point			
Day 30 post HSCT	**Intervention** N=21	**Control** N=24	**P value**
PGSGA Category, n (%			
Stage A	2 (9)	4 (17)	0.67
Stage B	18 (86)	18 (75)	
Stage C	1 (5)	2 (8)	
PGSGA Score, median (IQR)	15 (12-18)	11 (5-12)	0.51
Patients with PGSGA Score ≥ 4, n (%)	19 (95)	23 (96)	0.92
WN$_{AND/ASPEN}$, n (%)	7 (33)	6 (25)	0.54
Percent caloric intake, median (IQR)	92 (63 - 135)	71 (51 - 91)	0.04
Percent protein intake, median (IQR)	83 (58 - 100)	65 (54 - 78)	0.065
BMI (kg/m^2), median (IQR)	26.0 (22.0-29.6)	26.1 (23.3-29.2)	1
Significant weight loss, n (%)	4 (18)	1 (4.2)	0.13
FMI Category, n (%)			
Fat Deficit	0 (0)	1 (4)	0.91
Normal FMI	6 (29)	9 (38)	
High FMI	15 (71)	14 (58)	
WHR, median (IQR)	0.96 (0.91-1.0)	0.92 (0.87-1.0)	0.41
SMI (cm^2/m^2), median (IQR)	9.6 (8.2 – 10.5)	9.9 (8.5 – 10.7)	0.55
HGS (lb), median (IQR)	60 (48 - 87)	66 (50 - 87)	0.47
Diminished HGS, n (%)	17 (81)	19 (79)	0.88
Weekly physical activity (hours), median (IQR)	7.5 (2.9 – 10)	2.4 (0.1 – 7.5)	0.048
Serum albumin (gm/L), median (IQR)	40 (38-44)	40 (36-42)	0.52
Karnofsky Score, median (IQR)	70 (70-80)	70 (70-80)	0.74
Day 60 post HSCT	**Intervention** N=19	**Control** N=15	**P value**
PGSGA Category, n (%)			
Stage A	10 (53)	6 (40)	0.71
Stage B	8 (42)	8 (53)	
Stage C	1 (5)	1 (7)	
PGSGA Score, median (IQR)	8 (5-12)	9 (3-17)	0.81
Patients with PGSGA Score ≥ 4, n (%)	16 (84)	11 (73)	0.44
WN$_{AND/ASPEN}$, n (%)	9 (47)	5 (33)	0.41
Percent caloric intake, median (IQR)	120 (92 - 128)	90 (67 - 118)	0.028
Percent protein intake, median (IQR)	114 (82 - 137)	84 (67 - 111)	0.16

BMI (kg/m²), median (IQR)	27 (22.9-29.6)	24.4 (22.8-29)	0.57
FMI Category, n (%)			
Fat Deficit	0 (0)	0 (0)	0.49
Normal FMI	7 (41)	8 (57)	
High FMI	10 (59)	6 (43)	
WHR, median (IQR)	0.91 (0.85-0.95)	0.90 (0.88-0.99)	0.77
Significant weight loss, n (%)	1 (4.5)	2 (8.3)	0.60
SMI (cm²/m²), median (IQR)	10 (8.8 - 11)	10 (8.3 – 11)	0.48
HGS (lb), median (IQR)	60 (49 - 90)	71 (55 - 80)	0.37
Diminished HGS, n (%)	14 (74)	10 (67)	0.66
Weekly physical activity (hours), median (IQR)	8.8 (4.4 - 18)	9 (4.4 - 15)	0.75
Serum albumin (gm/L), median (IQR)	41 (37-44)	41 (38-47)	0.81
Karnofsky Score, median (IQR)	80 (70-90)	80 (80-90)	0.45
Day 100 post HSCT	**Intervention** N=18	**Control** N=21	**P value**
PGSGA Category, n (%)			
Stage A	13 (72)	9 (43)	0.063
Stage B	4 (22)	12 (57)	
Stage C	1 (6)	0 (0)	
PGSGA Score, median (IQR)	4 (3-13)	7 (4-12)	0.30
Patients with PGSGA Score ≥ 4, n (%)	13 (72)	18 (86)	0.38
WN$_{AND/ASPEN}$, n (%)	9 (50)	10 (48)	0.88
Percent caloric intake, median (IQR)	116 (87-164)	85 (76 - 111)	0.01
Percent protein intake, median (IQR)	94 (72 - 118)	77 (55 - 91)	0.067
BMI (kg/m2), median (IQR)	26.4 (20.4-30)	26.8 (23.9-28.8)	0.93
Significant weight loss, n (%)	3 (14)	1 (4.2)	0.26
FMI Category, n (%)			
Fat Deficit	1 (6)	1 (4)	0.92
Normal FMI	7 (39)	7 (33)	
High FMI	10 (56)	13 (62)	
WHR, median (IQR)	0.92 (0.85-1)	0.93 (0.86-1)	0.61
SMI (cm²/m²), median (IQR)	9.9 (8.4 - 11)	10.1 (8.6 – 10.8)	0.93
HGS (lb), median (IQR)	65 (38 - 86)	70 (46 - 91)	0.47
Diminished HGS, n (%)	13 (72)	15 (71)	0.96
Weekly physical activity (hours), median (IQR)	9 (4.4 - 18)	9 (4.4 - 15)	0.88
Serum albumin (gm/L), median (IQR)	43 (41-46)	44 (39-47)	0.70
Karnofsky Score, median (IQR)	90 (80-90)	80 (80-90)	0.81

PGSGA: Patient Generated Subjective Global Assessment, IQR: Inter Quartile Range, WN$_{AND/ASPEN}$: Well-nourished as per AND-ASPEN criteria, AND: Academy of Nutrition and Dietetics, ASPEN: American Society for Parenteral and Enteral Nutrition, BMI: Body

Mass Index, FMI: Fat Mass Index, Waist to Hip Ratio, SMI: Skeletal Muscle Index, FACT-BMT: Functional Assessment of Cancer Therapy- Bone Marrow Transplantation

Table 6: Frequency of well-nourished patients by transplantation type and allocation groups

Assessment Point	Autologous			Allogeneic		
	Intervention n (%)	Control n (%)	P value	Intervention n (%)	Control n (%)	P value
T0	5 (36)	7 (47)	0.83	5 (63)	5 (56)	0.62
T1	0 (0)	0 (0)	0.94	0 (0)	0 (0)	0.33
T2	2 (14)	3 (20)	0.55	0 (0)	1 (11)	0.24
T3	7 (58)	3 (43)	0.50	3 (43)	3 (38)	0.63
T4	9 (75)	5 (38)	0.066	4 (67)	4 (50)	0.28
Significant paired assessment	T1 vs T0 T4 vs T0 T4 vs T1 T4 vs T2	T1 vs T0		T1 vs T0 T2 vs T0	T1 vs T0 T4 vs T1	

Well-nourished patients are patients in Patient Generated Subjective Global Assessment category A. Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT. HSCT: Hematopoietic Stem Cell Transplantation

Table 7: FACT-BMT quality of life score evolution

QoL Subscale	Assessment Point	Intervention	Control	P value
Physical WB Score range: 0-28	D2	18 (11-21)	15 (9-21)	0.53
	T1	21 (15-25)	18 (13-22)	0.18
	T2	20 (15-25)	17 (11-24)	0.42
	T3	24 (19-26)	24 (19-27)	0.75
	T4	23 (19-28)	21 (16-26)	0.22
Paired Assessment	T4 vs D2	p=0.013	p<0.01	
Social WB Score range: 0-28	D2	26 (23-28)	24 (19-28)	0.09
	T1	26 (22-28)	23 (20-26)	0.15
	T2	24 (22-27)	22 (19-27)	0.25
	T3	25 (23-27)	24 (22-28)	0.68
	T4	27 (25-28)	23 (17-28)	**0.015**
Paired Assessment	T4 vs D2	p=0.66	p=0.097	
Emotional WB: 0-24	D2	17 (14-19)	17 (15-18)	0.63
	T1	18 (16-19)	18 (15-20)	0.97
	T2	19 (17-20)	17 (13-19)	0.026
	T3	18 (16-20)	18 (15-19)	0.53
	T4	18 (16-20)	15 (12-18)	**0.026**
Paired Assessment	T4 vs D2	p=0.054	p=0.026	
Functional Score range: 0-28	D2	19 (11-23)	17 (14-21)	0.75
	T1	20 (16-24)	17 (15-21)	0.19
	T2	17 (13-21)	18 (13-22)	0.69
	T3	21 (18-24)	22 (17-26)	0.67
	T4	22 (19-26)	19 (11-25)	0.091
Paired Assessment	T4 vs D2	p=0.028	p=0.70	
BMT specific questions Score range: 0-40	D2	28 (21-30)	25 (20-28)	0.33
	T1	26 (23-29)	27 (21-29)	0.69
	T2	27 (24-30)	26 (21-32)	0.82
	T3	31 (27-32)	29 (25-36)	0.93
	T4	29 (23-33)	29 (22-34)	0.8
Paired Assessment	T4 vs D2	p=0.24	p=0.035	
QoL BMT Score range: 0-148	D2	103 (86-116)	98 (81-110)	0.50
	T1	109 (95-118)	100 (93-109)	0.24
	T2	105 (94-114)	99 (84-115)	0.41
	T3	118 (106-130)	114 (87-121)	0.98
	T4	117 (106-130)	95 (87-121)	**0.036**
Paired Assessment	T4 vs D2	p <0.01	p=0.32	

Assessment points: D2: day 2 post HSCT, T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT. HSCT: Hematopoietic Stem Cell Transplantation

Table 8: Frequencies of participants' comments on fatigue, pain, sadness and sleep at T4

Symptom	Intervention	Control	P value
Nausea			
D2	6 (29)	6 (26)	0.17
T1	9 (47)	8 (33)	0.14
T2	11 (55)	8 (35)	0.48
T3	11 (61)	12 (75)	0.85
T4	15 (88)	14 (70)	0.27
Fatigue			
D2	3 (15)	7 (29)	0.41
T1	5 (26)	4 (17)	0.64
T2	6 (32)	7 (30)	0.93
T3	7 (39)	6 (38)	0.5
T4	3 (18)	4 (20)	0.91
Pain			
D2	4 (19)	4 (17)	0.49
T1	2 (11)	2 (8)	0.74
T2	9 (45)	11 (46)	0.83
T3	2 (11)	0 (0)	0.13
T4	8 (47)	11 (55)	0.91
Sadness			
D2	5 (24)	4 (17)	0.92
T1	3 (16)	2 (9)	0.82
T2	1 (5)	5 (22)	0.24
T3	1 (6)	0 (0)	0.27
T4	2 (12)	5 (25)	0.47
Sleeping Well			
D2	10 (50)	12 (50)	0.81
T1	13 (72)	21 (91)	0.27
T2	14 (70)	20 (87)	0.24
T3	15 (83)	14 (88)	1
T4	16 (94)	17 (85)	0.06

Symptoms were assessed using the FACT-BMT subscales combining the "much" and "very much" categories. Assessment points: D2: day 2 post HSCT, T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT. HSCT: Hematopoietic Stem Cell Transplantation

Figures
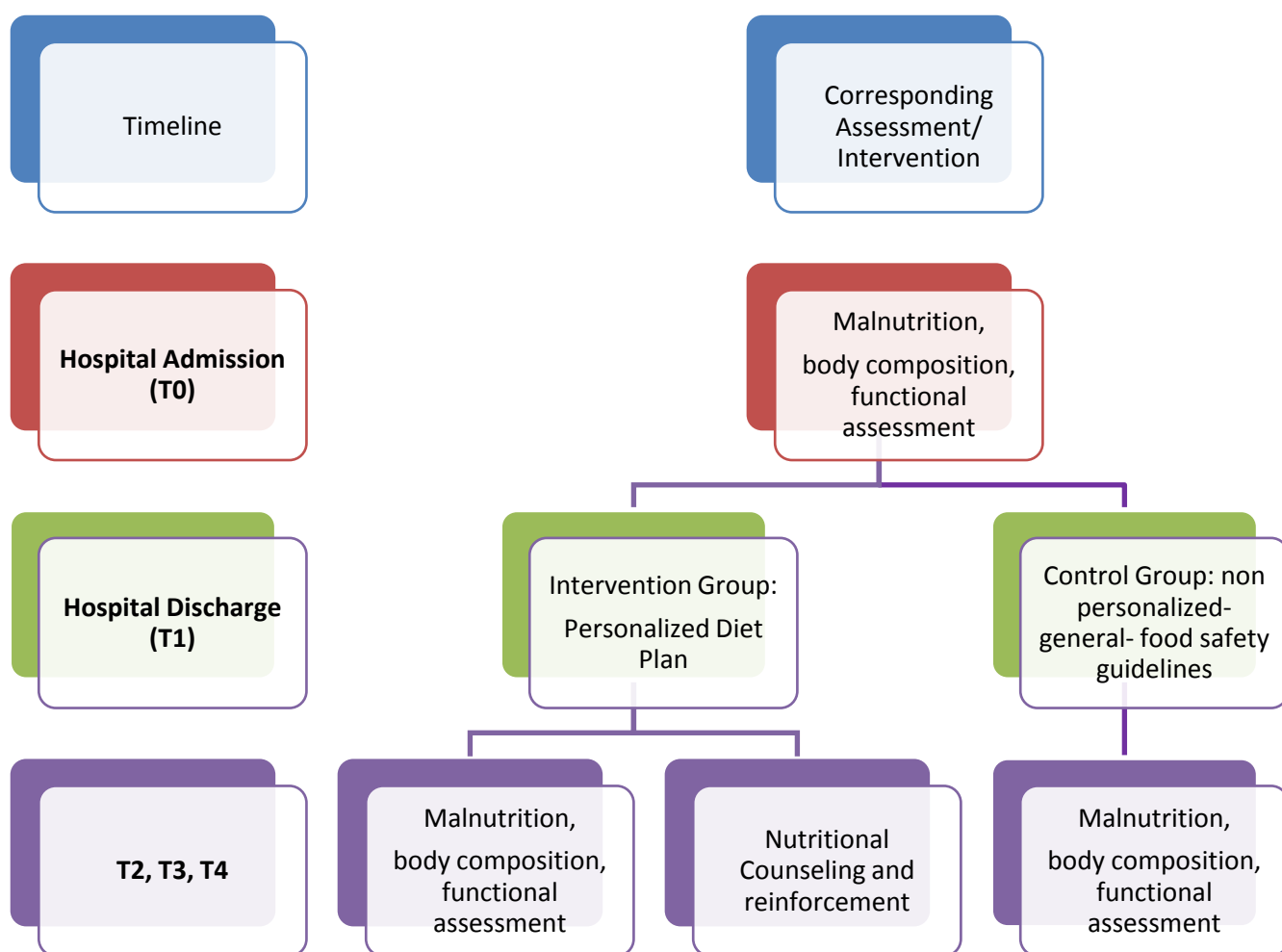
Figure 1: Research timeline

Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post transplantation.
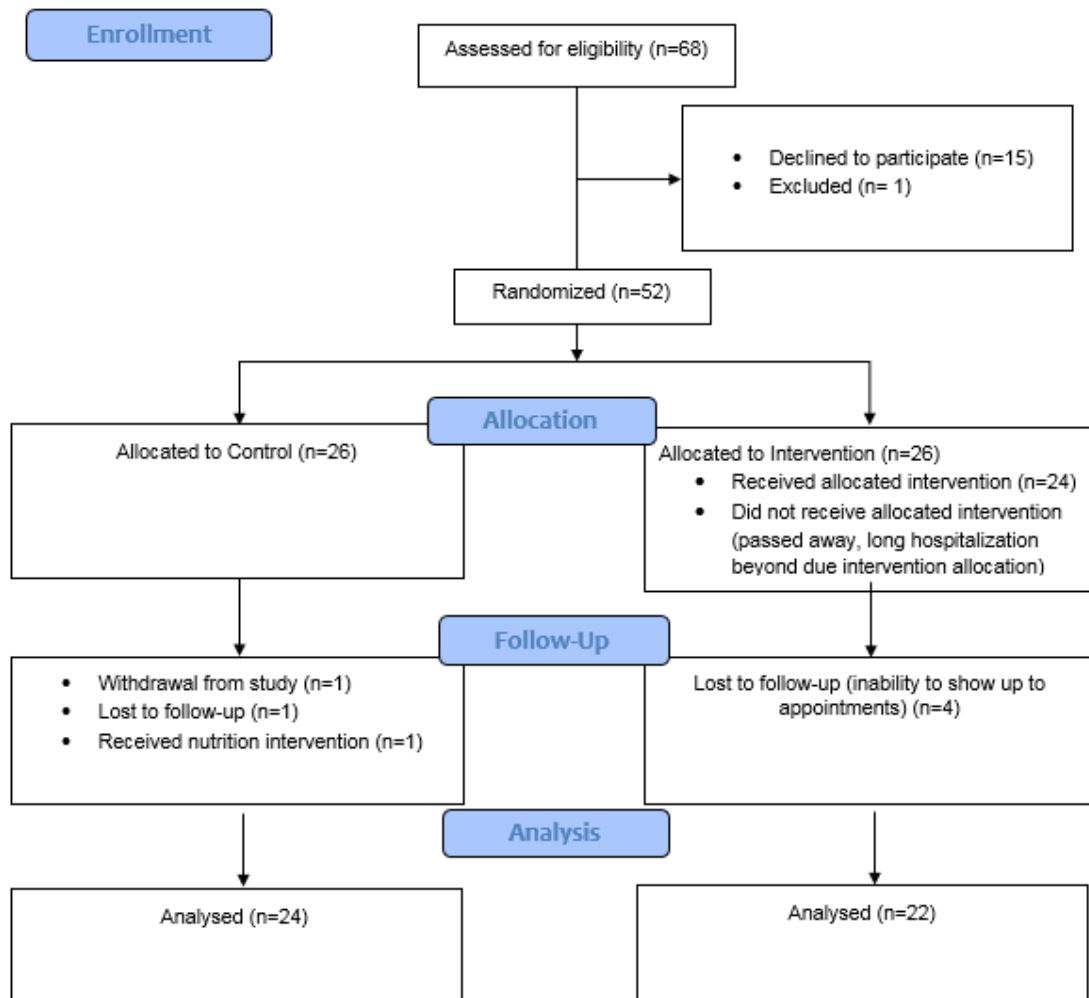
CONSORT 2010 Flow Diagram
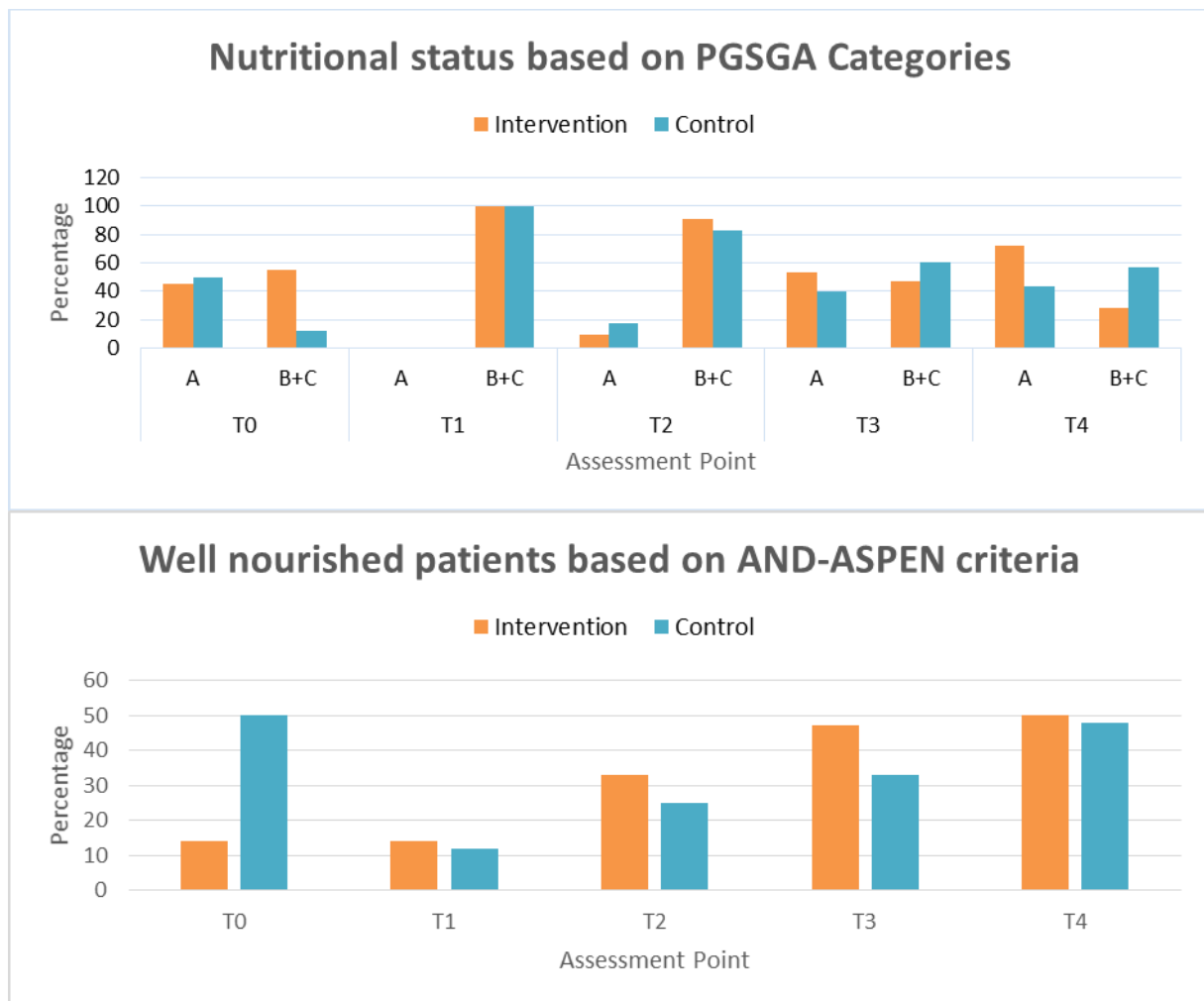
Figure 2: CONSORT diagram

Figure 3: Evolution of PGSGA and AND-ASPEN malnutrition scores by allocation group

PGSGA: Patient Generated Subjective Global Assessment. A, B and C reflect the PGSGA malnutrition categories. Letter A refers to malnourished patients and category B+C to patients with moderate and severe malnutrition. Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT. HSCT: Hematopoietic Stem Cell Transplantation, AND-ASPEN: Academy of Nutrition and Dietetics (AND)-American Society for Parenteral and Enteral Nutrition (ASPEN).

* reflects a p value <0.05 for differences between groups. Paired assessment comparing T0 to T4 for AND-ASPEN: p value =0.02 for IG and p value=1 for CG
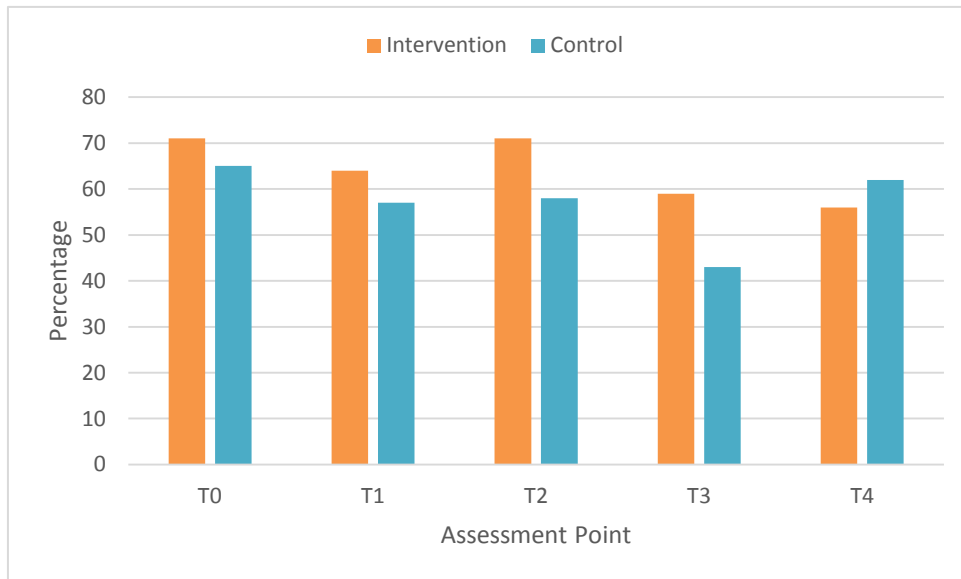
Figure 4: Frequency of patients with elevated Fat Mass Index

Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT.

Paired assessment comparing T0 to T4, revealed p values<0.05 in intervention group only
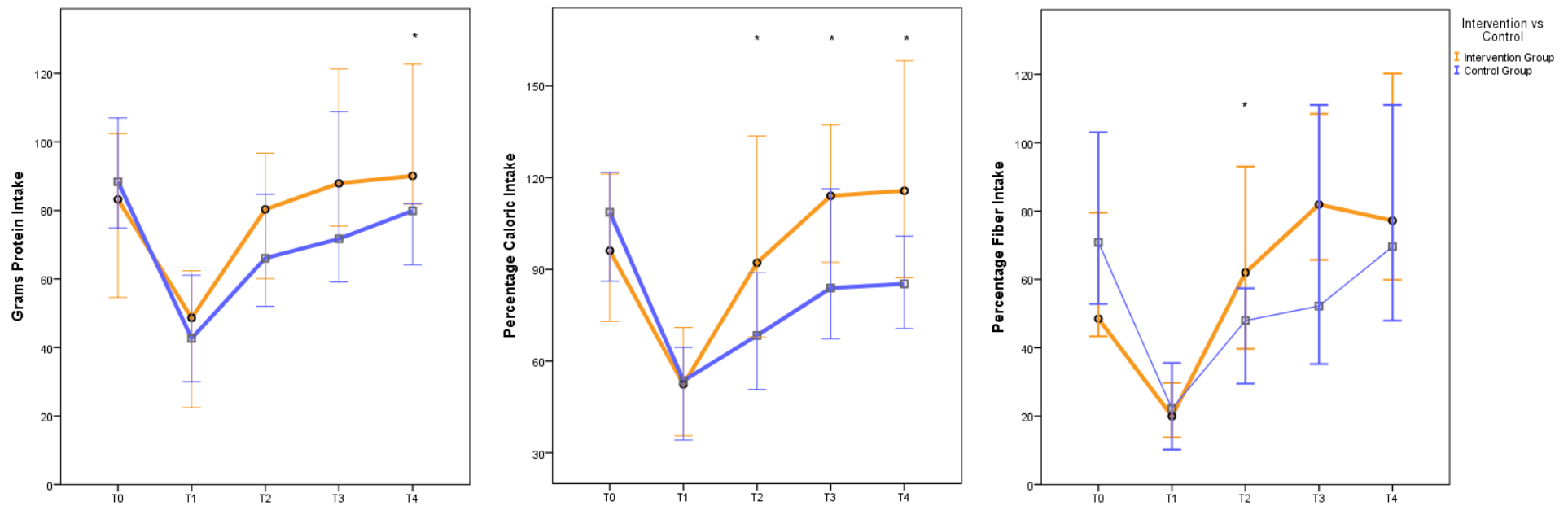
Figure 5: Evolution of protein, energy and fiber intake by allocation group

This figure presents median values and interquartile ranges of patients' protein intake (panel A) and percent intake compared to individual needs of calories (panel B) and fiber (panel C). Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post HSCT.

* reflects a p value <0.05 for differences between groups. Paired assessment comparing T0 to T4, revealed p values<0.05 for energy and fiber intake in intervention group only
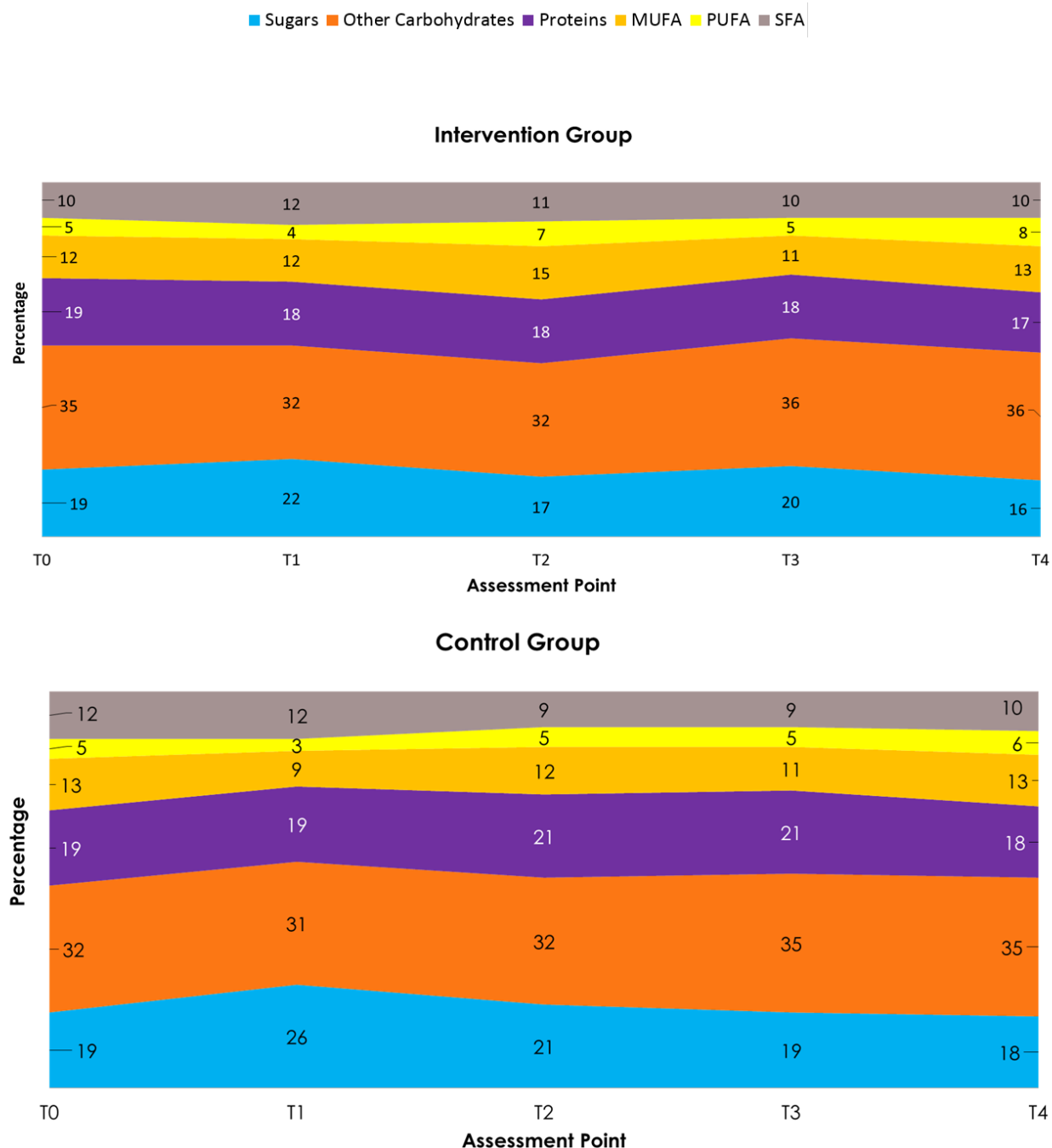
Figure 6: Contribution of macronutrients to total energy intake

MUFA: Monounsaturated fatty acids, PUFA: Polyunsaturated fatty acids, SFA: Saturated fatty acids. Assessment points: T0: hospital admission, T1: hospital discharge, T2: day 30 post HSCT, T3: day 60 post HSCT, T4: day 100 post transplantation.

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Appendix 1: CONSORT checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	10-15
	2b	Specific objectives or hypotheses	14-15
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	16
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	16
	4b	Settings and locations where the data were collected	16
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	17-21
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	21
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable

Sample size	7a	How sample size was determined	22
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	22
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	17
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	17
			21
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	No blinding
	11b	If relevant, description of the similarity of interventions	17
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	21
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	23
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Tables 1 & 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 4
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	24

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	25
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	34-35
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	34-35
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	26-35
Other information			
Registration	23	Registration number and name of trial registry	37
Protocol	24	Where the full trial protocol can be accessed, if available	Available in this manuscript
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	37

Appendix 2: Instruments

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight (See Worksheet 1)

In summary of my current and recent weight:

I currently weigh about _____ kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:

☐ decreased (1)   ☐ not changed (0)   ☐ increased (0)

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as

☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)   Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)

☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)   ☐ vomiting (3)
☐ nausea (1)   ☐ diarrhea (3)
☐ constipation (1)   ☐ dry mouth (1)
☐ mouth sores (2)   ☐ smells bother me (1)
☐ things taste funny or have no taste (1)   ☐ feel full quickly (1)
☐ problems swallowing (2)   ☐ fatigue (1)
☐ pain; where? (3) _____
☐ other (1)** _____
**Examples: depression, money, or dental problems   Box 3 ☐

4. Activities and Function:

Over the past month, I would generally rate my activity as:

☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Additive Score of Boxes 1-4 ☐ A

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Additive Score of Boxes 1-4 (See Side 1) ☐ **A**

Worksheet 1 – Scoring Weight Loss

To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

5. Worksheet 2 – Disease and its relation to nutritional requirements:

Score is derived by adding 1 point for each of the following conditions:

☐ Cancer   ☐ Presence of decubitus, open wound or fistula

☐ AIDS   ☐ Presence of trauma

☐ Pulmonary or cardiac cachexia   ☐ Age greater than 65

☐ Chronic renal insufficiency

Other relevant diagnoses (specify) _____

Primary disease staging (circle if known or appropriate) I II III IV Other ____

Numerical score from Worksheet 2 ☐ **B**

6. Worksheet 3 – Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. **Note:** Score fever intensity _or_ duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8 °C (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 37.2 and < 38.3	≥ 38.3 and < 38.8	≥ 38.8 °C
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ **C**

7. Worksheet 4 – Physical Exam

Exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid. Since this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = moderate, 3+ = severe. Rating in these categories is _not_ additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	**0**	**1+**	**2+**	**3+**

Fat Stores				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	**0**	**1+**	**2+**	**3+**

Fluid status				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	0	1+	2+	3+

Point score for the physical exam is determined by the overall subjective rating of the total body deficit. No deficit   score = 0 points   **Again, muscle deficit/loss takes precedence over fat loss or fluid excess.** Mild deficit   score = 1 point; Moderate deficit   score = 2 points; Severe deficit   score = 3 points

Numerical Score for Worksheet 4 ☐ **D**

Total PG-SGA Score (Total numerical score of A+B+C+D) ☐

Clinician Signature _____ RD RN PA MD DO Other _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C) ☐

Worksheet 5 – PG-SGA Global Assessment Categories

Category	Stage A Well-nourished	Stage B Moderate/suspected malnutrition	Stage C Severely malnourished
Weight	No weight loss OR recent non-fluid wt gain	≤ 5% loss in 1 month (≤10% in 6 months) OR Progressive weight loss	> 5% loss in 1 month (>10% in 6 months) OR Progressive weight loss
Nutrient intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	None OR significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR Recent significant deterioration
Physical Exam	No deficit OR chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).

First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score
- **0-1** No intervention required at this time. Re-assessment on routine and regular basis during treatment.
- **2-3** Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
- **4-8** Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
- **≥ 9** Indicates a critical need for improved symptom management and/or nutrient intervention options.

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email: faithotterymdphd@aol.com or info@pt-global.org

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

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Appendix 3: Institutional Review Board

Institutional Review Board | لجنة الأخلاقيات

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American University of Beirut
الجامعة الأمريكية في بيروت

APPROVAL OF RESEARCH

May 23, 2016

Jean El Cheikh, MD
American University of Beirut Medical Center
Email Address: je06@aub.edu.lb

Dear Dr. El Cheikh,

On May 23, 2016 the IRB reviewed the following protocol.

Type of Review:	Follow up, Expedited
Project Title:	Randomized controlled trial to assess the effect of a nutritional intervention on patients receiving stem cell transplant
Investigator:	Jean El Cheikh
IRB ID:	IM.J-EC.01
Documents reviewed:	• The IRB application • The modified study proposal(version received May 20, 2016) • The modified English & Arabic informed consent forms (version received April 28, 2016) • The email script to be sent to attendings

This is to grant you approval to the modified study proposal (version received May 20, 2016), the modified English & Arabic informed consent forms (version received April 28, 2016), the data collection sheet, the email script to be sent to attendings; for a period ending **May 22, 2017 inclusive**.

Before **March 22, 2017** or within 30 days of study close, whichever is earlier, you are to submit a completed "FORM: Continuing Review Progress Report" and required attachments to request continuing approval or study closure.

If continuing review approval is not granted before the expiration date of **May 22, 2017 approval** of this research expires on that date.

Kindly note that this approval does not grant permission for contacting patients who were enrolled in previous studies, unless it is specified in the signed consent form or if the principal investigator or research team member has a primary patient-physician relationship. In all other circumstances, the IRB needs to grant approval for alternative mechanisms.

Attached are stamped approved consent documents. Only these IRB approved consent forms and documents can be used for this research study.

It is a requirement to fill the official AUBMC Medical Records form titled "Enrollment in a Clinical Research Study" and place it in the inpatient chart or outpatient clinic chart for all patients enrolled in a clinical research study. The form will be stocked in the Materials Management Department and concerned units/departments can order it from there.

forms

The American University of Beirut and its Institutional Review Board, under the Institution's Federal Wide Assurance with OHRP, comply with the Department of Health and Human Services (DHHS) Code of Federal Regulations for the Protection of Human Subjects ("The Common Rule") 45CFR46, subparts A, B, C, and D, with 21CFR56; and operate in a manner consistent with the Belmont report, FDA guidance, Good Clinical Practices under the ICH guidelines, and applicable national/local regulations.

Sincerely,

Rami Mahfouz, MD
Vice-Chairperson of the IRB

Cc: Fuad Ziyadeh, MD, FACP, FRCP
Professor of Medicine and Biochemistry
Chairperson of the IRB

Ali K. Abu-Alfa, MD, FASN
Professor of Medicine

Consent to participate in a research study

Investigator: Dr. Jean El-Cheikh
Address: American University Hospital
                 Cairo Street
                 Beirut, Lebanon
Phone: 01-350 000 ext 7811
Study Site: Bone Marrow Transplantation Unit and nutrition private clinics
American University of Beirut Medical Center.

You are being asked to participate in a clinical research study conducted at the American University of Beirut. Please take time to read the following information carefully before you decide whether you want to take part in this study or not. Feel free to ask your doctor if you need more information or clarification about what is stated in this form and the study as a whole.

Study Purpose

Patients after stem cell transplantation are at risk of malnutrition as they might have decreased food intake due to nausea, vomiting and mucositis which would negatively affect their activities of daily living. Reversing malnutrition improves quality of life and reduces the associated complications. The proposed study aims to assess the impact of a nutrition intervention on the nutritional and functional statuses of patients receiving stem cell transplantation. Results of the study would guide the medical and nutritional standard of care post transplantation in Lebanon and the world.

During the pre-transplantation workup, you will be invited to participate in the study by the care coordinator in the Bone Marrow Transplantation (BMT) unit. If you are interested in the research, a Research Assistant (RA) will explain to you the study design and the benefits and risk of joining.

Participation in the study

If you decided to participate, you will be assigned to a control or an intervention group based on random sampling. Regardless of your group assignment, your body composition, physical activity level, functional status and nutritional status will be evaluated at regular intervals during the hospital stay (at admission and at days -2, +2, +5 and +10 of transplantation) and post discharge (days +30, +60 and +100 post transplantation).

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Body Composition

Your body composition will be evaluated using a body impedance analysis machine at admission, days +30, +60 and +100 post transplantation. During the analysis, that takes less than one minute, a small and safe electric current through your body. This current is safe on all patients except those who are pregnant and who have a pacemaker inserted. This measurement allows for the estimation of the percent of water and fat you have in your body.

Quality of Life

An assessment of your quality of life will be conducted using a dedicated questionnaire at days +2 post transplantation, at hospital discharge and at days +30, +60 and +100 post transplantation. You can fill the questionnaire yourself. An RA would be available for assistance.

Physical Activity Level

Your physical activity level will be assessed using a brief questionnaire the clinic.

Handgrip Strength

Your handgrip strength will be measured using a handgrip dynamometer. During measurement, you will be asked to hold the dynamometer and press against it as hard as you can. The measurement would take around 30 seconds.

Computed Tomography

If you have undergone a Computed Tomography (CT) scan in AUBMC, this CT might be reviewed by the research team to assess your body composition and compare it with the bioimpedance analysis results.

If you are in the nutrition intervention group, you will receive a tailored diet plan from a dietitian as well as regular follow-ups in the clinics measuring and reinforcing compliance. If you are in the control group, you will be assessed by a dietitian upon referral from the medical team. 52 patients should be recruited in the study.

The research team will communicate any new findings about the study if they appear.

Length of the study

This study extends from the hospital admission to the BMT unit until day +100 post transplantation. Assessments during hospital stay are expected to take around 20 minutes. Clinic visits are expected to take around 10 minutes for patients in the control group and around 25 minutes for patients in the intervention group.

The research team might decide to take you off from this study if it is in your best interest. You can choose to opt out from this study at any time. If you decide so, you need to inform a member of the research team.

Study Benefits
Direct benefits include:
- You will have a free measurement of your body composition.
- If you're in the intervention group, you will receive nutritional counseling to optimize your nutritional and functional statuses.

Indirect benefits include:
-This study allows us to have a better understanding of the nutritional and functional statuses of patients receiving stem cell cells and to assess the effectiveness of interventions to boost patients' nutritional statuses.

Study Risks
There are no foreseeable risks or discomfort of participating in the study.

Participation fees & Coverage
You will not be charged for participating in this study. Transportation coverage will be provided to all participants at a rate of 10,000 LL per clinic visit. Patients will receive reimbursement for each clinic visit, irrespective if they were able to complete the study. Moreover, reimbursement will be provided for serum albumin levels conducted at days +60 and +100 post SCT.

You are free to refuse participation in this research study. Refusal will involve no loss in medical or financial benefits. If you agree to participate in this research study, the information will be kept confidential. Unless required by law, only the study doctor and designee, the ethics committee and inspectors from governmental agencies will have direct access to your medical records. Study findings will be published in medical journals, yet you will not be identified in these publications in any way.

Investigator's Statement:
I have reviewed, in detail, the informed consent document for this research study with
_____ (name of patient or legal representative) the purpose of the study and its risks and benefits. I have answered to all the patient's questions clearly. I will inform the participant in case of any changes to the research study.

_____   _____

Name of Investigator or designee   Signature

_____

Date & Time

Patient's Participation:

I have read and understood all aspects of the research study and all my questions have been answered. I understand that the research team will have access to my medical files, ensuring confidentiality. I voluntarily agree to be a part of this research study and I know that I can contact Dr. Jean El-Cheikh at 01350000-7811 or any of his/her designee involved in the study in case of any questions. If I feel that my questions have not been answered, I can contact the Institutional Review Board for human rights at 01-350000 - 5445. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my care or benefits. I know that I will receive a copy of this signed informed consent.

_____   _____

Name of Patient or Legal Representative   Signature

_____

Date & Time

_____   _____

Witness's Name   Witness's Signature
(if patient, representative or parent do not read)

_____

Date & Time

- o I agree to be contacted from the research team for potential future research.
- o I do not agree to be contacted from the researchers for potential future research.

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Appendix 4: Clinicaltrial.gov registration documents

Detailed Description:

This study is a single center RCT with a parallel design. It aims to improve the SCT recipients' nutritional status and QoL and reduce the associated morbidities. Results of the study can guide the recommendations for the medical and nutritional outpatient assessment post SCT.

During the pre-SCT workup, patients will be invited to participate in the study. Around discharge from the hospital, recruited patients will be randomized to a control or an intervention group based on permuted block random sampling. Patients in the Nutrition Intervention group (NIG) will receive a tailored diet plan from the dietitian as well as regular outpatient follow-ups measuring and reinforcing compliance. Patients in the Control Group (CG) will receive usual care; they will only be assessed in the nutrition clinics upon referral by the medical team. The body composition, Quality of Life (QoL), Physical Activity (PA) level, nutrient intake, functional status and nutritional status of both groups will be evaluated at regular intervals during the hospital stay and post discharge through the Patient Generated Subjective Global Assessment (PGSGA), Body Impedance Analysis (BIA), handgrip strength, Functional Assessment of Cancer Therapy -Bone Marrow Transplantation (FACT-BMT), PA questionnaire and Karnofsky scale. Moreover, patients' food intake will be analyzed for its micronutrient and macronutrient content to assess the changes in nutrient analysis in the peri-transplantation phase. When applicable, BIA and Computed Tomography (CT) tests will be compared for their agreements.

Considering a power of 80%, an attrition rate of 30% and a difference of 40% between the NIG and CG groups, 52 patients need to be recruited in the study. Analysis will be done based on 'intention to treat' and 'per protocol' analysis.

Study Design

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Study Type ❶:	Interventional (Clinical Trial)
Actual Enrollment ❶:	52 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Supportive Care
Official Title:	Nutrition Intervention Among Stem Cell Recipients: a Randomized Controlled Trial Post Hospital Discharge
Actual Study Start Date ❶:	August 2016
Actual Primary Completion Date ❶:	November 2017
Actual Study Completion Date ❶:	January 2018

Resource links provided by the National Library of Medicine   NIH❯NLM

MedlinePlus related topics: Health Facilities   Malnutrition

U.S. FDA Resources

Arms and Interventions

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Arm ❶	Intervention/treatment ❶
No Intervention: Control Upon discharge from the medical center, patients would be advised on a qualitative, neutropenic diet. Participants' quality of life, physical activity level, functional and nutritional status would be assessed at days +30, +60 and +100 post transplantation. These participants will not receive nutritional counseling by the dietitian as outpatients except if referred by the medical team.	
Experimental: Nutrition Intervention Group Upon discharge from the medical center, NIG patients will receive tailored nutrition counseling with the provision of patient education material and oral nutritional supplements if needed. Patients will be advised on a diet high in energy and proteins and tailored to their medical condition in the	Other: Nutrition Intervention

Outcome Measures

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Primary Outcome Measures ❶:

1. Proportion of patients with a PGSGA score ≥4 [Time Frame: 100 days post transplantation]

Secondary Outcome Measures ❶:

1. Handgrip strength [Time Frame: 100 days post transplantation]

2. Lean Body Mass Changes [Time Frame: 100 days post transplantation]

3. Re-hospitalization Rate [Time Frame: 100 days post transplantation]

4. Quality of life (QoL) [Time Frame: 100 days post transplantation] [Time Frame: 100 days post transplantation]

Eligibility Criteria

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Ages Eligible for Study: 16 Years to 80 Years   (Child, Adult, Older Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Adults admitted to the adult BMT service at AUBMC
- Allogeneic or autologous SCT
- Malignant or non-malignant indication for SCT

Exclusion Criteria:

- Patients who pass away before day +100
- Patients who miss 2 assessment points

Contacts and Locations   Go to ▼

Information from the National Library of Medicine   NIH〉NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): **NCT02791347**

Locations

Lebanon

American University of Beirut Medical Center
Beirut, Lebanon

Sponsors and Collaborators

American University of Beirut Medical Center

Aix Marseille Université

More Information   Go to ▼

Responsible Party: Jean El Sheikh, Assistant Professor of Hematology Oncology- Department of Internal Medicine, American University of Beirut Medical Center
ClinicalTrials.gov Identifier: NCT02791347   History of Changes
Other Study ID Numbers: IM.J-EC.01
First Posted: June 6, 2016   Key Record Dates
Last Update Posted: February 8, 2018
Last Verified: February 2018

Additional relevant MeSH terms:
Malnutrition
Nutrition Disorders

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