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ORIGINAL RESEARCH REPORT

Functional capacity, lung function, and muscle strength in patients undergoing hematopoietic stem cell transplantation: A prospective cohort study

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Abstract
Objective/Background: Hematopoietic stem cell transplantation (HSCT) is a treatment for benign and malignant hematological diseases. These aggressive treatments cause reduced levels of physical activity, decreased lung function, and worse quality of life. Alterations in pulmonary function tests before HSCT are associated with the risk of respiratory failure and early mortality. The objective of this study was to evaluate functional capacity and lung function before and after HSCT and identify the predictors of mortality after 2 years.
Methods: A prospective cohort study was carried out with individuals with oncohematological diseases. The evaluations were carried out in two moments during hospitalization and at hospital discharge. Follow-up was carried out after 48 months. Assessments were carried out on 34 adults, using spirometry, manovacuometry, 6-Minute Walk Test (6MWT), Handgrip Strength Test, and 30-Second Chair Stand Test (30-s CST).
Results: There was a statistically significant reduction for the variables in forced vital capacity, forced expiratory volume predicted in the 1st second, Tiffeneau index, handgrip strength, and distance covered (% predicted) on the 6MWT ($p < .05$). There was a significant difference in

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the 30-s CST when individuals were compared according to the type of transplant. We found that a 10% reduction in the values of maximum inspiratory pressure (MIP) can predict an increased risk for mortality.

Conclusions: Individuals undergoing HSCT have reduced functional capacity, lung function, and muscle strength during the hospitalization phase. Reduction in the values of MIP increases the risk of nonrelapse mortality.

Introduction

The Brazil's National Cancer Institute estimates that 625,000 new cases of cancer will occur annually in Brazil between 2020 and 2022 [1]. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for a variety of malignant and nonmalignant hematological disorders [2—5]. Approximately 80 diseases at different stages and age groups can benefit from this treatment method [6]. Because of technological advances in transplantation and treatment, HSCT has become relatively safe and its applicability continues to expand [3].

The results of HSCT vary according to the baseline disease [5], type and intensity of conditioning, radiotherapy [7,8], and type of transplantation [9,10]. In addition, complications such as graft-versus-host disease [4], comorbidities related to previous treatments, and recipient age influence the success of the procedure [11,12].

Pulmonary complications are frequent and affect the success of autologous HSCT (auto-HSCT) or allogeneic HSCT (allo-HSCT). Auto-HSCT presents fewer pulmonary complications as it does not require immunosuppressive therapy [13]. Pulmonary infiltrates occur in 30—50% of HSCT receptors, can have infectious or noninfectious origin, and contribute significantly to pulmonary morbidity [14].

The underlying disease and aggressive treatment before HSCT lead to a decline in health status. In the skeletal muscular system, sarcopenia, fatigue, reduced muscle strength, health-related quality of life, and consequently reduced exercise capacity can occur [9,15—19]. These factors can hamper the recovery of activities of daily living after hospital discharge [17].

The evaluation of pulmonary function and exercise capacity before and after HSCT is essential in screening and monitoring patients with a higher risk of mortality. The 6-Minute Walk Test (6MWT) is commonly used to assess the pre-HSCT functional capacity and can be considered a predictor of post-HSCT mortality [20]. However, the factors associated with mortality after HSCT are still not well-established in the literature.

This study aims to verify alterations in functional capacity, lung function, and peripheral muscle strength before and after HSCT and to identify the predictors of mortality after 2 years of HSCT.

Methods

This is a prospective cohort study involving adult patients admitted to the bone marrow transplant sector at the Hospital de Clínicas de Porto Alegre (HCPA) that are scheduled to receive HSCT. This study was carried out in accordance with Resolution 466/12 of the National Health Council and was approved by the hospital's Research Ethics Committee (No. 16—0255).

The study population consisted of adult patients, aged over 18 years, with a hematological disease diagnosed by complementary examinations. Patients with cardiac, orthopedic, or trauma complications that limited the performance of the functional test, as well as those with recurrence of the disease were excluded.

After accepting to participate in the research and signing the informed consent form, patients were evaluated within the first 48 hours of hospitalization, mandatorily before starting chemotherapy or cell infusion, and re-evaluated at the time of hospital discharge. The monitoring of patients was carried out through electronic medical records for 48 months after HSCT to assess the outcome of nonrecurring mortality.

Follow-up of patients was performed using the electronic medical record for 48 months after HSCT to assess the nonrelapse mortality outcome.

Functional capacity was evaluated using the 6MWT, according to the guidelines published by the American Thoracic Society and European Respiratory Society [20]. Patients received standardized verbal stimuli and were instructed to do as many laps as possible in a 6-minute period. The distance covered was recorded in percentage of predicted value and the calculation was performed using normality equations for Brazilian adults [21]. The pulmonary function tests were performed with a computerized spirometer (Master Screen, Jaeger version 4.31a; Jaeger, Würzburg, Germany) at the Pulmonary Physiology Unit of the Pulmonology Service of HCPA. The test was carried out with the patient in a sitting position, and conducted in accordance with the Guidelines for Pulmonary Function Tests of the Brazilian Society of Pulmonology and Tisiology. The values of forced vital capacity (FVC), forced expiratory volume predicted in the 1st second (FEV_1), and Tiffeneau index (FEV_1/FVC) were recorded. The values were expressed as a percentage of the predicted value according to the reference equations for the Brazilian population [22]. Respiratory muscle strength was obtained using a device called a digital manometer (Homed, Microhard MVD 300, version 1.0; Porto Alegre, Brazil), where it was possible to obtain the values of maximum inspiratory pressure (MIP) and maximum expiratory pressure. The test was performed with the patients seated, using a nasal clip to prevent air from escaping during the maneuvers. At least three acceptable maneuvers (without air leak and lasting $\geq$ 2 seconds) and

reproducible maneuvers (without varying more than 10%) were performed. The highest value was computed and expressed as a percentage of the predicted value [21].

We performed the 30-Second Chair Stand Test (30-s CST) to assess lower limb strength [23]. Participants were seated in a chair with their hips and knees at 90°. The upper limbs were crossed at the level of the wrists at chest height. Patients were asked to sit down and rise up out of the chair as many times as possible in a period of 30 seconds. The result was determined by the maximum number of repetitions performed correctly in the 30-second period [24].

The handgrip strength was performed using a Dayhome digital dynamometer (E-Clear, model EH101). The individual should be seated with a 90° hip and knee flexion angle, erect spine, adducted shoulders, elbow flexed at 90°, and forearm and wrist in a neutral position. The dominant limb was used, according to the procedures of the American Society of Hand Therapists [25]. Three maneuvers were performed, with an interval of 20 seconds [26] and maximum contraction of 3—5 seconds [27]. The average value of the three maneuvers (expressed in kilograms) was accepted as an absolute value.

Body weight was checked using a Filizola electronic scale. Height was measured with the digital scale anthropometer. The body mass index (BMI) was obtained using the formula BMI = weight (kg)/height^2 (m), according to the references established by the World Health Organization [28].

Statistical analysis

The sample size was calculated using the WINPEPI program, version 11.43. The calculated sample size of 32 individuals had the ability to detect a 7.7% reduction between the FEV_1 averages before and after transplantation, considering the standard deviation of the differences of 17.12 (as per data from the pilot study carried out previously). A power of 80% and a significance level of 5% were considered. Data were analyzed using SPSS software version 18 (SPSS Inc., Chicago, IL, USA).

The primary outcome measure was FEV_1. The secondary outcomes were distance on the 6MWT, handgrip strength, result of 30-s CST, MIP, maximum expiratory pressure, and nonrelapse mortality without recurrence.

Quantitative variables were described by mean and standard deviation and categorical variables by absolute and relative frequencies.

In order to compare the parameters over time, generalized estimation equations model complemented by the least significant difference test was applied.

To evaluate the effect of these variations in relation to death, the regression model of Cox proportional hazards (univariate and multivariate analyses) was used. The criterion for entering the variable in the multivariate model is that it should have a value of $p < .20$ in the univariate analysis.

To obtain the best cutoff point for the MIP variation in the prediction of death, the receiver operating characteristic curve was used.

The level of significance adopted was 5% ($p < .05$) and the analyses were performed using SPSS version 21.0 (SPSS Inc.).

Results

Between September 2016 and June 2020, 45 patients were hospitalized at the HCPA for HSCT. Two patients refused to participate and nine others did not meet the inclusion criteria because they were unable to complete the proposed tests. The sample consisted of 34 adult patients, aged 18 years, who completed the assessments in the pre-HSCT phase; 32 patients completed the post-HSCT assessment and two did not complete the post-transplant assessments because they died after receiving the HSCT in the hospitalization phase. Data on clinical and demographic characteristics of the individuals in the sample who received HSCT are presented in Table 1.

In the studied sample, multiple myeloma was the most prevalent disease (32%) followed by non-Hodgkin lymphoma (18%) and Hodgkin lymphoma (15%; Table 2).

The variables used in analysis were weight, BMI, lung function, upper and lower limb muscle strength, distance covered on the 6MWT, and respiratory muscle strength. There was a statistically significant reduction in weight, BMI, FEV_1, FEV_1/FVC, handgrip strength, distance covered in the 6MWT (% predicted), and MIP ($p < .05$) following HSCT (Table 3).

Individuals were stratified according to the type of HSCT (allo- or auto-HSCT) in the pre- and post-transplant phases. There was no significant difference between the different types of transplant in clinical characteristics, exercise capacity, and lung function ($p > .05$). Allo-HSCT showed a significantly greater drop in the 30-s CST ($p < .05$; Table 4).

Univariate and multivariate Cox regression analyses were performed to predict death according to the variables. The multivariate analysis was adjusted in accordance with age, donor status, cell source, radiation therapy, bone marrow pick, and type of transplant. The variable that showed a significant difference was MIP ($p < .05$). A reduction of 1% in the value of MIP would increase the probability of death by 5% (Table 5).

In the 2-year follow-up after HSCT, eight deaths occurred. Among these, six occurred within the first 12 months and the others in the 2nd year of follow-up.

Assessment of survival time in 24 months according to the MIP values presented. The data were adjusted according to the variables, type of transplant and radiotherapy. The results show that if there is a 10% reduction in MIP, the probability of non-recurring mortality increases by 14.4 times (Fig. 1).

Discussion

A total of 34 individuals were included in this study; among them, 32 completed post-HSCT assessments. As much as 13 patients underwent allo-HSCT and 21 patients underwent auto-HSCT. The evaluation of the acute phase after HSCT showed a significant decline in lung function, exercise capacity, and peripheral and respiratory muscle strength. In the 2-year follow-up, eight

Table 1 Clinical and Demographic Characteristics of the Individuals Who Underwent HSCT.

Characteristics	Absolute frequency (*N* = 34)	Relative frequency, %
Gender		
Female	19	55.9
Male	15	44.1
Transplant type		
Autologous	21	62
Allogenic	13	38
Donor status		
Matched related	21	61.8
Matched unrelated	10	29.4
Haploidentical	3	8.8
Cells source		
Bone marrow	9	26.5
Peripheral blood	25	73.5
Conditioning		
Myeloablative	8	23.5
Nonmyeloablative	26	76.5
Total body irradiation		
Yes	5	14.7
No	29	85.3
Deaths during hospitalization		
Yes	2	5.9
No	32	94.1
Reported pre-HSCT fatigue		
Yes	17	50
No	17	50
Pre-HSCT musculoskeletal symptoms		
Yes	21	61.8
No	13	38.2
Pre-HSCT weight loss		
Yes	3	8.8
No	31	91.2

Note. HSCT = hematopoietic stem cell transplantation.

Table 2 Hematological Diseases of the Included Individuals.

Diagnostic	Absolute frequency (*N* = 34)	Relative frequency, %
Multiple myeloma	11	32
Non-Hodgkin lymphoma	6	18
Hodgkin lymphoma	5	15
Acute myeloid leukemia	3	9
Chronic myeloid leukemia	2	6
Myelodysplastic syndrome	2	6
Acute lymphocytic leukemia	2	6
Myelofibrosis	1	3
Aplastic anemia	1	3
POEMS syndrome	1	3

Note. *N* = absolute frequency sample; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; % = relative frequency sample.

deaths occurred, with the reduction of MIP being a predictor of mortality.

Pulmonary complications are considered barriers for the overall success of HSCT, and were an important cause of morbidity and mortality [29—32]. Individuals with impaired lung function before transplantation are at an increased risk of developing respiratory failure, increasing the risk of post-transplant mortality [33]. In our study, there was a statistically significant reduction in lung function in the acute phase after HSCT; however, this did not impact mortality. Despite the reduction in lung function, the values remained within the normal range, which may be the reason why

Table 3 Nutritional Characteristics, Lung Function, and Exercise Capacity of Pre- and Post-HSCT Patients.

Variable	Pre-HSCT (N = 34)	Post-HSCT (N = 32)	95% CI difference	p
	Mean ± SD	Mean ± SD		
Weight (kg)	78.1 ± 17.7	72.3 ± 14.6	−5.8 (−9.1 to −2.6)	<0.001*
BMI (kg/m^2)	27.7 ± 5.3	26.0 ± 4.3	−1.7 (−2.9 to −0.6)	0.002*
FVC (% predicted)	94.6 ± 13.8	89.5 ± 21.5	−5.1 (−10.5 to 0.3)	0.067
FEV_1 (% predicted)	97.1 ± 16.9	88.1 ± 23.2	−9.0 (−15.5 to −2.5)	0.006*
FEV_1/FVC (% predicted)	100.0 ± 11.3	92.1 ± 19.2	−7.9 (−15.1 to −0.7)	0.031*
Hand grip strength (kg)	29.5 ± 11.4	26.1 ± 10.9	−3.4 (−5.4 to −1.4)	0.001*
30-s CST (number of repetitions)	13.2 ± 4.4	12.2 ± 4.0	−1.0 (−2.2 to 0.3)	0.122
Distance 6MWT (% predicted)	73.0 ± 13.7	58.0 ± 21.5	−15.0 (−22.5 to −7.3)	<0.001*
MEP (% predicted)	63.7 ± 19.1	57.9 ± 17.7	−5.8 (−10.3 to −1.4)	0.011*
MIP (% predicted)	56.5 ± 18.6	53.2 ± 17.4	−3.3 (−7.9 to 1.4)	0.171

Note. 30-s CST = 30-Second Chair Stand Test; 6MWT = 6-Minute Walk Test; BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume predicted in the 1st second; FVC = forced vital capacity; HSCT = hematopoietic stem cell transplantation; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; SD = standard deviation; % predicted = percentage of predicted.

* Statistically significant values.

Table 4 Clinical Characteristics, Exercise Capacity, and Lung Function of Patients Who Underwent Allogenic or Autologous HSCT.

Variable	Allogenic transplant (n = 13)	Autologous transplant (n = 21)	p
	95% CI (difference: post − pre)	95% CI (difference: post − pre)	
Weight (kg)	−10.1 (−18.3 to −1.8)	−3.8 (−5.7 to −1.9)	0.149
BMI (kg/m^2)	−3.1 (−5.9 to −0.3)	−1.2 (−1.9 to −0.4)	0.192
FVC (% predicted)	−5.7 (−13.9 to 2.6)	−4.8 (−11.7 to 2.1)	0.872
FEV_1 (% predicted)	−4.3 (−14.4 to 5.8)	−11.9 (−20.1 to −3.7)	0.256
FEV_1/FVC (% predicted)	−0.1 (−9.7 to 9.4)	−12.6 (−21.8 to −3.4)	0.066
Hand grip strength (kg)	−5.5 (−10.1 to −0.9)	−2.3 (−4.1 to −0.5)	0.209
30-s CST (number of repetitions)	−3.6 (−6.0 to −1.3)	0.5 (−0.4 to 1.5)	0.001*
Distance 6MWT (% predicted)	−12.2 (−24.0 to −0.4)	−17.0 (−26.6 to −7.4)	0.533
MEP (% predicted)	−7.1 (−13.3 to −1.0)	−4.6 (−10.4 to 1.3)	0.125
MIP (% predicted)	2.7 (−3.3 to 8.6)	3.1 (−3.2 to 9.4)	0.921

Note. 30-s CST = 30-Second Chair Stand Test; 6MWT = 6-Minute Walk Test; BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume predicted in the 1st second; FVC = forced vital capacity; HSCT = hematopoietic stem cell transplantation; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; SD = standard deviation; % predicted = percentage of predicted.

* Statistically significant value.

these variables did not influence mortality during the 48-month follow-up after HSCT.

A previous study carried out a follow-up of approximately 60 months after HSCT and found that changes in lung function may also be present in asymptomatic individuals. Therefore, performing pulmonary function tests often could highlight which individuals may have pulmonary complications, such as the risk of pulmonary graft-versus-host disease [34,35].

In addition to spirometry, the evaluation of maximum static respiratory pressures allows investigating the strength of respiratory muscles [36]. In this study, MIP is considered a predictor of mortality with a 1% reduction in the MIP value increasing the probability of death by 5%. Previous studies in pre- and post-HSCT individuals have also identified a reduction in muscle strength [37,38], but without finding an association with mortality. In critically ill patients, respiratory muscle weakness, especially MIP, is associated with worse quality of life and mortality after hospital discharge [39–42].

In this study, we observed a significant reduction in handgrip strength in the allo- and auto-HSCT groups. The reduction in handgrip strength in patients with hematological disease may be associated with functional deconditioning [43]. Individuals who underwent HSCT showed a significant loss (6%) of handgrip strength test at 1 month after transplantation; however, their strength recovered in the next 2 months in the absence of graft-versus-host disease [44]. The reduction in handgrip strength may be associated with physical deconditioning and immobility during the hospital stay.

Table 5 Univariate and Multivariate Cox Regression Analyses to Predict Death.

Variable	Univariate analysis	Multivariate analysis*	*p*
	HR (95% CI)	HR (95% CI)	
Δ Weight (kg)	0.97 (0.84—1.12)	1.02 (0.80—1.29)	0.895
Δ BMI (kg/m^2)	0.96 (0.86—1.07)	0.93 (0.81—1.07)	0.286
Δ FVC (% predicted)	0.99 (0.95—1.03)	0.97 (0.91—1.04)	0.463
Δ FEV_1 (% predicted)	0.99 (0.96—1.03)	0.98 (0.91—1.05)	0.575
Δ FEV_1/FVC (% predicted)	1.01 (0.97—1.05)	0.97 (0.91—1.03)	0.268
Δ Hand grip strength (kg)	0.99 (0.95—1.05)	1.03 (0.95—1.11)	0.485
Δ 30-s CST (n. repetitions)	0.96 (0.92—1.01)	0.99 (0.92—1.08)	0.944
Δ Distance 6MWT (% predicted)	1.00 (0.97—1.03)	1.00 (0.97—1.03)	0.854
Δ MEP (% predicted)	1.00 (0.97—1.04)	0.99 (0.94—1.05)	0.789
Δ MIP (% predicted)	0.98 (0.95—1.01)	0.95 (0.90—0.99)	0.028**

Note. 30-s CST = 30-Second Chair Stand Test; 6MWT = 6-Minute Walk Test; BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume predicted in the 1st second; FVC = forced vital capacity; HR, hazard ratio; HSCT = hematopoietic stem cell transplantation; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; SD = standard deviation; % predicted = percentage of predicted; Δ = difference post − pre.

* Adjusted by age, donor status, cell source, radiation therapy, bone marrow, and transplant type.

** Statistically significant value.

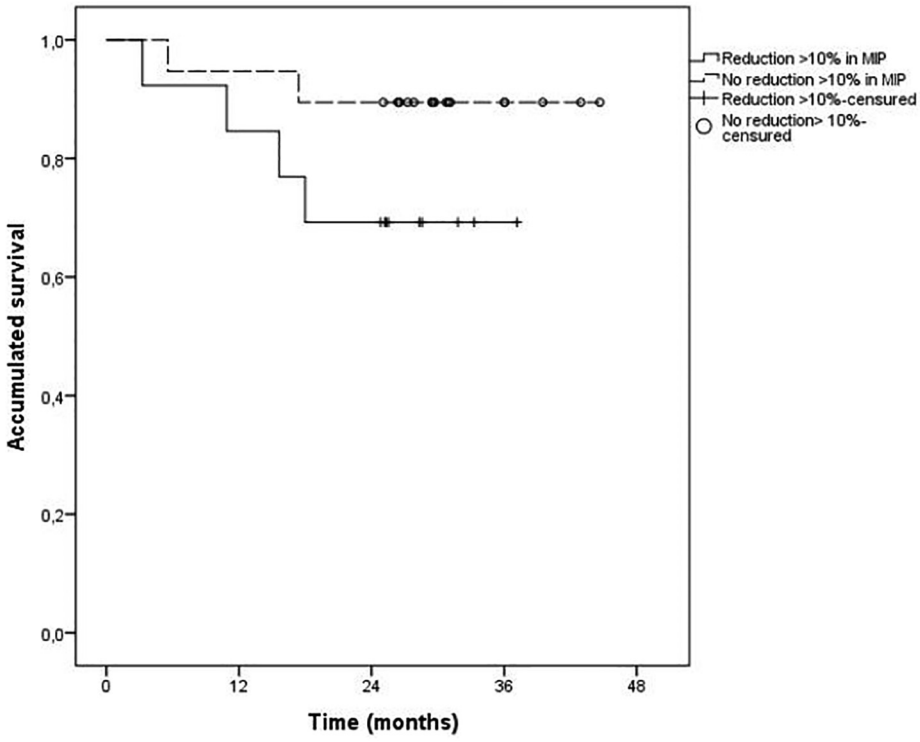

Fig. 1 Survival time 48 months after hematopoietic stem cell transplantation according to the presented values of maximum inspiratory pressure (MIP).

The 6MWT has been used in this population to assess exercise capacity, which is considered a quick and easy test. Jones et al. [45] evaluated 407 pre-HSCT individuals and found that the distance covered on the 6MWT less than 400 m was associated with an increased risk of mortality after the HSCT. These data differ from our findings because we did not find any correlation between the 6MWT and mortality despite the significant reduction in the distance covered in the 6MWT after HSCT. Other studies confirm our results that there is a significant reduction in functional capacity after HSCT [46—51].

Our study had some limitations, such as the different types of procedures, conditioning protocols, donor condition, prophylaxis and radiotherapy. In addition, there was a wide age group among the participants (18 to 67 years old). The diffusion capacity of carbon monoxide has not

been evaluated, although it is considered relevant in the diagnosis of obliterating lung disease and in the identification of pulmonary disease of the graft against the host, both of which are the main complications related to HSCT.

Conclusion

Based on our results, it can be concluded that adult patients present a deterioration of the clinical condition after HSCT, as evidenced by reduced pulmonary function, exercise capacity, and muscle strength in the hospitalization phase. Inspiratory muscle strength was considered a predictive variable for nonrelapse mortality after HSCT. Therefore, evaluations and ostensible follow-up in the hospitalization phase for HSCT can assist in the early management of alterations, avoiding complications and functional losses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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