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Running head: Altered exercise capacity in allo-HSCT survivors

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Abstract

Long–term survivors after allogeneic hematopoietic stem cell transplantation (allo-HSCT) are at high risk for treatment-related adverse events, that may worsen physical capacity and may induce fatigue and disability.

The aims of this prospective study were to evaluate exercise capacity in allotransplant survivors and its relationship with fatigue and disability. Patient-reported outcomes and exercise capacity were evaluated in 71 non-relapse patients one year after allo-HSCT, using validated questionnaires, cardiopulmonary exercise testing (CPET) with measure of peak oxygen uptake (peakVO_2) and deconditioning, pulmonary function testing, echocardiography and 6-minute walk test.

A high proportion (75.4%) of allo-HSCT survivors showed abnormal cardiopulmonary exercise testing parameters as compared to predicted normal values, including 49.3% patients who exhibited moderate to severe impairment in exercise capacity and 37.7% patients with physical deconditioning. PeakVO_2 values were not accurately predicted by 6-minute walk distances ($r = 0.53$). Disability and fatigue were strongly associated with decreased peakVO_2 values ($p = 0.002$ and $p = 0.008$, respectively).

Exercise capacity was reduced in most allo-HSCT long-term survivors. Because reduced exercise capacity was associated with fatigue, disability and a decrease in quality of life, cardiopulmonary exercise testing should be performed in every patient who reports fatigue and disability.

INTRODUCTION

Continuous progress in conditioning regimen and transplantation process in allogeneic hematopoietic stem cell transplantation (allo-HSCT) translates into an increasing population of long-term survivors who are at high risk of treatment-related late adverse events[1]. These events impact directly cardiopulmonary and musculoskeletal functions and may worsen physical capacity and reduce quality of life.[2-4] The need for cardiorespiratory fitness evaluation is becoming increasingly important, since physical activity has been highlighted as a modifiable non-pharmacological factor that may improve the length and quality of life among cancer survivors,[5-8] including haematological patients. [9-15]

Cardiopulmonary exercise testing (CPET) is the most accurate tool to evaluate cardiorespiratory fitness, to identify the main factors limiting exercise tolerance, and to set up an individual rehabilitation program with exercise targets if needed. Currently, CPET is not performed in the follow-up of allotransplants survivors in contrast to lung function tests and echocardiography, two tests performed at rest. A few studies analysed CPET findings on small numbers of allo-HSCT survivors (inferior to 20 patients) in the limited context of exercise intervention benefits.[11, 12] In auto-HSCT survivors, two studies evaluated cardiorespiratory fitness by CPET, including Stenehjem et al. who reported that 22% of patients from a 200-patient cohort had an impaired exercise capacity at 10 years post transplantation.[16, 17] Alternatively, physical function in chronic diseases such as chronic obstructive pulmonary disease (COPD) or heart failure is often assessed by submaximum exercise-testing such as the 6-minute walk test (6MWT), one of the most common field-tests used in the follow-up of such patients. However, the 6MWT only gives an extrapolation of cardiorespiratory fitness from submaximum exercise [18] and no data are available in the allotransplant setting.

In this prospective study we performed a full assessment of exercise capacity and quality of life (QOL) at one year in non-relapse allotransplanted patients. The aims of the present study were to evaluate the proportion of allo-HSCT survivors with impaired exercise capacity and the relationships between fatigue, disability and exercise capacity and to determine whether an simpler test such as 6MWT can substitute CPET in assessment of exercise capacity.

Materials and Methods

Study design

This was a single arm prospective and monocentric cohort study conducted at CHU of Nantes. As such, all consecutive adults (≥ 18 years old) receiving an allo-HSCT and alive one-year after transplant without relapse were included, for a 2-year period of inclusion. All tests were performed during a 1-day standard exploration at 1 year post transplantation. Furthermore, retrospective data were collected on the total of patients who underwent allo-HSCT one year before and after the beginning of inclusion. In those patients, death, relapse, hospitalisation at the time of 1-year evaluation, and one-year post-transplant check-up in other hospital were also collected between allo-HSCT and one-year post allo-HSCT. The study was approved by the Ethics Committee of Nantes, France (REF: 2013-12-08) and all patients provided written informed consent.

Quality of life

Various self-administered questionnaires were used : (i) the Medical Outcomes Study Short Form 36 (SF-36)[19], a 36 items generic multidimensional quality of life measure including Physical Functioning (PF), role physical (RP), Component Summary (PCS) and Mental Component Summary (MCS) scales allowing to compare scores with those observed for the general population,[20] (ii) the Hospital Anxiety and Depression scale (HAD), a score ≥11 defining patients suffering from anxiety or depression[21] and (iii) the St. George's Respiratory Questionnaire (SGRQ).[22]

Disability was self-reported by patients with a simple binary question: "In the daily life, do you experience disability?". We observed in the first enrolled patients that some of them reported "fatigue" as an important and persistent symptom in their daily life. The SF-36 provided self-report measurement of physical and mental health, but was not an effective tool for evaluating the "fatigue" symptom because of the lack of specific questions. Fatigue was then evaluated by a simple numeric rating scale (NRS) from 0 to 10, and defined as NRS ≥ 5. [23, 24]

Physical activity and exercise capacity measurements

To assess physical activity before, during and after (including at the time of the present study) transplant, bicycle ergometer practice in the sterile unit and reported one-time per week exercises were considered. Patients were required to retrospectively provide approximately the average duration in minutes (min) of physical activities for each period of time. Patients were then classified according to whether they had performed exercise less or more than 150 min per week, according to international exercise guidelines. [25]

The CPET was performed using the Ergocard® (Hyp'air, Medisoft, Sorinnes, Belgium) and the electronically braked cycle ergometer Ergoselect (ergoline GmbH, Bitz, Germany), with a 12-lead electrocardiogram (ECG) and blood pressure monitoring. The protocol included a 3-min rest period, a 3-min warm-up of unloaded pedalling followed by a 5-20W/min incremental phase, up to exhaustion.[26] Dyspnea and leg fatigue intensity were assessed with the Borg scale every 2-min up to exhaustion.[27] This includes the maximal or peak oxygen uptake (peakVO_2), the ventilatory threshold (VT), the VO_2 at VT (VO_2-VT), and the subjective perception of exertion. Peak aerobic exercise capacity (peakVO_2) was expressed in mL/min/kg and percentage of the predicted normal value (PNV). [28] Normal, mild, moderate or severe impaired exercise capacity were defined, respectively, as a peakVO_2 percentage > 80%, between 71 and 79%, between 51 and 70% or ≤ 50% of the predicted normal value.[28] A combined approach was used to calculate VT, based on the identification of the inflection point during the incremental exercise: i) of the respiratory equivalent for oxygen (VE/VO_2) curve with time, ii) of the minute-ventilation (VE) curve with time, or iii) the VO_2-VCO_2 relationship. The 9-panel graphical representation of Wasserman et al. was also used to optimize the VT position.[29] Deconditioning was defined by VT < 40% predicted VO_2max.

The 6MWT was performed according to the ERS/ATS guidelines.[30, 31] Patients were required to walk as fast as possible, without running, and to cover the longest possible distance during 6 minutes under the supervision of a certified physiotherapist (BlueNight Oximeter®). The 6MWD was expressed in meters and as a percentage of the predicted normal value for age and gender, according to Enright equation.[32]

Pulmonary and cardiac function at rest

All pulmonary function tests were performed in the Pulmonary Function Lab according to recommendations.[33] Transthoracic echocardiography was performed according to as standardized protocol (see Supplementary Material).

Statistical Analysis

To evaluate the association between exercise capacity and 6MWD, a linear regression model was used to correlate and predict peakVO_2 from the 6MWD. Residuals of the linear regression were analysed to evaluate departure between observed peakVO_2 and predicted peakVO_2 from 6MWD data. Differences between observed and predicted peakVO_2 were represented using histograms. All statistical analyses were performed using R statistical software.[34]

Continuous data were presented using mean $\pm$ standard deviation and with percentile p50 (p25-p75) when appropriate, categorical data were presented using raw counts and percentages. Association between categorical variables was expressed using odds ratios (ORs), with 95% confidence interval. The statistical significance of comparison between continuous variables (exercise capacity, quality of life score) was assessed using Mann Withney (2 groups) or Kruskall Wallis tests (more than 2 groups).

The statistical significance of association between variables was assessed using chi-square test, t-test (after exclusion of non-normal distribution) and Fisher's exact test when appropriate. Results were graphically illustrated using boxplots and spine plots. p-values were two-sided and reported without correction for multiple hypothesis testing. In a second step, major risk factors for post allo-HCST complications (including age, gender, conditioning intensity, GVHD presence) were introduced into a multivariate logistic regression analysis for prediction of peakVO_2 results (odds ratio with 95% CI). The threshold for statistical significance was defined as $p < 0.05$.

RESULTS

Patients

The study started in May 2012. Although a total of 153 patients underwent an allo-HSCT during the two following years, only 71 cases (46.4%) were enrolled in the present study. The reasons for exclusion at one year post-transplant were as follows: death (n = 55, 36%), relapse (n = 8, 5%), hospitalisation at the time of 1-year evaluation (n = 6, 4%) and one-year post-transplant check-up in other hospital (n = 13, 8%) (**Supplementary Figure S1**). Demographic and transplant characteristics of the 71 allo-HSCT one-year survivors are summarized in **Table 1**. Similar characteristics were shared by the 13 patients who underwent 1-year evaluation outside of our department (data not shown). Mean interval between allo-HSCT and one-year post-transplant evaluation was 14 months (range, 11-18 months). At this time, 14 (20%) patients were still under corticosteroid medication for GVHD treatment.

Lung function tests were normal in most patients (83%) and in the 69 patients who underwent echocardiography, results were normal with a mean LVEF of 64 ± 5.7% (**Table 2**). One patient out of 4 with obstructive lung function and 2/8 patients with restrictive lung defect were on steroid.

Self-reported symptoms and quality of life

Among the 71 patients, 26 (36.6%) reported disability at one year after allo-HSCT (**Table 2**). Importantly, 18/53 (34%) patients reported fatigue at one year post allo-HSCT. Interestingly, most patients with fatigue presented also disability (n = 11/18, 61%).

In QOL evaluation using self-administered questionnaires, scores related to physical health were the most impaired ones as compared to scores in the general population. Role limitations due to physical health were experienced by 62.3% of the patients (**Table 2**). Furthermore, PCS score (that represents the mean average of all of the physically relevant questions) was significantly lower than the general population in 69.2% of the patients (44.73 ± 8.32 vs 50.11 ± 5.79, $p < 0.001$). Finally, a lower general health perception was reported by 65.7% of the patients, showing a frequent alteration in QOL (**Table 2**). The MCS score was not significantly different from the general population (48.50 ± 10.39 vs 48.14 ± 6.66, $p = 0.78$), suggesting that impaired QOL was more related to physical impairment than mental health deficit. These

results were consistent with the low rate of patients reporting anxiety or depression on the HAD scale (**Table 2**, score > 11, n = 13/71 (18.3%)). No significant relationships were observed between peakVO_2 and SGRQ (data not shown), suggesting that this questionnaire is not relevant to detect patients with exercise capacity impairment.

Exercise capacity measurements

Despite normal lung function tests and echocardiography findings in most patients, only 17 (24.6%) had a normal exercise capacity on CPET and 52 (75.4%) and impaired exercise capacity (**Table 2**), while nearly half of the studied population (n = 34, 49.3%) showed moderate to severe impairment in exercise capacity, as defined by a peakVO_2 inferior to 70%pred. Importantly, deconditioning, defined by a ventilatory threshold < 40% predicted VO_2max, affected 26 patients (37.7% of the population).

Neither peakVO_2 nor deconditioning condition was associated with DLCO, conditioning regimen, chronic GVHD, or corticosteroid treatment (data not shown). An exploratory multivariate analysis including major risk factors for post allo-HSCT complications (age, gender, conditioning intensity, GVHD) did not predict peakVO_2 results (p = 0.4).

In parallel, mean 6MWD was 470.4 ± 85m (83 ± 16%pred). Interestingly, in 26 (37.7%) patients, the 6MWD was inferior to 80%pred (**Table 2**), a similar proportion to that of patients with impaired cardiorespiratory exercise capacity. However, only 19 patients presented both impaired cardiorespiratory exercise capacity and impaired 6MWD.

Relationship between peakVO_2 and 6MWD

There was a significant correlation between 6MWD and peakVO_2 (Pearson's coefficient correlation = 0.53, p = $3.95.10^{-6}$), the regression slope indicating that, on average, a 100m increase of the 6MWD performance was associated with a 4.0 ml/kg/min (95%CI: 2.4ml/kg/min; 5.5ml/kg/min) peakVO_2 increase (**Figure 1A).** However, peakVO_2values were not accurately predicted when based on the sole 6MWD (**Figure 1B**), as shown by the histogram of residuals of the linear regression (observed value minus predicted value): 14 patients (20.9%) had a predicted peakVO_2 overestimated and 17 patients

(25.4%) had a predicted peakVO_2 underestimated. These data suggest that 6MWD is not a relevant marker to detect exercise capacity impairment in patients conversely to peakVO_2.

Relationship between self-reported symptoms and exercise capacity impairment

Patients with disability or fatigue showed overall lower exercise capacity compared to other patients, with a mean peakVO_2 of 64 ± 18% pred. vs 75 ± 18% pred. (p = 0.01) and 66 ± 16% vs 79 ± 19% pred. (p = 0.02), respectively (**Supplementary Figure S2**). This result was consistent with results when patients were classified according to the degree of impairment of exercise capacity. Patients with disability had moderate to severe alteration of exercise capacity in 75%, vs a proportion of 35,6% patients with moderate to severe alteration of exercise capacity in patients that did not report disability (OR = 5.29, p = 0.002, **Figure 2A).** Patients with fatigue presented more frequently with moderate to severe alteration of exercise capacity : 66.7%, vs 27.3% patients without fatigue (OR = 5.14, p = 0.009, **Figure 2B)**. Fatigue but not disability was also significantly associated with deconditioning (patients with fatigue and deconditioning: 55.5% vs without deconditioning: 21.1% (OR = 4.49, p = 0.028, **Figure 2C & 2D)**). These data suggest that patients with disability or fatigue are at risk of moderate to severe exercise capacity impairment and deconditioning. Finally, patients who reported fatigue or disability did not exhibit any greater alteration of 6MWD as compared to patients who did not report disability or fatigue (**Supplementary Figure S3)**. Patients with severe alteration of exercise capacity (according to peakVO_2 value) showed significant impaired physical well-being when considering PF and PCS scores ($p < 0.05$, **Figures 3A & 3B**). No significant relationships were observed between peakVO_2 and MCS or HAD scores (data not shown).

Relationship between physical activity and exercise capacity impairment

Physical activities were reported by 44, 39 and 43 patients before, during and after transplant, respectively. This includes 9/69 cases with ≥ 150min/week of moderate to vigorous intensity exercise. During hospitalisation, the median duration of physical activity on bicycle ergometer was 17.9 $\pm$ 14.9 min/day for a median of 15.4 $\pm$ 13.4 days.

225 Physical activity before transplant was not associated with a better exercise capacity at 1 year post allo-
226 HSCT ($p = 0.2$, **Figure 4A**). Conversely, patients with physical activities during (**Figure 4B**) or after
227 hospitalisation (including at 1-year evaluation) were documented with significantly better exercise
228 capacity at 1 year, as evaluated by peakVO_2 ($p = 0.02$, and $p = 0.008$, respectively). Statistical
229 significance was reached whatever the duration of exercise activity ($<$ or $\geq$ 150 min/week) during
230 hospitalisation, but only in case of fulfillment of the recommendations about physical exercise (moderate
231 or vigorous intensity, $\geq$ 150min/week) after hospitalisation (data not shown).
232
233

DISCUSSION

Impaired exercise capacity at 1 year post transplantation despite normal lung and cardiac tests at rest

This prospective study highlighted a high proportion (75.4%) of non-relapse patients with mild to severe exercise capacity impairment at one year post allo-HSCT, while an important proportion of 40% were documented with deconditioning, despite normal lung and cardiac function tests at rest.

Exercise capacity should be evaluated, at least in patients who report fatigue and/or disability

Although most long-term survivors after allo-HSCT recover adequately from treatment, a substantial proportion continues to experience late effects that reduce health-related quality of life. One of the most prevalent and disturbing long-term symptoms is fatigue, evaluated from 28 % at 3 years post allo-HSCT [35] to 35% in another study (mean = 9.3 years) [36], a proportion close to that in our study. To avoid fatigue, cancer patients are often advised to rest and down-regulate their daily activities. However, these recommendations can cause paradoxical results. Since inactivity induces muscular wasting, prolonged rest can result in further loss of endurance. Our study shows disability and fatigue were both strongly associated to impaired exercise capacity, while recent studies suggest that exercise reduces fatigue and improves the performance status of cancer patients [37], including patients with allo-HSCT.[11, 35] Altogether these data show a strong and inverted link between fatigue and exercise capacity and suggest that fatigue should be systematically assessed and taken into account in long-term survivor follow-up and CPET should be performed in all long-term survivors post allo-HSCT, to detect low exercise capacity and to set up rehabilitation programs.

CPET is a better exercise capacity assessment tool than 6MWT

Our study reported a high proportion of patients with abnormal CPET (75%) and deconditioning (40%) at one year post allo-HSCT while 6MWD misevaluated exercise capacity in more than 50% patients. CPET provides a global noninvasive assessment of the integrative exercise responses which are not adequately

reflected through the measurement of individual organ system function.[26] Importantly, peakVO_2 is inversely associated with death from any cause in patients and healthy individuals [38], including patients with cardiovascular disease [39] and cancer patients in a large meta-analysis [40], and HSCT patients in a pilot study.[41]

Nevertheless, because CPET needs trained personnel, specialized equipment, and medical supervision, it is relatively expensive. As shown in our study and in others [26], resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity. 6MWT will not likely replace CPET [26] as studies in respiratory disease suggest that peakVO_2 measurement and 6MWD are not commutable [30], a data consistent with the poor correlation between 6MWD and peakVO_2 in our patients.

Long-term QOL is impaired mainly due to physical health and physical exercise should be encouraged

Similar to results reported by other authors [42, 43], the level of psychological distress was low in our population. Importantly, impairment of physical well-being on quality of life questionnaires was associated with the most altered exercise capacity, and the degree of physical health impairment (quantified by a PCS score of 44.73) was similar to that in Bevans et al. study.[43]

Our study does not address whether improvement in cardiorespiratory fitness via exercise training interventions is an effective strategy to reduce death risk in survivors post allo-HSCT. However, there is considerable evidence that aerobic training interventions following standard exercise prescription according to guidelines have beneficial effects on health-related quality of life domains in cancer survivors [44] including survivors post-HSCT[9-14], and recommendations about exercise training have been established for patients with cancer either during treatment or following treatment completion.[45, 46] In four studies where exercise program was performed during hospitalisation for HSCT among 18 to 100 patients, patients experienced improvement in fatigue, aerobic capacity, muscle strength and quality of life.[9, 47-49] Results from three other studies implementing exercise intervention 6 months to 3 years after HSCT showed similar benefits.[11, 12, 50]

In summary, long-term survivors after allo-HSCT are considered as a distinct, high-risk population that must be monitored for long-term transplant complications, including altered exercise capacity and deconditioning. Our study supports the recommendation of questioning about fatigue and disability into regular follow-up protocols for allo-HSCT survivors and of CPET measurement in every patient who reports fatigue or disability.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

Supplementary information is available at *Bone Marrow Transplantation*'s website.

REFERENCES

1. Gourraud PA, Balere ML, Faucher C, Loiseau P, Dormoy A, Marry E *et al.* HLA phenotypes of candidates for HSCT: comparing transplanted versus non-transplanted candidates, resulting in the predictive estimation of the probability to find a 10/10 HLA matched donor. *Tissue Antigens* 2014; **83**(1)**:** 17-26. e-pub ahead of print 2013/12/21; doi: 10.1111/tan.12263

2. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Rev Bras Hematol Hemoter* 2012; **34**(2)**:** 109-133. e-pub ahead of print 2012/10/11; doi: 10.5581/1516-8484.20120032

3. Clark CA, Savani M, Mohty M, Savani BN. What do we need to know about allogeneic hematopoietic stem cell transplant survivors? *Bone Marrow Transplant* 2016; **51**(8)**:** 1025-1031. e-pub ahead of print 2016/04/12; doi: 10.1038/bmt.2016.95

4. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. *Haematologica* 2017; **102**(4)**:** 614-625. e-pub ahead of print 2017/02/25; doi: 10.3324/haematol.2016.150250

5. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Cmaj* 2006; **175**(1)**:** 34-41. e-pub ahead of print 2006/07/05; doi: 10.1503/cmaj.051073

6. Dimeo FC, Tilmann MH, Bertz H, Kanz L, Mertelsmann R, Keul J. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer* 1997; **79**(9)**:** 1717-1722. e-pub ahead of print 1997/05/01;

7. Porock D, Kristjanson LJ, Tinnelly K, Duke T, Blight J. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care* 2000; **16**(3)**:** 30-36. e-pub ahead of print 2000/10/06;

8. Wilson RW, Taliaferro LA, Jacobsen PB. Pilot study of a self-administered stress management and exercise intervention during chemotherapy for cancer. *Support Care Cancer* 2006; **14**(9)**:** 928-935. e-pub ahead of print 2006/04/21; doi: 10.1007/s00520-006-0021-1

9. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L. A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplant* 2009; **43**(9)**:** 725-737. e-pub ahead of print 2009/02/24; doi: 10.1038/bmt.2009.27

10. van Haren IE, Timmerman H, Potting CM, Blijlevens NM, Staal JB, Nijhuis-van der Sanden MW. Physical exercise for patients undergoing hematopoietic stem cell transplantation: systematic review and meta-analyses of randomized controlled trials. *Phys Ther* 2013; **93**(4)**:** 514-528. e-pub ahead of print 2012/12/12; doi: 10.2522/ptj.20120181

11. Carlson LE, Smith D, Russell J, Fibich C, Whittaker T. Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. *Bone Marrow Transplant* 2006; **37**(10)**:** 945-954. e-pub ahead of print 2006/03/28; doi: 10.1038/sj.bmt.1705343

12. Wilson RW, Jacobsen PB, Fields KK. Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2005; **35**(7)**:** 721-727. e-pub ahead of print 2005/02/08; doi: 10.1038/sj.bmt.1704815

13. Persoon S, Kersten MJ, van der Weiden K, Buffart LM, Nollet F, Brug J *et al.* Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev* 2013; **39**(6)**:** 682-690. e-pub ahead of print 2013/03/15; doi: 10.1016/j.ctrv.2013.01.001

14. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N *et al.* Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood* 2011; **117**(9)**:** 2604-2613. e-pub ahead of print 2010/12/31; doi: 10.1182/blood-2010-09-306308

15. Steinberg A, Asher A, Bailey C, Fu JB. The role of physical rehabilitation in stem cell transplantation patients. *Support Care Cancer* 2015; **23**(8)**:** 2447-2460. e-pub ahead of print 2015/05/15; doi: 10.1007/s00520-015-2744-3

16. Stenehjem JS, Smeland KB, Murbraech K, Holte H, Kvaloy S, Thorsen L *et al.* Cardiorespiratory fitness in long-term lymphoma survivors after high-dose chemotherapy with autologous stem cell transplantation. *Br J Cancer* 2016. e-pub ahead of print 2016/06/29; doi: 10.1038/bjc.2016.180

17. Tuchman SA, Lane A, Hornsby WE, Bishop C, Thomas S, Herndon JE, 2nd *et al.* Quantitative measures of physical functioning after autologous hematopoietic stem cell transplantation in multiple myeloma: a feasibility study. *Clin Lymphoma Myeloma Leuk* 2015; **15**(2)**:** 103-109. e-pub ahead of print 2014/12/03; doi: 10.1016/j.clml.2014.09.002

18. ATS. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**(1)**:** 111-117. e-pub ahead of print 2002/07/02; doi: 10.1164/ajrccm.166.1.at1102

19. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**(6)**:** 473-483. e-pub ahead of print 1992/06/11;

20. Leplège A EE, Pouchot J, Coste J, Perneger T. *Le questionnaire MOS SF-3 6 : manuel de l'utilisateur et guide d'interprétation des scores.*, Estem: Paris, 2001.

21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6)**:** 361-370. e-pub ahead of print 1983/06/01;

22. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; **145**(6)**:** 1321-1327. e-pub ahead of print 1992/06/01; doi: 10.1164/ajrccm/145.6.1321

23. Butt Z, Wagner LI, Beaumont JL, Paice JA, Peterman AH, Shevrin D *et al.* Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. *J Pain Symptom Manage* 2008; **35**(1)**:** 20-30. e-pub ahead of print 2007/10/26; doi: 10.1016/j.jpainsymman.2007.02.040

24. Chauffier K, Paternotte S, Burki V, Durnez A, Elhai M, Koumakis E *et al.* Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients. *Clin Exp Rheumatol* 2013; **31**(6)**:** 864-870. e-pub ahead of print 2013/10/23;

25. *Global Recommendations on Physical Activity for Health*: Geneva, 2010.

26. ATS/ACCP. Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; **167**(2)**:** 211-277. e-pub ahead of print 2003/01/14; doi: 10.1164/rccm.167.2.211

27. Borg G. *Borg's Perceived Exertion and Pain Scales*, Human Kinetics, 1998.

28. Cooper CB, Storer TW. Exercise testing and interpretation: a practical approach. In. Cambridge University Press: New York, 2010.

29. Wasserman K HJ, Sue, SY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation.* , 4th edition edn Lippincott Williams & Wilkins. 2005. Philadelphia, USA, 2005.

30. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ *et al.* An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44**(6)**:** 1447-1478. e-pub ahead of print 2014/11/02; doi: 10.1183/09031936.00150414

31. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; **44**(6)**:** 1428-1446. e-pub ahead of print 2014/11/02; doi: 10.1183/09031936.00150314

32. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; **158**(5 Pt 1)**:** 1384-1387. e-pub ahead of print 1998/11/17; doi: 10.1164/ajrccm.158.5.9710086

33. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R *et al.* General considerations for lung function testing. *Eur Respir J* 2005; **26**(1)**:** 153-161. e-pub ahead of print 2005/07/05; doi: 10.1183/09031936.05.00034505

34. Team RC. *R: A language and environment for statistical computing*, R Foundation for Statistical Computing, Vienna, Austria, 2012.

35. Hjermstad MJ, Knobel H, Brinch L, Fayers PM, Loge JH, Holte H *et al.* A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. *Bone Marrow Transplant* 2004; **34**(3)**:** 257-266. e-pub ahead of print 2004/06/01; doi: 10.1038/sj.bmt.1704561

36. Gielissen MF, Schattenberg AV, Verhagen CA, Rinkes MJ, Bremmers ME, Bleijenberg G. Experience of severe fatigue in long-term survivors of stem cell transplantation. *Bone Marrow Transplant* 2007; **39**(10)**:** 595-603. e-pub ahead of print 2007/03/21; doi: 10.1038/sj.bmt.1705624

37. Dimeo F, Schwartz S, Fietz T, Wanjura T, Boning D, Thiel E. Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. *Support Care Cancer* 2003; **11**(10)**:** 623-628. e-pub ahead of print 2003/08/28; doi: 10.1007/s00520-003-0512-2

38. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol* 2008; **9**(8)**:** 757-765. e-pub ahead of print 2008/08/02; doi: 10.1016/S1470-2045(08)70195-5

39. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P *et al.* Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002; **106**(6)**:** 666-671. e-pub ahead of print 2002/08/07;

40. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015; **26**(2)**:** 272-278. e-pub ahead of print 2014/07/11; doi: 10.1093/annonc/mdu250

41. Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA *et al.* Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. *Bone Marrow Transplant* 2013; **48**(10)**:** 1342-1349. e-pub ahead of print 2013/04/16; doi: 10.1038/bmt.2013.58

42. McQuellon RP, Russell GB, Rambo TD, Craven BL, Radford J, Perry JJ *et al.* Quality of life and psychological distress of bone marrow transplant recipients: the 'time trajectory' to recovery over the first year. *Bone Marrow Transplant* 1998; **21**(5)**:** 477-486. e-pub ahead of print 1998/04/16; doi: 10.1038/sj.bmt.1701115

43. Bevans MF, Marden S, Leidy NK, Soeken K, Cusack G, Rivera P *et al.* Health-related quality of life in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2006; **38**(2)**:** 101-109. e-pub ahead of print 2006/06/06; doi: 10.1038/sj.bmt.1705406

44. Vijayvergia N, Denlinger CS. Lifestyle Factors in Cancer Survivorship: Where We Are and Where We Are Headed. *J Pers Med* 2015; **5**(3)**:** 243-263. e-pub ahead of print 2015/07/07; doi: 10.3390/jpm5030243

45. Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A *et al.* American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2006; **56**(5)**:** 254-281; quiz 313-254. e-pub ahead of print 2006/09/29;

46. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM *et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010; **42**(7)**:** 1409-1426. e-pub ahead of print 2010/06/19; doi: 10.1249/MSS.0b013e3181e0c112

47. Baumann FT, Zopf EM, Nykamp E, Kraut L, Schule K, Elter T *et al.* Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol* 2011; **87**(2)**:** 148-156. e-pub ahead of print 2011/05/07; doi: 10.1111/j.1600-0609.2011.01640.x

48. Mello M, Tanaka C, Dulley FL. Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2003; **32**(7)**:** 723-728. e-pub ahead of print 2003/09/18; doi: 10.1038/sj.bmt.1704227

49. DeFor TE, Burns LJ, Gold EM, Weisdorf DJ. A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. *Biol Blood Marrow Transplant* 2007; **13**(8)**:** 948-955. e-pub ahead of print 2007/07/21; doi: 10.1016/j.bbmt.2007.04.008

50. Shelton ML, Lee JQ, Morris GS, Massey PR, Kendall DG, Munsell MF *et al.* A randomized control trial of a supervised versus a self-directed exercise program for allogeneic stem cell transplant patients. *Psychooncology* 2009; **18**(4)**:** 353-359. e-pub ahead of print 2009/01/02; doi: 10.1002/pon.1505

FIGURES LEGENDS

Figure 1: **Correlation analysis of the association between exercise capacity and 6-minute walk distance (6MWD) using linear regression model.** Exercise capacity was evaluated by peakVO_2 assessed by cardiopulmonary exercise testing. PeakVO_2 was expressed in ml/kg/min and 6MWD in meters. Data from 67 patients were available. (*A)*: linear regression between peakVO_2 (ml/kg/min, Y axis) and 6MWD (m, X axis). Individual patient's data is depicted by a triangle. Linear regression (black continuous line) is provided with 95% confidence interval ($\pm$1.96 SD) dotted line. Departure between observed peakVO_2 and predicted peakVO_2 from 6MWD data is depicted by a dotted line. (*B)*: histogram of departures between observed peakVO_2 and predicted peakVO_2 associated with representation of their distribution using box-plot in the lower part of the figure. Data were computed using the differences between observed peakVO_2 (ml/kg/min) and peakVO_2 predicted in the linear model (observed value minus predicted value).

Figure 2: Spine plots representing univariate relationships between disability or fatigue, and decreased exercise capacity or deconditioning assessed by cardiopulmonary exercise testing. Disability was self-reported by patients with a binary question: "in the daily life, do you experience disability?". Fatigue was measured with a Numeric Rating Scale (NRS) from 0 to 10 and defined as NRS $\geq$ 5. Exercise capacity was evaluated by peakVO_2, expressed as percentage of sex- and age-predicted reference values from general population. Decrease in peakVO_2 was defined as normal to mild ($\geq$71%pred) or moderate to severe (< 70%pred). Deconditioning was defined as ventilator threshold $\leq$ 40% of peakVO_2. *Panels A, B*: proportion of patients with disability (A) or fatigue (B) and decreased exercise capacity, expressed as normal to mild ($\geq$ 71%pred) or moderate to severe (< 70%pred) alteration of peakVO_2. *Panels C, D*: proportion of patients with disability (C) or fatigue (D) and deconditioning. Odds ratio and p values were the following: (A) OR = 5.29 (IC 95% [1.61 ; 19.80]) p = 0.002, (B) OR = 5.14 (IC 95% [1.32 ; 22.48]) p = 0.009, (C) OR = 2.19 (IC95% [0.71 ; 6.91]) p = 0.19, (D) OR = 4.49 (IC95% [1.13; 19.46]) p = 0.028.

Figure 3: **Boxplots presenting physical health evaluation according to alteration in patient exercise capacity.** Physical health was assessed by the Physical Functioning (A) and the Physical Component Summary (B) scores of the SF-36 self-administered questionnaire. Exercise capacity was evaluated by peakVO_2, categorized into normal ($\geq$ 80% pred), mild (71-79% pred), moderate (51-69% pred), or severe ($\leq$ 50% pred). * $p < 0.05$.

Figure 4: Spine plots presenting univariate relationships between physical activity before (A) or during hospitalisation at the time of allo-HSCT (B), and patient exercise capacity at one year post allo-HSCT. Exercise capacity was evaluated by peakVO_2, expressed as percentage of sex- and age-predicted reference values from general population. Decrease in peakVO_2 was defined as "normal or mild" ($\geq$ 71%pred) or "moderate to severe" (< 70%pred). Physical activity during hospitalisation was evaluated by performing bicycle ergometer or not. Odds ratio and p values were the followings: (A) OR = 1.95 (IC95% [0.65 ; 6.07]) p = 0.2159, (B) OR = 3.50 (IC95% [1.18 ; 11.03]) p = 0.0155.

Table 1. Patient characteristics

Characteristics	Study population (n = 71) n (%)
Median age: years (range)	56 (29 – 70)
Gender: male	46 (65%)
Median time between allotransplant and study inclusion: months (range)	14 (11-18)
Median duration of protective isolation in the sterile unit: weeks (range)	4.5 (2-12)
Haematological diseases	
Acute lymphoblastic leukaemia	6 (8%)
Acute myelogenous leukaemia	28 (39%)
Lymphoma	15 (21%)
Myelodysplastic syndrome	9 (13%)
Others*	13 (18%)
History of smoking	
Former	34 (48%)
Current	8 (11%)
Non-smoker	29 (41%)
Conditioning regimen	
Non myeloablative	60 (85%)
Busulfan-based	54 (76%)
TBI-based	14 (20%)
Stem cell source	
Peripheral blood stem cell	56 (79%)
Bone marrow	5 (7%)
Cord blood	10 (14%)
Acute GvHD during the first 100 d	35 (49%)
Chronic GvHD	25 (35%)
Cutaneous	17 (68%)
Gastrointestinal	7 (28%)
Ongoing oral steroid treatment	14 (20%)

Abbreviations: TBI: total body irradiation, GvHD: graft-versus-host disease.
*Others: e.g., multiple myeloma, chronic lymphocytic leukaemia.

Table 2. Quality of life and functional assessments.

	Subjects n	Mean ± standard deviation	Patients with abnormal value n (%)
Disability	71		26 (36.6)
Fatigue	53	3.4 ± 2.0	NRS ≥ 5: 18 (34.0)
Health-related quality of life assessment (SF-36)			
Physical Functioning	70	79.05 ± 19	n < ref: 29 (41.4)
Role Physical	69	54.71 ± 41.19	n < ref: 43 (62.3)
Physical Component Summary	65	44.73 ± 8.32	n < ref: 45 (69.2)
General Health	70	59.02 ± 19.35	n < ref: 46 (65.7)
Mental Component Summary	65	48.50 ± 10.39	n < ref: 27 (41.5)
Hospital Anxiety and Depression (HAD)	71	10 ± 6	score ≥ 11: 13 (18.3)
Pulmonary function tests			
FEV1, liters	71	3.1 ± 0.8	
FEV1, %pred	71	103.9 ± 18.9	< 80%: 5 (7)
FEV1/FVC	71	78.2 ± 5.3	< 70%: 4 (5.6)
TLC, liters	69	6.1 ± 1.4	
TLC, %pred	69	101 ± 14	< 80%: 8 (11.6)
DLCO, %pred	70	72.3 ± 13.5	61-79%: 37 (52.9) 40-60%: 13 (18.6) < 40%: 1 (1.4)
Echocardiography			
Left ventricular ejection fraction, %	69	64.0 ± 5.7	< 55%: 1 (1.4)
Functional capacity			
PeakVO_2, ml/kg/min	69	19 ± 6	
PeakVO_2, %pred	69	71.3 ± 18.3	71-79%: 18 (26) 51-70%: 24 (34.8) ≤50%: 10 (14.5)
Ventilatory threshold, %peakVO_2	69	43.4 ± 12.3	< 40: 26 (37.7)
Median 6-minute walk distance, meters	69	470.4 ± 85	
6-minute walk distance, %pred	69	82.6 ± 16.4	< 80%: 26 (37.7)

Abbreviations: NRS: numeric rating scale; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; DLCO: lung carbon monoxide diffusing capacity; PeakVO_2: Peak oxygen uptake; SF-36: 36-item Short Form Health Survey; Pred: predicted normal value.

Figure 1

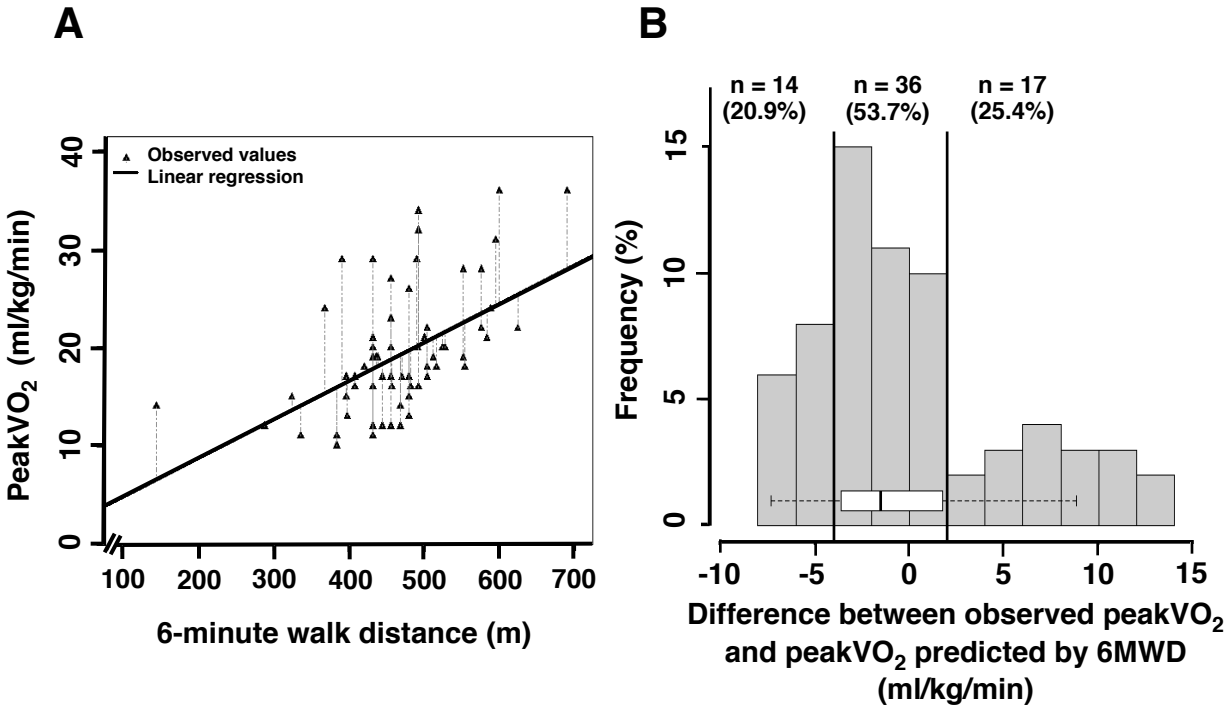

A
Observed values
Linear regression
PeakVO2 (ml/kg/min)
0
10
20
30
40
100
200
300
400
500
600
700
6-minute walk distance (m)
B
n = 14
(20.9%)
n = 36
(53.7%)
n = 17
(25.4%)
Frequency (%)
0
5
10
15
-10
-5
0
5
10
15
Difference between observed peakVO2
and peakVO2 predicted by 6MWD
(ml/kg/min)

Figure 2

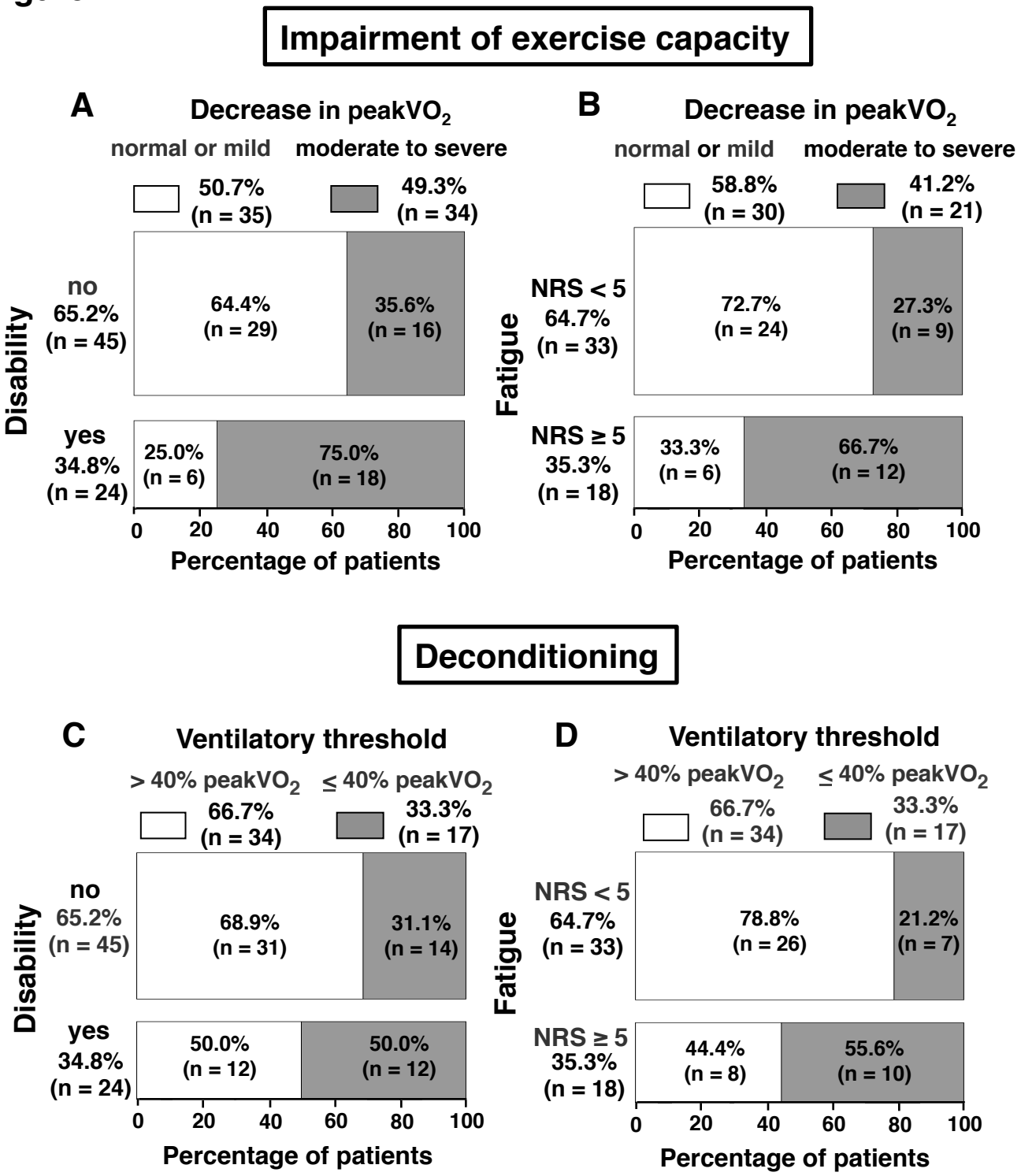

Impairment of exercise capacity
A
Decrease in peakVO2
normal or mild
moderate to severe
50.7% (n = 35)
49.3% (n = 34)
Disability
no 65.2% (n = 45)
64.4% (n = 29)
35.6% (n = 16)
yes 34.8% (n = 24)
25.0% (n = 6)
75.0% (n = 18)
0 20 40 60 80 100
Percentage of patients
B
Decrease in peakVO2
normal or mild
moderate to severe
58.8% (n = 30)
41.2% (n = 21)
Fatigue
NRS < 5 64.7% (n = 33)
72.7% (n = 24)
27.3% (n = 9)
NRS ≥ 5 35.3% (n = 18)
33.3% (n = 6)
66.7% (n = 12)
0 20 40 60 80 100
Percentage of patients
Deconditioning
C
Ventilatory threshold
> 40% peakVO2
≤ 40% peakVO2
66.7% (n = 34)
33.3% (n = 17)
Disability
no 65.2% (n = 45)
68.9% (n = 31)
31.1% (n = 14)
yes 34.8% (n = 24)
50.0% (n = 12)
50.0% (n = 12)
0 20 40 60 80 100
Percentage of patients
D
Ventilatory threshold
> 40% peakVO2
≤ 40% peakVO2
66.7% (n = 34)
33.3% (n = 17)
Fatigue
NRS < 5 64.7% (n = 33)
78.8% (n = 26)
21.2% (n = 7)
NRS ≥ 5 35.3% (n = 18)
44.4% (n = 8)
55.6% (n = 10)
0 20 40 60 80 100
Percentage of patients

Figure 3

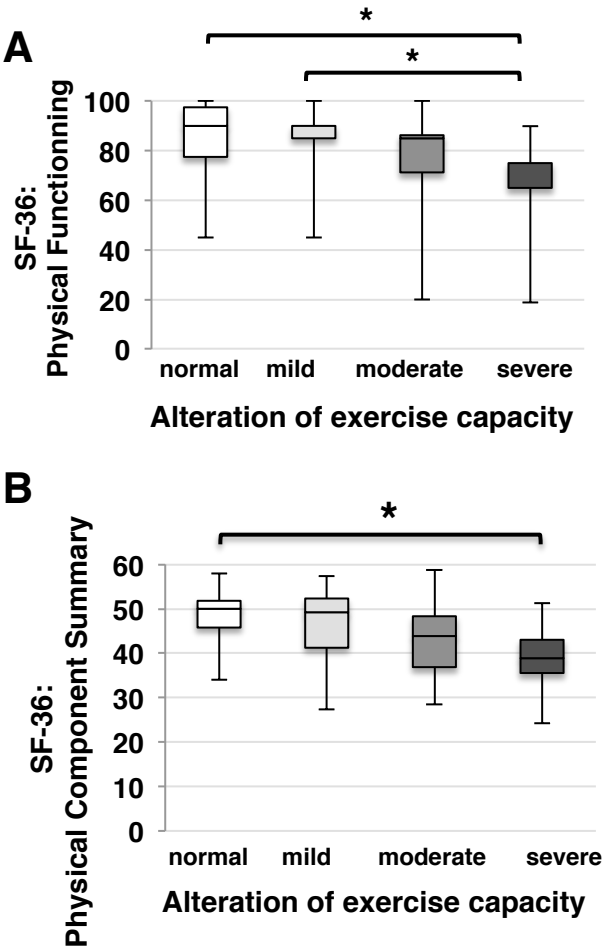
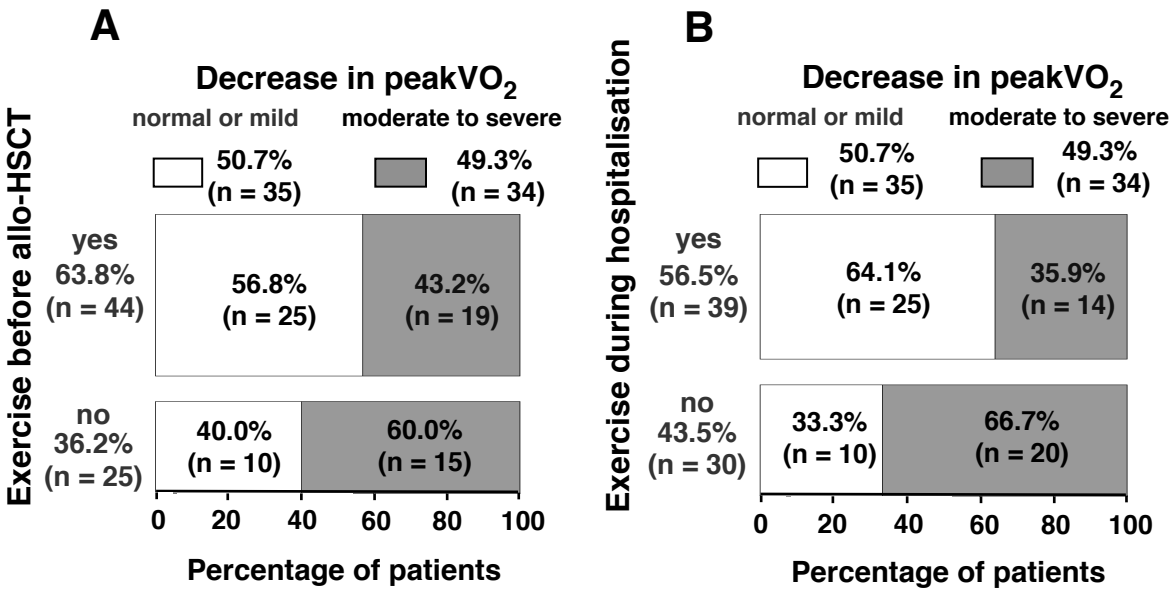

A
*
*
SF-36:
Physical Functionning
100
80
60
40
20
0
normal
mild
moderate
severe
Alteration of exercise capacity
B
*
SF-36:
Physical Component Summary
60
50
40
30
20
10
0
normal
mild
moderate
severe
Alteration of exercise capacity

Figure 4


A
Decrease in peakVO2
normal or mild
moderate to severe
50.7% (n = 35)
49.3% (n = 34)
Exercise before allo-HSCT
yes 63.8% (n = 44)
56.8% (n = 25)
43.2% (n = 19)
no 36.2% (n = 25)
40.0% (n = 10)
60.0% (n = 15)
0 20 40 60 80 100
Percentage of patients
B
Decrease in peakVO2
normal or mild
moderate to severe
50.7% (n = 35)
49.3% (n = 34)
Exercise during hospitalisation
yes 56.5% (n = 39)
64.1% (n = 25)
35.9% (n = 14)
no 43.5% (n = 30)
33.3% (n = 10)
66.7% (n = 20)
0 20 40 60 80 100
Percentage of patients