

# Deconditioning, fatigue and impaired quality of life in long-term survivors after allogeneic hematopoietic stem cell transplantation

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1                   **Deconditioning, fatigue and impaired quality of life in long-term survivors**  
2                   **after allogeneic hematopoietic stem cell transplantation**

3 **Running head:** Altered exercise capacity in allo-HSCT survivors

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28

29 **Abstract**

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

33 The aims of this prospective study were to evaluate exercise capacity in allotransplant survivors and its  
34 relationship with fatigue and disability. Patient-reported outcomes and exercise capacity were evaluated  
35 in 71 non-relapse patients one year after allo-HSCT, using validated questionnaires, cardiopulmonary  
36 exercise testing (CPET) with measure of peak oxygen uptake (peakVO<sub>2</sub>) and deconditioning, pulmonary  
37 function testing, echocardiography and 6-minute walk test.

38 A high proportion (75.4%) of allo-HSCT survivors showed abnormal cardiopulmonary exercise testing  
39 parameters as compared to predicted normal values, including 49.3% patients who exhibited moderate to  
40 severe impairment in exercise capacity and 37.7% patients with physical deconditioning. PeakVO<sub>2</sub> values  
41 were not accurately predicted by 6-minute walk distances ( $r = 0.53$ ). Disability and fatigue were strongly  
42 associated with decreased peakVO<sub>2</sub> values ( $p = 0.002$  and  $p = 0.008$ , respectively).

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

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48

## 49 INTRODUCTION

50

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

58 Cardiopulmonary exercise testing (CPET) is the most accurate tool to evaluate cardiorespiratory fitness,  
59 to identify the main factors limiting exercise tolerance, and to set up an individual rehabilitation program  
60 with exercise targets if needed. Currently, CPET is not performed in the follow-up of allotransplants  
61 survivors in contrast to lung function tests and echocardiography, two tests performed at rest. A few  
62 studies analysed CPET findings on small numbers of allo-HSCT survivors (inferior to 20 patients) in the  
63 limited context of exercise intervention benefits.<sup>11, 12</sup> In auto-HSCT survivors, two studies evaluated  
64 cardiorespiratory fitness by CPET, including Stenehjem et al. who reported that 22% of patients from a  
65 200-patient cohort had an impaired exercise capacity at 10 years post transplantation.<sup>16, 17</sup> Alternatively,  
66 physical function in chronic diseases such as chronic obstructive pulmonary disease (COPD) or heart  
67 failure is often assessed by submaximum exercise-testing such as the 6-minute walk test (6MWT), one of  
68 the most common field-tests used in the follow-up of such patients. However, the 6MWT only gives an  
69 extrapolation of cardiorespiratory fitness from submaximum exercise<sup>18</sup> and no data are available in the  
70 allotransplant setting.

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

## 76 **Materials and Methods**

77

### 78 **Study design**

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

### 88 **Quality of life**

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

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

### 101 **Physical activity and exercise capacity measurements**

102 To assess physical activity before, during and after (including at the time of the present study) transplant,  
103 bicycle ergometer practice in the sterile unit and reported one-time per week exercises were considered.  
104 Patients were required to retrospectively provide approximately the average duration in minutes (min) of  
105 physical activities for each period of time. Patients were then classified according to whether they had  
106 performed exercise less or more than 150 min per week, according to international exercise guidelines.<sup>25</sup>  
107 The CPET was performed using the Ergocard<sup>®</sup> (Hyp'air, Medisoft, Sorinnes, Belgium) and the  
108 electronically braked cycle ergometer Ergoselect (ergoline GmbH, Bitz, Germany), with a 12-lead  
109 electrocardiogram (ECG) and blood pressure monitoring. The protocol included a 3-min rest period, a 3-  
110 min warm-up of unloaded pedalling followed by a 5-20W/min incremental phase, up to exhaustion.<sup>26</sup>  
111 Dyspnea and leg fatigue intensity were assessed with the Borg scale every 2-min up to exhaustion.<sup>27</sup> This  
112 includes the maximal or peak oxygen uptake (peakVO<sub>2</sub>), the ventilatory threshold (VT), the VO<sub>2</sub> at VT  
113 (VO<sub>2</sub>-VT), and the subjective perception of exertion. Peak aerobic exercise capacity (peakVO<sub>2</sub>) was  
114 expressed in mL/min/kg and percentage of the predicted normal value (PNV).<sup>28</sup> Normal, mild, moderate  
115 or severe impaired exercise capacity were defined, respectively, as a peakVO<sub>2</sub> percentage > 80%,  
116 between 71 and 79%, between 51 and 70% or ≤ 50% of the predicted normal value.<sup>28</sup> A combined  
117 approach was used to calculate VT, based on the identification of the inflection point during the  
118 incremental exercise: i) of the respiratory equivalent for oxygen (VE/VO<sub>2</sub>) curve with time, ii) of the  
119 minute-ventilation (VE) curve with time, or iii) the VO<sub>2</sub>-VCO<sub>2</sub> relationship. The 9-panel graphical  
120 representation of Wasserman et al. was also used to optimize the VT position.<sup>29</sup> Deconditioning was  
121 defined by VT < 40% predicted VO<sub>2</sub>max.

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

126 **Pulmonary and cardiac function at rest**

127 **All pulmonary function tests** were performed in the Pulmonary Function Lab according to  
128 recommendations.<sup>33</sup> Transthoracic echocardiography was performed according to as standardized  
129 protocol (see Supplementary Material).

### 130 **Statistical Analysis**

131 To evaluate the association between exercise capacity and 6MWD, a linear regression model was used to  
132 correlate and predict peakVO<sub>2</sub> from the 6MWD. Residuals of the linear regression were analysed to  
133 evaluate departure between observed peakVO<sub>2</sub> and predicted peakVO<sub>2</sub> from 6MWD data. Differences  
134 between observed and predicted peakVO<sub>2</sub> were represented using histograms. All statistical analyses were  
135 performed using R statistical software.<sup>34</sup>

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

141 The statistical significance of association between variables was assessed using chi-square test, t-test  
142 (after exclusion of non-normal distribution) and Fisher's exact test when appropriate. Results were  
143 graphically illustrated using boxplots and spine plots. p-values were two-sided and reported without  
144 correction for multiple hypothesis testing. In a second step, major risk factors for post allo-HCST  
145 complications (including age, gender, conditioning intensity, GVHD presence) were introduced into a  
146 multivariate logistic regression analysis for prediction of peakVO<sub>2</sub> results (odds ratio with 95% CI). The  
147 threshold for statistical significance was defined as  $p < 0.05$ .

148

## 149 RESULTS

### 150 Patients

151 The study started in May 2012. Although a total of 153 patients underwent an allo-HSCT during the two  
152 following years, only 71 cases (46.4%) were enrolled in the present study. The reasons for exclusion at  
153 one year post-transplant were as follows: death (n = 55, 36%), relapse (n = 8, 5%), hospitalisation at the  
154 time of 1-year evaluation (n = 6, 4%) and one-year post-transplant check-up in other hospital (n = 13,  
155 8%) (**Supplementary Figure S1**). Demographic and transplant characteristics of the 71 allo-HSCT one-  
156 year survivors are summarized in **Table 1**. Similar characteristics were shared by the 13 patients who  
157 underwent 1-year evaluation outside of our department (data not shown). Mean interval between allo-  
158 HSCT and one-year post-transplant evaluation was 14 months (range, 11-18 months). At this time, 14  
159 (20%) patients were still under corticosteroid medication for GVHD treatment.

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

### 163 Self-reported symptoms and quality of life

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

167 In QOL evaluation using self-administered questionnaires, scores related to physical health were the most  
168 impaired ones as compared to scores in the general population. Role limitations due to physical health  
169 were experienced by 62.3% of the patients (**Table 2**). Furthermore, PCS score (that represents the mean  
170 average of all of the physically relevant questions) was significantly lower than the general population in  
171 69.2% of the patients ( $44.73 \pm 8.32$  vs  $50.11 \pm 5.79$ ,  $p < 0.001$ ). Finally, a lower general health perception  
172 was reported by 65.7% of the patients, showing a frequent alteration in QOL (**Table 2**). The MCS score  
173 was not significantly different from the general population ( $48.50 \pm 10.39$  vs  $48.14 \pm 6.66$ ,  $p = 0.78$ ),  
174 suggesting that impaired QOL was more related to physical impairment than mental health deficit. These



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

### 179 **Exercise capacity measurements**

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

185 Neither peakVO<sub>2</sub> nor deconditioning condition was associated with DLCO, conditioning regimen,  
186 chronic GVHD, or corticosteroid treatment (data not shown). An exploratory multivariate analysis  
187 including major risk factors for post allo-HSCT complications (age, gender, conditioning intensity,  
188 GVHD) did not predict peakVO<sub>2</sub> results (p = 0.4).

189 In parallel, mean 6MWD was 470.4 ± 85m (83 ± 16%pred). Interestingly, in 26 (37.7%) patients, the  
190 6MWD was inferior to 80%pred (**Table 2**), a similar proportion to that of patients with impaired  
191 cardiorespiratory exercise capacity. However, only 19 patients presented both impaired cardiorespiratory  
192 exercise capacity and impaired 6MWD.

### 193 **Relationship between peakVO<sub>2</sub> and 6MWD**

194 There was a significant correlation between 6MWD and peakVO<sub>2</sub> (Pearson's coefficient correlation =  
195 0.53, p = 3.95.10<sup>-6</sup>), the regression slope indicating that, on average, a 100m increase of the 6MWD  
196 performance was associated with a 4.0 ml/kg/min (95%CI: 2.4ml/kg/min; 5.5ml/kg/min) peakVO<sub>2</sub>  
197 increase (**Figure 1A**). However, peakVO<sub>2</sub> values were not accurately predicted when based on the sole  
198 6MWD (**Figure 1B**), as shown by the histogram of residuals of the linear regression (observed value  
199 minus predicted value): 14 patients (20.9%) had a predicted peakVO<sub>2</sub> overestimated and 17 patients

200 (25.4%) had a predicted peakVO<sub>2</sub> underestimated. These data suggest that 6MWD is not a relevant  
201 marker to detect exercise capacity impairment in patients conversely to peakVO<sub>2</sub>.

### 202 **Relationship between self-reported symptoms and exercise capacity impairment**

203 Patients with disability or fatigue showed overall lower exercise capacity compared to other patients, with  
204 a mean peakVO<sub>2</sub> of 64 ± 18% pred. vs 75 ± 18% pred. (p = 0.01) and 66 ± 16% vs 79 ± 19% pred. (p =  
205 0.02), respectively (**Supplementary Figure S2**). This result was consistent with results when patients  
206 were classified according to the degree of impairment of exercise capacity. Patients with disability had  
207 moderate to severe alteration of exercise capacity in 75%, vs a proportion of 35,6% patients with  
208 moderate to severe alteration of exercise capacity in patients that did not report disability (OR = 5.29, p =  
209 0.002, **Figure 2A**). Patients with fatigue presented more frequently with moderate to severe alteration of  
210 exercise capacity : 66.7%, vs 27.3% patients without fatigue (OR = 5.14, p = 0.009, **Figure 2B**). Fatigue  
211 but not disability was also significantly associated with deconditioning (patients with fatigue and  
212 deconditioning: 55.5% vs without deconditioning: 21.1% (OR = 4.49, p = 0.028, **Figure 2C & 2D**)).  
213 These data suggest that patients with disability or fatigue are at risk of moderate to severe exercise  
214 capacity impairment and deconditioning. Finally, patients who reported fatigue or disability did not  
215 exhibit any greater alteration of 6MWD as compared to patients who did not report disability or fatigue  
216 (**Supplementary Figure S3**). Patients with severe alteration of exercise capacity (according to peakVO<sub>2</sub>  
217 value) showed significant impaired physical well-being when considering PF and PCS scores (p < 0.05,  
218 **Figures 3A & 3B**). No significant relationships were observed between peakVO<sub>2</sub> and MCS or HAD  
219 scores (data not shown).

### 220 **Relationship between physical activity and exercise capacity impairment**

221 Physical activities were reported by 44, 39 and 43 patients before, during and after transplant,  
222 respectively. This includes 9/69 cases with ≥ 150min/week of moderate to vigorous intensity exercise.  
223 During hospitalisation, the median duration of physical activity on bicycle ergometer was 17.9 ± 14.9  
224 min/day for a median of 15.4 ± 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<sub>2</sub> ( $p = 0.02$ , 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,  $\geq 150$ min/week) after hospitalisation (data not shown).

232

233

234 **DISCUSSION**

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

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

240  
241 **Exercise capacity should be evaluated, at least in patients who report fatigue and/or disability**

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

255  
256 **CPET is a better exercise capacity assessment tool than 6MWT**

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

260 reflected through the measurement of individual organ system function.<sup>26</sup> Importantly, peakVO<sub>2</sub> is  
261 inversely associated with death from any cause in patients and healthy individuals<sup>38</sup>, including patients  
262 with cardiovascular disease<sup>39</sup> and cancer patients in a large meta-analysis<sup>40</sup>, and HSCT patients in a pilot  
263 study.<sup>41</sup>

264 Nevertheless, because CPET needs trained personnel, specialized equipment, and medical supervision, it  
265 is relatively expensive. As shown in our study and in others<sup>26</sup>, resting pulmonary and cardiac function  
266 testing cannot reliably predict exercise performance and functional capacity. 6MWT will not likely  
267 replace CPET<sup>26</sup> as studies in respiratory disease suggest that peakVO<sub>2</sub> measurement and 6MWD are not  
268 commutable<sup>30</sup>, a data consistent with the poor correlation between 6MWD and peakVO<sub>2</sub> in our patients.

269

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

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

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

286

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

292

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298

299

300 **CONFLICT OF INTEREST**

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

302

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



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523 **FIGURES LEGENDS**

524 **Figure 1: Correlation analysis of the association between exercise capacity and 6-minute walk**  
525 **distance (6MWD) using linear regression model.** Exercise capacity was evaluated by peakVO<sub>2</sub>  
526 assessed by cardiopulmonary exercise testing. PeakVO<sub>2</sub> was expressed in ml/kg/min and 6MWD in  
527 meters. Data from 67 patients were available. (A): linear regression between peakVO<sub>2</sub> (ml/kg/min, Y  
528 axis) and 6MWD (m, X axis). Individual patient's data is depicted by a triangle. Linear regression (black  
529 continuous line) is provided with 95% confidence interval ( $\pm 1.96$  SD) dotted line. Departure between  
530 observed peakVO<sub>2</sub> and predicted peakVO<sub>2</sub> from 6MWD data is depicted by a dotted line. (B): histogram  
531 of departures between observed peakVO<sub>2</sub> and predicted peakVO<sub>2</sub> associated with representation of their  
532 distribution using box-plot in the lower part of the figure. Data were computed using the differences  
533 between observed peakVO<sub>2</sub> (ml/kg/min) and peakVO<sub>2</sub> predicted in the linear model (observed value  
534 minus predicted value).

535 **Figure 2: Spine plots representing univariate relationships between disability or fatigue, and**  
536 **decreased exercise capacity or deconditioning assessed by cardiopulmonary exercise testing.**  
537 Disability was self-reported by patients with a binary question: "in the daily life, do you experience  
538 disability?". Fatigue was measured with a Numeric Rating Scale (NRS) from 0 to 10 and defined as NRS  
539  $\geq 5$ . Exercise capacity was evaluated by peakVO<sub>2</sub>, expressed as percentage of sex- and age-predicted  
540 reference values from general population. Decrease in peakVO<sub>2</sub> was defined as normal to mild  
541 ( $\geq 71\%$ pred) or moderate to severe ( $< 70\%$ pred). Deconditioning was defined as ventilator threshold  $\leq$   
542 40% of peakVO<sub>2</sub>. *Panels A, B:* proportion of patients with disability (A) or fatigue (B) and decreased  
543 exercise capacity, expressed as normal to mild ( $\geq 71\%$ pred) or moderate to severe ( $< 70\%$ pred) alteration  
544 of peakVO<sub>2</sub>. *Panels C, D:* proportion of patients with disability (C) or fatigue (D) and deconditioning.  
545 Odds ratio and p values were the following: (A) OR = 5.29 (IC 95% [1.61 ; 19.80]) p = 0.002, (B) OR =  
546 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  
547 (IC95% [1.13; 19.46]) p = 0.028.

548 **Figure 3: Boxplots presenting physical health evaluation according to alteration in patient exercise**  
549 **capacity.** Physical health was assessed by the Physical Functioning (A) and the Physical Component  
550 Summary (B) scores of the SF-36 self-administered questionnaire. Exercise capacity was evaluated by  
551 peakVO<sub>2</sub>, categorized into normal ( $\geq 80\%$  pred), mild (71-79% pred), moderate (51-69% pred), or severe  
552 ( $\leq 50\%$  pred). \* p < 0.05.

553 **Figure 4: Spine plots presenting univariate relationships between physical activity before (A) or**  
554 **during hospitalisation at the time of allo-HSCT (B), and patient exercise capacity at one year post**  
555 **allo-HSCT.** Exercise capacity was evaluated by peakVO<sub>2</sub>, expressed as percentage of sex- and age-  
556 predicted reference values from general population. Decrease in peakVO<sub>2</sub> was defined as “normal or  
557 mild” ( $\geq 71\%$ pred) or “moderate to severe” ( $< 70\%$ pred). Physical activity during hospitalisation was  
558 evaluated by performing bicycle ergometer or not. Odds ratio and p values were the followings: (A) OR =  
559 1.95 (IC95% [0.65 ; 6.07]) p = 0.2159, (B) OR = 3.50 (IC95% [1.18 ; 11.03]) p = 0.0155.

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561

**Table 1. Patient characteristics**

Characteristics	Study population (n = 71) n (%)
<i>Median age: years (range)</i>	56 (29 – 70)
<i>Gender: male</i>	46 (65%)
<i>Median time between allotransplant and study inclusion: months (range)</i>	14 (11-18)
<i>Median duration of protective isolation in the sterile unit: weeks (range)</i>	4.5 (2-12)
<i>Haematological diseases</i>	
Acute lymphoblastic leukaemia	6 (8%)
Acute myelogenous leukaemia	28 (39%)
Lymphoma	15 (21%)
Myelodysplastic syndrome	9 (13%)
Others*	13 (18%)
<i>History of smoking</i>	
Former	34 (48%)
Current	8 (11%)
Non-smoker	29 (41%)
<i>Conditioning regimen</i>	
Non myeloablative	60 (85%)
Busulfan-based	54 (76%)
TBI-based	14 (20%)
<i>Stem cell source</i>	
Peripheral blood stem cell	56 (79%)
Bone marrow	5 (7%)
Cord blood	10 (14%)
<i>Acute GvHD during the first 100 d</i>	35 (49%)
<i>Chronic GvHD</i>	25 (35%)
Cutaneous	17 (68%)
Gastrointestinal	7 (28%)
<i>Ongoing oral steroid treatment</i>	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)
<i>Health-related quality of life assessment (SF-36)</i>			
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)
<i>Hospital Anxiety and Depression (HAD)</i>	71	10 ± 6	score ≥ 11: 13 (18.3)
<i>Pulmonary function tests</i>			
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)
<i>Echocardiography</i>			
Left ventricular ejection fraction, %	69	64.0 ± 5.7	< 55%: 1 (1.4)
<i>Functional capacity</i>			
PeakVO <sub>2</sub> , ml/kg/min	69	19 ± 6	
PeakVO <sub>2</sub> , %pred	69	71.3 ± 18.3	71-79%: 18 (26) 51-70%: 24 (34.8) ≤50%: 10 (14.5)
Ventilatory threshold, %peakVO <sub>2</sub>	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<sub>2</sub>: Peak oxygen uptake; SF-36: 36-item Short Form Health Survey; Pred: predicted normal value.

Figure 1

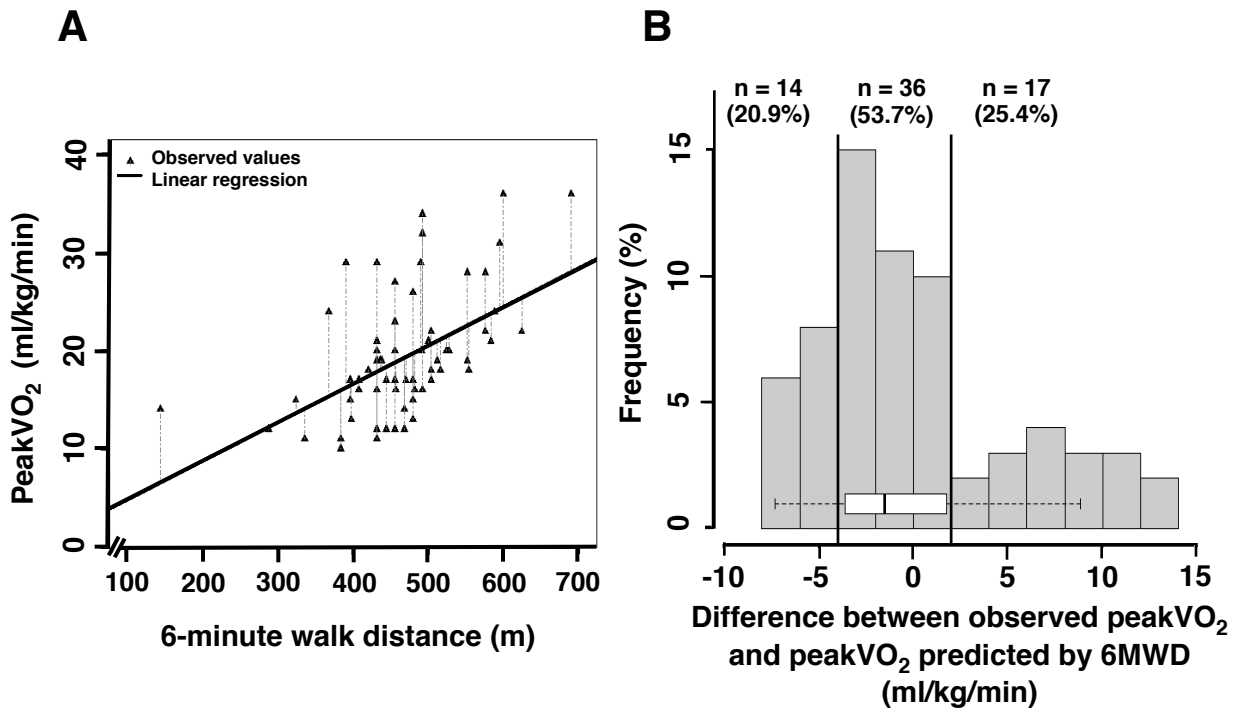
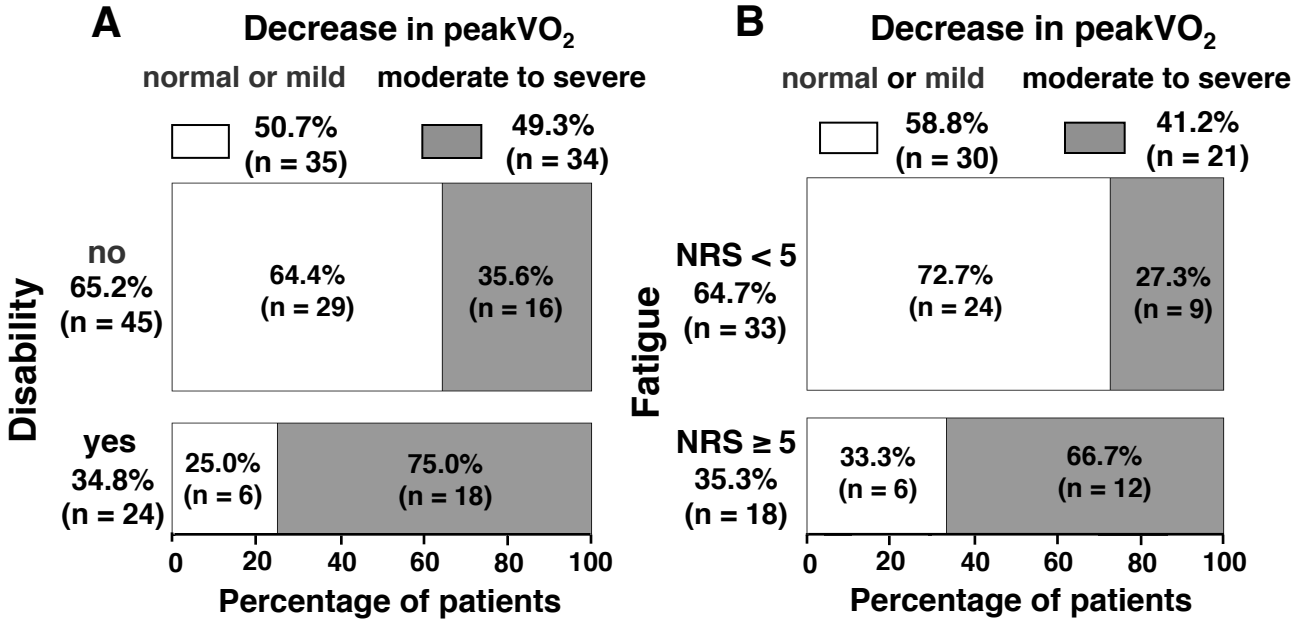
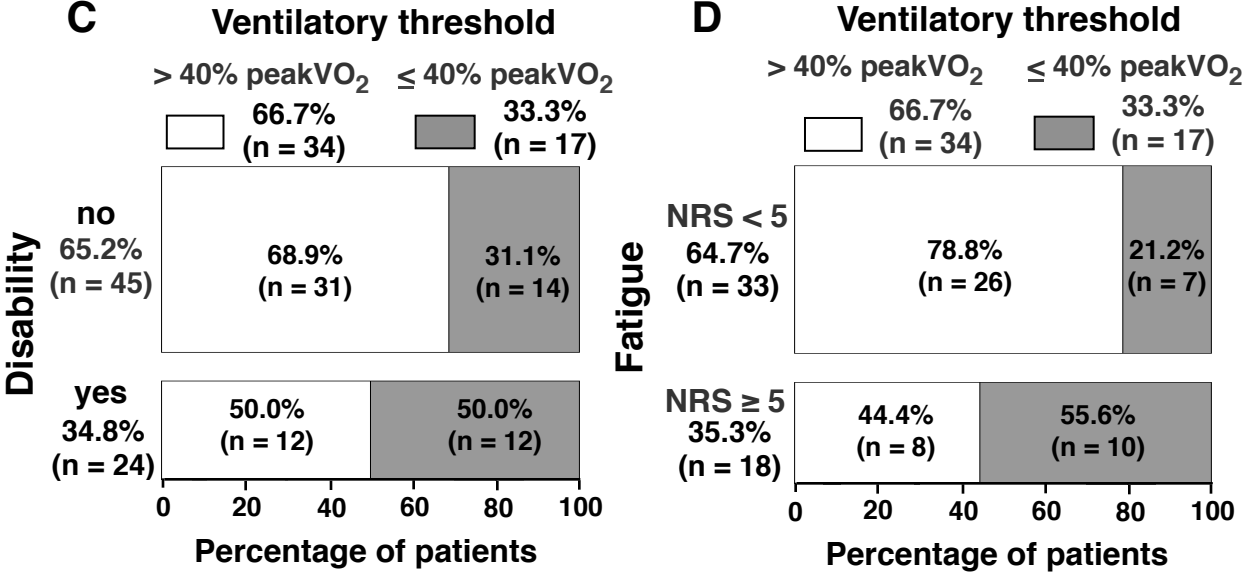


Figure 2

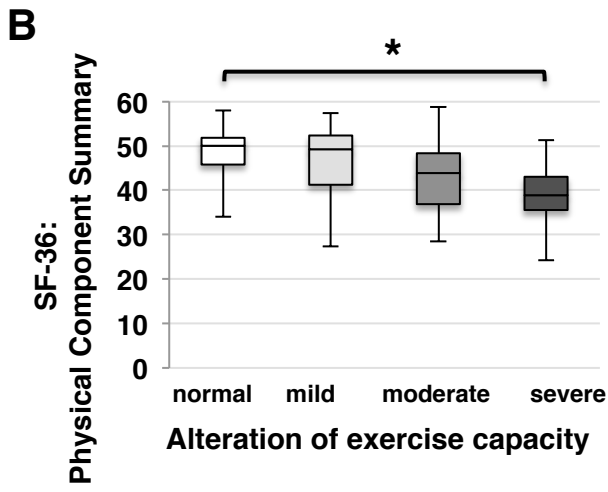
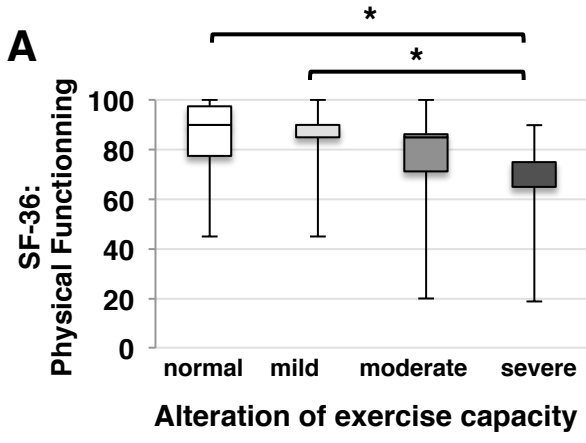
### Impairment of exercise capacity



### Deconditioning



**Figure 3**



**Figure 4**

