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Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation

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ABSTRACT

We have evaluated risk factors associated with fatigue in 220 cancer patients during hospitalization for stem-cell transplantation (SCT). Fatigue was assessed using a validated one-item energy scale and a comprehensive set of fatigue predictors, at hospital admission (baseline), day of SCT, and 7 days and 14 days after SCT. In cross-sectional multivariate analysis, depression was the variable most consistently and strongly associated with fatigue; other factors significantly associated with fatigue at some time during the study included older age, higher education, smoking, lower Karnofsky performance status, loss of appetite, nausea/vomiting, pain, higher regimen-related toxicity, low hemoglobin level, requirement for red blood-cell transfusions, and third year of the study period. In prospective multivariate analysis, baseline depression showed significance or a trend towards significance in its ability to predict subsequent measures of fatigue during hospitalization. Our findings may help to shed light on the mechanisms underlying fatigue and may also guide future interventions.

1. Introduction

Fatigue is one of the most prevalent and distressing symptoms of cancer. Reviews of cancer-related fatigue indicate prevalence rates ranging from 25% to 100% [1–3]. Fatigue has a major negative effect on the patient's quality of life, resulting in substantial adverse physical, psychosocial, and economic/occupational consequences [4–7]. Fatigue is a non-specific, multidimensional construct that is generally thought to involve subjective feelings of tiredness and/or lack of energy. Although research into the condition has increased in the past decade, little in-depth information regarding related clinical factors is available. The literature on this issue has been characterized by methodological limitations [1–3] such as retrospective or cross-sectional designs, sampling bias, use of questionnaires not validated, focus on a limited number of risk factors, use of global emotional distress measures that do not separate depression from anxiety, lack of assessment by multivariate statistical methods, and small sample size.

Haematopoietic stem-cell transplantation (SCT) is a highly aggressive and demanding medical therapy with a profound impact at both physical and psychological levels [8,9]. Only one study has reported clinical correlates of fatigue in patients hospitalized for SCT [6] and in fact their findings were

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limited by the small sample size ($n = 31$) and the lack of assessment by a multivariate statistical method.

In this 3-year prospective in-patient study, we evaluated fatigue using a validated one-item scale and a wide range of potential fatigue risk factors at four consecutive time points during hospitalization for SCT. The purpose of the current paper is to identify multivariate risk factors associated with fatigue during hospitalization for SCT. We hypothesized that depression would be associated with fatigue, even after adjusting for a comprehensive set of clinical confounding variables.

2. Patients and methods

2.1. Study population

The methods have been described in detail elsewhere [9,10]. Briefly, patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were haematologic malignancy, age at least 16, patient's first SCT, and verbal informed consent.

2.2. Study variables

2.2.1. Fatigue

Fatigue is a multidimensional concept with several modes of expression: physical (e.g., diminished energy, need to rest), cognitive (e.g., diminished concentration or attention), and affective (e.g., decreased motivation or interest) [1,3]. A methodological problem with regard to the relationship between fatigue and depression is that most depression scales contain items, which overlap with items of the fatigue questionnaires (e.g., energy level, ability to concentrate, and motivation). To solve in part this problem, in the current study, we measured the most physical dimension of fatigue, using energy level as a synonym for this construct. In a previous report, our one-item energy level scale was validated for use as a synonym of the most physical dimension of fatigue during hospitalization for SCT [10]. Patients rated their overall energy loss experienced during the past week in relation to what could be considered their healthy state. The energy loss was rated on a numerical scale from 0 to 100, and the energy level obtained by subtracting the energy loss from 100. In our previous report [10], the reliability and validity of the energy level scale during hospitalization for SCT were demonstrated: (1) we carried out test–retest reliabilities between three consecutive time points during hospitalization for SCT (all $P < 0.001$); (2) convergent validity was tested by examining associations with validated related scales measured at the time of hospital admission (energy and physical mobility scales from the Nottingham Health Profile [11]; all $P < 0.001$); (3) divergent validity was demonstrated by a non-significant association between the energy level scale and a validated unrelated scale measured at the time of hospital admission (health care orientation scale from the Psychosocial Adjustment to Illness Scale [12]; $P = 0.74$); (4) to evaluate criterion validity, we used the method of known-groups comparison to assess the ability of the energy level scale to distinguish between subgroups of patients with different Karnofsky performance status [13] at four different time points during hospitalization for SCT (all $P < 0.001$); (5) we assessed the responsiveness of the energy level scale to changes in Karnofsky performance status from hospital admission to hospital discharge, with the subgroup of patients whose Karnofsky performance status deteriorated the most reporting a significantly worse outcome in energy level ($P < 0.001$) compared to the subgroup of patients with less decline in Karnofsky performance status; and (6) predictive validity was demonstrated by the ability of the hospital admission energy level score to significantly predict hospital discharge energy level score after controlling for other baseline risk factors ($P < 0.001$).

2.2.2. Depression and anxiety

The patient-rated Hospital Anxiety and Depression Scale (HADS) contains two seven-item scales: one for depression and one for anxiety, with higher scores indicating greater distress [14]. Items that may also be attributable to illness or treatment side effects (e.g., fatigue) are not included in this questionnaire. However, in the depression subscale the retardation item ("I feel as if I am slowed down") appears to overlap with fatigue. The HADS scale has been extensively documented in patients with cancer [15–18] and its reliability and validity has been demonstrated [14,15]. Our study used an authorized Spanish translation. Internal consistency, reliability and correlation analysis for the HADS subscales were calculated from T1 to T4. Mean Cronbach's alphas for the depression and anxiety subscales were 0.88 and 0.80, and the mean Spearman rank order correlation between the depression and anxiety subscales was 0.47.

2.2.3. Loss of appetite and insomnia

Potential confounding exists in the measurement of fatigue because of its close association with depression. Since fatigue is primarily a subjectively experienced symptom, self-report measures are the most commonly described type of instrument for measuring fatigue [1]. It arises over a continuum, ranging from tiredness to exhaustion. As a part of our investigation, the nine diagnostic and statistical manual for mental disorders, fourth edition (DSM-IV [19]) criterion items required for the diagnosis of major depression (categorical variable) were rated by the clinician as absent/sub-threshold or present during the past week. The present report uses depression as defined by the HADS and not by DSM-IV because we wanted a depression measure that could be self-reported by the patient, spanning a continuum of depression levels, and not including somatic depressive symptoms such as fatigue or other symptoms that have been found to predict fatigue. One of the nine DSM-IV criterion items to diagnose major depression is fatigue, and two of the other criterion items, insomnia and loss appetite, have been found to predict higher levels of fatigue [1–5,18]. In the current report, we have only used the DSM-IV criterion items insomnia and loss of appetite to study its association with fatigue.

2.2.4. Nausea/vomiting and pain

The systemic symptom scale included the symptoms of vomiting/nausea, diarrhea, dry mouth, mouth pain, abdominalgia, headache, and other pain (the highest score of any other pain if several were present). In a previous report [10], the reliability and validity of the systemic symptom scale during hospitalization for SCT were demonstrated. In this study,

we used only those items that have been found in the literature to be related to fatigue [1–3]. Because odinia represents the main source of pain, we used two pain variables: one specifically for mouth pain and a new composite variable that included the other three pain symptoms of the systemic symptom scale. Symptoms were categorized as absent/mild or moderate/severe. We should state that the systemic symptom scale has not been validated for use with the modifications that the researchers made to include only items related to fatigue.

2.2.5. *Functional status*

The Karnofsky Performance Scale is an index of physical disability developed for the evaluation of oncology patients. Lower scores reflect greater impairment in normal activity, work, and self-care.

2.2.6. *Regimen-related toxicity*

The Bearman Toxicity Scale [20] was used to specifically rate the complications due to chemotherapy or chemoradiotherapy during hospitalization for SCT. Cardiac, bladder, renal, pulmonary, hepatic, central nervous system, gastrointestinal, and stomatitis toxicities are assigned a grade of 0–4 in increasing severity according to specific guidelines for each organ. The regimen-related toxicity score is the sum of the highest toxicity observed in each organ at any time.

2.2.7. *Other disease- and treatment-related data*

Haematological cancer diagnosis, disease risk status (low/intermediate versus high), conditioning regimen (chemotherapy versus chemoradiotherapy), type of SCT (autologous or syngeneic versus allogeneic), haemoglobin count, period of study entry (July 1994–June 1996 versus July 1996–August 1997), weekly requirement of red blood cell transfusions, and weekly requirement of opioid and benzodiacepine medications. Morphine and additional analgesics were converted to morphine equivalents using the conversion factors of Stimmel [21] and benzodiacepines medications were converted to diazepam equivalents [22].

2.3. *Study procedures*

Patients were assessed in a first structured interview within 48 h of hospital admission (T1, day −9 to day −4 depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (T2, day 0) until discharge or death (T3, day +7; T4, day +14; T5, day +21, and so on). In order to limit the number of dropouts (mainly due to hospital discharge) we only used data from the T1 to T4 interviews. At hospital admission and subsequently on a weekly basis, a Karnofsky performance status score was obtained from the haematologist. No inter-rater reliability assessment was carried out for this performance status measure. All structured interviews were carried out by three researchers: the main investigator was a psychiatrist (J.M.P.), the two others were a fourth year psychiatric resident (J.A.) who participated in the study for the first 11 months and a psychiatrist (J.B.) who participated in the rest of the study. Each patient was interviewed by only one of the researchers during the hospitalization period. The first interview included sociodemographic data, assessment of psychiatric status with DSM-IV criteria, energy level scale, and the HADS. After this first interview, patients were asked to complete two self-report instruments: the Nottingham Health Profile to measure health-related quality of life and the Psychosocial Adjustment to Illness Scale to assess psychosocial adaptation. In the following weekly assessments, we administered a structured interview that comprised assessment of psychiatric status with DSM-IV criteria, energy level scale, systemic symptom scale, and the HADS. After discharge, using a standardized form, J.M.P. abstracted medical data from hospital charts. The regimen-related toxicity, requirement of red blood cell transfusions, opioid treatment, and benzodiacepine treatment were obtained from T2 to T4. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

2.4. *Statistical analysis*

Univariate and multivariate linear regression analysis were used to identify predictors of energy level at T1, T2, T3, and T4. We dichotomized all weekly Karnofsky performance status variables (lowest quintile versus upper four quintiles), and all weekly benzodiazepine treatment variables (lower four quintiles versus highest quintile) because of their highly skewed distributions. Because their median energy levels were very similar, the time periods July 1994–June 1995 and July 1995–June 1996 were combined in the same category. For multivariate models, a stepwise selection method was used to select significant variables. Since poor health status can significantly increase both depression and fatigue [1–3,23,24], interaction terms between HADS depression and disease risk status, admission hemoglobin level, Karnofsky performance status, regimen-related toxicity, mouth pain, other pain, and requirement of red-blood cell transfusions were tested in their corresponding multivariate models. All multivariate models were adjusted for sex and age. Collinearity was assessed using variance inflation factors and standard residuals-based diagnostic procedures were used to assess model assumptions and adequacy of the model fit. Performance of the model was assessed by the adjusted explained variance (R^2). Patients with missing data on any scale were excluded from analyses. All reported P values are two-tailed. P values were considered significant if they were less than 0.05. No adjustment of the alpha level for multiple tests was made. Statistical analyses were done with SPSS (version 11.5).

2.5. *Attrition and missing data*

A total of 852 out of 871 possible observations (97.8%) were made from T1 to T4: 220, 217, 214, and 201. Missing observations were due to compromised medical status (3 at T2, 4 at T3, and 6 at T4) or scheduling difficulties (6 at T4). Attrition was due to hospital discharge (four patients had been discharged before the T4 assessment) and death (two patients had died by the time of the T3 assessment and 3 by the T4 assessment). Due to patient fatigue, in a few cases complete assessment of all predictor variables could not be performed. The total number of evaluations for energy level, loss of appetite, insomnia, and HADS decreased to 851, 851, 851 and 849,

respectively. For the haemoglobin count, information was missing from two patients.

3. Results

Of 253 patients that received SCT during the 3-year recruitment period, 235 met the eligibility criteria. Due to scheduling difficulties, 15 patients could not be interviewed at the first assessment and were excluded from the study. All patients who were approached agreed to be interviewed. Thus, the final study cohort included 93.6% of the eligible population (220/235). There were no differences in age, sex, haematologic diagnosis, or disease risk status between the 220 patients who participated in the study and the 15 excluded patients ($P > 0.20$). Baseline patient characteristics are displayed in Table 1. Measures in energy level and 12 fatigue risk factors from day of hospital admission (T1) to day +14 after SCT (T4) are listed in Table 2. Median energy level scores at T1, T2, T3, and T4 were 80, 50, 50 and 50, respectively.

Table 3 shows all tested univariate predictors of energy level from T1 to T4. Variables with $P < 0.10$ in univariate analysis were included in multivariate linear regression models. Full multivariate models estimating energy level from T1 to T4 (Table 4) included baseline data in addition to concurrent weekly values of those variables measured over time. Furthermore, the T1 energy level variable was incorporated in the full regression models used to predict energy level at T2, T3 and T4, to adjust for the effect of this variable at baseline. Adjusted explained variance for all these models ranged from 32% to 48%. After adjusting for the effect of other risk factors, low Karnofsky performance status at T1 and higher HADS depression at T2, T3, and T4 were the factors with the strongest association with low energy level in their corresponding regression models. Baseline multivariate models were used to study the predictive effect of those T1 risk factors on energy level at T2, T3, and T4 (Table 5). Compared to full multivariate models, a lower number of variables contributed to explaining the adjusted variance (range 6–19%). Baseline energy level was the strongest and most consistent predictor of subsequent measures of energy level. Baseline HADS depression was found to significantly predict T3 energy level ($P = 0.038$), showing a trend for significance in predicting T2 ($P = 0.093$) and T4 ($P = 0.16$) energy level. Tested interaction terms did not reach statistical significance in any full or baseline multivariate model (data not shown).

To investigate any confounding effect of the original HADS depression scale due to the fact that it contains the retardation item ("I feel as if I am slowed down") which appears to overlap with fatigue, we excluded this item from the scale and repeated the multivariate analysis. Although there was a reduction in the standardized β coefficients of the HADS depression after excluding this item (data not shown), we obtained the same significant results in predicting energy level in the full and baseline multivariate models.

To further explore the complex relation between fatigue and depression, we performed univariate and multivariate regression analyses to identify predictors of HADS depression from T1 to T4 (data not shown). For these analyses we used the same candidate risk factors as for the analyses predicting energy level. While low energy level was significantly associated with higher HADS depression in all corresponding multivariate full models, baseline energy level had no effect on

Table 1 – Baseline patient characteristics

Characteristic	T1 ($n = 220$)
Age (years)	38 (16–65)
Female sex, *n* (%)	91 (41.3)
Married/cohabitating, *n* (%)	141 (64.1)
Education, years	11 (4–12)
Current smoking, *n* (%)	41 (18.6)
Haematological cancer diagnosis, *n* (%)	
Acute myelogenous leukemia	50 (22.7)
Acute lymphoblastic leukemia	29 (13.2)
Chronic myelogenous leukemia	34 (15.5)
Non-Hodgkin's lymphoma	46 (20.9)
Hodgkin's disease	19 (8.6)
Multiple myeloma	27 (12.3)
Other[a]	15 (6.8)
High risk disease status, *n* (%)	100 (45.5)
Hemoglobin count (g/dl)	115 (62–159)
Chemoradiotherapy, *n* (%)	156 (70.9)
Allogeneic SCT,[b] *n* (%)	129 (58.6)
July 1996–August 1997, *n* (%)	75 (34.1)

Data are median (range) unless otherwise indicated. Comparison categories can be found in Section 2.2 and missing information in Section 2.5.
a Chronic lymphocytic leukemia ($n = 7$), myelodysplastic syndrome ($n = 5$), histiocytosis ($n = 1$), myeloproliferative syndrome ($n = 1$), and granulocytic sarcoma ($n = 1$).
b One syngeneic SCT was placed with the autologous SCT group.

Table 2 – Patient characteristics over time

Characteristic	T1 ($n = 220$)	T2 ($n = 217$)	T3 ($n = 214$)	T4 ($n = 201$)
Energy level score	85 (0–100)	50 (0–100)	50 (0–100)	50 (20–100)
Karnofsky score	100 (50–100)	70 (40–80)	70 (30–80)	70 (40–90)
HADS anxiety score	3 (0–21)	2 (0–17)	2 (0–16)	2 (0–17)
HADS depression score	1 (0–19)	3 (0–20)	3 (0–17)	3 (0–20)
Loss of appetite, *n* (%)	22 (10.0)	176 (81.5)	181 (84.6)	151 (75.1)
Insomnia, *n* (%)	23 (10.5)	55 (25.5)	53 (24.8)	39 (19.4)
Nausea/vomiting, *n* (%)		150 (69.1)	110 (51.4)	65 (32.3)
Mouth pain, *n* (%)		27 (12.4)	128 (59.8)	52 (25.9)
Other pain, *n* (%)		80 (36.9)	69 (32.2)	31 (15.4)
Regimen-related toxicity score		1 (0–4)	2 (0–6)	2 (0–8)
Red blood cell transfusions, *n*		0 (0–10)	2 (0–10)	2 (0–8)
Opioid treatment		0 (0–82)	9 (0–350)	21 (0–439)
Benzodiazepine treatment		0 (0–67)	0 (0–118)	2 (0–118)

Data are median (range) unless otherwise indicated. See Section 2.2 for comparison categories and Section 2.5 for missing information. Opioid treatment is expressed in mg of morphine equivalents and benzodiazepine treatment in mg of diazepam equivalents. Higher scores on energy level and Karnofsky scales and lower scores in all other scales represent better functioning.

Table 3 – Univariate predictors of energy level at T1, T2, T3, and T4

	T1 energy level (n = 220)	T2 energy level (n = 216)	T3 energy level (n = 214)	T4 energy level (n = 201)
T1 risk factors				
Age	−0.096	−0.060	−0.070	−0.086
Female	−0.031	−0.027	−0.061	−0.067
Married/cohabitating	0.077	0.011	0.141*	0.041
Education	0.095	0.026	−0.119*	−0.037
Current smoking	−0.122*	−0.033	−0.073	−0.074
High risk disease	−0.239***	−0.068	−0.159*	−0.111
Hemoglobin count	0.252***	0.101	0.202**	0.178*
Chemoradiotherapy	0.033	0.075	0.026	0.020
Allogeneic SCT	0.062	0.104	0.018	−0.077
July 1996–August 1997	0.259***	0.308***	0.204**	0.184**
HADS anxiety	−0.259***	−0.204**	−0.206**	−0.158*
HADS depression	−0.453***	−0.253***	−0.267***	−0.216**
Karnofsky status	0.484***	0.235***	0.224***	0.114
Loss of appetite	−0.429***	−0.141*	−0.118*	−0.097
Insomnia	−0.393***	−0.229***	−0.178**	−0.102
T2–T4 risk factors				
HADS anxiety		−0.247***	−0.266***	−0.380***
HADS depression		−0.482***	−0.573***	−0.513***
Karnofsky status		0.348***	0.337***	0.372***
Loss of appetite		−0.359***	−0.135*	−0.194**
Insomnia		−0.239***	−0.075	−0.243***
Nausea/vomiting		−0.251***	−0.304***	−0.223**
Mouth pain		−0.114*	−0.107	−0.244***
Other pain		−0.133*	−0.286***	−0.243***
Regimen-related toxicity		−0.158*	−0.213*	−0.216**
Red blood-cell transfusions		−0.055	−0.229***	−0.064
Opioid treatment		−0.103	−0.164*	−0.146*
Benzodiazepine treatment		−0.018	−0.118*	−0.163*

Each energy level outcome was analyzed for baseline T1 data in addition to concurrent weekly values of those risk factors measured from T2 to T4. Data are expressed as standardized β coefficients. See also footnote in Table 2.

* $P < 0.10$.

** $P < 0.01$.

*** $P < 0.001$.

predicting subsequent HADS depression at T2 ($P = 0.68$), T3 ($P = 0.50$), and T4 ($P = 0.74$) in multivariate baseline models.

4. Discussion

To our knowledge, this study is the largest in-hospital investigation studying risk factors for fatigue in any cancer sample. In cross-sectional multivariate analysis, depression was the variable most consistently and strongly associated with fatigue. Although there are some contradictory results [7,25,26], most studies have emphasized a significant cross-sectional association between depression and fatigue [5,6,16–18]. Failure to find a significant association may partly be explained by the nature of the patient sample and/or a low depression level. Stone and colleagues [25] found that depression had no effect on fatigue in a sample of patients with advanced disease and a very short prognosis. Under these circumstances, the role of depression may be more difficult to detect because of the strong cancer- or treatment-related biological processes at that moment. In another study [26], depression was not associated with fatigue in a sample of long-term cancer survivors with a low prevalence of depression. Visser and Smets [7] concluded that fatigue and depression were unrelated conditions with different patterns over time. However, in a recent study Tchekmedyian and colleagues [27] reported that improvement of fatigue was significantly associated with a reduction in depression.

Fatigue can occur as a symptom of depression [5,19,23,24] or, alternatively, it may precipitate feelings of depression because of its adverse effect on mood and functional ability. In our cross-sectional multivariate analysis, HADS depression was found to predict energy level, and energy level was found to predict HADS depression. However, in prospective multivariate analysis, baseline HADS depression showed significance or a trend towards significance for predicting subsequent measures of energy level, while baseline energy level did not predict subsequent measures of HADS depression. In addition, medical complications or treatment side effects that can significantly impact on fatigue may also cause or mimic depression [1–3,23,24]. However, our depression measure did not include somatic symptoms that could be attributed to illness or treatment side effects, and statistical analyses controlled for a comprehensive set of clinical confounding factors.

Table 4 – Full multivariate models: predictors of energy level at T1, T2, T3, and T4

	β	P	Adjusted R^2
T1 energy level ($n = 218$)			0.454
T1 Karnofsky	0.332	<0.001	
T1 loss of appetite	−0.263	<0.001	
T1 HADS depression	−0.214	<0.001	
July 1996–August 1997	0.193	0.001	
Current smoking	−0.148	0.010	
Hemoglobin count	0.123	0.032	
Age	−0.110	0.037	
T2 energy level ($n = 216$)			0.402
T2 HADS depression	−0.310	<0.001	
T1 energy level	0.212	<0.001	
T2 Karnofsky	0.176	0.002	
T2 nausea/vomiting	−0.161	0.004	
July 1996–August 1997	0.135	0.028	
T2 loss of appetite	−0.128	0.038	
T3 energy level ($n = 212$)			0.469
T3 HADS depression	−0.434	<0.001	
July 1996–August 1997	0.187	<0.001	
T3 other pain	−0.164	0.003	
Education	−0.159	0.003	
T1 energy level	0.153	0.006	
T3 red blood cell transfusions	−0.137	0.009	
T3 regimen-related toxicity	−0.135	0.012	
T4 energy level ($n = 199$)			0.321
T4 HADS depression	−0.440	<0.001	
July 1996–August 1997	0.154	0.016	
T4 Karnofsky	0.156	0.019	

All variables with $P < 0.10$ in univariate analysis were included in multivariate regression models. Only significant ($P < 0.05$) predictors are listed. See also footnote in Table 2.

Table 5 – Baseline multivariate models: predictors of energy level at T2, T3, and T4

	β	P	Adjusted R^2
T2 energy level ($n = 216$)			0.190
T1 energy level	0.329	<0.001	
July 1996–August 1997	0.229	0.001	
T3 energy level ($n = 212$)			0.150
T1 energy level	0.223	0.004	
Education	−0.170	0.010	
July 1995–June 1996	0.158	0.020	
T1 HADS depression	−0.152	0.038	
T4 energy level ($n = 199$)			0.058
T1 energy level	0.249	<0.001	

P values for T1 HADS depression at models T2 and T4 were 0.093 and 0.16. See also footnote in Table 4.

As expected from a clinical perspective and in agreement with other reports, we found that older age [16,26], lower Karnofsky performance status [4], higher disease or treatment burden [26], anaemia (low haemoglobin level/requirement of red-blood cell transfusions) [4,28], pain [5,17,25], or gastrointestinal symptoms such as nausea/vomiting [4] or loss of appetite [4] are significantly associated with fatigue. Pain can occur secondary to anticancer treatment and may lead to fatigue through its effects on mood, activity level, and/or sleep [5]. Fatigue may also be induced by loss of nutrients as a result of anorexia, nausea or vomiting [1].

Another noteworthy finding in this study was the significant association between smoking at the time of hospital admission and low energy level, even after adjusting for other clinical confounding variables. Consistent with our findings, several studies in the general population have described an association between smoking and fatigue [29,30]. We also found that degree of fatigue decreased in the last year of our study period, probably in relation to improvement in supportive care technologies and better patient selection. Our finding that higher education attainment, a surrogate of higher socioeconomic status [31], was predictive of lower energy level was contrary to expectations.

This study has several limitations. First, we did not perform a multidimensional assessment of fatigue. However, the advantages of the single-item fatigue scale include low burden to patients, simplicity, and ease of clinical use. Administering quality of life instruments in the SCT setting needs to be done with an acute awareness of the risk of patient overload. Second, although we did not measure inter-rater reliability for the haematological ratings of the Karnofsky performance status, our accurate knowledge of the patients' physical and functional status coupled with the use of strict guidelines for the assessment aided our estimation of performance status ratings. Third, we did not assess systemic symptomatology at T1, so as not to impose an undue burden on our patients. Based on clinical experience and the existing literature, systemic symptoms are at their lowest level previous to initiating the conditioning treatment at T1 [6,8]. Fourth, although our results provide support for the prognostic importance of depression, they do not establish that depression causes fatigue. To establish a causal relationship, we need longitudinal research combining repeated measurement of depression and its presumed pathophysiological mechanisms, followed by adequately powered, randomized trials targeting the implicated mechanisms. Finally, as in any single-institution study, some conclusions are specific to our center and reflect our patient characteristics and practice patterns. However, the findings of this study are strengthened by its prospective design, non-biased sample, high recruitment rates, large population, use of brief and previously validated instruments, use of serial evaluations, and use of multivariate regression models that included a comprehensive set of clinical confounding variables.

Our results support the multidimensional etiology of fatigue and may be useful in generating hypotheses about mechanisms underlying fatigue and directing intervention efforts for cancer-related fatigue. Although some clinical factors that we have found to be associated with fatigue are non-modifiable, other factors are treatable and may result in a decrease of fatigue levels. From a clinical perspective, we highlight the importance of carefully screening for depression in cancer patients who complain of fatigue. Short and simple self-reported questionnaires, such as the HADS, may help to detect depression in the clinical setting [15,16]. Many of the depressed patients can be treated effectively with medication and/or psychotherapy [1–3,23,24]. Furthermore, appropriate

treatment of pain, nausea/vomiting, or anaemia may be effective for reducing fatigue. In addition, help from smoking cessation services early in the disease process may have a role in promoting physical and psychological health. If this is not possible, evident restrictions for smoking during hospitalization for SCT provide an important opportunity for initially refractory patients to stop smoking. Clearly, further research is needed to gain a better understanding of the physiopathology and treatment of fatigue in cancer patients [1–3]. Among other outcomes, the course and predictors of fatigue during post-SCT follow-up and their impact on quality of life will be presented in future articles.

Conflict of interest statement

There is no any financial or personal relationship with other people or organisations that could inappropriately influence (bias) the authors' work.

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REFERENCES

1. Ahlberg K, Ekman T, Gaston-Johansson F, et al. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003;**362**:640–50.
2. Stasi R, Abriani L, Beccaglia P, et al. Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer* 2003;**98**:1786–801.
3. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer* 2002;**38**:27–43.
4. Wang XS, Giralt SA, Mendoza TR, et al. Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma. *J Clin Oncol* 2002;**20**:1319–28.
5. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol* 2000;**18**:743–53.
6. Hann DM, Garovoy N, Finkelstein B, et al. Fatigue and quality of life in breast cancer patients undergoing autologous stem cell transplantation: a longitudinal comparative study. *J Pain Symptom Manage* 1999;**17**:311–9.
7. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? *Support Care Cancer* 1998;**6**:101–8.
8. Fife BL, Huster GA, Cornetta KG, et al. Longitudinal study of adaptation to the stress of bone marrow transplantation. *J Clin Oncol* 2000;**18**:1539–49.
9. Prieto JM, Blanch J, Atala J, et al. Psychiatric morbidity and impact on hospital length of stay among haematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 2002;**20**:1907–17.
10. Prieto JM, Atala J, Blanch J, et al. Psychometric study of quality of life instruments used during hospitalization for stem-cell transplantation. *J Psychosom Res* 2004;**57**:201–11.
11. Hunt SM, McKenna SP, McEwen J, et al. The Nottingham Health Profile: subjective health status and medical consultations. *Soc Sci Med* 1981;**15**(Suppl A):221–9.
12. Derogatis LR. The Psychosocial Adjustment to Illness Scale (PAIS). *J Psychosom Res* 1986;**30**:77–91.
13. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. *Evaluation of chemotherapeutic agents*. New York: Columbia University Press; 1949. p. 199–205.
14. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
15. Bjelland I, Dahl AA, Haugh TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;**52**:69–77.
16. Fossa SD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. *J Clin Oncol* 2003;**21**:1249–54.
17. Haghighat S, Akbari ME, Holakouei K, et al. Factors predicting fatigue in breast cancer patients. *Support Care Cancer* 2003;**11**:533–8.
18. Okuyama T, Akechi T, Kugaya A, et al. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Support Care Cancer* 2000;**8**:215–22.
19. American Psychiatric Association. In: *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington (DC): American Psychiatric Association; 1994.
20. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988;**6**:1562–8.
21. Stimmel B. *Pain, analgesia, and addiction*. New York: Raven Press; 1993.
22. Ballenger JC. Benzodiazepine receptor agonists and antagonists. In: Sadock BJ, Sadock VA, editors. *Comprehensive textbook of psychiatry*. Philadelphia (PA)/Baltimore (MD): Lippincott/Williams & Wilkins; 2000. p. 2317–24.
23. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry* 2003;**54**:269–82.
24. Massie MJ, Popkin MK. Depressive disorders. In: Holland JC, editor. *Psycho-oncology*. New York: Oxford University Press; 1998. p. 518–40.
25. Stone P, Hardy J, Broadley K, et al. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Br J Cancer* 1999;**79**:1479–86.
26. Loge JH, Abrahamsen AF, Ekeberg O·, et al. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. *J Pain Symptom Manage* 2000;**19**:91–9.
27. Tchekmedyian NS, Kallich J, McDermott A, et al. The relationship between psychological distress and cancer-related fatigue. *Cancer* 2003;**98**:198–203.
28. Gabrilove JL, Cleeland CS, Livingston RB, et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001;**19**:2875–82.
29. Pattern CA, Gillin JC, Golshan S, et al. Relationship of mood disturbance to cigarette smoking status among 252 patients with a current mood disorder. *J Clin Psychiatry* 2001;**62**:319–24.
30. McDonough P, Moffatt RJ. Smoking-induced elevations in blood carboxyhaemoglobin levels. Effect on maximal oxygen uptake. *Sports Med* 1999;**27**:275–83.
31. Balfour JL, Kaplan GA. Social class/socioeconomic factors. In: Holland JC, editor. *Psycho-oncology*. New York: Oxford University Press; 1998. p. 78–90.