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Pre-transplant depression as risk factor for survival of patients undergoing allogeneic haematopoietic stem cell transplantation

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Abstract

***Introduction*: Depression is discussed as a possible risk factor for survival in cancer patients. We explored this relationship for patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT).**

***Patients and methods*: The depression subscale of the Hospital Anxiety and Depression Scale (HADS) served as a measure for depression. One hundred and thirty-eight patients (mean age 41 years; different diagnoses) participating in a psycho-oncology study filled in the HADS after admission for allogeneic HSCT. They were followed-up for at least two years; 72 patients died during follow-up.**

***Results*: Depression scores were not correlated with medical and psychosocial objective factors with the exception of having under-aged children. Controlling for medical factors that showed up as predictors for survival in our sample (patient's age at HSCT, having had a transplant before, risk for treatment failure) the HADS depression score (range 0–21) emerged as an independent predictor (Cox regression): hazard ratio = 1.087, 95% CI= 1.018–1.161.**

***Conclusion*: Depression is probably not a simple indicator of a worse health status. Further research is needed to decide if depression must be considered as an independent risk factor for survival when diagnosed in the pre-transplant period.**

Keywords: cancer; oncology; haematopoietic stem cell transplantation; depression; survival

Introduction

Depressive disorders are common with cancer patients, but often remain unrecognised. In general about 20–25% of patients with cancer develop a depressive disorder that requires treatment [1,2]. Although depression is discussed as a risk factor for the development of cancer and mortality, at date no convincing evidence exists that depression is a cause for the development of cancer [3–5]. Nevertheless there is a growing body of research on a negative effect of depression on the course of the disease [5], but results are disputed.

Several empirical studies addressed the relevance of psychosocial factors, amongst them depressive symptoms, on the course of recovery and survival following haematopoietic stem cell transplantation (HSCT). These studies were analysed by Hoodin and Weber [6] and Hoodin *et al*. [7] in two reviews. Their first review concludes that there is a scarce evidence for a negative influence of depressive mood on survival after HSCT [6]. Later, studies with higher quality were published suggesting that 'pre-transplant negative emotional profiles are associated with worse survival in the long term', even though the findings are not completely convincing [7, p. 255]. The present prospective study was intended to add to this body of evidence regarding depression during the pre-transplant period and survival time.

Our study was started in 1999 when neither the reviews by Hoodin and Weber [6] and Hoodin *et al*. [7] nor the five essential studies [8–12] linking negative emotions and survival as mentioned in Hoodin *et al*.'s latest review [7] were published. In his editorial addressing the study by Prieto *et al*. [8], Andrykowski stresses the point that research should 'move beyond ... demonstrations of a main effect relationship between depression and survival' [13, p. 5879]. Our chosen design does not allow one to clarify such research topics as demanded by Andrykowski [13], e.g. to identify interaction effects or biological mechanisms. However, in addition to performing 'conventional' survival analysis we will explore our data with respect to relationships between depression and objective data. In discussions with other researchers we often were confronted with the supposition that

depression merely reflects restricted physical condition. If this assumption is true, correlations between depression and objective factors should be found in our data. Thus, our paper addresses these two topics: (1) we assume that after controlling for objective factors depression measured after admission for HSCT is linked to overall survival and (2) we explore if objective factors known at that time are correlated with depression.

Patients and methods

The data were collected in the context of a psycho-oncology study (approved by the Ethics committee of Ulm University) aiming at the evaluation of additional psycho-social support during inpatient time for allogeneic HSCT compared with treatment as usual. In this study patients received treatment as usual (control group) or an additional behaviour medicine-oriented intervention programme (treatment group). Allocation to both groups depended on the time period during which patients were admitted to the hospital (four periods of seven months each, i.e. 28 months recruiting time in total; ABBA-design with A = control, B = treatment). The main outcome criterion for the intervention study was suffering from nausea and vomiting during inpatient time. The sample size of this study was aimed at detecting a difference of 0.5 standard deviations between the two groups that is considered clinically relevant in the quality of life research. With $\alpha = 5\%$ and power = 80%, 64 subjects were required both groups. More details on this study were reported elsewhere [14,15]. The data presented in this paper were collected after admission to hospital for allogeneic HSCT, and in the case of the treatment group before the start of the additional psychosocial intervention programme. With respect to the outcome *overall survival* the intervention programme had, as expected, no statistical effect on survival time [16]. Furthermore, there was no statistical significant difference between both groups regarding depression. Therefore, we considered the belonging to control or intervention group not as relevant for the results reported in this paper.

Patients

From September 1999 to December 2001, 230 patients were admitted for allogeneic HSCT at the transplant units for adults of the university hospitals in Ulm and Tübingen, Germany. The inclusion criteria were age (18+ years) and fluency in German language. After admission patients were informed about the psycho-oncology study. Once the patients had given informed consent for HSCT and participation in the psycho-oncology study, a package of questionnaires was administered to cover socio-demographic characteristics and psychological aspects as quality of life, mood, anxiety, and depression. The questionnaires were completed before the start of the conditioning regimen to avoid influences caused by the high-dose chemotherapy. One hundred and forty patients were enrolled in our psycho-oncology study (reasons for exclusion see Figure 1). Of these patients, data of 138 patients (mean age = 40.9 years, SD = 11.3, range = 18–61) could be evaluated for this report. For socio-demographic and medical characteristics of this sample see Table 1.

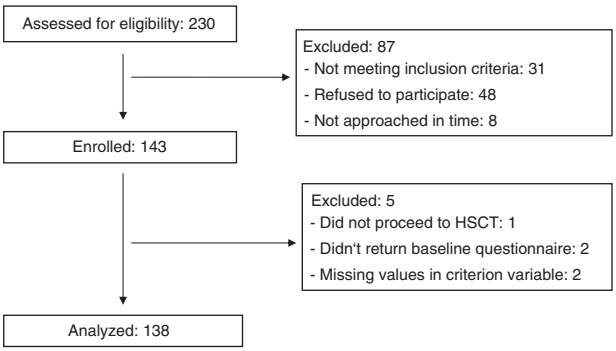

Figure 1. Recruitment

All patients were treated in accordance with the customary standards of the two transplant units. No specific differences between the two groups of study participants and non-participants were found with respect to the available data (sex, age, diagnosis). The survival time of a patient (overall survival) was calculated in days after HSCT till the day the patient died (event) or the day of his/her last documented visit to the transplant centre (censoring). Follow-up for each patient was planned for at least two years. Records could be checked with respect to survival in December 2003, i.e. 24 months after the recruitment of the last patient in December 2001. Seventy-two deaths (events) were registered at that time; the other participants were considered as censored cases.

Measures

We used the German version [17] of the well-validated Hospital Anxiety and Depression Scale (HADS) [18,19]. The HADS comprises two scales, a depression and an anxiety scale, each with seven items. The HADS was specifically developed for patients with physical illness omitting indicators of psychological distress such as weight loss or headache. All items are rated 0–3. A score for a scale is calculated by summing up the seven ratings of the scale, resulting in a range of 0–21. Furthermore, there are recommend cut-off scores to discriminate between the so-called cases (score > 10; probably clinical depression), borderline cases (score 8–10), and non-cases (score 0–7;

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Table 1. Medical and socio-demographic characteristics (frequency, percentage), $n = 138$

Variable	Subgroup	N	%
Study centre	Tübingen	67	48.6
	Ulm	71	51.4
Diagnosis	Acute leukaemia	70	50.7
	CML	29	21.0
	Non-Hodgkin lymphoma	19	13.8
	Others	20	14.5
Former HSCT	No	117	84.8
	Yes	21	15.2
Risk for treatment failure[a]	Low	23	16.7
	Intermediate	64	46.4
	High	51	37.0
Source of stem cells	Bone marrow	46	33.3
	Peripheral blood	92	66.7
HLA	Mismatch	12	8.7
	Ident	126	91.3
Relation to donor	Related	63	45.7
	Unrelated	75	54.3
Total body irradiation	No	38	27.5
	Yes	100	72.5
RIT[b]	No	108	78.3
	Yes	30	21.7
Sex	Female	56	40.6
	Male	82	59.4
Partnership[c]	Single	27	19.9
	Married	81	59.6
	Unmarried	28	20.6
Children under age of 18 years[c]	No	81	63.3
	Yes	47	36.7
Living alone[c]	No	120	91.6
	Yes	11	8.4
Education[c]	<12 years	99	73.3
	$\geqslant 12$ years	36	26.7

[a] This categorization discriminates three groups with low, intermediate and high risk for treatment failure based on diagnosis, stage of disease, and quality of stem cells [24].
[b] RIT, radioimmunotherapy.
[c] Difference to $n = 138$ due to missing values.

probably no depression) [17]. Our analysis is restricted to the HADS depression scale.

Statistical analysis

HADS depression scores were related to available variables. Comparisons of arithmetic means were carried out using *t*-tests or one-way analyses of variance (ANOVA). Homogeneity of variances was evaluated using the Levene statistic. In the case of inhomogeneity for *t*-tests the test statistic not assuming equal variances, and for the ANOVA the Brown–Forsythe and Welch robust tests of equality of means were chosen. Pearson correlation coefficients marked associations between continuous variables.

Survival times were analysed using Cox-regression models. To account for all possible objective factors influencing survival a much larger sample than ours would have been needed. For some diseases treated with allogeneic HSCT there exist prognostic indices based on objective factors, e.g. in the case of chronic myeloid leukaemia (CML) [20] or acute myeloid leukaemia in first relapse [21]. But unfortunately there exists no prognostic index that condenses all such factors for a broad range of diagnoses as in our sample. Therefore all collected objective variables in our study (e.g. the variables listed in Table 1 and patient's age at HSCT) were subjected to univariate survival analyses with overall survival as the outcome criterion. Four variables that showed up as significant univariate predictors were evaluated in multivariate Cox-regression models using forward and backward selection. In the context of the others one of these variables could be considered redundant, thus three variables were identified as relevant objective predictors. In the decisive evaluation these three variables were forced into a Cox-regression model (first step), and then, using forward stepwise selection (second step), the depression score was included to see if it significantly adds to the model with the three objective factors. The proportional hazard assumption was evaluated by plotting the log-minus-log graphs for categorical variables (e.g. former HSCT) and computing time-dependent covariates for continuous variables (e.g. age) [22]. For illustrative purposes Kaplan–Meier survival curves were plotted. *p*-Values <0.05 were considered as significant. Effect sizes to interpret differences between two groups were calculated as difference between the means divided by the pooled standard deviation. Interpretation followed the convention naming effect sizes >0.20 as small, >0.50 as medium and >0.80 as large effects [23]. All statistics were calculated using the package SPSS for Windows (Version 11.0.1; SPSS Inc., Chicago, IL).

Results

Admission took place about two weeks before HSCT (mean = 16, median = 14 days). The time from admission to HSCT in days did not correlate with the HADS-depression score ($r = 0.03$; $p > 0.70$).

Depression and survival

The median survival time for the 72 patients who died was 194 days (minimum 13, maximum 1056 days), for the 66 censored cases 923 days (minimum 21, maximum 1460 days), and for the total sample 535.5 days.

The mean HADS-depression score was 5.09 (SD = 3.83; minimum = 0, maximum = 17). According to the above-mentioned cut-off scores, 105 (76.1%) patients had to be classified as non-cases, 19 (13.8%) as borderline cases, and 14 (10.1%) as cases.

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Table 2. Univariate Cox-regression analyses for objective variables as covariates and overall survival: regression coefficients (*b*), significance (*p*), and hazard ratios (HR) with 95% confidence intervals

Variable	Subgroup	*b*	*p*	HR[a]	95% CI
Study centre	Tübingen	0.10	0.67	1.11	0.70–1.76
	Ulm			1	
Diagnosis	Acute leukaemia	0.41	0.21	1.51	0.79–2.89
	CML			1	
	Non-Hodgkin lymphoma	0.61	0.14	1.84	0.83–4.10
	Others	0.11	0.81	1.12	0.47–2.65
Former HSCT	No			1	
	Yes	0.91	0.001	2.49	1.44–4.32
Risk for treatment failure[b]	Low			1	
	Intermediate	0.41	0.30	1.51	0.69–3.30
	High	1.06	0.007	2.90	1.34–6.25
Source of stem cells	Bone marrow	0.02	0.93	1.02	0.63–1.67
	Peripheral blood			1	
HLA	Mismatch	0.27	0.50	1.31	0.60–2.85
	Ident			1	
Relation to donor	Related			1	
	Unrelated	0.51	0.036	1.67	1.03–2.69
Total body irradiation	No			1	
	Yes	0.30	0.28	1.35	0.79–2.33
RIT[a]	No			1	
	Yes	0.33	0.23	1.39	0.81–2.37
Sex	Female	0.06	0.81	1.06	0.66–1.70
	Male			1	
Partnership	Single			1	
	Married	0.16	0.60	1.18	0.64–2.18
	Unmarried	−0.28	0.49	0.76	0.35–1.66
Children under age of 18 years	No			1	
	Yes	0.13	0.61	1.14	0.70–1.86
Living alone	No			1	
	Yes	0.25	0.59	1.29	0.52–3.20
Education	<12 years	0.03	0.93	1.03	0.60–1.76
	$\geqslant 12$ years			1	
Age (years)[c]		0.03	0.020	1.03	1.004–1.048

[a] 1 Denotes the reference category.
[b] This categorization discriminates three groups with low, intermediate and high risk for treatment failure based on diagnosis, stage of disease, and quality of stem cells [24].
[c] An increase of one unit corresponds to an increased risk as given under HR.

The results of the univariate Cox-regression analyses are reported in Table 2. Former HSCT, risk for treatment failure, relation to donor, and age at HSCT were identified as significant predictors for overall survival. We explored these four variables as covariates in multivariate Cox-regression analyses. With the exception of the relation to donor the other three variables contributed independently to the outcome. As described in the methods section the HADS depression score was evaluated and showed up as an independent significant covariate. The resulting model is shown in Table 3.

To illustrate the impact of being a case, Figure 2 shows the Kaplan–Meier survival curves for these three groups without further adjustment for other variables (log rank = 6.4, df = 2, $p = 0.042$). Mean survival times for these three groups were: 848.4 days (95% CI = 730.9–965.9; median = 663) for non-cases; 699.3 days (95% CI = 473.8–924.9; median = 1056) for borderline cases; and 418.8 days (95% CI = 151.9–685.5; median = 100) for cases. Univariate Cox-regression with HADS depression as continuous covariate misses significance by a narrow margin: HR = 1.06 (95% CI = 0.996–1.12, $p = 0.069$).

Depression and objective factors

The age of the recipient at the time of HSCT and depression were virtually uncorrelated ($r = 0.11$, ns). The other results for the second focus of our analysis are shown in Table 4. Depression seems to be higher when the patient has children under the age of 18 years. This was the only significant difference between groups for the variables listed in Table 4. A possible ($p < 10\%$) difference may be seen for the risk of treatment failure, but the intermediate risk group shows highest depression scores, not as may be expected, the high-risk group. For all variables, effect sizes were small at best.

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Table 3. Multivariate Cox-regression model for the overall survival with four variables, namely former HSCT, risk for treatment failure, age at HSCT, and HADS depression: regression coefficients (*b*), significance (*p*), and hazard ratios (HR) with 95% confidence intervals

Variable		*b*	*p*	HR	95% CI
Former HSCT		0.585	0.053	1.795	0.993–3.246
Risk for treatment failure[b]	Intermediate[a]	0.230	0.571	1.259	0.567–2.796
	High[a]	0.950	0.019	2.585	1.170–5.709
Age at HSCT[c]		0.018	0.119	1.018	0.995–1.042
Depression[c]		0.084	0.013	1.087	1.018–1.161

Dummy coding: former HSCT and risk for treatment failure 'yes' = 1, 'no' = 0.
[a] Compared to low risk.
[b] This categorization discriminates three groups with low, intermediate, and high risk for treatment failure based on diagnosis, stage of disease, and quality of stem cells [24].
[c] An increase of one unit corresponds to an increased risk as given under HR.

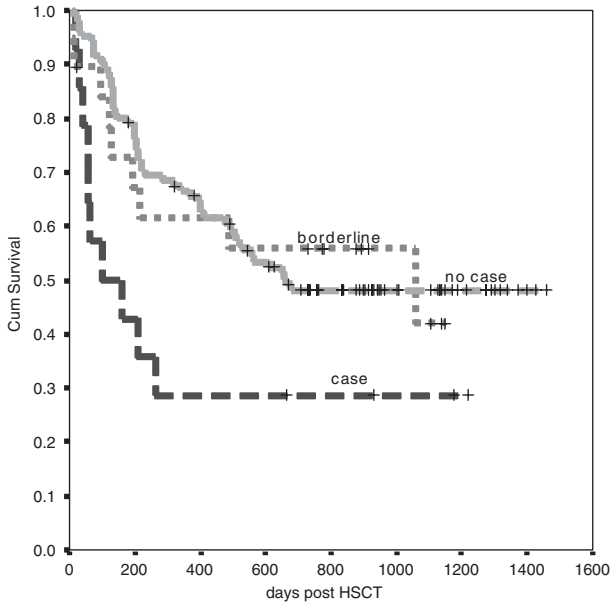

Figure 2. Kaplan–Meier survival curves for Hospital Anxiety and Depression Scale (HADS) depression groups. Scores on the HADS depression scale for 'no case': 0–7 ($n = 105$); 'borderline': 8–10 ($n = 19$); 'case': 11–21 ($n = 14$); +mark censored cases

Discussion

We explored the predictive value of self-reported depression during the pre-transplant period for allogeneic HSCT. To account for objective outcome-related factors we forced such factors as covariates into a Cox-regression analysis and found that depression independently and significantly contributed to overall survival. These identified objective factors are well known to be relevant for prognosis [20,24]. Holding these factors constant, an increase of one point on the HADS depression scale increases the risk to die about 9% (relative risk = 1.087). For illustrative purposes: a 10-point increase (that corresponds to a shift from e.g. non-depression, HADS-score = 0, to clinical depression, score = 10) results in a relative risk of HR = $e^{(10*0.084)} = 2.32$, thus more than doubling the risk to die. A patient faces a relevant risk factor for his (overall) survival when he/she suffers from depression (in terms of the HADS) in the pre-transplant period (cf. Figure 1). The prospects of HADS cases are clearly unfavourable, as is reflected in the mean and median survival times (approximately 419 and 100 days vs approximately 848 and 663 days for non-cases).

Prieto *et al.* [8] evaluated depression in clinical interviews using standardized diagnostic criteria (Diagnostic and Statistical Manual for Mental Disorders DSM-IV) and differentiated major depression, minor depression, and no depression. Depression predicted higher 1- and 3-year mortality in their sample after adjusting for other predictive factors. Nine per cent in their sample of 199 patients were diagnosed with major depression, 8.5% with minor depression. These numbers resemble roughly the numbers of 10% (cases) and 13.8% (borderline cases) in our study. Further, the curves shown in Figure 2 parallel to those shown in the paper by Prieto *et al.* [8], where patients with major depression show the worst, those with no depression the best outcome, and the curve for minor depression runs in between, slightly nearer to the no-depression curve.

If depression reflects objective unfavourable conditions we should assume that such factors would show a tendency towards differences in the expected directions. Apparently the depression scores were not correlated with age and the objective factors mentioned in Table 4 with one exception: being the parent of under-aged children. This relationship seems to be plausible. Being a responsible parent facing a life-threatening disease and treatment may induce depressive feelings when thinking about the future of one's children. Besides its significance this difference only represents a small effect (effect size 0.37). Some differences point towards the expected direction, e.g. lowest depression score for CML, amongst the diagnostic groups the one with the best prognoses, or slightly higher scores for patients who already experienced a prior transplantation. But other differences were

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Table 4. Depression scores (Hospital Anxiety and Depression Scale) for all subgroups (mean and standard deviation SD), *p*-values for differences between subgroups (independent samples *t*-test or analysis of variance), and effect sizes ES comparing two means

Variable	Subgroup	Mean	SD	*p*	ES
Study centre	Tübingen	5.43	4.12	0.32	0.17
	Ulm	4.77	3.54		
Diagnosis	Acute leukaemia	5.17	3.63	0.90[a]	0.16[b]
	CML	4.62	4.53		
	Non-Hodgkin lymphoma	5.26	3.54		
	Others	5.34	3.93		
Former HSCT	No	5.08	3.86	0.95	0.02
	Yes	5.14	3.76		
Risk for treatment failure[c]	Low	4.25	3.34	0.09[a]	0.26[d]
	Intermediate	5.86	4.06		
	High	4.51	3.62		
Source of stem cells	Bone marrow	4.91	4.13	0.69	0.07
	Peripheral blood	5.18	3.69		
HLA	Mismatch	4.25	4.54	0.43	0.24
	Ident	5.17	3.77		
Relation to donor	Related	5.30	3.76	0.57	0.10
	Unrelated	4.92	3.91		
Total body irradiation	No	5.66	4.24	0.29	0.20
	Yes	4.88	3.66		
RIT[e]	No	4.98	3.90	0.51	0.14
	Yes	5.50	3.60		
Sex	Female	5.16	4.13	0.87	0.02
	Male	5.05	3.64		
Partnership	Single	5.56	4.82	0.34[a]	0.15[f]
	Married	5.28	3.66		
	Unmarried	4.18	3.24		
Children under age of 18 years	No	4.56	3.70	0.045	0.37
	Yes	5.96	3.86		
Living alone	No	5.23	3.82	0.87	0.23
	Yes	4.36	3.61		
Education	<12 years	5.15	3.86	0.40	0.11
	$\geqslant 12$ years	4.75	3.62		

Sample sizes for all subgroups are given in Table 1.
[a] Analysis of variance.
[b] CML vs other groups.
[c] This categorization discriminates three groups with low, intermediate, and high risk for treatment failure based on diagnosis, stage of disease, and quality of stem cells [24].
[d] Low vs intermediate/high risk.
[e] RIT, radioimmunotherapy.
[f] Single vs married/unmarried.

contrary to expectations, e.g. less depression with mismatched graft, a known risk factor. All these evaluated differences were far from statistical significance, even when we increased the α-level to 0.20 to account for our interest in keeping the null-hypothesis. All *p*-values were >0.25 with the exception for the correlation coefficient (age−depression), in this case $p = 0.21$. Neither for somatic nor for psychosocial objective factors a trend towards a clear picture emerged.

All in all, we found no convincing statistical support for depression corresponding with objectively physical or socio-demographic characteristics. Therefore, the simple reasoning that unfavourable conditions lead to depression seems not to be justified. At the most there are small effects. This finding corresponds to the findings reported by Loberiza *et al*. [9] who did not find significant associations between the two groups of depressed and non-depressed patients and the objective factors of age, sex, marital status, number of children, race, religious affiliation, education, work at diagnosis, disease type, disease stage, TBI, and T-cell depletion. The only significant association was reported for the type of transplantation, i.e. non-depressed patients were over-represented in the group of autologous transplants as opposed to allogeneic, and we only looked at allogeneic HSCT.

The numbers of 'cases' (10.1%) and 'borderline cases' (13.8%) in our sample correspond to those in the general population in which the 90th and the 75th percentiles for men and women are 10 and 7, respectively [18]. With respect to depressiveness our sample of patients in the pre-transplant period reflects the German general population. The obvious assumption that facing HSCT causes more depression could not be found. This finding may be the result of known and unknown influences during the time period since the first diagnosis. Such

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influences that decrease the chances of proceeding to HSCT may be insufficient compliance, unhealthy lifestyle habits, lacking social support or deficient physical conditions, and these are the factors often seen in depressive patients. An example may be a severely depressed patient who decides to stop further treatment after an initial course of chemotherapy and hence, evidently, cannot proceed to HSCT. We assume that patients admitted for transplantation represent a selected sample with respect to depression. These selective influences belong to the pre-transplant period. To our knowledge, at least in the German-speaking countries, patients would not be rejected by the transplant team because of depression, but this could be disputed [25].

In another view one may speculate that facing a forthcoming HSCT is a reason not to be depressed but to be lucky because of the affording chance of becoming cured. At the time of admission those patients whose transplant had to be postponed during the next days did not know about this necessity. Therefore their answers should not be influenced by this fact. The zero-correlation between the numbers of days from admission to HSCT supports this interpretation.

We see our findings in concordance with those of Prieto *et al*. [8] and Loberiza *et al*. [9] and share their interpretation that depression is not simply an indicator of a worse health status. This conclusion relates to the main effects. We cannot exclude the hypothesis that depression is reducible to several objective factors (and maybe some of them are unknown yet). If they exist we expect quite complex interactions that need considerably larger sample sizes to identify their effects than those in the existing studies at date, including ours. Especially the fact that 'real' depression is a rather rare event (about 1 in 10) in this population requires huger sample sizes.

Other limitations of our study should be noted. We considered clinical relevant variables for risk adjustment that strengthens our finding of a significant effect of depression on survival in our limited sample. But we cannot rule out that other variables we did not cover would reduce the effect, e.g. immune function, blood counts, pre-morbid status.

With the HADS we used a well-validated questionnaire that is broadly accepted in the field of psycho-oncology. However, self-report questionnaires do not allow for a clinical diagnosis. Therefore, our conclusion must be considered as limited to depressiveness in the sense of HADS that was administered during the pre-transplant period. So, conclusions cannot be drawn for the effects of depression on survival when seen in the post-transplant period.

The mechanisms that mediate or explain the link of depression with shorter survival are explained approximately in parts only. Generally discussed pathways (e.g. [26–28]) are adherence to medical treatments, health behaviour (e.g. physics, diet, drugs, hygiene), and direct influences of depressive mood on psycho-neuro-endocrinal and psycho-neuro-immunological processes and vice versa. Our study does not allow definite conclusions in these directions.

Independent of the 'real' causes of depressive symptomatology, our study provides evidence that in the pre-transplant phase depression must be considered as a risk factor. This has several clinical implications that were extensively described by others, e.g. [7,8,13]. The main topic to be addressed is the hypothesis that treating depression by psychotherapeutic and/or psychopharmacological interventions might improve outcome, i.e. prolong the survival. This hypothesis is disputed and has no sufficient empirical support to date [27]. Nevertheless, we share Andrykowski's view that—whatever the role of depression for long-term survival may be—a 'better management of depression in the HSCT and oncology settings ... would be a desirable outcome strictly from a quality of life perspective' [13, p. 5879].

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