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Stem cell transplantation: Risk factors for psychiatric morbidity

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ABSTRACT

The aim of this study was to determine the risk factors for psychiatric disorder in haematological cancer patients during hospitalization for stem cell transplantation. In this 3-year prospective study, 220 patients received stem cell transplantation at a single institution. Structured psychiatric interviews applying standardized diagnostic criteria were performed at hospital admission and weekly during hospitalization until discharge or death, yielding a total of 1062 interviews. Psychiatric disorder (any depressive, anxiety, or adjustment disorder) prevalence at the time of hospital admission was 21% and psychiatric disorder incidence during post-admission follow-up was 22%. After adjusting for multiple confounders in multivariate logistic regression analyses, we found that younger age, women, a past psychiatric history, lower functional status, pain, smoking cessation, and higher regimen-related toxicity were significantly associated with psychiatric disorder risk. Our study findings may help to improve identification of the patients most at risk for psychiatric disturbances during hospitalization for stem cell transplantation.

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1. Introduction

Cancer is a life-threatening disease, and its psychological impact on patients has been an important aspect of clinical oncology. In most cancer patients with a positive psychiatric condition depression and/or anxiety are the central symptoms.[1–7] Methodological shortcomings in the cancer literature regarding risk factors for psychiatric disorders include retrospective or cross-sectional designs, sampling bias, only focusing on a limited number of risk factors, lack of assessment by multivariate statistical methods, or small sample size. Moreover, most of the published studies have used patient-rated depression or anxiety scale scores at a level suggestive of a clinical diagnosis, without using structured clinical interviews and/or standardized diagnostic criteria.[1–5] Clinician interviews and standardized diagnostic criteria such as the 'Diagnostic and Statistical Manual for Mental Disorders, 4th ed.' (DSM-IV[8]) or The World Health Organization International Classification of Disorders have long been held to be the gold standard for detecting psychiatric disorders.[1–5]

To the best of our knowledge only one study[6] has investigated multivariate risk factors for psychiatric disorders during hospitalization for stem cell transplantation (SCT). Sasaki and colleagues[6] diagnosed a mental disorder according

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to DSM-IV criteria in 16 (41%) of 39 allogeneic SCT patients. Higher anxiety prior to isolation, unrelated donor, and female sex predicted the occurrence of psychiatric disorders during isolation. However, their findings were limited by the small sample size and by the use of a very heterogeneous sample of psychiatric disorders for risk factor analysis.

Depression and/or anxiety may have a deleterious effect in many ways: it may impair quality of life;[9,10] increase symptom burden[2] and pain intensity;[2,4,5,11] lower compliance with medical treatment;[12] reduce overall survival time;[10] and increase health care costs[13] and hospital stay.[7] The high prevalence of depression or anxiety during hospitalization for SCT,[6,7] the associated complications mentioned above, and the fact that anxiety and depression tend to be under recognized in oncology patients[14] highlight the critical importance of identifying and treating these disorders in transplant patients.

In this 3-year prospective study carried out during hospitalization for SCT, we evaluated psychiatric disorders (depressive, anxiety, and adjustment disorders) based on structured psychiatric interviews and standardized DSM-IV diagnostic criteria. Weekly interviews were carried out from hospital admission until discharge or death. In an earlier report from our cohort,[7] we reported the general prevalence of DSM-IV psychiatric disorders and its association with a longer hospital stay. The purpose of the current paper was to identify risk factors associated with existing psychiatric disorders at the time of hospital admission or with new psychiatric disorders occurring during post-admission follow-up.

2. Patients and methods

2.1. Study population

Patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were haematological malignancy, at least 16 years of age, patient's first SCT, and verbal informed consent. Of 253 patients that received an SCT, 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 94% of the eligible population (220/235). There were no differences in age, sex, haematological diagnosis, or disease risk status between the 220 patients who participated in the study and the 15 who were excluded ($P > 0.20$).

2.2. Study procedures

Detailed information on transplant regimens, graft-versus-host disease prophylaxis and patient care has been published elsewhere.[7] Briefly, patients were assessed in a first structured interview within 48 h of hospital admission (day −9 to day −4, depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (day 0) until discharge or death (day +7; day +14; day +21 and so on). The first interview lasted 15–45 min and included sociodemographic data, assessment of past and current psychiatric status with structured interview and DSM-IV criteria, and the Nottingham Health Profile.[15] In the following weekly assessments, we administered a brief psychiatric structured interview with DSM-IV criteria lasting 5–15 min. At hospital admission a Karnofsky score[16] was obtained from the haematologist. After discharge, using a standardized form, J.M.P abstracted pertinent clinical data required to rate the regimen toxicity scale.[17] After discharge, using a standardized form, J.M.P abstracted pertinent clinical data required to rate the regimen toxicity scale.[17] For each particular patient, rating of the post-admission risk factors (regimen toxicity, graft-versus-host-disease, and documented infection) was obtained from the same in-hospital follow-up period used to rate the post-admission psychiatric disorder cases. For a patient who received the last psychiatric assessment at day +14 and was discharged on day +20, the rating of the post-admission risk factors was obtained from the period between the start of the conditioning regimen and day +14.

2.3. Psychiatric assessment

Three interviewers participated in the study: two psychiatrists (J.M.P. and J.B.) and a 4th year psychiatric resident (J.A.). Psychiatric information from the patient interviews was complemented with information from the family and medical and nursing staff. Psychiatric diagnoses were assigned at a diagnosis meeting held every two months, at which a consensus diagnosis was reached on each patient. No interrater reliability assessment was carried out.

2.3.1. Current psychiatric status

A complete description of the psychiatric assessment has been published elsewhere.[7] Briefly, the psychiatric interview followed a structured format with psychiatric diagnoses being defined according to DSM-IV criteria. Our aim was to conduct a relatively short psychiatric interview focusing on depressive, anxiety, and adjustment disorders known to be common in cancer patients.[1–5] The alterations in some depressive symptoms such as anorexia, and fatigue as a direct result of the neoplastic process or cytotoxic treatment present a methodological problem for the diagnosis of depression in cancer patients.[2,3,9,18] In our study setting, in which intensive conditioning treatment is used, most of the patients present fatigue and anorexia. The DSM-IV requires a symptom to be counted toward the diagnosis of depression only if it is thought not to be due to cancer or its treatment, with a consequent risk for under diagnosis in the SCT setting. As in our previous report,[7] we used the model of the Sloan-Kettering Cancer Institution group to diagnose major depression. For research purposes, this method is the best of the four possible diagnostic models available, as it maximizes specificity.[18] It ensures the most homogeneous depressed group possible, with the fewest confounding variables, thereby increasing the clinical and statistical significance of the research data.[18] The Sloan-Kettering method eliminates anorexia and fatigue from the list of nine major depression criteria, and requires only four (instead of five) of the remaining seven symptoms for diagnosis.

2.3.2. Psychiatric rates by time of diagnosis and overall prevalence rates

Depending on the time of psychiatric diagnosis, we made a distinction between admission prevalence and post-admis-

sion incidence. Admission prevalence is the rate at which existing disorders are diagnosed at hospital admission (first interview). Post-admission incidence is the rate with which new disorders occur during in-hospital follow-up (from the second interview until discharge or death). Post-admission incidence rates were calculated for patients with no psychiatric disorder at the time of hospital admission. Overall prevalence is the rate at which existing disorders are diagnosed during the hospitalization period (from hospital admission until discharge or death).

2.4. Instruments

2.4.1. Functional status

The Karnofsky Performance Scale[16] 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.

2.4.2. Nottingham health profile

This self-administered questionnaire contains 38 statements belonging to six dimensions of health: physical mobility, energy, pain, sleep, social isolation, and emotional reactions. Higher scores indicate more health problems. The reliability and validity of this scale have been demonstrated elsewhere.[15] In our investigation we used the validated Spanish version.[19] We planned the pain and social subscales to be used as risk factors for depression and anxiety. Cronbach's alphas for those pain and social isolation subscales measured at hospital admission were 0.77 and 0.34, respectively. Since the internal consistency of the social subscale was unacceptably low it was discarded to be used in statistical analysis.

2.4.3. Regimen-related toxicity

The Bearman Toxicity Scale[17] is used to specifically rate the complications due to chemotherapy or chemoradiotherapy during hospitalization for SCT, with higher scores reflecting higher toxicity.

2.5. Other study variables

2.5.1. Smoking cessation

Smoking cessation was defined as reporting active smoking within one month of hospital admission, since the onset of depressive or anxiety symptoms can range from 2 days up to several weeks after the initial abstinence from smoking.[8,20]

2.5.2. Alcohol intake

According to the units of alcohol consumption per week (1 unit = 8 g of alcohol), patients were subdivided into three groups:[21] low risk, hazardous, and dangerous. In our study we compared dangerous intake versus other categories since dangerous consumption is more likely to be associated with mental problems.[21]

2.6. Statistical analysis

Because of the frequent coexistence of depressive and anxiety symptoms,[3,4,6,7] the tendency in the hospital SCT setting for adjustment disorders to develop into specific depressive or anxiety disorders,[7] and our aim to increase sample size in order to reduce the possibility of a type II error, we pooled the depressive, anxiety, and adjustment disorders into a composite psychiatric disorder variable. Each patient was placed in one of two groups, according to their diagnosis of depressive, anxiety, or adjustment disorder. If patients were not diagnosed with either, then they were categorized in the no psychiatric disorder group. If they were diagnosed with either of them, then they were categorized in the psychiatric disorder group. In order to better delineate the risk factors associated with depression or anxiety, patients meeting criteria only for corticosteroid-induced depressive disorder ($n = 1$) or corticosteroid-induced anxiety disorder ($n = 6$) were either excluded from the statistical analysis or included in the "no psychiatric disorder" group. As the same significant factors were found in all multivariate models using either method, in our presentation of the results the corticosteroid-induced disorders are included in the "no psychiatric disorder" group.

Univariate and multivariate logistic regression analysis was used to identify risk factors for psychiatric disorder. Admission and post-admission risk factors used to predict psychiatric disorder were chosen based on past work in the field and due to their clinical relevance.[1,2,4] Admission risk factors included age (continuous variable), sex (male versus female), marital status (married/cohabitating versus not married/not cohabitating), living alone (no versus yes), education (continuous), past psychiatric history (no versus yes), smoking cessation (no active smoker versus stop smoking), alcohol intake (low risk and hazardous versus dangerous), score for pain on the Nottingham Health Profile (0 versus >0), Karnofsky score (90–100 versus <90), disease risk status (low, intermediate, and high), type of SCT (autologous or syngeneic versus allogeneic), and conditioning regimen (chemotherapy only versus chemoradiotherapy). Post-admission risk factors included regimen-related toxicity score (continuous), graft-versus-host disease (grades 0–1 versus 2–4), and occurrence of documented infection (no versus yes). We dichotomized the pain and Karnofsky scores because their distributions were highly skewed.

The results of the logistic regression are reported as odds ratios (ORs) with 95% confidence interval (CIs). Variables having a P-value <0.20 in univariate logistic regression analysis were entered as candidate risk factors in multivariate logistic regression models. In multivariate logistic analysis, we used a backwards stepwise regression process using the likelihood ratio test. Patients with a missing value on any scale were omitted from statistical analyses. All reported P-values were two-tailed. P-values were considered significant if they were less than 0.05. For this exploratory study, no adjustment of the alpha level for multiple tests was made. Data were analyzed using SPSS version 11.5 software (SPSS Inc., Chicago, IL).

3. Results

A total of 1062 psychiatric interviews were performed from hospital admission to discharge or death. Rates of specific DSM-IV psychiatric disorders by time of diagnosis and overall prevalence rates for the total sample ($n = 220$) are presented in

Table 1 – Rates of DSM-IV psychiatric disorders

Psychiatric disorder	Rates by time of diagnosis		Overall prevalence rates (n = 220)
	Admission prevalence (n = 220)	Post-admission incidence (n = 174)	
Any depressive disorder	19 (9)	7 (4)	28 (13)
Major depression	18 (8)	7 (4)	27 (12)[a]
Dysthymia	2 (1)	0 (0)	2 (1)
Any anxiety disorder	7 (3)	1 (1)	10 (5)
Phobia	4 (2)	0 (0)	4 (2)
Generalized anxiety disorder	4 (2)	0 (0)	4 (2)
Panic disorder	0 (0)	1 (1)	3 (1)[b]
Any adjustment disorder	22 (10)	32 (18)	50 (23)
With depressed mood	6 (3)	8 (5)	16 (7)[c]
With anxiety	7 (3)[b]	10 (6)	15 (7)
With mixed anxiety and depressed mood	9 (4)[a,c]	14 (8)	19 (9)
Any psychiatric disorder	46 (21)	39 (22)	85 (39)

Percentages do not add up to 100% because five patients had more than one diagnosis. Values are expressed as number (percentage). Incidence rates were calculated for patients with no psychiatric disorder at admission. DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, 4th ed.

a Two patients with an admission adjustment disorder evolved into a major depression.

b Two patients with an admission adjustment disorder evolved into a panic disorder.

c Two patients changed in adjustment disorder subtype.

Table 1. At hospital admission, we found 46 out of 220 (21%) patients meeting criteria for any psychiatric disorder (including any depressive, anxiety, or adjustment disorder). During post-admission follow-up 39 out of 174 (22%) patients developed new disorders meeting criteria for any psychiatric disorder. Of these post-admission psychiatric disorders, 85% (34/40) were diagnosed in the first two weeks after hospital admission.

Three multivariate logistic models were carried out: one to predict admission psychiatric disorder and two to predict post-admission psychiatric disorder. Three multivariate logistic models were carried out: one to predict admission psychiatric disorder and two to predict post-admission psychiatric disorder. An admission psychiatric disorder model included as independent variables all admission risk factors. A baseline post-admission psychiatric disorder model included as independent variables all admission risk factors and a full post-admission model, evaluated the additional contribution of post-admission risk factors to the baseline model. In the admission model, all patients were used for statistical analysis, whereas patients with a psychiatric disorder at the time of hospital admission were not included in the post-admission models. Table 2 shows the univariate predictors of psychiatric disorder by time of diagnosis.

Multivariate predictors of admission and post-admission psychiatric disorder are displayed in Table 3. A past psychiatric history and lower functional status were significantly associated with admission psychiatric disorder. In the baseline model predicting post-admission psychiatric disorder, younger age, presence of pain, a past psychiatric history, and smoking cessation emerged as multivariate risk factors. In the full model, post-admission psychiatric disorder was significantly associated with presence of pain, a past psychiatric history, smoking cessation, and higher regimen-related toxicity, with younger age showing a close to significant association (P = 0.056).

4. Discussion

The current report yields several findings regarding risk factors for psychiatric disorder during hospitalization for SCT. Given the paucity of data concerning risk factors associated with psychiatric disorders in the SCT setting,[6] we compared our results with studies in the general cancer literature analysing multivariate risk factors for depression, anxiety, or a global psychiatric measure including both depression and anxiety.

In our study, presence of a past psychiatric history was associated with an admission psychiatric disorder and also predicted subsequent psychiatric disorders during post-admission follow-up. A past psychiatric history may indicate patient vulnerability to develop a psychiatric disorder when confronted with a stressful environment. Many studies in the cancer literature have consistently reported an association between a past psychiatric history and depression[11,22–26] or anxiety.[23,24]

Research has shown that mental health declines along with physical status.[1–5] In accordance with these data, we found that higher regimen-related toxicity, lower functional status, and pain were significantly associated with psychiatric morbidity. Mini-transplants use moderately high-dose chemotherapy, appearing to be a safer and less toxic alternative to conventional allogeneic SCT. With the use of mini-transplant nowadays, we would expect a lower incidence of post-admission psychiatric morbidity. Studies should be performed to determine more precisely the psychiatric impact of this new transplant technique. Several cancer studies have reported a significant association between lower functional

Table 2 – Univariate predictors of psychiatric disorder by time of diagnosis

	Total sample (n = 220)	No psychiatric disorder (n = 135)	Psychiatric disorder			
			Admission cases (n = 46)	Admission models (n = 220)	Post-admission cases (n = 39)	Post-admission models (n = 174)
	Value	Value	Value	OR (95% CI)	Value	OR (95% CI)
Admission risk factors						
Age, years	38.0 (16–65)	40.0	39.5	1.00 (0.97–1.02)	36.0	0.98 (0.95–1.01)*
Female	91 (41)	37	39	0.89 (0.46–1.73)	59	2.44 (1.18–5.06)**
Not married	79 (36)	35	37	1.06 (0.54–2.08)	39	1.17 (0.56–2.44)
Living alone	9 (4)	4	7	1.95 (0.47–8.13)	3	0.68 (0.08–6.04)
Education, years	11.0 (4–22)	11.0	10.0	0.96 (0.89–1.04)	11.0	0.96 (0.88–1.05)
Past psychiatric history	84 (38)	26	67	4.71 (2.35–9.46)***	46	2.45 (1.17–5.12)**
Smoking cessation	41 (19)	15	24	1.51 (0.69–3.30)	26	1.98 (0.84–4.69)*
Dangerous alcohol intake	14 (6)	7	7	1.03 (0.28–3.87)	3	0.33 (0.04–2.65)
Pain score > 0	71 (34)	27	48	2.09 (1.05–4.15)**	42	1.97 (0.93–4.19)*
Karnofsky score < 90	34 (15)	11	28	2.87 (1.31–6.31)***	15	1.46 (0.52–4.04)
Disease risk status						
Intermediate risk	33 (15)	15	17	1.51 (0.57–4.00)	13	1.02 (0.33–3.19)
High risk	101 (46)	43	50	1.40 (0.68–2.88)	51	1.40 (0.65–3.05)
Allogeneic SCT	91 (41)	40	39	0.89 (0.46–1.73)	49	1.43 (0.70–2.92)
Chemoradiotherapy	156 (71)	69	74	1.21 (0.58–2.52)	74	1.31 (0.59–2.93)
Post-admission risk factors						
Regimen toxicity score	3.0 (0–10)	2.0			3.0	1.35 (1.12–1.64)***
GVHD, grades 2–4	10 (5)	3			13	4.82 (1.23–18.91)**
Documented infection	75 (34)	30			33	1.19 (0.56–2.54)

For the total sample column, values are reported as number (%) except for age, education, and regimen toxicity that are expressed as median (range). In all other columns values are expressed as % or median. Missing data: pain score, n = 10. GVHD, graft-versus-host disease; OR, odds ratio; 95% CI, 95% confidence interval. Levels of significance: *P < 0.20, **P < 0.05, ***P < 0.01.

Table 3 – Multivariate predictors of psychiatric disorder by time of diagnosis

	Admission psychiatric disorder model[a]		Post-admission psychiatric disorder			
			Baseline model[b]		Full model[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Admission risk factors						
Age	–	–	0.97 (0.94–1.00)	0.049		0.056
Female	–	–	2.50 (1.13–5.52)	0.024	2.41 (1.07–5.47)	0.035
Past psychiatric history	6.21 (2.87–13.43)	<0.001	2.34 (1.05–5.23)	0.039	2.49 (1.09-5.72)	0.031
Smoking cessation	–	–	2.57 (1.01–6.56)	0.048	2.95 (1.12–7.76)	0.029
Pain score > 0		0.12	2.33 (1.03–5.26)	0.042	2.33 (1.01–5.38)	0.049
Karnofsky score < 90	3.07 (1.23–7.67)	0.016	–	–	–	–
Post-admission risk factors						
Regimen-related toxicity	–	–	–	–	1.36 (1.11–1.67)	0.003
GVHD, grades 2–4	–	–	–	–		0.48

Variables with a P value <0.20 in univariate analysis (Table 2) were included in multivariate regression models. An admission psychiatric disorder model included admission risk factors as independent variables. A baseline post-admission psychiatric disorder model included admission risk factors as independent variables and a full model evaluated the additional contribution of post-admission risk factors to the baseline model. Due to missing data on the pain score: 10 patients were missing on the admission model and 6 patients on each of the post-admission models. GVHD, graft-versus-host disease; OR, odds ratio; 95% CI, 95% confidence interval.

a n = 210. Summary statistics: model χ^2 = 29.09, P < 0.001; goodness of fit, P = 0.87.

b n = 168. Summary statistics: model χ^2 = 19.40, P = 0.002; goodness of fit, P = 0.69.

c n = 168. Summary statistics: model χ^2 = 28.58, P < 0.001; goodness of fit, P = 0.51.

status and depression,[23–25] anxiety,[25] or an overall psychiatric disorder variable including major depression and adjustment disorders.[27] A substantial body of research suggests a relationship between pain and depression and/or anxiety, but the cause-and-effect nature of the association remains unclear.[4,5,11,26] Although our results provide support for the

prognostic importance of pain, they do not establish that pain causes psychiatric morbidity. To establish a causal relationship, we need longitudinal research combining repeated measurement of psychiatric disorders and its presumed pathophysiological mechanisms, followed by adequately powered, randomized trials targeting the implicated mechanisms. Our finding of a significant association between pain and psychiatric morbidity suggests the potential importance of the physician's role in reducing depression and/or anxiety through pain management, because pain is a factor that physicians can impact.

Another noteworthy finding in this study was that smoking cessation at the time of hospital admission was significantly predictive of a psychiatric disorder occurring during post-admission follow-up, even after adjusting for potential in-hospital confounding variables. The combination of case reports of cessation-associated severe depressions that can often be reversed by smoking, the need for sustained antidepressant treatment in some abstinent smokers, and the disproportionate development of depressive and anxiety symptoms during withdrawal among some smokers[8,20] reinforces the observation that cancer patients who smoke are at risk for psychiatric morbidity when they enter a medical care setting in which smoking restrictions are applied. Smoking cessation services early in the disease process may have a role in promoting physical and psychological health.

In line with our data, several oncological investigations have reported a significant association between female sex and anxiety[9,24,28] or depression.[28] Our data also corresponded with the large epidemiological studies linking female gender and higher rates of psychiatric morbidity.[29,30] Our finding of a significant association between younger age and depression and/or anxiety, is consistent with the results of previous cancer studies.[11,22,25,31] In younger patients compared to their older counterparts, anticancer treatment can lead to infertility, the entire disease and treatment process can represent a much greater loss of their role in the family, occupational and social activity, which overall may have a negative effect on their emotional status.

This study has several limitations. First, we only focused on a limited range of psychiatric conditions known to be common in cancer patients, [1–6] so as not to impose an undue burden on our patients. Second, although we did not measure interrater reliability, we sought to maximize the reliability of our psychiatric diagnoses by using standardized diagnostic criteria, serial observations, multiple sources of information, and discussion in regular meetings between investigators. Third, the use of only one data abstractor to rate the regimen-related toxicity scale represents another design limitation. However, strict guidelines were followed to rate the Bearman Toxicity Scale and clear definitions of in-hospital complications were applied. Fourth, due to the low Cronbach's alpha for the social isolation subscale we could not study the effect of perceived social support. Further research is needed on more sensitive social support measures to explore their role in predicting depression or anxiety. Finally, there are threats to generalizability in a study from a single institution. However, the findings of this study are strengthened by high recruitment rates, large population, and a comprehensive set of clinical risk variables considered for risk adjustment. Moreover, the use of a rigorous diagnostic method (structured psychiatric interview applying standardized diagnostic criteria) coupled with serial psychiatric evaluations during hospitalization for SCT (1062 psychiatric assessments were performed throughout the transplant process) may give a more accurate reflection of the psychiatric morbidity.

The risk factors examined in the current paper are mostly non-modifiable, a fact that limits the possibility of introducing successful prevention strategies. However, our study findings have clinical implications for physicians seeking to improve identification of patients most at risk for psychiatric disturbances during hospitalization for SCT. Because of our relatively high prevalence of psychiatric morbidity at hospital admission, it would be better to conduct first a comprehensive assessment after the patient agrees to undergo SCT, complemented by brief interviews during hospitalization for SCT. Although it remains to be determined whether early recognition and effective treatment of emotional deficits during the hospitalization period will result in better transplant outcomes, it has the potential to improve medical practice, reduce patient suffering, and enhance quality of life.[2,4,5,7,9–13]

Conflict of interest statement

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

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