Original Article

Short-Term Impact of Hematopoietic Stem Cell Transplantation on Psychiatric Morbidity and Quality of Life in Hematological Malignancies in Adults

Deeksha Elwadhi, S. K. Khandelwal[1], Lalit Kumar[2], Atul Sharma[2]

ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) is an established treatment for a number of malignancies. Quality of life (QOL) is an important marker for assessing arduous treatment modalities. Diagnosis of cancer, HSCT, and the physical and psychosocial sequelae of the intensive treatment lead to a deficit in the QOL of the recipient. This study aimed to assess the impact of HSCT on psychiatric morbidity and QOL in patients with hematological malignancies. **Methods:** A longitudinal pre-post study was conducted at a cancer research center. Thirty patients with hematological malignancies were assessed at three different time points for psychiatric symptoms and QOL. Sociodemographic and clinical variables were collected using a semi-structured questionnaire. Comprehensive psychopathological rating scale was used to assess the psychiatric symptoms. WHO QOL Bref and cancer-specific European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC-QLQ) were used to measure the quality of life. **Results:** The mean (SD) age of the sample was 42.3 (12.8) years, with 24 males and 6 females. Most patients reported anxiety and depressive symptoms, reaching a peak at 3 week post-HSCT. The maximum deficit in QOL scores was seen at 3 weeks, with further improvement at 3-month post-transplant. **Conclusions:** HSCT leads to an increase in symptoms and a decrease in QOL during the acute phase. In the long run, it leads to improvement in physical and psychological wellbeing, with improvement in QOL. The recent surge in the long-term survivors of the procedure calls for further research in this direction so as to aid in their full recovery.

Key words: *Hematological malignancies, Hematopoietic stem cell transplantation, psychiatric morbidity, quality of life*

Key messages:

- *Hematopoietic stem cell transplantation is an arduous but life-saving procedure*
- *Acute hospitalization is the period of maximum physical and psychological dysfunction*
- *Overall, it leads to a decrease in symptoms and improvement in quality of life.*

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Department of Health Research, [1]Department of Psychiatry, Holy Family Hospital, [2]Department of Medical Oncology, AIIMS, New Delhi, India

Address for correspondence: Dr. Deeksha Elwadhi
India Red Cross Society Building, 1 Red Cross Road, New Delhi - 110 001, India. E-mail: elwadhideeksha@gmail.com

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Hematopoietic stem cell transplantation (HSCT) is an established treatment modality for a number of hematological malignancies, such as chronic myeloid leukaemia, acute myeloblastic leukaemia, and multiple myeloma. Hematopoietic progenitor cells emerging from bone marrow, peripheral blood, or umbilical cord are injected intravenously to re-establish hematopoiesis in patients with defective bone marrow. High rates of physical complications have been reported with HSCT, the most common being opportunistic infections and graft-versus-host disease.[1] In addition, studies have shown that HSCT may be associated with significantly elevated rates of depression, anxiety, and cognitive difficulties.[2-4] A prospective study of 220 transplant recipients showed a total prevalence of psychiatric disorders to be 44.1%.[5] The complications of this procedure are likely to affect the Quality of Life (QOL) of the cancer survivors, among whom such issues are already of great concern because of the severity of the illness.[6]

World Health Organization (WHO) defines QOL as an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards, and concerns.[7] Prospective studies assessing QOL in HSCT patients showed physical functioning to be the most severely affected domain.[8-10] The majority of the studies have reported improved QOL 1-year post-HSCT.[11,12]

There is a dearth of data from low-income countries regarding psychiatric morbidities and QOL in hematological malignancies, and none in patients receiving HSCT.[13,14] The few studies regarding the prevalence of psychiatric disorders and QOL in malignancies pertain to either pediatric age group[15] or solid tumors like cancers of breast, cervix, and head and neck.[16,17]

This study aimed to assess the impact of HSCT on psychiatric morbidity and QOL in patients with hematological malignancies and to determine any correlation between the presence of psychiatric morbidity and the QOL.

MATERIALS AND METHODS

The study had a pre-post design, and the participants were assessed at three time points. Baseline interview was conducted one week prior to the HSCT, followed by assessments at three weeks and three months after the HSCT. All inpatients admitted for their first HSCT in the bone marrow transplant ward of the hospital were contacted 1 week prior to the procedure. They were provided with a brief description of the purpose of the study. Informed written consent was taken from those who expressed willingness to participate.

A convenience sample of 30 adult subjects admitted for HSCT, of either gender, who could understand the local language (Hindi) were recruited. Patients who were unwilling to take part in the study, were unable to understand the test questions, or had concurrent substance use disorder other than nicotine dependence were excluded from the study. Patients whose clinical condition made them unfit to sit through the interview, due to extreme pain or weakness, and those who had severe side effects from induction treatment regime were also excluded.

All participants were allowed to ask questions throughout the study and were free to withdraw at any point in time. Participant anonymity and confidentiality were guaranteed. Ethical clearance was taken from the Institute Ethics Committee.

A semi-structured proforma was used to collect the sociodemographic details and cancer-related clinically relevant information. Cognitive impairment was screened using the Hindi Mental State Examination (HMSE).[18] The HMSE is an Indian adaptation of the Mini Mental State Examination (MMSE), developed for the Hindi speaking population, and has a maximum score of 30. HMSE was preferred over MMSE, keeping in mind the relevant context of the study population. It is a highly sensitive (94%) and specific (98%) instrument to detect cognitive impairment, especially in the Indian populace,[19] and is freely available in the public domain for use in research. HMSE was used as a screening tool to exclude any cognitive deficits that could hamper further interviewing.

Comprehensive Psychopathological Rating Scale (CPRS)[20] was used to assess the psychiatric morbidity. It has 65 items, covers a wide range of psychiatric symptoms (depression, schizophrenia, obsessive compulsive disorder, and mental distress in connection with severe physical illness) and has high inter-rater reliability.[21] In addition to the full scale, two of its subscales – Brief Scale for Anxiety[22] and Montgomery Asberg Depression Rating Scale[23] – were also used, to assess anxiety and depression, respectively. Both these scales have a high degree of concordance.[24] The CPRS assesses symptoms and observed behavior and does not provide categorical diagnoses.[20]

QOL was assessed using two instruments. The first was the generic World Health Organization Quality of Life Questionnaire (WHOQOL- BREF) Hindi Version[7] – a 26-item, internationally applicable, cross-culturally comparable, multilingual, and multidimensional

instrument to measure QOL. In the study, four broad domains of QOL were assessed: physical health, psychological health, social relationship, and environment.

The second assessment instrument was the Hindi version of EORTC-QLQ (European Organization for Research in Treatment of Cancer Quality of Life Questionnaire) C30-version 3.0,[25] which is an integrated system for assessing the health-related QOL specifically of cancer patients. The QLQ C30-version 3.0 has five functional scales, three symptom scales, a global health status/QOL scale, and six single items. The total score in each domain ranges from 0 to100. Translations are available in 43 languages including Hindi. It is freely downloadable for research purposes. The two instruments were used to capture the cancer-specific effects on QOL in addition to the overall QOL.

The analysis was done using SPSS 20.0. Descriptive analysis of sociodemographic variables and outcome variables (scores in HMSE, CPRS, WHOQOL-BREF, and EORTC) was done. A comparison of the change in the mean scores of the variables over the three assessment points was done using repeat measure analysis of variance (ANOVA). The within-subject differences were taken into consideration, and in case Mauchly's test of Sphericity indicated that the assumption of sphericity has been violated, Greenhouse-Geisser correction was used to report the effect size. Correlation between the sociodemographic parameters and the outcome variables was assessed using Pearson's product–moment correlation analysis.

Table 1: Sociodemographic and clinical variables

Variables	Mean (SD) or frequency (%)
Age (years)	42.3 (12.8)
Gender	
Male	24 (80%)
Female	6 (20%)
Education	
Primary	7 (23.3%)
Middle	3 (10%)
High school	10 (33.3%)
Graduate	6 (20%)
Post graduate	4 (13.3%)
Occupation	
Professional	3 (10%)
Skilled worker	10 (33.3%)
Unskilled worker	4 (13.3%)
Student	5 (16.7%)
Homemaker	2 (6.7%)
Unemployed	6 (20%)
Marital status	
Married	8 (26.7%)
Unmarried	22 (73.3%)
Diagnosis	
Multiple myeloma	21 (70%)
Hodgkin's lymphoma	4 (13.3%)
Non-Hodgkin's lymphoma	2 (6.7%)
Acute Myelogenous lymphoma	3 (10%)
Duration of the Disease (years)	1.967 (1.07)
Type of HSCT	
Autologous	23 (76.7%)
Allogeneic	7 (23.3%)
Past-treatment received	
Chemotherapy	30 (100%)
Radiotherapy	12 (40%)
HSCT	0
Immunotherapy	0
Comorbidities	
Medical*	4 (13.3%)
Psychiatric†	1 (3.3%)

*Three had hypertension, whereas one had diabetes, †Adjustment disorder (6 months prior to the study); HSCT – Hematopoietic stem cell transplantation

RESULTS

Sociodemographic and clinical characteristics

The mean (SD) age was 42.3 years, and 24 (80%) were male. Multiple myeloma was the most common diagnosis (n = 21; 70%). Hodgkin's (4), non-Hodgkin (2), and AML (3) constituted the remaining 30%. Mean duration from the initial diagnosis to the first assessment point was around 2 years (6 months to 6 years). Twenty-three patients received autologous HSCT, while seven received allogeneic transplant with donor being HLA matched siblings. One patient was diagnosed with adjustment disorder 6 months prior to inclusion in the study and was not receiving any psychiatric treatment at the time of assessment.

The rest of the parameters are given in Table 1.

Psychiatric morbidity

The mean HMSE scores at all the three assessment points were within the normal range, indicating no cognitive deficits in the study population. The maximum mean HMSE score was at 3-month post-transplant, whereas the minimum was at 3 weeks post-transplant. The difference in means of the HMSE scores over three assessment points using repeat measure ANOVA [$F = 23.65$ $\eta^2 = 0.449$; $P < 0.001$], as shown in Table 2, was statistically significant. However, no clinical relevance can be inferred as none of the scores, at any of the assessment points, were below the threshold for cognitive deficits.

The mean total CPRS score was highest at three weeks post-transplant and lowest at three months post-transplant. Mean scores for anxiety and depression subscales showed a similar pattern.

At baseline, 19 patients (63%) had scores indicating mild depression. The most commonly reported CPRS items were inner tension, lassitude, and fatigability,

Table 2: RM ANOVA statistics of serial comparisons over three assessment points

Scale	Pre-transplant, mean scores (SD)	Three-week post-transplant, Mean scores (SD)	Three-month post-transplant, Mean scores (SD)	*F**	Effect size**	*P*
HMSE	30.37 (0.76)	29.70 (0.96)	30.83 (0.38)	23.65	0.449	<0.001
CPRS						
CPRS Total score	11.617 (4.5)	14.03 (5.33)	8.383 (4.19)	23.06	0.443	<0.001
Anxiety subscale	4.30 (2)	5.167 (2.52)	2.517 (1.63)	19.47	0.402	<0.001
Depression subscale	8.950 (4.44)	10.217 (4.64)	4.717 (3.27)	31.25	0.519	<0.001
WHOQOL-BREF						
Total	47.91 (6.14)	46.06 (5.2)	49.43 (4.22)	19.77	0.405	<0.001
Physical	44.978 (10.65)	36.232 (8.46)	47.716 (7.82)	24.42	0.457	<0.001
Psychological	49.391 (13.61)	48.275 (12.31)	50.801 (9.07)	1.68	0.055	0.19
Social relationship	52.081 (16.04)	51.807 (14.6)	59.033 (13.23)	12.77	0.306	<0.001
Environmental	53.02 (11.62)	51.562 (10.85)	51.562 (12.33)	5.89	0.169	0.005
EORTC						
Total	60 (13.2)	57.498 (13.02)	71.388 (12.32)	12.26	0.297	<0.001
Physical functioning	61.111 (15.96)	50.215 (14.52)	66.222 (14.54)	13.69	0.321	<0.001
Role functioning	69.445 (20.57)	50.556 (19.32)	60.556 (14.83)	12.51	0.301	<0.001
Emotional functioning	60 (15.7)	54.445 (15.43)	63.611 (12.85)	6.34	0.179	0.003
Cognitive functioning	80 (16)	67 (13.84)	75 (15.63)	9.62	0.249	<0.001
Social functioning	69.442 (27.36)	50 (29.03)	70 (26.41)	9.83	0.253	0.001

HMSE=Hindi mental state examination; CPRS=Comprehensive psychopathological rating scale, WHOQOL- Bref=World Health Organisation Quality of Life questionnaire - Bref; EORTC=European Organization for Research in Treatment of Cancer Quality of Life Questionnaire, *Degrees of freedom (within groups) = 29, **In case Mauchly's test for spherical assumption ruled no sphericity assumed, Greenhouse Geisser correction used

with no reports of sadness of mood. At three weeks post-transplant, 22 patients (73%) had scores suggestive of mild depression, and one had moderate depression. At 3 months post-transplant, six patients (20%) met the cut-off for mild depression. Difficulty in concentration was the most reported symptom at the latter two assessments. None of the subjects reported psychotic symptoms or suicidal ideations. ANOVA for mean total CPRS scores showed significant difference at the three time points [$F = 23.06\ (1, 29)$; η^2=0.443; $P < 0.001$].

Quality of life

The maximum deficit in all the four domains of WHOQOL Bref was seen at 3 weeks, with improvement at 3-month post-transplant. The highest scores out of the four domains at all the time points were seen in the social relationship, and the lowest scores, in physical functioning.

Overall QOL showed a statistically significant rise at 3-week and 3-month post-transplant as compared to the baseline. In separate scales (physical, role, cognitive, and social functioning), a statistically significant fall at 3 weeks and an increase at 3-month post-transplant were noted. In the emotional functioning scale, the fall from 3-week to 3-month post-transplant was statistically significant. Similar pattern was found in both WHOQOL Bref and EORTC QLQ.

In the EORTC symptom scales, fatigue, nausea and vomiting, pain and dyspnea, sleep difficulties, appetite difficulties, and constipation were maximum at 3-week post-transplant and showed a significant fall at 3-month post-transplant. Financial problems showed a rising curve with the passage of time. Overall, 3-week period appears to be the period of maximum symptoms, with significant improvement at 3-month post-transplant.

Correlation analysis

A correlation analysis was done to explore the direction and strength of the linear association within the same outcome variables at different time points and also between the different outcome variables. It was assumed that the *P* value achieved 'statistical significance' at $P < 0.01$ considering multiple measurements. The CPRS score at baseline was positively correlated with scores at 3 weeks ($r = 0.47$, $P = 0.008$) and negatively correlated with the role functioning domain of EORTC QLQ at baseline ($r = -0.50$, $P = 0.005$). The CPRS score at 3 weeks had a strong positive correlation with CPRS total score at 3-month post-transplant ($r = 0.73$, $P < 0.001$). The HMSE score at baseline and at 3-week post-transplant did not show any statistically significant correlation with each other. However, the HMSE scores at three months post-transplant were positively correlated with the EORTC global health domain at three months. The WHOQOL Bref mean scores at baseline were positively correlated with the scores at 3-week and 3-month post-transplant. Also, they were correlated with the EORTC global health domain and role function subdomain at pre-transplant. Further, WHOQOL Bref scores at three weeks post-transplant were significantly correlated with the mean scores at the three months post-transplant ($r = 0.87$; $n < 0.001$)

indicating that an earlier improvement heralds a later improvement in QOL. A statistically significant positive correlation was seen between various subdomains of EORTC QLQ at various assessment points, as shown in the supplementary file.

An important point of note was the statistically significant negative correlation seen between a particular combination of WHOQOL Bref and EORTC QLQ, that is, WHOQOL Bref scores at 3 weeks and EORTC global health domain at 3 months, even though intuitively one may expect a positive correlation between these two.

DISCUSSION

This study assessed the impact of HSCT on psychiatric morbidity and QOL in hematological malignancies in a pre-post design. It is the first of its kind in an Indian setting.

No mortality was reported in our small sample during the follow-up period of 3 months. The majority (23, 76.7%) were recipients of autologous HSCT, which is not associated with graft versus host disease a nd has lower mortality rates.

None of the study participants had any cognitive deficits at any assessment point. Some studies have shown that the deficits in cognition do occur in HSCT recipients as a long-term sequelae.[26] This could not be commented upon in our study, as we followed up patients only for 3 months.

CPRS has been used in many studies to assess the impact of various interventions on psychiatric symptoms and offers the advantage of objective assessment like "observation of sad mood." In our study, 63% of the subjects were rated to have mild baseline depression on CPRS, which increased to 73% at 3 weeks. These rates are higher than the prevalence found in other studies, which were in the range of 20%–40%.[2,27,28] The higher rates could be due to the differences in the patient population, treatment protocols and the instrument used, as none of the previous studies had used CPRS. Interestingly, none of our subjects reported sadness of mood, and observed sadness was present in only one patient at 3-week assessment. The vegetative symptoms such as sleep and appetite disturbances may have led to higher scores on CPRS in these patients.

The trajectories for the total scores, as well as the depression and anxiety subscales of CPRS, were similar. All three showed maximum scores during hospitalization, with a decrease thereafter, as found in previous studies.[29-31] Patients recover from the acute effects of HSCT in 4–6 weeks. Post-transplant patients are isolated (usually for the first two weeks) to prevent opportunistic infections, which may give them less chance for allaying their fears and anxieties regarding the outcome. Once the acute period is over, patients are discharged and nursed in more comfortable and less stringent settings at home, and the pain and dysfunction caused by malignancy also improve, which aids in the decrement of the scores. Some previous studies have also shown improvement in psychiatric outcomes with the passage of time after the procedure.[9,32]

Two instruments were used to assess the QOL. WHO QOL Bref assessed the generic overall QOL, whereas EORTC was used to measure cancer-specific QOL, bringing the effect of malignancy and side effects of treatment in its fold. QOL is an important parameter to be assessed, especially in cases with a terminal diagnosis and in arduous procedures such as HSCT, to judge the overall effect of the treatment.

The mean overall QOL score in both the scales decreased from baseline to reach a nadir at three weeks post-transplant, with a significant increase at three months post-transplant. Physical functioning was the most affected domain and psychological/emotional functioning, the least. In previous studies too, the physical functioning had declined rapidly immediately after transplantation, reaching its lowest at 30 days.[33,34] Wettergren *et al*.[12] found physical functioning at 8- to 12-month post-transplantation to be as good as prior to the procedure. In our study, social relationships improved with time, which was also seen in one of the first prospective studies.[10] Mc Quellon *et al*.[9] showed a parabolic curve in QOL, which was also seen in the physical and social relationship domains of our sample. Chang *et al*.[2] showed a linear improvement in the QOL at six- and twelve-months post-transplant. A linear trend was seen in the environmental domain, but it was a worsening than an improvement; satisfaction with the environment decreased over time. Return to the home increases the interaction and functioning of the individual but adds to the difficulties in going back for tertiary care.

Role functioning was maximum before HSCT, with a significant decrease at 3 weeks after it ($P < 0.001$), corresponding to the period of acute side effects. The poor role fulfillment may be a result of various factors such as the patient's poor physical health, over-involvement from the family leading to role reversal, precautions as advised by the oncologist, apprehensions regarding the long-term success, and reluctance to join back normal functioning after a long break due to the malignancy and its treatment.

Emotional functioning also was seen to improve with the passage of time. HSCT exerts a toll on the recipients early in the process. Emotional functioning for survivors is most compromised before transplantation and immediately after the procedure.[9,33] As in our study, significant improvement was seen in a previous study as early as at hospital discharge to 100-day post-HSCT,[35] with stabilization over time.[36]

All symptom scale items showed maximum dysfunction at 3-week post-transplant. The financial problem showed a linear increase until three months post-transplant. With limited role function and continuing medical care costs, the financial situation worsens in these patients. The worsening financial situation can be a major impeding factor in overall QOL. The increased financial burden can also lead to the advent of anxiety and depressive symptoms in the patients. Both prospective and cross-sectional studies have shown greater financial difficulties at varied time points ranging from 1- to 7-year post-transplant.[8,37]

A negative correlation was found between the mean duration of disease before the assessment and CPRS scores at baseline (−0.44). It can be inferred that longer the duration of the malignancy, the psychiatric symptoms decrease, as the patient accepts the diagnosis and the prognosis. Due to acceptance, the patient's anxiety and concerns start falling, which leads to better coping. However, in a study by Rodrigue *et al*.,[38] significant positive association was found between disease duration and depression.

A correlation between the CPRS score at baseline and the scores at 3-week and 3-month post-transplant can indicate that patients with better coping skills and good functioning at baseline might tolerate the effects of the procedure better as compared to the others. This calls for liaison between psychiatry and oncology, as a baseline assessment and intervention early in the course could lead to a better overall outcome. Frequent contact with a trained therapist can ensure good psychological recovery and better QOL.

A negative correlation was found between the CPRS scores at baseline and the EORTC role functioning subdomain scores at baseline (−0.50). Higher scores, signifying more psychiatric symptoms, lead to a higher toll on the QOL of the individual and a restriction in the fulfillment of roles, which can explain the negative correlation.

We may not be able to tender a concrete response as to how a statistically significant negative correlation between WHOQOL Bref scores at 3 weeks and EORTC global health domain at three months was seen, but we suppose that the small sample size of our study might have contributed to this, which is a major limitation of our study. In addition, it might be that the focus of WHO QOL Bref is to evaluate the overall generic QOL, whereas EORTC QLQ specifically focuses on cancer-specific domains.

Even though the biological correlates of psychiatric morbidity in HSCT have not been adequately described, a few possible mechanisms can be inferred. First, in many conditions of chronic stress, an imbalance in the hypothalamic-pituitary-adrenal axis underlies the development of psychiatric symptoms, which could also lead to such a development in malignancies.[39] HSCT itself is quite a tenuous procedure and can lead to significant stress to the body. Second, the chemotherapy regimen for immunosuppression prior to the procedure might lead to changes in the immune system, which might lead to the development of psychiatric symptoms.[40] All the more, isolation periods essential in the prevention of infections post-HSCT might lead to under-stimulation and can lead to cognitive deficits or development of psychiatric symptoms, in a similar way to the development of ICU psychosis.

The longitudinal assessment, with a baseline measure pre-transplant, is the major strength of this study. Assessment time points represented different landmarks for the transplant recipients – admission, discharge, and follow-up. Validated instruments were used for the assessment of outcome variables, and no attrition was reported in the above sample.

Small sample size, the fact that the group was heterogeneous in terms of type and diagnosis, and a short follow-up period are the limitations of this study. In addition, neuropsychological assessment could not be done in this study, due to time constraints. Even though a single-arm pre-post study design is a well-accepted methodology, the study could have been made more robust by including a control group. As it was an exploratory study, further research can take that into consideration.

This study infers that HSCT leads to an increase in psychological symptoms and a decrease in various domains of QOL during the acute phase, with significant improvement in the long run.

With the advancement in technology, newer procedures have forayed into the medical practice. It has become increasingly important to assess the impact of these procedures, not only on the underlying disease but also on the other important aspects of the patient's life. It is prudent to assess whether these procedures unintentionally increase morbidity in the race to

decrease it. Studies with a larger, homogeneous sample should be followed up for a longer period to corroborate the above findings further. Descriptive studies addressing the main concerns of the patient and finding the locus of distress should be undertaken for designing targeted psychological interventions.

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Conflicts of interest
There are no conflicts of interest.

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