

# The Relationship Between Anxiety and Adverse Events During Hematopoietic Stem Cell Transplantation in Cancer Patients: A Cross-Sectional Study

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## ABSTRACT

### Objective

Anxiety, negatively affects the response to transplantation and the recovery process after transplantation. Anxiety prevalence is high pre and post transplantation but no information is known about during transplantation. This study was conducted to determine anxiety and adverse events during hematopoietic stem cell transplantation (HSCT) and to explain the association between these two conditions.

### Methods

The sample consisted of 93 patients with cancer who received hematopoietic stem cell transplantation at the Bone Marrow Transplant Centre in Türkiye. The data were collected using a patient information form and the State Anxiety Inventory (STAI-S). Significance between the descriptive characteristics of the participants and the scale was calculated using a one-way ANOVA and Student-T test. Logistic regression analysis was performed to determine the effect of adverse events on the level of anxiety.

### Results

We found that there was a significant difference between the variables of age ( $F = 2.497$ ,  $p = 0.020$ ), gender, years after diagnosis ( $F = 1.381$ ,  $p = 0.035$ ), the state of believing that transplant will be successful and previous transplant history, and the STAI-S mean score. The Nagelkerke  $R^2$  value of the model was 0.167. The goodness of fit of the model was assessed using Hosmer and Lemeshow's test ( $X^2 = 8.900$ ,  $p = 0.203$ ). When analyzing the adverse events during HSCT that affected the occurrence of anxiety, we found that nausea and vomiting increased the anxiety score by 6.1-fold ( $\beta: 0.613$ ,  $p = 0.010$ ), abdominal pain by 4.4-fold ( $\beta: 0.449$ ,  $p = 0.030$ ), and tachycardia by 2.6-fold ( $\beta: 0.267$ ,  $p = 0.020$ ).

### Conclusions

The results of this study showed that patients experienced nausea and vomiting, hypertension and abdominal pain during stem cell transplantation, respectively; anxiety level was above the moderate level; nausea and vomiting, abdominal pain and palpitations increased anxiety. Preventing anxiety during stem cell transplant can reduce adverse effects depend on HSCT.

### Keywords

Hematopoietic Stem Cell Transplant; Anxiety; Adverse Events; Nursing

## INTRODUCTION:

Hematopoietic stem cells (HSC) are cells found in bone marrow, peripheral blood, and umbilical cord that can turn into blood and immune system cells<sup>1</sup>. These cells can be transplanted into patients in need to produce healthy cells instead of cells that have lost their function and pose a threat. This procedure, known in the literature as hematopoietic stem cell transplantation (HSCT), stands as a significant treatment choice that has achieved considerable success in recent times. It has been particularly effective in treating blood-related or organ-specific cancers, along with diverse non-cancerous conditions<sup>1,2</sup>.

Hematopoietic stem cell transplantation requires a high degree of tissue compatibility between donor and recipient. The higher the compatibility, the greater the success after transplantation. Bone marrow, peripheral

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stem cells and umbilical cord blood are the sources used for stem cell transplantation. These sources are obtained autologously or allogeneically. Autologous transplantation involves the reinfusion of stem cells obtained from the individual's own bone marrow or blood through specialized techniques. Allogeneic transplants are transplants in which compatibility with the human leukocyte antigen (HLA) is sought<sup>1,2</sup>. With this type of transplant, stem cells from a donor whose tissue type is very similar to the patient's are transplanted into the patient to establish compatibility. For this reason, the donor is usually a member of the family, usually a sibling. However, if a suitable donor is not found among the siblings, screening is extended to the general population. There are thousands of possible combinations of different HLA tissue types. Therefore, it may take months or years to find a matching HLA type.

Patients who go through a very difficult process and have the option of transplantation may face many physical and psychological complications before, during, and after transplantation<sup>3-6</sup>. Anxiety is a condition that has a psychological origin but whose effects can also be seen physiologically and is common in patients undergoing stem cell transplantation<sup>7-10</sup>. It has been reported that uncertainty about the treatment process, the possibility of graft rejection, mandatory isolation before and after transplantation, etc. cause anxiety<sup>11</sup>. This situation, which seems to be inevitable in stem cell transplantation, negatively affects the response to transplantation and the recovery process after transplantation, prolongs the length of hospitalization, and increases the number of hospitalizations after transplantation<sup>12-14</sup>. The literature generally includes studies examining anxiety before and after transplantation in stem cell transplant patients. However, no study was found that investigated the association between anxiety during transplantation and adverse events (AEs). Therefore, the aim of our study is to identify anxiety and AEs during HSCT and to explain the association between these two conditions. We anticipate that data obtained from this study will contribute to the planning of care interventions that can be applied to patients during transplantation.

## MATERIALS AND METHOD:

### Study design and participants

This single-centre, cross-sectional study was completed

at the Faculty of Medicine of İnönü University, in Malatya, Türkiye, within Bone Marrow Transplant Centre. Data were collected between May 01, 2021 and May 01, 2022. The study population consisted of 123 patients who had registered for HSCT (peripheral blood) at the bone marrow transplant centre. Twenty-two patients did not meet the inclusion criteria, and eight patients refused to participate in the study and were excluded in the sample. The study was terminated with 93 subjects. The inclusion criteria were as follows:  $\geq 18$  years who were able to understand and communicate in the Turkish language, the lack of any psychological conditions, such as depression, anxiety disorders, or psychotic disorders, being hospitalized for HSCT, having received stem cells from peripheral blood, consenting to participating in the study.

The patient's AEs during the infusion and  $\leq 1$  hour after transplantation were recorded by the researcher. The vital signs were collected at the time of infusion at 15th minute. Hypertension was  $\geq 140/90$  mm Hg, hypotension  $\leq 90/60$  mm Hg, bradycardia  $< 60$  bpm, tachycardia  $> 100$  bpm, and fever  $> 37.5$ . We obtained the presence of other symptoms according to the nursing records. On the day of transplantation, the patient information form was filled out before premedication. Care was taken to ensure that routine practices were not interfered with and that no anxiety-provoking stimuli occurred. Patients completed the STAI-S Anxiety scale after expressing that they felt ready during the intravenous administration.

### Measures

The data were collected using a patient information form prepared by the researchers based on previous literature; and the STAI-S.

### Patient Information Form

This form consisted of 11 items inquiring about patient's sociodemographic characteristics (gender, age, education level, marital status, economic status etc.) and diagnosis, type of stem cell transplant, adverse events and assessing the individual's thoughts about transplantation.

**The State Anxiety Inventory (STAI-S):** The State Anxiety Inventory was developed by Spielberger et al.<sup>15</sup>. The State-Trait Anxiety Inventory Form (STAI) is the authoritative tool used for assessing anxiety in adults. It effectively distinguishes between the transient state of "state anxiety" and the more enduring characteristic

of “trait anxiety”. We used the section “state anxiety”, only. The STAI-S Anxiety scale assesses fundamental qualities such as apprehension, tension, nervousness, and worry. Scores on the STAI-S Anxiety scale increase in response to physical danger and psychological stress, and decrease following relaxation training. It provides valuable insights into individuals’ anxiety levels and responses to various situations. It is a 20-question, four-point Likert-type scale with “Not at all”, “A little”, “A lot” and “Completely” rating options. The validity and reliability of the scale in its Turkish form was conducted N. Öner and Le Compte<sup>16</sup>. Among the statements in the scale, the direct ones express negative emotions and the inverted ones express positive emotions. The inverted statements in the STAI-S Anxiety scale are items 1,2,5,8,10,11,15,16,19 and 20. High scores on this scale indicate high levels of anxiety and low scores indicate low levels of anxiety. In the reliability analysis, we found that the cronbach alpha internal consistency coefficient was between 0.94 and 0.96. The test-retest reliability coefficients ranged between 0.26 and 0.68. In this study, the cronbach alpha value of the scale was found to be 0.90.

### Data analysis

Data analysis was performed using the SPSS 25.0 program. Mean and standard deviation were used for the descriptive statistics of the variables, and number and percentage were used for the descriptive statistics of the categorical data. Significance between the descriptive characteristics of the participants and the scale was calculated using a one-way ANOVA. Logistic regression analysis was performed to determine the effect of AEs on the level of anxiety. The statistical significance level in the study was  $p < 0.05$ .

### ETHICAL CONSIDERATIONS:

The study conformed to the principles of the Declaration of Helsinki. Participants gave their written informed consent to take part in the study, ethical approval (decision numbered: 2021/01-05) was obtained from the the Ethics Review Boards of Batman University in Türkiye, and written permissions were obtained from the institution where the study was done.

### RESULTS:

We found that 41.9% of the patients were in the age

group of 29 to 37 years, 56.0% were married, 43.0% had secondary education, 51.6% had children, and 45.2% had income equal to their expenses. We also found that 32.3% of patients had been diagnosed with acute myeloid leukemia, 53.8% had been ill for 6-11 years, 40.9% had received chemotherapy before transplantation, 53.8% had received allogeneic transplantation, 54.9% were undecided about the success of the transplantation process, 86.6% had never undergone a transplantation before, and 85.0% had experienced AEs during transplantation (Table 1). The mean score of the STAI was  $52.70 \pm 3.7$ .

**Table 1.** Descriptive and disease characteristics of participants (N=93)

Sociodemographic Characteristics	n (%)	Disease related characteristics	n (%)
<b>Age</b>		<b>Diagnosis</b>	
20-28	28 (30.1)	Multiple myeloma	9 (9.7)
29-37	39 (41.9)	Acute myelogenous leukemia	30 (32.3)
38-46	26 (28.0)	Acute lymphocytic leukemia	27 (29.0)
<b>Gender</b>		Hodgkin's lymphoma	15 (16.1)
Male	50 (53.8)	Non-Hodgkin's lymphoma	12 (12.9)
Female	43 (46.2)	<b>Years after diagnosis</b>	
<b>Marital status</b>		0-5 years	12 (12.9)
Married	52 (56.0)	6-11 years	50 (53.8)
Single	41 (44.0)	12-17 years	31 (33.3)
<b>Educational status</b>		<b>Type of HSCT</b>	
Elementary School Grad.	25 (26.9)	Autologous	43 (46.2)
Middle School Grad.	40 (43.0)	Allogeneic	50 (53.8)
Higher Education Grad.	28 (30.1)	<b>Status of get transplantation previously</b>	
<b>Having children</b>		Yes	13 (13.4)
Yes	45 (48.4)	No	80 (86.6)
No	48 (51.6)	<b>Status of thinking that the transplantation process will be successful</b>	
<b>Income status</b>		Yes	23 (24.7)
Income less than expenses	32 (34.4)	No	19 (20.4)
Equal to income and expense	42 (45.2)		

Sociodemographic Characteristics	n (%)	Disease related characteristics	n (%)
Income more than expenses	19 (20.4)	Undecided	51 (54.9)
Total	93 (100)	The status of experiencing AEs during HSCT.	
		Yes	79 (85.0)
		No	14 (15.0)
		Total	93 (100)

n: number, %: percent

**Table 2** compared the patients’ descriptive characteristics and their mean STAI scores. We found that there was a significant difference between the variables of age, gender, years after diagnosis, belief in a successful transplant process, and previous transplantation status and the mean STAI score. The supplemental post-hoc analysis conducted to determine the causes of the differences found that mean anxiety scores were higher in the age group of 20 to 28 years, women, those with a disease diagnosis of 0 to 5 years, those who believed that the transplant process would not be successful, and those who had never undergone a transplantation (Table 2).

**Table 2.** Distribution of mean of STAI scores of the participants

Sociodemographic Characteristics	State Anxiety Inventory (M ± SD)	Test
Age		
20-28	62.15 ± 3.0	F= 2.497 p= 0.020
29-37	42.09 ± 2.1	
38-46	43.50 ± 2.6	
Gender		
Male	47.63 ± 2.2	t= 0.895 p= 0.012
Female	58.17 ± 2.8	
Educational status		
Elementary School Grad.	52.25 ± 3.0	F= 2.521 p= 0.306
Middle School Grad.	52.00 ± 2.9	
Higher Education Grad.	52.14 ± 3.5	
Diagnosis		
Multiple myeloma	51.9 5± 3.0	F= 3.108 p= 0.630
Acute myelogenous leukemia	52.30 ± 2.2	
Acute lymphocytic leukemia	53.47 ± 2.4	
Hodgkin’s lymphoma	52.61 ± 3.6	
Non-Hodgkin’s lymphoma	51.38 ± 3.7	

Sociodemographic Characteristics	State Anxiety Inventory (M ± SD)	Test
Years after diagnosis		
0-5 years	59.84 ± 3.5	F= 1.381 p= 0.035
6-11 years	46.53 ± 2.2	
12-17 years	47.92 ± 3.0	
Type of HSCT		
Autologous	51.16 ± 3.1	t= 0.259 p= 0.507
Allogeneic	53.00 ± 3.5	
Status of thinking that the transplantation process will be successful		
Yes	45.11 ± 2.0	t= 0.073 p= 0.040
No	60.08 ± 3.7	
Undecided	48.01 ± 3.5	
Status of get transplantation previously		
Yes	48.59 ± 2.2	t= 0.977 p= 0.010
No	56.40 ± 3.6	

M±SD: mean plus/ minus standard deviation

\*One-Way Anova Test and t test was performed.

**Table 3.** Rates of HSCT infusion-related AEs (n:79)

Type of AEs	n	%
Nausea and Vomiting	27	34.2
Abdominal pain	11	14.0
Itching	4	5.1
Hypertension	14	17.6
Hypotension	8	10.1
Tachycardia	9	11.4
Fever	6	7.6

n: number, %: percent

Nausea and vomiting (34.2%), hypertension (17.6%), abdominal pain (14.0%), tachycardia (11.4%), hypotension (10.1%), fever (7.6%), and itching (5.1%) were the problems experienced by patients during transplantation (Table 3).

**Table 4.** Adverse events affecting the state anxiety scores of patients during HSCT.

Type of AEs	β Value	SE	OR	CI 95 %	p*
Itching	0.035	0.011	0.895	0.447-1.793	0.940
Hypertension	0.020	0.005	0.764	0.416-1.404	0.316
Hypotension	0.004	0.002	0.605	0.153-2.289	0.105
Tachycardia	0.267	0.136	0.913	0.605-1.567	0.020



Type of AEs	$\beta$ Value	SE	OR	CI 95 %	$p^*$
Nausea and Vomiting	0.613	0.218	1.186	0.669-2.105	0.010
Abdominal pain	0.449	0.145	1.316	0.768-2.253	0.030
Fever	0.008	0.001	0.506	0.447-1.790	0.407

\*Backward Stepwise (Conditional) logistic regression analysis;

OR: Odds ratio; CI: Confidence interval. SE: Standard error, Durbin-Watson=1.530

Logistic regression analysis was performed using the backward method. The Nagelkerke R<sup>2</sup> value of the model was 0.167. The goodness of fit of the model was assessed using Hosmer and Lemeshow's test ( $X^2=8.900$ ,  $p=0.203$ ). When analyzing the side effects during bone marrow transplantation that affected the occurrence of anxiety, we found that nausea and vomiting increased the anxiety score by 6.1-fold ( $\beta: 0.613$ ), abdominal pain by 4.4-fold ( $\beta: 0.449$ ), and tachycardia by 2.6-fold ( $\beta: 0.267$ ) (Table 4).

## DISCUSSION

Studies conducted to determine anxiety levels in stem cell transplant patients have mainly focused on the pretransplant and posttransplant periods. In this study, we assessed patients' anxiety levels during transplantation. Our study differs from other studies in this regard. We found that patients were more than moderately anxious during transplantation. In addition, individuals in the age group 20-28 years, women, individual with a diagnosis of 0-5 years, individuals who believed that the transplantation process would be unsuccessful, and individuals who had never undergone transplantation previously had higher mean anxiety scores, and the difference between variables was statistically significant. Additionally, there was no significant difference between the patients' anxiety according to the type of HSCT.

We hypothesized that patients thinking that they would not live long, inadequacy in the process of accepting and learning to cope with the disease, and uncertainty regarding the progression of the illness and the treatment procedures may be responsible elevated anxiety levels in both the younger age group and in patients with years after diagnosis of less than 5 years<sup>17</sup>. Another striking finding of the present study was that those who believed

that the transplant process would fail and those who had never had undergone a transplantation previously had higher mean anxiety scores. Nelson et al. examined the effects of illness perception on mental health after stem cell transplantation and found that anxiety scores were higher in those who perceived the illness negatively; Larson et al.<sup>18</sup> found that anxiety was lower in those who internalized and did not make judgement the illness while<sup>19</sup> Wells et al. also found an inverse relationship between coping and anxiety depression in patients after transplantation<sup>20</sup>. Our study's findings align with the outcomes of the aforementioned studies in this aspect. These results show the effect of negative thinking and uncertainty on anxiety and how important it is to manage anxiety to prevent negative effects of the transplantation process.

Interventions such as interactive education, informing with visual methods and problem-solving training are performed for anxiety experienced before and after transplantation<sup>21-24</sup>. Some of these interventions were found to be effective and some ineffective. The findings obtained in our study show that patients also experience anxiety during transplantation therefore, interventions to prevent anxiety should also be performed during transplantation. There are a few studies in the literature on the prevention of anxiety during stem cell transplantation<sup>25,26</sup>. These studies found that the interventions had a positive effect on anxiety. Since there was no previous study determining the level of anxiety during transplantation, studies on anxiety were conducted considering the possibility of anxiety. Therefore, our study will provide a scientific rationale for planned studies on anxiety during stem cell transplantation.

Patients who have the opportunity of transplantation after tens of troublesome processes may encounter AEs in the process. Many factors, especially the source and type of transplantation, cause AEs. For example, with an allogeneic transplant, the incidence of AEs varies according to the source of peripheral stem cells, bone marrow stem cells and cord blood stem cells<sup>27</sup>. Cardiovascular, pulmonary and gastrointestinal complications are commonly seen in stem cell transplants<sup>28,29</sup>. Most of these complications are not life-threatening, but some patients may develop life-threatening events such as stroke, myocardial infarction and cardiac arrest<sup>29,30</sup>. In our study, nausea/vomiting, hypertension, and abdominal pain were the most common complications

during stem cell transplantation. Pruritus, hypotension, tachycardia, and fever were other complications. None of these complications was life-threatening. In the composite of adverse events, gastrointestinal complications (nausea/vomiting and abdominal pain) ranked first at 48.2% and cardiovascular complications (hypertension, hypotension, and tachycardia) ranked second at 39.1%.

Anxiety has been associated with AEs during stem cell transplantation<sup>11,12,31</sup>. Seo et al.<sup>11</sup> found that anxiety was associated with fatigue and shortness of breath after transplantation, while Pasyar et al.<sup>31</sup> found that it had to do with pain, fatigue, nausea, and vomiting. Connor Johnson et al.<sup>12</sup> studied the association between patient-reported pretransplant symptoms and posttransplant complications and found that depression occurring before transplantation was associated with acute graft-versus-host disease. In our study, nausea and vomiting, abdominal pain, and tachycardia were found to increase anxiety scores. This finding indicates that nursing interventions should be taken to prevent nausea, vomiting, abdominal pain, and tachycardia that cause anxiety.

Nurses play a critical role in the assessment and management of patients with transplantations. Through routine assessments at the bedside and in transplantation rooms, nurses are often the first to identify AEs related to symptoms. Failure of the transplant process, which is associated with high hopes, leads to great disappointment. Although it is possible to start the process again, it is a great loss considering the time lost in treating the disease and finding a suitable donor. Therefore, managing the anxiety that occurs during the transplant process can increase the patient's well-being during the transplant and prevent AEs that may occur after the transplant. Our finding show that nurses should plan nursing interventions to prevent anxiety during HSCT.

## CONCLUSION

The results of this study showed that patients experienced nausea and vomiting, hypertension and abdominal pain during stem cell transplantation, respectively; anxiety

level was above the moderate level and no significant difference according to the type of HSCT; nausea and vomiting, abdominal pain and palpitations increased anxiety. The findings indicates that nursing interventions should be taken to prevent nausea-vomiting, abdominal pain, and tachycardia that cause anxiety during HSCT.

## Study limitations

This study has several limitations. This study only included individuals receiving stem cell treatment at the Bone Marrow Center, a only center, faculty of medicine hospital that receives limitation patients and visitors. This clinic primarily treats patients coming from the eastern part of Türkiye. Thus, The findings of this study may not be generalizable to people receiving stem cell transplant in all Türkiye. Anxiety may be both the cause and effect of psychological reactions to stem cell transplant. This statu may not explain adequately demonstrate the cause-effect relationship between the variables. Also other limitation, the administration in the short duration of stem cell transplantation and the implementation of infection control protocols made data collection for the study quite challenging. Researchers need to be very careful because it is a very sensitive treatment. Additionally, Further studies using a large population sample are recommended to confirm the findings of the present study.

## Conflict of Interest

None

## Funding sources

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## Data Availability Statement

The datasets used during the current study are available from the corresponding author upon reasonable request.

## Author Contributions

Nuriye Efe Ertürk: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - Original Draft Preparation, Writing - Review & Editing Preparation.

Tuğba Menekli: Conceptualization, Methodology, Formal analysis, Investigation, Data collection, Writing - Review & Editing Preparation.

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