Pain, Fatigue, Nausea, and Vomiting as Predictors of Anxiety in Patients Undergoing Hematopoietic Stem Cell Transplantation: A Cross-sectional Study

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Abstract

Purpose

The present study aimed to determine the predictive roles of pain, fatigue, nausea, and vomiting in anxiety among the patients undergoing Hematopoietic Stem Cell Transplantation (HSCT).

Methods

The present cross-sectional study was conducted on 200 patients treated by HSCT referred to the centers affiliated to Shiraz University of Medical Sciences, Iran. The data were collected using Spielberger Anxiety Questionnaire, Numerical Pain Scale, Brief Fatigue Inventory, and Rhodes Nausea and Vomiting Index. Then, the data were analyzed using Spearman's test and multiple regression analysis.

Results

The means of state anxiety, trait anxiety, pain, fatigue, and nausea, vomiting and retching were 41.67 (SD = 9.71), 43.78 (SD = 9.00), 3.79 (SD = 2.79), 4.23 (SD = 2.48), 6.31 (SD = 7.53), respectively. The results showed that the participants with higher pain and fatigue scores had higher anxiety levels. The individuals who had more nausea and vomiting had higher anxiety levels, as well. It indicated that fatigue, pain, amount of vomiting, and severity of nausea, vomiting and retching were the predictors of trait anxiety. This study showed the predictor role of pain, fatigue, and severity of retching in state anxiety.

Conclusion

The study findings revealed an association between anxiety and pain, fatigue, nausea, and vomiting among the HSCT patients. The results also showed that fatigue and pain were the predictors of anxiety among the patients. Yet, future studies are recommended to determine the other factors contributing to anxiety among the HSCT patients.

1. Introduction

Hematologic malignancies have been defined as the tumors that arise from bone marrow or lymphoid tissue, affect blood, bone marrow, and the lymphatic system, and are directly related to the circulatory system and immune system (1). Chemotherapy, target therapy, and Hematopoietic Stem Cell Transplantation (HSCT) have been commonly used to treat hematologic malignancies (2). Although HSCT has good clinical outcomes (3), the long course of the disease and the unpredictability of the treatment process are among its main challenges (4). HSCT is also an invasive and complex procedure that causes many complications for patients due to the pre-bone marrow preparation regimen, which includes receiving high doses of chemotherapy drugs and whole-body radiation therapy (5). Anxiety is one of the consequences of cancer diagnosis and treatment. It is in fact one of the common psychological complications (6). The prevalence of anxiety has been found to be high in patients with hematologic malignancies treated by HSCT (7). Before transplantation, 30% of patients experienced

increased anxiety levels (8). Patients with hematologic malignancies who were transplanted and had COVID-19 were also prone to anxiety and depression (9). Overall, anxiety could have negative effects on cancer patients, including increased complications-related treatment, slow physical recovery, decreased quality of life, and reduced survival rate (10). The risk of COVID-19 infection and discontinuation of cancer treatment could further exacerbate the symptoms of anxiety and depression in cancer patients and have a greater impact on their clinical prognosis (11). Anxiety can also affect the sensation of pain experienced by HSCT patients (12). Pain is the most common and debilitating symptom among HSCT patients (13). Pain can result from the side effects of chemotherapy drugs or acute complications after HSCT (14). Psychological distress, which is an important component of cancer pain, has increased during the COVID-19 crisis due to quarantine and social isolation (15). Besides, anxiety can lead to fatigue in HSCT patients (16). One study found that most HSCT survivors experienced fatigue continuously one year (62.3%), three years (68%), and six years (63.8%) after transplantation (16). It should also be noted that patients' psychological problems before HSCT could affect the severity of their perceived fatigue (17). Moreover, mental fatigue after HSCT could be associated with cognitive dysfunction (18). One of the main causes of anxiety in cancer patients is nausea and vomiting (19). Chemotherapy-induced nausea and vomiting is a global experience among HSCT patients (20). Chemotherapy regimens before HSCT are the most common cause of nausea and vomiting within the first week after transplantation (21). The studies performed amongst patients undergoing HSCT have mainly assessed the physical and psychological complications of treatment, such as anxiety (7, 8), pain (13, 22), fatigue (16, 23), and nausea and vomiting (21, 24). However, less attention has been paid to the association between complications following treatment and the predictive role of these complications in the level of anxiety among the patients undergoing HSCT. Therefore, the present study aims to investigate the predictive roles of pain, fatigue, nausea, and vomiting in anxiety among the patients undergoing HSCT.

2. Methods

This was a cross-sectional and correlational study. The data were collected in Nemazee Hospital and Motahhari Clinic affiliated to Shiraz University of Medical Sciences from September 2020 to March 2021.

The sample size was based on a pilot study on 10 HSCT patients in which all of the correlation coefficient between state and trait anxiety and pain, fatigue, severity and frequency of nausea, vomiting, and retching and amount of vomiting were ≥ 0.250 . However, the correlation between state anxiety and duration of nausea was 0.227 and had lowest correlation. Therefore, considering 90% power, 5% error, $r = 0.227$; 200 people were determined as the sample size. Finally, this study was performed on 200 patients by convenience sampling.

$$n = \frac{\left(\frac{z_{1-\alpha} + z_{1-\beta}}{u_p}\right)^2}{u_p^2} + 3 = 200$$

$$u_p = \frac{1}{2} \ln \frac{1+r}{1-r}$$

$$r = 0.227$$

The inclusion criteria were having undergone HSCT, aging 18 years and above, being oriented to time and place, and being willing to participate in the study. The exclusion criteria were unwillingness to take part in the research and death.

The study data were collected using five questionnaires, including the demographic and clinical information questionnaire, Spielberger State-Trait Anxiety Inventory (STAI), numerical pain scale, Brief Fatigue Inventory (BFI), and Index of Nausea, Vomiting, and Retching.

Demographic and clinical information questionnaire: This form included information, such as age, gender, level of education, marital status, diagnosis, and type of transplant.

STAI: This inventory had 40 questions. The first 20 questions were related to state anxiety and the second 20 questions were related to trait anxiety. The answer to each question was based on a four-point Likert scale, ranging from one to four. Accordingly, the scores were divided into three levels; i.e., mild (20-39), moderate (40-59), and severe (60-80) anxiety. Cronbach's alpha coefficient was reported as 0.92 for state anxiety and 0.90 for trait anxiety. Additionally, the test-retest coefficient was 0.62 for state anxiety and 0.68 for trait anxiety (25). The content validity of the Persian version of STAI was confirmed and its reliability was reported to be 0.81 (26).

Numerical pain scale: This tool is a standard scale for measuring pain. It is a horizontal ruler divided from 0 to 10. According to this scale, scores 0, 1-3, 4-6, and 7-10 indicated pain, mild pain, moderate pain, and severe pain, respectively. The validity of this tool was 0.80 and its reliability was 0.80 (27). In addition, the reliability of the Persian version of the scale was 0.94 (28).

BFI: This inventory was designed to measure the level of fatigue and consisted of 10 questions. The first question determined the presence or absence of unusual fatigue in the last week using a yes/no question. In questions 2 to 10, the degree of fatigue was examined by different conditions, each being measured on a scale numbered from 0 to 10. Scores 0 and 10 indicated no fatigue the most severe state of fatigue, respectively. Finally, the patient's fatigue was determined by adding the scores of questions 2 to 10 and dividing it by 9. Accordingly, scores 0, 1-3, 4-6, and 7-10 represented no fatigue, mild fatigue, moderate fatigue, and severe fatigue, respectively. The validity of this questionnaire was found to be 0.76 and its reliability was reported as 0.96. Overall, this inventory had the highest reliability for measuring fatigue compared to other questionnaires (29). In another study, the validity of this questionnaire was confirmed and its reliability was reported to be 0.90 (30). In the present study, the reliability of BFI was approved by the Cronbach's alpha coefficient of 0.95.

Index of Nausea, Vomiting, and Retching: This index aimed at evaluating multiple objective and subjective cases of nausea, vomiting, and retching. This index contained eight questions and was scored based on a five-point Likert scale. The index included three questions about nausea (frequency, severity, and duration of nausea), three questions about vomiting (frequency, severity, and amount of vomiting), and two questions about retching (frequency and severity). These questions could be assigned zero (absence of or minimum symptoms) to four (the worst condition) scores. Thus, the total score of this index could range from 0 to 32, with higher scores representing more severe nausea and vomiting. The validity of this questionnaire was 0.87 and its reliability was 0.98 (31). In another study, the reliability of this index was reported to be 0.88 (32). In the current study, the reliability of the index was confirmed by Cronbach's alpha coefficient of 0.97.

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1398.1329). The questionnaires were coded and the study data were collected anonymously. In addition, the patients were assured about the confidentiality of their data and the voluntary nature of the study. Written consent forms were also obtained from the patients.

Descriptive and inferential statistics were used to analyze the data. Spearman and Pearson correlation coefficient were used to determine the association between the variables. In addition, multiple regression analysis was used to determine the predictive roles of pain, fatigue, nausea, and vomiting in anxiety. These data were analyzed using the SPSS 26 software and $p < 0.05$ was considered statistically significant.

3. Results

The study sample included 200 patients who had undergone HSCT. Among the patients, 112 (56%) were male and 88 (44%) were female. The participants' ages ranged from 20 to 66 years (mean = 42.78, SD = 12.57). Besides, 67% of the participants were married and 33.5% had middle and high school degrees. Regarding the clinical characteristics, 50.7% of the participants had leukemia (acute myeloid or lymphocytic leukemia). Furthermore, 76.5% and 23.5% of the patients had undergone allogeneic and autologous transplantations, respectively. The demographic and clinical characteristics of the HSCT patients have been presented in Table 1.

The mean score of trait anxiety (43.78, SD = 9.00) was higher compared to state anxiety (41.67, SD = 9.71). Fig 1 and 2 shows the levels of state and trait anxiety. Among the participants, 53% and 63.0% had moderate state and trait anxiety levels, respectively.

The total scores of pain ranged from 0 to 10, with a mean of 3.79 (SD = 2.79). Moreover, 18.6%, 46.1%, and 35.5% of the participants had high, moderate, and low pain levels, respectively.

This study showed 165 patients (82.5 %) felt fatigue in the last week. The mean score of fatigue was 4.23 (SD = 2.48), and the total scores of fatigue ranged from 0 to 9.78. Fatigue was mild in 37.5 % of participants, moderate in 42.6 % and severe in 19.9 % of them.

The total scores of nausea, vomiting, and retching ranged from 0 to 31, with the mean score of 9.46 (SD = 8.50). As Table 2 shows approximately, half of the HSCT patients experienced nausea, vomiting and retching and their severity was from mild to severe. One third of them reported 1 - 4 times nausea, vomiting and retching at the last 12 hours. Moreover, 140 (70%) of the subjects did not throw up vomiting and 44% of them felt nausea for 1 hour or less to 3 hours.

The results of correlation coefficient have been presented in Table 3. Accordingly, a significant association was found between state and trait anxiety and fatigue ($p < 0.001$). A significant association was also observed between state and trait anxiety and pain ($p < 0.05$). In addition, there were correlation between state and trait anxiety and severity of nausea, vomiting, and retching ($p < 0.05$). Significant association were also observed between state and trait anxiety and frequency of nausea, vomiting, and retching, amount of vomiting, and duration of nausea in HSCT patients ($p < 0.05$).

The results of regression analysis have been presented in Table 4. Based on this analysis fatigue, pain, severity and frequency of nausea, vomiting and retching, amount of vomiting, and times of nausea predicted 42% of the HSCT patients state anxiety variance ($R = 0.67$, $R^2 = 0.45$, ADJ. $R^2 = 0.42$). The results revealed the predictor roles of pain ($p < 0.001$), fatigue ($p < 0.001$) and severity of retching in state anxiety.

This study showed above mentioned variables predicted 44% of the HSCT patients' trait anxiety variance ($R = 0.68$, $R^2 = 0.47$, ADJ. $R^2 = 0.44$). Moreover, pain, fatigue, amount of vomiting, and severity of nausea, vomiting and retching predicted the HSCT patients' trait anxiety (Table 4).

4. Discussion

In this study, all HSCT patients showed mild to severe anxiety and 53% and 63% of the participants had moderate state and trait anxiety, respectively. It was reported that HSCT patients had moderate anxiety levels during the COVID-19 pandemic (33). On the other hand, the prevalence of anxiety was 17.53% among cancer patients during the COVID-19 pandemic (11). It should be noted that the prevalence of anxiety was higher among the HSCT patients in the present study compared to cancer patients during the COVID-19 pandemic. The HSCT patients' anxiety levels were also higher in comparison to other times than the COVID-19 pandemic. COVID-19 as infectious disease is easily transmitted to others, increases the risk of infections in HSCT patients, disturbs the transplantation process, and may lead to death. Therefore, these complications of COVID-19 might elevate the level and mean score of anxiety in these patients.

In the present study, the mean score of pain was 3.79, and 64.7% of the participants had moderate and high levels of pain. Similarly, another study reported moderate to severe pain intensity among the patients undergoing HSCT (13). Another study also indicated that the pain burden could be potentially high in the hematology patients, especially those treated by HSCT (34). In fact, excessive bone marrow activity in the patients undergoing HSCT may lead to bone pain in these patients.

Based on the present study findings, the mean score of fatigue was 4.23, and 82.5% of the patients had mild to severe fatigue. Moreover, 42.6% and 19.9% of the participants reported moderate and severe fatigue levels, respectively. It was previously observed that the HSCT patients experienced high fatigue levels during their treatment period (35). In another study evaluating fatigue in allogeneic stem cell transplant recipients, patients reported 68% fatigue on the day of transplantation, 90% in the first month, and 81% on day 100 after transplantation (36).

In the present study, the mean score of nausea, vomiting and retching was 6.31. In another study, the mean score of nausea and vomiting was 7.2 (SD=8.7) in patients undergoing chemotherapy (37). Overall, 70-80% of the patients undergoing chemotherapy experienced nausea and vomiting, which could be both acute (36%) and delayed (59%) (38).

The present study investigated the association between anxiety and pain, fatigue, nausea, and vomiting in the patients treated by HSCT. The results demonstrated that state and trait anxiety and fatigue had relationship with each other. In another research, patients undergoing chemotherapy with moderate to severe fatigue had higher anxiety scores and showed significantly more anxiety symptoms (39). Another research also revealed a moderate correlation between anxiety and fatigue, so that anxiety could be continuously associated with fatigue (40).

In the present study, state and trait anxiety were associated with pain. In another study also, there was a positive correlation between anxiety and pain among cancer patients (41). Anxiety was also directly related to pain in cancer patients in the COVID-19 pandemic, such a way that increase in pain might increase the anxiety level (42).

In the current study, nausea, vomiting and retching were associated with state and trait anxiety. Researchers have indicated that nausea and vomiting could be one of the main causes of anxiety in cancer patients. In other words, the presence of nausea and vomiting might lead to several mental problems, such as anxiety and depression, among these patients (19). Hence, controlling nausea and vomiting during and after the HSCT could significantly prevent or reduce the physical and psychological effects of transplantation, such as fatigue and anxiety. It could improve the patients' quality of life, as well (20).

The results of regression test in the present study demonstrated that the most important factors affecting the participants' state and trait anxiety were fatigue and pain. Moreover, severity of nausea, vomiting, and retching, duration of nausea and amount of vomiting were the predictors of trait anxiety in the study participants. A prior study disclosed that anxiety and depression were positively associated with psychological distress in HSCT patients, and fatigue might play a positive predictive role in anxiety among these patients (43). Furthermore, anxiety was significantly associated with pain in cancer patients, and pain intensity might predict anxiety in these patients (12).

Because of the current crisis in the world due to the COVID-19 pandemic, the situation has become sensitive and worrying for certain patients, such as HSCT recipients. The unknown nature of COVID-19,

lack of studies on the disease, and lack of unique treatments and vaccines have increased the psychological burden and anxiety levels among patients, especially HSCT recipients, as well as their physicians (44). If the crisis persists, these patients will need more psychological support in addition to their main treatment (45).

One of the limitations of the present study was its cross-sectional design. Nevertheless, the study results may increase efforts to evaluate and manage common transplant complications among HSCT patients. In addition, etiological research in this field should be done in the future to determine the other factors associated with anxiety during the COVID-19 pandemic.

5. Conclusion

This study showed an association between state and trait anxiety and pain, fatigue, nausea, and vomiting among the HSCT patients. Considering the correlation between physical complications such as pain and fatigue and mental complications such as anxiety among the HSCT patients, healthcare workers are recommended to evaluate these patients in terms of both physical and mental problems and control and manage these complications by complementary and integrative interventions.

Declarations

Funding

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Conflicts of interest/Competing interests

There are not conflicts of interest.

Availability of data and material

The data transparency was approved by FZ, NP, and MR. Data are available by MR, and NP, FZ in the form of SPSS software. Data is available on request based on the privacy and ethical limitations.

Code availability

Not applicable.

Authors' contributions

Nilofar Pasyar, Masoume Rambod, Fatemeh Zahedi, and Mani Ramzi contributed in this study. All of the authors participated in conceptualization, design, draft, read, and revised the manuscript and approval of the study and manuscript. Nilofar Pasyar, Masoume Rambod, Fatemeh Zahedi participated in data collection management. Masoume Rambod, Fatemeh Zahedi collaborated in data analysis and interpretation.

Ethics approval

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1398.1329).

Consent to participate

Written consent forms were obtained from the patients. The questionnaires were coded and the study data were collected anonymously. In addition, the patients were assured about the confidentiality of their data and the voluntary nature of the study.

Consent for publication

The data were published anonymously.

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Tables

Table 1. Demographic and clinical characteristics of the HSCT patients (N = 200)

Variable	n (%)
Gender	
Male	112 (56.0)
Female	88 (44.0)
Education levels	
illiterate	15 (7.5)
Primary school	51 (25.5)
Secondary and high school	67 (33.5)
Academic	67 (33.5)
Marital status	
Single	52 (26.0)
Married	134 (67.0)
Divorced	10 (5.0)
Widowed	4 (2.0)
Disease diagnosis	
Multiple Myeloma	78 (39.6)
Acute Myeloid leukemia	41 (20.8)
Acute lymphocytic leukemia	47 (23.9)
Lymphoma	25 (12.7)
Aplastic anemia	6 (3.0)
Type of HSCT	
Autologous	75 (37.5)
Allogeneic	125 (62.5)

Table 2. Nausea, Vomiting and Retching in the HSCT patients the last12 hours

Variables	Nausea	Vomiting	Retching
Severity			
No	94 (47.0)	119 (59.5)	115 (57.5)
Mild	48 (24.0)	36 (18.0)	41 (20.5)
Moderate	36 (18.0)	33 (16.5)	27 (13.5)
Great	17 (8.5)	8 (4.0)	11 (5.5)
Severe	5 (2.5)	4 (2.0)	6 (3.0)
Frequency ^a			
No	102 (51.0)	139 (69.5)	108 (54.0)
1-2	46 (23.0)	34 (17.0)	47 (23.5)
3-4	29 (14.5)	12 (6.0)	18 (9.0)
5-6	9 (4.5)	7 (3.5)	18 (9.0)
7 or more	14 (7.0)	8 (4.0)	9 (4.5)
Amount			
Very large ^b		5 (2.5)	
Large ^c	————	7 (3.5)	————
Moderate ^d		7 (3.5)	
Small ^e		41 (20.5)	
I did not throw up		140 (70.0)	
How much times			
Not at all	88 (44.0)		
1 hour or less	55 (27.5)	————	————
2-3 hours	33 (16.5)		
4-6 hours	7 (3.5)		
More than 6 hours	17 (8.5)		

^a times, ^b Very large (3 cups or more), ^c large (2-3 cups), ^d moderate (1/2-2 cups), ^e small (up to 1/2 cup)

Table 3. The association between state and trait anxiety and fatigue, pain, nausea, vomiting and retching in HSCT patients

Variables	State anxiety	Trait anxiety
Fatigue	$r = 0.61, P < 0.001$	$r = 0.58, p < 0.001$
Pain	$r = 0.54, p < 0.001$	$r = 0.56, p < 0.001$
Severity of nausea	$r = 0.33, p < 0.001$	$r = 0.26, p < 0.001$
Severity of vomiting	$r = 0.31, p < 0.001$	$r = 0.23, p = 0.001$
Severity of retching	$r = 0.41, p < 0.001$	$r = 0.33, p < 0.001$
Frequency of nausea	$r = 0.29, p < 0.001$	$r = 0.18, p = 0.008$
Frequency of vomiting	$r = 0.28, p < 0.001$	$r = 0.25, p < 0.001$
Frequency of retching	$r = 0.34, p < 0.001$	$r = 0.27, p < 0.001$
Amount of vomiting	$r = 0.27, p < 0.001$	$r = 0.22, p = 0.001$
Duration of nausea	$r = 0.26, p < 0.001$	$r = 0.22, p = 0.002$

Table 4. The results of regression analysis for determining the predictive roles of pain, fatigue, nausea, and vomiting in the HSCT patients' state anxiety (n = 200)

	Unstandardized Coefficients		Standardized Coefficients	<i>t</i>	P-value	95% CI ^a
	B	Std. Error	Beta			
1 (constant)	31.27	1.10		28.27	< 0.001	29.08, 33.45
Fatigue	1.71	0.28	0.43	6.06	< 0.001	1.15, 2.27
Pain	0.71	0.25	0.20	2.83	0.005	0.21, 1.21
Severity of nausea	1.39	1.06	0.15	1.31	0.19	- 0.69, 3.49
Severity of vomiting	1.11 •	1.31	- 0.11	- 0.85	0.39	- 3.71, 1.47
Severity of retching	2.69	1.24	0.29	2.16	0.03	0.23, 5.14
Frequency of nausea	0.87 •	0.83	- 0.10	- 1.49	0.29	- 2.52, 0.77
Frequency of vomiting	0.60	0.99	0.06	0.60	0.54	- 1.36, 2.56
Frequency of retching	0.05	0.80	0.007	0.07	0.94	- 1.53, 1.64
Amount of vomiting	1.46 •	0.98	- 0.13	- 1.49	0.13	- 3.41, 0.47
Duration of nausea	0.97 •	0.78	- 0.12	- 1.23	0.21	- 2.52, 0.58

a 95.0 % confidence interval for B

Table 5: Multiple linear regression analysis predicting HSCT patients' trait anxiety (n = 200)

95% CI ^a	P-value	t	Standardized Coefficients	Unstandardized Coefficients		Factors
			Beta	Std. Error	B	
32.42, 36.41	< 0.001	34.05		1.01	34.42	1 (constant)
0.74, 1.76	< 0.001	4.85	0.34	0.25	1.25	Fatigue
0.32, 1.23	0.001	3.35	0.24	0.23	0.77	Pain
1.16, 4.99	0.002	3.17	0.37	0.97	3.08	Severity of nausea
- 4.92, -0.18	0.03	- 2.12	- 0.28	1.20	• 2.65	Severity of vomiting
0.41, 4.89	0.02	2.33	0.31	1.13	2.65	Severity of retching
- 2.36, 0.66	0.27	- 1.10	-0.11	0.76	• 0.84	Frequency of nausea
- 0.35, 3.23	0.11	1.58	0.16	0.90	1.44	Frequency of vomiting
- 1.25, 1.65	0.78	0.27	0.02	0.73	0.20	Frequency of retching
- 3.80, - 0.25	0.02	- 2.25	- 0.20	0.90	• 2.03	Amount of vomiting
0.41, 4.89	0.02	2.33	- 0.16	0.71	• 1.19	duration of nausea

a 95.0 % confidence interval for B

Figures

Figure 1

The HSCT patients' state anxiety levels

Figure 2

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