Anxiety, depression, physical symptoms, and activity in patients with hematological malignancy undergoing chemotherapy: A cross-sectional study

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Abstract

Objective: The purpose of this study was to investigate the prevalence and characteristics of depression and anxiety in patients with hematological malignancy including examining their relationship with physical functioning and physical symptoms.

Method: Japanese inpatients (n = 173, mean age: 62.7 ± 15.0 years) with hematological malignancy undergoing chemotherapy and 115 age- and sex-matched healthy controls participated. All participants completed the Hospital Anxiety and Depression Scale. For patients with hematological malignancy, muscle strength, physical activity, activities of daily living, and quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30) were assessed.

Results: We revealed that 32.9% and 45.7% of patients had anxiety and depression, respectively, which were both significantly higher than the values among healthy controls. Patients with hematological malignancy who had anxiety and depression displayed lower physical functioning scores and higher symptom scores on the QLQ-C30. Logistic regression analyses revealed that age, nausea, and cognitive functioning were significantly associated with anxiety in patients with hematological malignancy, and insomnia was significantly associated with depression.

Significance of Discussion: The prevalence of anxiety and depression was high in Japanese inpatients with hematological malignancy undergoing chemotherapy. Anxiety and depression may be affected more by physical symptoms than by physical functioning or activity; therefore, the relationship between psychological distress (anxiety and depression) and physical symptoms should be focused on when treating patients with hematological malignancy undergoing chemotherapy.

Introduction

Patients with hematological malignancy present with a variety of physical and mental symptoms such as cytopenia derived from nutritional deficiencies and bone marrow suppression [1], nausea/vomiting [2], anorexia [3], and cancer-related fatigue [4]. In addition, among these patients, anxiety and depression can potentially impair their physical and social functioning and quality of life (QoL) [5,6]. However, the severity of anxiety and depression among patients with hematological malignancy has not been compared with that of healthy people in previous studies.

Notably, a few reports compared anxiety and depression between patients with other cancers and healthy people. Concerning breast cancer, some reports revealed that anxiety and depression did not differ between patients and healthy controls [7-9]. Further, it was reported that anxiety and depression among patients with lung cancer was severer than that of healthy people who lived in suburban areas, but not urban areas [10]. Severer depression and anxiety were also observed in inpatients with colorectal and testicular cancer as compared to healthy people [11,12].

Key factors associated with anxiety and depression have been addressed in several reports examining patients with cancer; however, some did not compare against healthy people. For example, in a study about inpatients with hematological malignancy in Saudi Arabia, the associated factors of anxiety and depression were multiple comorbidities and a tense home atmosphere, but not age, income, or treatment [13]. Further, research in China revealed that optimism and resilience, but not self-efficacy, were associated with depression and anxiety among inpatients with hematological malignancy [14]. In outpatients, depression and anxiety are aggravated by smoking and having to relocate for treatment [15]. Moreover, in a study that investigated QoL

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and physical symptoms, social functioning, nausea, insomnia, and financial difficulties were all associated with depression and anxiety among patients with hematological malignancy [16]. Lastly, fatigue and sex also influenced mental distress in patients with hematological malignancy [4,17].

Consequently, various factors are associated with depression and anxiety; however, the affecting factors in patients with hematological malignancy have not been fully clarified. Especially, few studies have demonstrated the relationship between depression and anxiety and physical functioning such as muscle strength, activities of daily living (ADL), and physical activity in patients with hematological malignancy. It has been posited that physical functioning of patients with hematological malignancy decreases during hospital treatment (e.g., receiving chemotherapy) [18]. There is also a high possibility that anxiety and depression are affected by physical functioning [19].

Therefore, we investigated the prevalence and characteristics of anxiety and depression in Japanese inpatients with hematological malignancy undergoing chemotherapy including examining their relationship with physical functioning and physical symptoms. Moreover, we explored the risk factors of anxiety and depression.

Methods

Study design and participants

This cross-sectional observational study was conducted at Nagasaki University Hospital, from January 2014 to March 2019. Inpatients with hematological malignancy undergoing chemotherapy in Nagasaki University Hospital and age- and sex-matched healthy controls in Nagasaki city participated. Informed consent was obtained from all participants. Inclusion criteria of patients included the following: 1) inpatients diagnosed with hematological malignancy including lymphoma, acute myeloid leukemia and Acute lymphoblastic leukemia, 2) hospitalized to receive chemotherapy, and 3) aged > 20 years. Exclusion criteria included the following: 1) difficulty communicating, 2) critical condition, 3) had received radiotherapy or transplant treatment, 4) severe heart disease, 5) severe respiratory disease, 6) hepatic or renal failure, or 7) cerebrovascular or orthopedic disease that greatly influenced physical functioning. Healthy controls were recruited at health-related events and welfare businesses for citizens.

General information about participants such as age, sex, height, weight, and body mass index (BMI) were recorded. For patients, clinical information was also collected, including diagnosis; days from hospitalization; disease duration; treatment type; and blood chemistry data such as serum albumin, serum C-reactive protein, and hemoglobin concentration. Anxiety, depression, and muscle strength were also measured for all participants. Additionally, ADL, physical activity, and QoL were assessed for patients.

This study was approved by a hospital ethics committee before study commencement (approval number 15072757). Study objectives were explained to all participants before they were invited to participate. Written consent was obtained from all consenting participants.

Psychological distress

The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress [20]. This is a widely used valid questionnaire to measure psychological morbidity in cancer patients [20]. It consists of a 7-item anxiety subscale and a 7-item depression subscale. Each item is rated on a scale from 0 (best status) to 3 (worst status); possible scores for each subscale range from 0 to 21. Scores between 0 and 7 suggest "no case," 8 to 10 represents a "possible case," and 11 to 21 indicates a "probable case of anxiety/depression" [21]. In this study, a score of 8 was set as the cut-off value of anxiety/depression per a previous study [21].

Muscle strength

Handgrip strength was measured as a marker of general muscle strength using a standard adjustable-handle dynamometer (TKK 5101; Takei Scientific Instruments Co. Ltd., Japan). Measurements were taken in standardized position with participants standing with their arm held in zero abduction flush against their body. A single attempt of maximum right- and left-hand grip strength was recorded in kilogram force, and higher values were adopted for analyses.

Additionally, the strength of the quadriceps femoris muscle was assessed. Muscle strength was quantified using maximum voluntary isometric contraction for knee joint extension, per a previous study [22]. Participants were seated at the corner of a bed or chair with their knees at about 90 degrees flexion. A portable muscle force dynamometer (μ-tas MF-01, ANIMA Corp., Japan) was placed against the anterior side of participants' legs just proximal to the malleoli. The dynamometer stabilizing belt passed around the legs of the bed/chair. Participants were then asked to continue trying to straighten their knee as hard as possible until the tester asked them to stop. The measurement was performed for both the right and left legs, and data from the stronger leg were used for analyses.

Activities of daily living

In patients with hematological malignancy, ADL was evaluated using the Functional Independence Measure, which assesses physical and cognitive functioning and the need for assistance. It consists of an 18-item scale that measures independence in performing tasks involved in feeding, grooming, dressing, toileting, mobility, and cognition [23]. Each item is rated on a scale from 1–7 (1 = total assistance, 2 = maximal assistance, 3 = moderate assistance, 4 = minimal assistance, 5 = needs supervision, 6 = modified independence, and 7 = Complete independent).

Physical activity

The Eastern Cooperative Oncology Group performance status was defined as follows: 0 = fully active and able to perform all pre-disease activities without restriction; 1 = restricted in physically strenuous activity; however, ambulatory and able to perform work of a light or sedentary nature; 2 = ambulatory and capable of all selfcare; however, unable to complete any work activities, and "up and about" for more than 50% of waking hours; 3 = capable of only limited selfcare and confined to bed or chair for more than 50% of waking hours; and 4 = completely disabled, cannot perform any selfcare, and totally confined to a bed or chair.

Daily steps were measured as a marker of physical activity using a pedometer with accelerometer. Participants were instructed to wear the accelerometer (Kenz Lifecorder GS; Suzuken Co., Ltd., Japan) on their belt or waistband, above the right midline of the thigh, from the moment they got out of bed in the morning until they went to bed in the evening, except while bathing. The wearing period was 1 week and mean daily step count was calculated.

Quality of life

QoL was measured using The European Organisation for Research and Treatment of Cancer QoL Questionnaire-C30 (EORTC QLQ-C30).

The EORTC QLQ-C30 is a cancer-specific self-report questionnaire and consists of a global QoL scale (two items), functional scales (physical, role, emotional, cognitive, and social functioning), and symptom scales (fatigue, pain and nausea/vomiting, insomnia, dyspnea, appetite loss, diarrhea, constipation, and financial difficulties). The items are scored on a 4-point categorical scale ranging from 1 (not at all) to 4 (very much), except the global QoL scale, which utilizes a modified 7-point linear analogue scale. All scales are transformed to a score from 0–100. For the global QoL scale and functional scales, higher scores represent better functioning. For the symptom scales, higher scores indicate severe symptoms [24].

Data analyses

Data were analyzed using SPSS 22.0 (IBM, NY, USA). Data were shown as means ± standard deviation for continuous data and as frequencies (%) for categorical data. First, patients were compared with healthy controls regarding anxiety and depression. Second, patients were divided into two groups based on their HADS anxiety/depression subscale scores (≥ 8 = anxious/depressed group and < 8 = non-anxious/depression group). Variables between groups were compared using independent samples t-tests and $\chi 2$ tests. Third, all variables with a significant association with anxiety/depression were entered into a multiple stepwise logistic regression model, with the dichotomous anxiety/depression as the dependent variable, to explore psychological status factors. $P < .05$ was considered statistically significant.

Results

One-hundred seventy-three patients with hematological malignancy being treated at Nagasaki University Hospital were recruited, and data were collected from 115 healthy controls. There were no differences between patients and controls regarding general characteristics (Table 1).

Anxiety and depression in patients with hematological malignancy increased compared with healthy controls. Patients had significantly higher mean HADS-anxiety and HADS-depression scores than did controls; however, when the presence of anxiety was judged using the cut-off value (HADS-anxiety > 8 points), the prevalence of anxiety in patients and healthy controls was not significantly different. Further, regarding muscle strength, both handgrip and knee extension strength significantly decreased in patients compared with controls (Table 1).

Patients' general and clinical characteristics are shown in Table 2. Most cancer type was lymphoma (45.7%), followed by acute myeloid leukemia (24.8%) and acute lymphoblastic leukemia (29.5%). From data of blood chemistry, typical physical symptoms of hematological malignancy undergoing chemotherapy such as anemia and nutritional deprivation were observed. ECOG performance status was Grade 1 (39.9%), 2 (31.2%) and 3 (26.6%), which showed that physical activity of patients decreased in hospital to a varying extent. The mean hospitalization duration was 17.5±22.7 days.

As indicated in Table 3, demographic and clinical variables were compared between the anxious/depressed group and the non-anxious/depressed group among patients with hematological malignancy. There were no differences concerning age, BMI, blood chemistry, muscle strength, physical activity, ADL, or hospitalization period between groups. Concerning the EORTC QLQ-C30, global health status and emotion, cognitive, and social functioning significantly decreased in the anxious/depressed group compared with the non-anxious/

Table 1. Comparing psychological distress and muscle strength between patients with hematological malignancy and healthy controls

	Patients (n = 173)	**Controls (n = 115)**	*p*
Age (years)	62.7±15.0	66.0±13.5	.062
Sex			
Male, n (%)	87 (50.3)	55 (47.8)	.680
Female, n (%)	86 (49.7)	60 (52.2)	
Body mass index	20.7±3.3	22.7±2.9	< .001
HADS-anxiety			
Mean	6.3±3.7	5.3±3.6	.031
< 8, n (%)	116 (67.1)	83 (72.2)	.357
≤ 8, n (%)	57 (32.9)	32 (27.8)	
HADS-depression			
Mean	7.4±3.7	5.6±3.5	< .001
< 8, n (%)	94 (54.3)	80 (69.6)	.009
≤ 8, n (%)	79 (45.7)	35 (30.4)	
Handgrip, Kgf	22.0±9.6	30.4±10.2	< .001
Knee extension strength, Kgf	44.9±20.1	52.1±19.2	.003

HADS: Hospital Anxiety and Depression Scale, Kgf: kilogram-force.

Table 2. Clinical characteristics among patients with hematological malignancy

Clinical characteristics	
Cancer type, n (%)	
Lymphoma	79 (45.7)
Acute myeloid leukemia	43 (24.8)
Acute lymphoblastic leukemia	51 (29.5)
Blood chemistry	
Hemoglobin, g/dL	9.8±2.0
Albumin, g/dL	3.5±0.6
Total protein, g/dL	6.2±1.0
C-reactive protein, mg/dL	1.4±3.1
ECOG performance status	
Mean	1.9±0.9
Grade 0, n (%)	1 (0.6)
Grade 1, n (%)	69 (39.9)
Grade 2, n (%)	54 (31.2)
Grade 3, n (%)	46 (26.6)
Grade 4, n (%)	3 (1.7)
Hospitalization, days	17.5±22.7
Drug	
Opioid, n (%)	31 (17.9)
Sleeping drug, n (%)	23 (13.3)
Anti-anxiety, n (%)	6 (3.5)
Anti-depression, n (%)	5 (2.9)
Stabilizer, n (%)	3 (1.7)
Psychotropic drug, n (%)	27 (15.6)

ECOG: The Eastern Cooperative Oncology Group.

depressed group. Concerning cancer-related symptoms, the anxious/depressed group had more serious nausea, fatigue, insomnia, and appetite loss compared with the non-anxious/depressed group. Pain, dyspnea, constipation, and diarrhea did not differ between groups.

We used logistic regression analyses to investigate factors related to anxiety and depression. Emotion functioning (from the QLQ-C30) was excluded from independent variables intentionally because it predominantly assesses anxiety and depression [25, 26]. The results revealed that age, nausea, and cognitive functioning were significantly associated with anxiety among patients (Table 4). Further, insomnia was significantly associated with depression (Table 5). All functions and physical symptoms were correlated anxiety (data not shown).

Table 3. Differences between the anxious/depressed group and the non-anxious/depressed group among patients with hematological malignancy

	Non-anxious	Anxious		Non-depressed	Depressed	
	n = 116	n = 57	p	n = 94	n = 79	p
Age (years)	63.7±14.9	60.5±17.3	.207	62.4±16.7	63.0±14.7	.798
Body mass index	20.9±3.5	20.4±2.8	.233	20.7±2.9	20.6±3.7	.888
Hemoglobin, g/dL	9.7±2.0	10.1±1.9	.186	9.8±2.0	9.8±2.0	.881
Albumin, g/dL	3.5±0.6	3.5±0.7	.884	3.5±0.6	3.5±0.7	.982
C-reactive protein	1.4±3.5	1.3±2.0	.814	1.2±2.9	1.5±3.3	.551
ECOG performance status						
Mean	1.9±0.9	1.9±0.8	.189	1.9±0.9	1.9±0.9	.631
Grade 0, n (%)	1 (0.9)	0 (0.0)		0 (0.0)	1 (1.3)	
Grade 1, n (%)	50 (43.1)	19 (33.3)		41 (43.6)	28 (35.4)	
Grade 2, n (%)	30 (25.9)	24 (42.1)		28 (29.8)	26 (32.9)	
Grade 3, n (%)	32 (27.6)	14 (24.6)		23 (24.5)	23 (29.1)	
Grade 4, n (%)	3 (2.6)	0 (0.0)		2 (2.1)	1 (1.3)	
Handgrip, Kgf	22.1±9.8	21.6±9.3	.703	21.4±8.4	22.6±8.4	.562
Knee extension strength, Kgf	45.1±20.0	44.5±20.7	.862	44.2±19.6	45.6±20.9	.650
FIM	117.5±14.1	118.5±8.1	.630	117.8±12.6	117.8±12.3	.983
Physical activity, daily steps	1492.1±1074.5	1625.6±1448.6	.635	1469.8±981.5	1604.8±1404.3	.605
EORTC QLQ-C30						
Global health status	53.9±21.5	45.9±19.6	.020	54.2±22.2	47.8±19.5	.049
Physical functioning	69.4±18.3	61.7±20.2	.133	68.7±19.4	64.7±19.0	.174
Role function	60.8±29.8	49.7±33.4	.289	61.9±30.4	51.5±31.8	.030
Emotion functioning	79.5±15.7	63.9±20.3	< .001	78.0±17.8	70.0±19.1	.005
Cognitive functioning	77.3±21.1	65.2±24.9	< .001	77.7±23.0	68.8±22.4	.013
Social functioning	77.7±24.7	60.8±31.1	< .001	76.6±28.6	66.9±26.5	.023
Nausea	6.3±11.6	12.9±17.5	.004	8.5±13.6	8.4±14.8	.974
Fatigue	40.1±20.1	47.4±22.1	.033	41.2±21.4	44.0±20.5	.389
Dyspnea	23.6±24.5	28.1±23.4	.250	25.0±24.1	22.3±22.1	.108
Pain	24.9±23.3	28.1±24.6	.404	25.9±23.7	27.8±23.4	.328
Insomnia	30.2±27.1	43.9±33.4	.004	29.1±28.6	41.4±30.3	.007
Appetite loss	30.7±29.9	40.3±29.4	.047	29.8±28.7	38.8±30.9	.048
Constipation	22.1±26.7	24.6±23.2	.557	19.5±23.7	27.0±27.3	.054
Diarrhea	17.8±24.3	22.8±3.6	.221	18.4±24.7	20.7±25.8	.562
Financial impact	21.0±28.3	33.9±29.2	.006	21.3±28.0	23.0±30.0	.051
Hospitalization, days	17.1±23.1	18.3±22.0	.741	18.8±23.5	15.9±21.7	.418

ECOG: The Eastern Cooperative Oncology Group, Kgf: kilogram-force, FIM: Function Independence Measure, EORTC: The European Organization for Research and Treatment of Cancer.

Table 4. Results from forward stepwise ordered logistic regression analyses regarding anxiety

Factor	β	SE	p	OR (95% CI)
Age	-0.023	0.012	.052	0.977 (0.955, 1.000)
Nausea	0.026	0.014	.057	1.026 (0.999, 1.054)
Cognitive functioning	-0.22	0.007	.005	0.977 (0.961, 0.993)

SE: standard error, CI: confidence interval, OR: odds ratio.

Table 5. Results from forward stepwise ordered logistic regression analyses regarding depression

Factor	β	SE	p	OR (95% CI)
Insomnia	0.013	0.006	.015	1.014 (1.003, 1.025)

SE: standard error, CI: confidence interval, OR: odds ratio.

Discussion

In the present study, the prevalence of depression was significantly higher among patients with hematological malignancy than healthy controls in Japan. However, the difference in the prevalence of anxiety between patients and healthy controls did not reach significance. The patients with hematological malignancy were more likely to suffer depression than healthy control, which might be a characteristic of patients with hematological malignancy.

We believed our results are meaningful because comparisons between patients with hematological malignancy and age-matched healthy controls are affected by various factors, including culture. In a French study, the mean HADS-anxiety and depression scores were 6.1 ± 3.6 and 3.8 ± 3.4 in healthy workers aged > 50 years, respectively [27]. In Colombia, the mean HADS-anxiety and depression scores were 4.0 ± 3.4 and 4.7 ± 3.9 in healthy men aged > 60 years, respectively [28]. One study showed severer depression among Japanese individuals compared to Americans [29]. Further, patients in the present study displayed more depression but less anxiety than did Brazilian patients with the same disease (5.9 ± 4.2 and 7.9 ± 4.7, respectively) [17]. Therefore, depression and anxiety may be affected more by culture than disease-specific factors.

Patients with anxiety had decreased global health status, emotion functioning, cognitive functioning, and society functioning, as well as increased nausea, fatigue, insomnia, appetite loss, and financial impact compared with non-anxious patients. Regarding the QLQ-C30, nearly identical results were reported in a previous study that examined Turkish patients with hematological malignancy [5].

Further, depression was also associated with physical functioning and physical symptoms among patients. However, several differences between depression and anxiety were observed. Concretely, nausea and fatigue were related to anxiety but not depression. The relationship between anxiety and nausea can be explained by classical conditioning: state anxiety directly facilitates the classical conditioning of nausea, and state anxiety exacerbates the magnitude of post-chemotherapy nausea experienced [30,31]. On the other hand, depressive symptoms and fatigue may share the same neuroendocrine-immune pathophysiologic mechanisms [32]. Therefore, a relationship between fatigue and depression was expected. However, in the present study, a relationship between fatigue and depression was not observed in patients with hematological malignancy, even though fatigue was associated with anxiety. Several prior studies also found no evidence for a cause-and-effect relationship between depression and fatigue among cancer patients [33-35].

Significant relationships between anxiety and age, nausea, and cognitive functioning were detected in patients with hematological malignancy. Consistently, it was previously reported that anxiety increase with age in healthy people [27,36,37]. The relationship between nausea and anxiety is likely identical to that of nausea and depression (explained above). Further, cognitive functioning was previously affected by anxiety in a study examining older adults [38]. Moreover, a significant relationship between depression and insomnia was detected among patients with hematological malignancy. It is well known that insomnia and depression have a bidirectional relationship in patients without cancer [39,40]. Therefore, the fact that age, cognitive functioning, and insomnia were associated with anxiety/depression in the present study is not surprising. However, the relationship between anxiety and nausea may be critical for inpatients with hematological malignancy receiving chemotherapy, because anxiety can exacerbate the nausea felt during chemotherapy [30,31].

An unexpected result was that physical functioning and activity was not significantly related to either anxiety or depression in patients with hematological malignancy. There are many reports that showed a significant relationship between physical activity and psychological health in patients with/without cancer and healthy people [41-44]. However, in the present study, among healthy controls, physical functioning such as knee extension strength was related to depression (data not shown: r = -0.186, p = .047, 95% CI: -0.357, -0.002). It is also known that physical exercise can reduce psychological symptom such as anxiety/depression in patients with cancer [45,46]. In contrast, several studies showed that physical functioning was not associated with anxiety/depression in patients with cancer [47,48]; however, the number of these studies is negligible. The physical symptoms associated with chemotherapy might affect the relationship between physical function and psychological distress; therefore, further studies are necessary to elucidate this relationship.

Despite our large sample size, this study had some limitations. First, this study was conducted at a single-center. The observation research should be performed in multiple institutions. Second, several results could not be explained logically, even with referencing prior studies. The analysis of more detail factors should be added. Third, the cross-sectional design inhibits inferring causal relationships between variables. Prospective studies about anxiety and depression among patients with hematological malignancy should be conducted to support the development of effective interventions to manage their anxiety and depression.

In conclusion, the prevalence and severity of depression was higher than that of anxiety among Japanese inpatients with hematological malignancy, which differed from prior cross-cultural results. Regarding cancer-related physical symptoms in patients with hematological malignancy, nausea was greatly relevant to anxiety, and insomnia was associated with depression. On the other hand, physical functioning and activity were not related to either anxiety or depression in patients with hematological malignancy. Clinicians should focus on the mutual relationship between psychological distress and physical symptoms more. Early identification and proper intervention are therefore vital to minimize the negative effects of anxiety/depression on patients' QoL and the outcomes of their physical symptoms. Our findings can be used for both prevention and intervention among patients with hematological malignancy. Further studies are indispensable to discover potential pathophysiologic pathways between anxiety and depression in patients with hematological malignancy.

Acknowledgments

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