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RESEARCH

Associations of nutrition impact symptoms with depression in patients with advanced cancer

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Abstract

Purpose Advanced cancer patients have nutrition impact symptoms (NISs), while many of them have depressive moods. This study aimed to determine the associations of NISs with depression.

Methods This study was a secondary analysis. The dietary intake and 19 NISs in patients receiving palliative care were evaluated using 10-point scales, and the patients were categorized into two groups (non-depression and depression groups) using the cutoff based on the Patient Health Questionnaire-9 (PHQ-9). To determine associations between depression and the number of NISs with a score of ≥ 4, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the logistic regression model were calculated.

Results A total of 225 participants were divided into the non-depression group ($n = 148$) and the depression group ($n = 77$). The prevalence of depression was 34.2%. Dietary intake was lower, and the number of NISs with a score of ≥ 4 was higher in the depression group (both $p < 0.001$). All NISs were more severe in the depression group. Significant differences were observed in 15 of the 19 NISs. In the logistic regression model, significantly higher adjusted ORs were observed in the groups with 4–6 NISs and 7 or more NISs with a score of ≥ 4 (10.76 [95% CI, 2.07–55.91], $p = 0.016$; 17.02 [95% CI, 3.08–94.22], $p < 0.001$) than in the group with no NISs with a score of ≥ 4.

Conclusion Having four or more NISs with a score ≥ 4 was associated with depression.

Keywords Nutrition · Dietary intake · Symptom · Depression · Advanced cancer · Palliative care

Abbreviations

NIS	Nutrition impact symptom
ECOG	Eastern Cooperative Oncology Group
BMI	Body mass index
%WL	Weight loss rate
Ingesta-VVAS	Ingesta-Verbal/Visual Analog Scale
QOL	Quality of life
FAACT ACS	Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale
PHQ-9	Patient Health Questionnaire-9
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval

Introduction

Cancer cachexia is defined as a multifactorial syndrome involving the ongoing loss of skeletal muscle mass, with or without fat mass, that cannot be completely reversed by conventional nutritional care and can progressively lead to impaired physical function in various cancers [1, 2]. In pathophysiology, cancer cachexia is also characterized by protein and energy imbalances induced by the combination of reduced dietary intake and abnormal metabolism due to systemic inflammation [1, 2]. Cancer cachexia has a typical pattern of physical symptoms (e.g., lack of appetite, nausea, pain, and impaired physical function) and psychological symptoms (e.g., feeling sad, anxiety, sleep disruption, and drowsiness), leading to emotional distress (e.g., eating-related distress and weight-related distress) in patients with advanced cancer [3, 4]. Many of these physical and psychological symptoms are considered nutrition impact symptoms

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(NISs) because they are generally related to dietary intake, deteriorated nutritional status, and weight loss [5–10]. NISs can interfere with the desire to eat, appetite, and the ability to ingest and digest food in patients with cancer; however, there has been no consensus on the definition of NISs [3]. Overall, the management of NISs is considered a pivotal component of the assessment and management of cachexia in supportive and palliative care [11–14].

A large retrospective matched cohort study was performed using population data from the United Kingdom and reported the probabilities of cancer and depression, as well as diabetes, dementia, and thyroid dysfunction, among patients presenting with unexpected weight loss. The study emphasized that clinicians need to prioritize screening for cancer and depression in patients with unexpected weight loss who are over 60 years old, regardless of their sex [15]. Moreover, a Mendelian randomization study showed a potential bidirectional relationship between depression-induced cachexia and sarcopenia with implications for both mental and physical health. The authors concluded that decreased muscle strength due to cachexia and sarcopenia may lead to a higher risk of depression [16]. Furthermore, a scoping review suggested that there are associations among cachexia, sarcopenia, and depression in elderly people with a high frequency of cancer [17]. In addition to these studies on mixed populations of cancer and non-cancer patients, several studies have recently shown that correlations exist among malnutrition, cachexia, sarcopenia, and depression in patients with cancer [18–23]. There are also some papers reporting from a nutritional perspective that the incidence of vitamin B1 deficiency is high in cancer patients with Wernicke–Korsakoff syndrome and delirium [24, 25]. However, there is a lack of focus on the associations of NISs, which are connected to reduced dietary intake, malnutrition, cachexia, and sarcopenia, with depression in patients with advanced cancer. Therefore, this study aimed to investigate the prevalence of depression and assess the associations of NISs with depression in patients with advanced cancer in palliative care.

Materials and methods

Sites and participants

This study involved the secondary analysis of a multicenter survey using a self-reported questionnaire to develop a tool assessing eating-related distress experienced by patients with advanced cancer [26]. In brief, the survey was performed in palliative care outpatient services, hospital palliative care teams, and palliative care units in Japan. The development phase of the survey was conducted at five hospitals between July and September 2020, and the validation phase was performed at 11 hospitals between January and July 2021. In this study, the data obtained in the validation phase were exclusively used because no information on depression was obtained in the development phase.

Eligible patients were enrolled in the survey based on the following inclusion criteria: (1) patients newly referred to palliative care, (2) adult patients (20 years or older), (3) patients diagnosed with locally advanced or metastatic cancer and hematologic neoplasms, (4) patients aware of the diagnosis of malignancy, and (5) patients with the capability of completing a self-reported questionnaire. Patients forbidden to eat through the mouth by the primary physician and patients with serious psychological distress recognized in an interview with the palliative care physician were excluded. Patients who declined to participate in the survey were also excluded.

This study was conducted following the ethical standards outlined in the Helsinki Declaration and the ethical guidelines for medical and health research involving human subjects presented by the Ministry of Health, Labor, and Welfare in Japan [27]. This study was approved by each of the local institutional review boards at all participating institutes, including the Research Ethics Board of the National Cancer Center (No. 2020–070). Acquiring written or oral informed consent was not employed, because individual informed consent from participants is not necessarily required by Japanese law in a non-invasive observational trial like this study. However, completing and returning the questionnaire was regarded as their agreement to participate in the study. When patients did not want to participate in the study, they were requested to return the questionnaire with "no participation" indicated.

Measurement

Patients' demographic and characteristic data, such as age, sex, Eastern Cooperative Oncology Group (ECOG) performance status [28], presence of symptomatic fluid retention (e.g., edema, pleural effusion, and ascites), and treatment status (i.e., pre-chemotherapy, chemotherapy, and never treated/previous treatment), were collected. Both patients who did not receive cancer treatment because of their bad condition and patients who decided to cease cancer treatment were categorized into the never treated/previous treatment group.

Patients' anthropometric measurement data (height [m] and current and previous body weight [kg]) were also obtained. The body mass index (BMI) was calculated by dividing the body weight by the height squared, and the weight loss rate (%WL) over 6 months was calculated as follows: (current body weight − previous body weight) / previous body weight × 100). Patients with a 6-month %WL of > 5% or BMI < 20 kg/m^2 + 6-month %WL of > 2% were

diagnosed with cachexia based on the international diagnostic criteria [1].

Patients' dietary intake was measured using the Ingesta-Verbal/Visual Analog Scale (Ingesta-VVAS), which consists of 10 points (a scale from 0 "nothing at all" to 10 "as usual") to assess energy food intake and nutritional risk in patients with cancer. Higher scores indicate better dietary intake. The Ingesta-VVAS was well-correlated with energy intake. An ingesta-VVAS score of ≤ 7 detected patients with nutritional risk of weight loss in medical oncology [29, 30].

In this study, NISs were tentatively defined as symptoms that compromise dietary intake and drive malnutrition. The NIS cluster was considered to have a broad range of physical and psychological symptoms that interfere with the desire to eat and the ability to ingest and digest food [3, 4]. Patients rated the levels of 19 NISs, namely oral pain, pain, shortness of breath, fatigue, drowsiness, lack of appetite, early satiety, nausea, vomiting, constipation, diarrhea, abnormal taste, abnormal smell, dry mouth, dental problems, difficulty swallowing, food bolus obstruction, anxiety, and feeling sad, with a score ranging between 0 and 10 (0, no; 1–3, mild; 4–6, moderate, 7–9, severe; 10, unbearable). These symptoms were adopted from the Edmonton Symptom Assessment System [31, 32] and Patient-Generated Subjective Global Assessments [33, 34] and edited by the authors based on the findings of our previous studies because of no consensus definition of NISs [3–5, 7, 10].

Patients were asked to measure their quality of life (QOL) using the Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale (FAACT ACS), which involves 12 items. The FAACT ACS can be used to specifically assess patients' cachexia-related symptoms and concerns. The five-item anorexia symptoms and four-item anorexia concern subscales were derived from the 12 items. Higher scores indicate better QOL [35, 36].

Patients were also requested to answer the Patient Health Questionnaire-9 (PHQ-9), which is a self-administered questionnaire with nine items that help screen for depression. A PHQ-9 score of ≥ 10 indicates that the respondent may suffer from major depression [37–39]. The validity of the PHQ-9 for depression in patients with cancer was previously evaluated in two large studies [40, 41].

Statistical analysis

Patients were categorized into two groups (the non-depression and depression groups) using the cutoff value (< 10 and ≥ 10) based on the PHQ-9 score. Their demographic, characteristic, and anthropometric measurement data were presented as proportions (%) for categorical variables or medians (interquartile range [IQR]) for continuous variables, where appropriate. The dietary intake measured using the Ingesta-VVAS, 19 NISs rated using a 10-point scale, and cachexia-related QOL evaluated using the FAACT ACS were also presented as medians (IQR). Comparisons between groups were performed using the Mann–Whitney U test or chi-squared test, where appropriate.

To determine the association between the PHQ-9 score and the number of NISs with a score of ≥ 4, crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the logistic regression model were calculated. The PHQ-9 score was dichotomized using the cutoff value (< 10 and ≥ 10) as a dependent variable. The patients were categorized into four subgroups based on the number of NISs with a score of ≥ 4 (0, 1–3, 4–6, and 7 or more), which was one of the independent variables because four or more NISs with a score of ≥ 4 was significantly associated with decreased dietary intake and higher eating-related distress [10]. A multivariate model was adjusted for the number of NISs with a score of ≥ 4 (0, 1–3, 4–6, and 7 or more), age, sex (male and female), ECOG performance status (0–1, 2, and 3–4), and treatment status (pre-chemotherapy, chemotherapy, and never treated/previous treatment).

The results were considered to be significant for p-values < 0.05. Complete case analyses were performed, and no multiplicity adjustments were made in the analyses because this study aimed to determine the association between NISs and depression in an exploratory manner. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Among 495 patients asked to participate in this study, 378 responded (response rate, 76.4%), and no one directly refused to participate. All 144 patients participating in the development phase and nine patients participating in the validation phase were excluded for missing data in the PHQ-9. Thus, 225 patients were included in the final analysis. They were divided into the non-depression group ($n = 148$) and the depression group ($n = 77$) using the cutoff value (< 10 and ≥ 10) for the PHQ-9 score. The prevalence of depression was 34.2% in this population. The study is summarized in Fig. 1.

Patient demographics and characteristics are presented in Table 1. The median age was 62.0 (IQR 52.0–72.0) years, and 116 of the 225 patients (52.3%) were male. Regarding the proportions of primary cancer sites, 25.1% were in the lung, 15.5% were in the liver, biliary system, and pancreas, and 14.6% were in the upper and lower gastrointestinal tract. The proportions of ECOG performance status 0–1, 2, 3, and 4 were 54.6%, 19.7%, 20.2%, and 5.5%, respectively. Of the 225 patients, 23.4% had symptomatic fluid retention, 47.0% had cancer cachexia or refractory cachexia, and 67.6% were receiving chemotherapy. A comparison between patients

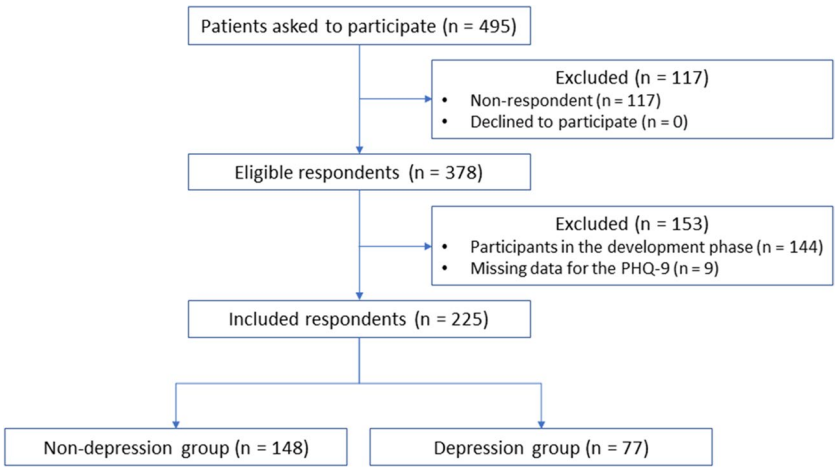

Fig. 1 Study diagram. PHQ-9, Patient Health Questionnaire-9

Table 1 Patient demographics and characteristics

	Total	Non-depression group	Depression group	*P*-value
N	225	148	77	
Age in years	62.0 (52.0–72.0)	63.0 (53.0–73.0)	57.0 (51.0–70.0)	0.095
Sex				0.140
Male	116 (52.3%)	82 (55.8%)	34 (45.3%)	
Female	106 (47.7%)	65 (44.2%)	41 (54.7%)	
Primary cancer site				0.821
Lung	55 (25.1%)	33 (22.8%)	22 (29.7%)	
Liver, biliary system, and pancreas	34 (15.5%)	25 (17.2%)	9 (12.2%)	
Upper and lower gastrointestinal tract	32 (14.6%)	24 (16.6%)	8 (10.8%)	
Breast	15 (6.8%)	10 (6.9%)	5 (6.8%)	
Urinary system and prostate	14 (6.4%)	10 (6.9%)	4 (5.4%)	
Head and neck	9 (4.1%)	6 (4.1%)	3 (4.1%)	
Hematologic malignancy	8 (3.7%)	4 (2.8%)	4 (5.4%)	
Uterus and ovaries	7 (3.2%)	5 (3.4%)	2 (2.7%)	
Others	45 (20.5%)	28 (19.3%)	17 (23.0%)	
ECOG performance status				0.003
0–1	119 (54.6%)	91 (63.6%)	28 (37.3%)	
2	43 (19.7%)	24 (16.8%)	19 (25.3%)	
3	44 (20.2%)	22 (15.4%)	22 (29.3%)	
14	12 (5.5%)	6 (4.2%)	6 (8.0%)	
Body mass index (kg/m^2)	20.9 (18.8–23.9)	21.3 (18.9–24.3)	20.2 (18.6–23.2)	0.103
Weight loss rate over 6 months (%)	3.4 (0.0–8.5)	3.3 (0.0–8.0)	3.8 (0.0–11.3)	0.416
Symptomatic fluid retention, yes	51 (23.4%)	26 (17.9%)	25 (34.2%)	0.007
Cachexia/refractory cachexia, yes	95 (47.0%)	62 (47.0%)	33 (47.1%)	0.981
Treatment status				0.372
Pre-chemotherapy	14 (6.5%)	7 (4.9%)	7 (9.7%)	
Chemotherapy	146 (67.6%)	100 (69.4%)	46 (63.9%)	
Never treated/previous treatment	56 (25.9%)	37 (25.7%)	19 (26.4%)	

Values represent proportions (%) or medians (interquartile range) where appropriate

ECOG, Eastern Cooperative Oncology Group

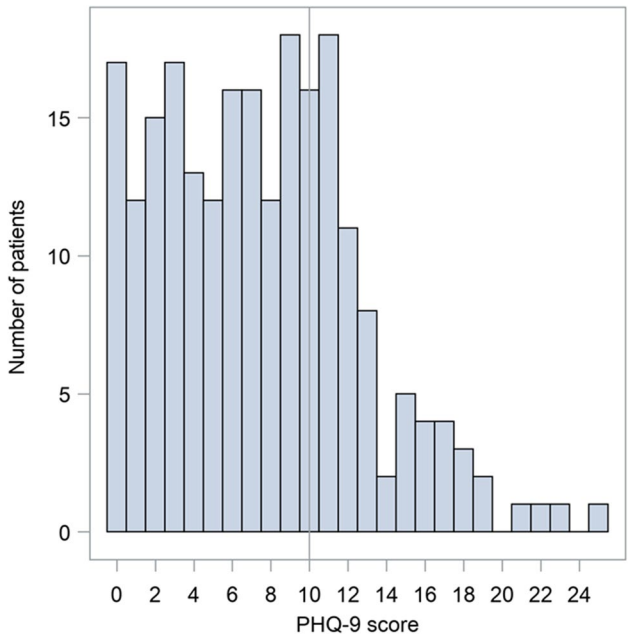

Fig. 2 Relationship between the number of patients and the PHQ-9 score. PHQ-9, Patient Health Questionnaire-9

with and without depression yielded the following results. Significant differences were observed in ECOG performance status ($p = 0.003$) and symptomatic fluid retention ($p = 0.007$). Patients with depression had a significantly worse performance status and more severe symptomatic fluid retention than those without depression.

The number of patients for each PHQ-9 score is illustrated in Fig. 2. The number of patients was relatively high in the lower point range but highest for the scores of 9 and 11, and then, the number of patients decreased as the scores increased further.

The relationships among dietary intake, NISs, and depression are shown in Table 2. The median value for the dietary intake assessed using the Ingesta-VVAS was 6.0 (IQR 5.0–8.0), and that for the number of NISs with a score of ≥ 4 was 3.0 (IQR 1.0–6.0) in the total cohort. Dietary intake was significantly lower, and the number of NISs with a score of ≥ 4 was significantly higher in the depression group than in the non-depression group (both $p < 0.001$). Furthermore, all NIS scores were higher in the depression group. Significant differences were observed between the non-depression and depression groups for 15 of the 19 NISs.

Table 2 Relationship between dietary intakes, NISs, and depression

	Total	Non-depression group	Depression group	*P*-value
N	225	148	77	
Dietary intake	6.0 (5.0–8.0)	7.0 (5.0–8.0)	5.0 (3.0–7.0)	< 0.001
NISs				
Oral pain	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.394
Pain	3.0 (0.5–6.5)	3.0 (0.0–6.0)	4.5 (2.0–7.0)	0.003
Shortness of breath	0.0 (0.0–2.0)	0.0 (0.0–2.0)	2.0 (0.0–4.0)	0.004
Fatigue	3.0 (0.0–5.0)	2.0 (0.0–4.0)	4.0 (2.5–6.0)	< 0.001
Drowsiness	3.0 (0.0–5.0)	2.0 (0.0–3.0)	4.0 (2.0–6.0)	< 0.001
Lack of appetite	3.0 (0.0–5.0)	1.0 (0.0–4.0)	5.0 (3.0–6.0)	< 0.001
Early satiety	3.0 (0.0–5.5)	2.0 (0.0–4.0)	5.0 (3.0–7.0)	< 0.001
Nausea	0.0 (0.0–2.0)	0.0 (0.0–1.0)	1.0 (0.0–3.0)	< 0.001
Vomiting	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.003
Constipation	2.5 (0.0–5.0)	2.0 (0.0–5.0)	4.0 (1.0–7.0)	0.005
Diarrhea	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.707
Abnormal taste	0.0 (0.0–2.0)	0.0 (0.0–1.0)	0.0 (0.0–3.0)	0.028
Abnormal smell	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	< 0.001
Dry mouth	0.0 (0.0–3.0)	0.0 (0.0–2.0)	2.0 (0.0–5.0)	< 0.001
Dental problems	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.025
Difficulty swallowing	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.050
Food bolus obstruction	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.172
Anxiety	2.0 (0.0–4.0)	1.0 (0.0–3.0)	3.0 (2.0–7.0)	< 0.001
Feeling sad	2.0 (0.0–5.0)	1.0 (0.0–3.0)	4.0 (2.0–7.0)	< 0.001
Number of NISs with a score of ≥ 4	3.0 (1.0–6.0)	2.0 (1.0–4.0)	6.0 (3.0–8.0)	< 0.001

Values represent the medians (interquartile range). Dietary intakes were assessed using the Ingesta-Verbal/Visual Analog Scale (10-point scale). High scores indicate better dietary intake. NISs were rated between 0 and 10 (0, no; 1–3, mild; 4–6, moderate, 7–9, severe; 10, unbearable)

NISs, nutrition impact symptoms

Table 3 Relationship between cachexia-related QOL and depression

	Total	Non-depression group	Depression group	*P*-value
N	225	148	77	
FAACT ACS 12-item score	32.0 (28.0–38.0)	36.0 (30.0–40.0)	28.0 (23.0–32.0)	< 0.001
FAACT ACS 5-item score	14.0 (11.0–17.0)	16.0 (13.0–18.0)	11.0 (7.0–14.0)	< 0.001
FAACT ACS 4-item score	11.0 (9.0–12.0)	12.0 (10.0–13.0)	9.0 (7.0–11.0)	< 0.001

Values represent the medians (interquartile range)

QOL, quality of life; *FAACT ACS*, Functional Assessment of Anorexia/Cachexia Therapy Anorexia Cachexia Subscale

The relationship between the cachexia-related QOL measured using the FAACT ACS and depression is presented in Table 3. The scores obtained for the 12-item FAACT ACS, five-item anorexia symptoms, and four-item anorexia concerns in the depression group were significantly lower than those in the non-depression group (all $p < 0.001$). Patients with depression had a more impaired cachexia-related QOL.

Adjusted ORs for the number of NISs with a score of ≥ 4 and other variables associated with depression are shown in Table 4. In the logistic regression model, significantly higher adjusted ORs were observed in the groups with 4–6 NISs and 7 or more NISs with a score of ≥ 4 (10.76 [95% CI, 2.07–55.91], $p = 0.016$; 17.02 [95% CI, 3.08–94.22], $p < 0.001$, respectively) than in the group with no NISs with a score of ≥ 4. Having four or more NISs with a score of ≥ 4 was associated with depression.

Discussion

To the best of our knowledge, this is the first study to determine the associations of NISs with depression in patients with advanced cancer in palliative care settings. The results demonstrated that having four or more NISs with a score of ≥ 4 on the 10-point analog scale was a risk of depression and that depression was correlated with poor cachexia-related QOL in this population.

The prevalence of depression in this study population was 34%, which was relatively higher than that reported in previous investigations in patients with cancer. The higher prevalence may be attributed to the difficult situation (i.e., death is imminent without effective treatment) in which the participants were placed and a broad spectrum of depression from the adjustment disorder level to severe depression. A meta-analysis of 211 studies with 82,426 patients reported

Table 4 Association between NISs and depression

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Number of NISs with a score ≥ 4				
0	1.00 (reference)		1.00 (reference)	
1–3	3.89 (0.83, 18.22)	0.154	2.98 (0.60, 14.87)	0.134
4–6	14.00 (3.01, 65.16)	0.005	10.76 (2.07, 55.91)	0.016
7 or more	24.00 (4.95, 116.35)	< 0.001	17.02 (3.08, 94.22)	< 0.001
Age in years	0.98 (0.96, 1.00)	0.096	0.99 (0.96, 1.02)	0.556
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	1.52 (0.87, 2.66)	0.141	2.34 (1.11, 4.95)	0.026
ECOG performance status				
0–1	1.00 (reference)		1.00 (reference)	
2	2.57 (1.23, 5.37)	0.312	1.40 (0.55, 3.55)	0.856
3–4	3.25 (1.66, 6.37)	0.031	1.66 (0.68, 4.07)	0.423
Treatment status				
Pre-chemotherapy	1.00 (reference)		1.00 (reference)	
Chemotherapy	0.46 (0.15, 1.39)	0.206	0.46 (0.11, 1.95)	0.301
Never treated/previous treatment	0.51 (0.16, 1.68)	0.485	0.54 (0.11, 2.60)	0.661

The multivariate model is adjusted for NISs, age, sex, ECOG performance status, and treatment status

OR, odds ratio; *CI*, confidence interval; *ECOG*, Eastern Cooperative Oncology Group; *NISs*, nutrition impact symptoms

that the mean prevalence of depression in patients with cancer ranged from 8 to 24% and differed according to the type of instrument, type of cancer, and treatment phase. It also revealed that the prevalence of depression was highest during cancer treatment (14%) [42]. A multicenter observational study of 528 adult patients with cancer reported that the prevalence of depression was 23% [21], and a retrospective study of 90 patients in a single cancer center showed that the prevalence of depression was 8% [22]. Unlike the present study, the settings of these studies were not limited to palliative care settings.

This study revealed that having four or more NISs with a score of ≥ 4 was associated with depression diagnosed using the PHQ-9 in patients with advanced cancer. The results also indicated the correlation between depression and cachexia-related QOL measured using the FAACT ACS in this population. Furthermore, our previous research demonstrated that patients having four or more NISs with a score of ≥ 4 were likely to have poorer dietary intake and higher eating-related distress [10]. Presenting four or more NISs with a score of ≥ 4 may be one indicator for the start of multimodal interventions in supportive and palliative care. A case series and mini-review suggested that simple assessments and inexpensive interventions to manage NISs may have beneficial effects on patients referred to a cancer cachexia clinic [8]. Thus, prompt assessment and management of NISs is a key component of supportive and palliative care for patients with cancer cachexia. However, no standard guidelines have been adopted regarding the specific management of NISs in cancer care [3]. Further research is needed to understand NISs and develop holistic, multimodal care for patients affected by cancer cachexia [43].

Many NISs (e.g., pain, fatigue, drowsiness, lack of appetite, nausea, anxiety, and feeling sad) are likely to be induced through alternations in the central nervous system (CNS)/hypothalamic–pituitary–adrenal (HPA) axis, or central neurotransmitters, due to systemic inflammation, which is considered one of the mechanisms responsible for cancer cachexia. These NISs often generate emotional distress, which can disrupt circadian rhythm, accelerate systemic inflammation, and alter the CNS/HPA axis. There are complex relationships among systemic inflammation, CNS inflammation, NISs, and emotional distress, which generally coexist and amplify one another in cachectic patients with advanced cancer. Thus, it appears that there is a common pathogenesis between cancer cachexia and depression and that they interact with each other [1–4].

This study has several limitations. Given the observational nature of a cross-sectional study, potential confounders may not have been obtained or accounted for in this study. It was difficult to determine the confounders of the association between NISs and depression other than the factors used in this study. Moreover, causality could not be determined in the current study design/analysis. Furthermore, the presence or absence of cachexia was excluded from the logistic regression model because the prevalence of symptomatic fluid retention was relatively high (23%), which may impair the diagnostic ability of the international criteria [44–46]. Additionally, patients with major depressive disorders may be excluded by the exclusion criteria. No data on previous diagnoses of depressive disorders or taking antidepressants were obtained, and the degree of depression may change over time during the cancer treatment journey. Finally, no information on systemic inflammation or the types of cancer treatments, including cytotoxic chemotherapy, targeted therapy, immunotherapy, or a combination of them, were collected, although approximately 70% of participants were receiving cancer treatments. Nevertheless, the findings of this study were representative of the real situations for patients with advanced cancer receiving palliative care in Japan.

Conclusion

The prevalence of depression was relatively high among patients with advanced cancer receiving palliative care in Japan. The NIS cluster was associated with depression in this study population. The higher the number of NISs, the higher the risk of depression. Presenting four or more NISs with a score of ≥ 4 may be one indicator for the start of multimodal interventions. The medical management of NISs should be a major component in holistic, multimodal care for cancer cachexia provided by a multidisciplinary team.

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Author contribution This study involved the secondary analysis of a multicenter survey using a self-reported questionnaire to develop a tool assessing eating-related distress experienced by patients with advanced cancer [26]. Authors who conducted the survey as a team contributed to this study.

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Declarations

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