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ORIGINAL RESEARCH

The Relationship Between Nutrition Impact Symptoms, Intake Status, and Systemic Inflammation for Cancer Patients

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Purpose: Cancer-related malnutrition (CRM) is characterized by nutrition impact symptoms (NIS), prominently reduced intake, and irreversible systemic inflammation (SI). This study aimed to use NIS as a phenotype to explore the etiological mechanisms of CRM and facilitate a more precise classification approach for CRM patients by symptomatic clusters.

Patients and Methods: 147 CRM patients were included in this study. Exploratory factor analysis (EFA) was used to identify the NIS clusters, analyze their regression factor score (RFS), and explore potential patient groups. Spearman correlation, Kruskal–Wallis tests, and regression analysis were used to analyze the correlation and interaction between RFS and nutrition, SI, and intake status.

Results: EFA identified 4 factors: RFS-1 was significantly correlated with mid-arm circumference (MAC) ($r = -0.28$, $p = 0.001$), calf circumference ($r = -0.32$, CC) ($p < 0.001$), hand grip strength ($r = -0.24$, $p = 0.004$), hemoglobin ($r = -0.19$, $p= 0.023$), albumin ($r = -0.18$, ALB) ($p = 0.026$), pre-albumin (PAB) ($r = -0.26$, $p = 0.002$), C-reactive protein (CRP) ($r = 0.33$, $p < 0.001$), neutrophil-to-lymphocyte ratio (NLR) ($r = 0.32$, $p < 0.001$), and systemic immune-inflammation index (SII) ($r = 0.28$, $p = 0.001$). RFS-2 was also significantly correlated with MAC ($r = -0.21$, $p =0.010$), CC ($r = -0.19$, $p = 0.030$), ALB ($r = -0.23$, $p = 0.010$), and PAB ($r = -0.21$, $p = 0.010$). Two-step cluster analysis identified 3 patient groups: Group 1 and Group 2 had higher MAC than Group 3 ($p = 0.001$) and had higher CC than Group 3 ($p = 0.029$). Group 1 and Group 2 had lower CRP than Group 3 ($p = 0.007$), presented lower NLR than Group 3 ($p = 0.004$), and had lower SII than Group 3 ($p = 0.014$). Group 2 ($p < 0.001$) had a lower risk of developing anorexia than Group 3, and Group 2 ($p = 0.010$) had a lower risk of decreasing intake.

Conclusion: This exploratory study identified 4 NIS clusters, 2 significantly related to SI and intake status. Based on CAM etiological mechanisms, 3 potential patient groups were explored, which established a robust phenotypic framework for subsequent large-scale investigations, addressing a critical gap in CRM research and providing a standardized phenotypic tool for future multi-center analyses. These efforts will contribute significantly to enhancing the prevention, treatment, and clinical management of CRM.

Keywords: cancer-related malnutrition, nutrition impact symptom, intake status, systemic inflammation, symptomatic clusters

Introduction

Globally, the prevalence of cancer-related malnutrition (CRM) among hospitalized patients reaches approximately 70%,[1] with even higher incidence reported in China, where CRM affects up to 80.4% of patients,[2] positioning it as one of the most serious complications of cancer. Due to elevated resting energy expenditure, aberrant metabolic reprogramming, and treatment-associated factors,[3] cancer patients face a greater risk of malnutrition compared to other chronic diseases, characterized by nutrition impact symptoms (NIS), prominently reduced intake, and irreversible systemic inflammation (SI). NIS refers to a series of symptoms affecting nutrient intake, digestion, and absorption,[4] directly contributing to dietary insufficiency and the progression of malnutrition. In turn, it diminishes the tolerance and efficacy of anti-tumor

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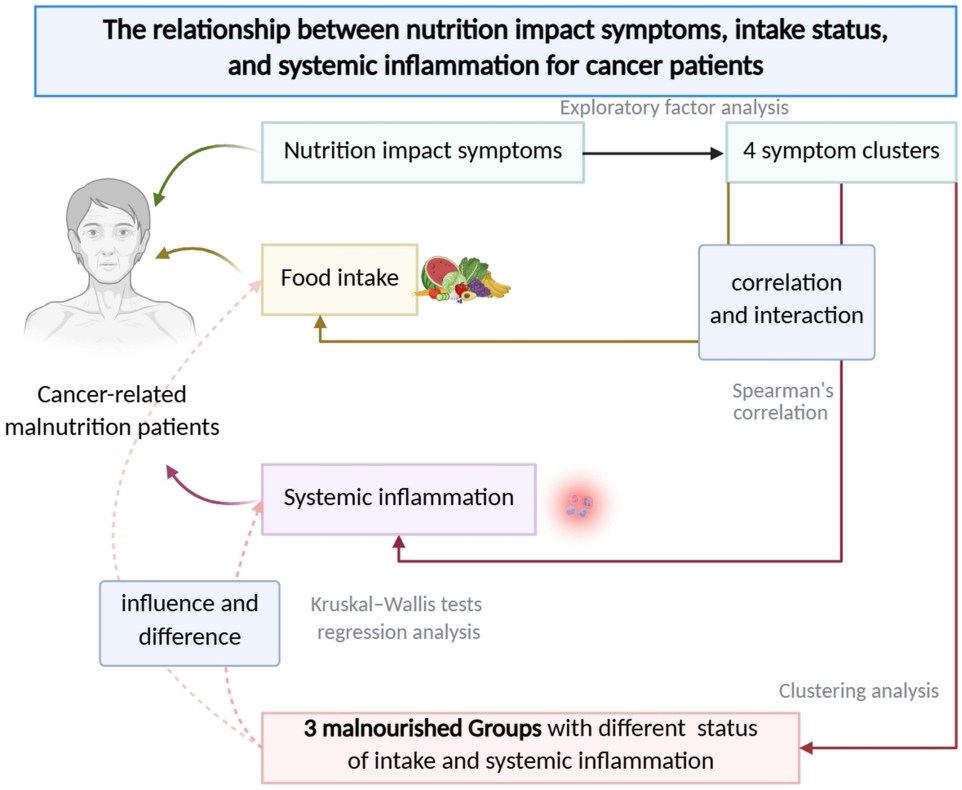
Graphical Abstract



therapies and prolongs the hospitalization time, thus increasing the burden of medical care and significantly impairing the quality of life and survival outcome.[5] Additionally, reduced dietary intake independently correlates with increased inpatient mortality risk.[6] CRM usually trends to progressive worsening, closely related to the chronic and irreversible SI state,[7] while the onset or worsening of NIS often signals further exacerbation of SI.[3]

Currently, a patient-generated subjective global assessment (PG-SGA)[8] scale classifies a score of 2–8 as moderate malnutrition and a score of 9 or above as severe, primarily utilized for evaluating CRM. Within the PG-SGA, the significance of NIS is underscored by its contribution to nearly 50% of the symptom scores. However, the qualitative assessment of CRM remains limited due to insufficient categorization of malnourished patients (distinguished only as moderately or severely malnourished) and a lack of etiological differentiation, particularly regarding key factors such as low food intake and SI, as emphasized in the Global Leadership Initiative on Malnutrition (GLIM).[9] This limits the utility of PG-SGA in guiding diagnostic and therapeutic strategies for CRM. Furthermore, NIS frequently manifests in patients with moderate to severe malnutrition,[10] suggesting it is a phenotype that could support more nuanced qualitative assessment and exploration of etiological mechanisms, thereby facilitating a novel and more precise classification approach for CRM patients.

Previous studies have primarily focused on the impact of individual NIS on nutritional or intake status and examined correlations between NIS and inflammatory markers. These findings suggested that inflammation may serve as an important mediator in the relationship between NIS and prognosis, with symptoms such as anorexia, vomiting, and dysphagia identified as key contributors to poor outcomes.[11,12] However, they often lack in-depth analysis of their underlying relationships and symptomatic clusters influencing CRM. Therefore, this study will collect data on NIS, intake, and inflammation for CRM patients, exploring symptom clusters by exploratory factor analysis and appraising

their correlations and interactions. Furthermore, clinical implications for nutritional assessment, etiological classification, and severity stratification of CRM will be determined based on the weighting of these symptom clusters.

Materials and Methods

Study Design

This study employed a descriptive design. The sample size was calculated a priori based on a pre-survey result indicating a Cronbach's α of 0.71. With an expected Cronbach's α of 0.8, 12 NIS items as independent variables, a power of 80%, and a significance level (α) of 0.05, the minimum required sample size was estimated to be 121 using PASS version 15.0 (NCSS, LLC). To accommodate an anticipated 10% rate of invalid responses, the sample size was adjusted to 133. Ultimately, a total of 147 participants were included in the study.

Population

147 CRM patients, treated in the Department of Oncology at Wangjing Hospital, China Academy of Traditional Chinese Medicine, from July 2023 to September 2024, were included in this study, which was deemed sufficient for the observational objectives of this study. The inclusion criteria were as follows: i) malnutrition assessed according to PG-SGA ≥ 2 points;[13] ii) patients aged ≥18 years; iii) Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 3. Exclusion criteria: i) patients who defecate through gastrointestinal fistula; ii) pregnant and lactating women; iii) patients who are receiving radiotherapy and chemotherapy. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Wangjing Hospital (approval number: WJEC-KT-2023-020-P001). Written informed consent was obtained from all individual participants prior to their enrollment in the study.

Baseline Clinical Assessment

All demographic and clinical information of patients was collected through the electronic medical record system of the hospital information system. The demographic information profile included age, sex, height, and weight, and clinical information included tumor type, pathological stage, and comorbid chronic diseases (hypertension, diabetes, and hyperlipidemia).

Clinical Characteristics Assessment

Nutritional Status

PG-SGA[8] was used to evaluate the malnutritional status (a score of 2–8 as moderate malnutrition and outweighs or equals 9 as severe). NIS including loss of appetite, nausea, vomiting, constipation, diarrhea, sore mouth, dry mouth, taste alteration, altered smell, dysphagia, early satiety, and abdominal bloating.[13] Body mass index (BMI) was calculated as weight (kg) per squared height (m2), which was divided into 4 groups according to the BMI characteristics of the Chinese population[14] including lean group (<18.5 kg/m2), normal group (18.5–23.9 kg/m2), overweight group (24–27.9 kg/m2), and obese group (≥28 kg/m2). The data of mid-arm circumference (MAC, cm), calf circumference (CC, cm), and hand grip strength (HGS, kg) were measured by tape rule and electronic grip strength indicator (Camry, model EH101, Guangdong, China). Nutritional blood indexes were collected on the day of admission, including hemoglobin (HGB), albumin (ALB), and pre-albumin (PAB).

Intake Status

Appetite was assessed using the Visual Analog Scale (VAS)[15] for appetite, consisting of a 100 mm line, where 0 mm denotes "no appetite at all" and 100 mm indicates "very good appetite". A VAS score of ≤ 50 mm was considered indicative of anorexia risk. Intake status was also evaluated using the PG-SGA scale; in this study, intake was classified as normal if the patient's intake was unchanged or greater than usual, and as abnormal if it was less than usual.

SI Level

The neutrophil-to-lymphocyte ratio (NLR),[16] systemic immune-inflammation index (SII),[17] and C-reactive protein (CRP) were collected to evaluate the SI level. The NLR is the ratio of neutrophils to the number of lymphocytes, and SII is the multiplication of NLR by platelets.

Statistical Analyses

Exploratory factor analysis was conducted using SPSS software (Microsoft) on 12 symptoms (loss of appetite, nausea, vomiting, constipation, diarrhea, sore mouth, dry mouth, taste alteration, altered smell, dysphagia, early satiety, and abdominal bloating). The observed variables (12 symptoms) were categorized and downgraded based on their internal correlation and intrinsic data structure. Clusters with similar characteristics within the variables were obtained and extracted to be the factor. The explained variance of each factor was then analyzed, and when the total value was ≥50%, the result of the exploratory factor analysis was justified. Each symptom has a loading on each factor. When the absolute value of the loading is greater than 0.5, it is retained, thus forming a component matrix. The greater the absolute value of the loading, the higher the degree of contribution to the factor. When the loading is positive, it is a positive contribution; a negative value represents a negative contribution. Based on the explained variance and loading of the factors, the regression factor scores (RFS) of each subject were calculated using the regression method, illustrating the characteristics of each symptom cluster. Based on the RFS value of each subject, 147 cases were analyzed using a two-step cluster analysis to obtain patient groups.

Correlations were analyzed using Spearman correlation between RFS and MAC, CC, GPS, HGB, ALB, PAB, CRP, NLR, and SII. Given the unequal sample sizes across groups in this study, the exact significance was estimated via Monte Carlo simulation with 10,000 resamples to ensure the robustness of the results and to circumvent potential limitations of asymptotic methods. The starting seed was set to 2,000,000 to ensure reproducibility. Differences in RFS were analyzed between patient groups with different nutritional, SI, and intake statuses using Kruskal–Wallis tests. The effects of patient groups on nutritional, SI, and intake statuses were analyzed using linear, ordered, and logistic regression. Model diagnostics were performed for all regression models. For linear regression, we assessed linearity and homoscedasticity using residual-versus-predicted plots and evaluated normality with Q-Q plots. Influential observations were identified using Cook's distance. For logistic regression, model fit was assessed with the Hosmer-Lemeshow test and discriminative ability using AUC. Multicollinearity was evaluated with variance inflation factors (VIF). The above data analysis was done using IBM SPSS Statistics for Windows, version 25.0. (IBM Corp; Armonk, NY, USA).

Results

The Characteristics of Patients and NIS

Table 1 presents the demographic and clinical information related to malnutrition, SI, and intake statuses of the 147 patients, a total of whom 92 (62.6%) were male, with a mean age of 67.8 (±11.1) years. The most common types of

Table 1 Patient Characteristics

Sex (n=147), n (%)	
Female	55 (37.4)
Male	92 (62.6)
Age, years (n=147), mean (SD)	67.8 (11.1)
Cancer sites (n=147), n (%)	
Lung	43 (29.3)
Upper gastro-intestinal	40 (27.2)
Colorectal	21 (14.3)
Pancreatic	21 (14.3)
Breast	8 (5.4)
Others [a]	14 (9.5)

(*Continued*)

Table 1 (Continued).

Cancer stage (n=147), n (%)	
1	3 (2.0)
2	5 (3.4)
3	12 (8.2)
4	127 (86.4)
Malnutrition [b] (n=147), n (%)	
Moderate	25 (17)
Severe	122 (83)
VAS [c] of appetite (n=139), mean (SD)	55.04 (27.62)
Anorexia [c]	
Yes	72 (51.8)
No	67 (48.2)
Intake status (n=147), n (%)	
Unchanged or more than unusual	36 (24.5)
Less than unusual	111 (75.5)
Body mass index (n=147), n%	
<18.5 kg/m2	39 (26.5)
18.5–23.9 kg/m2	77 (52.4)
24-27.9 kg/m2	26 (17.7)
≥28 kg/m2	5 (3.4)
MAC, cm (n=145), median (IQR)	22 (21,24.75)
CC, cm (n=130), median (IQR)	30 (27,32)
HGS, kg (n=145), median (IQR)	15.05 (10.3,20.83)
HGB, g/L (n=147), median (IQR)	111.5 (97.25,125.75)
ALB, g/L (n=146), median (IQR)	37.25 (33.01,40.33)
PAB, g/L (n=146), median (IQR)	0.16 (0.10,0.22)
CRP, (n=119), median (IQR)	9.27 (1.57,42.86)
NLR, (n=147), median (IQR)	3.09 (2.05,5.08)
SII, (n=147), median (IQR)	592.39 (356.26,1176.55)

Notes: [a] Other sites included prostate (n=2), ovary (n=2), bladder (n=1), gall bladder (n=2), liver (n=2), womb (n=1), kidney (n=1), lymphoma (n=1), and unknown cancer site (n=1). [b] PG-SGA was used to evaluate the state of malnutrition: moderate malnutrition (PG-SGA: 2–8), severe malnutrition (PG-SGA ≥ 9). [c] Appetite was evaluated using the VAS score of appetite, which consists of a 100 mm line in length, with the leftmost (0 mm) representing "I have no appetite at all", the rightmost (100 mm) representing "I have a very good appetite", and when the VAS score is less than or equal to 50 mm it represents anorexia risk.
Abbreviations: VAS, visual analog scale; MAC, mid-arm circumference; CC, calf circumference; HGS, hand grip strength; HGB, hemoglobin; ALB, albumin; PAB, pre-albumin; CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte ratio; SII, systemic immune-inflammation index.

cancer were lung (29.3%) and upper gastrointestinal (27.2%), and 86.4% of patients had stage IV cancer. 122 patients (83%) were severely malnourished, 72 patients (51.8%) had the risk of anorexia, and only 77 patients (52.4%) were in the normal BMI (18.5 kg/m^2–23.9 kg/m^2) group. The mean values of MAC, CC, GPS, HGB, ALB, PAB, CRP, NLR, and SII are demonstrated in Table 1.

Figure 1 demonstrates the frequency of the 12 NIS in 147 patients, loss of appetite (n = 110), dry mouth (n = 105), and abdominal bloating (n = 86) occurring in more than half of whom, while the proportion of diarrhea (n = 34), altered smell (n = 24), sore mouth (n = 22), and dysphagia (n = 16) was lower. Figure 2 illustrates the distribution of the cases with less than 3 NIS or more. With only 50 patients possessing less than 3 symptoms, half were moderate malnutrition, and half were severe. 97 patients had more than or equal to 3 symptoms, and all of them were severely malnourished.

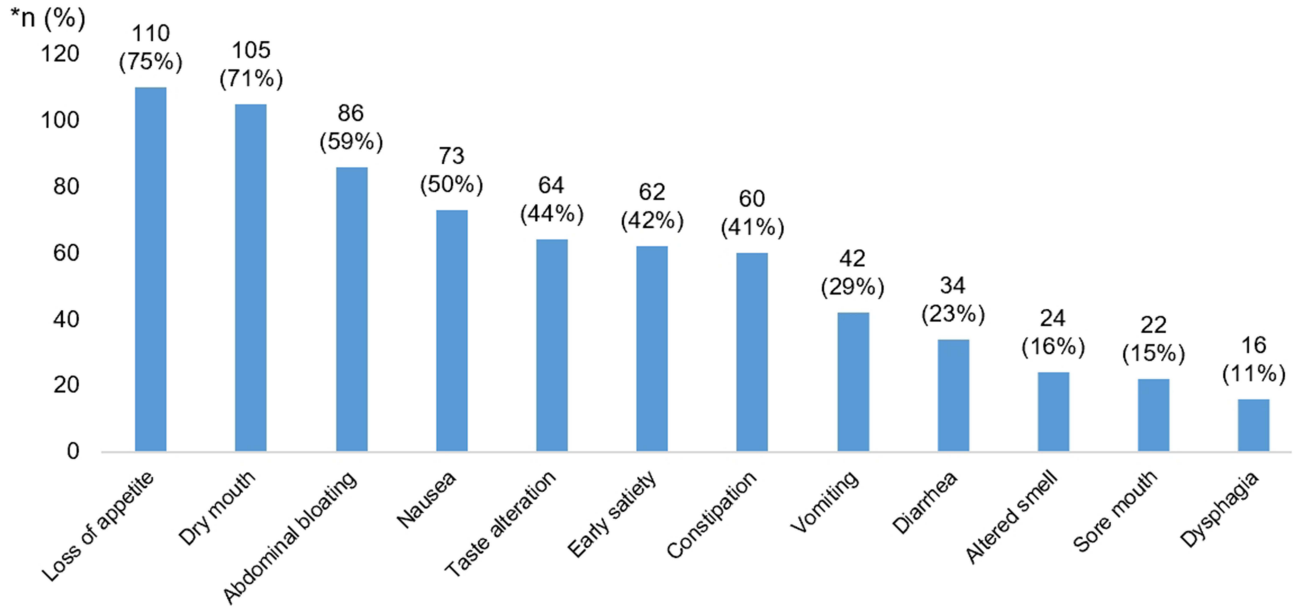


Figure 1 The frequency of nutrition impact symptoms.
Notes: * n indicates the number of patients with the symptom.

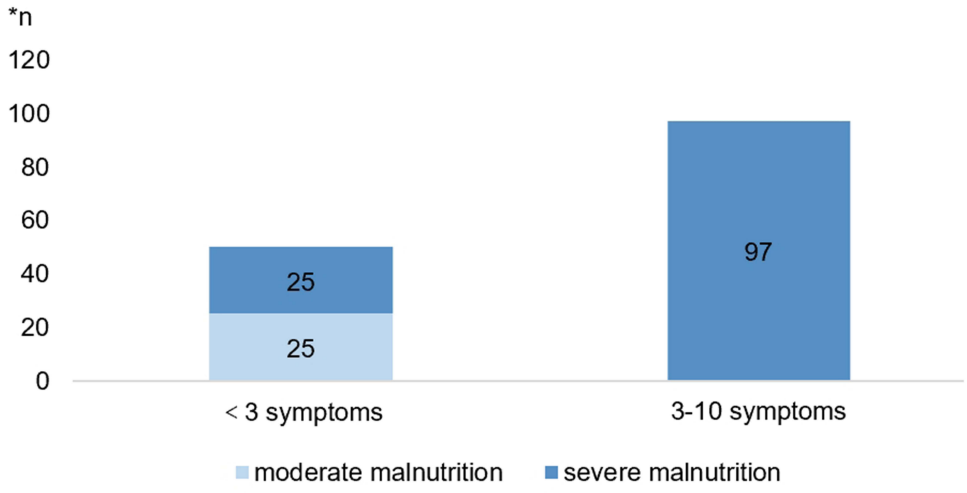


Figure 2 The distribution of the number of nutrition impact symptoms.
Notes: * n represents the number of patients (grouped based on having either <3 or 3–10 symptoms).

The results of EFA for NIS

Table 2 presents the results of the exploratory factor analysis of the 12 NIS, with four factors extracted and a total explanation variance of 57.2%, which is a moderate yet acceptable level for exploratory research in complex clinical domains. Factor 1 includes vomiting, nausea, and altered smell, all have positive loadings, but dysphagia was excluded, whose loading value was less than 0.5. Factor 2 includes early satiety, loss of appetite, taste alteration, and abdominal bloating, which all have positive loadings. Factor 3 includes diarrhea with negative loading and constipation with positive loading. Factor 4 includes dry mouth and sore mouth, whose loadings are positive. In addition, the median (interquartile range [IQR]) RFS of four factors was also described at the bottom of Table 2. For example, the Factor 1 RFS (RFS-1) (median: −0.29, IQR: −0.83, 0.70) provides an overall score for the positive loadings of nausea, vomiting, and altered smell. Table 3 presents the median (IQR) RFS for the 3 groups from specific RFS cluster profiles. Group 1 (n=47) was characterized by a negative RFS-1, RFS-3, and RFS-4 and a positive RFS-2; Group 2 (n=71) was featured with a negative RFS-1 and RFS-2 and a positive RFS-3 and RFS-4; Group 3 (n=29) marked by a positive RFS-1, RFS-2, RFS-3 and RFS-4.

The Relationship Between NIS, Intake Status, and SI Level

Tables 4 and 5 respectively demonstrate the correlations between the 4 RFS and nutritional and SI indicators. RFS-1 was significantly correlated with MAC ($r = -0.28$, $p = 0.001$), CC ($r = -0.32$, $p < 0.001$), GPS ($r = -0.24$, $p = 0.004$), HGB ($r = -0.19$, $p = 0.023$), ALB ($r = -0.18$, $p = 0.026$), PAB ($r = -0.26$, $p = 0.002$), CRP ($r = 0.33$, $p < 0.001$), NLR ($r = 0.32$, $p < 0.001$), and SII ($r = 0.28$, $p = 0.001$). RFS-2 was significantly correlated with MAC ($r = -0.21$, $p = 0.010$), CC ($r = -0.19$, $p = 0.030$), ALB ($r = -0.23$, $p = 0.010$), and PAB ($r = -0.21$, $p = 0.010$). RFS-3 and RFS-4 did not correlate significantly with the above indicators.

The Differences Between Nutrition and Intake Status and SI Level for the 3 Groups

Table 6 presents the differences in RFS between different nutritional statuses (moderately or severely malnourished subgroups, BMI subgroups). Severely malnourished patients had higher RFS-1 (−0.08; 95% CI: −0.78, 0.94; $p < 0.001$) and RFS-2 (0.42; 95% CI: −0.49, 0.95; $p < 0.001$), and the lean group (BMI <18.5 kg/m2) had higher RFS-1 (0.19; 95% CI: −0.83, 1.28; $p = 0.003$) and RFS-2 (0.38; 95% CI: −0.39, 0.90; $p = 0.010$). Table 7 presents the differences in RFS between different intake statuses (anorexia or not subgroups, normal or abnormal intake subgroups). The anorexia patients had higher RFS-1 (−0.59; 95% CI: −0.85, 0.08; $p < 0.001$) and RFS-2 (−0.56; 95% CI: −1.33, 0.58; $p < 0.001$), and abnormal

Table 2 Nutrition Impact Symptoms Factor Loading Patterns [a], Regression Factor Scores, and Factor Score Cluster Profiles (n = 147)

	Factor 1	Factor 2	Factor 3	Factor 4
Vomiting	0.834			
Nausea	0.777			
Altered smell	0.523			
Dysphagia	- [b]			
Early satiety		0.703		
Loss of appetite		0.688		
Taste alteration		0.629		
Abdominal bloating		0.621		
Diarrhea			−0.789	
Constipation			0.676	
Dry mouth				0.853
Sore mouth				0.537
Eigenvalue	2.17	2.04	1.44	1.23
Explained variance, %: Total (57.2%)	18.0	17.0	12.0	10.2
Regression factor scores, median (IQR)	−0.29 (−0.83, 0.70)	0.06 (−0.69, 0.90)	−0.05 (−0.52, 0.81)	−0.22 (−0.89, 0.67)

Notes: [a] The KMO value of 0.678, along with a significant Bartlett's test ($\chi^2(66) = 296.749$, $p < 0.001$), indicates that the data are sufficient for factor analysis despite a modest KMO value. [b] The score of dysphagia is under 0.5 points.

Table 3 Patient Grouping by Regression-factor-score Cluster Profiles, Median (IQR)

	Factor 1	Factor 2	Factor 3	Factor 4
Group 1: 47 patients (31.97%)	−0.09 (−0.74, 0.69)	0.61 (−0.42, 0.95)	−0.52 (−1.43, −0.1)	−1.19 (−1.57, −0.12)
Group 2: 71 patients (48.30%)	−0.74 (−0.93, −0.29)	−0.35 (−1.18, 0.6)	0.10 (−0.1, 0.84)	0.44 (0.09, 0.96)
Group 3: 29 patients (19.73%)	1.33 (0.9, 1.99)	0.13 (−0.56, 0.89)	0.83 (0.23, 1.28)	0.34 (−0.11, 0.68)

Table 4 Relationships Between Nutritional Indicators and Regression Factor Scores

Variable (N)	RFS-1	*p*	RFS-2	*p*	RFS-3	*p*	RFS-4	*p*
MAC (145)	−0.28	0.001	−0.21	0.010	−0.04	0.680	−0.16	0.050
CC (130)	−0.32	<0.001	−0.19	0.030	−0.09	0.310	−0.16	0.060
HGS (145)	−0.24	0.004	0.09	0.310	0.01	0.920	−0.15	0.080
HGB (147)	−0.19	0.023	−0.13	0.110	−0.04	0.610	−0.01	0.860
ALB (146)	−0.18	0.026	−0.23	0.010	0.03	0.760	−0.11	0.180
PAB (146)	−0.26	0.002	−0.21	0.010	−0.03	0.760	−0.05	0.590

Abbreviations: RFS, regression factor score; MAC, mid-arm circumference; CC, calf circumference; HGS, hand grip strength; HGB, hemoglobin; ALB, albumin; PAB, pre-albumin.

Table 5 Relationships Between Systemic Inflammation Indicators and Regression Factor Scores

Variable (N)	RFS-1	*p*	RFS-2	*p*	RFS-3	*p*	RFS-4	*p*
CRP (119)	0.33	<0.001	0.03	0.730	0.07	0.470	0.06	0.520
NLR (147)	0.32	<0.001	0.10	0.220	0.04	0.670	−0.03	0.700
SII (147)	0.28	0.001	-	0.970	0.08	0.340	0.01	0.910

Abbreviations: RFS, Regression factor score; CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte ratio; SII, systemic immune-inflammation index.

Table 6 Regression Factor Scores by Nutritional Status

Variable (N)	RFS-1, Median (IQR)	*p*	RFS-2, Median (IQR)	*p*	RFS-3, Median (IQR)	*p*	RFS-4 Median (IQR)	*p*
Malnutrition		<0.001		<0.001		0.080		0.900
Moderate (25)	−0.78 (−0.85, −0.52)		−1.33 (−1.70, −0.96)		0.09 (−0.09, 0.84)		0.44 (−1.16, 0.55)	
Severer (122)	−0.08 (−0.78, 0.94)		0.42 (−0.49, 0.95)		0.01 (−0.86, 0.77)		0.16 (−0.78, 0.67)	
BMI		0.003		0.010		0.970		0.150
<18.5 kg/m2 (39)	0.19 (−0.83, 1.28)		0.38 (−0.39, 0.90)		−0.01 (−0.9, 0.84)		0.36 (−0.04, 0.71)	
18.5–23.9 kg/m2 (77)	−0.2 (−0.77, 0.88)		0.19 (−0.55, 1.08)		0.05 (−0.49, 0.78)		0.09 (−0.90, 0.68)	
24-27.9 kg/m2 (26)	−0.7 (−0.94, −0.3)		−0.73 (−1.35, −0.09)		0.09 (−0.39, 0.67)		−0.57 (−1.18, 0.44)	
≥28 kg/m2 (5)	−0.83 (−1.09, −0.08)		−0.14 (−0.92, 0.33)		0.03 (−0.87, 0.81)		0.39 (−0.68, 0.70)	

Abbreviations: RFS, regression score factor; BMI, body mass index.

Table 7 Regression Factor Scores by Food Intake Status

Variable (N)	RFS-1, Median (IQR)	*p*	RFS-2, Median (IQR)	*p*	RFS-3, Median (IQR)	*p*	RFS-4 Median (IQR)	*p*
Anorexia		<0.001		<0.001		0.990		0.330
Yes (72)	−0.59 (−0.85, −0.08)		−0.56 (−1.33, 0.58)		0.09 (−0.27, 0.47)		0.27 (−0.89, 0.67)	
No (67)	0.29 (−0.67, 1.19)		0.41 (−0.32, 0.93)		0.22 (−0.84, 0.89)		0.07 (−1.01, 0.67)	
Intake quantity		0.004		<0.001		0.070		0.500
Normal (25)	−0.72 (−0.85, −0.13)		−0.97 (−1.52, −0.27)		0.22 (−0.1, 0.84)		0.40 (−0.89, 0.61)	
Abnormal (127)	−0.08 (−0.75, 0.9)		0.42 (−0.51, 1.03)		−0.01 (−0.86, 0.7)		0.09 (−0.91, 0.67)	

Abbreviation: RFS, regression factor score.

intake group had higher RFS-1 (−0.08; 95% CI: −0.75, 0.90; $p = 0.004$) and RFS-2 (0.42; 95% CI: −0.51, 1.03; $p < 0.001$). Table 8 presents the differences in RFS between different groups (Group 1, Group 2, and Group 3). Group 1 had the higher RFS-2 (0.61; 95% CI: −0.42, 0.95; $p = 0.003$) and lower RFS-3 (−0.52; 95% CI: −1.43, −0.10; $p < 0.001$) and RFS-4 (−1.19; 95% CI: −1.57, −0.12; $p < 0.001$), group 2 had the higher RFS-4 (0.44; 95% CI: 0.09, 0.96; $p < 0.001$) and lower RFS-1 (−0.74; 95% CI: −0.93, −0.29; $p < 0.001$) and RFS-2 (−0.35; 95% CI: −1.18, 0.60; $p = 0.003$), and Group 3 had the higher RFS-1 (1.33; 95% CI: 0.90, 1.99; $p < 0.001$) and RFS-3 (0.83; 95% CI: 0.23, 1.28; $p < 0.001$).

Table 9 presents the differences in nutritional indicators between different groups. Group 1 and Group 2 had higher MAC than Group 3 (22; 95% CI: 20, 22; $p = 0.001$), and had higher CC than Group 3 (27.75; 95% CI: 26, 30.13; $p = 0.029$). Differences for other nutritional indicators were not statistically significant. Table 10 presents the differences in SI indicators between different groups. Group 1 and Group 2 had lower CRP than Group 3 (37.41; 95% CI: 10.62, 91.42; $p = 0.007$), had lower NLR than Group 3 (5.14; 95% CI: 2.73, 14.00; $p = 0.004$), and had lower SII than Group 3 (1171.50; 95% CI: 447.78, 2196.72; $p = 0.014$).

The Influences of 3 Groups on Nutrition and Intake Status and SI Level

Tables 11–13 presents the results of the regression analysis of the patient groups on nutrition, SI, and intake indicators. MAC was significantly higher for patients in Group 1 (1.85; 95% CI: 0.35, 3.35; $p = 0.020$) and Group 2 (2.21; 95% CI:

Table 8 Regression Factor Scores by Group of Patients

Variable (N)	Overall (147) Median (IQR)	Group 1 (47) Median (IQR)	Group 2 (71) Median (IQR)	Group 3 (29) Median (IQR)	*p*
RFS-1	−0.29 (−0.83, 0.70)	−0.09 (−0.74, 0.69)	−0.74 (−0.93, −0.29)	1.33 (0.9, 1.99)	<0.001
RFS-2	0.06 (−0.69, 0.90)	0.61 (−0.42, 0.95)	−0.35 (−1.18, 0.60)	0.13 (−0.56, 0.89)	0.003
RFS-3	−0.05 (−0.52, 0.81)	−0.52 (−1.43, −0.1)	0.10 (−0.1, 0.84)	0.83 (0.23, 1.28)	<0.001
RFS-4	−0.22 (−0.89, 0.67)	−1.19 (−1.57, −0.12)	0.44 (0.09, 0.96)	0.34 (−0.11, 0.68)	<0.001

Abbreviation: RFS, regression factor score.

Table 9 Nutritional Indicators by Groups of Patients

Variable (N)	Overall (128) Median (IQR)	Group 1(39) Median (IQR)	Group 2 (63) Median (IQR)	Group 3 (26) Median (IQR)	*p* (MC) [a]
MAC	22 (20, 24)	23 (21, 25)	23 (20.5, 25)	22 (20, 22)	0.001
CC	30 (27, 32)	30 (27, 32)	30 (27, 34)	27.75 (26, 30.13)	0.029
HGS	15.05 (10.30, 20.83)	17.6 (12, 21.8)	15 (10, 21.9)	12.05 (7.65, 17.75)	0.120
HGB	111.5 (97.25, 125.75)	114 (95, 125)	111 (102, 127)	105 (81, 124.25)	0.379
ALB	37.06 (33.01, 40.12)	37.40 (33.31, 40.38)	38.05 (33.58,41.08)	34.80 (31.70, 38.49)	0.447
PAB	0.16 (0.10, 0.22)	0.16 (0.10, 0.21)	0.18 (0.12,0.24)	0.13 (0.09,0.165)	0.070

Notes: [a] MC = Monte Carlo (10,000 samples, seed = 2,000,000).
Abbreviations: MAC, mid-arm circumference; CC, calf circumference; HGS, hand grip strength; HGB, hemoglobin; ALB, albumin; PAB, pre-albumin.

Table 10 Systemic Inflammation Indicators by Groups of Patients

Variable (N)	Overall (119) Median (IQR)	Group 1 (42) Median (IQR)	Group 2 (53) Median (IQR)	Group 3 (24) Median (IQR)	*p* (MC) [a]
CRP	10.80 (1.61, 49.72)	9.12 (1.44, 39.10)	5.96 (1.53, 41.30)	37.41 (10.62, 91.42)	0.007
NLR	3.48 (2.24, 5.51)	3.60 (2.04, 6.30)	3.04 (2.05, 4.72)	5.14 (2.73, 14.00)	0.004
SII	634.29 (368.63, 1402.09)	666.32 (433.33, 1267.13)	555.70 (347.23, 985.88)	1171.50 (447.78, 2196.72)	0.014

Notes: [a] MC = Monte Carlo (10,000 samples, seed = 2,000,000).
Abbreviations: CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte ratio; SII, systemic immune-inflammation index.

Table 11 Linear Regression Analyses of Patient Groups on Malnutrition-related Outcomes

Linear Regression	Patient Groups	N (%)	B (95% CI)	*p*
MAC (N=145)	Group 1	46 (31.72)	1.85 (0.35, 3.35)	0.020
	Group 2	70 (48.28)	2.21 (0.82, 3.61)	0.002
	Group 3	29 (20.00)	Reference	–
CC (N=130)	Group 1	40 (30.77)	2.46 (0.35, 4.58)	0.020
	Group 2	64 (49.23)	2.49 (0.54, 4.44)	0.010
	Group 3	26 (20.00)	Reference	–
PAB (N=146)	Group 2	71 (48.63)	0.04 (0.01, 0.07)	0.030
	Group 3	29 (19.86)	Reference	–
CRP (N=119)	Group1	42 (35.29)	−33.79 (−56.53, −11.04)	0.004
	Group2	53 (44.54)	−30.46 (−52.33, −8.99)	0.010
	Group 3	24 (20.17)	reference	–
NLR (N=147)	Group 1	47 (31.97)	−3.51 (−5.73, −1.28)	0.002
	Group2	71 (48.30)	−4.06 (−6.14, −1.99)	<0.001
	Group3	29 (19.73)	reference	–

Abbreviations: MAC, mid-arm circumference; CC, calf circumference; PAB, pre-albumin; CRP, C-reactive protein; NLR, Neutrophil-to-Lymphocyte ratio.

Table 12 Ordered Logical Regression Analyses of Patient Groups on Malnutrition-related Outcomes

Ordered Logical Regression	Patient Groups	N (%)	OR (95% CI)	*p*
BMI (N=147)	Group 1	47 (31.97)	3.00 (1.21, 7.40)	0.020
	Group 2	71 (48.30)	3.51 (1.50, 8.23)	0.004
	Group 3	29 (19.73)	reference	–

Abbreviation: BMI, body mass index.

Table 13 Logistic Regression Analyses of Patient Groups on Malnutrition-related Outcomes

Logistic Regression	Patient Groups	N (%)	OR (95% CI)	*p*
Anorexia (N=139)	Group 2	67 (48.20)	0.16 (0.06, 0.44)	<0.001-
	Group 3	28 (20.14)	reference	
Intake quantity (N=147)	Group 2	71 (48.30)	0.16 (0.04, 0.57)	0.010-
	Group 3	29 (19.73)	reference	

0.82, 3.61; $p = 0.002$) than those in Group 3. CC was significantly higher for patients in Group 1 (2.46; 95% CI: 0.35, 4.58; $p = 0.020$) and Group 2 (2.49; 95% CI: 0.54, 4.44; $p = 0.010$) than those in Group 3. PAB was significantly higher for patients in Group 2 (0.04; 95% CI: 0.01, 0.07; $p = 0.030$) than in Group 3. CRP was significantly lower for patients in Group 1 (−33.79; 95% CI: −56.53, −11.04; $p = 0.004$) and Group 2 (−30.46; 95% CI: −52.33, −8.99; $p = 0.001$) than those in Group 3. NLR was significantly lower for patients in Group 1 (−3.51; 95% CI: −5.73, −1.28; $p = 0.002$) and Group 2 (−4.06; 95% CI: −6.14, −1.99; $p < 0.001$) than those in Group 3. BMI was significantly higher for patients in Group 1 (3.00; 95% CI: 1.21, 7.40; $p = 0.020$) and Group 2 (3.51; 95% CI: 1.50, 8.23; $p = 0.004$) than those in Group 3. Group 2 (0.16; 95% CI: 0.06, 0.44; $p < 0.001$) had a lower risk of developing anorexia than Group 3, and Group 2 (0.16; 95% CI: 0.04, 0.57; $p = 0.010$) had a lower risk of decreasing intake.

Discussion

The Relationship Between NIS and CRM

In this study, we investigated the frequency and distribution of NIS among 147 CRM patients. Loss of appetite (n=110), dry mouth (n=105), and abdominal bloating (n=86) exhibited the highest incidence, whereas diarrhea (n=34), altered smell (n=24), sore mouth (n=22), and dysphagia (n=16) were less common. Prior studies have similarly demonstrated loss of appetite[12] and dry mouth[18] as frequent NIS; however, the interviewers held negative treating attitudes, perceiving them as requiring no specific intervention.[19] Dry mouth is a warning symptom of oral mucositis representing reduced salivary secretion, which predisposes to chewing and swallowing difficulties[20] and a decreased sensitivity of taste carriers, leading to taste alteration.[21] In our study, taste alterations were also prevalent (n=64) and were shown to correlate with dry mouth.[22] Additionally, nausea (n=73) occurred in more patients than vomiting (n=42). Previous studies have found that patients viewed nausea as a more unpleasant symptom than vomiting, but the latter was more in need of intervention.[19] Acute diarrhea, frequently triggered by radiotherapy or gastrointestinal infections,[23] tends to receive immediate medical attention, resulting in a lower incidence. For another reason, patients in our study were not in the anti-tumor therapeutic phase, which may have reduced the occurrence of treatment-related side effects. Sore mouth is often accompanied by oral pain, prompting patients to seek timely treatment,[19] and symptomatic treatment is generally effective, leading to a relatively low incidence. Dysphagia mainly occurs in head and neck cancer (HNC) patients,[24] a subgroup with limited representation in our cohort, contributing to its lower frequency. In addition, our study found that more than half of the patients reported abdominal distension, suggesting suppressed gastrointestinal peristalsis and delayed gastric emptying, triggered loss of appetite,[25] abdominal pain, and constipation[26] that interfere with digestion and absorption of nutrients. Notably, the PG-SGA scale does not incorporate this symptom, underscoring the need to enhance nutritional assessments of this symptom. Furthermore, our findings indicate that 97 patients experienced more than three NIS, all of whom were severely malnourished, consistent with previous studies indicating a higher nutritional risk among patients with multiple symptoms.[27]

The Characteristics of RFSs and Patient Groups

This study performed an exploratory factor analysis of the 12 NIS, identifying 4 factors (symptom clusters). Factor 1 includes nausea, vomiting, and altered smell, which are interconnected, as the altered smell may induce nausea, potentially leading to vomiting. Factor 2 encompasses loss of appetite, early satiety, taste alteration, and abdominal bloating. Prior research has established a strong relationship between anorexia and taste alteration.[28] Additionally, early satiety, taste alteration, and abdominal bloating all contribute to appetite suppression,[18] and the coincidence of loss of appetite and early satiety increases patients' nutritional risk even more. Factor 3 comprises diarrhea and constipation, with diarrhea representing more frequent and thin stools but constipation representing less frequent and dry stools. In this analysis, constipation showed a positive loading while diarrhea showed a negative loading, with the progression from negative to positive values reflecting decreasing stool frequency and moisture. We proposed a hypothesis that constipation held a tighter relation with malnutrition than diarrhea, aligning with other studies that reported a weak correlation between diarrhea and reduced intake.[29] Factor 4 contains dry mouth and sore mouth, both of which are common symptoms of oral mucositis, with a degree of association. Previous studies have shown that both dry mouth and sore mouth impair swallowing and eating abilities, directly leading to reduced intake.[30] Mechanistically, cancer treatments induced oxidative stress that damaged the basal epithelial cells of the oral mucosa, leading to excessive generation of reactive oxygen species, which not only caused direct cellular damage but also promoted the pro-inflammatory cytokines, such as interleukin- 6/1β.[31] Furthermore, disruption of the mucosal barrier facilitates microbial colonization, which may lead to secondary infection and delayed healing.[32] Using cluster analysis based on RFS, we categorized the malnourished population into three groups. We hypothesized that the patients in Group 1 (n=47) had more severe symptoms of loss of appetite, early satiety, taste alteration, and bloating, and Group 2 (n=71) had more severe symptoms of dry mouth and sore mouth, whereas Group 3 (n=29) had more severe symptoms of nausea, vomiting, altered smell, and constipation.

The Correlations Between RFSs and SI, Nutritional, and Intake Indicators

In our study, we investigated the correlations between regression factor scores (RFS) and nutritional and systemic inflammation (SI) indicators. We found that RFS-1 was negatively correlated with nutritional indicators (MAC, CC, GPS, HGB, ALB, and PAB), while RFS-2 was negatively correlated with a subset of these indicators (MAC, CC, ALB, and PAB) with lower correlation coefficients. Additionally, RFS-1 showed a significant positive correlation with SI markers (CRP, NLR, and SII index), whereas RFS-2 showed no significant correlation with these markers. The results indicated that nausea, vomiting, and altered smell had a greater impact on nutritional indicators than other symptoms and may directly reflect patients' SI status. Previous studies have confirmed that 5-hydroxytryptamine (5-HT) and substance P are key neurotransmitters and pro-inflammatory mediators that promote gastrointestinal inflammation, thereby triggering nausea and vomiting.[33] Notably, our study is the first to report an association between altered smell and SI status. When comparing differences in RFS between intake subgroups, significant differences were observed between RFS-1 and RFS-2. RFS-2 was significantly higher than RFS-1 in anorexia and decreased intake subgroups, indicating that RFS-2 plays a more substantial role in intake status. However, it should be noted that the relatively low correlation coefficients may indicate that RFS-2, while statistically associated with certain nutritional markers, has limited utility as a standalone clinical predictor of nutritional status, and should be interpreted with caution in practice. Factor 2 consists of loss of appetite, taste alteration, and early satiety. Loss of appetite is the direct cause of triggering a reduction in intake,[34] while taste alteration can cause unpleasant food flavors, such as excessive sweetness, acidity, or bitterness, which also reduce intake.[35] Early satiety also resulted in decreased appetite, making it a crucial factor influencing intake. Based on the effects of RFS-1 and RFS-2 on SI and intake, we hypothesized the following etiological mechanisms among the 3 malnutrition groups: Group 1 experienced severe intake reduction with moderate inflammation, Group 2 had mild intake reduction with mild inflammation, and Group 3 had moderate intake reduction with severe inflammation. These differences could predict the degree of malnutrition for the 3 groups: Group 3 presented the most severely malnourished, and Group 2 suffered less severely. In terms of SI status, Group 3 was heavier than Group 1, and Group 2 was the least severe. The results of the regression analysis likewise confirmed that Group 3 presented the most severe malnutrition and SI statuses.

The Current Treatment for NIS

Presently, the therapy for malnutrition primarily relies on nutritional support and the management of NIS.[36] The latter is crucial in nutritional therapy, as NIS can directly reduce patients' oral nutritional intake, thereby impacting the effectiveness of nutritional support.[37] Consequently, improving NIS is not only symptomatic management but also enhances the efficacy of nutritional support. In symptomatic management, multiple NIS usually take place at the same time. However, the use of multiple medications can lead to adverse reactions or toxic side effects, increasing patients' metabolic burden. For instance, although glucocorticosteroids can improve appetite and promote weight gain, they may also induce nausea, headache, and elevate thrombosis risk.[38] Similarly, 5-HT inhibitors are effective in alleviating nausea and vomiting but may cause constipation, dizziness, and other side effects.[39] Lactulose is commonly used to treat constipation but is prone to induce bloating, anorexia, and diarrhea.[40] Our study demonstrated that the occurrence of NIS tends to cluster, forming symptom clusters with varying degrees of nutritional impact for CRM patients. Therefore, when addressing multiple concurrent NIS, it may be beneficial to first categorize NIS to identify those that are primary contributors to malnutrition, based on their impact on intake and SI. For instance, our study demonstrated that Group 3 exhibited severe nausea and vomiting accompanied by elevated SI. Therefore, nutritional therapy for this group should incorporate antiemetics and anti-inflammatory agents alongside conventional nutritional support. In contrast, management for Group 1, which is predominated by anorexia, bloating, and early satiety, should prioritize prokinetic agents and appetite stimulants. This approach allows for targeted intervention, potentially reducing the adverse effects associated with overmedication.

Managing the SI Status in CRM Benefits From Reducing the Incidence of NIS

This study identified a strong and clear correlation between nutritional impact symptoms (NIS) and systemic inflammation (SI), suggesting that anti-inflammatory treatment may help alleviate NIS and thereby improve nutritional status. Previous research has confirmed that non-steroidal anti-inflammatory drugs (NSAIDs) can enhance patient appetite and

food intake.[41] However, the prolonged use of NSAIDs might stimulate the gastrointestinal mucosa, causing gastrointestinal tract adverse reactions, and even the occurrence of gastrointestinal tract ulcers.[42] Therefore, how to safely and effectively ease the SI environment in CRM remains one of the current dilemmas in nutritional therapy. An anti-inflammatory diet has been found to improve the prognosis of tumor patients,[43] and there is a strong correlation between dietary habits with a high nutritional inflammatory index (DII) and the occurrence of abdominal pain[44] and constipation.[45] Therefore, adopting an anti-inflammatory diet may represent a safer approach to managing the SI status in CRM and reducing the incidence of NIS, thereby enhancing overall nutrition. Carbohydrates, fats, and proteins are the three essential nutrients and whole grain carbohydrates are an important component of an anti-inflammatory diet, intake of polyunsaturated fatty acids and monounsaturated fatty acids are beneficial for the body to develop an anti-inflammatory internal environment,[46] whereas fish, poultry, and legume proteins have lower DII scores, and are better suited for oncology patients than red and processed meats.[47] Beyond the three fundamental macronutrients, consideration should be given to the qualitative aspects of nutrients and their anti-inflammatory properties. Plant polyphenols, widely present in vegetables, fruits, and tea, are non-nutrient compounds with anti-inflammatory properties. Among them, flavonoids and phenolic acids exhibit notable anti-inflammatory and antioxidant activities.[48] From a nutrient perspective, ω-3 polyunsaturated fatty acids, including α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, also play an important role in anti-inflammatory diets.[49] In addition to choosing the right food for the anti-inflammatory diet, the cooking method is also essential. Frying and grilling are considered pro-inflammatory and carcinogenic[47] while steaming is considered a healthier way of cooking. Despite these associations, no studies have definitively confirmed a causal relationship between DII scores and the occurrence of NIS. Further research is needed to elucidate these connections and establish evidence-based dietary recommendations.

Limitations and Future Directions

Despite our interesting findings, this study has several limitations that should be considered. (i) The study population predominantly comprised patients with lung and gastrointestinal cancers, whereas HNC, which also has a high prevalence of NIS,[12] was underrepresented, resulting in a lower prevalence of dysphagia and milder mucositis in this cohort. The lower incidence of diarrhea and sore mouth may be the reason for the promoting statistical results for RFS-3 and RFS-4. To robustly validate these findings, it is imperative that future research employs a multicenter framework aimed at accruing a larger sample size, particularly from undersampled subgroups like HNC patients. (ii) This study utilized the PG-SGA, which classifies NIS dichotomously without assessing their severity or frequency. This methodological limitation may have led to an underestimation of the statistical contribution of certain symptoms in the factor analysis, potentially introducing bias into the final factor structure. Future methodological approaches should incorporate instruments that quantify symptom severity and frequency to obtain more precise and clinically informative data. (iii) Although patients currently receiving chemoradiotherapy were excluded to avoid acute treatment-related symptoms, the study did not account for the history or timing of prior anticancer therapies. Residual chronic symptoms from previous treatments, such as persistent taste changes, may have confounded the assessment of NIS. (IV) The use of a qualitative rather than a quantitative tool for assessing dietary intake may have limited the accuracy and sensitivity of our nutritional evaluations. Future studies would benefit from employing validated quantitative instruments, such as food frequency questionnaires (FFQs) or multiple 24-hour dietary recalls, to obtain more precise and continuous data on energy and protein intake. (V) SI indicators did not include cytokines such as interleukin-1β and interleukin-6, nor were anorexia-related hormones such as leptin and ghrelin assessed. Future research should focus on these neuroendocrine factors to deepen understanding of the underlying mechanisms. Moreover, the RFS identified in this study is based on statistical correlations, and its underlying biological pathways have not been empirically validated. Future studies should incorporate biomarker analyses, such as measuring serum 5-HT levels or assessing heart rate variability as an indicator of vagal tone, to verify the biological basis of these symptom clusters.

Conclusions

This study analyzed NIS, intake, and SI status as the three primary factors influencing nutritional status, using NIS as a disease phenotype to preliminarily explore the underlying mechanisms of malnutrition. This approach enabled a more

detailed, population-based categorization of moderately and severely malnourished patients, providing insights that may inform the etiological treatment of malnutrition. These findings carry substantial clinical implications, as they advocate for a paradigm shift from supportive nutritional management toward mechanism-targeted interventional strategies. For instance, the identification of symptom clusters dominated by inflammatory manifestations may justify the use of anti-inflammatory agents, while phenotypes characterized primarily by NIS may indicate underlying neurophysiological mechanisms, with the potential to improve clinical outcomes and quality of life in CRM patients.

Abbreviations

CRM, cancer-related malnutrition; NIS, nutrition impact symptoms; SI, systemic inflammation; PG-SGA, patient-generated subjective global assessment; GLIM, Global Leadership Initiative on Malnutrition; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; MAC, mid-arm circumference; CC, calf circumference; HGS, hand grip strength; HGB, hemoglobin; ALB, albumin; PAB, pre-albumin; VAS, visual analog scale; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; CRP, C-reactive protein; RFS, regression factor scores; NIS, nutritional impact symptoms; HNC, head and neck cancer; NSAIDs, non-steroidal anti-inflammatory drugs; DII, nutritional inflammatory index.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Wangjing Hospital on 19 July 2023 (approval number: WJEC-KT-2023-020-P001). Informed consent was obtained from all subjects involved in the study.

Ethics Approval and Informed Consent

Approval was granted by the Medical Ethics Committee of Wangjing Hospital, China Academy of Chinese Medical Sciences (ethical approval number: WIEC-KT-2023-020-P001). The participants provided their written informed consent to participate in this study, which confirmed their agreement for access to their medical records and their full understanding of the study details. All research activities strictly adhere to the ethical principles outlined in the Declaration of Helsinki and relevant national research ethics regulations.

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Disclosure

The authors declare no conflicts of interest in this work.

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