Associations of inflammation with neuropsychological symptom cluster in patients with Head and neck cancer: A longitudinal study

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ARTICLE INFO

ABSTRACT

Purpose: Head and neck cancer (HNC) patients may experience multiple co-occurring neuropsychological symptoms (NPS) cluster, including fatigue, depression, pain, sleep disturbance, and cognitive impairment. While inflammation has been attributed as a key mechanism for some of these symptoms, its association with the NPS as a cluster of symptoms is unknown. Thus, the aim of this study was to examine the association between peripheral inflammation and NPS cluster among HNC patients over cancer treatment (radiotherapy with or without chemotherapy).

Methods: HNC patients were recruited and followed at pre-treatment, end of treatment, three months and one-year post-treatment. Plasma inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNFA), soluble tumor necrosis factor receptor-2 (sTNFR2), interleukin-1 beta (IL1-β), interleukin-6 (IL-6), interleukin-10 (IL-10), monocyte chemotactic protein-1 (MCP-1), and interleukin-1 receptor antagonist (IL-1RA) and patient-reported NPS cluster were collected at the 4 time points. Associations between inflammatory markers and the NPS cluster were analyzed using linear mixed-effects models and generalized estimating equations (GEE) models controlling covariates.

Results: 147 HNC patients were eligible for analysis. 56% of the patients received chemoradiotherapy as treatment. The highest NPS cluster score was reported at the end of treatment, which gradually decreased over time. An increase in inflammatory markers including CRP, sTNFR2, IL-6 and IL-1RA was associated with higher continuous NPS cluster scores ($p<0.001$, $p = 0.003$, $p<0.001$, $p<0.001$; respectively). GEE further confirmed that patients with at least two moderate symptoms had elevated sTNFR2, IL-6, and IL-1RA ($p = 0.017$, $p = 0.038$, $p = 0.008$; respectively). Notably, this positive association between NPS cluster and inflammatory markers was still significant at one-year post-treatment for CRP ($p = 0.001$), sTNFR2 ($p = 0.006$), and IL-1RA ($p = 0.043$).

Conclusions: Most HNC patients experienced NPS clusters over time, especially immediately after the end of treatment. Elevated inflammation, as represented by inflammatory markers, was strongly associated with worse NPS cluster over time; this trend was also notable at one-year post-treatment. Our findings suggest that peripheral inflammation plays a pivotal role in the NPS cluster over cancer treatment, including long-term follow-ups. Interventions on reducing peripheral inflammation may contribute to alleviating the NPS cluster in cancer patients.

1. Introduction

As a broad medical term, head and neck cancer (HNC), includes malignancies in the nasopharynx, oropharynx, hypopharynx, oral cavity, paranasal sinuses and nasal cavity, larynx, and salivary glands (Luo et al., 2018; Institute, 2021). HNC represents the seventh most common cancer worldwide, accounting for 15,400 deaths in 2023 in the US (HeadNeck Cancer, 2020; Vigneswaran and Williams, 2014; HeadNeck Cancer, 2023). While advanced therapies such as surgery, chemotherapy, radiation therapy (RT), and/or their combination improve

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survival rates, this population experiences less adherence to the treatment plan, poor quality of life (QoL), and low functional status due to the side effects of cancer treatment on swallowing, hearing and speech (Calver et al., 2018; Xiao et al., 2014; Zimmaro et al., 2018; Gomes et al., 2020).

One of the main factors influencing QoL and treatment interruption is the presence of co-occurring symptoms, including fatigue, pain, sleep disturbance, depressive symptoms, and cognitive dysfunction (Zimmaro et al., 2018; Chiang et al., 2018; Li et al., 2020). According to a literature review of 158 papers about symptom clusters, 83% of the studies assessed co-occurring symptoms in cancer population and 49% of these studies have reported the co-occurrence of at least three of these symptoms, including fatigue, depression, pain and sleep disturbance (Miaskowski et al., 2017). This set of co-occurring symptoms, known as neuropsychological symptoms (NPS) cluster, may have a common underlying biological mechanism (Xiao et al., 2014; Bai et al., 2020). The discovery of common mechanistic pathways may lead to the development of novel approaches to manage these co-occurring symptoms simultaneously and improve patients' QoL in a cost-effective way (Kim et al., 2012).

Basic research on neural-immune signaling has determined that inflammatory markers signal the central nervous system to trigger co-occurring symptoms such as fatigue, sleep disturbance, and depressive-like symptoms using animal models (Dantzer et al., 2008). While the exact mechanism of this association is still unknown, it has been suggested that peripheral inflammatory markers can activate the brain resident macrophages (Cattaneo et al., 2015). The activated microglia can promote central inflammation, influences neuroplasticity, neurogenesis, and neurotransmitter metabolism, leading to behavioral symptoms (Sforzini et al., 2019; Brites and Fernandes, 2015; Bhattacharya et al., 2016).

In patients, cancer itself and various cancer treatment such as surgery, radiotherapy and chemotherapy can stimulate the immune system response and lead to inflammation and numerous symptoms (McFarland et al., 2021). To support this, clinical studies show that inflammatory cytokines are one of the possible common biological pathways that underlie symptoms of the NPS cluster (Kim et al., 2012). Some studies have shown the associations of inflammatory markers such as interleukin-1 (IL-1), interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFA), and C-reactive protein (CRP) with individual symptoms in the NPS cluster, such as fatigue, depression, pain, and cognitive impairment in cancer patients (Xiao et al., 2016a; Bower et al., 2007; Li et al., 2017; Jara et al., 2020; Seruga et al., 2008). Most of the current literature evaluated associations between peripheral inflammation with behavioral symptoms had a cross-sectional design and did not include multiple co-occurring symptoms in the model (Kwekkeboom et al., 2018; Ji et al., 2017).

The high prevalence and persistence of co-occurring symptoms across the cancer continuum make it crucial to understand the associations between these multiple co-occurring symptoms as a cluster and peripheral inflammation over cancer treatment (Stark et al., 2012). This can shed light on the biological underpinning of multiple co-occurring symptoms to develop precise interventions to manage them. To the best of our knowledge, no study evaluated the association between peripheral inflammation and the NPS cluster in HNC over the course of treatment. Thus, in this study, we aimed to evaluate the longitudinal relationship between inflammatory markers and NPS cluster in HNC patients.

2. Methods

2.1. Participants and setting

One hundred forty-seven participants were recruited from the Radiation Oncology Clinics at Emory Winship Cancer Institute. Inclusion criteria were ≥21 years of age; histological proof of squamous cell carcinoma of the head and neck region with no distant metastasis; and no evidence of uncontrolled metabolic, cardiovascular, renal, hematologic, neurologic, or hepatic disease. Exclusion criteria were previous invasive malignancies but disease-free for <3 years; simultaneous primaries (existence of other primary cancers); pregnancy; and presence of a major psychiatric disorder (e.g., schizophrenia or bipolar disorder) or inability to understand English; chronic medical conditions involving the immune system (e.g., hepatitis B or C, HIV) or regular use of immunosuppressive medications (e.g., glucocorticoids and methotrexate) within six months of study entry. Antidepressants and over-the-counter anti-inflammatory medications were allowed.

Participants were followed at four time points, including pre-treatment (approximately one week prior to radiotherapy), end of treatment (last day of the radiotherapy), and three months and one year post-radiotherapy. The study was approved by the Institutional Review Board of Emory University (Protocol# IRB00070167). The information of the research study was explained to the participants, and written informed consent was obtained from all the participants.

2.2. Data collection

Participants completed all questionnaires at clinic sites; blood samples were collected into chilled EDTA tubes for plasma isolation by a phlebotomist or certificated nurse on the same day as the questionnaires. The collected blood samples were centrifuged at $1000 \times g$ for 10 min at 4 °C, and then plasma was aliquoted into siliconized polypropylene tubes and stored at −80 °C until inflammatory marker analysis.

2.3. Outcome measures

2.3.1. Clinical outcomes

2.3.1.1. Fatigue. Fatigue was measured using the Multidimensional Fatigue Inventory (MFI)-20. MFI contains 20 items that cover five fatigue dimensions, including general fatigue (impairment of overall daytime functioning), physical fatigue (body tiredness), mental fatigue (fatigue related to cognition), reduced activity, and reduced motivation. Each dimension contains four items with a possible score from 4 to 20. The total score was calculated as the sum of five dimensions ranging from 20 to 100, which a higher score representing more fatigue (Smets et al., 1995). A score of ≥43 was used to define moderate to severe fatigue (Andic et al., 2020). The validity and reliability of the MFI-20 have been established in cancer patients receiving RT (Smets et al., 1996).

2.3.1.2. Depression. Depression was measured using the Patient Health Questionnaire (PHQ-8) questionnaire. This questionnaire contains eight questions with four answer categories. Depression score was determined based on the sum of the answers (Kroenke et al., 2009). The PHQ-8 has a validated threshold cutoff score ≥10, which has been used as the presence of depression (Kroenke et al., 2009; Shin et al., 2019). The PHQ-8 has been well validated in cancer patients (Oancea and Cheruvu, 2016).

2.3.1.3. Pain. Pain was measured using the Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). PRO-CTCAE is a self-reported tool to measure symptomatic toxicities in cancer patients (Institue, 2021). The severity score of each item ranges from 0 to 4, with 0 meaning no symptom, 1 mild, 2 moderate, 3 severe, and 4 very severe. One item addressing general pain in the PRO-CTCAE was used for the current study, and a cutoff score ≥2 indicates moderate to severe pain (Lee et al., 2020).

2.3.1.4. Cognitive impairment. Two items (concentration and memory) in PRO-CTCAE were used to measure cognitive impairment. The total score was calculated based on the average of the two items, with a

higher score indicating a higher cognitive impairment. A cutoff score ≥2 was used to define moderate to severe cognitive impairment (Lee et al., 2020).

2.3.1.5. Sleep disturbance. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality (Buysse et al., 1989). This tool consists of seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction due to sleepiness. The scoring of answers was based on a scale of 0–3 (total score of 21). A higher score reflects poor sleep quality (Buysse et al., 1989). A cutoff score ≥5 for the presence of sleep disturbance was considered (Al Maqbali et al., 2020). Several studies have evaluated the validity and reliability of the PSQI as a measurement for sleep quality in the cancer population (Fontes et al., 2017; Akman et al., 2015; Beck et al., 2004).

2.3.1.6. Covariates: demographic and clinical variables. Demographic and clinical characteristics of the participants were collected by standard questionnaires or chart review. Variables included: age, body mass index (BMI), sex, race (White vs. Non-White), marital status (married vs. unmarried), history of smoking status (yes vs. no), history of alcohol use (<1 drink per week during the past year vs. 1+ drink per week during the past year), antidepressants medication use (yes vs. no), antiinflammation medication use (yes vs. no), education (below college vs. college and above), human papillomavirus (HPV) status (associated vs. unassociated), cancer site (oropharynx vs. non-oropharynx), cancer stage (≤III vs. IV), and treatment regimen (RT ± surgery vs. RT + chemotherapy vs. RT + chemotherapy + surgery).

2.3.2. Inflammatory markers

Selected inflammatory markers were used to measure peripheral inflammation according to literature (McFarland et al., 2022; Bower and Lamkin, 2013a). Plasma CRP level was determined using standard turbidimetric assay techniques. Plasma concentration of TNF-α, sTNFR2, IL-1B, IL-6, IL-10, and IL-1RA were determined using Magnetic Luminex Screening Assay (R&D Systems, Minneapolis, MN) (Xiao et al., 2018). All samples were run in duplicate, and the mean inter- and intra-assay coefficients of variation for control samples were 10% or less. The detection limit of each inflammatory marker has been shown in Supplementary Table 1.

2.4. Data analysis

Descriptive statistics, including mean (standard deviation [SD]) and frequency (n, percentage), were performed for demographic and clinical variables. The NPS cluster was defined as both continuous and categorical variables. For the continuous NPS cluster, raw scores were normalized using a Z score for each symptom to make the scores from different questionnaires comparable. Then a mean Z score of the five symptoms (fatigue, depression, pain, sleep disturbances, and cognitive dysfunction) was computed as the total score of the NPS cluster. For the categorical NPS cluster, patients were defined to have the NPS cluster if they experienced at least two symptoms based on the defined validated cut-off point for the presence of that symptom described above (Ji et al., 2017; Liu et al., 2009). Also, the Pearson correlation was used to evaluate the correlation between every two individual symptoms.

To evaluate the association between NPS cluster and inflammatory markers over time, a linear mixed-effects model was used for the continuous NPS cluster, and a generalized estimating equations (GEE) model was employed for the categorical NPS cluster. In these models, NPS at all four time points was the outcome variable. Also, inflammatory markers at all four time points and the measurement time were the predictor. Covariates were selected based on their correlations with NPS (Xiao et al., 2016b, 2021). Separate models were performed for each inflammatory marker. Post hoc independent samples T-Tests were

further conducted to examine whether patients with NPS cluster at one-year post-treatment still experience high inflammatory responses, compared to patients without NPS cluster. The log value of inflammatory markers was used in data analysis to achieve normality. Demographic and clinical characteristics were considered as covariates in all models. All analyses were carried out using R version 4.0.2. A two-tailed test of significance with a significance level of 0.05 was used.

3. Results

3.1. Demographics and clinical characteristics of the participants

The present study included 147 HNC patients with a mean age of 59 years (59 ± 10). The majority of the patients were White (80%), male (71%), and married (69%). Sixty percent of patients had a history of smoking, and 42% used alcohol for more than one drink per week during the past one year. Most patients had no history of antidepressant use (79%), no history of antiinflammation use (82%), and had a below college education level (62%). The majority of the patients were diagnosed with oropharynx cancer (53%) and with stage IV (78%). More than half of the patients had HPV-associated tumors (53%). All patients were treated with RT and, more than half of them received concurrent chemoradiotherapy (56%). Demographic and clinical characteristics are shown in Table 1.

3.2. NPS changes from baseline to one-year post-treatment

The continuous NPS cluster scores changed significantly over time, in which the highest NPS cluster occurred at the end of treatment (p= <0.001) compared to the pre-treatment time point. Also, patients experienced lower NPS cluster scores at one-year post-treatment compared to pre-treatment (p = 0.022) (Supplementary Fig. 1). According to the results of categorical NPS cluster, among all patients, 62%

Table 1
Demographic and clinical characteristics of the participants.

Variable	(n = 147)	Mean ± SD or N (%)
Age (years)		59.36 ± 10.08
BMI		27.65 ± 5.28
Sex	Male	105 (71.4%)
	Female	42 (28.6%)
Race	White	118 (80.3%)
	Non-White	29 (19.7%)
Marital status	Married	102 (69.4%)
	Unmarried	45 (30.6%)
Smoking	Yes	88 (59.9%)
	No	59 (40.1%)
Alcohol use[a]	<1 drink per week	86 (59.3%)
	1+ drink per week	59 (40.7%)
Antidepressants use[a]	No	116 (79.4%)
	Yes	30 (20.5%)
Antiinflammation use[a]	No	118 (82.5%)
	Yes	25 (17.5%)
Education[a]	Below college	91 (62.3%)
	College and above	55 (37.7%)
HPV	Associated	78 (53%)
	Un-associated	69 (47%)
Cancer site	Oropharynx	79 (53.7%)
	Non-Oropharynx	68 (46.3%)
Cancer stage[a]	≤III	31 (21.2%)
	IV	115 (78.8%)
Treatment	RT ± Surgery	28 (19%)
	RT + Chemotherapy	83 (56.5%)
	RT + Surgery + Chemotherapy	36 (24.5%)

RT = radiation therapy.
[a] Having missing cases: alcohol use (2); antidepressant use (1); antiinflammation use (4); education (1); cancer stage (1).

of the participants experienced categorical NPS cluster (at least two moderate symptoms simultaneously) at pre-treatment, 85% at the end of treatment, 61% at three-month post-treatment, and 46% at one year post-treatment (Fig. 1). Among different symptoms, fatigue and sleep disturbance were the most commonly reported symptoms at all time points: at least half of the participants reported moderate fatigue and sleep problems, with the highest rates at the end of treatment (92% and 87% for fatigue and sleep, respectively). Cognitive impairment was reported the least (pre: 8%; end of treatment: 19%; 3 months: 11%; one year: 15%), followed by depressive symptoms (pre: 13%; end of treatment: 42%; 3 months: 18%; one year: 15%; Supplementary Table 2). Moreover, each of these individual symptoms was significantly correlated with each other (r ranging from 0.34 to 0.75, all p-values were significant), further suggesting the importance of the NPS; Supplementary Table 3).

3.3. Association between inflammatory markers and neuropsychological symptoms over time

Our results from the mixed-effect model showed that the higher concentration of inflammatory markers, including CRP (estimate = 3.189; p<0.001), sTNFR2 (estimate = 7.203; p = 0.003), IL-6 (estimate = 4.289; p<0.001), and IL-1RA (estimate = 7.115; p<0.001), was significantly associated with higher continuous NPS cluster scores over time while controlling for covariates, including age, sex, race, BMI, marital status, alcohol use, smoking, antidepressants use, antiinflammation use, cancer stage, HPV status, treatment, and feeding. These associations remained significant after Bonferroni correction (p = 0.05/8 = 0.006) (Table 2, Supplementary Fig. 2).

Notably, patients with high CRP ($\geq$3) had a significantly elevated NPS cluster score at one year post-treatment compared to end of treatment (p = 0.047), while patients with low CRP ($\leq$1) had a decreased NPS cluster score from the end of treatment to one year post-treatment (p = 0.001) (Fig. 2).

We also examined the associations of inflammatory markers with the categorical NPS cluster (at least two moderate symptoms simultaneously) using the GEE model. After adjusting for covariates, the categorical NPS cluster was also associated with inflammatory markers

including TNFR2 (estimate = 2.044; p = 0.017), IL-6 (estimate = 0.981; p = 0.038), as well as IL-1RA (estimate = 1.679; p = 0.008) (Supplementary Table 4). Comparison of inflammatory markers between patients with and without categorical NPS cluster showed high CRP and IL-6 levels (p = 0.012, p = 0.036) at pre-treatment and high IL-1RA level (p = 0.042) at the end of treatment in patients with categorical NPS cluster. Moreover, at one-year post-treatment, patients with NPS cluster still had significantly higher inflammatory makers compared to those who did not (CRP (p = 0.001), sTNFR2 (p = 0.006), and IL-1RA (p = 0.043) (Supplementary Table 5, Fig. 3).

4. Discussion

To the best of our knowledge, this is the first longitudinal study to examine the associations between inflammatory markers and NPS clusters in patients with HNC. The findings of this study revealed that NPS cluster scores were high at pretreatment, increased significantly following the end of treatment and gradually decreased over one year. The majority of the participants experienced at least two moderate symptoms at each time point. It was notable that at one-year post-treatment, almost half the patients still experience moderate to severe NPS. Among different symptoms, fatigue and sleep disturbance were most commonly reported over time. Elevated peripheral inflammation, as represented by inflammatory markers of CRP, sTNFR2, IL-6, and IL-1RA, was associated with higher NPS cluster scores over time. Notably, patients with NPS clusters still had significantly higher peripheral inflammatory markers compared with patients without NPS cluster at one-year post-treatment.

4.1. Neuropsychological symptoms cluster in HNC

Behavioral symptoms, as the most common adverse effects of cancer diagnosis and treatment, cause significant impairment in patients' QoL (Bower et al., 2011). According to our findings, 62% of patients reported NPS clusters at pre-treatment. However, Tometich et al. revealed that only 16% of breast cancer survivors had high NPS clusters before treatment (Tometich et al., 2019). Our results also showed that high NPS clusters were mostly reported after the end of treatment. Similarly, Kim
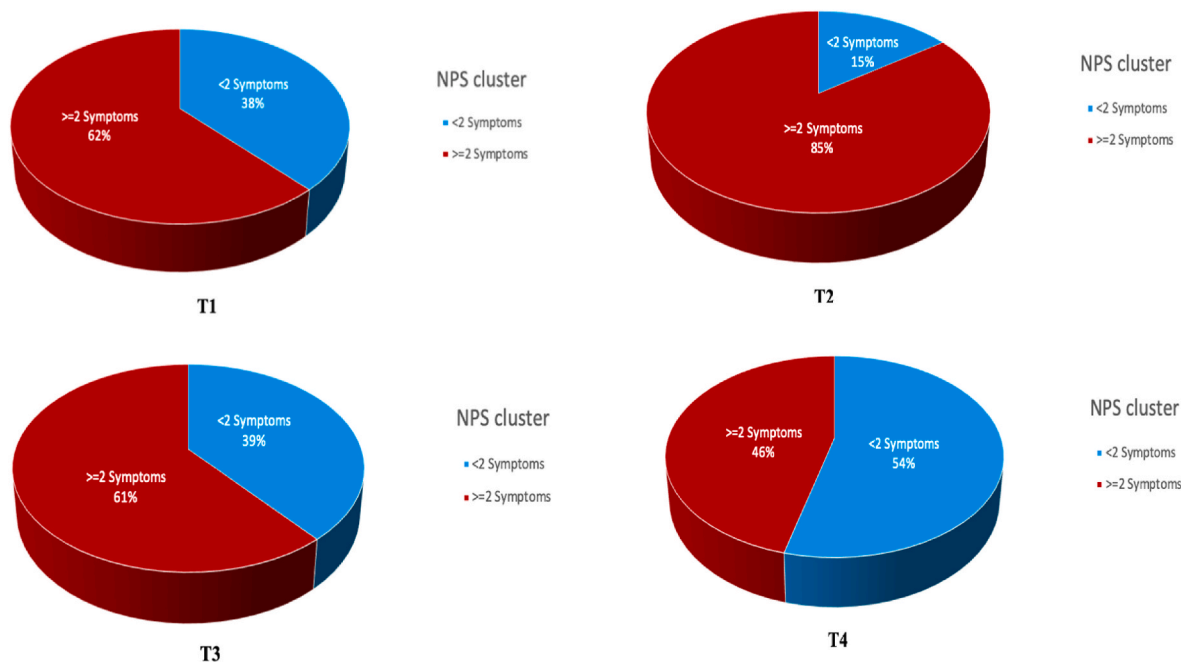

Fig. 1. Frequency of the categorical NPS cluster over time.
NPS cluster = neuropsychological symptoms cluster, T1 = pre-treatment, T2 = end of treatment, T3 = three months post-treatment, T4 = one year post-treatment.

Table 2
Mixed effect model of for the association between each inflammatory marker and continuous neuropsychological symptom cluster scores over time adjusting for covariates.

Predictors	CRP Model		TNF-α Model		sTNFR2 Model		IL-1β Model		IL-6 Model		IL-10 Model		IL-1RA Model	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Inflammatory markers	3.189	**<0.001**	-0.845	0.679	7.203	**0.003**	1.379	0.503	4.289	**<0.001**	1.710	0.373	7.115	**<0.001**
T2	6.338	**<0.001**	8.278	**<0.001**	6.757	**<0.001**	8.127	**<0.001**	5.840	**<0.001**	7.528	**<0.001**	7.833	**<0.001**
T3	-0.092	**0.017**	-0.870	0.349	-1.805	0.053	-0.831	0.374	-0.922	0.301	-1.083	0.235	-0.351	0.696
T4	-1.228	0.169	-1.944	**0.038**	-2.028	**0.024**	-2.207	**0.018**	-2.244	**0.012**	-2.106	**0.022**	-0.744	0.428
Age	-0.110	0.064	-0.096	0.117	-0.137	**0.025**	-0.097	0.100	-0.120	**0.047**	-0.101	0.105	-0.115	0.056
Sex[a]	2.535	0.074	2.523	0.083	2.240	0.117	2.231	0.113	2.339	0.105	2.540	0.088	1.917	0.187
Race[a]	-0.734	0.642	-0.935	0.564	-0.651	0.683	-0.299	0.849	-0.897	0.575	-0.553	0.740	-0.194	0.904
BMI	-0.185	0.075	-0.125	0.242	-0.160	0.127	-0.113	0.273	-0.137	0.191	-0.133	0.216	-0.212	**0.047**
Marital status[a]	4.992	**<0.001**	5.091	**<0.001**	5.281	**<0.001**	5.149	**<0.001**	5.221	**<0.001**	5.115	**<0.001**	5.315	**<0.001**
Alcohol use[a]	-0.315	0.787	-0.772	0.520	-0.743	0.457	-0.866	0.457	-0.732	0.539	-0.755	0.540	-0.599	0.614
Smoking[a]	1.198	0.336	1.600	0.209	1.476	0.204	1.568	0.204	1.357	0.282	1.693	0.191	1.512	0.231
Antidepressants use[a]	-2.688	**0.023**	-2.182	0.071	-1.974	0.099	-2.431	**0.047**	-2.258	0.061	-2.115	0.093	-2.343	0.053
Antinflammation use[a]	1.139	0.264	1.231	0.241	1.257	0.227	0.962	0.368	1.054	0.312	1.280	0.232	1.221	0.238
Cancer stage[a]	2.449	0.147	2.294	0.185	2.308	0.175	2.814	0.094	2.410	0.163	2.199	0.214	2.597	0.130
HPV status[a]	3.924	0.091	3.346	0.160	3.592	0.125	3.695	0.110	3.768	0.110	3.530	0.144	3.715	0.115
Treatment[b]	-4.118	**0.012**	-3.820	**0.023**	-4.346	**0.009**	-4.329	**0.008**	-4.144	**0.013**	-3.911	**0.022**	-3.647	**0.029**
Treatment[c]	-6.764	**0.001**	-6.472	**0.002**	-6.793	**0.001**	-7.114	**<0.001**	-6.693	**0.001**	-6.159	**0.004**	-5.827	**0.005**
Feeding	3.365	**0.007**	4.152	**0.001**	3.724	**0.003**	4.318	**0.001**	3.984	**0.002**	3.873	**0.003**	3.830	**0.002**

CRP—C-reactive protein, TNF-α = Tumor necrosis factor-alpha, sTNFR2 = soluble Tumor necrosis factor receptor-2, IL-1β = Interleukin 1 beta, IL-6 = Interleukin 6, IL-10 = Interleukin 10, IL-1RA = Interleukin 1 receptor antagonist, T2 = end of treatment, T3 = three months post-treatment, T4 = one-year post-treatment, [a] The reference point for the categorical variables were: sex = female, race = White, marital status = married, alcohol use = +1 drink per week, antidepressant use = yes, antinflammation use = yes, cancer stage = IV, HPV status = associated, treatment [b] = radiation therapy + chemotherapy, treatment [c] = radiation therapy + chemotherapy + surgery.

et al. showed that 71% of cancer patients who received treatment, had high NPS clusters, and only 29% reported low NPS cluster (Kim and Malone, 2019). According to our results, there were significant changes in NPS clusters over time. However, in a longitudinal study, Kim et al. showed that breast cancer patients experienced stable NPS clusters from pre-treatment to one month post-treatment (Kim et al., 2008). Conflicts in the results of various studies in reporting NPS cluster severity over treatment trajectory can be attributed to the types of cancer and treatments and the methods for clustering symptoms. Further investigations are warranted.

Although we have reported five symptoms in NPS cluster, some studies reported only three out of the five symptoms as a cluster. For instance, Laird et al. found that pain, depression, and fatigue as a cluster co-existed in cancer patients with cachexia (Laird et al., 2011). Similarly, Jhamb et al. showed that fatigue, pain, and depression were highly correlated in patients with advanced gastrointestinal (GI) cancers (Jhamb et al., 2019). Also, in a longitudinal study, Thomas et al. showed a cluster of pain, fatigue, and sleep disturbance from baseline to 12 months later (Thomas et al., 2014). While various studies reported limited co-existed symptoms as a cluster, there is substantial evidence to support the existence of the NPS cluster in cancer patients (Aktas, 2013). A potential explanation for the difference in included symptoms in a cluster can be related to the type and number of measured symptoms as well as statistical methodology in clustering symptoms (Xiao, 2010). Future studies may include more symptoms of the NPS and use standard statistical methods for symptom clustering to verify our findings.

Our study is among few studies that assessed a cluster of co-occurring symptoms longitudinally (Kim et al., 2008, 2014; Thomas et al., 2014), and further extends our understanding of NPS cluster in patients with HNC. Since symptoms usually occur in a cluster rather than in isolation in cancer patients, more studies are required to evaluate the presence and severity of NPS cluster in other cancer populations (Jhamb et al., 2019; Murphy et al., 2019). Additionally, our findings show that symptoms in NPS cluster co-occur among a high percentage of cancer patients. These co-existing symptoms as a cluster may be a clue in explaining the common underlying biological mechanisms of multiple symptoms.

4.2. Associations of peripheral inflammatory markers with NPS cluster over time

Our findings showed a statistically significant association between higher inflammatory markers and higher continuous NPS cluster scores, and further demonstrated that patients with NPS cluster (having at least two moderate symptoms simultaneously) had higher inflammatory markers compared to those without NPS cluster. The consistency of our results for both the continuous and categorial NPS cluster further verified our findings for the association between inflammation and the NPS cluster. This finding is also relatively consistent with limited, earlier studies, where fewer symptoms or cross-sectional designs were used. For instance, with a longitudinal design (before and during chemotherapy), Liu et al. reported positive associations between fatigue and IL-6 as well as between sleep problems and IL-6 along with IL-1RA in 53 breast cancer patients (Liu et al., 2012). Yet, this study did not examine fatigue and sleep problems as a cluster and did not report any other symptoms in NPS. Similarly, a few studies using a cross-sectional design investigated fewer symptoms in the NPS cluster and found that increased inflammatory markers (IL-6 or TNF-α) was associated with higher NPS (Kwekkeboom et al., 2018; Ji et al., 2017). Nevertheless, some studies did not show significant associations among cancer-related NPS and inflammatory markers. For example, Laird et al. did not find an association between a symptom cluster of pain, depression, and fatigue and CRP in patients with advanced GI, lung, and pancreatic cancers post-treatment (Laird et al., 2011). While Bower et al. found a positive association between fatigue and sTNF-R2 in breast cancer patients following chemotherapy, they did not report any association between
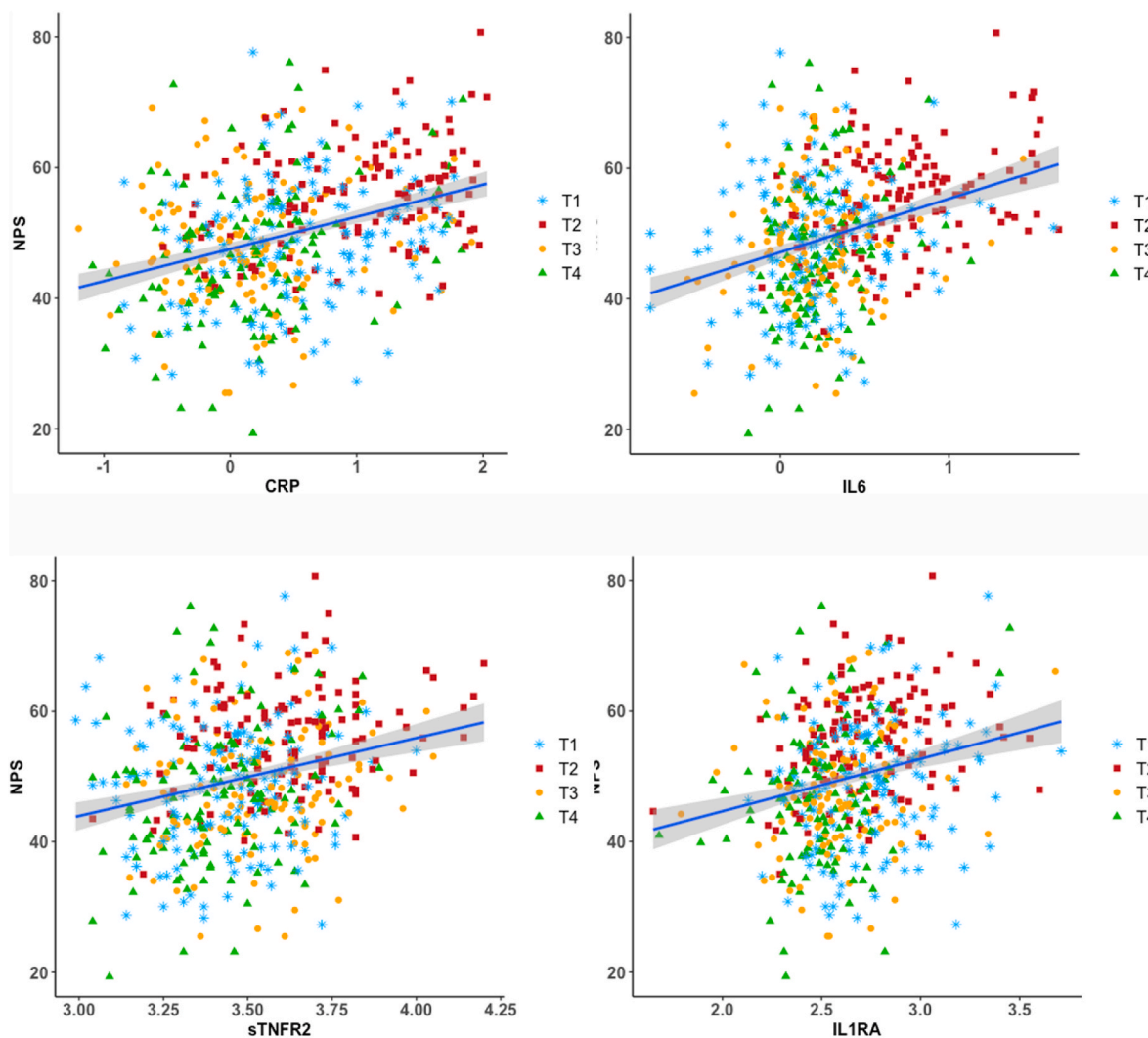
Fig. 2. The association among inflammatory markers and the continues NPS cluster over time.
NPS = neuropsychological symptoms, CRP=C-reactive protein, sTNFR2 = soluble Tumor necrosis factor receptor-2, IL-6 = Interleukin 6, IL-1RA = Interleukin 1 receptor antagonist. T1 = pre-treatment, T2 = end of treatment, T3 = three months post-treatment, T4 = one-year post-treatment.

depressive symptoms and sleep problems with inflammatory markers (Bower et al., 2011). Similarly, Paulsen et al. found a positive association between fatigue and IL-1RA, but no association was reported between inflammatory markers and pain in patients with advanced cancer following corticosteroid treatment (Paulsen et al., 2017). Given the cross-sectional design of most studies and limited symptoms in NPS, the longitudinal design of the present study by including more co-occurring symptoms in NPS illuminates the association between inflammation and NPS cluster over cancer treatment and during a long follow up period.

As a longitudinal study, we also found that this positive association continues at one-year post-treatment: patients with NPS cluster had significantly higher CRP, IL1RA, and sTNFR2 compared to those without NPS cluster at a long-term follow-up. These findings reliably suggest a strong and long-term inflammatory effect on NPS cluster. The existence of high inflammatory markers such as CRP for patients with NPS cluster, particularly at one year post-treatment can be a reliable parameter of low-grade inflammation as suggested in literature among chronic cancer-related symptoms (Orre et al., 2009a). Thus, controlling peripheral inflammation could be important for managing NPS clusters. Studies on reducing inflammation, particularly low-grade inflammation from before cancer treatment to after one year post-treatment, could be critical for NPS cluster management in a clinical setting.

The exact mechanism by which peripheral inflammation contributes

to the NPS cluster is not well understood. Mountain evidence from animal models and clinical studies suggests that the administration of pro-inflammatory cytokines to animals and healthy humans has resulted in "sickness behavior" (Eisenberger et al., 2010; Raison et al., 2010; Voll-mer-Conna et al., 2004; Bluthé et al., 2000). Moreover, targeting inflammation with anti-inflammatory markers may reduce symptoms such as fatigue in cancer patients (Monk et al., 2006). Similarities in the symptom profile of the NPS cluster and sickness behavior support that inflammation may cause the NPS cluster through the same biological pathways as sickness behavior (Kim et al., 2012). Inflammatory markers can be released from tumor microenvironment, or tissue damage from cancer treatments. (Bower and Lamkin, 2013b). They can be transmitted to the specific brain regions through different pathways, including afferent nerves, hormonal pathways, blood-brain barrier, and activation of inflammatory receptors in the brain (Kim et al., 2012; Dantzer et al., 2008; George et al., 2020). Involvement of these immune-to-brain communication pathways ultimately leads to activating sensory afferents of cranial nerves and stimulating the microglial cells to secrete an immune-active substance, which influences neural activity and causes behavioral symptoms (Kim et al., 2012). The mechanism by which the brain circuitry mediates the diverse behavioral actions of inflammatory markers remains elusive, which warrants further investigations (Dantzer et al., 2008).
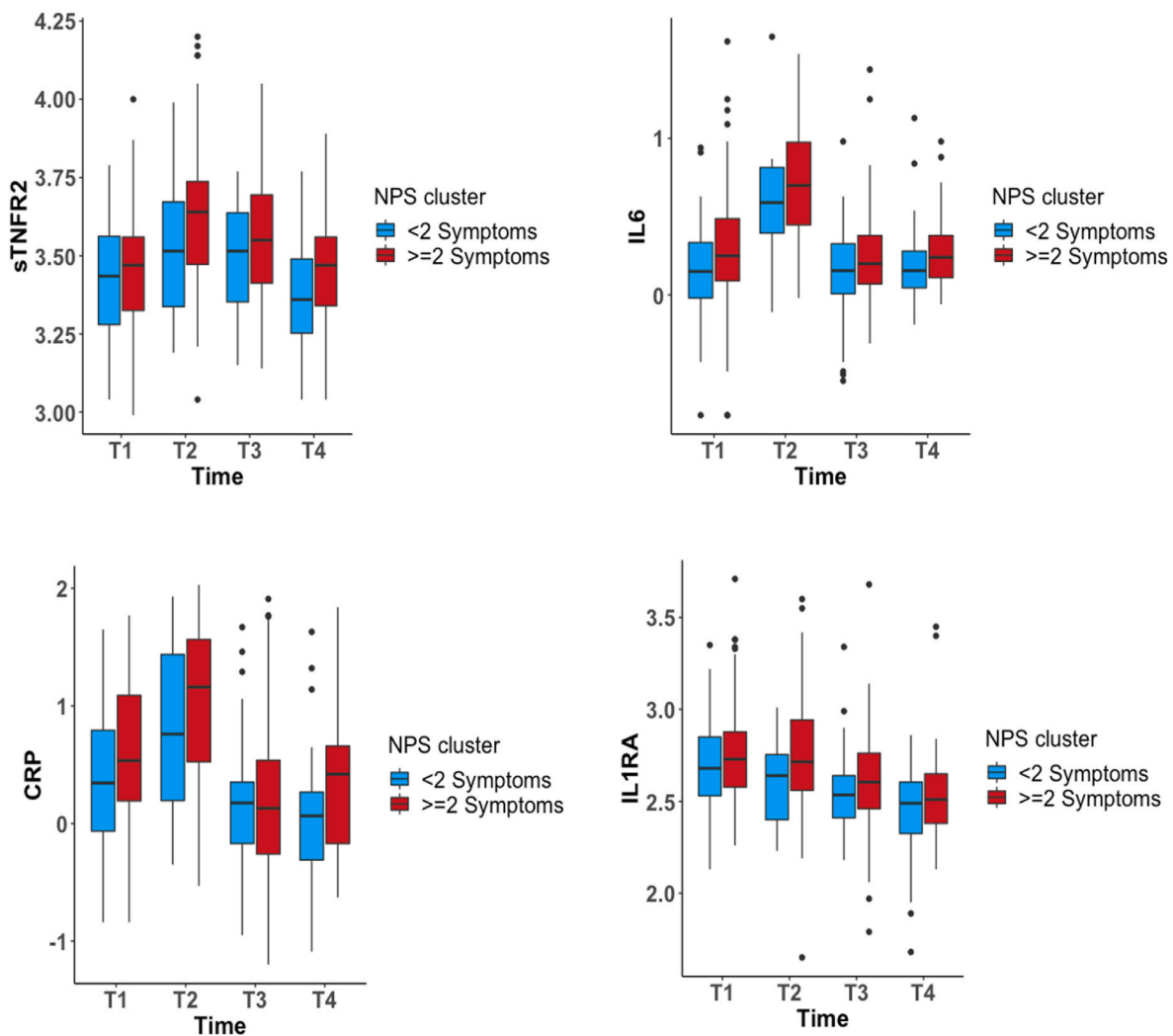
Fig. 3. Changes in inflammatory markers along with the categorical NPS cluster over timeNPS cluster = neuropsychological symptoms cluster, CRP═C-reactive protein, sTNFR2 = soluble Tumor necrosis factor receptor-2, IL-6 = Interleukin 6, IL-1RA = Interleukin 1 receptor antagonist. T1 = pre-treatment, T2 = end of treatment, T3 = three months post-treatment, T4 = one-year post-treatment.

Our results also indicate that CRP, sTNFR2, IL-6, and IL-1RA appeared to be key inflammatory markers that were significantly associated with either continuous or categorical NPS clusters among a variety of inflammatory markers. The significance of these inflammatory markers has been supported by other studies on fatigue, pain, depression, sleep disturbance, and cognitive impairment in patients with various cancers (Ji et al., 2017; Xiao et al., 2016b; Murphy et al., 2019; Paulsen et al., 2017; Fung et al., 2013). IL-6, as an indicator of chronic inflammation, is mostly reported in these studies, which can stimulate the production of other inflammatory markers such as CRP and IL-1RA (Paulsen et al., 2017; Thomsen et al., 2016; Orre et al., 2009b; Lee et al., 2011). Subsequently, the cascade of these inflammatory markers contributes to the development of symptoms (Murphy et al., 2019; Asslih et al., 2021). Future studies on the NPS cluster may focus those commonly identified inflammatory markers.

The main strength of the current study is its longitudinal design covering pre-treatment and until one-year post-treatment with a relatively large sample size. We also used well-validated questionnaires to measure symptoms in the NPS cluster. The major limitation is that the questionnaires for symptom measurements were not on the same scale. However, we used a standard process to calculate NPS cluster scores to ensure that the scores were comparable (Bai et al., 2020). Moreover, most of the participants were White and males, and the interpretation of

the study findings needs to be cautious when referring to patients with more diverse backgrounds.

5. Conclusion

Our findings revealed that most HNC patients experienced NPS cluster from pre-treatment until one-year post-treatment, and elevated inflammatory markers were associated with higher NPS cluster score over time. Furthermore, patients with NPS clusters experienced elevated peripheral inflammation compared to those without NPS clusters, and this positive association continues at one-year post-treatment. These results support the hypothesis that elevated inflammatory markers play a key role in the development of NPS clusters among cancer patients. Since studying the association between peripheral inflammation and NPS clusters is at an early stage, further longitudinal studies may validate this association to reach a consensus, including the involved inflammatory markers. Also, interventional studies designed to reduce peripheral inflammation may benefit cancer patients by alleviating multiple concurrent neuropsychological symptoms simultaneously and eventually improving cancer patients' QoL and daily functional status.

Financial support

Code availability

N/A.

Consent to participate

The information of the research study was explained to the participants, and written informed consent was obtained from all the participants.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100649.

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