Changes in and predictors of pain characteristics in patients with head and neck cancer undergoing radiotherapy

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Abstract

Pain is a common symptom in patients with head and neck cancer (HNC) that is associated with significant decrements in physical and psychological functioning. Only four studies have evaluated for changes in, as well as predictors of different pain characteristics in these patients. In this longitudinal study of patients with HNC, changes in pain intensity (i.e., average pain, worst pain), pain interference with function, and pain relief were evaluated from the initiation of radiotherapy and through the following six months. Hierarchical linear modeling was used to evaluate for changes over time in these four pain characteristics, as well as to identify predictors of inter-individual variability in each characteristic. Overall, pain intensity and interference with function scores were in the mild to moderate range, while pain relief scores were in the moderate range. The occurrence of pain, as well as scores for each pain characteristic, increased from the initiation to the completion of radiotherapy, followed by a gradual decrease to near pre-treatment levels at six months. However, inter-individual variability existed in patients' ratings of each pain characteristic. Predictors of more severe pain characteristic scores were: more comorbidities; worse physical functioning; not having surgery prior to radiotherapy; difficulty swallowing; mouth sores; sleep disturbance; fatigue; more energy, and less social support. Patients with more depressive symptoms had better pain relief. Although some of the predictors cannot be modified (e.g., occurrence of surgery), other predictors (e.g., symptoms) can be treated. Therefore, information about these predictors may result in decreased pain in HNC patients.

1.0 Introduction

Patients with head and neck cancer (HNC) have the highest prevalence of pain among cancer patients [53] and it is often a reason for seeking care [13]. Pain is associated with both the disease and its treatment (e.g., sequela of surgery, radiotherapy [RT]-associated mucositis, chemotherapy [CTX]-associated peripheral neuropathy, osteonecrosis, oral infections) [13]. Approximately 50% of HNC patients report orofacial pain prior to, 81% during, and 70% at the completion of treatment. In addition, 36% report pain six months after treatment and ~30% experience pain beyond six months [10]. The severity of pain varies among different disease sites and over the treatment course [3].

Pain in HNC patients is often assessed as one component of quality of life (QOL) evaluations [10;30]. Over the past 15 years, seven longitudinal studies have evaluated changes in the occurrence [33], severity [11;21;57], or both the occurrence and severity [15;27;35] of pain in HNC patients who received RT. When occurrence rates were reported, pain was present in 53% [15] to 93% [27] of patients prior to, and peaked to 100% [15;27] at the completion of RT. Sample sizes varied from 30 [27] to 135 [35] patients, with follow-up of 2 to 3 months. One study evaluated changes in pain intensity, pain interference, and pain relief [15].

Four studies evaluated a few potential predictors of pain [11;15;27;35]. In one study [15], the occurrence of pain prior to RT predicted worse pain intensity during RT. Findings on the association between pain intensity and the receipt of chemoradiotherapy were not consistent [11;15;27;35]. Among three cross-sectional [29;43;56] and three longitudinal [6;45;47] studies that evaluated pain after HNC treatment, higher pain intensity scores were associated with younger age [43;45], older age [6], less education [47], smoking [29], surgery combined with RT [56], neck dissection [47], higher RT doses [6], feeding tube [47], xerostomia [47], difficulty with speech or swallowing [6], pre-treatment pain [47], use of pain

medication [47], worse physical and mental health [45], less activity [47], sleep problems [47], and depressive symptoms [6;45;47]. None of these studies evaluated all of these characteristics in the same sample or whether they predicted changes in pain scores across the treatment trajectory.

Limitations in previous studies highlight the need for additional research on changes in and predictors of pain during and following RT for HNC. Newer methods of longitudinal analysis, like hierarchical linear modeling (HLM), allow for evaluation of changes over time, as well as identification of characteristics that predict variability in initial levels and trajectories of pain. This approach may provide insights into which characteristics place patients at higher risk for more severe pain, so that treatments can be initiated sooner.

Therefore, the purposes of this longitudinal study of HNC patients were to determine: whether different pain characteristics (i.e., average pain, worst pain, pain interference with function, pain relief) changed from the initiation of RT through the following six months and whether specific demographic, clinical, symptom, and psychosocial characteristics were associated with initial levels of, or changes in, these pain characteristics.

2.0 Methods

2.1 Patients and settings

This study is part of a larger, longitudinal study of symptoms and QOL in oncology patients. Study procedures were described in detail elsewhere (Astrup et al, in press [1]). In brief, patients with HNC were recruited approximately one week prior to the initiation of RT at the Norwegian Radium Hospital (NRH), Oslo University Hospital. These HNC patients were recruited consecutively from an unselected cohort in a health-region covering approximately 60% of the Norwegian population. Inclusion criteria were age ≥18 years; ability to read, write and understand Norwegian; and being scheduled to receive RT for HNC. Exclusion criteria were having RT for brain metastases or a disease that affected the patients'

cognitive ability. Before initiation of RT, patients completed self-report questionnaires to obtain information on demographic and clinical characteristics, as well as several instruments that assessed symptoms and QOL. The questionnaires were completed again at approximately 1, 2, 3, and 6 months after enrollment. Patients in the current study were examined weekly by physicians, and offered frequent follow-up by nurses. In addition, oral hygiene specialists were available for consultation. The study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Directorate of Health, the privacy ombudsman at the hospital, and the institutional review board at NRH.

2.2 Demographic and clinical characteristics

Patients completed a demographic questionnaire about marital status, living situation, level of education, and employment status. Medical records were reviewed for information on the patients' diagnosis, TNM staging [49], and previous treatments.

Karnofsky Performance Status (KPS) scale - Physical functioning was assessed using a version of the KPS scale [17;18] that ranged from 40 (disabled; requires special care and assistance) to 100 (normal; no complaints; no evidence of disease) in 10-point increments.

Self-Administered Comorbidity Questionnaire-19 (SCQ-19) - Comorbidities were assessed using the SCQ-19 [44] which includes 16 common and three optional medical conditions. In the current study, the total number of comorbidities was used in the analyses.

2.3 Symptom characteristics

Brief Pain Inventory (BPI) - Pain occurrence, pain intensity (i.e., average pain, worst pain), pain interference with function, and pain relief were evaluated using the BPI [7;9]. Patients were asked to indicate whether they had pain (yes/no). If they had pain, they rated the severity of their average and worst pain using a 0 (no pain) to 10 (pain as bad as you can imagine) numeric rating scale (NRS). Pain intensity item scores can be categorized into mild pain (1-4), moderate pain (5-6), and severe pain (7-10) [46]. Pain interference with seven

domains (i.e., daily activity, mood, walking ability, normal work, sleep, enjoyment of life, relations with others) was rated using a 0 (does not interfere) to 10 (completely interferes) NRS. A total interference score was calculated as the mean of these seven items. Pain relief was rated using a 0% (no relief) to 100% (complete relief) rating scale. The BPI has well-established validity and reliability among cancer patients, including sensitivity to change in longitudinal studies [19;22;59]. In this study, Cronbach's alpha for the BPI interference scale was .92.

Memorial Symptom Assessment Scale (MSAS) - The MSAS consists of 32 symptoms rated on occurrence, frequency, severity, and distress. The MSAS has well-established validity and reliability [36]. The occurrence of three common symptoms associated with HNC (i.e., dry mouth, mouth sores, difficulty swallowing) were assessed using single items from the MSAS.

General Sleep Disturbance Scale (GSDS) - Sleep disturbance was assessed using the 21-item GSDS [25] that evaluates various aspects of sleep disturbance in the past week. The total score ranges from 0 (no sleep disturbance) to 147 (extreme sleep disturbance). A score of ≥43 indicates high levels of sleep disturbance [25]. In this study, Cronbach's alpha for the GSDS was .86.

Lee Fatigue Scale (LFS) - Fatigue and energy levels were assessed using the 18-item LFS [26] that evaluates each item based on how patients feel "right now" and consists of two subscales (i.e., fatigue and energy). The subscale scores range from 0 to 10. A score of ≥4.4 indicates high levels of fatigue and a score of ≤4.8 indicates low levels of energy [31]. In this study, Cronbach's alpha for the fatigue and energy subscales were .95 and .91, respectively.

Center for Epidemiologic Studies - Depression (CES-D) scale - Depressive symptoms were assessed using the 20-item CES-D [38]. Patients rated how often over the past week they experienced symptoms, using a 0 to 3 scale. The total score ranges from 0 to 60. A score of

≥16 indicates a clinically meaningful level of depressive symptoms. In this study, Cronbach's alpha for the CES-D was .87.

2.4 Psychosocial characteristics

Multidimensional Quality Of Life Scale - Cancer (MQOLS-CA) Nutrition subscale - Nutrition was assessed using the 4-item MQOLS-CA Nutrition subscale [12] that evaluates appetite, food intake, taste, and weight concerns. This subscale score ranges from 0 to 10. Higher scores indicate better nutritional status. In this study, Cronbach's alpha for the MQOLS-CA Nutrition subscale was .73.

MQOLS-CA Interpersonal Well-Being subscale - Social support and social/role functioning, shortened to social support, was assessed using the 5-item MQOLS-CA Interpersonal Well-Being subscale [12] that evaluate these two constructs. The subscale score ranges from 0 to 10. Higher scores indicate better social support. In this study, Cronbach's alpha for the MQOLS-CA Interpersonal Well-Being subscale was .65.

2.5 Data analysis

Descriptive statistics and frequency distributions for the sample characteristics and symptom severity scores at enrollment were calculated using SPSS version 20 (SPSS Inc., Chicago, Illinois). Mean pain intensity, interference with function, and relief scores were calculated for each of the five assessments, for use in the subsequent statistical analyses.

HLM, based on full maximum likelihood estimation, was done using the software developed by Raudenbush and colleagues [40;41]. Four separate HLM analyses were performed to evaluate for changes over time in ratings of pain intensity (i.e., average pain, worst pain), pain interference with function, and pain relief. Each HLM analysis proceeded in two levels. In the first level, intra-individual variability in each of the pain characteristics over time was examined. For each pain characteristic, four different level 1 models were compared to determine whether the patients' ratings did not change over time (i.e., no time effect);

changed at a constant rate either accelerating or decelerating (i.e., linear effect); changed at a rate that accelerated and decelerated over time (i.e., quadratic effect); or changed at a rate that accelerated, decelerated, and accelerated over time (i.e., cubic effect). At this point, the models were constrained to be unconditional (i.e., no predictors) and likelihood ratio tests (i.e., comparison of the deviance values among the models) were used to determine the best fitting models.

The second level of the HLM analyses examined inter-individual differences in the trajectories of the pain characteristics by modeling the individual change parameters (i.e., intercept and slope) as a function of proposed predictors at level 2. A list of proposed predictors was developed based on a review of the literature on pain in patients with HNC (Table 1) [6;11;15;27;29;35;43;45;47;56]. To improve estimation efficiency and to construct parsimonious models, exploratory analyses were done in which each potential predictor was assessed to determine whether it would result in a better fitting model if it alone was added as a level 2 predictor. Predictors with a *t*-value of <2, which indicates a lack of significant effect, were dropped from subsequent model testing. All of the significant predictors from the exploratory analyses, indicated with an "x" in Table 1, were entered into the models to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other variables were retained in the final models (i.e., *p*-value of <.05). The effects of each of these predictors are illustrated in the figures as adjusted change curves for the different pain characteristics that were estimated based on differences in dichotomous outcome predictors (yes/no) or continuous outcome predictors (higher/lower score calculated based on 1 SD above and below the mean score of the predictor).

Non-opioids, opioids and co-analgesics were introduced early in the course of RT during the weekly clinical consultation. Based on patients' self-reports of their current use of analgesic medications, their responses were categorized at each assessment point as either

using or not using analgesics. The use of oral agents such as local anesthetics and mouthwash was not recorded.

3.0 Results

3.1 Patient characteristics

A total of 207 patients scheduled for RT were invited to participate, 163 (79%) consented, but five were excluded after enrollment because they did not meet the pre-specified inclusion criteria. Of the remaining 158 patients, 133 patients (84%) completed the questionnaires prior to RT. The attrition rate was 37% throughout the study period. Differences in demographic and clinical characteristics between patients who did and did not enroll and between patients who did and did not complete the study were described elsewhere (Astrup et al, in press [1]).

Demographic, clinical, and treatment characteristics are presented in Table 2. Most patients were married, middle-aged men, and had oropharyngeal cancer. The most common comorbid conditions were neck/back pain (35%), hypertension (29%), and osteoarthritis (20%). The majority of the patients received a total RT dose of 70 Gray over a period of six weeks (mean dose 61.5 [SD 11.6]).

3.2 Pain occurrence

Figure 1 illustrates the occurrence of none, mild, moderate, and severe pain based on patients' ratings of worst pain at each assessment. The overall occurrence of pain ranged from 48% prior to RT to a peak of 75% during RT, and was 59% at six months. Among the patients with pain prior to RT, 10% reported no pain at one month and 30% reported no pain at two months. On the other hand, the occurrence of pain following the initiation of RT was common. Among the patients who did not report pain prior to RT, 65% reported pain at one month and 56% reported pain at two months.

3.3 Individual and mean change in pain characteristics

The goodness-of-fit tests of the deviance among the models indicated that a cubic model fit the data best for all four pain characteristics ($p<.001$). Table 3 presents the estimates of the unconditional cubic change models from the level 1 analysis. Because the models had no covariates, the intercepts represent the estimated levels of average pain (2.6), worst pain (3.2), pain interference with function (2.0), and pain relief (5.0 [=50%]) prior to RT. Figures 2A through 2D present the cubic trajectories for the four pain characteristics that all display the same pattern (i.e., an increase from enrollment to completion of RT, followed by a decrease after three to six months). The mean scores depicted in the figures are estimated or predicted means based on the HLM analyses.

Inter-individual differences in the trajectories of average pain - Four patient characteristics were associated with initial levels of average pain. Figures 3A through 3D display the effects of each of these characteristics with adjusted change curves for average pain estimated based on differences in number of comorbidities (higher/lower levels calculated based on ± 1 SD of the mean number of comorbidities [Figure 3A]); occurrence of HNC surgery in the six weeks prior to RT (yes/no [Figure 3B]); difficulty swallowing (yes/no [Figure 3C]); and sleep disturbance (higher/lower levels calculated based on ± 1 SD of the mean GSDS score [Figure 3D]).

Inter-individual differences in the trajectories of worst pain - Three patient characteristics were associated with initial levels of worst pain. Figures 4A through 4C display the effects of differences in difficulty swallowing (Figure 4A); sleep disturbance (Figure 4B); and social support (higher/lower levels calculated based on ± 1 SD of the mean MQOLS Interpersonal Well-Being subscale score [Figure 4C]) on initial levels of worst pain.

Inter-individual differences in the trajectories of pain interference with function - Several patient characteristics were associated with initial levels and the trajectory of pain interference with function. Figures 5A through 5F display the effects of differences in

functional status (higher/lower levels calculated based on ± 1 SD of the mean KPS score [Figure 5A]); difficulty swallowing (Figure 5B); sleep disturbance (Figure 5C); fatigue (higher/lower levels calculated based on ± 1 SD of the mean LFS fatigue subscale score [Figure 5D]); energy (higher/lower levels calculated based on ± 1 SD of the mean LFS energy subscale score [Figure 5E]); and social support (Figure 5F) on initial levels of pain interference with function. Figure 6 displays the effect of number of comorbidities on the trajectory of pain interference with function.

Inter-individual differences in the trajectories of pain relief - Three patient characteristics were associated with initial levels or the trajectory of pain relief. Figures 7A and 7B display the effects of differences in occurrence of mouth sores (yes/no [Figure 7A]) and depressive symptoms (higher/lower levels calculated based on ± 1 SD of the mean CES-D score [Figure 7B]) on initial levels of pain relief. Figure 7C displays the effect of number of comorbidities on the trajectory of pain relief.

3.4 Analgesic treatments

Patients' use of analgesics is presented in Table 4. At each assessment, between 7% and 28% of the patients who had pain, reported that they did not use pain medications.

4.0 Discussion

4.1 Pain characteristics

While slightly lower than previous reports [15;27] , the occurrence rates for pain were relatively high throughout this study. Prior to RT, 48% of patients had pain, a presenting symptom that may be severe at diagnosis [23]. In addition, 14% of patients had recurrent disease with previous single- or multimodal treatments, which can cause pain [30]. At six months, 59% of the patients reported pain; 17% in the moderate to severe range, which suggests that persistent pain is a significant problem [5]. Pain prior to initiation of RT is presumably associated with the tumor or secondary to surgery, while pain at six months is

most likely associated with treatment. Treatment-related pain can result from multiple mechanisms (i.e., nociceptive (e.g., tumor expansion, inflammation), neuropathic (e.g., RT-induced neuritis)), and occur in multiple locations [2]. While the current study included patients with mixed HNC diagnoses, the majority had oropharyngeal cancer that is often associated with HPV-infection. Additional research is needed to determine if pain characteristics differ among the various HNC diagnoses.

Pain intensity scores in this study were in the mild to moderate range, slightly lower than previous reports [15;27]. Pain interference with function scores were similar to one previous report [15]. As expected, the patterns of change in ratings of average and worst pain, as well as pain interference with function, increased during RT and decreased to near pre-treatment levels following RT. The parallel increase in pain relief scores suggests that patients received additional analgesics during RT without sufficient level/doses to relieve pain associated with RT-induced injury to the oral and oropharyngeal mucosa.

Potential explanations for the lower pain intensity scores are that Norwegian patients may seek medical care earlier and or that their physicians prescribe more potent or higher doses of analgesics. Despite the provided interventions from clinicians and consistent with a previous report [15], ratings of pain relief, as well as use of analgesics (Table 4), suggest that improvements in pain management are warranted. Sub-optimal pain relief may be associated with barriers to pain management (e.g., fears of tolerance and addiction [34;52]). Reasons for the persistence of pain and its interference with function were not assessed. However, it may be related to the adverse effects of RT or surgery [5;13] or to other comorbid conditions. Persistent post-treatment pain may be complex and more difficult to treat [10].

Lower levels of pain interference with function may be explained by the specific items on the BPI interference scale. For example, HNC-pain may not interfere with ability to walk or perform general activities. However, HNC patients reported that pain does interfere with

their ability to eat, swallow, or speak [6], which are not assessed on the BPI. This finding calls for the use of disease-specific pain assessment tools (e.g., see references [4;8;28]) in order to increase the sensitivity and specificity for changes between groups and over time, for better identification of the concept of pain in these patients. Our finding that difficulty swallowing predicted initial levels of pain intensity and pain interference supports this recommendation.

4.2 Predictors of each pain characteristic

Several symptom and psychosocial characteristics were associated with the severity of one or more of the pain characteristics. Pre-RT sleep disturbance was associated with higher initial levels of average and worst pain as well as pain interference with function. Similar associations were found in other studies of oncology patients [20;47]. Pain is one of the primary factors that precipitate sleep disturbance in cancer patients [51]. In addition, sleep disturbance increases one's sensitivity to pain [48]. Our patients' mean GSDS score was above the clinically meaningful cut-off score. As part of effective pain management, sleep disturbance needs to be assessed in these patients.

Consistent with a study of symptom clusters in patients with HNC [60], fatigue was associated with higher initial levels of pain interference with function. In contrast, patients with more energy reported higher initial levels of pain interference with function. This finding may be explained by the fact that even though HNC patients often experience pain in the head and neck region as well as weight loss, they still have high energy levels at the initiation of RT.

Pre-RT difficulty swallowing was associated with higher initial levels of average and worst pain and pain interference with function, consistent with a previous report [6]. In contrast, the presence of mouth sores pre-RT was only associated with higher initial levels of pain relief. Pre-RT mouth sores may be caused by the tumor or mucosal injury. The necessity to swallow saliva may result in a severe and almost continuous pain compared to mouth sores.

An alternative hypothesis is that medications for mouth sores were more effective than those for difficulty swallowing.

While positive associations were found between depressive symptoms and worst pain [6;45;47], in this study higher levels of depressive symptoms were associated with higher pain relief scores. One potential explanation is that our patients with depressive symptoms received antidepressants with analgesic effects.

Consistent with previous reports in patients with heterogeneous cancer diagnoses [32] and breast cancer [16], patients with less social support reported higher initial levels of worst pain and pain interference with function. Previous research demonstrates that caregivers assist patients to manage their pain by helping them monitor symptoms, comply with medical treatments, deal with side effects, and communicate with clinicians [37].

Three clinical characteristics were associated with one or more of the pain characteristics. The occurrence of surgery in the six weeks prior to RT was associated with lower initial levels of average pain. These patients may have had cancer-related pain relieved by surgery [54]. In a previous study, pain in patients with HNC was tumor-related in 81% of cases [14]. Patients who underwent surgery may have received analgesics as part of their postoperative treatment.

Patients with a lower KPS score reported higher initial levels of pain interference with function. This finding supports previous work that found associations between poorer physical health and more severe post-treatment pain [45] and between lower functional status and a higher dose of prescribed analgesics [24]. The fact that both lower functional status scores and higher energy scores predicted higher levels of pain interference is interesting. The mean KPS score in this study (i.e., 86 ±13) was relatively high, while the mean energy score [i.e., 5.4 ±2.2) is just above the clinically meaningful cut-off score. The correlation between the two scales was 0.50 ($p<.001$). This finding warrants exploration in future studies.

Finally, the number of comorbidities predicted initial levels of average pain (Figure 3A) as well as the trajectories of pain interference with function (Figure 6) and pain relief (Figure 7C). Patients with more comorbidities reported higher average pain scores pre-RT. Previous studies of patients with HNC [50] and heterogeneous cancer diagnoses [39;52;55] reported similar results. This finding may be associated with the co-occurrence of other painful conditions (e.g., neck/back pain, osteoarthritis). Patients with more comorbidities reported less pain interference with function during RT, but slightly more at the end of the study. Patients with other painful conditions may experience less impact from RT-associated pain or adjust their activities to reduce their pain. Patients with more comorbidities reported less pain relief during RT, which may be attributed to inadequate treatment of their comorbid conditions and/or the new pain associated with cancer and its treatment. A previous study found that patients with more comorbidities were less likely to receive adequate analgesics [58].

The lack of significant predictors of the trajectories of average and worst pain may be explained by the sample size and attrition rate of 37%. Support for predictors of a cubic rate of change may require more patients and a larger amount of variability in the assessed outcome [42]. Other limitations may have influenced our results. Patients were not asked about the etiology of their pain, the inclusion of patients with a variety of HNC diagnoses results in a more heterogeneous sample, generalizability of the findings is limited due to the recruitment of mostly White, married, and well-educated patients and characteristics found to be associated with pain in previous studies (e.g., presence of a feeding tube, smoking) were not assessed.

4.3 Implications for practice and research

Clinicians can use the information on the severity and predictors of the different pain characteristics to identify and intervene with higher risk patients. More comorbidity, difficulty

swallowing, and sleep disturbance were associated with three out of the four pain characteristics, suggesting that these predictors need to be assessed in patients with HNC. Furthermore, findings suggest that patients warrant more intensive pain management strategies during and after treatment.

Pain severity and interference with function scores did not return to pre-RT levels at six months. Future studies with a longer follow-up can explore duration of and potential mechanisms for persistent pain. Replication of findings on predictors of the different pain characteristics is warranted in independent samples. Future studies should test the efficacy of interventions targeted at mitigating modifiable risk factors for more severe pain.

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Table 1 Exploratory analysis of potential predictors of levels of different pain characteristics in patients with head and neck cancer

Characteristics	Average pain				Worst pain				Pain interference				Pain relief			
	I	LC	QC	CC	I	LC	QC	CC	I	LC	QC	CC	I	LC	QC	CC
Demographic																
Age												x				
Gender																
Marital status						x	x	x								
Education level																
Employment status																
Clinical																
Time since diagnosis																
Karnofsky Performance Status	x				x				x					x	x	x
Number of comorbidities	x				x	x	x	x	x	x	x	x		x	x	x
Tumor site																
Stage of disease at enrollment																
Current treatment intent																
Surgery prior to radiotherapy	x				x				x				x	x		
Concomitant chemotherapy																
Radiotherapy dose in Gray																
Symptom																
Pain at enrollment (for slope)		x	x	x		x	x	x								
Mouth sores	x				x				x				x			
Dry mouth	x				x				x							
Difficulty swallowing	x			x	x	x	x	x	x				x	x	x	x
Sleep disturbance	x				x				x				x	x	x	x
Fatigue	x				x				x							
Energy									x							
Depressive symptoms	x				x				x				x			
Psychosocial																
Nutrition	x				x	x	x	x	x				x	x	x	x
Social support	x				x		x	x	x							

Note: Potential predictors that had a *t*-value of 2 or higher in the exploratory analysis are indicated with an "x"
Abbreviations: CC=Cubic Component; I=Intercept; LC=Linear Component; QC=Quadratic Component

Table 2 Demographic, clinical, symptom, and psychosocial characteristics of patients with head and neck cancer (n=133)

Characteristic		**Mean (SD)**	**Min/max**
Age, *years*		60 (11)	24/87
Time since diagnosis, *weeks*	Primary disease	5 (9)	0/90
	Residual/recurrent disease	159 (159)	10/581
Clinical characteristic scores at enrollment	KPS score (40-100)	86 (13)	40/100
	Number of comorbidities (0-19)	2 (2)	0/16
Symptom and psychosocial characteristic scores at enrollment	Sleep disturbance (0-147)	46.1 (22.0)	8.4/108.2
	Fatigue (0-10)	2.5 (2.0)	0.0/8.0
	Energy (0-10)	5.4 (2.2)	0.0/10.0
	Depressive symptoms (0-60)	12.6 (9.5)	0.0/42.0
	Nutrition (0-10)	7.9 (2.2)	0.5/10.0
	Social support (0-10)	8.0 (1.5)	1.8/10.0
		N	**%** [a]
	Pain (yes)	68	51
	Mouth sores (yes)	44	33
	Dry mouth (yes)	73	55
	Difficulty swallowing (yes)	64	48
Gender	Male	94	71
	Female	39	29
Ethnicity	White	132	99
	Asian	1	1
Marital status	Married/Partnered	91	68
	Unmarried/Divorced/Widowed	42	32
Education level	Primary	29	22
	Secondary	66	50
	College/University	38	29
Employment status	Full/Part time work	14	11
	Sick leave/Disability benefit	85	64
	Retired/Other	34	26
Tumor site	Oral cavity	36	27
	Oropharynx	61	46
	Larynx	15	11
	Other	21	16
Stage of disease at enrollment	I	10	8
	II	12	9
	III	11	8
	IV	81	61
	Residual/recurrent	19	14
Previous treatment	Surgery	18	14
	Radiotherapy (RT)	15	11
	Chemotherapy (CTX)	6	5
Current treatment intent	Curative [b]	120	90
	Palliative [c]	13	10
Current treatment [d]	Surgery prior to RT [e]	65	49
	RT	25	19
	RT and concomitant CTX	35	26
	Post-operative RT	46	35
	Post-operative RT and concomitant CTX	11	8
	Hyperfractioned/palliative RT	16	12
	Post-RT surgery primary tumor/lymph node	28	21
	Post-RT symptomatic/palliative surgery	15	11
Status after 6 months	Disease free	113	85

	Alive with disease	9	7
	Death by index tumor	7	5
	Death by other disease	4	3

Abbreviations: CTX=Chemotherapy, KPS=Karnofsky Performance Status, RT=Radiotherapy, SD=Standard Deviation

Notes:

[a] Percentages may add up to >100 because decimals are rounded up

[b] Including 9 patients with recurrent disease

[c] Including 3 patients with primary disease

[d] Patients may have undergone more than one treatment

[e] Including 5 patients who underwent primary RT and 3 patients who underwent hyperfractioned/palliative RT

Table 3 Hierarchical linear models of pain characteristics in patients with head and neck cancer

Average pain	Coefficient (SE)					
	Unconditional model			Final model		
Fixed effects						
Intercept	2.581	(0.225)	***	2.427	(0.200)	***
Time [a] (linear rate of change)	2.344	(0.437)	***	2.575	(0.431)	***
$Time^2$ (quadratic rate of change)	-1.046	(0.208)	***	-1.128	(0.203)	***
$Time^3$ (cubic rate of change)	0.110	(0.024)	***	0.118	(0.023)	***
Time invariant covariates						
Intercept:						
Number of comorbidities				0.211	(0.073)	**
Surgery prior to RT				-0.534	(0.256)	*
Difficulty swallowing				0.958	(0.268)	***
Sleep disturbance				0.022	(0.006)	***
Variance component						
In intercept	3.036		***	1.829		***
In linear rate	9.474		***	9.039		**
In quadratic rate	1.950		**	1.742		*
In cubic rate	0.023		*	0.020		*
Goodness-of-fit deviance (df)	1410.520	(15)		1357.963	(19)	
Model comparison ($\chi 2$)				52.557	(4)	***

Worst pain	Coefficient (SE)					
	Unconditional model			Final model		
Fixed effects						
Intercept	3.167	(0.277)	***	3.019	(0.249)	***
Time [a] (linear rate of change)	2.877	(0.537)	***	3.061	(0.536)	***
$Time^2$ (quadratic rate of change)	-1.308	(0.264)	***	-1.366	(0.263)	***
$Time^3$ (cubic rate of change)	0.139	(0.030)	***	0.144	(0.030)	***
Time invariant covariates						
Intercept:						
Difficulty swallowing				0.903	(0.317)	**
Sleep disturbance				0.027	(0.008)	***
Social support				-0.312	(0.098)	**
Variance component						
In intercept	4.599		***	2.913		***
In linear rate	14.004		***	13.959		***
In quadratic rate	3.238		***	3.182		**
In cubic rate	0.042		**	0.041		**
Goodness-of-fit deviance (df)	1568.679	(15)		1525.929	(18)	
Model comparison ($\chi 2$)				42.750	(3)	***

Pain interference with function	Coefficient (SE)					
	Unconditional model			Final model		
Fixed effects						
Intercept	2.045	(0.231)	***	1.860	(0.164)	***
Time [a] (linear rate of change)	2.275	(0.412)	***	2.550	(0.382)	***
$Time^2$ (quadratic rate of change)	-1.069	(0.200)	***	-1.163	(0.188)	***
$Time^3$ (cubic rate of change)	0.116	(0.023)	***	0.125	(0.022)	***
Time invariant covariates						
Intercept:						
KPS score				-0.034	(0.010)	***
Difficulty swallowing				0.588	(0.242)	*
Sleep disturbance				0.028	(0.007)	***
Fatigue				0.234	(0.089)	**

Energy				0.203	(0.062)	***
Social support				-0.500	(0.073)	***
Change over time:						
Number of comorbidities						
Time [a] (linear rate of change)				-0.434	(0.179)	*
Time^2 (quadratic rate of change)				0.208	(0.095)	*
Time^3 (cubic rate of change)				-0.022	(0.011)	*
Variance component						
In intercept	3.479		***	0.699		*
In linear rate	7.323		***	5.381		**
In quadratic rate	1.613		***	1.159		*
In cubic rate	0.020		***	0.015		*
Goodness-of-fit deviance (df)	1460.701	(15)		1341.284	(24)	
Model comparison (χ2)				119.417	(9)	***

Pain relief	Coefficient (SE)					
	Unconditional model			Final model		
Fixed effects						
Intercept	4.955	(0.447)	***	4.831	(0.423)	***
Time [a] (linear rate of change)	2.514	(0.749)	***	2.814	(0.713)	***
Time^2 (quadratic rate of change)	-1.260	(0.360)	***	-1.377	(0.340)	***
Time^3 (cubic rate of change)	0.139	(0.042)	***	0.151	(0.039)	***
Time invariant covariates						
Intercept:						
Mouth sores				1.195	(0.488)	*
Depressive symptoms				0.078	(0.026)	**
Change over time:						
Number of comorbidities						
Time [a] (linear rate of change)				0.887	(0.270)	***
Time^2 (quadratic rate of change)				0.461	(0.149)	**
Time^3 (cubic rate of change)				-0.052	(0.018)	**
Variance component						
In intercept	11.446		***	9.557		***
In linear rate	25.373		***	20.653		***
In quadratic rate	5.877		***	4.605		***
In cubic rate	0.076		***	0.060		***
Goodness-of-fit deviance (df)	1466.995	(15)		1446.156	(20)	
Model comparison (χ2)				20.839	(5)	***

Note: [a] Time was coded as zero at the visit prior to radiotherapy; * p<.05; ** p<.01; *** p<.001
Abbreviations: KPS=Karnofsky Performance Status; RT=Radiotherapy; SE=Standard error

Table 4 Self-reported use of analgesic medications among patients in pain at each assessment

	Enrollment % [a]	Month 1 %	Month 2 %	Month 3 %	Month 6 %
None	19	7	12	21	28
Analgesic treatment	63	87	83	74	61
Missing	18	6	5	5	12

Note: [a] Percentages may add up to >100 because decimals are rounded up

Figure legends

Figure 1 - Percentage of patients with no, mild, moderate, and severe pain at each assessment. Footnote: Worst pain severity scores were used to categorize mild (1-4), moderate (5-6), and severe (7-10) pain

Figure 2 - Mean trajectories of average pain (A), worst pain (B), pain interference with function (C), and pain relief (D) from initiation of radiotherapy (RT) and for six months following

Figure 3 - Trajectories of average pain by number of comorbidities (A), occurrence of surgery prior to radiotherapy (B), occurrence of difficulty swallowing (C), and sleep disturbance (D)

Figure 4 - Trajectories of worst pain by occurrence of difficulty swallowing (A), sleep disturbance (B), and social support (C)

Figure 5 - Trajectories of pain interference with function by functional status (A), occurrence of difficulty swallowing (B), sleep disturbance (C), fatigue (D), energy (E), and social support (F)

Figure 6 - Trajectories of pain interference with function by number of comorbidities

Figure 7 - Trajectories of pain relief by occurrence of mouth sores (A), depressive symptoms (B), and number of comorbidities (C)

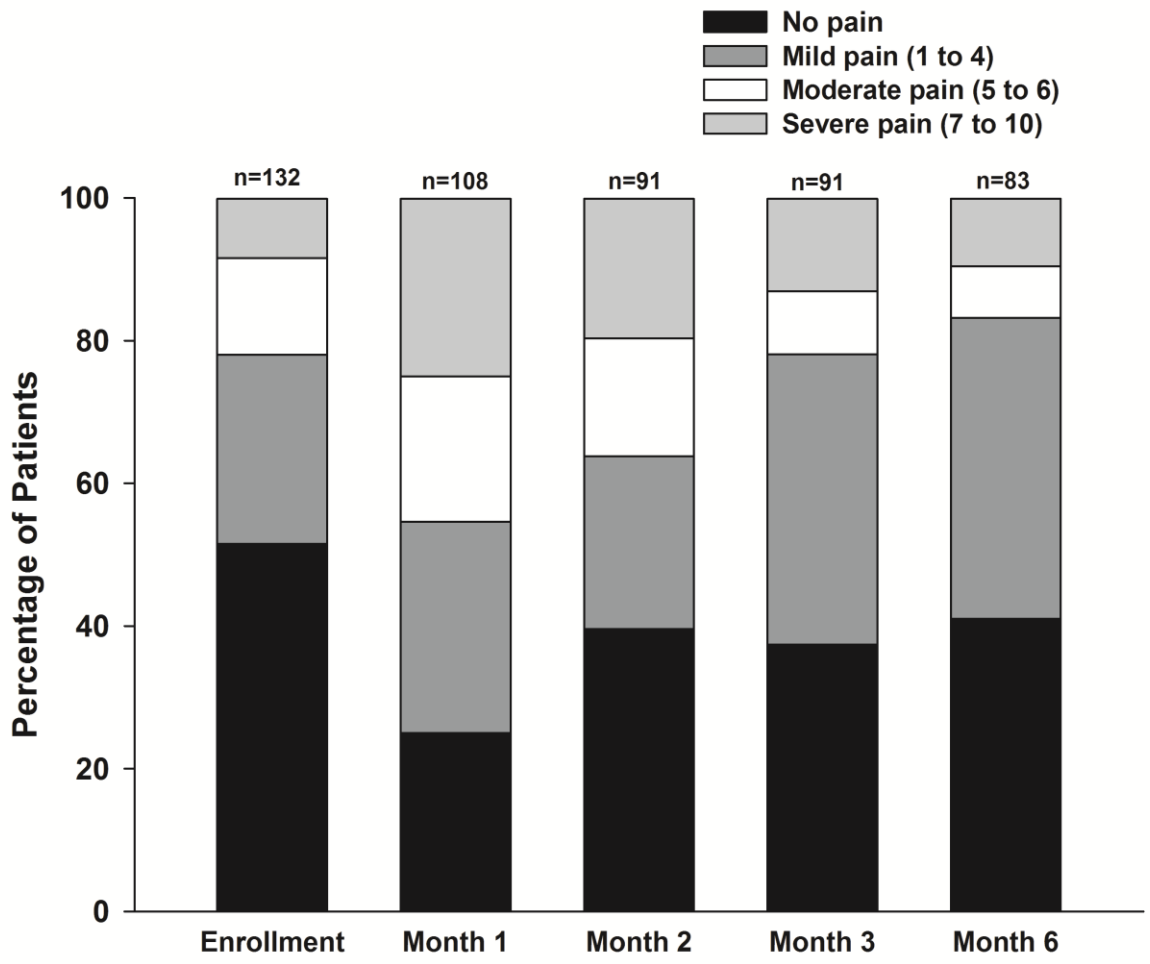
No pain
Mild pain (1 to 4)
Moderate pain (5 to 6)
Severe pain (7 to 10)
n=132
n=108
n=91
n=91
n=83
100
80
60
40
20
0
Percentage of Patients
Enrollment
Month 1
Month 2
Month 3
Month 6

Figure 1

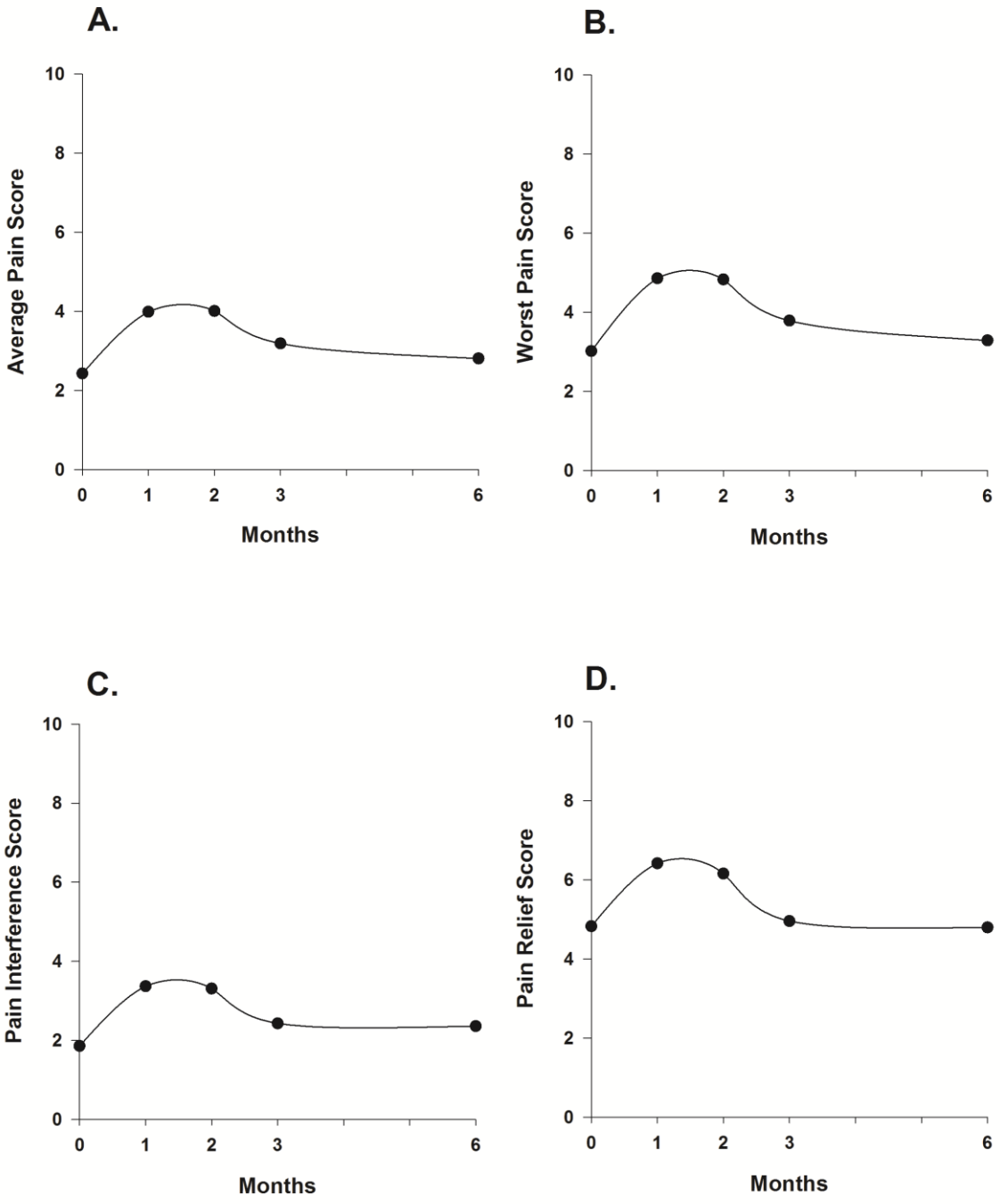
A.
Average Pain Score
10
8
6
4
2
0
0
1
2
3
6
Months
B.
Worst Pain Score
10
8
6
4
2
0
0
1
2
3
6
Months
C.
Pain Interference Score
10
8
6
4
2
0
0
1
2
3
6
Months
D.
Pain Relief Score
10
8
6
4
2
0
0
1
2
3
6
Months

Figure 2

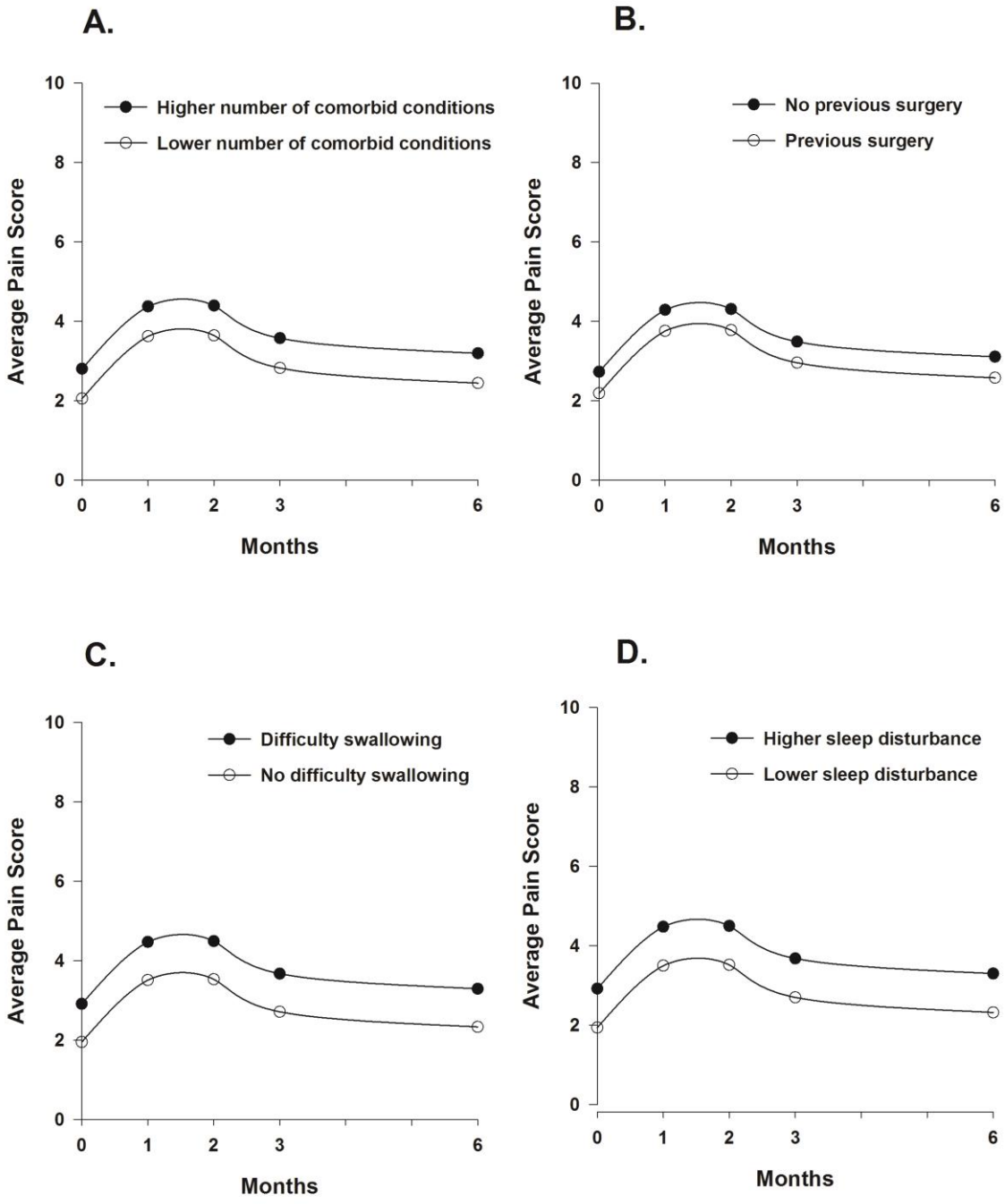
A.
Higher number of comorbid conditions
Lower number of comorbid conditions
Average Pain Score
Months
B.
No previous surgery
Previous surgery
Average Pain Score
Months
C.
Difficulty swallowing
No difficulty swallowing
Average Pain Score
Months
D.
Higher sleep disturbance
Lower sleep disturbance
Average Pain Score
Months

Figure 3

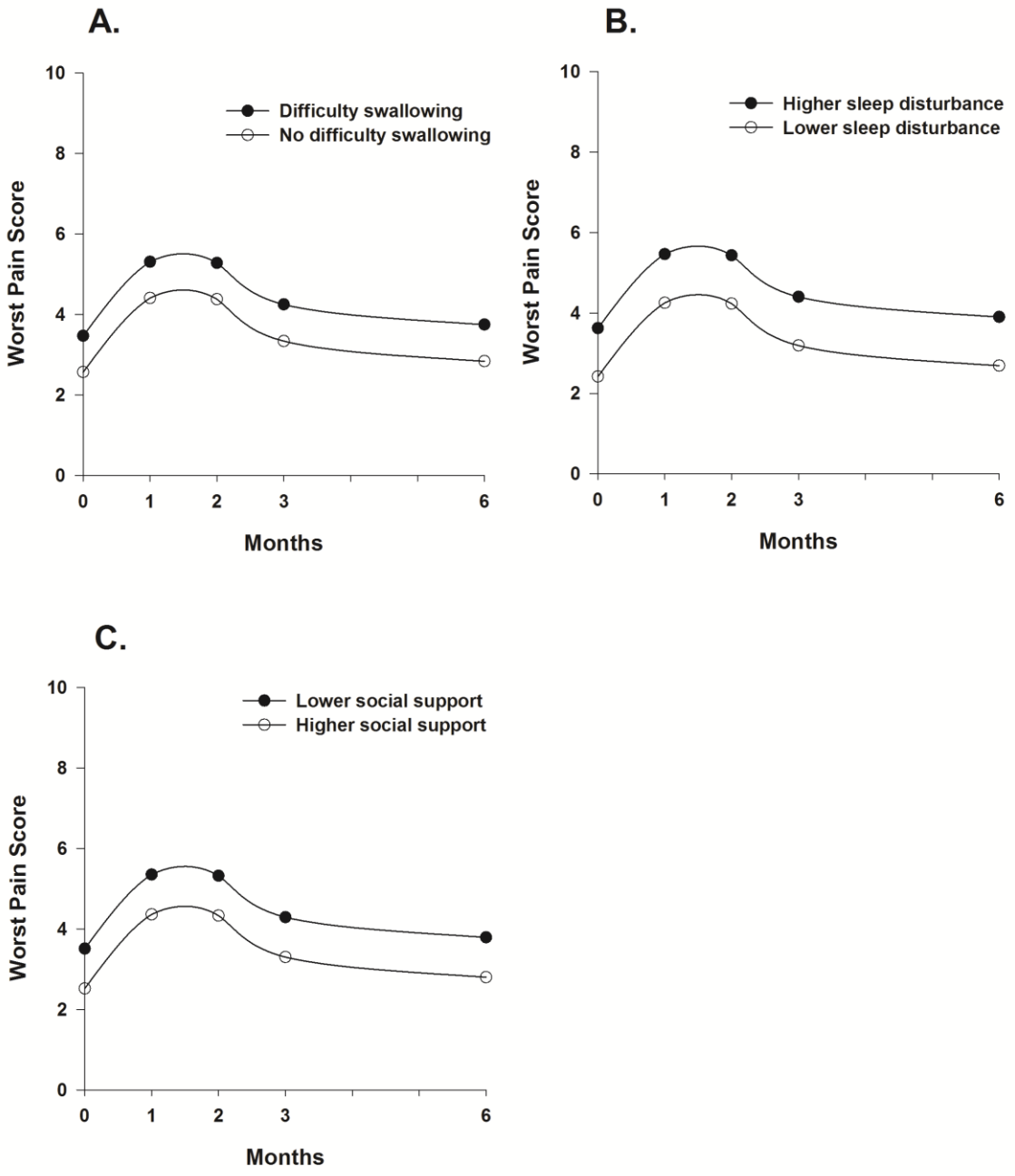
A.
Worst Pain Score
Difficulty swallowing
No difficulty swallowing
Months
B.
Worst Pain Score
Higher sleep disturbance
Lower sleep disturbance
Months
C.
Worst Pain Score
Lower social support
Higher social support
Months

Figure 4

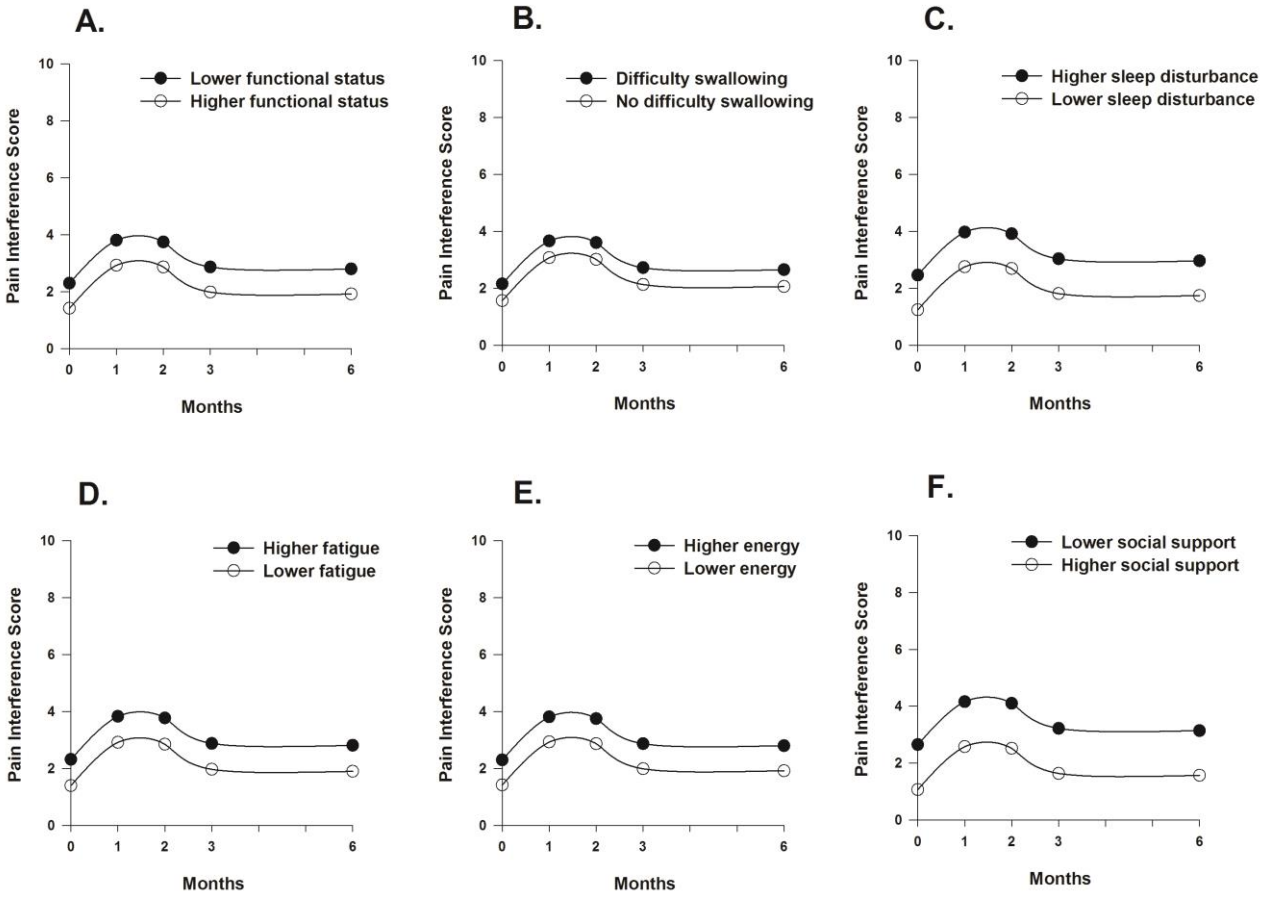

Figure 5

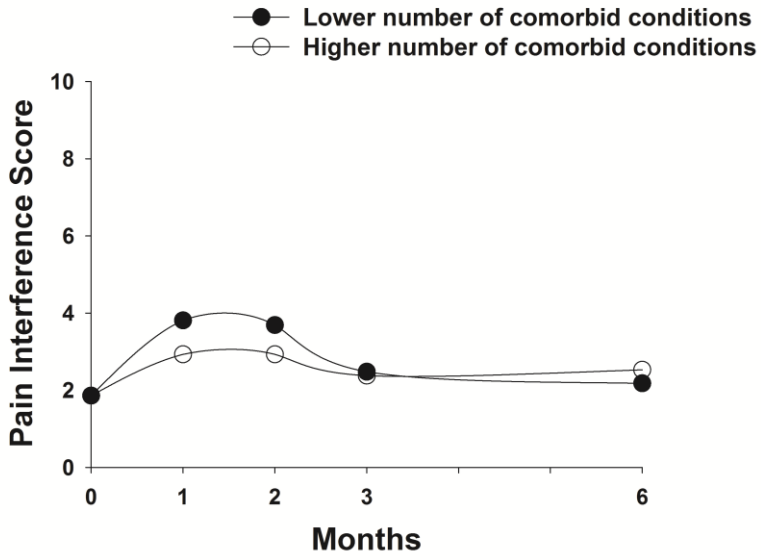

Figure 6

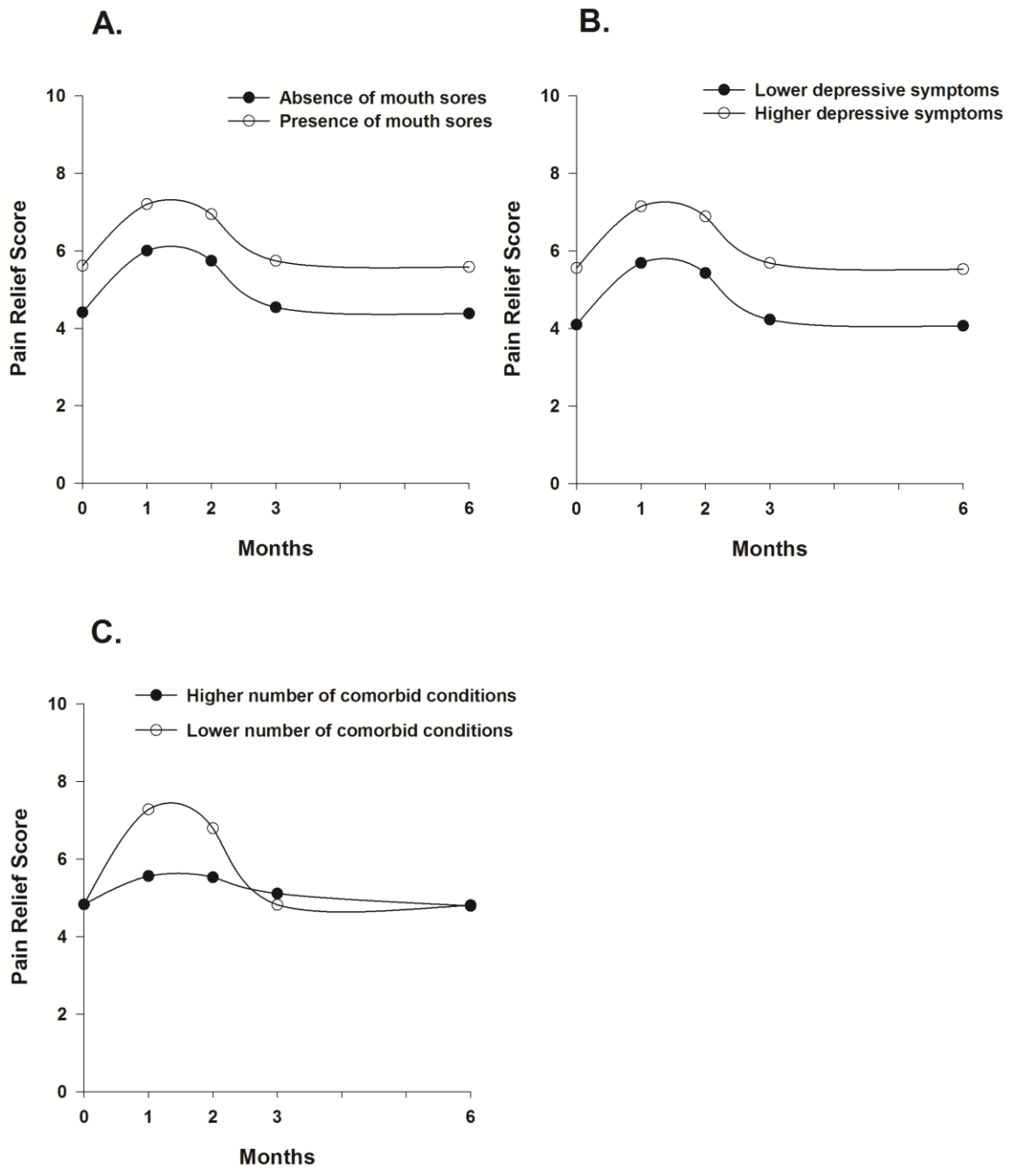
A.
Absence of mouth sores
Presence of mouth sores
Pain Relief Score
Months
B.
Lower depressive symptoms
Higher depressive symptoms
Pain Relief Score
Months
C.
Higher number of comorbid conditions
Lower number of comorbid conditions
Pain Relief Score
Months

Figure 7