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Correlation of symptom clusters, fatigue, and quality of life in pituitary tumor patients

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Abstract: This longitudinal study investigated the composition, progression, and clinical implications of symptom clusters among patients with pituitary adenomas across four perioperative time points. A total of 104 patients undergoing transsphenoidal surgery were assessed using validated instruments, including the MDASI-BT, MFI-20, HADS, PSQI, and SF-36. Three major symptom clusters were identified: neurological, endocrine, and fatigue–emotional–sleep disturbance (FES). The FES cluster was associated with the most severe fatigue, poorest sleep quality, and lowest quality of life scores, particularly during the early postoperative period. While patients in the neurological cluster experienced significant recovery over time, those in the endocrine and FES clusters showed more prolonged or fluctuating symptom trajectories. The minimal overlap between clusters revealed a high degree of heterogeneity in symptom experiences, underscoring the importance of tailored management. To the best of the authors’ knowledge, this is one of the first longitudinal studies in a Chinese population to examine symptom cluster dynamics in pituitary tumor patients across multiple time points using multidimensional patient-reported outcomes. These findings contribute to novel insights for precision symptom management, with implications for improving recovery, reducing fatigue, and enhancing quality of life in this unique clinical population.

Keywords: Symptom trajectory; transsphenoidal surgery; cluster-based management; emotional distress; postoperative recovery; brain tumor rehabilitation

1. Introduction

Pituitary adenomas (PAs) are benign neoplasms that originate from adenohypophysis cells or remnants of the craniopharyngeal duct. These tumors, although non-malignant, can produce significant clinical manifestations due to their anatomical location and hormonal activity. The underlying pathogenesis typically involves genetic mutations or epigenetic changes affecting cell cycle regulation [1]. PAs represent the third most prevalent primary intracranial tumor, following gliomas and meningiomas, accounting for approximately 10% to 15% of all intracranial neoplasms [2]. Globally, the prevalence of PAs is estimated at 89.1 per 100,000 individuals, with an annual incidence of about 5.1 per 100,000 [1]. Although comprehensive epidemiological data from China are still limited, advancements in imaging and endocrinological diagnostics have enhanced the detection rate of PAs [3]. Reports from cancer registries indicate 130 to 230 cases per million, while some population-based estimates suggest even higher figures ranging from 190 to 280 per million [4].

PAs can develop at any age, with bimodal peaks in incidence during the ages of 30 to 40 and 60 to 70 [5]. These tumors are classified by size into microadenomas (<10

mm), macroadenomas (10–40 mm), and giant adenomas (≥ 40 mm), and by functionality into functioning and non-functioning adenomas. This dual classification aids in predicting clinical behavior and guiding treatment strategy. Non-functioning PAs comprise 15% to 54% of all cases and may remain undiagnosed due to the absence of hormonal symptoms. Functioning adenomas may secrete prolactin (32% to 66%), growth hormone (8% to 16%), ACTH (2% to 6%), and rarely TSH or gonadotropins [6]. The 2017 WHO classification introduced the term pituitary neuroendocrine tumors (PitNETs), reflecting the heterogeneous and neuroendocrine nature of these tumors [7].

Clinical manifestations of PAs depend on hormonal activity or mass effect. The symptomatology often overlaps with other neurological or endocrine disorders, which can delay diagnosis. Hypersecreting tumors lead to symptoms such as galactorrhea, infertility, acromegaly, or Cushing's disease, while large tumors may cause visual field deficits, headaches, and cranial nerve impairments [8]. Although histologically benign, PAs may invade surrounding structures including the cavernous sinus and sphenoid sinus, contributing to surgical challenges and recurrence [9].

Surgical resection remains the cornerstone of treatment, especially for non-functioning and secreting hormone-secreting adenomas. The endoscopic endonasal transsphenoidal approach is widely favored for its minimally invasive nature and superior visual outcomes [10]. Nevertheless, complications such as cerebrospinal fluid (CSF) leakage, diabetes insipidus, electrolyte imbalance, olfactory dysfunction, and infection persist [11]. Transient diabetes insipidus typically occurs within the first 48 hours and resolves spontaneously in most cases. Hormonal dysregulation may persist postoperatively, necessitating long-term endocrine management [12]. Visual recovery generally improves within six weeks, though complete normalization may take up to six months [13]. Residual symptoms including headache, nasal discomfort, and fatigue can linger, substantially affecting quality of life. These postoperative effects often require multidisciplinary care and psychological support to facilitate full recovery and enhance patient well-being [14].

Most prior studies have examined isolated symptoms or outcomes such as visual or hormonal recovery. However, emerging evidence highlights the importance of evaluating symptom cluster groups of interrelated symptoms that co-occur and interact synergistically to increase patient burden. These clusters often include fatigue, emotional distress, and neurocognitive symptoms, which are frequently reported among PA patients. Recognizing and managing these symptom clusters can provide a more holistic and impactful approach to care.

This study addresses the current gap by employing a prospective longitudinal design to analyze the composition, temporal changes, and subgroup patterns of symptom clusters in PA patients. By correlating symptom cluster patterns with fatigue and quality of life outcomes, this study aims to generate practical insights for individualized symptom management. The novelty of this study lies in its longitudinal scope, subgroup stratification, and use of validated measurement tools to explore symptom trajectories across four postoperative time points. Ultimately, it aims to offer evidence that can directly support proactive clinical decision-making and patient education.

2. Literature review

2.1. Concept of symptom clusters

The concept of symptom clusters was introduced by Dodd et al. [15] in 2001 to describe three or more concurrent symptoms that are interrelated but may not share the same etiology. The modern definition has evolved to include two or more symptoms that are correlated and form a stable grouping. These symptom clusters often exert compounded physiological and psychological effects, surpassing the burden of individual symptoms alone. Clinically, symptom clusters are increasingly viewed as a more meaningful unit for intervention, as they reflect underlying biological or psychosocial mechanisms. Understanding how symptoms interact can help healthcare professionals anticipate trajectories, tailor supportive care plans, and improve health outcomes.

2.2. Instruments for symptom cluster assessment

A variety of tools have been validated to measure symptom clusters in chronic and oncologic populations. The Memorial Symptom Assessment Scale (MSAS) evaluates 32 symptoms in terms of frequency, severity, and distress. It includes physical and psychological subscales and has demonstrated high internal consistency (Cronbach's alpha 0.79 to 0.87) [16].

The MD Anderson Symptom Inventory (MDASI), including its Brain Tumor module (MDASI-BT), contains 28 items and has been validated for Chinese populations. It assesses both symptom severity and interference with daily functioning [17].

The Edmonton Symptom Assessment System (ESAS) includes nine core symptoms, later expanded to eleven by adding constipation and sleep quality (ESAS-CS) [18]. Although ESAS is simple to use, it may not capture the full complexity of symptom interactions.

The Symptom Distress Scale (SDS) measures symptom severity and distress using a 5-point Likert scale, but lacks granularity in differentiating severity from interference, limiting its utility in detailed cluster analysis [19]. In practice, the choice of instrument depends on the clinical context, desired level of detail, and patient population. More comprehensive tools like MDASI-BT offer richer data for clustering analysis, while brief scales such as ESAS are more feasible for routine monitoring.

2.3. Methods for symptom cluster analysis

Several analytical approaches have been applied to explore symptom clusters in oncology and neurology populations. Exploratory Factor Analysis (EFA) is one of the most frequently used methods. It reduces many observed variables into a smaller set of latent factors by identifying patterns of shared variance, without requiring prior assumptions about the structure of the data. EFA has been successfully used to reveal symptom cluster structures and their evolution over time in pituitary adenoma patients and other cancer populations [20]. Principal Component Analysis (PCA), a related dimensionality reduction method, transforms correlated variables into uncorrelated components. This technique helps simplify complex symptom profiles and has been

used to identify core symptom domains in patients with central nervous system tumors [21].

Cluster analysis, particularly hierarchical clustering using Ward's method, has been widely employed to classify patients into symptom burden groups based on the intensity and similarity of reported symptoms. Studies have shown that patients with high-symptom cluster profiles often report significantly poorer functional outcomes and quality of life compared to those in low-symptom groups [22].

Latent Class Analysis (LCA) and Latent Profile Analysis (LPA) are person-centered approaches that identify unobserved subgroups within a population by analyzing patterns of symptom occurrence or severity. These methods are particularly useful when researchers hypothesize the existence of distinct patient classes that are not immediately observable. LCA has demonstrated strong predictive value for both symptom progression and patient-reported outcomes such as quality of life and functional status in advanced cancer and glioma populations [23,24].

Although these statistical methods offer robust insights, they often require large samples and strong modeling assumptions. In the present study, symptom clusters were classified manually based on clinically reported initial and accompanying symptoms, allowing for a more practical and observation-based framework that reflects real-world patient experiences.

2.4. Current status and implications

Numerous studies have validated the clinical relevance of symptom clusters in cancer and brain tumor populations. Previous studies have demonstrated that certain symptom clusters, especially those involving fatigue, mood disturbances, or neurological symptoms, are significantly associated with lower quality of life [22]. Dong et al. reported that worsening symptom clusters were associated with poorer outcomes [24]. These findings emphasize the need for early identification and intervention to mitigate the progression of symptom burden.

In neuro-oncology, common clusters include neurofunctional (fatigue, dry mouth, impaired activity), emotional (anxiety, depression), and fatigue-sleep disturbance clusters [14]. These groupings are not only consistent across different tumor types but also appear to persist over time, highlighting their clinical importance. Kim et al. [22] and Coomans et al. [23] found that patients in high-symptom clusters exhibited significantly worse quality of life, reduced physical functioning, and limited mobility. Such observations support the argument that symptom clusters can serve as important markers for treatment planning, patient counseling, and prognosis estimation.

2.5. Symptom clusters in PA patients

Studies on PA patients remain limited but show consistent findings. Liu et al. [25] observed symptom evolution across time, with fatigue and sleep disturbance dominant pre- and post-surgery, later transitioning to cognitive and sensory symptoms. Liu [26] applied PCA and identified neurofunctional and emotional clusters in postoperative PA patients.

These findings suggest that symptom clusters offer greater clinical utility than

single-symptom assessments by capturing interactions, predicting risk, and guiding personalized management. For instance, identifying a subgroup characterized by fatigue-sleep disturbance may lead to early supportive care or psychosocial interventions tailored to their specific needs. The recognition of subgroups within symptom clusters further enables tailored interventions.

This study builds upon these foundations by longitudinally identifying symptom cluster compositions, trajectories, and high-risk subgroups in a Chinese PA cohort, ultimately contributing to improved symptom control and quality of life.

3. Methodology

3.1. Study design

This study adopted a prospective longitudinal design. A multi-time-point questionnaire survey was conducted at four time points: the day of hospital admission (T1), one week after surgery (T2), one month after surgery (T3), and three months after surgery (T4). The aim was to understand the number, severity, and composition of symptom clusters at different time points, identify their longitudinal trajectory, classify symptom cluster subgroups, and analyze differences in general demographic and clinical characteristics across subgroups.

3.2. Participant selection

Participants were selected using convenience sampling from the Affiliated Hospital of Nantong University. All participants were undergoing endoscopic transsphenoidal resection for pituitary adenomas. The inclusion criteria were as follows: patients diagnosed with pituitary adenoma by preoperative MRI; age 18 years or older; clear consciousness and the ability to cooperate in completing questionnaires; good communication skills; and voluntary participation with signed informed consent. The exclusion criteria included patients with severe comorbid diseases or dysfunction of the heart, lungs, or kidneys (such as serious infections, respiratory diseases, cardiovascular conditions, renal diseases, or a history of other malignant tumors), as well as those who had experienced major personal or family events in the past two months, such as divorce, bereavement, unemployment, or financial hardship that could influence their emotional state. Patients diagnosed with recurrent or malignant pituitary adenomas were also excluded. In addition, elimination criteria included those who developed severe postoperative cognitive impairment that rendered them unable to cooperate, those who failed to complete the questionnaires, or those who voluntarily withdrew during the study.

3.3. Data collection procedure

Five researchers received unified training and independently collected data at four time points: T1 (hospital admission), T2 (one-week post-surgery), T3 (one-month post-surgery), and T4 (three months post-surgery). For the initial data collection at admission, after obtaining informed consent via phone or in person, researchers informed participants that there would be four rounds of questionnaires and maintained contact through personal information and WeChat groups (e.g., “Pituitary

Tumor Support Group”) for convenience.

Researchers were postgraduate nursing students trained in scientific research methods. They were familiar with the ward environment and able to communicate effectively with patients. Before data collection, they were required to familiarize themselves with the questionnaires and undergo standardized training to ensure accurate data collection. During the investigation, researchers introduced themselves, explained the purpose of the study, and confirmed patient consent and cooperation. If participants could fill in the questionnaire independently, the researcher only provided instructions using a standardized script. If the participant could not read, the researcher read each item aloud and recorded responses verbatim.

All questionnaires were collected immediately and checked item-by-item for completeness and accuracy. If items were missing or incorrectly filled, the researcher verified them with the participant on the spot. For hospitalized patients, data collection was conducted face-to-face in the ward. For patients at home, data was collected via telephone or during outpatient follow-up visits. Young participants were also given the option of completing the survey online via Wen Juan Xing. All other procedures followed the same standards as the initial collection.

3.4. Data collection instruments

This study employed a structured, multi-component survey approach to comprehensively assess symptoms, fatigue, emotional distress, sleep quality, and quality of life among patients with pituitary adenomas. Demographic and disease-related information such as sex, age, height, weight, body mass index (BMI), marital status, education level, occupation, residence, income, and disease duration were collected using a custom-designed case report form.

Symptom severity and interference were evaluated using the Chinese version of the MD Anderson Symptom Inventory–Brain Tumor module (MDASI-BT), which comprises 28 items assessing both core and tumor-specific symptoms as well as their interference with daily functioning [17]. Fatigue levels were measured using the Multidimensional Fatigue Inventory (MFI-20), a validated 20-item instrument covering five domains: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue [27]. Emotional distress was assessed using the Hospital Anxiety and Depression Scale (HADS), which includes two subscales for anxiety and depression, each containing seven items scored on a four-point scale [28]. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), which evaluates sleep across seven domains, with a global score above five indicating poor sleep [29]. Quality of life was measured using the 36-Item Short Form Survey (SF-36), which includes eight dimensions such as physical functioning, bodily pain, vitality, and mental health [30]. This instrument provides both a physical and a mental component summary score.

All scales used in this study have been validated in Chinese populations, including those with brain and endocrine tumors, and demonstrated good internal consistency and construct validity (Cronbach’s $\alpha > 0.80$) in prior research. These tools allowed for the repeated assessment of patient-reported outcomes across the four study time points (T1–T4), offering robust longitudinal insight into symptom progression

and recovery trajectories.

3.5. Data analysis

All data were entered and analyzed using SPSS version 16.0. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables such as age, fatigue scores, sleep quality, anxiety and depression levels, and quality of life indicators were reported as means and standard deviations. Categorical variables including sex, marital status, education level, and employment status were reported as frequencies and percentages.

Symptom cluster patterns were identified manually based on initial and accompanying symptoms reported by participants at admission. These symptoms were grouped into three clinical categories: neurological, endocrine, and fatigue–emotional–sleep (FES) disturbance clusters. This classification was based on common co-occurrence observed in clinical records rather than statistical modeling, and was used descriptively to examine differences in symptom trends across time.

Longitudinal changes in fatigue (MFI-20), emotional distress (HADS), sleep quality (PSQI), and quality of life (SF-36) across the four timepoints (T1 to T4) were analyzed using repeated measures ANOVA. Significance was set at $p < 0.05$ for all statistical tests.

4. Results and discussion

4.1. Demographic and clinical characteristics

A total of 104 patients diagnosed with pituitary adenoma were included in this study. The mean age was 58.0 ± 12.4 years. Among the participants, 48.1% were female. Most patients were married (98.1%), and only 5.8% had attained a college-level education or higher. A total of 63.5% of the patients were employed at the time of data collection. The mean body mass index (BMI) was 23.5 ± 3.4 kg/m², calculated from recorded height and weight data.

4.2. Symptom burden over time (MDASI-BT)

The MDASI-BT symptom severity scores exhibited a dynamic pattern across the perioperative trajectory. Symptom burden initially increased from T1 (4.71 ± 0.95) to a peak at T2 (6.13 ± 0.97), which corresponds to the first postoperative week. A subsequent decline was observed at T3 (3.63 ± 0.99), with further improvement noted at T4 (2.97 ± 1.09). Repeated measures ANOVA confirmed a significant main effect of time on symptom severity, $F(3, 309) = 198.44$, $p < 0.001$. Trend analysis demonstrated significant linear, quadratic, and cubic components (all $p < 0.001$), indicating a non-linear trajectory characterized by early postoperative exacerbation followed by progressive recovery.

This trajectory reflects the physiological and psychological stress of surgery, with early postoperative symptom intensification likely related to acute inflammatory response, pain, and disruption in neuroendocrine regulation following transsphenoidal resection. Previous studies have reported similar peaks in symptom burden shortly after surgery, particularly related to fatigue, pain, and cognitive complaints in brain

tumor populations, including pituitary tumor patients [13]. The subsequent decline in symptom severity by T3 and T4 aligns with expected post-surgical recovery, hormonal stabilization, and adaptation, although the persistent symptom presence at T4 suggests ongoing subacute rehabilitation needs [14]. **Figure 1** illustrates this fluctuating trajectory, highlighting the critical need for close symptom monitoring in the first postoperative month.

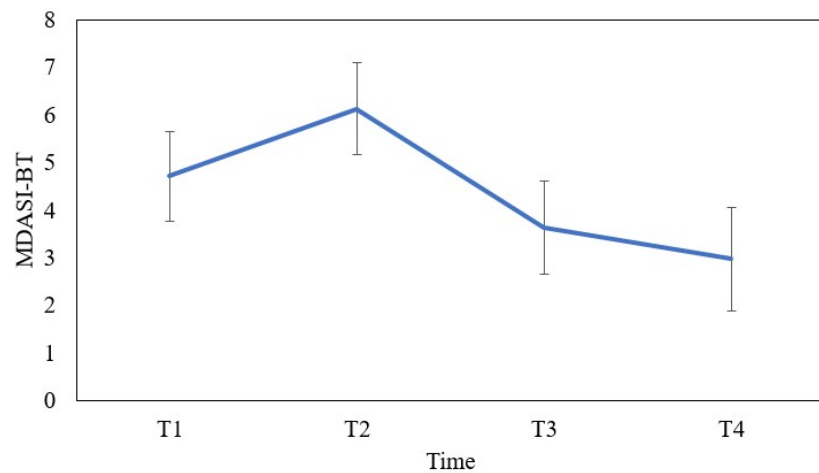


Figure 1. Mean MDASI-BT scores over time among pituitary tumor patients.

4.3. Fatigue trends (MFI-20)

Fatigue severity, measured by the MFI-20, varied significantly over time. The mean score increased from T1 (55.60 ± 6.29) to a peak at T2 (65.19 ± 6.72), reflecting heightened fatigue in the immediate postoperative period. Subsequently, fatigue scores decreased at T3 (45.38 ± 5.44) and reached their lowest at T4 (39.58 ± 6.33). Repeated measures ANOVA demonstrated a significant main effect of time, $F(3, 309) = 350.23$, $p < 0.001$, and trend analysis confirmed significant linear, quadratic, and cubic components (all $p < 0.001$), indicating a non-linear fatigue trajectory with postoperative aggravation and gradual resolution.

This postoperative fatigue spike is consistent with previous findings indicating that surgical stress, disrupted circadian rhythm, and transient hormonal dysregulation can lead to pronounced fatigue in the early recovery phase. In a large cross-sectional study in China, Zhang et al. [31], founds that fatigue was highly prevalent among patients with primary pituitary adenomas, and strongly influenced by psychological distress, sleep quality, and employment status. Similarly, Ghadirzadeh et al. [32] showed that macroadenoma patients had significantly higher fatigue scores compared to those with microadenomas, and that fatigue was positively correlated with prolactin levels and tumor size, while inversely associated with physical activity levels.

These results reinforce the importance of structured postoperative rehabilitation programs, incorporating sleep regulation, mental health support, and gradual physical activity. **Figure 2** illustrates this fatigue trajectory, highlighting the need for targeted interventions especially in the subacute recovery phase.

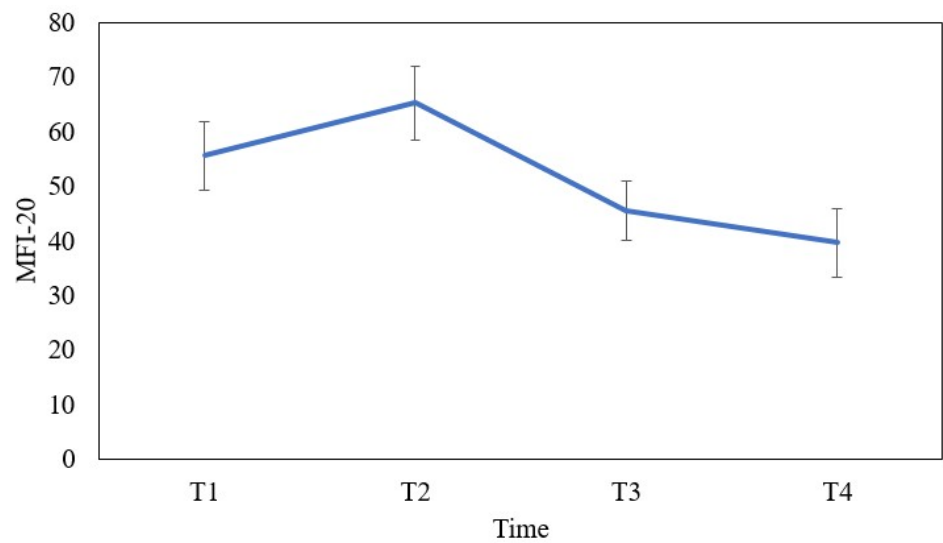


Figure 2. Mean MFI-20 scores over time among pituitary tumor patients.

4.4. Anxiety and depression (HADS-A and HADS-D)

Anxiety levels, measured by HADS-A, showed a gradual decline over time. Scores decreased from T1 (7.72 ± 2.22) to T2 (7.61 ± 2.08), then more notably at T3 (5.67 ± 1.98) and T4 (5.38 ± 1.95). Repeated measures ANOVA confirmed a significant time effect, $F(3, 309) = 94.44$, $p < 0.001$, with significant linear, quadratic, and cubic trends (all $p < 0.001$). In contrast, depression levels (HADS-D) followed a delayed peak trajectory, increasing from T1 (6.91 ± 2.00) to T2 (7.66 ± 1.93), peaking at T3 (9.63 ± 2.12), and then declining by T4 (7.41 ± 2.17). The effect of time on depression was also significant, $F(3, 309) = 35.73$, $p < 0.001$, with all polynomial trends significant.

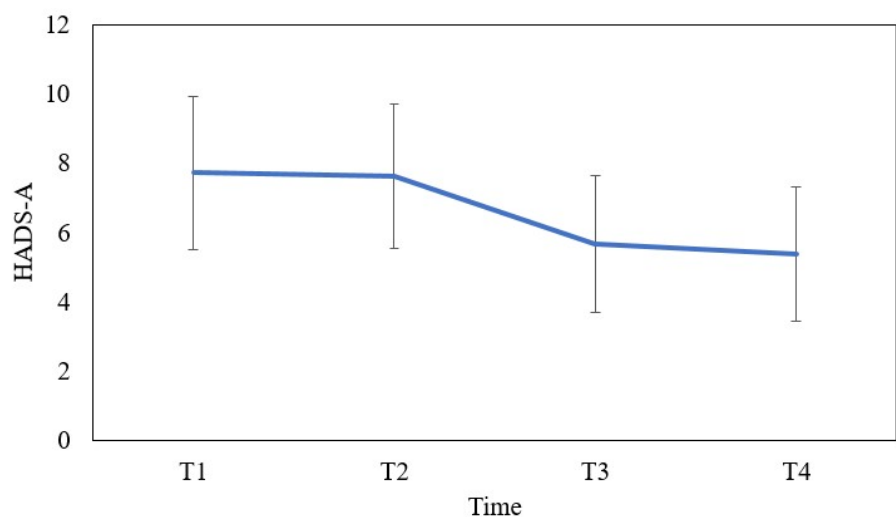


Figure 3. Mean HADS-A scores over time among pituitary tumor patients.

These distinct trajectories suggest that anxiety is highest around diagnosis and preoperative hospitalization, possibly due to fear of surgery and uncertainty about prognosis, and tend to alleviate as patients transition into recovery and gain reassurance from surgical outcomes [33,34]. Depression, however, tends to escalate postoperatively, especially around one month (T3), likely reflecting delayed

psychosocial stressors such as prolonged fatigue, hormonal imbalances, or unmet recovery expectations [35]. This T3 peak may also coincide with patients' return to daily life, during which physical limitations and reduced quality of life become more apparent [13]. Although both anxiety and depression declined by T4, the sustained levels indicate the need for continued emotional support beyond the immediate postoperative period. **Figures 3 and 4** demonstrate these differing temporal dynamics.

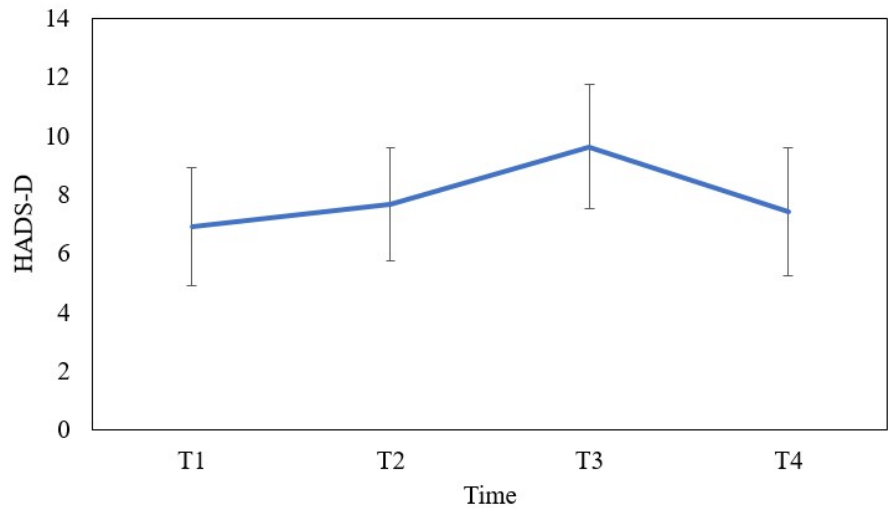


Figure 4. Mean HADS-D scores over time among pituitary tumor patients.

4.5. Sleep quality (PSQI)

Pittsburgh Sleep Quality Index (PSQI) scores revealed fluctuating sleep disturbances over the four timepoints. Sleep quality was moderately poor at baseline (T1: 8.48 ± 1.76), worsened significantly at T2 (9.59 ± 1.93), and subsequently improved at T3 (7.44 ± 2.00) and T4 (6.67 ± 2.08). Repeated measures ANOVA demonstrated a significant effect of time, $F(3, 309) = 136.39, p < 0.001$, with linear, quadratic, and cubic components all significant ($p < 0.001$). As shown in **Figure 5**, sleep quality deteriorated markedly in the early postoperative period and gradually recovered thereafter.

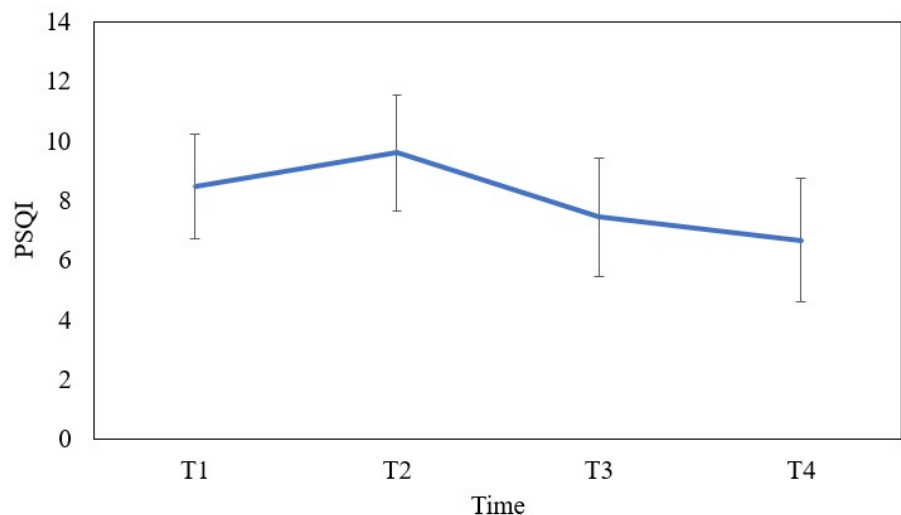


Figure 5. Mean PSQI scores over time among pituitary tumor patients.

4.6. Quality of life (SF-36)

Health-related quality of life, measured by the SF-36 total score, improved progressively across the study timeline. Baseline scores were moderate at T1 (49.95 ± 7.04), followed by an increase at T2 (55.24 ± 7.99), with continued improvements at T3 (59.51 ± 7.61) and T4 (63.59 ± 7.80). Repeated measures ANOVA revealed a significant main effect of time, $F(3, 309) = 58.79$, $p < 0.001$. Interestingly, only the cubic trend was statistically significant ($p < 0.001$), suggesting a non-linear trajectory, where initial improvement may have plateaued or accelerated unevenly during recovery.

This upward trend indicates that patients generally experienced steady recovery in physical and psychological functioning after pituitary surgery. Early improvement in quality of life may be attributed to symptom relief and psychological reassurance postoperatively, particularly after T2 when acute complications begin to subside. Subsequent gains likely reflect restored functional status, better fatigue and sleep control, and hormonal stabilization by T3 and T4 [36]. However, the non-linear pattern suggests individual variability in recovery pace, as some patients may continue to experience residual symptoms or psychosocial adjustment issues [23]. **Figure 6** visually demonstrates this trend, reinforcing the importance of ongoing multidimensional rehabilitation in the months following surgery to optimize recovery outcomes [37].

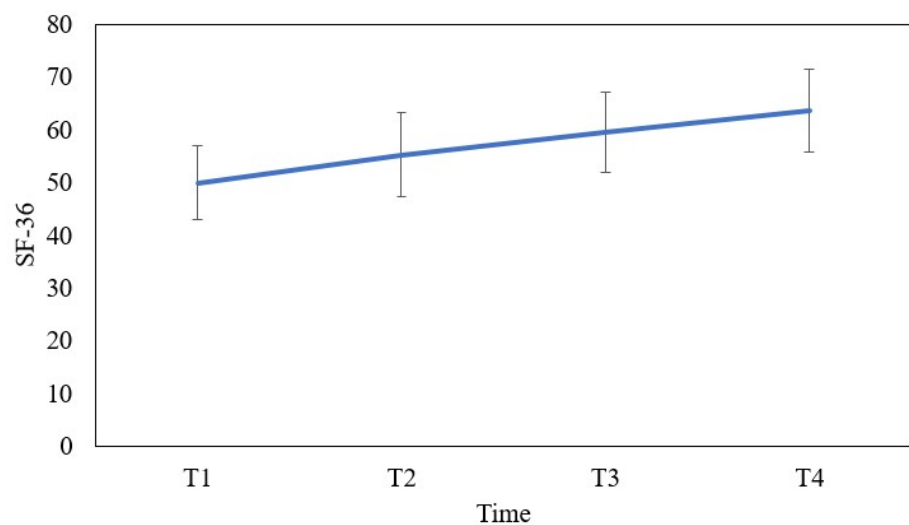


Figure 6. Mean SF-36 scores over time among pituitary tumor patients.

4.7. Symptom clusters and their relationship with fatigue, sleep, and quality of life

4.7.1. Cluster identification and prevalence

Symptom co-occurrence patterns among patients with pituitary adenoma were examined through a manual classification process based on clinically reported initial and accompanying symptoms. The research team reviewed symptom profiles and grouped them into three commonly observed clinical clusters: The Neurological Cluster, the Endocrine Cluster, and the Fatigue–Emotional–Sleep disturbance (FES) Cluster. This classification was guided by clinical experience and literature-informed

interpretation rather than statistical modeling. Patients could belong to one or more clusters depending on their reported symptoms.

The Neurological Cluster was the most prevalent, encompassing 75 patients (72.1%). Symptoms in this group included headache ($n = 33$), dizziness ($n = 16$), nausea or vomiting ($n = 3$), and visual disturbances such as blurred vision, diplopia, or visual field defects ($n = 43$). The Endocrine Cluster was identified in 21 patients (20.2%) and was characterized by hormonal or somatic features, including galactorrhea ($n = 5$), amenorrhea ($n = 2$), menstrual irregularities ($n = 2$), and extremity enlargement suggestive of excess growth hormone ($n = 9$). A smaller subset of 13 patients (12.5%) constituted the FES Cluster, which involved fatigue, disrupted sleep, reduced appetite, or heightened emotional reactivity.

Cluster overlap was minimal. Three patients (2.9%) presented with both neurological and endocrine symptoms, while two patients (1.9%) were categorized in both the neurological and FES clusters. Notably, no patients exhibited all three clusters simultaneously, and no overlap was observed between the endocrine and FES groups. These distributions are illustrated in **Figure 7**.

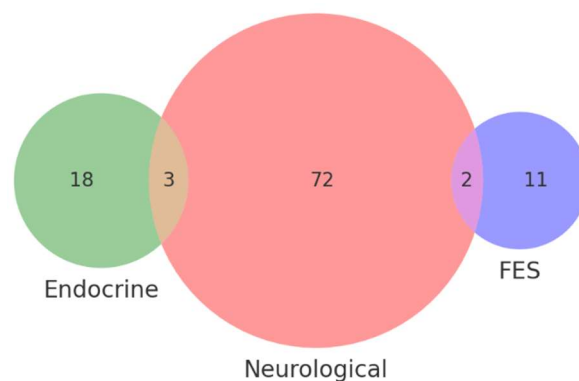


Figure 7. Overlap of symptom clusters in pituitary tumor patients.

4.7.2. Associations with fatigue, sleep quality, and quality of life

Table 1 presents the group means and standard deviations for MFI-20 (fatigue), PSQI (sleep quality), and SF-36 (physical and mental health domains) across four timepoints (T1–T4). Among the three clusters, patients in the FES cluster exhibited the most severe symptom burden. Their fatigue levels peaked at T2, with a mean MFI-20 score of 67.9, and they reported the poorest sleep quality at the same timepoint (PSQI = 11.29). Across all timepoints, this group maintained the lowest SF-36 scores, reflecting a persistently diminished quality of life.

In contrast, patients in the neurological cluster experienced a similar spike in symptom severity at T2 (MFI-20 = 65.6; PSQI = 10.96), but their scores improved markedly by T4. Fatigue levels decreased to 39.8, and sleep quality also improved substantially (PSQI = 5.81), accompanied by parallel gains in SF-36 scores.

Patients classified in the endocrine cluster demonstrated a more stable recovery pattern. Although they reported moderate fatigue and impaired sleep early on, their outcomes improved steadily over time. By T4, this group had the most favorable sleep scores among all clusters (PSQI = 5.48) and showed significant gains in quality of life.

These findings align with prior evidence that fatigue and emotional symptoms

often co-occur as symptom clusters with a stronger association to quality-of-life outcomes than isolated symptoms [22,24]. The rapid improvement observed in neurological cluster patients may reflect surgical decompression of optic pathways or neurovascular structures, as noted in postoperative studies of pituitary surgery [38]. Endocrine-related symptoms often persist or fluctuate post-surgically without adjuvant hormone therapy, which may explain the delayed quality of life recovery [35].

The distinct trajectories and minimal overlap among clusters reinforce the utility of a cluster-based framework. This approach enables personalized management strategies based on cluster characteristics. Psychological interventions may be prioritized for patients in the FES cluster, while hormone and metabolic therapies are more appropriate for those with endocrine-related symptoms. For individuals in the neurological cluster, targeted neurosurgical rehabilitation may offer the greatest benefit [23,39].

Table 1. Fatigue, sleep quality, and quality of life scores (Mean $\pm$ SD) by symptom cluster across timepoints.

	FES cluster	Neurological cluster	Endocrine cluster
MFI-20			
T1	57.29 $\pm$ 6.7	55.15 $\pm$ 5.84	56.14 $\pm$ 7.33
T2	67.86 $\pm$ 6.01	65.6 $\pm$ 6.74	61 $\pm$ 6.07
T3	46.21 $\pm$ 6.18	45.39 $\pm$ 5.39	44.33 $\pm$ 5.37
T4	39.86 $\pm$ 6.32	39.81 $\pm$ 6.	38 $\pm$ 6.65
PSQI			
T1	8.29 $\pm$ 1.68	8.49 $\pm$ 1.77	8.52 $\pm$ 1.81
T2	11.29 $\pm$ 1.98	10.96 $\pm$ 2.29	10.86 $\pm$ 1.88
T3	7.79 $\pm$ 1.53	6.91 $\pm$ 2.17	6.81 $\pm$ 1.69
T4	5.29 $\pm$ 2.05	5.81 $\pm$ 2.07	5.48 $\pm$ 2.11
SF-36			
T1	50.13 $\pm$ 5.64	49.42 $\pm$ 6.43	51.79 $\pm$ 9.14
T2	54.26 $\pm$ 5.18	55.08 $\pm$ 8.21	55.44 $\pm$ 8.9
T3	58.28 $\pm$ 5.67	59.18 $\pm$ 8.15	61.06 $\pm$ 7.3
T4	62.21 $\pm$ 6.81	63.67 $\pm$ 7.96	64.22 $\pm$ 7.3

4.8. Limitations

Several limitations should be acknowledged in this study. First, the study did not include objective biochemical or imaging indicators, such as hormone levels or radiological assessments, which limits the ability to directly link symptom clusters to physiological recovery. Second, all symptom assessments were based on patient self-reports, which may have introduced recall bias or subjective interpretation, especially among those experiencing emotional distress or cognitive fatigue. Third, participants were selected through from one hospital within a single province, which may affect the generalizability of the findings to other regions or populations. Fourth, although the longitudinal design provided insight into symptom changes over time, the three-month follow-up period may not fully capture long-term recovery patterns or delayed

symptoms. Finally, some potential influencing factors, including the use of hormone replacement therapy or informal support systems, were not controlled in the analysis and may have affected patient-reported outcomes.

5. Conclusion

This longitudinal study provides strong evidence that symptom clusters in pituitary adenoma patients exhibit distinct trajectories and are closely associated with fatigue severity, sleep quality, and health-related quality of life. The identification of three main symptom clusters, including neurological, endocrine, and fatigue emotional sleep disturbance (FES), reflects the complexity of postoperative recovery. Among these clusters, the FES group showed the most sustained negative impact on patient outcomes, indicating the need for targeted interventions that address psychological burden and persistent fatigue.

Although neurological symptoms tended to improve more rapidly after surgical decompression, endocrine-related symptoms followed a steadier course, and emotional and fatigue-related symptoms often persisted beyond three months after surgery. These findings suggest that routine follow-up should be supplemented by cluster-specific symptom management. The low overlap between symptom clusters also highlights the heterogeneity in patient experiences and supports the use of individualized care strategies based on cluster assignment.

To the best of the authors' knowledge, this is one of the first longitudinal studies in a Chinese population to examine the evolution of symptom clusters in pituitary tumor patients across multiple time points using validated instruments. By offering a dynamic and multidimensional understanding of cluster patterns and their clinical implications, this study provides an important foundation for designing personalized symptom management protocols. Future research should consider longer follow-up periods and interventional trials that specifically target high-burden symptom clusters, especially those involving fatigue, emotional distress, and sleep disturbance.

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