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ORIGINAL RESEARCH

Differences in Polysomnographic and Craniofacial Characteristics of Catathrenia Phenotypes: A Cluster Analysis

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Purpose: Catathrenia is a rare sleeping disorder characterized by repetitive nocturnal groaning during prolonged expirations. Patients with catathrenia had heterogeneous polysomnographic, comorbidity, craniofacial characteristics, and responses to treatment. Identifying phenotypes of catathrenia might benefit the exploration of etiology and personalized therapy.

Patients and Methods: Sixty-six patients diagnosed with catathrenia by full-night audio/video polysomnography seeking treatment with mandibular advancement devices (MAD) or continuous positive airway pressure (CPAP) were included in the cohort. Polysomnographic characteristics including sleep architecture, respiratory, groaning, and arousal events were analyzed. Three-dimensional (3D) and 2D craniofacial hard tissue and upper airway structures were evaluated with cone-beam computed tomography and lateral cephalometry. Phenotypes of catathrenia were identified by K-mean cluster analysis, and inter-group comparisons were assessed.

Results: Two distinct clusters of catathrenia were identified: cluster 1 (n=17) was characterized to have more males (71%), a longer average duration of groaning events (18.5±4.8 and 12.8±5.7s, p=0.005), and broader upper airway (volume 41,386±10,543 and 26,661 ±6700 mm^3, p<0.001); cluster 2 (n=49) was characterized to have more females (73%), higher respiratory disturbance index (RDI) (median 1.0 [0.3, 2.0] and 5.2 [1.2, 13.3]/h, p=0.009), more respiratory effort-related arousals (RERA)(1 [1, 109] and 32 [13, 57)], p=0.005), smaller upper airway (cross-sectional area of velopharynx 512±87 and 339±84 mm^2, p<0.001) and better response to treatment (41.2% and 82.6%, p=0.004).

Conclusion: Two distinct phenotypes were identified in patients with catathrenia, primary catathrenia, and catathrenia associated with upper airway obstruction, suggesting respiratory events and upper airway structures might be related to the etiology of catathrenia, with implications for its treatment.

Keywords: subtype, groaning, upper airway, treatment, OSA, sleep-disordered breathing

Introduction

Catathrenia is a rare sleeping disorder, characterized by recurrent episodes of prolonged expiration with the production of groaning sounds during sleep.[1] Patients with catathrenia often complained about social embarrassment, and some patients also suffer from unrefreshing sleep and daytime fatigue.[2] Since the disease was first reported in 1983,[3] there have been controversial findings of its polysomnographic characteristics, classification, combination with obstructive sleep apnea (OSA), craniofacial characteristics, and treatment efficacy.

Early investigations have documented that groaning events tend to occur predominantly in rapid eye movement (REM) sleep,[4–7] whereas cases with the predominance in non-REM (NREM) sleep[8–10] and equal distribution across sleep

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stages[11,12] were also reported. A close association between groaning and arousal events has been observed in several studies,[13–16] however, a similar association was not replicated in other studies.[17] Besides, catathrenia patients combined with OSA seemed to have a better response to the treatment of continuous positive airway pressure (CPAP) or mandibular advancement devices (MAD).[8,11,18–20] With the above heterogeneous findings, there has been an ongoing debate about the classification of catathrenia, whether it is a parasomnia or sleep-related breathing disorder.[1,21–23]

Limited consistency often exists in sleeping disorders, and different subtypes exist.[24] Recently, unsupervised cluster analysis has been used to identify subtypes of various sleeping disorders. Gool et al utilized a data-driven clustering algorithm with symptoms, demographics, objective and subjective sleep measures, and laboratory biomarkers and identified 7 clusters of phenotypes of central disorders of hypersomnolence.[25] The heterogeneity of OSA, the most common sleep-related breathing disorder, has also been explored by cluster analysis with combinations of symptoms,[26–29] polysomnography,[30–33] comorbidities,[26,27,31,34–36] craniofacial pattern,[37–39] and treatment.[35,40–43] Similarly, knowledge of the heterogeneity might benefit the exploration of etiology and personalized treatment of catathrenia. Therefore, this study aims to examine the heterogeneity of catathrenia with regard to patients' demographics, polysomnographic parameters, craniofacial anatomical characteristics, and treatment response with cluster analysis. We hypothesized that there are different phenotypes of catathrenia.

Materials and Methods

Study Participants

This prospective cohort study was conducted at the Department of Orthodontics, Peking University Hospital of Stomatology. From August 2004 to April 2023, a total of 66 patients seeking treatment for catathrenia were included with informed consent. All the patients were diagnosed with catathrenia by full-night audio/video polysomnography at the Sleep Division of Peking University People's Hospital and Peking University International Hospital. This study was approved by the Institutional Review Board of Peking University School of Stomatology (No. PKUSSIRB 201631128). This study was registered at the Chinese Clinical Trial Registry (No. ChiCTR-COC-17013239). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Polysomnography

Full-night audio/video polysomnography was recorded using Compumedics E-series (Compumedics, Abbotsford, Victoria, Australia). The details of the polysomnography recording were described elsewhere.[17] All the records were evaluated manually by two certified technicians and verified by a researcher. The sleep technicians and researcher who scored the PSG did not participate in data analysis. Standards from the 2012 American Academy of Sleep Medicine (AASM) manual were used to score sleep stages, arousals, and respiratory events.[44] Apneas were defined as the oronasal thermal sensor drops by ≥90% of baseline for ≥ 10s. Hypopneas were defined as a ≥ 30% reduction of nasal pressure excursions of baseline amplitude for ≥ 10s, associated with ≥ 3% oxygen desaturation or arousal. Respiratory effort-related arousals (RERA) were defined as an increasing respiratory effort or flattening of the nasal pressure waveform followed by arousal. Since some patients were combined with OSA, the apnea-hypopnea index (AHI) was calculated as apnea and hypopnea events per hour of sleep. The respiratory disturbance index (RDI) was as equal to the AHI + RERA index. Groaning events were defined as deep inspiration followed by a prolonged expiration during which a monotonous vocalization was produced, or an exhalation like a sigh produced at the end of the expiration, without oxygen desaturation. Groaning events were scored separately to calculate the groaning index (GI, groaning events per hour of sleep). Arousal events were defined if there is an abrupt shift of electroencephalogram (EEG) frequency that lasts ≥ 3 s, and a concurrent increase in submental electromyography (EMG) in the REM stage. Groaning events-related arousals were defined in accordance with previous studies, with EEG arousal occurring before the onset of groaning events.[45,46]

Craniofacial and Upper Airway Structures Measurement

Informed choices were made by the patients to undergo cone-beam computed tomography (CBCT) to analyze craniofacial and upper airway structures. All images were obtained on a CBCT scanner (VATECH, DCTPRO-050Z, Vatech Co, Korea), with a scanning protocol of 120 kV, 5 mA, 13×17cm field of view, 0.25mm voxels, and a scanning time of 40s. All patients were asked to maintain centric occlusion, breathe evenly, and refrain from swallowing.

All the measurements of the craniofacial, upper airway, and surrounding soft tissue structures were assessed using Dolphin Imaging (Version 11.8 Premium; Dolphin Imaging, Chatsworth, CA) by the same examiner. The digital points of skeletal structures, the measurement of cross-sectional area, and the upper airway diameter are shown in Figures 1 and 2.

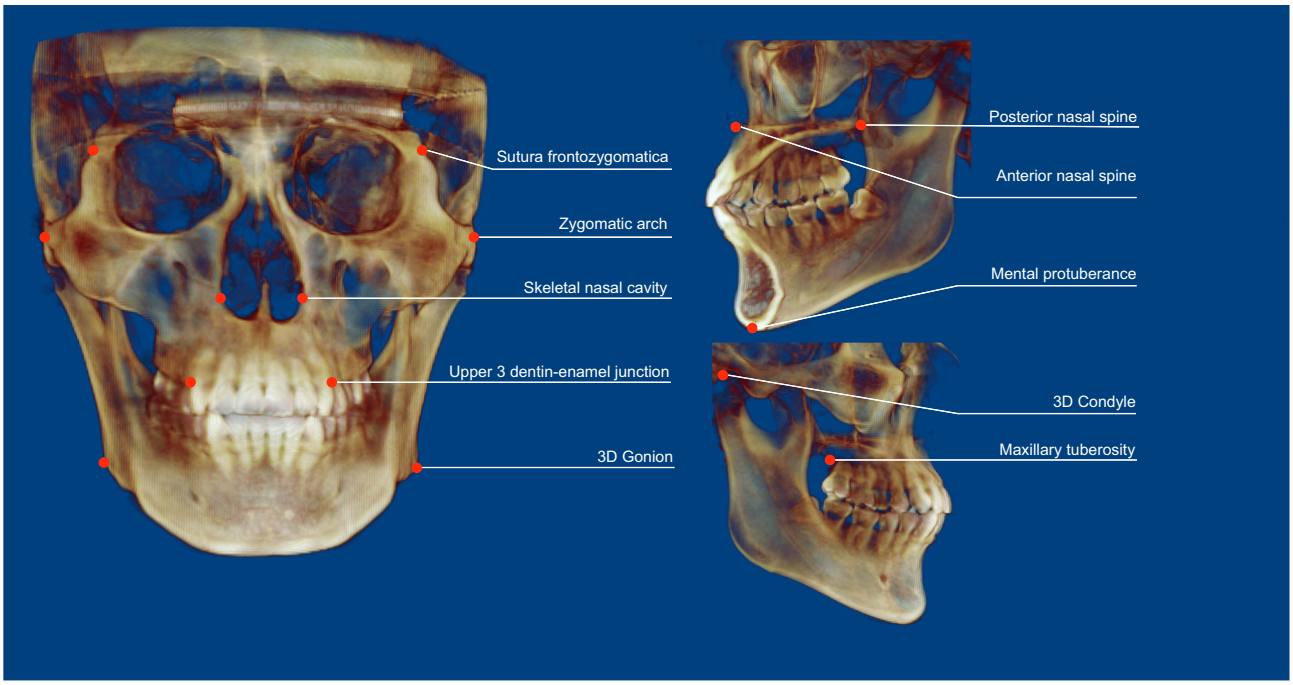

Figure 1 Measurements of craniofacial skeletal parameters on cone-beam computed tomography (CBCT). Maxillary length: distance between anterior and posterior nasal spine; anterior maxillary width: distance between left and right upper 3 dentin-enamel junction; posterior maxillary width: distance between the left and right maxillary tuberosity; mandibular width: distance between left and right 3D Gonion; mandibular total length: distance between the 3D condyle and mental protuberance; mandibular body length: distance between the angle of the mandible and mental protuberance; mandibular ramus height: distance between the 3D Gonion and condyle.

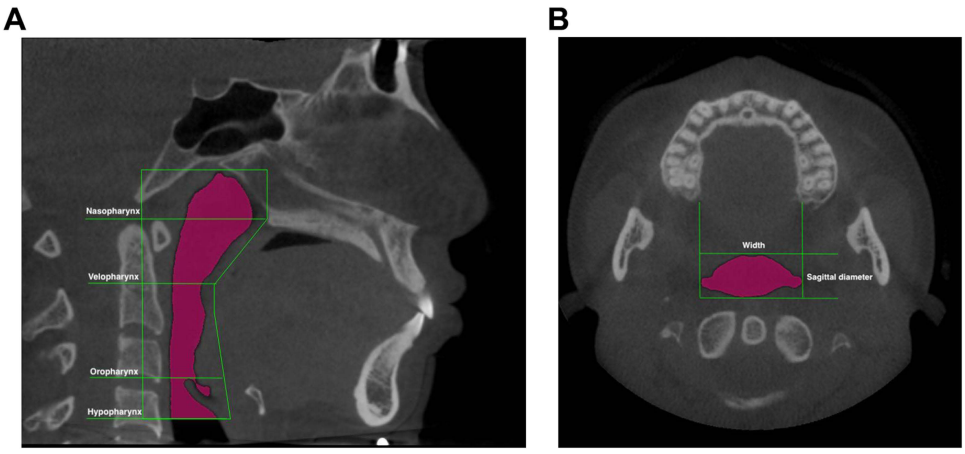

Figure 2 Measurement of upper airway structures. The upper airway is marked in pink. (**A**) Segmentation of upper airway and measurement of height; (**B**) measurement of cross-sectional area, width, and sagittal diameter.

Lateral cephalograms, radiographs commonly utilized in orthodontic practice, could be built from CBCT. The parameters of maxillofacial structures, upper and lower teeth, and upper airway were illustrated in Figure S1.

Six patients (9%) were randomly selected for the replicated measurement, and the intra-reliability was tested with an intra-class correlation coefficient of 0.87 to 1.00.

Treatment Response

Informed decisions were made by 63 patients to either receive manually-titrated CPAP (n=7) at the Sleep Division of Peking University People's Hospital or a custom-fit MAD (n=56) at the Department of Orthodontics, Peking University Hospital of Stomatology. Three patients have made the decision to forgo treatment. The design of MAD and the detailed efficacy in the treatment of catathrenia were detailed elsewhere.[20] The objective efficacy of treatment was evaluated with full-night audio/video PSG. The decrease of the groaning index (GI) with treatment was considered effective, and patients were classified into effective and ineffective groups.

Statistical Analysis

Normal distribution was analyzed using the Shapiro–Wilks test. Data with normal and skewed distribution were summarized as mean ± standard deviation (SD) and median (interquartile range, IQR), respectively, for continuous variables, and frequencies (percentages) for categorical variables. The K-means cluster analysis was performed using R 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). Firstly, correlation analyses were conducted to identify parameters significantly related to GI. Secondly, the average silhouette width (ASW) analysis was used with significantly correlated parameters to determine the optimal number of clusters with the larger ASW, the better the split of clustering.[47] Thirdly, the independent *t*-test and Mann–Whitney test were used to perform inter-group comparisons. Pearson Chi-square test was used for categorical variables comparisons. A *p*-value less than 0.05 was considered statistically significant.

Results

Patients' Characteristics

There were 25 males and 41 females included in the study, with an average age of 30.7±10.5 y. The average body mass index (BMI) was 21.9±3.1 kg/m^2. The median apnea-hypopnea index (AHI) was 1.5 (IQR 0.4, 4.4) events/h, with fourteen (21.2%) patients diagnosed with OSA. The median RDI was 3.2 (IQR 1.0,12.8) events/h.

Clustering of Patients

A total of 157 parameters, including patients' demographic characteristics (sex, age, BMI), polysomnographic characteristics (sleep architecture, respiratory events, oxygen saturation, arousal and groaning events), craniofacial and upper airway structures (volume, cross-sectional area, diameter, soft palate, and tongue), were used to explore significant correlation with GI as an initial screening. Thirteen parameters, including arousal index (ArI), number of groaning events, average duration of groaning events, etc, were included in the cluster analysis.

Two homogeneous clusters were identified by ASW (Figure S2) and K-means cluster analysis (Figure 3). Cluster 1 consisted of 17 patients (25.8%), with a higher proportion (70.6%) of males (12 males, 5 females). Cluster 2 consisted of 49 patients (74.2%), with a higher proportion (73.4%) of females (13 males, 36 females). The distribution of patients' sex was significantly different between clusters (p=0.003). There were no significant differences in age (34.3±12.6 and 29.5±9.6 y, p=0.106) and BMI (22.3±3.4 and 21.8±3.0 kg/m^2, p=0.291) between clusters. Patients' Epworth sleepiness scale was not statistically different between clusters either (8.1±4.0 and 8.2±3.1, p=0.962). Patients in cluster 1 mainly complained about headaches and difficulty falling asleep, whereas patients in cluster 2 mostly complained about restless sleep, dry mouth, and morning fatigue.

Subgroup Comparisons of Polysomnographic Characteristics

All the included patients had a median GI of 6.6 (IQR 2.4, 15.7) events/h and a median AHI of 1.5 (IQR 0.4, 4.4) events/h. The polysomnographic characteristics between clusters are shown in Table 1. There were no significant differences in sleep architecture between clusters in all patients. The AHI was not statistically different between clusters. However, the

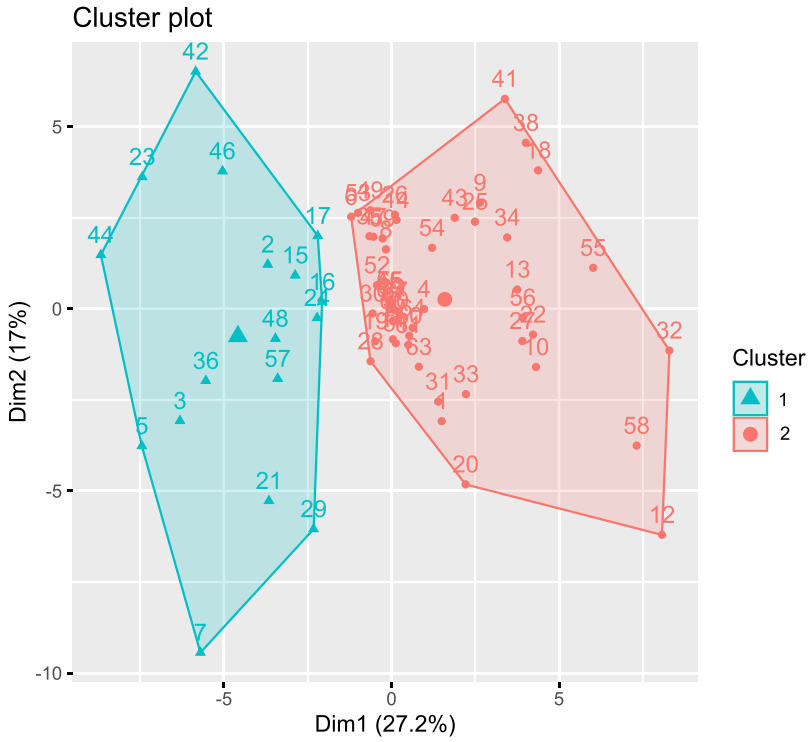

Figure 3 Scattergram for two clusters segregated by cluster analysis.

RDI of cluster 2 was significantly higher than that of cluster 1 (1.0 [0.3, 2.0] and 5.2 [1.2, 13.3]/h, p=0.009), with more RERA in cluster 2 (1[1, 109] and 32[13, 57], p=0.005) (Figure 4).

The inter-cluster differences in groaning events are shown in Table 2. The number of groaning events and groaning index was slightly higher in cluster 1, without statistical difference. However, the shortest and average durations of groaning events were significantly higher in cluster 1 (average duration 18.5±4.8 and 12.8±5.7s, p=0.005) (Figure 5). The

Table 1 The Polysomnographic Characteristics Between Subgroups

	Total (n=66)	**Cluster 1 (n=17)**	**Cluster 2 (n=49)**	***p***
Demographic characteristics				
Sex (M/F)	25/41	12/5	13/36	0.003**
Age (y)	30.7±10.5	34.3±12.6	29.5±9.6	0.106
BMI (kg/m^2)	21.9±3.1	22.3±3.4	21.8±3.0	0.291
ESS	8.2±3.4	8.1±4.0	8.2±3.1	0.962
Sleep architecture				
Total sleep time (min)	422.6±41.8	424.8±39.6	421.9±42.9	0.806
Sleep efficiency (%)	88.3±7.8	88.0±8.2	88.4±7.7	0.857
Sleep onset latency (min)	18.6±20.6	18.6(8.5,32)	9.5(4,18.8)	0.126
REM latency (min)	124.9±53.1	128.0±63.9	123.8±49.5	0.783
R(%)	17.8±5.8	16.9±9.3	18.2±4.1	0.579
N1(%)	12.7±7.0	13.5±6.3	12.4±7.3	0.593
N2(%)	51.7±10.3	54.0±9.5	50.9±9.5	0.285
N3(%)	17.8±9.9	15.7±10.7	18.5±9.6	0.308

(*Continued*)

Table 1 (Continued).

	Total (n=66)	Cluster 1 (n=17)	Cluster 2 (n=49)	*p*
Respiratory events				
Obstructive apnea (/h)	0.1 (0, 1.0))	0.1 (0, 1.0)	0.1 (0, 0.6)	0.858
Mixed apnea (/h)	0 (0, 0.1)	0 (0, 1.5)	0 (0, 1.0)	0.596
Central apnea (/h)	0 (0, 0.8)	0 (0, 0.4)	0 (0, 0.8)	0.155
Hypopnea (/h)	0.5 (0, 2.0)	0.1 (0, 0.7)	0.7 (0.1, 2.3)	0.160
AHI (/h)	1.6 (0.4, 4.6)	1.7 (0.3,2.1)	1.5 (0.3,4.6)	0.265
RDI (/h)	3.2 (1.0,12.8)	1.0 (0.3, 2.0)	5.2 (1.2, 13.3)	0.009**
Oxygen saturation				
Average (%)	96.6±1.3	96.6±1.1	96.5±1.3	0.952
Lowest (%)	89.8±5.5	89.6±5.6	89.9±5.4	0.831
Arousal events				
Arousal index (/h)	15.8±7.4	13.6±4.4	14.9±6.6	0.441
RERA	31 (5, 56)	1 (1, 109)	32 (13, 57)	0.005**
Groaning events related arousals	11 (5, 32)	8 (6, 50)	12 (5, 34)	0.436

Notes: Data were summarized as mean ± standard or median (interquartile range). **$p<0.01$.
Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; REM, rapid eye movement sleep; R, REM sleep; N, non-REM sleep; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; RERA, respiratory efforts-related arousal.

distribution of groaning events across sleep stages (REM-predominance) was similar between clusters. Patients in cluster 2 showed a better response to treatment of CPAP or MAD (41.1% and 82.6%, p=0.004).

Subgroup Comparisons of Craniofacial Characteristics

The characteristics of craniofacial and upper airway structures measured with CBCT are shown in Table 3. Inter-cluster analyses were performed according to patients' sex to reduce the significantly different sex distribution on craniofacial anatomical structures. Overall, the 3D skeletal measurements did not show significant inter-cluster differences, except that the posterior maxillary width was larger in cluster 1 (p=0.022). Distinct characteristics were observed in the upper airway structures of different clusters. The upper airway volume was significantly smaller in cluster 2, from the nasopharynx to the hypopharynx, with the inter-cluster trend remaining consistent in both sexes. The minimum and average cross-sectional area and diameter in all the segments of the upper airway tend to be smaller in cluster 2 as well. The inter-cluster difference was slightly different in women, who showed significant differences only in the velopharynx and oropharynx. The characteristics of maxillofacial, upper and lower teeth, and upper airway structures measured with lateral cephalograms are shown in Table S1. Maxillofacial structures were fairly similar between clusters, except female patients in cluster 2 had more proclined upper incisors than those in cluster 1 (99.5±7.7 and 106.9±5.0°, p=0.006). Patients in cluster 1 showed significantly larger upper airways (Figure 6), consistent with results measured on CBCT. Parameters of the soft palate, tongue, and hyoid bone did not differ between clusters.

Overall, the polysomnographic and craniofacial characteristics of two phenotypes of catathrenia identified in the study are shown in Figure 7.

Discussion

With regard to the heterogenous clinical manifestations and etiology assumptions of catathrenia, this study used a data-driven approach of cluster analysis to explore the phenotypes of catathrenia, combining polysomnographic and craniofacial and upper airway characteristics. This study identified two phenotypes in patients with catathrenia: cluster 1, primary catathrenia, consisting of mainly male patients with longer duration of groaning events, lower RDI, and broader upper airway; cluster 2, catathrenia associated with upper airway resistance, consisting of mostly female patients with shorter duration of groaning events, higher RDI, smaller upper airway, and better response to treatment with MAD or CPAP. The characteristics of hard tissue in the maxillofacial area were similar between clusters.

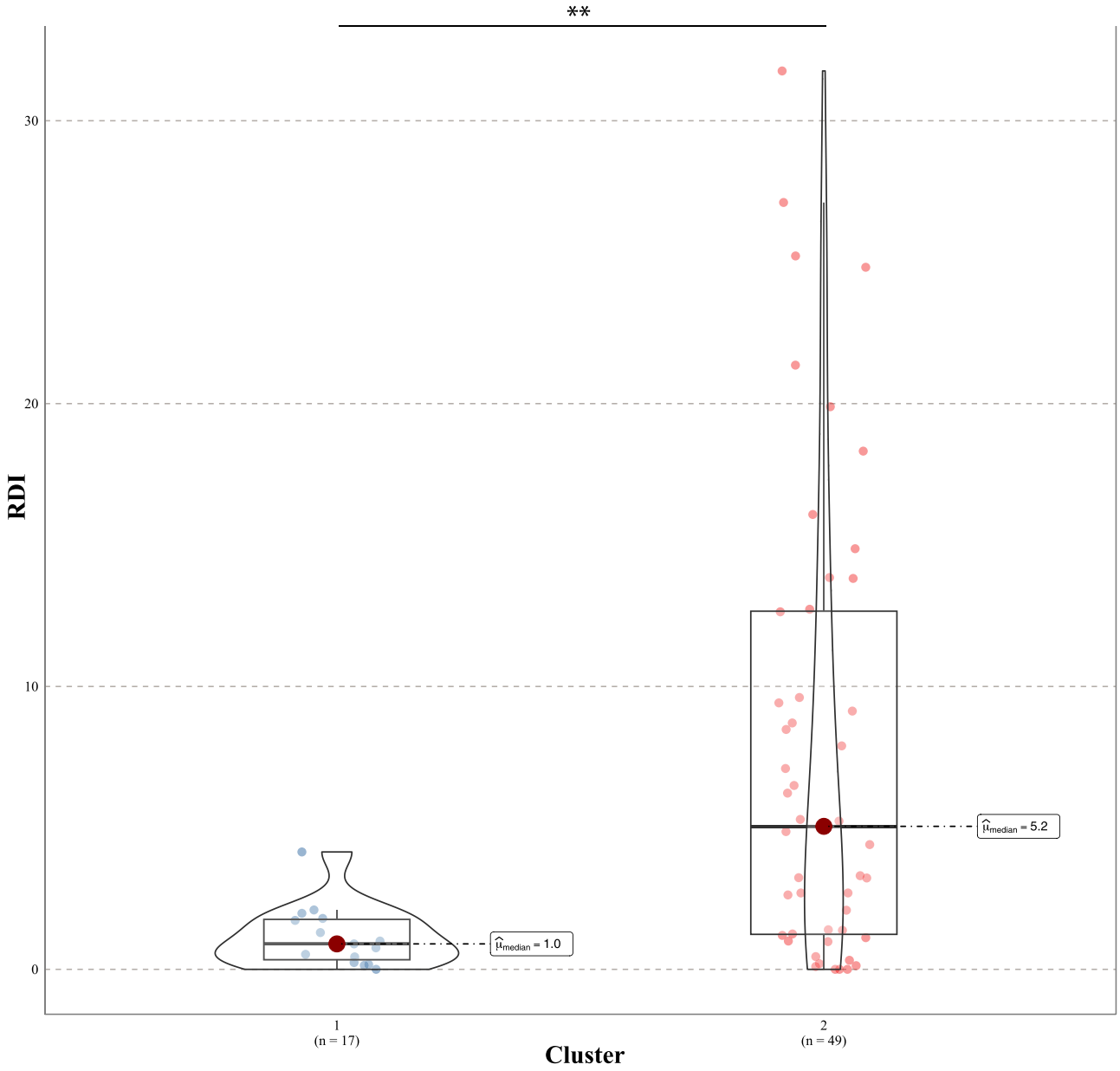

Figure 4 The difference in respiratory disturbance index (RDI) between clusters. **p<0.01.

Distinct craniofacial structures of patients with catathrenia have been discussed in previous studies. In this study, certain parameters of craniofacial structures were also found to vary between clusters of catathrenia. Hao et al compared the lateral cephalograms of catathrenia, OSA, and those without any sleep disorders. They observed that patients with catathrenia had broader upper airways and well-developed mandibles compared to the other two groups.[48] Yu et al confirmed these findings with more subjects with catathrenia, and used CBCT for measurement.[49] Furthermore, the study also observed patients with catathrenia had a steep cranial base. In the present study, the 3D and 2D measurements of hard tissue, including cranial base and maxillas, were consistently similar between clusters. Two distinct clusters can be identified based on the parameters of the upper airway, with cluster 2 having smaller upper airways despite the patients' sex.

In this study, the polysomnographic and craniofacial characteristics of patients in cluster 2 were similar to those in patients with sleep-disordered breathing (SDB) – higher RDI, more RERA, relatively narrower upper airway, and better response to treatment options of SDB. On the other hand, patients in cluster 1 had well-developed upper airway

Table 2 The Characteristics of Groaning Events Between Subgroups

	Total (n=66)	Cluster 1 (n=17)	Cluster 2 (n=49)	*p*
Number (total)	48 (18, 112)	24 (14, 70)	61 (18, 113)	0.155
Number (REM)	35 (4, 76)	19 (6,36)	39 (3,79)	0.110
Number (NREM)	13 (6, 41)	9 (1,33)	13 (6,45)	0.224
Shortest duration (s)	5.2±4.2	9.0±6.2	4.7±3.6	0.019*
Average duration (s)	13.9±6.2	18.5±4.8	12.8±5.7	0.005**
Longest duration (s)	33.9±15.5	34.2±12.4	31.6±15.1	0.620
Groaning index (/h)	7.3 (2.5, 16.1)	3.4 (1.9,9.9)	8.4 (3.0,16.7)	0.155
Groaning index (REM)	25.2 (4.1, 48.8)	9.7 (3.2,29.1)	27.4 (3.6,52.8)	0.104
Groaning index (NREM)	2.2 (1.1, 7.4)	1.7 (0.2,6.0)	2.2 (1.1,8.3)	0.199
REM-predominance	29/37	9/8	20/29	0.753
Duration <5s	2 (0, 12)	0 (0,0,3)	3 (0,20)	0.082
Duration 5 to 15s	26 (6, 60)	12 (1,35)	30 (6,63)	0.218
Duration 15 to 30s	9 (3, 20)	8 (2,22)	9 (3,21)	0.669
Duration 30 to 50s	2 (0, 5)	3 (0,8)	1 (0,4)	0.362
Treatment effectiveness (effective/ineffective)	45/18	7/10	38/8	0.004**

Notes: Data were summarized as mean ± standard or median (interquartile range). *$p<0.05$; **$p<0.01$.
Abbreviations: REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep.

structures. Characteristics of cluster 2 might correspond to questions raised by Guilleminault et al that catathrenia is an SDB-related phenomenon that responds appropriately to interventions for SDB,[9] who reported seven female catathrenia patients with small upper airways. Besides, cases of catathrenia reported by other investigators also resembled cluster 2 of the current study. Iriarte et al reported a 62-year-old female patient combined with OSA and responded well to CPAP.[11] A 40-year-old female case of catathrenia and OSA reported by Songu, with Mallampati grade 3 upper airways, resulted in a marked improvement with CPAP treatment.[18] Craniofacial examinations of previous studies have revealed inconsistent findings on catathrenia, from normal maxillas and upper airway,[11,50,51] mandible retrognathia[8,9] to obstructive upper airway,[18] and even broad upper airway.[48,49] The treatment efficacy of CPAP on catathrenia also varied greatly across studies.[8,10,11,19,52] These heterogeneous findings might derive from the phenotypes of catathrenia identified in the study.

Some investigations suggested there is a close association between arousal and groaning events. In this study, patients in cluster 2 had significantly more RERA; however, the arousal index did not differ between clusters, nor did arousals caused by groaning episodes. Muraki et al reported that more than 50% of the groaning episodes occurred after arousal.[53] Drakatos et al observed that arousals preceded or coincided with the onset of 84% of groaning events, which were of longer duration than those not associated with arousal.[45] Although the cluster analysis of the current study has documented significantly more RERA in cluster 2, the duration of groaning events in cluster 2 was significantly shorter. It might be speculated that arousal events may result from decreased airflow, and groaning events may act as an active maneuver to reduce upper airway resistance. Unfortunately, the results of the current study were unable to reproduce the findings of earlier studies. The association of groaning and arousal events requires further investigation.

The overall AHI of the two clusters was not significantly different in the study, whereas the RDI in cluster 2 was higher than in cluster 1. This study has found that patients in cluster 2 had a better response to treatment interventions for SDB. Some investigators have noticed a close association between catathrenia and OSA.[54] Songu et al reported a catathrenia patient combined with OSA treated with CPAP, which resulted in the resolution of groaning sounds and a decrease of AHI.[18] Several treatment trials have been conducted for catathrenia, including medications, CPAP, MAD, and surgery.[4,9,20,55,56] Yu et al observed that MAD had a better efficacy with respiratory events than groaning events, and anatomical structures of the upper airway might affect efficacy.[20] The etiology in cluster 2 might be resistance or

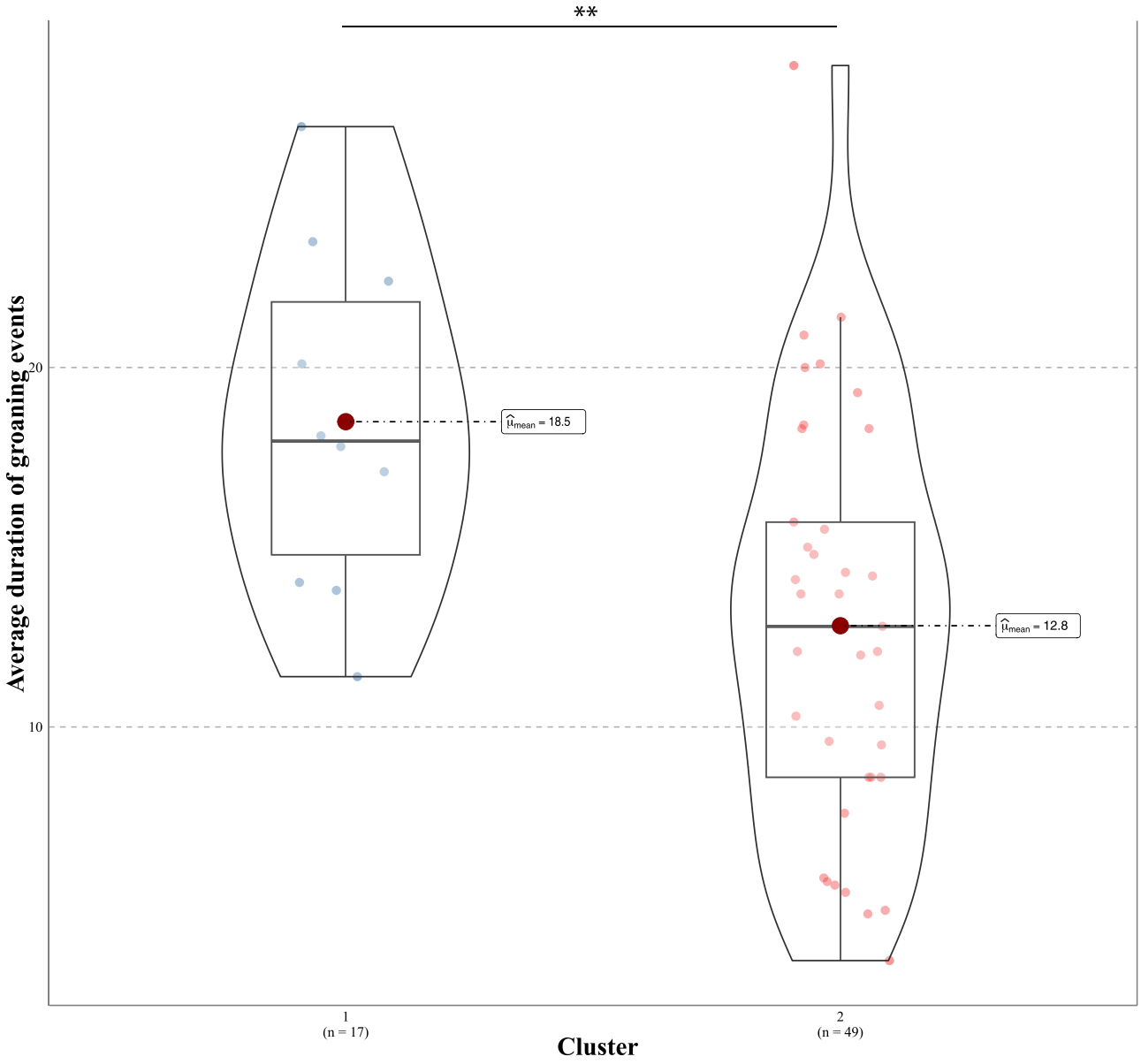

Figure 5 The difference in the average duration of groaning events between clusters. **$p<0.01$.

obstruction of the upper airway. Patients with relatively smaller upper airway phenotypes responded better in the elimination of groaning events than those with broad upper airway dimensions. On the other hand, the etiology of cluster 1 was not clear, possibly associated with the instability of the neural structures controlling ventilation during sleep, as Poli et al suggested.[57] Alternative treatment options might be required to achieve the desired efficacy for patients in cluster 1.

The similarities between cluster 2 catathrenia identified in the current study and OSA have raised another question – whether catathrenia tends to occur in patients with OSA, who have even smaller upper airway structures and more respiratory events at night. Previous studies have pointed out that groaning events, with a flat airflow signal similar to apneas, could be misclassified in home sleep apnea tests (HSAT) and PSG.[58,59] Therefore, catathrenia might be common in patients with OSA and has been underdiagnosed. These assumptions considering associations between catathrenia and OSA, need future investigations.

Table 3 The Craniofacial Anatomical Characteristics Between Subgroups Measured with Cone-Beam Computed Tomography (CBCT)

	Total (n=66)	Cluster 1 (n=17)	Cluster 2 (n=49)	*P* total	*P* Males	*P* Females
3D skeletal measurement (mm)						
Inter-sutura frontozygomatica width	103.4±5.9	105.6±7.1	102.7±5.3	0.085	0.578	0.793
Inter-zygomatic arch width	129.7±6.4	131.5±8.4	129.1±5.5	0.197	0.635	0.392
Skeletal nasal width	25.9±2.0	26.7±2.9	25.6±1.6	0.169	0.963	0.038*
Anterior maxillary width	37.8±3.0	38.7±3.9	37.5±2.6	0.263	0.873	0.057
Posterior maxillary width	63.5±4.6	65.7±6.2	62.7±3.7	0.022*	0.387	0.277
Maxillary length	43.5±4.4	44.0±3.6	43.3±4.7	0.568	0.670	0.898
Inter-condyle width	113.0±7.7	115.1±7.1	112.2±7.8	0.177	0.840	0.801
Mandibular width	95.9±5.4	96.8±7.1	95.6±4.8	0.533	0.759	0.108
Mandibular body length	82.1±10.3	84.4±5.8	81.2±11.3	0.272	0.692	0.458
Mandibular total length	125.1±8.9	126.6±6.7	124.6±9.5	0.411	0.352	0.912
Mandibular ramus height	66.2±15.3	69.4±19.9	65.1±13.3	0.326	0.590	0.501
Upper airway volume (mm^3)						
Total	30,454±10,130	41,386±10,543	26,661±6700	0.000***	0.001**	0.000***
Nasopharynx	8861±2887	10,260±2939	8376±2734	0.019*	0.021*	0.048*
Velopharynx	10,377±3997	14,887±3365	8812±2855	0.000***	0.000***	0.000***
Oropharynx	7395±4305	11,220±6008	6068±2468	0.003**	0.012*	0.018*
Hypopharynx	3821±1886	5019±2821	3405±1216	0.035*	0.203	0.248
Upper airway cross-sectional area (mm^2)						
Velopharynx (minimum)	234±101	336±94	199±78	0.000***	0.001**	0.000***
Oropharynx (minimum)	230±108	345±117	190±70	0.000***	0.003**	0.000***
Hypopharynx (minimum)	225±83	299±100	199±59	0.001**	0.009**	0.101
Nasopharynx (average)	436±116	533±127	402±91	0.001**	0.000***	0.209
Velopharynx (average)	384±113	512±87	339±84	0.000***	0.000***	0.000***
Oropharynx (average)	283±115	410±125	238±70	0.000***	0.001**	0.000***
Hypopharynx (average)	283±93	372±112	252±61	0.000***	0.003**	0.048*
Nasopharynx (maximum)	574±160	712±176	526±124	0.000***	0.001**	0.027*
Velopharynx (maximum)	644±168	816±139	585±134	0.000***	0.001**	0.000***
Oropharynx (maximum)	340±124	476±137	292±74	0.000***	0.001**	0.000***
Hypopharynx (maximum)	352±99	440±117	322±71	0.001**	0.011*	0.057
Upper airway diameter (mm)						
Height	86.8±10.2	92.7±14.2	84.8±7.6	0.041*	0.174	0.586
Nasopharynx width	36.5±5.5	41.3±5.2	34.8±4.6	0.000***	0.000***	0.270
Velopharynx width	32.4±5.5	38.6±3.6	30.2±4.3	0.000***	0.000***	0.000***
Oropharynx width	30.2±4.6	35.3±3.8	28.5±3.4	0.000***	0.000***	0.003**
Hypopharynx width	33.4±3.7	36.0±4.0	32.5±3.1	0.000***	0.044*	0.329
Nasopharynx sagittal diameter	23.2±4.6	26.5±4.7	22.0±4.0	0.000***	0.003**	0.078
Velopharynx sagittal diameter	16.4±3.1	19.6±2.1	15.3±2.6	0.000***	0.000***	0.000***
Oropharynx sagittal diameter	13.4±3.7	17.0±4.1	12.2±2.5	0.000***	0.011*	0.000***
Hypopharynx sagittal diameter	14.5±3.1	16.9±4.1	13.6±2.2	0.006**	0.051	0.019*

Notes: Data were summarized as mean ± standard. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

There are some strengths of the study. First, the identification of subtypes of catathrenia improves the knowledge and awareness of the heterogeneity of catathrenia clinical presentations. Second, identifying distinct clinical profiles of catathrenia might be beneficial for personalized therapies in the future. However, there are several limitations of the study. First, all the participants included in the study came from two independent sleep

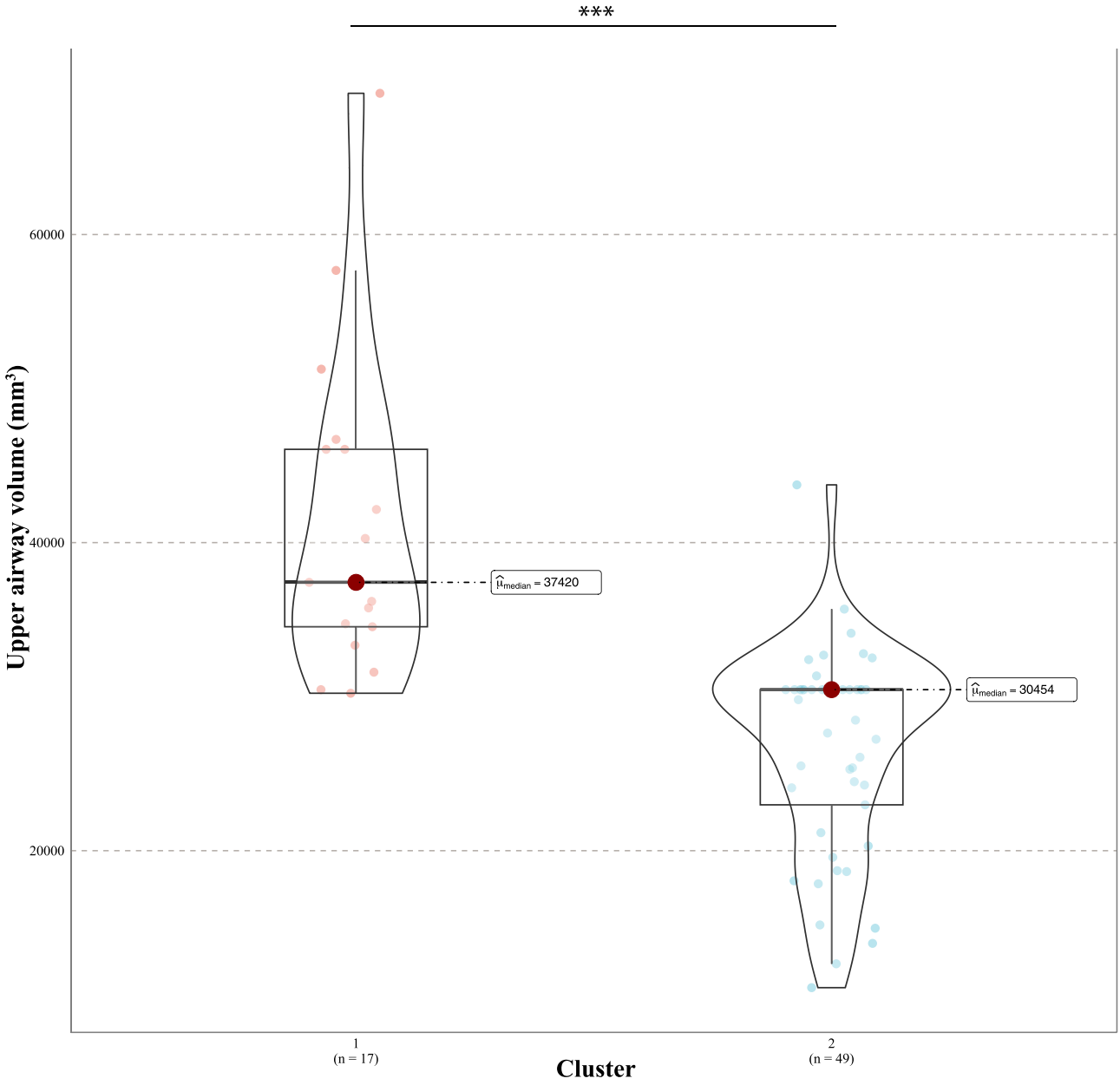

Figure 6 The difference in the upper airway volume between clusters. ***$p<0.001$.

centers, indicating moderate referral bias. The sample size is relatively large for catathrenia. However, it is important to acknowledge that a larger sample size would have potentially yielded more accurate results. Second, the participants in the study were Asian, and racial and ethnic factors were not considered. It is important to note that this study did not cover all possible clinical presentations of catathrenia, including associated symptoms, comorbidities, and acoustic characteristics of groaning sounds. This is because the symptoms exhibited by patients with catathrenia were quite diverse, and the sample size of the study was relatively insufficient for thorough analysis. The robustness and generalizability of phenotypes identified in the study need to be verified in future investigations with more diverse samples.

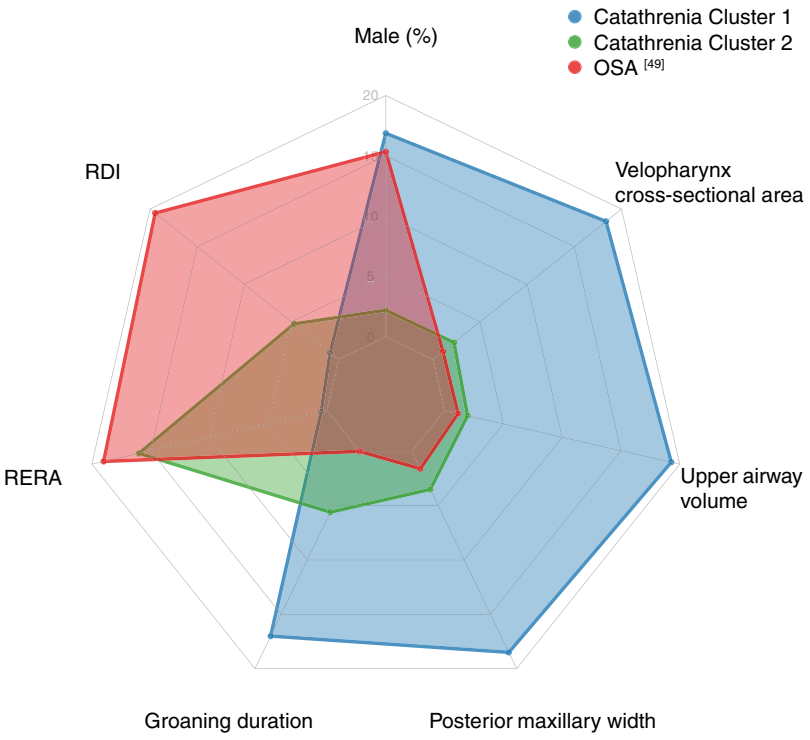

Figure 7 Two phenotypes of catathrenia identified in the study, compared with OSA. Data of OSA was extracted from reference.[49] Patients with catathrenia in cluster 2 exhibit similarities to those with OSA on several parameters, while those in cluster 1 do not.
Abbreviations: RERA, respiratory effort-related arousals; RDI, respiratory disturbance index; OSA, obstructive sleep apnea.

Conclusion

Two distinct phenotypes were identified in patients with catathrenia, primary catathrenia and catathrenia associated with upper airway obstruction, suggesting respiratory events and upper airway structures might be related to the etiology of catathrenia, with implications for its treatment. There might exist a close association between catathrenia and OSA.

Statement of Significance

The clinical manifestations including polysomnographic characteristics and upper airway evaluations of catathrenia (nocturnal groaning) have been heterogeneous, possibly due to various disease subtypes. In this study, we used K-mean cluster analysis on 66 patients diagnosed with catathrenia to explore phenotypes and identified two distinct clusters of catathrenia, primary catathrenia, and catathrenia associated with upper airway obstruction. Patients' sex, respiratory and groaning events, and upper airway dimension differ between subgroups. It is suggested respiratory events and upper airway structures might be related to the etiology of catathrenia, with implications for its treatment.

Data Sharing Statement

The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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