Multidimensional Prediction of Continuous Positive Airway Pressure Adherence

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Abbreviations: AHI, apnea-hypopnea index; APAP, auto-titrating positive airway pressure; ArI, arousal index; BMI, body mass index; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; %N1, proportion spent in NREM sleep stage 1; NREM, non-rapid eye movement; ODI, 3% oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; PSG, polysomnography; REM, rapid eye movement; RPSGT, registered polysomnographic technologist; T90, total sleep time spent with arterial oxygen saturation <90%

ABSTRACT

Objective/Background: Continuous positive airway pressure (CPAP) is the standard treatment for obstructive sleep apnea (OSA). Unsatisfactory adherence to CPAP is an important clinical issue to resolve. Cluster analysis is a powerful tool to distinguish subgroups in a multidimensional fashion. This study aimed to investigate the use of cluster analysis for predicting CPAP adherence using clinical polysomnographic (PSG) parameters and patient characteristics.

Patients/Methods: Participants of this multicenter observational study were 1,133 patients with OSA who were newly diagnosed and implemented CPAP. Ward's method of cluster analysis was applied to in-laboratory diagnostic PSG parameters and patient characteristics. CPAP adherence was assessed during 90- and 365-day periods after CPAP initiation in each cluster. We adopted the Centers for Medicare and Medicaid Services criterion for CPAP adherence, i.e., CPAP use ≥4 h per night for 70% or more of the observation period. Logistic regression analysis was performed to stratify clusters according to CPAP adherence.

Results: Five clusters were identified through cluster analysis. Clustering was significantly associated with CPAP adherence at 90- and 365-day periods after CPAP initiation. Logistic regression revealed that the cluster with features including apnea predominant sleep-disordered breathing, high apnea-hypopnea index, and relatively older age demonstrated the highest CPAP adherence.

Conclusion: Cluster analysis revealed hidden connections using patient characteristics and PSG parameters to successfully identify patients more likely to adhere to CPAP for 90

days and up to 365 days. When prescribing CPAP, it is possible to identify patients with OSA who are more likely to be non-adherent.

Keywords: Cluster analysis, CPAP adherence, Obstructive sleep apnea, Prediction of CPAP adherence

1. Introduction

Continuous positive airway pressure (CPAP) is a standard treatment for obstructive sleep apnea (OSA). It can improve sleep quality and reduce the risk of cardiovascular complications and mortality in patients with OSA [1]. It also improves intermediate markers of systemic inflammation and endothelial function [2,3]. However, these benefits are limited to those patients with CPAP adherence, as defined as >4 h of use during the night, with non-adherence rates ranging from 46–83% [4].

Predicting patient CPAP adherence would allow clinicians to focus on those who might be non-adherent and consider other treatment options for them earlier in patient management. Thus, it is helpful to consider known predictors of CPAP adherence. Reported independent predictors of CPAP adherence include age [5-10], sex [9], apnea-hypopnea index (AHI) [6,7,10], 3% oxygen desaturation index (ODI) [6,10], total sleep time spent with arterial oxygen saturation <90% (T90) [6], pre-treatment Epworth Sleepiness Scale (ESS) [7], and body mass index (BMI) [7]. However, these predictive factors differ among studies; furthermore, several independent factors have been simultaneously identified in the same study [5-10]. For instance, Sabil et al. reported age was a significant independent factor, whereas AHI, BMI, ESS, sex, ODI, and T90 were not [8]. McArdle et al. reported that age, AHI, BMI, and ESS were significant independent factors, but significance was not seen in sex [7]. Thus, CPAP adherence is inherently multidimensional.

Clinicians who prescribe CPAP integrate multiple aspects of known and unpublished predictors. Thus, one may consciously or unconsciously apply a combination rather than an independent factor. An unbiased cluster analysis could be useful for a clinician to

attempt adherence prediction. Recently, cluster analysis has been employed in studies on sleep-disordered breathing [11-15]. Most have been to identify OSA or AHI phenotype presentations; that is, cluster classifications have been reported without outcomes. In contrast, only a few studies have outcomes such as adverse cardiovascular events and symptom changes over time [14,16]. In the current study, we aimed to investigate the use of cluster analysis of which outcome was CPAP adherence using more detailed diagnostic PSG parameters and patient characteristics.

2. Methods

2.1. Study design and population

This was a multicenter, retrospective, and observational study. The study sites comprised five institutes: two university hospitals, two regional hospitals, and a private sleep clinic. All institutes were certified by the Japanese Society of Sleep Research (JSSR). Consecutive patients diagnosed with OSA and newly initiated CPAP therapy were enrolled in this study. Non-naïve patients with CPAP were excluded. The enrolment period was two years from 1 January 2017. None of the patients in this study were managed by telemedicine. During enrolment, 1,261 patients with OSA had newly prescribed CPAP therapy. One hundred twenty-eight patients diagnosed with home sleep apnea testing were excluded, then the remaining 1,133 patients were eligible for the analysis in this study. The study protocol was approved by the ethics committee of Nara Medical University on April 1, 2021 (No. 2951).

2.2. Single-night PSG for OSA diagnosis

In-laboratory PSG was performed to diagnose OSA for a single night. Regarding the PSG device, three institutes used the Alice 6 LDx or Alice 5 (Philips, Murrysville, PA), and two hospitals used the PSG-100 system (Nihon Kohden, Tokyo, Japan). All procedures, scoring, and reporting parameters for the PSG were standardized as per the AASM Manual for the Scoring of Sleep and Associated Events; Rules, Terminology, and Technical Specifications, Version 2.2 or 2.3 [17,18]. PSG was scored by JSSR-certified technicians and a registered polysomnographic technologist (RPSGT) and reviewed by certified sleep physicians at each site. Investigator meetings were held multiple times to evaluate and minimize inter-scorer variability between the institutes.

2.3. CPAP prescription and adherence

Certified sleep physicians initiated CPAP treatment at each site if the AHI was ≥20, which is the cut-off value for CPAP prescription according to the Japanese health insurance system regulation. For all patients prescribed CPAP, CPAP therapy was adjusted following a sleep study with manual titration or auto-titrating positive airway pressure (APAP). It is mandatory that patients using CPAP visit the sleep clinic every month. Usually, certified sleep physicians check patients and review the CPAP adherence data extracted from a CPAP memory card or cloud-based data system. At the monthly visit, CPAP settings, including the pressure range or CPAP mode, are modified by certified physicians if necessary. If acceptance and adherence were adequate for three to four months with CPAP therapy, sleep physicians could extend the visit interval to a maximum of every three months, which is also a Japanese health insurance system regulation for CPAP users.

We defined good CPAP adherence as achieving the Centers for Medicare and Medicaid Services (CMS) criterion, which is CPAP use ≥4 h per night for 70% or more of the observation period [19]. Patients who did not meet the CMS criterion were defined as having poor CPAP adherence, and those who refused CPAP during the follow-up period were defined as dropouts. CPAP adherence was assessed during 90- and 365-day periods after CPAP initiation. Adherence was calculated as the percentage of good cases out of the total number of patients, excluding those with missing adherence data.

2.4. Cluster analysis

Both the k-means and Ward's methods were utilized for cluster analysis. Details are described in Appendix S1. Then, eventually, a hierarchical clustering method, called Ward's method, was adopted using 12 factors, including patient characteristics and PSG parameters related to CPAP adherence, converting categorical variables into dummy variables (1,0). The effects of both factor, data standardization and the missing value imputation, were not significant in preliminary study; therefore, standardization and imputation were not adopted in the analysis. This analysis was performed based on complete case data since the mechanism of missing values was considered as missing completely at random. Details of missing values are provided in Appendix S1.
The optimal number of clusters was determined to be five based on the cluster dendrogram, the elbow plot, and clinical significance. The detailed rationale for choosing five for the number of clusters, including the consideration of alternative cluster numbers, is provided in Appendix S1.

Regarding the 12 adopted variables for the cluster analysis, we selected patient profiles, including sex, age, BMI, ESS, and PSG parameters, presumably related to CPAP

adherence, based on an expert's suggestion. The rationale for this expert suggestion is described in Appendix S1. Briefly, factors which have been previously reported as independent predictors of CPAP adherence and others which are considered to affect CPAP treatment according to the clinical experience of experts were selected for the variables for the cluster analysis. Those of PSG parameters included the proportion spent in non-rapid eye movement (NREM) sleep stage (N) 1 (%N1), arousal index (ArI), AHI, apnea ratio, which is calculated as (apneas)/(apneas+hypopneas), sleep positional dependency, rapid eye movement (REM) dependency, ODI, and T90. As for positional and REM dependency, we used the formula of (supine AHI+1.0)/(non-supine AHI+1.0) and (REM-AHI+1.0)/(NREM-AHI+1.0), respectively, based on previous reports [20,21].

2.5. Statistical analysis

To ensure the robustness of our findings, we performed a sensitivity analysis including the adjusted analysis. ANOVA and Fisher's exact test were conducted to assess the significance of differences between clusters for various parameters. Post-hoc analysis using the Tukey-Kramer method were conducted to confirm these differences. The details are shown in Appendix S2.

Logistic regression analyses were performed on CPAP adherence during 90- and 365-day observational periods after CPAP initiation. The predictor variables were clusters classified by Ward's method, and the response variable was CPAP adherence (good = 1, others = 0). In addition, the odds ratio (OR) for good CPAP adherence between the clusters was calculated. The association between the response variable (CPAP adherence) and the predictor variables (cluster) in the model was statistically significant. We

compared the *P*-value for the predictor to 0.05 to assess the null hypothesis. The null hypothesis was that the predictor coefficient equals zero, indicating no association between the predictor and response. The OR between clusters indicated the strength and direction of the association (OR = 1: cluster did not affect the odds of CPAP adherence; OR > 1: cluster associated with higher odds of CPAP adherence; OR < 1: cluster associated with lower odds of CPAP adherence).

Cluster analysis was performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and logistic regression analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Continuous variables are expressed as mean ± standard deviation, depending on the data distribution. Discrete variables are expressed as numbers and percentages.

We performed cross-validation with k = 5 to validate the robustness of our clustering results. This involved dividing the dataset into five subsets, where one subset was used as a validation set while the remaining four subsets served as the training set. This process was repeated five times, ensuring each subset was used as a validation set once. Details of the cross validation are shown in Appendix S3.

Statistical analyses were performed by statisticians from ClinChoice (Tokyo, Japan).

3. Results

3.1. Description of the study cohort

The demographic characteristics of the analyzed patients (N = 1,133) are summarized in the right column of Table 1. The age, BMI, and ESS were 55.6±13.9 years, 27.7±5.5 kg/m^2, and 8.6±4.8, respectively, and 81.2% were male. Overall, the average CPAP usage during

90- and 365-day periods after CPAP initiation was 4 h 33 min ± 2 h 5 min and 4 h 44 min ± 1 h 55 min, respectively. A total of 46.8% and 45.6% of patients achieved the CMS criterion for CPAP adherence for 90 and 365 days, respectively. Details of CPAP adherence in each cluster are shown in Table S6 in Appendix S4. Regarding the CPAP device, 51.5% of patients used AirSense 10 AutoSet (ResMed, San Diego, CA), 47.1% used DreamStation (Philips, Best, Netherlands), and the remaining patients used SleepStyle (Fisher & Paykel Healthcare, Auckland, New Zealand). APAP was used by 901 (79.5%) patients.

Table 1. Demographic characteristics of patients in each cluster and all patients

Parameter	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Total**
N	318	239	429	67	80	1,133
Age (years)	52.3 ± 13.1	57.0 ± 12.7	58.9 ± 14.1	55.0 ± 16.2	46.8 ± 11.3	55.6± 13.9
Male sex	237 (74.5)	212 (88.7)	348 (81.1)	51 (76.1)	72 (90)	920 (81.2)
BMI (kg/m^2)	26.4 ± 4.5	27.7 ± 4.5	26.6 ± 4.9	33.0 ± 7.6	34.2 ± 5.8	27.7 ± 5.5
ESS	8.7 ± 4.8	8.4 ± 4.7	8.2 ± 4.8	8.4 ± 4.9	10.9 ± 5.2	8.6 ± 4.8
%N1, %	17.8 ± 7.1	38.6 ± 15.4	29.9 ± 13.2	50.6 ± 25.9	51.8 ± 16.1	31.1 ± 17.4
ArI	25.9 ± 7.8	58.6 ± 18.1	41.0 ± 12.8	60.6 ± 17.9	87.8 ± 19.2	44.9 ± 22.0

Apnea ratio, %	22.2 ± 15.0	69.5 ± 17.6	31.1 ± 23.0	11.5 ± 12.8	73.9 ± 23.8	38.6 ± 28.4
AHI	26.3 ± 5.5	64.5 ± 14.5	41.0 ± 13.4	74.6 ± 17.4	94.7 ± 17.7	47.6 ± 23.8
REM dependency	1.6 ± 1.0	0.8 ± 0.3	1.1 ± 0.6	0.9 ± 0.2	0.7 ± 0.2	1.1 ± 0.8
Sleep position dependency	5.3 ± 5.9	2.2 ± 2.1	10.2 ± 16.9	1.8 ± 1.7	14.2 ± 31.7	7.0 ± 14.5
ODI	20.5 ± 7.0	59.0 ± 13.9	33.3 ± 14.1	71.6 ± 22.6	94.1 ± 20.4	41.7 ± 26.0
T90	1.9 ± 3.5	12.3 ± 10.7	4.2 ± 7.8	14.6 ± 14.4	36.7 ± 18.6	8.2 ± 13.1
Cluster features	Hypopnea-predominant moderate OSA with low N1 appearance	Apnea-predominant severe OSA with relatively older age	Older-aged relatively severe OSA	Hypopnea-predominant severe OSA with severe obesity	Younger-aged apnea-predominant severe OSA with sustained hypoxia and morbid obesity	

AHI, apnea-hypopnea index; apnea ratio = (apnea/apnea+ hypopnea) × 100; ArI, arousal index; BMI, body mass index; ESS, pre-treatment Epworth Sleepiness Scale; N1, non-rapid eye movement sleep stage 1; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; %N1, proportion spent in non-rapid eye movement sleep stage 1; T90, total sleep time spent with arterial oxygen saturation <90%; REM, rapid eye movement; REM

dependency = REM-AHI+1.0/NREM-AHI+1.0; Sleep position dependency = supine AHI+1.0/non-supine AHI+1.0.

3.2. Characteristics of each cluster

Based on cluster analysis, we identified five clusters (Figures 1). Table 1 presents the variables in each cluster.

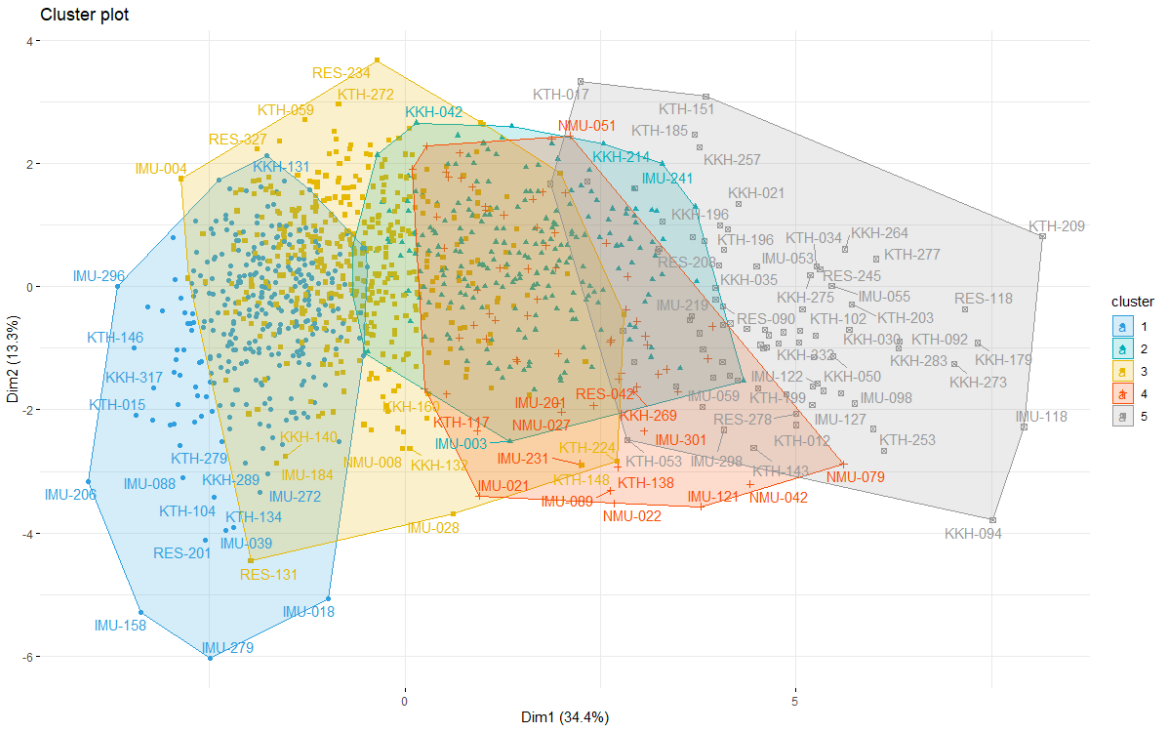

Figure 1. Cluster plot. A hierarchical clustering method called Ward's method was performed using 12 factors, including patient characteristics and polysomnographic parameters related to continuous positive airway pressure adherence. The optimal number of clusters was determined as five based on the cluster plot.

3.2.1. Cluster 1

Cluster 1 was the second-largest cluster, comprising 318 patients (28.1%). Compared to the other clusters, this cluster exhibited relatively low AHI (26.3±5.5/h) and apnea ratio

(22.2±15.0%), which implies hypopnea-predominant OSA, and relatively high REM-dependency (1.6±1.0) and low %N1 (17.8±7.1%). Considering these characteristics, we named it “hypopnea-predominant moderate OSA with low N1 appearance”.

3.2.2. Cluster 2

Cluster 2 was the third-largest cluster, comprising 239 patients (21.1%), and was called “apnea-predominant severe OSA with relatively older age” because the apnea ratio was the second highest value (69.5±17.6%), and AHI was more than 60/h (64.5±14.5/h).

3.2.3. Cluster 3

Cluster 3 was the largest, comprising 429 patients (37.9%). The age was the oldest among the five clusters (58.9±14.1 years). Patients were similar to those in Cluster 2 regarding BMI (26.6 kg/m2). The ArI was 41.0±12.8/h, and AHI was 41.0±13.4/h. This cluster was named “older-aged relatively severe OSA”.

3.2.4. Cluster 4

Cluster 4 was the smallest, comprising 67 patients (5.9%). AHI was extremely high (74.6±17.4/h), and BMI was the second highest (33.0±7.6 kg/m^2). The apnea ratio was the lowest (11.5±12.8%) among all clusters, implying hypopnea-predominant OSA. Thus, we called this cluster “hypopnea-predominant severe OSA with severe obesity”.

3.2.5. Cluster 5

Cluster 5 comprised 80 patients (7.1%). This cluster was similar to Cluster 4 regarding the extremely high AHI and BMI (94.7±17.7/h and 34.2±5.8 kg/m^2, respectively). However, patients in this cluster were the youngest (46.8±11.3 years) and revealed the highest T90 (36.7±18.6%) and apnea ratio (73.9±23.8%). ESS was 10.9±5.2, the highest among all

clusters. Thus, we named this cluster “younger-aged apnea-predominant severe OSA with sustained hypoxia and morbid obesity”.

3.3. Differences in CPAP adherence among clusters

ANOVA and Fisher’s exact test revealed significant differences in parameters among the clusters. Post-hoc analysis using the Tukey-Kramer method confirmed these differences, identifying specific cluster pairs with significant differences at a significance level of 0.05. The details are shown in Appendix S2.

The results of the logistic regression analyses for CPAP adherence in the 90 days after CPAP initiation are summarized in Table 2. CPAP adherence rates were 38.4% (Cluster 1), 58.6% (Cluster 2), 48.9% (Cluster 3), 42.2% (Cluster 4), and 38.7% (Cluster 5). Logistic regression revealed that clustering was significantly different in CPAP adherence and that Cluster 2 (apnea-predominant severe OSA with relatively older age) was significantly more adherent than the other clusters. Considering the OR of each reference, the CPAP adherence of Cluster 2 was 2.27, 1.48, 1.94, and 2.24 times higher than those of Clusters 1, 3, 4, and 5, respectively. Regarding the characteristics of each cluster, Cluster 2 was similar to Cluster 5, with both clusters having apnea-predominant severe OSA. However, CPAP adherence was significantly higher in Cluster 2 than in Cluster 5.

Table 2. Odds ratios for CPAP adherence during 90-day period

Cluster (CPAP adherence)	Cluster 1 (38.4%)	Cluster 2 (58.6%)	Cluster 3 (48.9%)	Cluster 4 (42.2%)	Cluster 5 (38.7%)
Cluster 1 (38.4%)	(reference)	2.27 [1.60-3.23] *P*<0.01	1.54 [1.14-2.08] *P*=0.01	1.17 [0.68-2.03] *P*=0.57	1.01 [0.60-1.70] *P*=0.96
Cluster 2 (58.6%)	0.44 [0.31-0.63] *P*<0.01	(reference)	0.68 [0.49-0.94] *P*=0.02	0.52 [0.29-0.91] *P*=0.02	0.45 [0.26-0.76] *P*=0.00
Cluster 3 (48.9%)	0.65 [0.48-0.88] *P*=0.01	1.48 [1.06-2.06] *P*=0.02	(reference)	0.76 [0.45-1.30] *P*=0.32	0.66 [0.4-1.09] *P*=0.11
Cluster 4 (42.2%)	0.85 [0.49-1.47] *P*=0.57	1.94 [1.10-3.40] *P*=0.02	1.31 [0.77-2.23] *P*=0.32	(reference)	0.86 [0.44-1.71] *P*=0.67
Cluster 5 (38.7%)	0.99 [0.59-1.66] *P*=0.96	2.24 [1.31-3.83] *P*=0.00	1.52 [0.92-2.51] *P*=0.11	1.16 [0.59-2.28] *P*=0.67	(reference)

Odds ratio
2.7
2.4
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0

CPAP, continuous positive airway pressure.

Each crossing cell contains the odds ratio [95% confidence interval] and *P*-value for CPAP adherence in the cluster listed horizontally relative to CPAP adherence in the cluster listed vertically. The Heatmap visually represents the odds ratio for CPAP adherence in each cell. The intensity of the red color indicates the magnitude of the odds ratio, with darker and lighter shades representing higher and lower odds ratios, respectively.

The results of the logistic regression analyses for CPAP adherence in the 365 days after CPAP initiation are summarized in Table 3. CPAP adherence rates were 34.1% (Cluster 1), 56.7% (Cluster 2), 48.3% (Cluster 3), 47.4% (Cluster 4), and 40.0% (Cluster 5). Importantly CPAP adherence was not significantly different from the 90-day period and exhibited similar trends across clusters. Logistic regression revealed that Cluster 2 was

significantly more adherent than Clusters 1 and 5. Although not statistically significant, CPAP adherence in Cluster 2 was higher than in Cluster 3. Moreover, CPAP adherence was significantly higher in Cluster 2 than in Cluster 5, as observed in CPAP adherence in the 90 days.

Table 3. Odds ratios for CPAP adherence during 365-day period

Cluster (CPAP adherence)	Cluster 1 (34.1%)	Cluster 2 (56.7%)	Cluster 3 (48.3%)	Cluster 4 (47.4%)	Cluster 5 (40.0%)
Cluster 1 (34.1%)	(reference)	2.54 [1.74-3.27] *P*<0.01	1.81 [1.31-2.50] *P*=0.00	1.74 [0.97-3.10] *P*=0.06	1.29 [0.76-2.18] *P*=0.35
Cluster 2 (56.7%)	0.40 [0.27-0.57] *P*<0.01	(reference)	0.71 [0.51-1.00] *P*=0.05	0.69 [0.38-1.24] *P*=0.21	0.51 [0.30-0.87] *P*=0.01
Cluster 3 (48.3%)	0.55 [0.40-0.76] *P*=0.00	1.40 [1.00-1.97] *P*=0.05	(reference)	0.96 [0.55-1.68] *P*=0.89	0.71 [0.43-1.18] *P*=0.19
Cluster 4 (47.4%)	0.58 [0.32-1.03] *P*=0.06	1.46 [0.81-2.62] *P*=0.21	1.04 [0.60-1.81] *P*=0.89	(reference)	0.74 [0.37-1.49] *P*=0.40
Cluster 5 (40.0%)	0.78 [0.46-1.32] *P*=0.35	1.97 [1.15-3.37] *P*=0.01	1.40 [0.85-2.32] *P*=0.19	1.35 [0.67-2.71] *P*=0.40	(reference)

Odds ratio
2.7
2.4
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0

CPAP, continuous positive airway pressure.

Each crossing cell contained the odds ratio [95% confidence interval] and *P*-value for CPAP adherence in the cluster listed horizontally relative to CPAP adherence in the cluster listed vertically. The Heatmap visually represents the odds ratio for CPAP adherence in each cell. The intensity of the red color indicates the magnitude of the odds ratio, with darker and lighter shades representing higher and lower odds ratios, respectively.

3.4. Cross-validation of clustering

Based on cross-validation to verify the clustering, the two clusters for each of the five data sets were similar in the shape of the plot of clusters vs. gap statistics and in the position of the hierarchy of clusters in the hierarchical tree, respectively. The details are shown in Appendix S3.

4. Discussion

The cluster analysis successfully identified five clusters comprising patient characteristics and PSG parameters that affect CPAP adherence at 90 days. The cluster of patients with features including apnea-predominant sleep-disordered breathing, high AHI, and relatively older age (Cluster 2) demonstrated significantly higher CPAP adherence than the other clusters. Moreover, patients in Cluster 2 maintained the highest CPAP adherence during the 365 days after CPAP initiation. Furthermore, the stratification in terms of CPAP adherence among five clusters persisted for 365 days, implying identified cluster in the current study would predict short-term as well as intermediate-term CPAP adherence. Clusters 2 and 4 showed significant differences in 90-day CPAP adherence but not in 365-day CPAP adherence. In Cluster 4, 18.8% of the patients with poor 90-day adherence improved their adherence by the 365-day mark. We believe that the inclusion of these cases contributed to the lack of significant difference in long-term adherence. This indicates that with appropriate measures to improve adherence, some patients may enhance their long-term CPAP adherence.

One may concern about whether dividing into five clusters and adopting Ward's Method were not the appropriate way for our demonstration, in another word, other methods or different numbers of clusters could give different results. However, we selected five clusters because this choice balanced well both statistically and clinically. Details about testing other cluster numbers and methods we performed are provided in Appendix S1.

Various single, independent predictors of CPAP adherence have been explored. As presented in Table 4, the independent predictors of CPAP adherence proposed by previous studies have been inconsistent and/or controversial [5-10]. CPAP adherence in clinical practice appears multifactorial, and each relevant factor implicitly has associated factors at different levels. We adopted cluster analysis to overcome this challenge. Cluster 2 was predicted to have higher CPAP adherence; this group exhibited apnea-predominant characteristics with a high AHI and relatively older age. However, when considering the previously reported independent predictors for CPAP adherence, we observed that AHI, ODI, and BMI were much higher in Clusters 4 and 5. These findings indicate that CPAP adherence is likely influenced by combinations of factors rather than by individual factors alone. There could be an interaction between factors and/or limited dose-dependent correlations between CPAP adherence and AHI, ODI, and BMI. Thus, higher AHI, ODI, or BMI might not necessarily predict CPAP adherence, that is, the correlation might not completely be a linear dose-response pattern.

Table 4. Significant and non-significant factors predicting CPAP adherence in previous studies

	Significant factor	Non-significant factor	Criteria of adherence	Adherence
Budhiraja et al.[5]	Age	AHI, ESS, sex	Average usage ≥ 4h	63.5% (30 days)
Hoshino et al.[6]	Age, AHI, ODI, REM-related OSA, T90	BMI, ESS, sex, %N1+N2	CPAP use ≥4 h per night for 70% or more	26.7% (6 months)
McArdle et al.[7]	Age, AHI, BMI, ESS	sex	Long-term CPAP use	N/A
Sabil et al. [8]	Age	AHI, BMI, ESS, sex, ODI, T90	Average usage ≥ 4h	87% (3 months)
Sin et al.[9]	Age, sex	AHI, BMI, %N1	Average usage ≥ 4h	87.1% (3 months), 83.8% (6 months)
Lee et al.[10]	AHI, ODI	Age, BMI, ESS, sex	CPAP use ≥4 h per night for 70% or more	52.6% (1 year)

REM, rapid eye movement; OSA, obstructive sleep apnea; BMI, body mass index; ESS, Epworth Sleepiness Scale; ODI, 3% oxygen desaturation index; %N1, proportion spent in

non-rapid eye movement sleep stage 1; %N1+N2, proportion spent in non-rapid eye movement sleep stage 1 and 2; T90, total sleep time spent with arterial oxygen saturation <90%.

In our study, the apnea ratio was one of the key predictors for CPAP adherence. To our knowledge, there have been no reports of apnea ratio associated with CPAP adherence. Regarding the possible explanation, a higher apnea ratio, which was seen in Cluster 2, reflects a collapsible upper airway. Thus, pressure splint with CPAP might have worked effectively. Moreover, older age has been more often positively reported among known predictors for CPAP adherence (Table 4). In our study, the highest CPAP adherence of Cluster 2 presenting a relatively older age supports this reported association. Thus, it could be reasonable that Cluster 2 (apnea-predominant severe OSA with relatively older age) showed the highest CPAP adherence among the identified five clusters. From a clinical perspective, medical providers can actively continue to prescribe CPAP for patients in Cluster 2. For other clusters with lower adherence, it is helpful to anticipate the possibility of intolerance of CPAP adherence from its introduction and to prepare to propose alternative treatments.

Since AHI has been reported as an independent predictor of CPAP adherence, clusters 4 and 5 with higher AHI were expected to have high CPAP adherence. However, their adherence was significantly lower than that of Cluster 2.

In Cluster 5, factors of younger age and morbid obesity were assumed to contribute more negatively to CPAP adherence. There might be a background of inappropriate lifestyles in the younger and obese population. REM dependency is another

possible issue. One study reported that REM-related OSA (REM-AHI/NREM-AHI ≥ 2.0) is associated with lower CPAP adherence [6]. Supporting this report, our data of Cluster 1 presented the lowest CPAP adherence and the highest REM-dependency value (1.6±1.0) among clusters. Furthermore, Cluster 1 demonstrated the lowest %N1. It has been reported that a higher proportion of light sleep (N1 and N2) was observed in patients with severe OSA than in those with mild or moderate OSA [22]. AHI and ArI values were the lowest in Cluster 1 (26.3±5.5/h and 25.9±7.8/h, respectively), and fewer apneic events existed during light sleep, which may reflect the dependency of REM-related OSA.

Cluster analysis has recently been adopted for sleep-disordered breathing [15]. Zinchuk et al. published the report in which a certain group of patients identified with cluster analysis was significantly associated with a specific outcome, i.e., the risk of cardiovascular disease. Moreover, they demonstrated that clustering was a more useful marker for cardiovascular events rather than OSA severity based on AHI values [16]. Pien et al. adopted a cluster analysis with symptom changes over time as the outcome [14]. They reported three distinct clinical phenotypes of OSA identified with cluster analysis: Disturbed Sleep, Minimally Symptomatic, and Sleepy. They found that CPAP adherence affected the symptom changes over time differently between those 3 clusters [14]. Gagnadoux et al. adopted a cluster analysis with CPAP adherence as the outcome [23]. They conducted the cluster analysis with 13 variables including patients characteristics, symptoms and comorbidities. They reported a significant the association between the clusters and CPAP adherence after adjusting for criteria commonly used to assess OSA severity and to prescribe CPAP therapy, including socioeconomic status, apnea-hypopnea index, and ESS.

However, the cluster analysis in our study used detailed PSG data and patient characteristics as variables and 90- and 365-day CPAP adherence as outcomes. To our knowledge, this is the first study using cluster analysis with variables, including detailed PSG parameters with a large sample size of which the outcome is CPAP adherence.

Our study has some limitations. First, all participants in this study were Japanese, a population with relatively low ethnic diversity. However, Japanese individuals vary in terms of attitudes, craniofacial form, or regional food customs. To provide a comprehensive view of Japan, this study was conducted as a multicenter study across various regions. Nonetheless, the backgrounds of patients in different countries differ in terms of ethnic distribution, healthcare and insurance systems, education, socioeconomic status, food customs, and obesity levels, which may vary widely from country to country. Therefore, the clusters identified in this study may not be directly applicable to other countries. However, we believe that the concepts in this study provides an opportunity for researchers in other countries to develop their own clusters for predicting CPAP adherence. Second, the AHI of participants in our study was ≥20, since the Japanese national health insurance system does not allow the prescription of CPAP in cases of AHI < 20. Thus, the population who uses CPAP in Japan is different from that the United States and other countries. However, our findings should be still helpful for the prediction of CPAP adherence in patients with moderate-to-severe OSA. Third, more than 80% of the patients in the present study were male; however, the sex distribution is similar to that of former reports from Japan [24]. When cluster analysis was performed with only men, the results were not different (data were not shown). However, further studies with

a population including more females are needed. Fourth, we did not consider socioeconomic or educational status. However, socioeconomic and educational disparities in Japan are not as large as those in other countries. In addition, the national health insurance system allows anyone in Japan to access any hospital, including university hospitals. Fifth, comorbidities were not included in the variables. Comorbidities can be considered as possible confounders for CPAP adherence. Sixth, the mean ESS score in our study population was 8.6. Thus, we could not fully elucidate the effect of sleepiness on our results. Finally, this was a retrospective observational study; thus, causality between clusters and CPAP adherence could not be proven. A prospective validation study using this clustering is needed to address this.

In this study, we used an unbiased approach to reveal hidden connections using patient characteristics and PSG parameters to successfully identify patients more or less likely to adhere to CPAP for 90 days and found this continued for up to 365 days. In addition, this real-time approach can be optimized to compare or design other interventions for sleep apnea treatment.

Author Contributions:

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MY: Conceptualization (equal), Data curation (lead), Formal analysis (equal), Investigation (equal), Methodology (lead), Resources (supporting), Supervision, Validation (equal), Writing-review & editing (lead)

YF: Conceptualization (supporting), Data curation (lead), Investigation (equal), Resources (supporting), Validation (equal), Writing-review & editing (supporting)

TN: Data curation (equal), Investigation (equal), Methodology (supporting), Resources (equal), Validation (equal), Writing-review & editing (supporting)

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KPS: Conceptualization (supporting), Methodology (supporting), Resources (equal), Validation (equal), Writing-review & editing (lead)

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