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Sleep-disordered breathing and markers of morbidity in children and adolescents with cystic fibrosis

Roberta Ribeiro Batista Barbosa PhD[1] | Fernanda Mayrink Gonçalves Liberato PhD[2] | Pitiguara de Freitas Coelho PhD[1] | Pâmela dos Reis Vidal PT[1] | Roberta Barcellos Couto Olimpio de Carvalho MD[3] | Márcio Vinícius Fagundes Donadio PhD[4]

[1]Department of Physiotherapy, Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Vitória, Espírito Santo, Brazil

[2]Cystic Fibrosis Reference Center, Hospital Infantil Nossa Senhora da Glória, Vitória, Espírito Santo, Brazil

[3]Medsono Sleep Medicine and Pulmonology, Vitória, Espírito Santo, Brazil

[4]Laboratory of Pediatric Physical Activity, Centro Infant, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil

Correspondence
Roberta Ribeiro Batista Barbosa, Department of Physiotherapy, Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, 2190, Nossa Senhora da Penha Avenue, Vitória, Espírito Santo 29027-502, Brazil.
Email: robertaribeirob@hotmail.com

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Abstract

Background: Studies have shown that sleep disorders occur in cystic fibrosis (CF) patients and may be present before daytime clinical manifestations.

Objectives: To evaluate the presence of sleep disorders among children and adolescents with CF, attempting to identify associations with pulmonary function, nutritional status, days in hospital, and days taking antibiotics.

Methods: Individuals with a diagnosis of CF aged between 6 and 18 years were included. Information on sociodemographic, clinical profile, history of hospitalizations, and use of antibiotics in the last year were collected. Spirometry, bioimpedance, and polysomnography were performed. The presence of nocturnal hypoxemia and obstructive sleep apnea syndrome (OSAS) were evaluated and participants divided according to their presence.

Results: Thirty-one patients were included. The prevalence of OSAS was 32.3% and nocturnal hypoxemia was 29.0%. Average nocturnal peripheral oxyhemoglobin saturation (SpO_2) correlated ($P < .001$) with forced vital capacity ($r = .55$) and forced expiratory volume in the first second ($r = .62$). The higher the percentage of total sleep time (TST) with SpO_2 less than 90%, the lower the pulmonary function. Individuals with OSAS and nocturnal hypoxemia had lower spirometric values compared to patients without these disorders, but the nocturnal hypoxemia group also had lower Shwachman-Kulczycki score, longer hospitalization time and antibiotic use. TST with SpO_2 less than 90% was associated with length of hospitalization ($r^2 = .53$).

Conclusion: Children and adolescents with CF have sleep disorders, including OSAS (32.3%) and nocturnal hypoxemia (29%). Individuals with nocturnal hypoxemia presented lower lung function, worse clinical score, and higher morbidity. TST with SpO_2 less than 90% was associated with length of hospitalization.

KEYWORDS

cystic fibrosis, hospitalization, nocturnal hypoxemia, obstructive sleep apnea syndrome

1 | INTRODUCTION

Sleep disorders have a significant negative impact on mood, behavior, academic performance, and cognitive function in childhood.[1] Poor sleep increases susceptibility to infections and is associated with elevated serum levels of inflammatory markers.[2] In people with cystic fibrosis (CF) hypoxemia during sleep is common and drops in peripheral oxyhemoglobin saturation (SpO_2) primarily occur during rapid eye movement sleep (REM), because of the reduced activity of intercostal muscles, irregular respiratory pattern, and hypoventilation caused by falling minute ventilation.[3,4] Additionally, patients with CF often have chronic infections and nasal polyps, which can contribute to airway obstruction, provoking the development of obstructive sleep apnea syndrome (OSAS).[5]

Poor quality sleep, caused by increasing intermittent collapse of the upper airways, contributes to the deterioration of pulmonary function.[6] Borriello et al[7] have also suggested that hypoxemia can exacerbate pulmonary inflammation and affect the bacterial profile in the lungs of these patients. Evidence in the literature suggest that severe episodes of oxyhemoglobin desaturation occur during sleep in adolescents and adults with CF and that brief episodes of desaturation can increase pressure in the pulmonary artery, demonstrating that hypoxemia can be a stimulus in breaking the normal sleep pattern and degrading the quality of life in these patients, playing an important role in the pathogenesis of pulmonary damage and development of *cor pulmonale*.[4,8,9]

While sleep-disordered breathing is more relevant in children than in adults, since they have a longer duration of REM sleep,[10] data on the sleep of CF children and adolescents, as well as individuals with mild lung disease are limited.[11-13] In the majority of studies and in clinical practice, sleep analysis using polysomnography is usually conducted at more advanced stages of the disease, when the pulmonary function is already compromised, which may imply that sleep-disordered breathing is being detected late and that the consequences are already in course, worsening prognosis.[9]

Therefore, considering that the main cause of morbidity and mortality in individuals with CF is the result of respiratory disorders and that there is evidence of sleep-disordered breathing in this population,[12,14] the objective of this study is to evaluate the presence of sleeping disorders among children and adolescents with CF, attempting to identify associations with pulmonary function, nutritional status, days in hospital, and days taking antibiotics. Improved understanding of the relationships between these variables and early detection of sleep disorders could contribute to better prevention and treatment for individuals with CF.

2 | MATERIALS AND METHODS

This is a cross-sectional observational study with nonhospitalized CF patients aged from 6 to 18 years being treated at a referral center. Sample size was calculated using data from a study by Veronezi et al,[15] taking the rate of apnea and hypopnea as reference variable. Considering a standard deviation of 2.0, 95% power, significance of 5%, and a minimum correlation between variables of 0.5, the sample size was estimated at 30 participants. The study enrolled children and adolescents with a clinical diagnosis of CF confirmed by the sweat test or genetic testing, in stable clinical conditions, and with preserved cognitive function. The exclusion criteria were the presence of intercurrent conditions during the preceding 30 days, use of oxygen therapy, and individuals who exhibited comprehension difficulties or were unable to complete the tests. The study complies with ethical criteria for research with human beings and was approved by the Research Ethics Committee under protocol number 2.459.354.

2.1 | Study design

Children and adolescents were selected according to the inclusion criteria from a database maintained by the referral clinic and those who agreed to take part were scheduled for inclusion on the same day as their routine consultation.

The experimental protocol was conducted on 2 consecutive days. First, a free and informed consent form and a free and informed assent form were provided, read, and signed. Next, information was collected on the participant's sociodemographic and clinical profile, including age, date of diagnosis, type of mutation, chronic colonization of airways by *Pseudomonas aeruginosa*, Shwachman-Kulczycki (SK) score, number of days in hospital, and days on antibiotics in the previous year. Next, a pulmonary function assessment was performed by spirometry, and a nutritional status assessment, with bioimpedence. On the same day, in the evening, participants were referred to a specialist sleep study clinic for preparation for overnight polysomnography. At the clinic, polysomnography equipment was fitted and the participant and their guardian were given instructions about the test and then went home with the equipment. On the following day, at 8 AM, the participant returned to the clinic for removal of the equipment, validation of the test, and download of the data. Chronic colonization by *P. aeruginosa* was defined as the persistent presence of this bacteria in samples collected by oropharynx swab or in sputum samples over the preceding 6 months or in three consecutive samples.[16]

2.2 | Procedures

2.2.1 | Pulmonary function

Spirometry was performed using a duly calibrated KoKo spirometer (nSpire Health, Inc., Circle Longmont, CO). All participants were instructed to perform one expiration, followed by one inspiration, slowly and deeply, and then, with verbal encouragement, performed a maximum forced expiration. At least three maneuvers were performed, considered acceptable when the curves and their respective values were reproducible with differences of less than 5% or 150 mL between them, in accordance with American Thoracic Society

criteria.[17] The variables studied were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), forced expiratory flow from 25% to 75% of FVC ($FEF_{25\%-75\%}$), and the FEV_1/FVC ratio. The international reference equation was used to calculated predicted values (The Global Lung Initiative, 2012).[18]

2.2.2 | Nutritional status

Bioelectrical impedance analysis was conducted with an Inbody 720 system (InBody Co., Los Angeles, CA), using a direct segmental multi-frequency measurement method, with an 8-point tactile electrode system, two for each foot, and two for each hand, at the frequencies 1, 5, 50, 250, 500, and 1000 kHz. Before taking this test, participants and/or their guardians were instructed to follow certain recommendations, including absolute fasting for 12 hours, no strenuous physical exercises during the previous 24 hours, no consumption of drinks containing caffeine for 24 hours beforehand, no diuretics within the 7 days preceding the test. Data were obtained on weight, skeletal muscle mass, fat mass, body fat percentage, and body mass index (BMI). The BMI *z*-score was calculated and values less than or equal to 2 were defined as indicative of malnutrition.

2.2.3 | Polysomnography

Baseline nocturnal polysomnography is the gold standard examination for assessing sleep disorders. All participants underwent type II baseline nocturnal polysomnography, conducted at home, using an Alice PDx portable sleep diagnostic system (Philips Respironics, Murrysville, PA). Setup and preparation for the examination were performed from 19 to 21 hours at a specialist sleep laboratory, according to American Academy of Sleep Medicine criteria.[19] All of the transducers were calibrated and all channels tested and then the participant was discharged to sleep at home, with instructions on how to start the test. The examination was completed the next morning, attempting to achieve a mean duration of 8 hours of recordings, and the equipment was removed at the same laboratory.

The polysomnography traces were read manually by a specialist professional trained in pediatric sleep medicine. The stages of sleep were analyzed every 30 seconds, or 1 epoch, using the standard criteria, and respiratory parameters were analyzed at 120 second intervals (four epochs), because of the slower occurrence of respiratory events. For each epoch, the following were analyzed: phases of sleep, number of apneas and hypopneas, arousals according to the electroencephalogram, and oxyhemoglobin desaturation. Respiratory events were analyzed using the amplitude of airflow provided by the nasal sensor signal, signals from the chest and abdominal effort belts, and the SpO_2 graph, enabling detection of sleep-disordered breathing.

According to the American Academy of Sleep Medicine's 2017 Manual for Scoring of Sleep and Associated Events,[19] obstructive apnea is defined as when there is a greater than 90% reduction in the flow detected by the oronasal thermal flow sensor or alternative apnea flow sensor; for at least two respiratory cycles and with continued respiratory effort throughout the period. Hypopneas are defined as a greater than 30% drop at the nasal flow pressure sensor transducer or alternative apnea flow sensor, lasting more than two respiratory cycles, and with a fall of more than 3% in oxyhemoglobin saturation and/or arousal, and are considered obstructive when combined with at least one of the following attributes: snoring, paradoxical thoracoabdominal movement, or flattening of the nasal transducer flow curve.[19] The apnea and hypopnea index (AHI) was defined as the number of apneas/hypopneas per hour of sleep. The OSAS was defined as an obstructive AHI (OAHI) greater than or equal to 2 per hour.[20] Nocturnal hypoxemia was defined as present when SpO_2 was less than 90% for 5% or more of total time asleep.[14,21]

2.3 | Statistical analysis

The normality of data was assessed with the Kolmogorov-Smirnov test. Continuous data with normal distribution were expressed as mean and standard deviation, while asymmetrical data were expressed as median and interquartile range. Categorical variables were expressed as absolute and relative frequencies. Spearman's coefficients were calculated to test for correlations between polysomnography variables and clinical variables. Clinical variables were compared between groups with and without OSAS and between groups with and without nocturnal hypoxemia using Student's *t* test for independent variables for those with normal distribution and the Mann-Whitney test for nonparametric variables. The Pearson χ^2 test was also used to test for associations. A multivariate linear regression model (forward stepwise) was constructed to detect associations between the variables age, sex, chronic colonization, BMI, FVC, FEV_1, OSAS, % of total time asleep at SpO_2 less than 90%, and mean nocturnal saturation and the variables time spent in hospital and use of antibiotics. All analyses and data processing were performed using SPSS 25.0. The significance level was set at 5% ($P < .05$).

3 | RESULTS

A total of 57 patients being seen at the referral center were invited to participate. Twenty did not agree to take part because of transport difficulties, one was excluded because of dependence on oxygen therapy, four had exacerbation episodes or were in the hospital on the assessment day, and one did not complete the polysomnography test. The flow diagram of study selection is presented in Figure 1. Therefore, the sample comprised a total of 31 patients with a median of age of 9.6 years, 64.5% females and 45.2% heterozygotes for the F508del mutation. Mean FEV_1 (%) was 68.1 ± 24, and 18 patients (58%) had values below 80% of predicted. As to nutritional status, mean BMI was 16.6 ± 2.6 kg/m^2 and 6 (19.4%) participants exhibited

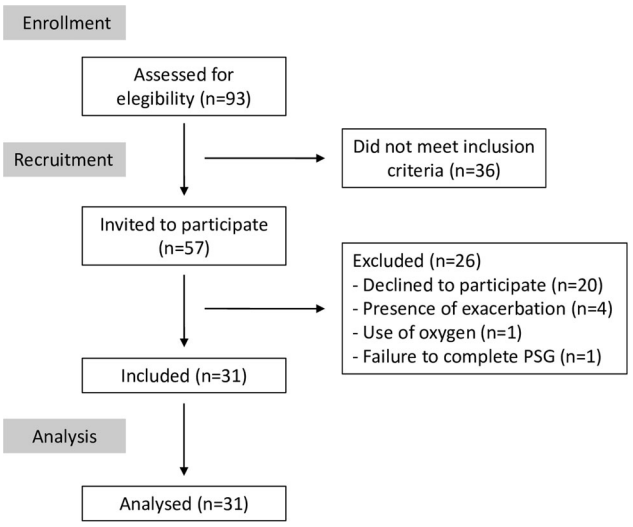

FIGURE 1 Flow diagram of study selection

TABLE 1 Demographic, clinical and pulmonary function variables

Variables evaluated	n = 31
Age[a]	9.6 (7.9–15.1)
Male, n (%)	11 (35.5)
Anthropometry	
Height, cm	139.2 ± 16.6
Weight, kg	33.3 ± 12.2
BMI, kg/m^2	16.6 ± 2.6
BMI (z-score)[a]	−0.4 (−1.7–0.1)
Skeletal muscle mass[a]	11.9 (8.8– 9.4)
Fat mass[a]	5.3 (3.3–10.3)
Body fat percentage[a]	20.1 (12.1–27.2)
Malnutrition, n (%)	6 (19.4)
Genotype	
F508del homozygous, n (%)	7 (22.6)
F508del heterozygote, n (%)	14 (45.2)
Other mutations, n (%)	10 (32.3)
Age at diagnosis (months)[a]	6.0 (2.0–32.0)
Chronic colonization	
Pseudomonas aeruginosa, n (%)	10 (32.3)
Nasal polyposis, n (%)	10 (32.3)
SK score[a]	90.0 (75.0–95.0)
Hospitalization (days in the last year)	5.8 ± 14.1
Antibiotic use (days in the last year)	33.0 ± 28.0
Pulmonary function	
FEV_1, %	68.1 ± 24.4
FVC, %	77.8 ± 21.4
$FEF_{25\%-75\%}$, %	53.8 ± 29.4
FEV_1/FVC	0.8 ± 0.1

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of FVC; SK, Shwachman-Kulczycki.
[a]Median and 25-75 interquartile range.

a reduction (<−2) in *z*-score. Table 1 lists demographic, anthropometric, and clinical characteristics for the sample studied.

The sleep study revealed reduced sleep efficiency, an increased number of arousals, comprising increased time awake after sleeping and a high rate of arousal. The sample studied exhibited sleep-disordered breathing with a median index of 2.6 per hour. The majority of the respiratory events were obstructive hypopnea. The median OAHI during sleep was 1.3 per hour, and the OSAS was present (OAHI ≥ 2/h) in 10 patients (32.3%). Mean SpO_2 during sleep was 95% and nine participants (29%) exhibited nocturnal hypoxemia, that is, SpO_2 less than 90% for more than 5% of the total time asleep (Table 2). No reductions of SpO_2 at rest were found during daylight. Although nasal polyposis was found in 32.3% of patients, no associations with OSAS ($P = .57$) and nocturnal hypoxemia ($P = .37$) were identified.

Table 3 lists the correlations found between the main clinical and polysomnographic variables. In relation to pulmonary function (%), the number of obstructive hypopnea episodes correlated with $FEF_{25\%-75\%}$ ($r = -.40$) and the OAHI was correlated with FEV_1 and $FEF_{25\%-75\%}$ ($r = -.36$ and $r = -.43$, respectively). Mean nocturnal SpO_2 was correlated with FVC ($r = .55$), FEV_1 ($r = .62$), and $FEF_{25\%-75\%}$

TABLE 2 Main polysomnographic variables

Variables evaluated	n = 31
Sleep latency, min	104.6 ± 59.8
REM sleep latency, min	167.2 ± 70.1
TST, min	449.5 ± 68.1
Sleep efficiency, %	67.0 ± 12.1
NREM stages, %TST	
Stage 1[a]	4.2 (2.8–6.0)
Stage 2	45.5 ± 10.7
Stage 3	27.7 ± 7.9
REM sleep, %TST	20.9 ± 6.3
WASO, min[a]	123.0 (98.3–149.3)
Arousal, n[a]	69.0 (49.0–89.0)
Arousal index, events/h[a]	8.8 (6.7–11.2)
Respiratory events, n[a]	20.0 (14.0–33.0)
Obstructive apnea, n[a]	0.0 (0.0–1.0)
Obstructive jypopnea, n[a]	9.0 (6.0–17.0)
Respiratory events index, n/h[a]	2.6 (1.9–4.4)
AHI/h[a]	2.1 (1.3–3.9)
OAHI/h[a]	1.3 (1.0–2.2)
Mean sleep SpO_2, %[a]	95.0 (94.0–97.0)
Minimum sleep SpO_2, %[a]	88.5 (83.0–91.0)
REM sleep desaturation index, n/h[a]	3.5 (1.1–7.0)
NREM sleep desaturation index, n/h[a]	1.6 (0.6–3.0)
SpO_2 < 90%, % of TST[a]	0.3 (0.1–5.6)

Abbreviations: AHI, apnea hypopnea index; NREM, non-rapid eye movement; OAHI, obstructive apnea hypopnea index; REM, rapid eye movement; SpO_2, peripheral oxyhemoglobin saturation; TST, total sleep time; WASO, wake after sleep onset.
[a]Median and 25-75 interquartile range.

TABLE 3 Correlations between clinical and sleep disorder variables

Clinical variables	Respiratory events (n)	Obstructive hypopnea (n)	AHI/h	OAHI/h	Mean SpO_2 (%)	SpO_2 < 90% (%TST)
FVC, %						
r	−.03	−.24	−.18	−.32	.55	−.55
P	.883	.187	.348	.079	.001[a]	.001[a]
FEV_1, %						
r	−.01	−.27	−.12	−.36	.62	−.55
P	.976	.138	.514	.048[a]	.000[a]	.001[a]
$FEF_{25\%-75\%}$, %						
r	−.03	−.40	−.16	−.43	.66	−.51
P	.855	.026[a]	.389	.015[a]	.000[a]	.004[a]
BMI, kg/m^2						
r	−.42	−.27	−.41	−.30	.08	−.34
P	.018[a]	.150	.023[a]	.105	.690	.058
BMI (z-score)						
r	−.02	−.02	−.08	−.03	.39	.01
P	.906	.908	.678	.857	.031[a]	.958
Hospitalization (days in the last year)						
r	.03	.31	.19	.28	−.50	.47
P	.894	.086	.307	.129	.004[a]	.007[a]
Antibiotics use (days in the last year)						
r	.15	.17	.31	.24	−.41	.40
P	.422	.348	.085	.202	.022[a]	.028[a]

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of FVC; OAHI, obstructive apnea hypopnea index; *r*, Spearman's correlation coefficient; SpO_2, peripheral oxyhemoglobin saturation; TST, total sleep time.
[a]$P < .05$.

(*r* = .66), while total time asleep with SpO_2 less than 90% had moderate, negative, and significant correlations with all pulmonary function variables. With relation to nutritional status, the higher the BMI, the lower the number of respiratory events and OAHI (*r* = −.42 and *r* = −.41 respectively), and the higher the mean nocturnal SpO_2 (*r* = .39). Additionally, both the mean nocturnal SpO_2 (*r* = −.50 and *r* = .41) and percentage of total time asleep with SpO_2 lower than 90% (*r* = .47 and *r* = .40) were correlated with number of days in hospital and days on antibiotics (Table 3).

Comparisons between groups with and without OSAS demonstrated that presence of OSAS was associated with pulmonary function in patients with CF, since the group with OSAS had values (%) for FEV_1, FVC, and $FEF_{25\%-75\%}$ that were significantly lower than the group without OSAS (Figure 2). Furthermore, presence of nocturnal hypoxemia was associated not only with pulmonary function values (FEV_1, FVC, and $FEF_{25\%-75\%}$), but also with lower SK score, more days in the hospital, and more days on antibiotics during the previous year when patients with hypoxemia were compared with those without hypoxemia (Figure 3).

The multivariate linear regression model including demographic and clinical variables (age, sex, chronic colonization, BMI, FVC, FEV_1, OSAS, % total time asleep with SpO_2 less than 90%, and mean nocturnal SpO_2) showed that mean nocturnal SpO_2 was associated with time taking antibiotics (r^2 = .22), while the percentage of total time asleep with SpO_2 less than 90% was associated with time in hospital (r^2 = .53). These data are shown in Table 4.

4 | DISCUSSION

The results of this study demonstrate that children and adolescents with CF have reduced sleep efficiency and frequent arousals and that the most common respiratory sleep disorders were obstructive hypopnea and nocturnal hypoxemia. Additionally, the presence of sleep disorders was associated with pulmonary function parameters and morbidity.

The precise origin of sleep disorders in children and adolescents with CF is not fully understood. However, one of the main hypothesis is the presence of upper airway obstruction caused by chronic rhinosinusitis and nasal polyposis, frequently found in this population,[22] although our results have shown no association of nasal polyposis with OSAS and nocturnal hypoxemia. Another possible pathophysiology for the occurrence of OSAS in CF is that patients with frequent cough have lesions of the upper airways with epithelial damage and inflammation with neutrophil infiltration, resulting in an increase in the soft tissues surrounding the oropharynx, decreasing the caliber

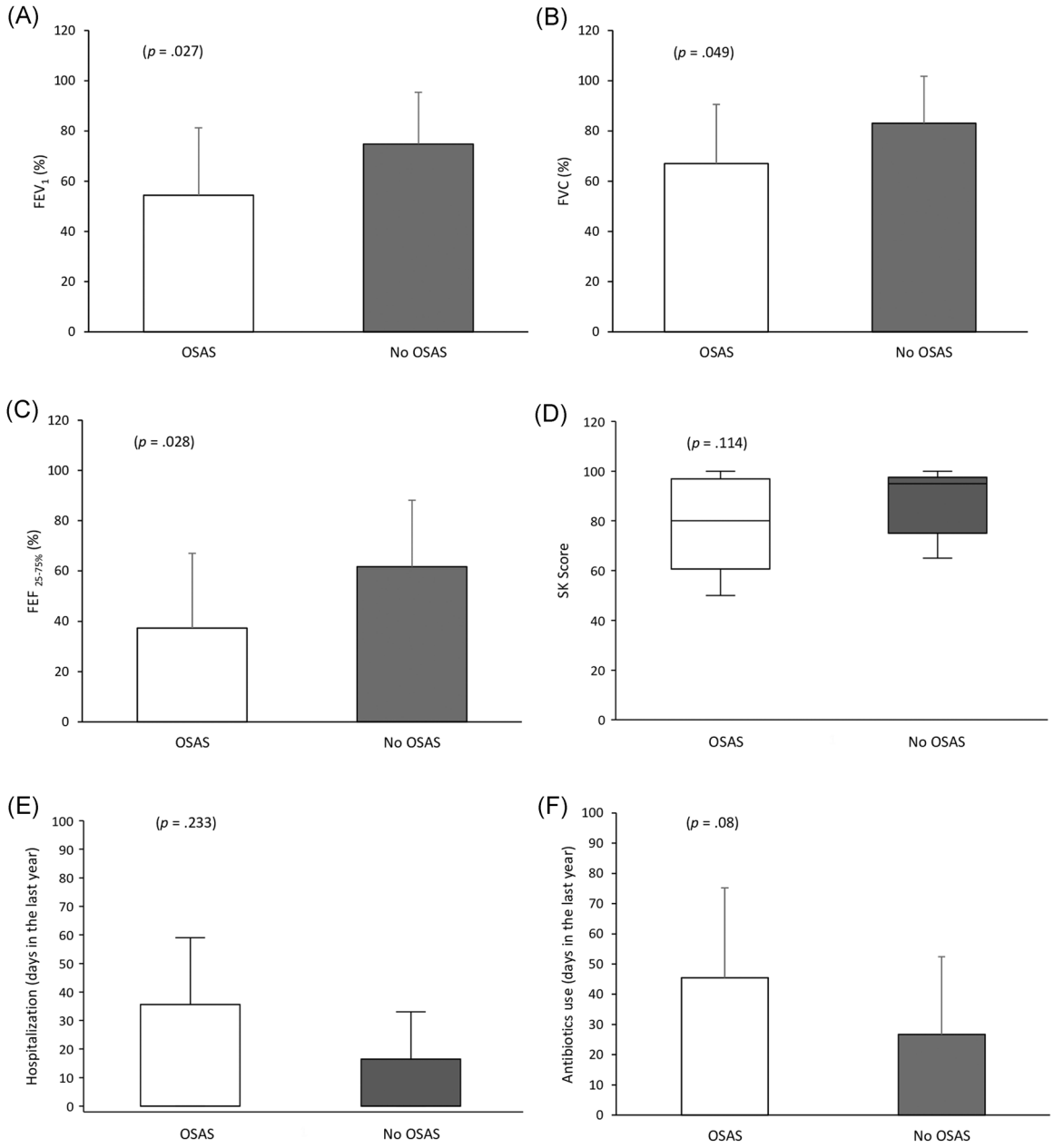

FIGURE 2 Comparison of clinical variables according to the presence of obstructive sleep apnea syndrome (OSAS). A, forced expiratory volume in 1 second (FEV_1); (B) forced vital capacity (FVC); (C), forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$); (D) Shwachman-Kulczycki score (SK); (E) hospitalization; (F) antibiotic use. Graphs in (A), (B), (C), and (F) are presented as mean and standard deviation and data were compared using Student's *t* test. In graphs (D) and (E), variables are expressed in box-plots (median, interquartile range, minimum, and maximum) and the Mann-Whitney test was used

of the airways.[23] It is possible that the occurrence of hypopneas and nocturnal hypoxemia in the present study may result from a combination of several factors, including lung function impairment, upper airway alterations, and nutritional status. Impairment of lung function may facilitate the occurrence of nocturnal hypoxemia, although, as an isolated factor, it does not explain the alterations in total. In our results, 58% of patients presented impaired lung function, but only 29% showed nocturnal hypoxemia. In addition, none of the patients included presented resting daylight SpO_2 reductions.

Studies demonstrate that patients with CF have reduced sleep efficiency, greater number of nighttime arousals and shorter duration of REM sleep, compromising the quality of their sleep,[24] and with the potential to cause behavioral problems, such as attention, concentration, and learning deficits.[25-27] The OSAS is common among children and adolescents, although its epidemiology is not clearly defined because of methodological limitations related to the different diagnostic criteria adopted in different studies and the low number of population-based studies.[28] In pediatrics, the definition of OSAS is

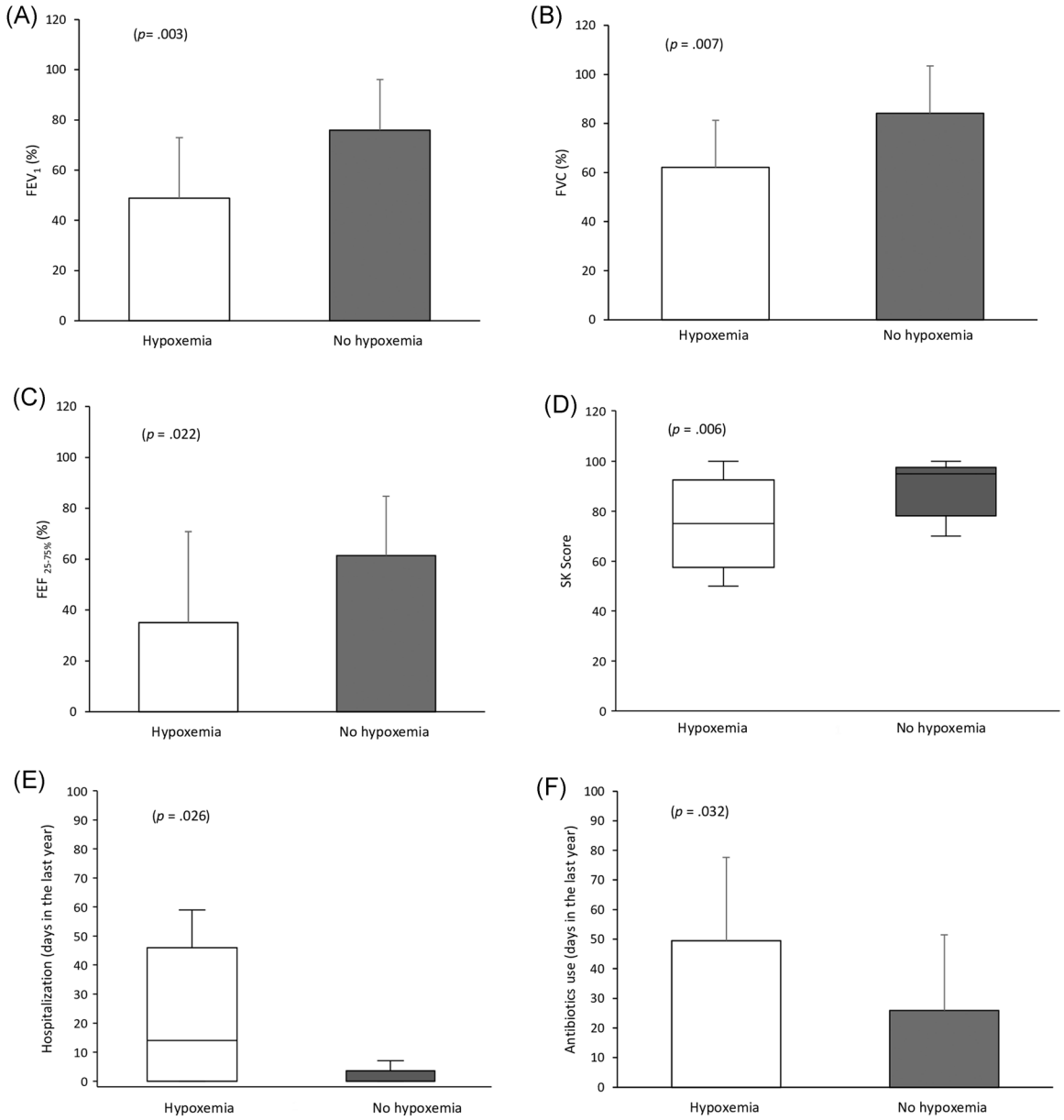

FIGURE 3 Comparison of clinical variables according to the presence of nocturnal hypoxemia. A, Forced expiratory volume in 1 second (FEV_1); (B) forced vital capacity (FVC); (C) forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$); (D) Shwachman-Kulczycki score (SK); (E) hospitalization; (F) antibiotic use. Graphs in (A), (B), (C), and (F) are presented as mean and standard deviation and data were compared using Student's *t* test. In graphs (D) and (E), variables are expressed in box-plots (median, interquartile range, minimum, and maximum) and the Mann-Whitney test was used

highly controversial, and can variously be considered to be an AHI greater than or equal to 1 per hour,[14] or OAHI greater than or equal to 1 per hour[15,29] or OAHI greater than or equal to 2 per hour,[20] and an obstructive apnea index (OAI) greater than or equal to 1 per hour.[20,30] Studies demonstrate an estimated prevalence of OSAS among healthy children and adolescents of 1.2% to 5.7%.[1,31] However, when individuals with CF from the same age group were evaluated, studies have shown a much higher prevalence of OSAS, reaching more than 50% of the individual.[14,30] In our study, the prevalence of OSAS was 32.3%, which is in accordance with the literature.

The OSAS can cause disorders of ventilation and gaseous exchange in patients with CF, which can be aggravated by the presence of advanced lung disease. Despite this, OSAS does not appear to be considered an important cause of sleep disorders or even an integral part of the etiology of the nocturnal hypoxemia frequently observed in these patients. There are few correlations between OSAS and clinical variables in the literature. Veronezi et al[15] only observed

TABLE 4 Regression analysis to assess the influence of sleeping disturbances on hospitalization and antibiotic use

			95% CI			
	β	*SE*	Minimum	Maximum	*P*	R^2 adjusted
Hospitalization (days in the last year)						
Constant	1.17	1.90	−2.72	5.05	0.544	0.534
SpO_2 < 90% (%TST)	.56	0.09	0.37	0.75	0.000	
Antibiotics use (days in the last year)						
Constant	529.98	160.28	202.18	857.78	0.003	0.223
Nocturnal mean SpO_2 (%)	−5.25	1.69	−8.72	−1.79	0.004	

Abbreviations: CI, confidence interval; R^2, coefficient of determination; *SE*, standard error; SpO_2, peripheral oxyhemoglobin saturation; TST, total sleep time.

correlations between OSAS and BMI and age and, in common with other studies,[30,32] did not detect a significant correlation between OSAS and pulmonary function. However, in the present study, percent FEV_1 and FVC values were significantly lower in the group of patients with OSAS than in patients who did not have OSAS.

In common with OSAS, the prevalence of nocturnal hypoxemia in CF is unclear, since there are divergent criteria used for this definition in the literature. A large proportion of studies use total time asleep with SpO_2 lower than 90% as the variable to determine hypoxemia. However, the value of total time asleep used can vary, and greater than 5 minutes,[29] greater than 5%,[13,14,28] greater than 10%[33] and greater than 30%[34] have all been used. Other criteria that have been used include mean nocturnal SpO_2 lower than 95%,[12,35] an oxyhemoglobin desaturation index greater than or equal to 4 per hour,[21] and a minimum SpO_2 of 85%.[28,34] It should be pointed out that studies also disagree on the criterion for desaturation, which ranges from 3%[32] to 4%.[21,28] In the present study, we observed nocturnal hypoxemia in 29% of the children and adolescents with CF, but results in the literature for the prevalence of nocturnal hypoxemia in this population vary widely, from 6% to 57.9%.[14,21,28,33,36] On the other hand, mean SpO_2 during sleep in healthy children is around 97% and desaturation below 92% is uncommon.[37]

The results presented here indicate that nocturnal oxyhemoglobin saturation appears to have the strongest relationship with clinical pulmonary function variables, SK score, length of hospital stay, and antibiotics usage. The relationship between nocturnal oxyhemoglobin saturation and pulmonary function has been demonstrated in several studies. Frangolias et al[13] demonstrated that nocturnal desaturation is uncommon when FEV_1 is greater than 65%. Another study, by Isaiah et al,[14] found that FEV_1 less than 53% was the best predictor of nocturnal hypoxemia, which is in agreement with this study, in which we observed that total time asleep with SpO_2 less than 90% and mean SpO_2 had moderate correlations with all of the pulmonary function variables. Another easily obtained clinical variable that has a relationship with nocturnal hypoxemia is a mean SpO_2 at the rest of 93%.[13] In our study, the percent of FEV_1, FVC, $FEF_{25\%-75\%}$, as well as the SK score, number of days in the hospital, and days taking antibiotics in the previous year exhibited significant differences between patients with and without nocturnal hypoxemia. In agreement with these findings, Ramos et al[28] also observed lower values for SK score, FVC, and FEV_1 in a group of patients with CF and nocturnal hypoxemia. However, as to correlations between sleep and nutritional status, in common with Veronezi et al,[15] we observed a negative and moderate correlation between BMI and number of respiratory events and the AHI. Waters et al[36] observed a correlation between BMI and baseline nocturnal SpO_2. Although the precise causal effect underlying this association was not precisely described yet, it is possible that nutritional status may indirectly contribute to sleep disorders through lung function compromise and inflammatory status in CF patients.

It is known that sleep disorders, pulmonary exacerbations, and hospital admissions accelerate disease progression and contribute significantly to a worse prognosis. Reduced efficiency and quality of sleep has been associated with the presence of elevated serum levels of inflammatory markers[2] and the harmful effects they have on inflammation are relevant to patients with CF, since these patients have a chronic inflammatory process in the airways. Furthermore, the presence of *P. aeruginosa* in the lungs of patients with CF has been recognized as a risk factor for early mortality.[38] Studies show that this pathogen can change phenotype and potentially become more resistant to host defenses in the presence of hypoxemia.[7,39] Therefore, in an attempt to understand the influence of sleep disorders on number of days in hospital and days taking antibiotics, we constructed a linear regression model that showed that, although mean SpO_2 had a weak association with antibiotic use (r^2 = .22), percentage total time asleep with SpO_2 less than 90% was the variable with the strongest association with days in hospital in the study period (r^2 = .53). Regarding therapeutic options, the treatments most often discussed and recommended by the CF team, considering the alterations found, were the use of nocturnal oxygen therapy, optimization of drug prescription, noninvasive ventilation, and recommendation for moderate-to-vigorous physical activity practice.

Limitations of this study include the cross-sectional design, which does not allow causal relationships between the variables studied to be determined, unavailability of a capnograph for polysomnography and the absence of data on tonsil size and Mallampati score. The use of home-based polysomnography may also be subjected to error, although traces were read manually by a specialist professional trained in pediatric sleep medicine. In addition, although significance was reached, the sample size may also be considered as a limitation of the study, as well as the lack of comparisons with healthy subjects.

In conclusion, the results observed demonstrated the presence of sleep disorders in children and adolescents with CF, including OSAS (32.3%) and nocturnal hypoxemia (29%). Participants with nocturnal hypoxemia had reduced pulmonary function, worse clinical scores, and greater morbidity (hospitalizations and use of antibiotics), and the percentage of total time asleep with SpO_2 lower than 90% was associated with the total number of days in the hospital. Our findings emphasize the need to include nocturnal polysomnography in the routine assessment of these patients, to identify sleep disorders early, optimize treatment, and reduce exacerbations, thereby improving prognosis and quality of life.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Pitiguara de Freitas Coelho http://orcid.org/0000-0001-7547-5041
Márcio Vinícius Fagundes Donadio http://orcid.org/0000-0001-8836-9109

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