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Predictors of obstructive sleep apnea in patients with chronic obstructive pulmonary disease

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Abstract

Background The co-existence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) is known as overlap syndrome, and both conditions share common risk factors and are associated with co-morbidities and poor outcomes.

Methodology Sixty stable COPD patients were included in the study. We assessed body measurements, pulmonary functions to diagnose and assess COPD severity, arterial blood gases, STOB-BANG questionnaire (SBQ), Epworth sleepiness scale (ESS), and polysomnography (PSG) for diagnosis and classification of OSA severity. The aim of the study is to assess predictors of OSA among COPD patients.

Results The prevalence of overlap syndrome was 70% among studied stable COPD patients, with a male-to-female ratio of 2:1, and SBQ and ESS were statistically higher in overlap syndrome with p values < 0.001 and 0.002, respectively. Oxygen desaturation index (ODI) was 42.72 ± 30.02 for overlap in comparison to 13.18 ± 5.80 for COPD with a significant p value of < 0.001, and T90 was significantly increased in the overlap group (26.75 ± 10.37) than the COPD-only group (1.8 ± 0.98, p value ≤ 0.001). We found a direct correlation between the GOLD stage and severity of OSA in overlap syndrome. The best cutoff value for the detection of overlap syndrome was ESS = 9 (sensitivity = 88.6% and specificity = 62.5%) and SBQ = 5 (sensitivity = 63.6% and specificity = 93.8%).

Conclusion Overlap syndrome represents 70% of stable COPD patients. A direct relation was found between the GOLD stage and OSA severity in overlap syndrome. ESS and SBQ can be used for screening for OSA in COPD patients but with a lower cutoff value than those used for the general population.

Trial registration Retrospectively registered, registration number is NCT05605431, date of registration October 29, 2022.

Keywords COPD, OSA, Overlap syndrome

Background

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are common disorders, and the co-existence of both conditions is called overlap syndrome [1]. Smoking, obesity, airway resistance, and inflammation are considered risk factors for both conditions, and interestingly, both COPD and OSA are associated with increased cardiovascular complications with further increased risk in overlap syndrome [2].

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Multiple theories could explain that one disorder can predispose or exaggerate the other. For example, in COPD, cigarette smoking and inhaled steroids are linked to myopathy of upper airway dilator muscles. Moreover, in cor pulmonale redistribution of edema fluid in a supine position during sleep can also contribute to or exacerbate OSA [3, 4].

On the other hand, OSA patients might smoke frequently and more heavily to compensate for excessive daytime sleepiness and to help them lose weight, which results in exaggerated airway inflammation and exacerbates COPD [5]. The rationale of the study was to assess the prevalence and predictors of OSA among patients with stable COPD.

Methodology

The present study is an observational cross-section study that was carried out in the Chest Department, Faculty of Medicine, Cairo University, during the period from March 2020 to November 2020. The research ethical committee of Cairo University has approved the study (IRB: MS-81–2020). Based on the following equation [6], the calculated sample size is 60 patients with COPD is enough to detect 66% (± 14%) prevalence of OSA in COPD patients at a 95% level of confidence [7]. Sample size equation; $n = (Z_{1\text{-}\alpha/2}/d)^2 * p * (1\text{-}p)$, where n is the calculated sample size, $Z_{\alpha/2}$ is the critical value that the central 95% of the Z distribution from the tail (= 1.96), p is the estimated prevalence of OSA among COPD patients (about 66%), and d is the width of confidence interval as % (± 14%).

Eighty-two patients with COPD were registered to the study, 22 patients were excluded (7 patients were in exacerbation, 10 refused to do polysomnography, and 5 patients suffered from end organ failure), and 60 COPD patients were registered in the final analysis. COPD diagnosis and severity classification were based on GOLD guidelines 2020 [8]. In symptoms suggestive of sleep apnea, smoking index, history of co-morbidities, body measurements [BMI (in kg/m^2), and neck circumferences], Epworth Sleepiness Scale (ESS) is widely used as a subjective measure of a patient's sleepiness. The test is a list of eight situations in which the patient rates his tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When a patient finishes the test, the sum of the values estimates the total score which ranges from 0 to 24, and the eight situations are sitting and reading, watching TV, and sitting inactive in a public place (e.g., a theater or a meeting). As a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, and sitting quietly after lunch without alcohol. In a car, while stopped for a few minutes in traffic, interpretation of the ESS scale as follows: 0–7: It is unlikely that you are abnormally sleepy. 8–9: You have an average amount of daytime sleepiness. 10––15: You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention. 16–24: You are excessively sleepy and should consider seeking medical attention [9].

STOP-BANG questionnaire consisting of 4 self-reportable (STOP: snoring, tiredness, observed apnea, and high blood pressure) and 4 demographic (Bang: [BMI, age, neck circumference, and gender) items—interpretation scores from 0 to 2 low risk of obstructive sleep apnea, 3 to 4 intermediate risk of obstructive sleep apnea, and 5 to 8 high risk of obstructive sleep apnea [10], was evaluated in all participants. Spirometry was done using Master screen PFT 2012, CareFusion 234 GmbH, Germany (V-781267–057 version 03.00). Post-bronchodilator FEV1/FVC and FEV1% were obtained to meet the diagnosis and severity of COPD, respectively, according to GOLD guidelines 2020 [8], arterial blood gases (ABGs), polysomnography study (7 h per night) with detailed analysis, and manual scoring of the recorded data using Medicom-MTD, Model: Encephalan-EEGR-19/26) screen TM plus (cardio-respiratory screening), which is a computer-based high technology polysomnography (level 1). It included electroencephalography (EEG), electrooculography (EOG) electrodes, electromyography (EMG) electrodes for the chin and anterior tibialis muscle, nasal cannula and nasal thermistor, thoracic and abdominal belt, pulse oximetry sensor to detect arterial oxygen saturation (SpO_2), ECG electrodes, snoring microphone applied on the neck beside the larynx, and body position sensor. From the recording, the following data are obtained: apnea–hypopnea index (AHI) is the total number of apneas and hypopneas/hour of sleep, and respiratory disturbance index (RDI) is the number of apneas and hypopneas plus RERAS (respiratory effort related arousals). The oxygen desaturation index is the number of desaturation episodes/hour. Oxygen desaturation is defined as a decrease in the mean oxygen saturation of ≥ 4% that lasts for at least 10 s, $SpO_2 < 90\%$ time (T90 is the percentage of time spent with O_2 saturation below 90% from total sleep time). The snoring index is the number of snoring events per hour of sleep, and the arrhythmia index is the number of cardiac arrhythmias/sleep hour. OSA was defined based on the American Academy of Sleep Medicine Guidelines 2014 [11]. The study population was classified based on a concomitant diagnosis of OSA into two groups: the overlap group and the COPD-only group. The aim of the study is to assess predictors of OSA among COPD patients.

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp.,

Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [12]. For comparing categorical data, a chi-square (χ^2) test was performed. The exact test was used instead when the expected frequency was less than 5 [13]. Logistic regression was done to detect independent predictors of overlap syndrome [14]. *P* values less than 0.05 were considered statistically significant.

Results

The current study included 60 COPD patients, they were classified into two groups: COPD alone (18 patients) and overlap syndrome (42 patients). There was no significant difference between groups regarding age, BMI, neck circumference, pulmonary functions, and ABGs. In the overlap syndrome group, systemic hypertension was detected in (59.5%), diabetes (61.9%), tachyarrhythmia (61.9%), dyslipidemia (47.6%), and ischemic heart disease (35.7%) in comparison to the COPD-only group (38%, 50%,33%, 44%, and 22%, respectively) with no statistical difference. The male-to-female ratio in COPD patients was 1:1, while in overlap syndrome patients was 2:1. Smoking index in the overlap group was 31.93 ± 32.97 versus 13.53 ± 19.69 in COPD alone group with *p* value = 0.05. ESS and STOP-BANG questionnaires were significantly increased in the overlap group than the COPD-only group (15.67 ± 5.75 versus 9.44 ± 8.48, *p* value 0.002, and 4.80 ± 1.41 versus 3.13 ± 0.89, *p* value < 0.001. respectively). Regarding polysomnographic data, O_2 desaturation index (ODI) was 30.67 ± 26 and 3.09 ± 3.15 for overlap syndrome and COPD alone, respectively, with significant *p* value (< 0.001), and T90 was significantly increased in the overlap group (26.75 ± 10.37) than the COPD-only group (1.8 ± 0.98), *p* value = < 0.001. AHI and RDI were significantly increased in the overlap group (36.18 ± 18.65 and 37.22 ± 18.68, respectively) in comparison to the COPD-only group (2.92 ± 1.02 and 3.73 ± 2.22, respectively) with *p* value equals < 0.001. It was found that sleep latency was significantly reduced in the overlap group (5.05 ± 1.75) in comparison to the COPD-only group (13.5 ± 1.54), and the *p* value was < 0.001 (Table 1). The correlation between the degree of airway obstruction

Table 1 Comparison of both groups regarding body measurements, pulmonary functions, ABGs, and polysomnographic findings

	Overlap syndrome (*N* = 42)					COPD alone (*N* = 18)					*P* value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age (years)	56.86	10.20	60.00	25.00	76.00	52.44	10.20	51.50	37.00	74.00	0.067
smoking index	31.93	32.97	30.00	0.00	135.00	13.53	19.69	2.50	0.00	70.00	**0.05**
BMI (kg/m$^{2)}$	42.81	11.31	39.60	29.00	73.50	39.12	11.03	37.25	23.00	64.40	0.256
Neck (cm) circumference	46.47	8.43	44.00	35.00	70.00	42.88	4.98	42.50	33.00	52.00	0.209
FEV1%	45.88	15.56	46.00	16.00	79.00	44.50	17.93	49.00	16.00	68.00	0.927
FVC %	58.70	16.51	61.00	30.00	105.00	52.43	16.85	53.00	30.00	86.00	0.228
FEV1/FVC %	58.92	10.35	63.00	37.10	69.30	60.11	6.87	63.00	48.39	69.00	0.770
ESS	15.67	5.75	16.50	6.00	24.00	9.44	8.48	6.00	1.00	29.00	**0.002**
STOP-BANG score	4.80	1.41	5.00	2.00	8.00	3.13	0.89	3.00	2.00	5.00	**< 0.001**
Sleep efficiency	87.98	17.83	93.95	0.00	100.00	87.39	14.38	93.50	58.90	100.00	0.795
AHI[b]	36.18	18.65	30.60	10.30	83.00	2.92	1.02	3.00	1.00	4.00	< 0.001
RDI[b]	37.22	18.68	31.10	11.00	85.00	3.73	2.22	3.00	1.00	10.00	< 0.001
T90	26.75	10.37	24.00	13.00	43.00	1.83	0.98	1.50	1.00	3.00	< 0.001
ODI[b]	30.67	17.25	26.00	0.80	80.30	3.09	3.15	2.00	0.00	12.00	< 0.001
Sleep latency[a]	5.05	1.75	5.00	2.00	8.00	13.50	1.54	13.50	10.00	15.00	< 0.001
Snoring index[b]	134.38	168.11	29.50	0.00	656.00	71.19	92.96	24.50	0.00	279.00	0.407
Min SpO_2%	68.45	16.52	71.50	30.00	95.00	73.00	17.05	71.50	35.00	93.00	0.332
Mean SpO_2%	88.05	7.49	89.50	64.00	98.00	89.63	7.28	90.00	71.00	98.00	0.426
Wake after sleep	32.37	84.96	5.70	0.00	545.00	24.62	36.97	11.40	1.00	151.00	0.558
Tachycardia[b]	8.58	15.81	1.15	0.00	64.00	8.36	12.99	3.05	0.00	40.00	0.609
Asystole[b]	0.19	0.93	0.00	0.00	6.00	0.37	1.50	0.00	0.00	6.00	0.969
Bradycardia[b]	7.30	17.94	0.00	0.00	77.00	6.25	14.75	0.00	0.00	48.60	0.881

[a] Sleep latency in minutes

[b] Events/hour of sleep

Table 2 Correlation of degree of airway obstruction (GOLD stage) and severity of OSA in overlap syndrome

OSA severity	GOLD stage	Overlap group, $n=42$	*P* value
Mild OSA (AHI 5–15/h)	**Stage 2** FEV1 (50–79%)	3 (42.8%)	**< 0.001**
	Stage 3 FEV1 (30–49%**)**	2 (28.5%)	
	Stage 4 FEV1 (< 30%)	2 (28.5%)	
Moderate OSA (AHI 15–30/h)	**Stage 2** FEV1 (50–79%)	4 (28.5%)	**0.040**
	Stage 3 FEV1 (30–49%**)**	8 (57.3%)	
	Stage 4 FEV1 (< 30%)	2 (14.3%)	
Severe OSA (AHI > 30/h)	**Stage 2** FEV1 (50–79%)	6 (27.27%)	**0.004**
	Stage 3 FEV1 (30–49%**)**	8 (40.9%)	
	Stage 4 FEV1 (< 30%)	7 (31.8%)	

FEV1 Forced expiratory volume in the 1st second, *AHI* Apnea hypopnea index, *OSA* Obstructive sleep apnea

Table 3 Predictors of OSA among COPD patients

	Area under the curve	*P* value	95% confidence interval				
			Lower bound	Upper bound	Cutoff	Sensitivity %	Specificity %
ESS	.759	**0.002**	.597	.920	**9**	88.6	62.5
STOP-BANG	.828	**< 0.001**	.724	.932	**4**	63.6	93.8

ESS Epworth sleepiness scale

and severity of OSA in the overlap group revealed a high statistical difference in the mild OSA group as described in (Table 2). The best cutoff value for detection of overlap syndrome was ESS = 9 with sensitivity = 88.6% and specificity = 62.5% with area under curve = 75.9% (95% CI 59.7 to 92%). The best cutoff value for detection of overlap syndrome using STOP-BANG questionnaire = 4 with sensitivity = 63.6% and specificity = 93.8% with area under curve = 82.8% (95% CI 72.4 to 93.2%) (Table 3).

The significant independent predictors of overlap syndrome are ESS with OR = 1.168 (95% CI 1.018 to 1.341) and STOP-BANG with OR = 2.609 (95% CI 1.278 to 5.324) Table (4).

Discussion

The overlap of both OSA and COPD is associated with common factors affecting the pathophysiology of each disease and its outcome. The current study included 60 stable COPD patients to assess predicting factors of OSA co-existence, and 42 patients (70%) were diagnosed with overlap syndrome.

Table 4 Multivariate logistic regression to detect independent predictors of overlap syndrome

		P value	OR	95% C.I	
				Lower	Upper
Overlap syndrome	**Age**	.689	.984	.907	1.067
	Smoking index	.291	1.019	.984	1.054
	BMI	.318	1.057	.948	1.177
	Neck circumference	.552	1.046	.902	1.213
	FEV1%	.086	1.065	.991	1.144
	FEV1/FVC %	.368	.949	.848	1.063
	PaO_2	.950	1.002	.946	1.061
	SaO_2	.633	1.029	.915	1.157
	ESS	**0.027**	1.168	1.018	1.341
	STOP-BANG	**0.008**	2.609	1.278	5.324

BMI Body mass index, PaO_2 Partial pressure of oxygen in arterial blood gases, SaO_2 Oxygen saturation in arterial blood gases

The prevalence of OSA among COPD patients was variable in previous studies, and it ranges from 35 to 77% [15–18], with one meta-analysis done by Shawon and his colleagues, reporting OSA prevalence in COPD patients between 2.9 and 65.9%. The difference in the prevalence of OSA among COPD patients may be attributed to differences in the methodology, diagnostic, and demographic criteria [19].

In our study, the mean age of overlap syndrome patients was 56.86 ± 10.20 years and in COPD patients was 52.44 ± 10.20 years with no significant difference, which is consistent with the findings of another study which was conducted on 90 COPD participants. They found that the majority of their overlap syndrome patients were under 60 years (54%) and 12% between 61 and 65 years [20].

We found that overlap syndrome was more prevalent in males (male-to-female ratio 2:1) which is consistent with the finding of one study that showed 62% of overlap syndrome patients were males [21], and in another study, 85.5% of overlap syndrome patients were men [20].

In contrast, another study revealed that the prevalence of overlap syndrome was higher in women, and this could be explained that women in their study were post-menopausal and the gender difference disappears after women go through menopause [22, 23].

The smoking index in the overlap group was 31.93 ± 32.97 versus 13.53 ± 19.69 in the COPD alone group with p value = 0.05. Smoking has an aggravated effect on the risk of development of OSA in COPD patients as smoking can lead to inflammation of the upper airway which in turn could lead to swelling and narrowing and thus increasing the tendency to airway closure [24].

The risk factors for the coexistence of OSA such as age, gender, and smoking may not provide clinical relevance in determining the probability of OSA, especially that in advanced COPD, they may have different predictors from the general population [21].

In the current work, the mean BMI of overlap syndrome patients was 42.81 ± 11.31 kg/m^2 and that of COPD patients was 39.12 ± 11.03 kg/m^2 with no significant difference between COPD and overlap syndrome patients. This goes with another study, where they found no significant difference in BMI between COPD and overlap syndrome groups [25]. However, in a study done by Gunduz et al., BMI was significantly higher in the overlap syndrome group compared to the COPD group [26].

The findings that there was no significant difference in BMI between overlap syndrome and COPD patients in our research might be explained by the fact that we did not perform additional measures of central adiposity, which may be increased among OSA patients in the setting of a normal or high BMI. It is well known that low body weight is common in COPD patients, but previous data suggested that about 65% of COPD patients might be overweight or obese and that low BMI in advanced COPD carries a poor prognosis [27].

We found no significant difference in neck circumference between COPD and overlap syndrome participants, and it was 42.88 ± 4.98 cm and 46.47 ± 8.43, respectively.

This matches the findings of another study performed on 54 COPD patients where PSG was done to screen for OSA, and the mean neck circumferences were 40.7 cm and 35.1 cm for males and females, respectively, showing that OSA is common in patients with advanced COPD even among those with small neck circumference. The use of corticosteroids in COPD patients is responsible for increased fat deposition in the neck leading to increased OSA risk and may produce changes in airway collapsibility and ventilatory control that overcomes neck size [21].

Our study showed that the most common co-morbidities in overlap syndrome patients were diabetes type 2 and tachyarrhythmia (61.9%) for each of them followed by systemic hypertension (59.5%), hyperlipidemia (47.6%), and ischemic heart disease (35.7%).

Our results matched another study which had demonstrated that overlap syndrome patients suffered from multiple co-morbidities compared to COPD patients and matched for sex, age, and BMI. The most common conditions were diabetes, followed by hypertension, tachyarrhythmia, and dyslipidemia. However, the difference between the type and percent of co-morbidities did not reach a statistically significant level [28].

Asystole (no electrical heart activity and my last 2–6 s) is one of the bradyarrhythmias that may occur in up to 18% of OSA patients even in the absence of cardiac diseases was also reported in literature [29].

Papachatzakis and co-authors concluded that COPD and OSA share common risk factors and pathophysiological mechanisms, and both conditions had systemic inflammatory state, oxidative stress, and endothelial dysfunction which contribute to the development of co-morbidities [28].

We did not find a significant difference between both groups regarding pulmonary functions and ABGs. Similarly, previous studies found no difference between both groups regarding ABGs, and they concluded that ABGs cannot be used to predict OSA in COPD patients [30]. Also, many studies found no significant difference in pulmonary function tests between COPD and overlap syndrome groups [7, 31, 32].

As expected, we found higher RDI, AHI, T90, and ODI in the overlap group than in COPD alone with a significant p value < 0.001. Previous researchers showed the same findings [33, 34]. In well recognized that breathing

cessation, nocturnal hypoxemia, sleep fragmentation, and frequent arousals in OSA could activate the sympathetic system, trigger oxidative stress, and result in low-grade systemic inflammatory state. This explains the link between OSA and endothelial dysfunction and cardiometabolic risks [28].

In contrast, other studies found that ODI is not sensitive or specific for screening for OSA in COPD as it may result in underestimation of OSA, and this may be related to the use of oxygen therapy in some COPD patients making ODI non-diagnostic [30, 35].

Comparison of both groups regarding the ESS and STOP-BANG questionnaire (15.67 ± 5.75, p value 0.002 and 4.80 ± 1.41, p value < 0.001, respectively) revealed a significant increase of both scales in the overlap group as described in Table 2.

The best cutoff value for detection of overlap syndrome was ESS = 9 with sensitivity = 88.6% and specificity = 62.5% and the best cutoff value for detection of overlap syndrome using STOP-BANG questionnaire = 4 with sensitivity = 63.6% and specificity = 93.8% (Table 3). We found that the significant independent predictors of overlap syndrome are ESS and STOP-BANG (Table 4).

This goes with the findings of a previous study conducted by Schreiber et al., where they found a significant increase in ESS in overlap syndrome than COPD patients, with lower cutoff values of ESS (< 10) [30]. Another study found that an ESS cutoff value of 10 was not accurate in predicting or excluding OSA in COPD patients, which means that the usual cutoff values may be misleading and could underestimate OSA prevalence in COPD patients [36], which is matched with our findings.

Previous studies found a higher STOP-BANG questionnaire in the overlap group than in COPD patients, and they concluded that it could be used in screening for OSA in COPD patients [17, 18].

One study revealed that a STOP-BANG questionnaire ≥ 3 can predict OSA in COPD patients while a score ≥ 4 had higher possibility to predict OSA and could be used to predict disease severity [37].

When describing the relation between the severity of airway obstruction and the severity of OSA in the overlap group (as in Table 2), we found a direct correlation between the GOLD stage and severity of OSA with a statistically significant difference of p value < 0.001, 0.040, and 0.004 for mild, moderate, and severe OSA, respectively.

Many studies found a positive association between the severity of OSA and GOLD stages [7, 38, 39] which matches our findings.

On the other hand, studies found an inverse correlation between the degree of airway obstruction and severity of OSA in COPD patients, which means the more severe the obstruction the lower AHI, and they concluded that lower FEV1 could play a protective role against OSA severity [5, 40]. Severe airflow obstruction is associated with increased end-expiratory volume which prevents upper airway collapse and maintains its patency [36], which does not match our results.

However, a more recent study found a lack of relationship between the severity of airway obstruction and the severity of OSA [41].

This conflict of studies regarding the direction of the correlation of severity of both conditions may be related to the difference in the studied population, and whether different phenotypes of OSA and COPD may have a certain relationship, this hypothesis needs further research.

Limitations of the study are as follows: it is a single-center study and has a small number of patients, we did not study the effect of initiating NIV on prognosis and mortality, and we did not identify different OSA and COPD phenotypes which may show different relationships.

Conclusions

Our data revealed that 70% of COPD patients included in the study had overlap syndrome. We found a direct relationship between the GOLD stage and the severity of OSA in the overlap group. ESS and SBQ can be used for screening for OSA in COPD patients but with lower cutoff values (8.5 and 4.5, respectively) than used for the general population.

Abbreviations

COPD	Chronic obstructive pulmonary disease
OSA	Obstructive sleep apnea
SBQ	STOP-BANG questionnaire
ESS	Epworth sleepiness scale
PSG	Polysomnography
ODI	Oxygen desaturation index
T90	Percentage of cumulative time with oxygen saturation < 90% in total sleep time
AHI	Apnea–hypopnea index
RDI	Respiratory disturbance index
GOLD	Global initiative of chronic obstructive lung disease
BMI	Body mass index
PFT	Pulmonary function test
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
ABGs	Arterial blood gases
EEG	Electoencephalogram
EOG	Electrooculogram
EMG	Electromyogram
Sao2	Arterial oxygen saturation
ECG	Electrocardiogram
RERAs	Respiratory effort-related arousals
SpO2	Oxygen saturation by pulse oximetry
NIV	Non-invasive ventilaton

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Authors' contributions
1) Safy Zahid Kaddah was responsible for the conception and design, revising, and final approval of the article. 2) Yousef Mohamed Amin Soliman is responsible for the acquisition of the data, analysis, drafting of the article, and final approval of the manuscript. 3) Heba Mousa is responsible for the acquisition of the data and analysis, drafting of the article, and final approval of the manuscript. 4) Naglaa Moustafa is responsible for the acquisition of the data and analysis, revising, and final approval of the article. 5) Eman Kamal Ibrahim is responsible for the conception and design, revising and writing, and final approval of the article.

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Availability of data and materials
The data of the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant regulations and guidelines, informed consent was obtained from all participants and/or their legal guardian, and the study was approved by the research ethical committee, Cairo University, with IRB (MS-81–2020).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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