Original Article

Risk factors analysis of noninvasive positive pressure ventilation in inpatients with overlapping syndrome of chronic obstructive pulmonary disease combined with obstructive sleep apnea

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Abstract:

OBJECTIVE: The aim of the study was to analyze the clinical data of patients with chronic obstructive pulmonary disease and obstructive sleep apnea overlap syndrome (OS) during hospitalization and to evaluate the risk factors of patients treated with Non-Invasive Ventilation (NIV).

METHODS: Demographic and clinical data of patients with confirmed OS during hospitalization were retrospectively collected. The patients were divided into two groups according to whether noninvasive ventilator was used during hospitalization, including OS treated with NIV (244 cases) and OS without NIV (239 cases). The *t*-test, χ^2 test, and Kaplan–Meier curve were used to compare the two groups, and multiple logistic regression was used to analyze the risk factors of NIV in patients with OS.

RESULTS: Compared with the OS group without NIV, the pulmonary hypertension, lymphocyte count, and left ventricular ejection fraction% of OS patients with NIV were lower, whereas PCO_2, uric acid, *C-reactive protein*, procalcitonin, and N-terminal pro-B-type natriuretic peptide were higher, with statistical differences ($P < 0.05$). During hospitalization and follow-up, OS patients with NIV had a longer hospital stay ($P < 0.001$), and there was no significant difference in the rate of readmission within 28 days. The logistic regression analysis showed that the history of diuretic use, previous history of noninvasive ventilator use, and ischemic heart disease were independent risk factors for NIV treatment in OS patients during hospitalization.

CONCLUSION: Patients with OS undergoing NIV during hospitalization exhibited more severe overall illness and had prolonged hospital stays compared to OS patients not receiving NIV. History of diuretic use, history of NIV use, and ischemic heart disease are independent risk factors for NIV treatment in OS patients during hospitalization.

Keywords:

Chronic obstructive pulmonary disease-obstructive sleep apnea, noninvasive ventilator treatment, overlap syndrome

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease in clinical practice. Currently, reports show that 10% of the general population worldwide suffers from moderate to severe COPD.[1]

Obstructive sleep apnea syndrome (OSAS) is the most common sleep-related breathing disorder, with a prevalence of at least 10% and a rising trend over the years, possibly due to increasing obesity.[2] COPD and OSAS share similar influencing factors and clinical

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characteristics, and there is a relatively high possibility of coexistence in the same patient. This simultaneous occurrence of both diseases is referred to as overlap syndrome (OS). Currently, it is estimated that at least 1% of the general population will have both diseases to some extent. Recent studies have shown a significantly increased prevalence of OSAS in severe COPD patients, especially in overweight individuals.[3] It is worth noting that the two diseases do not simply overlap; they mutually exacerbate or worsen the conditions. Compared to patients with COPD or OSAS alone, OS patients are more prone to develop carbon dioxide retention and nocturnal hypoxemia during sleep, which is significantly related to respiratory failure, pulmonary heart disease, pulmonary hypertension (PH), and ultimately disease survival rates.[4]

Noninvasive positive pressure ventilation is an important therapeutic approach for the management of acute exacerbations of COPD respiratory failure. However, the role of noninvasive pressure support ventilation in the treatment of nocturnal sleep-disordered breathing in COPD patients is still unclear.[5] A long-term follow-up study spanning 12 years demonstrated a significantly increased mortality rate in patients with OS compared to those with COPD alone, particularly in relation to cardiovascular-related deaths. Effective continuous positive airway pressure treatment for OSAS can reduce the mortality rate in OS patients. OS patients who did not receive continuous positive airway pressure treatment had a significantly higher risk of severe COPD exacerbations, leading to hospitalization compared to the group with COPD alone, whereas continuous positive airway pressure treatment significantly reduced this risk.[6] However, the risk factors for initiating noninvasive ventilation in OS patients hospitalized for acute exacerbations of COPD are still unclear. This study retrospectively analyzed the differences in clinical data between OS patients treated with combined noninvasive ventilation and those without noninvasive ventilation to identify the propensity and warning parameters for implementing noninvasive ventilation during hospitalization for OS patients.

Methods

Study participants

A retrospective selection was made of patients diagnosed with OS who were admitted to the Respiratory and Critical Care Medicine Department of our hospital due to acute exacerbations of COPD between October 2018 and September 2022. Inclusion criteria were as follows: (1) meeting the diagnostic criteria for COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines in 2018 and the diagnostic criteria for obstructive sleep apnea (OSA)-hypopnea syndrome according to the guidelines in 2011;[7,8] (2) patients not requiring invasive ventilation support; (3) patients undergoing portable sleep respiratory monitoring and pulmonary function tests; and (4) patients who provided informed consent by signing an informed consent form. Exclusion criteria were as follows: (1) presence of contraindications to noninvasive ventilation or to pulmonary function and sleep monitoring; (2) presence of severe cardiovascular diseases such as uncontrolled PH, severe arrhythmias, shock, and acute myocardial infarction; (3) presence of complications such as upper gastrointestinal perforation, gastrointestinal obstruction, significant bleeding, recent gastrointestinal surgery, or other major systemic diseases (e.g., acute cerebral infarction, autoimmune diseases, hematological disorders, uremia, and malignant tumors); and (5) poor compliance during hospitalization, leading to unplanned discharge or incomplete clinical data. A total of 483 hospitalized OS patients were selected based on the inclusion and exclusion criteria, with 244 patients in the combined noninvasive ventilation treatment group and 239 patients in the group without noninvasive ventilation treatment. This study obtained the approval of the Clinical Trials Ethics Committee of Harrison International Peace Hospital Affiliated to Hebei Medical University.

Noninvasive ventilation method

After admission, all patients underwent comprehensive laboratory examinations, and their lung function was assessed using a spirometer (Masterscope, Germany). Following the GOLD guidelines, all patients should receive bronchodilators, antispasmodics, antimicrobial therapy, and oxygen therapy. In addition to these treatments, patients in the combined noninvasive ventilation group were treated with noninvasive positive pressure ventilation (BiPAP Synchrony, Philips Respironics, USA). This therapy utilized a bilevel positive airway pressure approach, specifically the S/T mode. The parameters were adjusted gradually based on the patient's baseline condition and tolerance. The oxygen flow rate was set between 4 and 8 L/min, the frequency between 12 and 20 breaths per minute, tidal volume between 8 and 10 mL/kg, inspiratory positive airway pressure between 4 and 20 cmH_2O, and an initial expiratory positive airway pressure of 2 cmH_2O, which was increased gradually to an appropriate level.

Outcome measures

General clinical data

Upon admission, general clinical data were collected, including age, gender, smoking history within the past 6 months, body mass index (BMI), history of noninvasive ventilation therapy, history of oral diuretic use, and history of oral antiplatelet aggregation drugs. Records of comorbidities such as cerebrovascular disease, ischemic heart disease, hypertension, and diabetes were also included.

Pulmonary function tests and sleep respiratory monitoring

Pulmonary function tests included the forced expiratory volume in 1 s (FEV_1), the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), and FEV_1 as a percentage of the predicted value. Sleep respiratory monitoring included the observation of the apnea–hypopnea index (AHI). COPD severity was classified as follows: Stage I (mild COPD): FEV_1/FVC% <70%, FEV_1 ≥80% of predicted value; Stage II (moderate COPD): FEV_1/FVC% <70%, 50% ≤FEV_1 <80% of predicted value; Stage III (severe COPD): FEV_1/FVC% <70%, 30% ≤FEV_1 <50% of predicted value.

Laboratory tests

Blood biochemical markers included total white blood cell count, neutrophil count, lymphocyte count, N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and procalcitonin (PCT). Arterial blood gas analysis included pH value and partial pressure of oxygen.

Hospitalization and follow-up

The length of hospital stay was recorded, and a follow-up visit was conducted 1 month after discharge. The proportion of readmissions due to exacerbation of COPD within 28 days of discharge was documented.

Statistical analysis

The recorded data were analyzed using SPSS 24.0 software package (International Business Machines Corporation, Armonk, New York). Continuous variables were expressed as mean ± standard deviation, and the *t*-test was used for between-group comparisons. Categorical variables were presented as counts (percentages), and the Chi-square test was used for between-group comparisons. Kaplan–Meier cumulative event curves were constructed to analyze the hospitalization rate and 28-day readmission rate between the two groups, and the log-rank test was used to compare the differences. Binary logistic regression analysis was performed to identify the risk factors for noninvasive ventilation treatment in OS patients. The dependent variable was the use of noninvasive ventilation (yes or no), and the independent variables were the history of previous noninvasive ventilation use, diuretic use, and ischemic heart disease. The results were reported as odds ratio (OR), 95% confidence interval (CI), and *P* value. A $P < 0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics between two groups of overlap syndrome patients

The average age of OS patients receiving combined noninvasive ventilation was 68.82 ± 8.15 years, with 190 (77.9%) males. The average age of OS patients without noninvasive ventilation was 68.41 ± 8.66 years, with 184 (77.0%) males. There were no statistically significant differences between the two groups in terms of age ($P = 0.626$) and gender ($P = 0.809$). However, compared to OS patients without noninvasive ventilation, OS patients receiving combined noninvasive ventilation had significantly increased BMI (28.34 ± 3.21 vs. 27.23 ± 2.98, $P = 0.036$), previous use of noninvasive ventilation (42.2% vs. 31.8%, $P = 0.012$), previous use of oral diuretics (15.6% vs. 8.4%, $P = 0.015$), and higher prevalence of ischemic heart disease (18.9% vs. 10.9%, $P = 0.009$), renal insufficiency (7.0% vs. 2.9%, $P = 0.042$), and lower extremity venous complications (22.1% vs. 13.4%, $P = 0.012$). In addition, the COPD classification and AHI grading were significantly higher in OS patients receiving combined noninvasive ventilation compared to those without ventilation ($P < 0.001$). The baseline characteristics of the two groups of OS patients are shown in Table 1. Laboratory tests and arterial blood gas analysis upon admission showed that OS patients receiving combined noninvasive ventilation exhibited more severe arterial hypercapnia, lower lymphocyte count, and higher levels of uric acid, CRP, PCT, and NT-proBNP ($P < 0.05$). The laboratory tests and arterial blood gas analysis upon admission are shown in Table 2.

Comparison of hospitalization and follow-up between two groups of overlap syndrome patients

The average length of hospital stay was recorded for both groups. OS patients receiving combined noninvasive ventilation had an average hospital stay of 12 days, significantly longer than the 10 days for OS patients without noninvasive ventilation ($P < 0.001$). The Kaplan–Meier curve showed a significantly longer hospital stay in OS patients receiving combined noninvasive ventilation compared to those without ventilation, with a significant difference between the two groups [Log-rank = 96.217, $P < 0.001$, Figure 1]. During the 28-day follow-up after discharge, there was no significant difference in the readmission rate due to exacerbation of COPD between the two groups [Log rank = 1.094, $P = 0.296$, Figure 2].

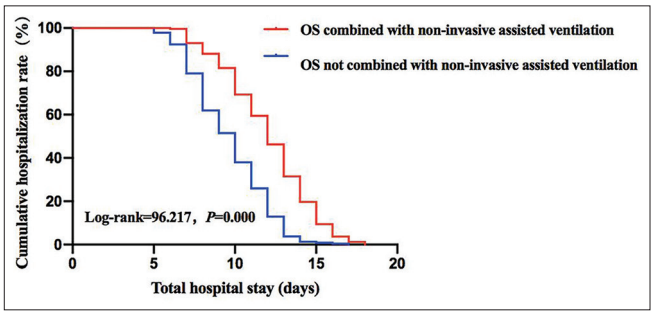

Figure 1: Survival analysis of cumulative hospitalization rate in two groups. OS = Overlap syndrome

Table 1: Baseline characteristics of the two groups of overlap syndrome patients

Variable	The combined noninvasive ventilation treatment group (*n*=244), *n* (%)	The without noninvasive ventilation treatment group (*n*=239), *n* (%)	*P*
Age	68.82±8.15	68.41±8.66	0.626
Male	190 (77.9)	184 (77.0)	0.809
BMI	28.34±3.21	27.23±2.98	0.036
Previous use of NIV	103 (42.2)	76 (31.8)	0.012
Previous use of diuretics	38 (15.6)	20 (8.4)	0.015
Ischemic heart disease	46 (18.9)	26 (10.9)	0.009
Renal insufficiency	17 (7.0)	7 (2.9)	0.042
Lower extremity venous complications	54 (22.1)	32 (13.4)	0.012
COPD classification			
Mild (stage I)	5 (2.0)	18 (7.5)	<0.001
Moderate (stage II)	68 (27.9)	121 (50.6)	
Severe (stage III)	122 (50.0)	85 (35.6)	
Very severe (stage IV)	49 (20.1)	15 (6.3)	
AHI grading			
Mild (5–15)	38 (15.6)	79 (33.1)	<0.001
Moderate (15–30)	72 (29.5)	96 (40.2)	
Severe (>30)	134 (54.9)	64 (26.8)	

BMI=Body mass index, AHI=Apnea–hypopnea index, COPD=Chronic obstructive pulmonary disease, NIV=Noninvasive pressure support ventilation

Table 2: Laboratory tests and arterial blood gas analysis of the two groups of overlap syndrome patients

Variable	The combined noninvasive ventilation treatment group (*n*=244)	The without noninvasive ventilation treatment group (*n*=239)	*P*
pH	7.35±0.04	7.38±0.03	<0.001
$PaCO_2$	55.21±8.32	48.16±7.14	<0.001
Lymphocyte count	1.24±0.51	1.42±0.58	0.002
Uric acid	420.13±96.25	389.27±87.34	0.001
CRP	28.17±19.43	21.34±15.27	<0.001
PCT	0.23±0.18	0.17±0.14	0.001
NT-proBNP	1256.34±832.17	876.21±621.34	<0.001

CRP=C-reactive protein, PCT=Procalcitonin, NT-proBNP=N-terminal pro-B-type natriuretic peptide

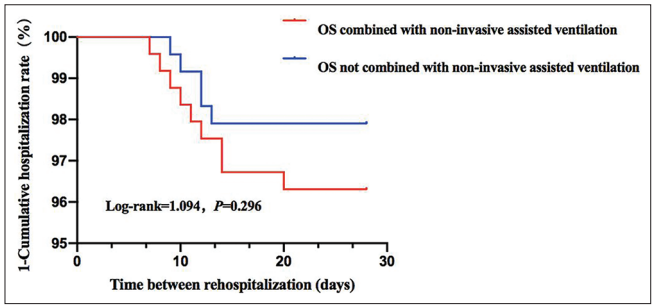

Figure 2: Survival analysis of readmission rate within 28 days in both groups. OS = Overlap syndrome

The hospitalization and follow-up outcomes of the two groups of OS patients are shown in Table 3.

Risk factors analysis for noninvasive ventilation during hospitalization in overlap syndrome patients

A multivariable binary logistic regression analysis was performed on the baseline data of OS patients to determine the factors associated with the use of noninvasive ventilation during hospitalization. The results showed that a history of previous noninvasive ventilation use (OR = 1.716, 95% CI: 1.097–2.687, P = 0.018) and a history of diuretic use (OR = 1.947, 95% CI: 1.082–3.505, P = 0.026) were independent risk factors for the use of combined noninvasive ventilation in hospitalized OS patients [Figure 3]. Furthermore, a multivariable binary logistic regression analysis was conducted on the comorbidities, and the results showed that ischemic heart disease (OR = 1.493, 95% CI: 1.017–2.19, P = 0.041) was an independent risk factor for the use of combined noninvasive ventilation in hospitalized OS patients [Figure 4].

Discussion

With the increasing prevalence of obesity, the incidence of OSA in adults is estimated to be around 10% to 20%, particularly higher in individuals aged 50 years and above. This may be attributed to common risk factors such as obesity, smoking, increased airway resistance, and local and systemic inflammation.[9] In recent years, there has been growing attention to OS, but there is still a lack of systematic clinical research on OS. Noninvasive

Table 3: Hospitalization and follow-up outcomes of the two groups of overlap syndrome patients

Variable	The combined noninvasive ventilation treatment group (*n*=244)	The without noninvasive ventilation treatment group (*n*=239)	*P*
Length of hospital stay (days)	12.32±4.21	10.27±3.16	<0.001
Readmission within 14 days, *n* (%)	12 (4.9)	9 (3.8)	0.578
Readmission within 28 days, *n* (%)	18 (7.4)	15 (6.3)	0.674

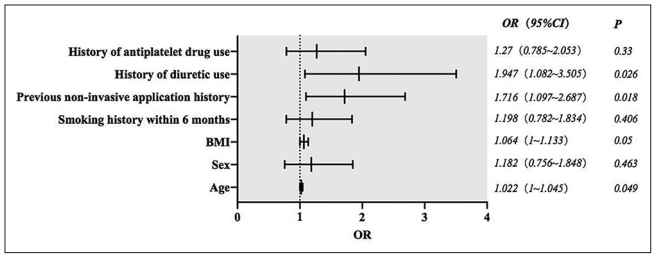

Figure 3: Multivariate binary logistic regression analysis was used to analyze the general condition of patients. OR = Odds ratio, CI = Confidence interval, BMI = Body mass index

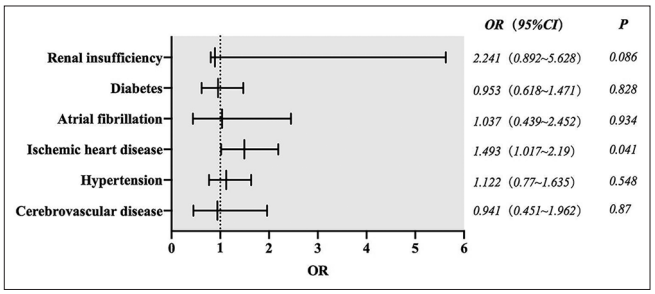

Figure 4: Multivariate binary logistic regression analysis of previous comorbidities. OR = Odds ratio, CI = Confidence interval

ventilation is a commonly used treatment modality for OS patients, and this study aims to analyze the clinical characteristics of hospitalized OS patients to establish effective predictive parameters for noninvasive ventilation.

This study found that hospitalized OS patients, irrespective of whether they received noninvasive ventilation, were more commonly observed in elderly patients around the age of 68, with males accounting for over 70%. This could be attributed to a gender bias related to long-term smoking history, where smoking leads to chronic inflammation in the airways and serves as an independent risk factor for developing COPD and OSA. Other studies have also demonstrated that COPD patients who smoke are more likely to have comorbid OSA.[10,11] Conversely, with regard to BMI, OS patients receiving combined noninvasive ventilation had higher BMI. Smoking index and BMI can be used in epidemiology to predict the development of airflow limitation risk.[12] The higher the smoking index and BMI, the greater the risk of developing airflow limitation, COPD, OSA, and OS. Obesity associated with OSA can also have a negative impact on lung function.[13]

Retrospective recording of comorbidities in patients revealed that among OS patients, those who received combined noninvasive ventilation during hospitalization were more likely to have lower extremity venous thrombosis, ischemic heart disease, and chronic renal insufficiency. Studies have shown that COPD is a moderate risk factor for venous thromboembolism (VTE), with approximately 10% of COPD patients experiencing lower extremity venous thrombosis during acute exacerbation hospitalization, but this proportion may be underestimated.[14,15] It is evident that the incidence of lower extremity venous thrombosis in Asian COPD patients is significantly higher than in non-COPD patients.[16] In this study, the prevalence of lower extremity venous thrombosis among all OS patients was approximately 17.8%, with no reported international or domestic data on this topic. OSA may be an additional influencing factor promoting the occurrence of VTE in COPD patients. Therefore, VTE is relatively common in hospitalized COPD patients, and routine prophylactic anticoagulation therapy may be considered for COPD inpatients at risk of VTE.[17] Similarly, meta-analysis results have also demonstrated a higher incidence of OSA in VTE patients, highlighting the necessity of screening for OSA in VTE patients to establish effective treatment strategies.[18]

Ischemic heart disease is more common in patients with OS who receive combined noninvasive ventilation. Research has shown that OSA is a risk factor for cardiovascular syndrome. Long-term chronic intermittent hypoxia can lead to endothelial dysfunction, promoting the formation of vascular wall plaques. It also affects coagulation activity, platelet function, and fibrinolysis system. When combined with COPD, these factors synergistically contribute to the development of cardiovascular complications. Noninvasive ventilation therapy can improve these conditions.[19] In an international clinical study involving 1698 COPD patients, approximately 45% of the cases were taking aspirin daily.[20] In comparison, the usage rate of antiplatelet drugs in OS patients in this study was around 17.9%, slightly higher in patients receiving combined noninvasive ventilation compared to those with OSA alone, but the difference was not statistically significant. This indicates a lack of emphasis on the treatment and prevention of cardiovascular diseases in the current domestic setting. Another meta-analysis suggested that antiplatelet therapy may

help reduce overall mortality in COPD patients.[21] Future studies with larger sample sizes and multicenter follow-ups can further investigate this topic.

When patients present with symptoms of heart failure, the combination of diuretics is often used to reduce overall fluid load. This study shows a higher rate of diuretic use in patients receiving combined noninvasive ventilation for OS, accounting for approximately 15.6% of the patients in this group. This suggests that OS patients with concomitant heart failure symptoms are more likely to receive combined noninvasive ventilation treatment. The prevalence of renal insufficiency in patients receiving combined noninvasive ventilation for OS is approximately 7.0%, compared to 2.9% in the group with OSA alone. When COPD is combined with OSA, it exacerbates nocturnal hypoxemia. Studies have shown that nocturnal hypoxemia is independently associated with an increased risk of renal insufficiency,[22] and the relationship between OSA and chronic kidney disease (CKD) may be bidirectional.[23,24] On one hand, OSA can lead to intermittent hypoxia, abnormal sympathetic nervous system activity, and hypertension, all of which can have detrimental effects on renal function. On the other hand, in patients with end-stage renal disease, fluid overload plays a significant role in the pathogenesis of OSA, leading to its exacerbation. Intensified renal replacement therapy has been shown to alleviate the severity of OSA. Therefore, in patients with more severe OS receiving combined noninvasive ventilation, clinicians need to be vigilant about the occurrence of CKD in clinical diagnosis and treatment.

Approximately 70.1% of patients receiving combined noninvasive ventilation for OS have severe to very severe COPD, with a predominance of severe COPD. In contrast, in OS patients without noninvasive ventilation, the majority have moderate COPD. This suggests that patients with more severe lung function impairment, in a state of decompensation with hypercapnia and/or respiratory failure, require combined noninvasive ventilation during hospitalization. Furthermore, for stable COPD patients, long-term noninvasive ventilation is recommended as it can reduce arterial carbon dioxide levels and subsequently decrease long-term mortality.[25] Regardless of the severity of OSA, when OSA is combined with COPD, noninvasive positive pressure ventilation is the preferred and initial treatment. This study also compared hospitalization and follow-up outcomes for all OS patients. The results showed that OS patients receiving combined noninvasive ventilation had significantly longer hospital stays. On one hand, this may be attributed to the presence of multiple comorbidities that require simultaneous treatment during hospitalization. On the other hand, it may be related to higher levels of infectious markers, which affect the duration of antimicrobial therapy. However, there were no significant differences in readmission rates within 14 and 28 days after discharge between the two groups. The observation showed that readmissions in both groups were more concentrated within 14 days after discharge. Considering that the severity of illness in both groups at admission was managed with active symptomatic treatment, there were no significant differences in short-term readmission rates. Further investigations are needed to determine the causes of readmission in these patients.

Conclusion

The history of previous noninvasive ventilation use, diuretic use, and ischemic heart disease are independent risk factors for combined noninvasive ventilation treatment in hospitalized patients with OS. Previous studies[26] have confirmed that OSA is an independent risk factor for cardiovascular disease. The use of diuretics aims to alleviate peripheral edema caused by chronic hypercapnia and reduce cardiac load. Therefore, OS patients with poor lung function and concurrent heart disease are more likely to receive combined noninvasive ventilation during hospitalization. Given the high prevalence of OSA in the COPD population, it is necessary to conduct routine sleep-breathing monitoring to avoid missed diagnosis in hospitalized COPD patients. In addition, for OS patients with a history of previous noninvasive ventilation use, diuretic use, and concurrent ischemic heart disease, it is important to raise awareness of standardized noninvasive ventilation treatment during hospitalization.

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Conflicts of interest

There are no conflicts of interest.

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