

Impact of Severe Vitamin D Deficiency on Antibiotic Use in Hospitalized COPD Patients with Exacerbations: A Retrospective Analysis

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Background: Exacerbations of chronic obstructive pulmonary disease (ECOPD) often require antibiotic treatment. Vitamin D deficiency has been implicated in influencing the outcomes of ECOPD; however, its role in antibiotic usage during hospitalization remains unclear.

Patients and Methods: We conducted a retrospective analysis of 125 hospitalized ECOPD patients, stratified into two groups based on the presence of severe vitamin D deficiency (SVDD, 25-hydroxyvitamin D < 10 ng/mL) and non-severe vitamin D deficiency (NSVDD). Clinical outcomes, including duration of antibiotic treatment, cumulative defined daily doses (cDDD), hospital length of stay (LOS) and associated costs, were compared between subgroups. Multivariate linear regression was used to assess the association between 25-hydroxyvitamin D levels and antibiotic use, adjusting for demographic and clinical variables.

Results: Patients with SVDD exhibited significantly longer durations of antibiotic use (13.50 vs. 11.00 days, $P=0.023$), higher cDDDs (16.16 vs. 12.00, $P=0.012$) and longer LOS (15.00 vs. 12.00, $P=0.026$) compared to those with NSVDD. Patients with SVDD and pneumonia had more antibiotics use, longer LOS and higher cost than those with NSVDD and AECOPD ($P<0.05$). Multivariate linear regression analysis revealed that lower 25-hydroxyvitamin D levels were independently associated with increased antibiotic duration (coefficient -0.20 , 95% CI -0.32 , -0.08 , $P<0.001$) and higher cDDDs (coefficient -0.24 , 95% CI -0.46 , -0.01 , $P=0.041$) after adjustment, although the magnitude was smaller than that observed for some other variables.

Conclusion: SVDD is independently associated with antibiotic burden in hospitalized COPD patients with exacerbation. Prospective studies are warranted to further explore this potential relationship and its clinical implications.

Keywords: chronic obstructive pulmonary disease, exacerbation, hospitalization, 25-hydroxyvitamin D, severe deficiency, antibiotic use

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, characterized by progressive airflow limitation and frequent exacerbations.¹ Exacerbation of COPD (ECOPD), particularly those requiring hospitalization, are associated with increased mortality, worsened lung function, and reduced quality of life.² Antibiotic treatment is commonly required during these episodes, as it has been shown to shorten recovery time, reduce the risk of treatment failure, and decrease the duration of hospitalization when indicated.^{3,4} Despite its widespread use, the factors influencing antibiotic consumption during ECOPD remain poorly understood.

Vitamin D, a crucial nutrient involved in immune function,⁵⁻⁸ has been implicated in the pathogenesis and exacerbation of COPD. Systematic reviews and meta-analyses of randomized controlled trials (RCT) have demonstrated that vitamin D supplementation may help protect against respiratory infections.^{8,9}

Severe vitamin D deficiency (SVDD, 25-hydroxyvitamin D < 10 ng/mL) is commonly observed in COPD patients.¹⁰ Low vitamin D levels are associated with an increased risk of exacerbations in COPD patients, and vitamin D supplementation may reduce the frequency of these episodes.^{11–15} However, the impact of SVDD on antibiotic use during ECOPD has received limited attention.

This study aimed to explore the association between vitamin D deficiency status and antibiotic use in hospitalized COPD patients with exacerbations. We hypothesized that SVDD would be associated with longer antibiotic treatment durations and higher cumulative antibiotic doses (cDDD). To address this hypothesis, we performed a retrospective analysis.

Materials and Methods

Patients

Demographic and clinical data of hospitalized COPD patients with exacerbations were retrospectively collected at Beijing Chao-Yang Hospital, Capital Medical University (Beijing, China), as previously described.¹⁴ After excluding nine patients without available procalcitonin (PCT) or c-reactive protein (CRP) measurements, 125 patients were included in the final analysis.

Data Collection

Data on demographic information, comorbidities, antibiotic use, associated cost, hospital length of stay (LOS), and infection and inflammation indices were collected. The diagnosis of pneumonia was established based on the presence of a new infiltrate observed in the chest CT scan. Antibiotic use was assessed in terms of treatment duration (defined as the number of days from initiation to discontinuation of antibiotic therapy) and cDDDs (calculated according to WHO recommendations),¹⁶ which served as the primary study outcomes.

The study received approval from the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (No. 2023-ke-390), in accordance with the Declaration of Helsinki. To protect participants' privacy and mitigate the risk of breaches, all sensitive information has been erased and de-identified in the statistical data. Due to the anonymous nature of the data, the consent was exempted for this study by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University.

Statistical Analysis

Continuous variables were reported as mean $\pm$ standard deviation (SD) or as median with interquartile range (IQR). Categorical variables were presented as counts and percentages. Between-group comparisons were performed using the Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, depending on data distribution, and the χ^2 test for categorical variables. Multivariable linear regression analysis was applied to assess the associations between serum 25-hydroxyvitamin D levels and antibiotic use outcomes (treatment duration and cDDDs), using a stepwise variable selection procedure. All statistical analyses were conducted with R software (version 4.4.0) and IBM SPSS Statistics (version 27). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Patients' Characteristics

A total of 125 hospitalized COPD patients were divided into a SVDD group (median 25-hydroxyvitamin D 8.26 ng/mL) and a NSVDD group (median 25-hydroxyvitamin D 17.06 ng/mL) (Table 1). Patients with SVDD had a lower proportion of males compared with those in the NSVDD group (67.86% vs. 87.63%, *P* = 0.021). The proportion of patients with hospitalization for exacerbations in the past year was higher in the SVDD group (60.71% vs. 30.93%, *P* = 0.008), and the eosinophil counts were lower (0.11 vs. $0.18 \times 10^9/L$, *P* = 0.022). The distribution of 25-hydroxyvitamin D measurement season differed significantly between groups (*P* = 0.007), with severe deficiency more frequently in winter.

Table 1 Baseline Characteristics

Variable	Overall N = 125 ^a	SVDD N = 28 ^a	NSVDD N = 97 ^a	P ^b
Sex, male	104 (83.20%)	19 (67.86%)	85 (87.63%)	0.021*
Age, y	70.92 (8.64)	71.71 (8.64)	70.69 (8.67)	0.584
BMI, kg/m ²	22.66 (20.98,24.22)	22.09 (21.31,25.25)	22.83 (20.90,24.22)	0.983
Current smoker	38 (30.40%)	4 (14.29%)	34 (35.05%)	0.061
Comorbidities				
Pneumonia	45 (36.00%)	12 (42.86%)	33 (34.02%)	0.526
Respiratory failure	36 (28.80%)	7 (25.00%)	29 (29.90%)	0.789
Cardiac insufficiency	24 (19.20%)	8 (28.57%)	16 (16.49%)	0.247
Diabetes	26 (20.80%)	7 (25.00%)	19 (19.59%)	0.721
Cerebral infarction	16 (12.80%)	2 (7.14%)	14 (14.43%)	0.521
Hypoalbuminemia	75 (60.00%)	17 (60.71%)	58 (59.79%)	1.000
GOLD grades				0.351
1	7 (5.60%)	2 (7.14%)	5 (5.15%)	
2	21 (16.80%)	7 (25.00%)	14 (14.43%)	
3	21 (16.80%)	6 (21.43%)	15 (15.46%)	
4	6 (4.80%)	0 (0.00%)	6 (6.19%)	
N/A	70 (56.00%)	13 (46.43%)	57 (58.76%)	
Hospital for exacerbation last year	47 (37.60%)	17 (60.71%)	30 (30.93%)	0.008**
System corticosteroids use	57 (45.60%)	10 (35.71%)	47 (48.45%)	0.329
25-(OH)D, ng/mL	15.30 (10.56,21.30)	8.26 (7.84,9.04)	17.06 (13.37,22.77)	<0.001***
Season of 25-hydroxyvitamin D examined				0.007**
Spring	33 (26.40%)	6 (21.43%)	27 (27.84%)	
Summer	39 (31.20%)	4 (14.29%)	35 (36.08%)	
Autumn	24 (19.20%)	5 (17.86%)	19 (19.59%)	
Winter	29 (23.20%)	13 (46.43%)	16 (16.49%)	
Leukocytes, ×10 ⁹ /L	7.73 (6.52,9.35)	7.66 (6.57,9.19)	7.88 (6.52,9.49)	0.769
Neutrophils, ×10 ⁹ /L	5.09 (3.94,6.74)	5.19 (3.86,6.64)	5.00 (4.00,6.83)	0.906
Lymphocytes, ×10 ⁹ /L	1.60 (1.21,2.02)	1.54 (1.29,1.98)	1.62 (1.18,2.06)	0.932
Monocytes, ×10 ⁹ /L	0.52 (0.41,0.68)	0.60 (0.45,0.69)	0.49 (0.38,0.68)	0.126
Eosinophils, ×10 ⁹ /L	0.15 (0.09,0.26)	0.11 (0.05,0.18)	0.18 (0.09,0.28)	0.022*
CRP, mg/L	0.48 (0.25,1.24)	0.66 (0.28,4.04)	0.43 (0.24,0.99)	0.138
PCT, µg/L	14 (11.20%)	3 (10.71%)	11 (11.34%)	1.000

Notes: ^aAll values represent mean (SD) or No. (%) or Median (IQR). ^bStudent's t-test, Mann-Whitney U-test, the X2 test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ severe deficiency group vs. non-severe deficiency group.

Clinical Outcomes by Vitamin D Status and ECOPD Types

The outcomes of interest were antibiotic utilization, including treatment duration, cDDD, antibiotic-related costs, and LOS. As shown in [Figure 1](#), patients with SVDD had significantly higher treatment duration (13.50 vs. 11.00 days, $P = 0.023$), cDDD (16.16 vs. 12.00, $P = 0.012$) and LOS (15.00 vs. 12.00 days, $P = 0.022$) compared with those without severe deficiency ([Figure 1a](#)).

Patients with COPD often suffer acute exacerbations (AECOPD) and pneumonia (COPD + pneumonia). Similar trends were observed in COPD patients with pneumonia, who received longer antibiotic therapy, higher cDDD, longer LOS, and incurred greater costs (all $P < 0.05$) ([Figure 1b](#)).

Notably, COPD patients with both SVDD and pneumonia showed the greatest antibiotic burden, with significantly prolonged treatment duration, higher cDDD, longer LOS, and higher costs ([Figure 1c](#)).

Association of 25-Hydroxyvitamin D Levels with Antibiotic Use

We assessed the association between serum 25-hydroxyvitamin D levels and antibiotic use, focusing on treatment duration and cDDD. Covariates included sex, age, BMI, season of hospitalization, comorbidities (pneumonia,

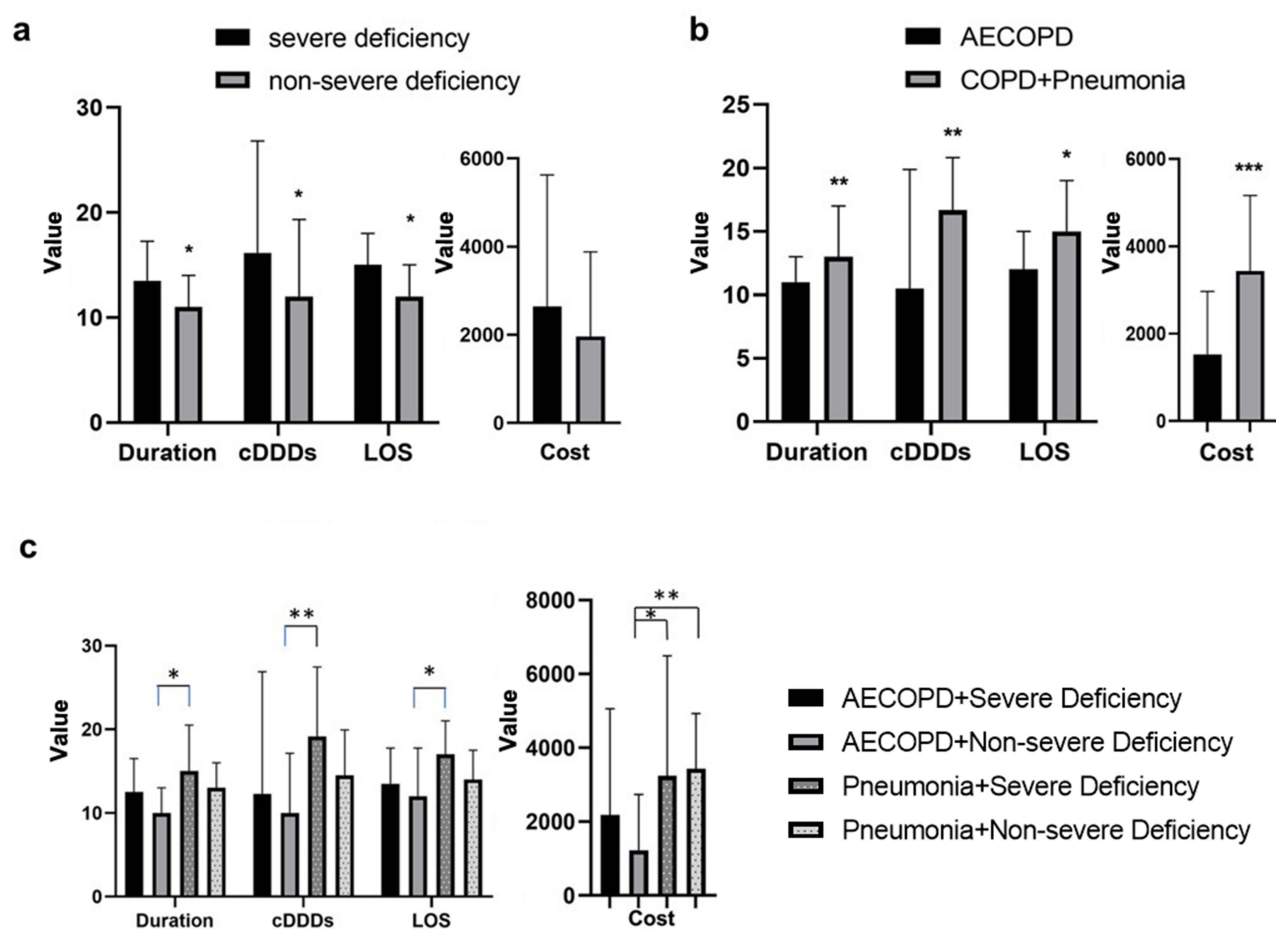


Figure 1 Outcomes in hospitalized ECOPD grouped by vitamin D deficiency and pneumonia status. Outcomes included antibiotic treatment duration, cDDD, LOS, and antibiotic-related costs. (a) Severe vs. non-severe vitamin D deficiency. (b) AECOPD vs. COPD + pneumonia. (c) Four subgroups stratified by vitamin D deficiency and pneumonia status. Data are presented as median (interquartile range). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

respiratory failure, cardiac insufficiency, diabetes, cerebral infarction and hypoalbuminemia), and infection-related indices (leukocyte count, CRP, and PCT). Lower 25-hydroxyvitamin D levels were independently associated with prolonged antibiotic duration (coefficient = -0.20 , 95% CI -0.32 to -0.08 , $P < 0.001$) and higher cDDDs (coefficient = -0.24 , 95% CI -0.46 to -0.01 , $P = 0.041$), although the magnitude of these associations was smaller than that observed for some other variables. Respiratory failure, leukocytosis, male sex, and pneumonia were positively associated with longer antibiotic duration. Elevated CRP, respiratory failure, and winter season were positively associated with higher cDDDs (all $P < 0.05$) (Figure 2).

Association of Vitamin D Status with AECOPD versus Pneumonic COPD

Lower vitamin D levels were significantly associated with longer antibiotic treatment duration in both AECOPD and pneumonic COPD patients (AECOPD: coefficient = -0.19 , 95% CI -0.34 to -0.05 , $P = 0.011$; pneumonic COPD: coefficient = -0.26 , 95% CI -0.49 to -0.03 , $P = 0.028$). Regarding cDDDs, in AECOPD patients, 25-hydroxyvitamin D was associated with cDDDs in the univariate analysis (coefficient = -0.33 , $P = 0.026$), but the association did not persist after multivariate adjustment. In pneumonic COPD patients, lower vitamin D levels remained independently associated with higher cDDDs (coefficient = -0.55 , 95% CI -0.97 to -0.13 , $P = 0.011$) (Supplementary Figure 1).

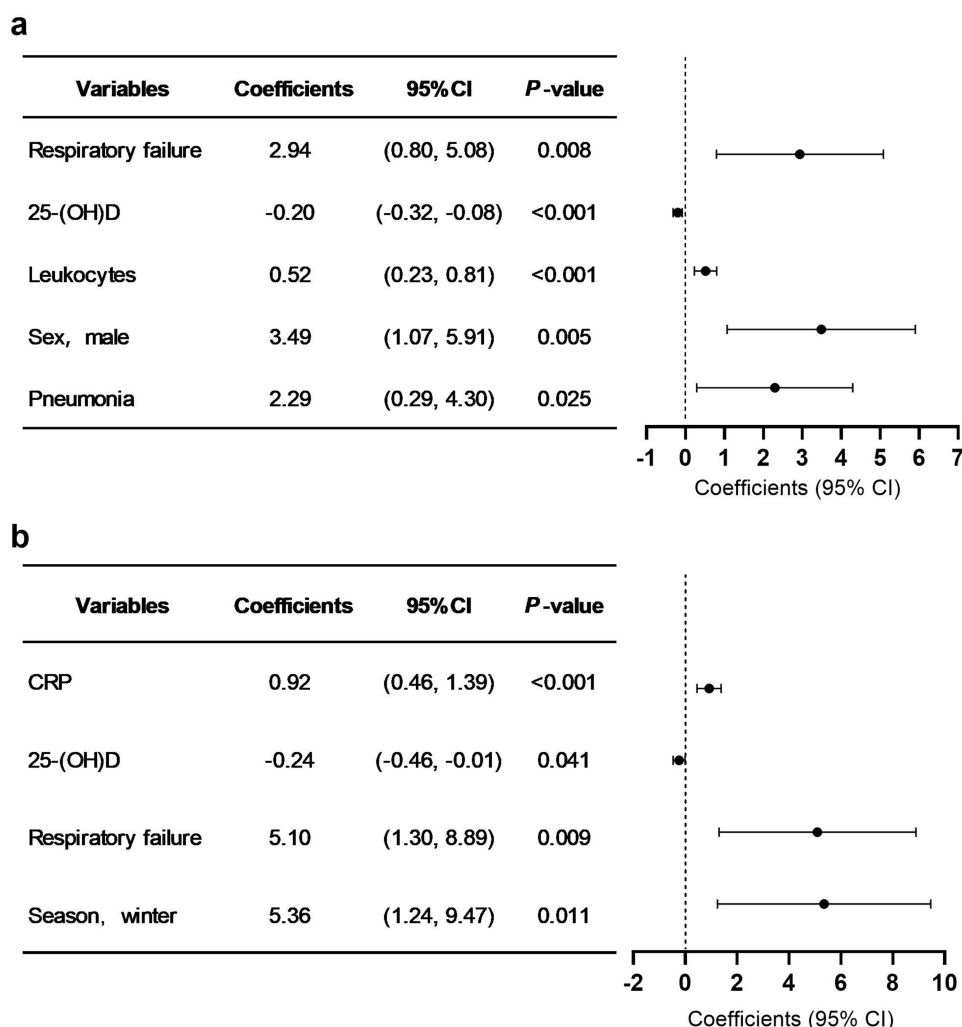


Figure 2 Multivariate linear regression analysis assessing association of 25-hydroxyvitamin D with antibiotic use duration (a) and cDDD (b) in hospitalized COPD patients with exacerbation.

Discussion

In this retrospective study of hospitalized patients with exacerbated COPD, we found that patients with SVDD tended to have prolonged antibiotic treatment, higher cDDD and longer hospital stay compared with those with NSVDD. After adjusting for sex, age, BMI, season of hospitalization, comorbidities, and infection-related indices, lower serum 25-hydroxyvitamin D levels remained independently associated with antibiotic duration and cumulative exposure in hospitalized COPD patients with exacerbation. Our results extend previous studies that primarily focused on the association between vitamin D status and the risk or severity of ECOPD by specifically quantifying its relationship with antibiotic utilization during hospitalization.

COPD patients often exhibit compromised innate immunity, including reduced phagocytic cells functions, dysregulated cytokine production and deficient antimicrobial peptides.^{17,18} Vitamin D plays a well-established immunomodulatory role by enhancing antimicrobial peptide synthesis, regulating inflammatory pathways, and maintaining epithelial barrier function.⁶ Deficiency in vitamin D may impair host defense against infections, potentially leading to more severe or prolonged respiratory infections and increased antibiotic requirements. Therefore, it is reasonable that low vitamin D levels may have independent clinical associations with antibiotic use beyond exacerbation severity alone.

The discrepant associations of vitamin D with antibiotic use between AECOPD and pneumonic COPD may reflect differences in pathophysiology and treatment strategies.¹⁹ AECOPD is a heterogeneous condition, not all bacterial

infection driven,²⁰ yet lower vitamin D levels remained associated with both prolonged antibiotic duration and higher cDDD, suggesting that impaired host immunity related to vitamin D deficiency may contribute to greater antibiotic use in AECOPD. In contrast, pneumonic COPD represents a more infection-predominant phenotype, in which vitamin D levels were associated with cDDD but not duration, possibly because disease severity more strongly determines treatment duration in pneumonia, attenuating the independent association with vitamin D.

Vitamin D varies seasonally, with deficiency more commonly observed in winter and spring, reported by a cross-sectional study of urban Beijing residents.²¹ Seasonal factors may also influence respiratory infection risk and antibiotic use. In our study, winter hospitalization was associated with higher cDDD, which is consistent with the observed association between severe vitamin D deficiency and antibiotic burden.

The potential association between low vitamin D levels and different antibiotic regimens or combinations is clinically meaningful and deserves further investigation. A better understanding of this relationship may help optimize antibiotic stewardship strategies and improve individualized management in patients with COPD exacerbations.

This study has several limitations. First, its retrospective single-center design and relatively small sample size may limit the generalizability of the findings. Second, lung function data were incomplete for a substantial proportion of patients, which restricted adjustment for baseline COPD severity. Although previous studies have not consistently demonstrated a direct association between lung function impairment and the risk of respiratory infections, residual confounding related to disease severity cannot be fully excluded. Third, antibiotic prescribing practices and treatment duration are also influenced by baseline disease severity and clinical judgment; therefore, residual confounding cannot be completely excluded, despite adjustment for comorbidities and infection-related indices. Future studies with larger sample sizes and prospective designs are warranted to further clarify the relationship between vitamin D status and antibiotic utilization in ECOPD.

Conclusion

In this study, we demonstrated that SVDD is independently associated with antibiotic burden in hospitalized patients with COPD exacerbations after adjusting for demographic and clinical variables, although the magnitude was smaller than that observed for some other variables. This finding may support more comprehensive clinical assessment and risk stratification in hospitalized ECOPD patients. Prospective studies are needed to further investigate this relationship and its clinical implications.

Abbreviations

SVDD, severe vitamin D deficiency; NSVDD, non-severe vitamin D deficiency; BMI, body mass index, GOLD, Global Initiative for Chronic Obstructive Lung Disease, 25-(OH)D, 25-hydroxyvitamin D, cDDD, cumulative defined daily doses, CRP, c-reactive protein, PCT, procalditonin.

Ethics Approval and Informed Consent

The study received approval from the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (No. 2023-ke-390), in accordance with the Declaration of Helsinki. To protect participants' privacy and mitigate the risk of breaches, all sensitive information has been erased and de-identified in the statistical data. Given the anonymous nature of the data, informed consent was waived for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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