

# Evaluation of plasma leptin, tumor necrosis factor- $\alpha$ , and prealbumin as prognostic biomarkers during clinical recovery from acute exacerbations of chronic obstructive pulmonary disease

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## ABSTRACT

**Background:** Inflammatory and nutritional biomarkers have an important bearing on outcomes of acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but the temporal profile of these compounds during an acute episode is unclear. **Patients and Methods:** Plasma leptin, prealbumin, and tumor necrosis factor-alpha (TNF- $\alpha$ ) were estimated at baseline and before hospital discharge in patients with AECOPD. **Results:** A total of 82 patients were evaluated (66 males; mean (standard deviation) age, 61.6 (10.1) years. Of these, 74 subjects (90.2%) were current or former smokers, with median (range) pack-years of 15 (0–96), duration of COPD of 8 years (range, 2–25 years) and duration of current symptoms being 5 days (range, 1–30 days). Majority (41.5%) had type I (severe) exacerbation. During the current episode, 46 patients (58.9%) required mechanical ventilation for a median of 6 days (range, 1–34). The median duration of hospital stay was 13 days, (range, 1–110). At discharge, significant reduction was observed in dyspnea, total leukocyte count, erythrocyte sedimentation rate (ESR), partial pressure of carbon dioxide, hemoglobin, urea, creatinine, potassium, aspartate transferase, and TNF- $\alpha$  levels compared to baseline, whereas arterial pH, PO<sub>2</sub>, serum albumin, prealbumin, and leptin significantly improved. No difference was seen in leptin, prealbumin, and TNF- $\alpha$  between patients with mild/moderate and severe exacerbation, or between patients who required or did not require mechanical ventilation. Change in leptin correlated with body mass index and change in ESR; no associations were observed between leptin, prealbumin, and TNF- $\alpha$  with other clinico-laboratory variables. **Conclusion:** Plasma levels of novel inflammatory and nutritional biomarkers, i.e., leptin, TNF- $\alpha$ , and prealbumin are altered in AECOPD episodes and lag behind other parameters during recovery. These biomarkers are not reliable predictors of clinical outcomes in these patients.

**KEY WORDS:** Chronic obstructive pulmonary disease, inflammatory, leptin, prealbumin, tumor necrosis factor-alpha

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## INTRODUCTION

The interaction between systemic inflammation and malnutrition in chronic obstructive pulmonary

disease (COPD) continues to remain a subject of interest and research. It is known that during an acute exacerbation

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of COPD (AECOPD), an inflammatory burst causes increased sputum levels of interleukin-6 (IL-6), IL-8, tumor necrosis factor-alpha (TNF- $\alpha$ ), myeloperoxidase, neutrophil elastase, and leukotriene B<sub>4</sub>.<sup>[1,2]</sup> In addition, the identification of these cytokines in plasma/serum of COPD patients strongly suggests a possible communication of the local inflammatory response with the systemic circulation.<sup>[3]</sup> Extensively studied inflammatory biomarkers in AECOPD include C-reactive protein (CRP), IL-6, and more recently, fibrinogen. However, the clinical utility of these markers as a reliable prognostic and monitoring tool has not yet been established.<sup>[4-8]</sup> There is, thus, a need to evaluate other compounds as potential monitoring tools during the clinical course of AECOPD. Leptin is one such biomarker that is increased in inflammatory states and is also a marker of nutritional status<sup>[9]</sup> while TNF- $\alpha$  is an inflammatory cytokine that has been reported to predict mortality and exacerbation rates in acute COPD.<sup>[5,10-13]</sup>

On the other hand, the frequent occurrence of malnutrition in COPD has a direct adverse effect on disease course and prognosis.<sup>[14,15]</sup> Among the various anthropometric and biochemical tools available, prealbumin possesses certain advantages of relatively short half-life and ability to detect acute changes in nutritional status.<sup>[16,17]</sup> However, most previous reports have evaluated the change in inflammatory and nutritional profile from a stable state to an episode of exacerbation in follow-up cohorts.<sup>[18-21]</sup> The changes occurring during an acute episode and their relation with clinical response have not been well-characterized. We thus attempted to evaluate the temporal course of these relatively novel biomarkers (leptin, TNF- $\alpha$ , and prealbumin) during recovery from AECOPD and their prognostic utility for morbidity indices.

## PATIENTS AND METHODS

Consecutive patients admitted with a diagnosis of AECOPD to the pulmonary medical wards and Intensive Care Unit of the All India Institute of Medical Sciences, New Delhi, (a tertiary care center in North India) were recruited. Patients requiring admission to the hospital by the criteria of the American Thoracic Society/European Respiratory Society were included in the study.<sup>[22,23]</sup> The diagnosis of AECOPD was made by eliciting a history of acute symptomatic worsening from the stable state and beyond normal day-to-day variations and necessitating a change in regular medication.<sup>[24]</sup> Patients were further classified into three types of exacerbation depending on the presence of at least one of the following symptoms: Dyspnea; increased sputum volume; and sputum purulence in addition to at least one of the following: An upper respiratory tract infection lasting 5 days, fever, or an increase in wheeze. The presence of all the above three symptoms classifies the exacerbation as type I (most severe); two symptoms as type II and one symptom as type III.<sup>[25]</sup> Admission for any other primary diagnosis such as acute coronary syndrome, congestive heart failure, pneumonia, pneumothorax,

pulmonary embolism, and bronchiectasis were excluded. Patients' consent was taken and approval obtained from the Institute Ethics Review Board.

Detailed demographic and clinical data was recorded, including the duration of disease, total duration of current symptoms, history of previous hospitalizations for AECOPD, requirement of noninvasive or invasive mechanical ventilation, and evidence of cor pulmonale on the basis on engorged jugular veins, pedal edema, loud pulmonary sounds, and electrocardiogram. Active smokers were defined as having smoked within the past 6 months. Major co-morbidities such as diabetes mellitus, hypertension, ischemic heart disease, and past pulmonary tuberculosis were noted. Charlson co-morbidity Index<sup>[26,27]</sup> was calculated after excluding COPD as a variable. Glasgow coma scale and Acute Physiologic and Chronic Health Evaluation II score were recorded at the time of admission. Baseline arterial blood gas analyses and chest radiography was done in all patients, and respiratory secretions were sent for Gram stain and bacterial culture. Other laboratory tests such as hemoglobin, total leukocyte counts (TLCs), renal/hepatic function tests and serum electrolytes for sodium and potassium were monitored serially.

All patients were managed by the treating medical unit with nebulized bronchodilators, steroids, and antibiotics as clinically indicated. The decision to institute noninvasive or invasive mechanical ventilation was taken by the treating unit as per guidelines and clinical indication. Complications occurring during hospital stay, (e.g., pneumothorax) were recorded. All patients were followed to discharge or death; the decision to discharge was taken by the treating physicians; survivors were subsequently analyzed for the purpose of this study.

### Estimation of plasma biomarkers

Within 24 h of admission in hospital, 4–5 ml of blood was collected from an antecubital vein without venostasis and placed into vacuum collection tubes containing heparin. The blood was centrifuged at 3000 rpm for 10 min at ambient temperature, plasma separated in aliquots and immediately stored at  $-80^{\circ}\text{C}$  until the immunoassays were performed. Plasma levels of leptin, prealbumin, and TNF- $\alpha$  were estimated on samples collected twice – one within 48 h of hospitalization and subsequently at predischarge. The change in the levels were evaluated and correlated with clinical and laboratory response. The laboratory analysis was conducted by investigators who had no information related to the patients being studied; the clinicians on the other hand, were unaware of these laboratory results. For performing laboratory analysis, plasma samples were thawed, diluted 1:3 in the appropriate buffer and used for estimation by ELISA using commercially available antibodies and according to the supplier's laboratory protocol. The normal range for leptin, prealbumin, and TNF- $\alpha$  were taken as 2.0–5.6 ng/ml, 10–40 mg/dl, and 25–800 pg/ml, respectively according to the manufacturer's protocol.

### Statistical analysis

The data were entered into an Excel spreadsheet and analyzed using STATA version 11.0 (StataCorp, Texas). Baseline data were computed for each of the two main groups. All numerical data were expressed as mean standard deviation (SD) or median (range). The differences in laboratory parameters, including levels of inflammatory markers, were calculated using the paired *t*-test and Wilcoxon sign rank test for continuous variables, and Pearson's Chi-square test and the Fisher's exact test for nominal variables. Prealbumin was categorized into two subgroups with <10 mg/dl (moderate/severe deficiency), and >10 mg/dl (normal/mild deficiency).

### RESULTS

The baseline demographics of the patient population are depicted in Table 1. A total of 82 patients were evaluated (66 males; mean (SD) age, 61.6 (10.1) years. Of these, 74 subjects (90.2%) were current or former smokers, with median (range) pack-years of 15 (0–96), duration of COPD of 8 years (range, 2–25 years), and duration of current symptoms being 5 days (range, 1–30 days). Hypertension was the most common comorbidity, recorded in 51% subjects, followed by diabetes (22%). Regular use of inhaled bronchodilators and inhaled steroids was noted in 68 (82.9%) and 39 (47.6%) patients, respectively, while 13 patients (15.8%) were on domiciliary oxygen. Thirty-four patients (41.5%) had clinical features of right heart failure and 48.8% presented with clinical and/or radiological features of chest infection. Type I (severe) exacerbation of COPD was most commonly observed (41.5%). Previously, 34% of patients had been hospitalized for AECOPD, with 50% of them requiring mechanical ventilation. During the current hospital stay, 46 patients (58.9%) required mechanical ventilation for a median of 6 days (range, 1–34 days). The median duration of hospital stay was 13 days, (range, 1–110 days). Majority had TNF- $\alpha$ , leptin and prealbumin levels below the normal range as defined above.

At the time of reassessment before planned discharge, significant reduction was observed in dyspnea scores, TLC, erythrocyte sedimentation rate (ESR), partial pressure of carbon dioxide, hemoglobin, urea, creatinine, potassium, aspartate transferase, and TNF- $\alpha$  levels compared to baseline, whereas arterial pH, PO<sub>2</sub>, serum albumin, prealbumin, and leptin significantly improved [Table 2]. Respiratory rate, TLC, PO<sub>2</sub>, and ESR normalized, whereas leptin, prealbumin and TNF- $\alpha$  remained outside their respective normal range at the time of reassessment. The correlations between the baseline prealbumin, leptin and TNF- $\alpha$  level with other clinico-laboratory parameters are shown in Table 3. Baseline leptin correlated with body mass index, potassium and albumin. There was no significant difference in the levels of these markers

**Table 1: Demographic profile of the patients**

Variables	Total (n=82)
Age (years)	61.6±10.1
Smoker	
No	8 (9.8)
Current	42 (51.2)
Previous	32 (39.0)
Pack years	15 (0, 98)
Duration of COPD (years)	8 (2, 25)
Current duration of symptoms (days)	5 (1, 30)
Type of exacerbation	
Severe	36 (43.9)
Moderate	24 (29.3)
Mild	22 (26.8)
APACHE II score	17.6±5.2
BMI	21.7±3.6
Chest infection	
No	42 (51.2)
Yes	40 (48.8)
Respiratory rate	26.8±5.5
Dyspnea MRC score	4 (1, 5)
pH	7.3±0.1
PCO <sub>2</sub> (mmHg)	70.7±21.7
PO <sub>2</sub> (mmHg)	70.2±30.9
HCO <sub>3</sub> (mEq/L)	29.0±9.1 (n=47)
Hb (g %)	13.4±2.8 (n=80)
TLC (/cmm)	15,075.6±5950.5
ESR (cm)	37.9±13.3
Urea	46 (4.6, 196)
Creatinine	1.1 (0.5, 6.9)
Albumin	3.5±0.6
Duration of hospital stay (days)	13 (1, 110)
Ventilation duration (days) <sup>#</sup>	9 (1, 34)

Data are expressed in mean±SD, median (minimum, maximum) or n (%), #n=51. SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, APACHE II: Acute Physiologic and Chronic Health Evaluation II, BMI: Body mass index, MRC: Medical Research Council, TLC: Total leukocyte count, ESR: Erythrocyte sedimentation rate

**Table 2: Baseline and predischarge clinical characteristics of the study group (n=82)**

Variables	At admission	At discharge	P
Respiratory rate (/min)	26.8±5.5	14.6±1.6	<0.001
Dyspnea MRC score	3.7±1.3	1.7±0.6	<0.001
pH	7.3±0.1	7.4±0.1	<0.001
PCO <sub>2</sub>	70.7±21.7	50.1±10.3	<0.001
PO <sub>2</sub>	76.2±30.9	88.3±16.2	0.001
HCO <sub>3</sub> (mEq/L)	29.0±9.1 (n=47)	28.2±6.5 (n=47)	0.575
Hb (g %)	13.4±2.8	12.6±1.2	0.002
Hematocrit (%)	44.2±8.5	41.2±5.9	<0.001
TLC (/cmm)	15,075.6±5950.5	9598.3±4196.4	<0.001
ESR (mm/1 <sup>st</sup> h)	37.9±13.3	24.4±9.5	<0.001
Sodium (mEq/L)	138.6±6.0	139.0±5.1	0.662
Potassium (mEq/L)	4.4±0.9	3.9±0.6	<0.001
Albumin (g/dl)	3.5±0.6	3.7±0.7	0.012
Urea (mg/dl)	46 (4.6, 196)	31 (13.0, 800)	<0.001
Creatinine (mg/dl)	1.1 (0.5, 6.9)	0.8 (0.4, 1.6)	<0.001
SGPT (U/L)	42.5 (12, 2710)	32 (10, 639)	<0.001
TNF- $\alpha$ (pg/ml)*	5.6 (0, 1321.2)	0.8 (0, 379.0)	0.039
Leptin (pg/ml)	1.1 (0, 88.8)	2.3 (0, 80.9)	0.001
Prealbumin (mg/dl)	11.7±5.6	15.2±2.8	0.001

Values are expressed in mean±SD/median (minimum, maximum), \*n=50. SD: Standard deviation, TLC: Total leukocyte count, ESR: Erythrocyte sedimentation rate, TNF- $\alpha$ : Tumor necrosis factor-alpha, SGPT: Serum glutamate pyruvate transaminase, MRC: Medical Research Council

between patients with mild/moderate and severe exacerbation, or between patients who required or did not require mechanical ventilation. A negative correlation was observed between baseline prealbumin and pH ( $r = -0.32$ ) as well as between the % increase in prealbumin and the % increase in pH ( $r = -0.2$ ). Baseline prealbumin was significantly correlated with duration of mechanical ventilation [Table 3]. However, this association was lost after adjusting for various confounders [Table 4]. No other associations were observed between leptin, prealbumin, and TNF- $\alpha$  with other clinico-laboratory variables.

## DISCUSSION

The results of this study indicate that plasma levels of leptin, prealbumin, and TNF- $\alpha$  are initially abnormal during an episode of AECOPD and lag behind other clinic-laboratory parameters during normalization with

**Table 3: Correlation between baseline values of measured biomarkers with various clinical and demographic parameters**

Variable	Leptin ( <i>r</i> )	TNF- $\alpha$ ( <i>r</i> )	Prealbumin ( <i>r</i> )
Age	0.05	0.05	-0.04
Duration of COPD	-0.01	0.16	-0.09
Smoking index	-0.27*	-0.02	-0.09
Duration of symptoms	0.05	-0.07	-0.08
Ventilation duration	0.08	-0.11	-0.23*
Duration of hospital stay	-0.09	-0.11	-0.07
APACHE II	0.03	0.17	-0.15
SBP	0.14	0.10	0.19
BP	0.22	0.12	0.11
BMI	0.45*	0.03	0.01
RR	0.05	0.04	-0.07
MRC	0.08	-0.09	-0.19
pH	-0.13	-0.03	-0.32*
PCO <sub>2</sub>	-0.04	-0.05	-0.03
HCO <sub>3</sub>	-0.13	0.02	-0.09
Hb	0.18	0.02	0.11
Hematocrit	0.12	0.06	-0.04
TLC	0.07	-0.03	0.18
SGPT	0.08	-0.02	0.14
ESR	-0.01	0.09	-0.18
Urea	-0.17	-0.18	0.11
Creatinine	-0.09	0.17	0.02
Sodium	0.04	-0.45*	-0.07
Potassium	-0.28*	0.16	-0.09
Albumin	0.22*	0.09	0.18
PO <sub>2</sub>	0.18	0.07	0.01

\*Significant at 0.05. *r*: Spearman correlation, TLC: Total leucocyte count, ESR: Erythrocyte sedimentation rate, TNF- $\alpha$ : Tumor necrosis factor-alpha, SGPT: Serum glutamate pyruvate transaminase, MRC: Medical Research Council, BMI: Body mass index, BP: Blood pressure, SBP: Systolic blood pressure, RR: Relative risk, COPD: Chronic obstructive pulmonary disease, APACHE II: Acute Physiologic and Chronic Health Evaluation II

clinical recovery. However, these biomarkers are unreliable prognostic indicators of morbidity indices such as duration of hospital stay and need of mechanical ventilation.

The presence of increased systemic inflammation during AECOPD has been demonstrated previously by measuring using various biomarkers.<sup>[4,7,11,12,28]</sup> Leptin levels increase acutely in patients with infection or inflammation<sup>[29]</sup> as well as during weight loss.<sup>[30]</sup> In addition, leptin is reported to be a predictor for physical and functional disability and quality of life in stable COPD.<sup>[31]</sup>

The relation between the TNF- $\alpha$  and leptin systems has not always been consistent, and reports have been conflicting.<sup>[28,31]</sup> Previous reports have demonstrated lower plasma levels of leptin and higher levels of TNF- $\alpha$  in stable COPD compared with controls, especially in those who were malnourished and belonged to the emphysema phenotype.<sup>[28]</sup> Breyer *et al.*<sup>[32]</sup> reported that circulating leptin correlated with CRP and fibrinogen, but not with IL-6 in 186 patients with stable COPD. These results contrasted with those observed in a similar previous study, where no such correlation was found.<sup>[33]</sup> In a large population-based study, plasma leptin was not found to be a reliable predictor for the presence of COPD compared to controls, thereby indirectly refuting the role of leptin in the pathogenesis of COPD. Another large prospective 3-year follow-up of 400 COPD subjects did not demonstrate a significant role of inflammation, but found an association between higher TNF- $\alpha$  and progressive loss of fat-free mass.<sup>[10]</sup> The mean TNF- $\alpha$  among our patients was lower than the normal range, thereby indicating that possibly the inflammatory process did not impact the TNF axis to a significant degree.

Reports of leptin in AECOPD are few and show conflicting results. Higher baseline levels of leptin among AECOPD patients compared to stable COPD and healthy controls have been documented.<sup>[34]</sup> In another analysis of 52 patients with AECOPD, higher leptin and TNF- $\alpha$  levels were observed on day 1 compared to day 15 of hospitalization, along with a positive correlation among both biomarkers. Conversely, no change in serum TNF- $\alpha$  levels were observed in 20 patients admitted with AECOPD over an 8-week period, although TNF- $\alpha$  correlated with change in forced expired volume in 1 s (FEV<sub>1</sub>).<sup>[12]</sup> In other reports, an independent correlation between circulating leptin and TNF- $\alpha$  has been demonstrated, regardless of age, sex, nutritional aspects, and the severity of disease.

The temporal profile of inflammatory mediators during an acute episode of COPD has been less extensively

**Table 4: Correlation of measured biomarkers with duration of ventilation and duration of hospital stay**

Variables	<i>n</i>	Median (minimum, maximum)	Duration of mechanical ventilation			Duration of hospital stay		
			<i>P</i>	Unadjusted $\beta$	Adjusted $\beta^*$	<i>P</i>	Unadjusted $\beta$	Adjusted $\beta^*$
TNF- $\alpha$	50	0 (0, 1321.2)	0.08	0.0006	0.0196	0.17	-0.0165	-0.1867
Leptin	82	1.08 (0, 88.8)	0.09	0.025	0.1002	0.17	-0.0324	-0.0531
Prealbumin	82	11.21 (2.02, 28.5)	0.07	-0.2402	-0.2159	0.18	-0.1685	-0.0623

\*Adjusted for BMI, PCO<sub>2</sub>, HCO<sub>3</sub>, sodium, home oxygen. BMI: Body mass index, TNF- $\alpha$ : Tumor necrosis factor-alpha



studied. Although sufficient evidence is available regarding increased inflammation as a risk factor for future exacerbations, the relationship of systemic inflammation with mortality and morbidity indices and recovery from exacerbation is undefined. Some reports have documented a definite association between inflammatory cytokines such as IL-6, IL-8, TNF-alpha, and fibrinogen with clinical recovery,<sup>[11,12,35]</sup> while others have failed to show such an association.<sup>[36,37]</sup> Similarly, although malnutrition *per se* may be associated with difficult weaning, specific inflammatory markers have not shown reliable correlation with important hospital outcomes. We have previously reported that the duration of mechanical ventilation in AECOPD is significantly related to baseline levels of IL-6 and fibrinogen.<sup>[35]</sup> However, no such association was found in the current study using a different panel of markers.

In addition, the lack of correlation between leptin and TNF- $\alpha$  in our group implies that leptin metabolism is perhaps not inflammation – induced. The reduced leptin levels among our patients at baseline might represent a down-regulation of leptin mRNA induced by several factors, leading to reduced leptin production. This appears to get corrected as clinical recovery occurs but still lags behind the rate of normalization of other parameters such as respiratory rate, PO<sub>2</sub>, TLC, and ESR.

Plasma prealbumin is a well-established indicator of nutritional status, and has been validated as a reliable marker of mortality, duration of hospital stay, and other adverse outcomes in several conditions, including heart failure,<sup>[38]</sup> stroke,<sup>[39]</sup> acute kidney injury,<sup>[40]</sup> and decompensated liver cirrhosis.<sup>[41]</sup> Prealbumin is the earliest serum protein that is altered during conditions of acute malnutrition and is most sensitive toward normalization following nutritional supplementation. Prealbumin presents quite a small body reserve and a short half-life (of approximately 2 days).<sup>[42]</sup> In states of systemic inflammation, hepatic production of prealbumin falls and is rapidly reflected in serum levels.<sup>[21]</sup> Conversely, prompt recovery occurs if adequate supplementation is provided. Gil Canalda *et al.*<sup>[43]</sup> found a positive correlation between the evolution time of AECOPD in 43 patients and the levels of albumin, PO<sub>2</sub> and FEV1. Gocmen *et al.*<sup>[14]</sup> demonstrated a significant correlation of prealbumin with parameters defining disease severity (duration of hospital stay, and FEV1 and FEV1/FVC values). Majority of our patients had normal/mildly deficient prealbumin levels at baseline, which improved with clinical recovery. We also observed an inverse association between baseline prealbumin and pH. This may be due to the fact that although both parameters increased with clinical recovery, the rate of normalization is likely to differ. pH tends to change acutely and rapidly, whereas the rate of prealbumin recovery depends on the adequacy of nutritional replacement. It was observed that our patients with severe exacerbation had a longer mean hospital stay (14.7 days), compared to patients with mild exacerbation (12.8 days; *P* = not significant), thereby allowing longer time for prealbumin

recovery. In previous reports, prealbumin has not been found to be a reliable marker of mortality; however, change in prealbumin following nutritional supplements, strongly predicted survival in cancer patients.<sup>[44]</sup>

It was also noted that although leptin and prealbumin improved from baseline until discharge, they were still below the recommended normal range. This perhaps implies that longer recovery time is needed for normalization, even in the case of prealbumin that has a relatively short half-life. It also indicates that these biomarkers lag behind other clinical and laboratory parameters as far as recovery to normal is concerned following an acute COPD episode.

Our study had some limitations. Since we did not have a healthy control group, we were unable to compare levels of the markers under study with non-COPD patients. In addition, concerns may be raised regarding increased leptin due to exogenous steroid administration as part of the management protocol of AECOPD. Data to this effect has been conflicting, with some reports on healthy subjects demonstrating increased leptin after a short course of oral steroids,<sup>[45,46]</sup> while others showed no such effect.<sup>[47]</sup> Since virtually all patients among our group received steroids for a variable period, a conclusive statement cannot be given on this issue. We did not have baseline spirometric data on majority of patients, since most of them were 1<sup>st</sup> time emergency visits, and, therefore, the diagnosis of COPD was made mainly on clinical grounds and past treatment records. Data regarding anthropometric measurements were not available. In addition, although it is likely that the acidosis observed in our patients was predominantly of respiratory etiology, other confounding factors such as renal dysfunction could not be accounted for when calculating change in pH and correlation with prealbumin. In spite of these shortcomings, the temporal trend observed in these biomarkers provides some useful information of their status in hospitalized patients with AECOPD.

## CONCLUSION

Plasma levels of leptin, TNF- $\alpha$ , and prealbumin are abnormal during episodes of AECOPD and lag behind other clinical and laboratory parameters during recovery. However, they are not reliable predictors of clinical outcomes in these patients.

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## Conflicts of interest

There are no conflicts of interest.

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