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Plasma 4-hydroxynonenal estimates severity and prognosis in patients with acute exacerbation of chronic obstructive pulmonary disease

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4-Hydroxynonenal (4-HNE), a product of lipid peroxidation, is recognized as a biomarker of oxidative stress. However, its relationship with the severity and prognosis of acute exacerbation in chronic obstructive pulmonary disease (AECOPD) remains unclear. This prospective cohort study aimed to investigate the associations between plasma 4-HNE levels and disease severity and prognosis in AECOPD patients. A total of 150 AECOPD patients, 80 stable COPD (SCOPD) patients, and healthy volunteers were enrolled. Plasma 4-HNE and inflammatory cytokines were measured using enzyme-linked immunosorbent assay (ELISA). Compared to healthy individuals, plasma 4-HNE levels were significantly elevated in both SCOPD and AECOPD patients, with progressively increasing alongside worsening pulmonary function and higher mMRC, CAT, and CCQ scores. In AECOPD patients, plasma 4-HNE was positively correlated with inflammatory cytokines, and linear regression analysis revealed that elevated plasma 4-HNE was associated with increased disease severity. Furthermore, higher plasma 4-HNE levels at admission were linked to prolonging hospital stays and AECOPD, indicating a poorer prognosis. Compared with several conventional biomarkers, plasma 4-HNE demonstrated superior predictive value for AECOPD and clinical outcomes. These findings suggest that plasma 4-HNE may be a useful biomarker for assessing severity and prognosis in AECOPD patients, potentially playing a role in the underlying pathophysiology of the disease.

Keywords COPD, 4-Hydroxynonenal, Cohort study, Pulmonary function, Prognosis

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and death worldwide and is characterized by airflow limitation[1]. COPD has become the fourth leading cause of death, and 328 million people were diagnosed with COPD globally in 2015[2]. In China, 13.7% of people over 40 years old suffer from COPD[3]. Tobacco smoke, ambient air pollution, underweight status and genetic factors are significant risk factors for COPD[4]. Symptoms of COPD include breathlessness, sputum production, and excessive mucus production. COPD decreases the ability to exercise in daily life and quality of life[5]. COPD is a chronic disease, and its course is characterized by acute exacerbation of respiratory impairment. Every acute exacerbation may promote disease progression and increase the risk of death and hospital admission for COPD patients[6–8]. Unfortunately, the prevalence of COPD is gradually increasing annually. Many studies have demonstrated that various clinical indicators have been broadly applied as prognostic factors for mortality in acute exacerbation of COPD (AECOPD) patients[9,10]. However, the predictive effectiveness of clinical indicators varies across studies. Therefore, it is essential to identify new biomarkers to monitor disease severity and guide the management of AECOPD patients.

The most important pathogeny for AECOPD is infection[8]. During the infection process, the body produces a series of antibacterial responses, including the generation of reactive oxygen species (ROS)[11]. ROS can react with cellular lipids and initiate lipid peroxidation[12]. 4-Hydroxynonenal (4-HNE) is an oxygen-containing unsaturated

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aldehyde originating from the lipid oxidation process of polyunsaturated fatty acids, including linoleic acid, linolenic acid and arachidonic acid[13]. 4-HNE is an important product of endogenous lipid peroxidation[14]. 4-HNE is maintained at a very low physiological level in cells or the body. Nevertheless, 4-HNE is evidently elevated when the body is subjected to oxidative stress[15,16]. As a significant product of oxidative stress in body, 4-HNE is also an important cell signaling molecule. Several studies have demonstrated that 4-HNE can react with enzymes and kinases in a variety of cell pathways, indicating that 4-HNE is involved in the physiological activities[17,18]. Lipid peroxidation induced by oxidative stress is related to many diseases in humans. There is growing evidence that oxidative stress is increased in patients with community-acquired pneumonia, airway inflammation, acute lung injury, and pulmonary fibrosis[19–23]. Moreover, oxidative stress plays a significant role in the pathogenesis of COPD[21].

4-HNE is also considered a biomarker of oxidative stress[24]. Previous studies have revealed that 4-HNE is increased in airway epithelial cells, alveolar epithelial cells and endothelial cells in COPD rat models. Moreover, an in vivo study indicated that 4-HNE is increased in a mouse model of cigarette smoke-evoked COPD[25]. Immunohistochemistry has revealed that 4-HNE is located in the lung tissues of COPD patients and mice[26,27]. Moreover, a previous study revealed that 4-HNE is increased in the lung tissues of COPD patients[26]. Therefore, we assume that 4-HNE may participate in the pathogenesis of AECOPD. However, the function of 4-HNE in AECOPD has not been clarified. Consequently, the purpose of this study was to explore the associations of plasma 4-HNE levels with disease severity and prognosis in patients with AECOPD.

Materials and methods

Subjects

In this study, AECOPD and stable COPD (SCOPD) patients were all enrolled from September 2020 to April 2021 in the Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Anhui Medical University. Pulmonary function tests were conducted in all COPD patients. A pulmonary function test was performed when the patient's condition was stable. We also recruited 150 healthy volunteers (CTRL) without respiratory diseases from the physical examination. Each healthy volunteer was matched with one AECOPD patient according to age, sex, and BMI. The diagnosis of COPD must meet the following criteria: forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) less than 0.7 and an FEV1% less than 80%[28]. The COPD patients were classified into three ranks according to pulmonary function: Grade 1–2, FEV1%>50; Grade 3, 30 < FEV1%<50; and Grade 4, FEV1%<50[29]. The exclusion criteria for patients were as follows: complicated with other respiratory diseases; serious complications and asthma; serious infection; malignant tumor patients; younger than 30 years; and organ transplants. All COPD patients were hospitalized for acute exacerbation of COPD. When AECOPD patients were admitted to the hospital before treatment on the first day, fasting blood samples were collected. SCOPD patients were recruited from the outpatients. Moreover, clinical information and demographic characteristics, including the length of hospital stay, history of smoking, number of exacerbations, and clinical laboratory results, were obtained from the electronic medical records system. The length of hospital stay was considered a prognostic outcome and was calculated from hospitalization. Additionally, a questionnaire survey was performed to evaluate disease severity in all COPD patients. This questionnaire included the modified British Medical Research Council (mMRC), COPD assessment test (CAT) score and Clinical COPD Questionnaire (CCQ)[30,31]. The study was approved by the Ethics Committee in The Second Affiliated Hospital of Anhui Medical University. All COPD patients and controls agreed to participate in this study and signed the informed consent form by themselves or their authorized children.

Enzyme-linked immunosorbent assay (ELISA)

Fasting blood samples were collected from all participants. Each blood sample was divided into two parts: one was placed in common blood collection tubes, and the other was placed in anticoagulant tubes containing EDTA-K2. After centrifugation (3500 g/min), the supernatant was collected from common blood collection tubes and anticoagulant tubes. Then, the plasma and serum were isolated. The samples were immediately stored at -80 °C[32,33]. 4-HNE-protein adducts were detected in plasma, and inflammatory cytokines were measured in serum through ELISA. Monocyte chemoattractant protein-1 (MCP-1) and 4-HNE ELISA kits were obtained from Cusabio, Wuhan, China (http://www.cusabio.com/). Tumor necrosis factor-α (TNF-α) ELISA kits (JYM0110Hu) were purchased from Wuhan Colorful Gene Biological Technology Co., Ltd. (http://www.jymbio.com/). The levels of 4-HNE in plasma, TNF-α and MCP-1 in serum were measured following the instructions with minor adjustments[34]. The standard 4-HNE in protein adducts was diluted, and a standard curve was established. The plasma samples and dilutions were added to each well. HRP-conjugated and enzyme-IgG antibodies were subsequently added to the ELISA plate and incubated. The ELISA plate was washed with wash buffer. Finally, the absorbance was measured at a wavelength of 450 nm[35,36].

Statistical analysis

All the statistical analyses were conducted via SPSS 21.0. Demographic information and clinical characteristics are expressed as the mean (standard error) or median (interquartile range). Differences in continuous variables were compared with two independent samples t tests. Differences in categorical variables were compared via the chi-square test. Associations between the plasma 4-HNE level and the clinical characteristics of AECOPD patients were analyzed through Pearson correlation analysis or Spearman correlation analysis. Linear and logistic regression analyses were performed to analyze the associations between plasma 4-HNE and severity and prognosis in AECOPD patients. Statistical significance was regarded as $P < 0.05$.

RESULTS

Demographic information and clinical characteristics

The demographic information and clinical characteristics are summarized in Table 1. No significant differences in sex, age, or body mass index (BMI) were observed among the AECOPD patients, SCOPD patients and healthy controls. The results suggested that the level of pulmonary function was greater in SCOPD patients than in AECOPD patients. Moreover, the severity was evaluated by the CAT, mMRC, and CCQ scores in AECOPD patients. We also detected several inflammatory cytokines in the three groups. While there was no difference of interleukin-6 (IL-6) contents in three groups, the levels of tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and monocyte chemotactic protein (MCP)-1 were significantly elevated in AECOPD patients compared to SCOPD patients and control subjects, particularly higher in AECOPD patients (Table 1).

The levels of plasma 4-HNE in different groups

Plasma 4-HNE levels were measured in different groups. As shown in Fig. 1A, the level of plasma 4-HNE was significantly higher in AECOPD and SCOPD patients than those in healthy volunteers. Moreover, the levels of plasma 4-HNE were greater in AECOPD patients compared with SCOPD patients (Fig. 1A). Moreover, we compared the levels of plasma 4-HNE in patients with different grades of AECOPD. The levels of plasma 4-HNE gradually increased with elevating grades among AECOPD patients (Fig. 1B). Moreover, the levels of plasma 4-HNE were further compared in AECOPD patients with different scores. As shown in Fig. 1C, the levels of plasma 4-HNE gradually increased in line with the mMRC score. The CAT score revealed that the levels of plasma 4-HNE was lower in patients with scores ≤ 23 than in those with scores > 23 in patients with AECOPD (Fig. 1D). There was no difference in plasma 4-HNE among AECOPD patients with different CCQ scores (Fig. 1E).

Associations of plasma 4-HNE with clinical characteristics in AECOPD patients

The associations between plasma 4-HNE levels and routine blood indices were analyzed in AECOPD patients via Pearson correlative analysis or Spearman correlative analysis. Pearson correlation analysis revealed that plasma 4-HNE was negatively associated with lymphocytes (r=-0.258, P=0.031) (Table 2). Moreover, the associations of plasma 4-HNE with renal function, liver function and myocardial function were assessed in AECOPD patients. As shown in Table 2, Spearman correlative analysis found that plasma 4-HNE was positively associated with alanine aminotransferase (ALT) (r=0.272, P=0.022), aspartate aminotransferase (AST) (r=0.261, P=0.030), total bilirubin (TBIL) (r=0.249, P=0.040), direct bilirubin (DBIL) (r=0.209, P=0.007), and lactate dehydrogenase (LDH) (r=0.354, P=0.012) levels. In addition, the levels of plasma 4-HNE were positively associated with D-dimer (r=0.209, P=0.007), procalcitonin (PCT) (r=0.331, P=0.043), and fibrinogen (FIB) (r=0.235, P=0.045) in patients with AECOPD. Moreover, the association between plasma 4-HNE and pulmonary function was assessed in AECOPD patients. As shown in Fig. 2A and D, Pearson correlative analysis indicated that plasma 4-HNE was negatively correlated with FEV1% (r=-0.500, P<0.001), FVC (r=-0.298, P<0.001), FEV1 (r=-0.410, P<0.001), and FEV1/FVC% (r=-0.259, P=0.002) in AECOPD patients. Additionally, serum 4-HNE was positively associated with the levels of inflammatory cytokines (MCP-1, TNF-α, IL-6, and CRP) in AECOPD patients (Fig. 2E and H).

Association of plasma 4-HNE with severity in AECOPD patients

As shown in Table 3, although there was no association of plasma 4-HNE with the scores of CAT or mMRC, linear regression analysis indicated that plasma 4-HNE was positively associated with the CCQ score (β = 0.171, 95% CI: 0.018 ~ 0.398) and inversely associated with the FEV1% (β=-0.512, 95% CI: -0.899~-0.018) in AECOPD

Variables	Control (n = 150)	SCOPD (n = 80)	AECOPD (n = 150)	P
Age (years)	75.54 ± 3.65	70.32 ± 1.21	73.84 ± 0.69	0.300
Male, n (%)	99 (66.0)	56 (70.0)	112 (74.8)	0.214
BMI	22.35 ± 0.32	23.01 ± 0.14	22.65 ± 0.29	0.087
FEV1 (%)	N.A.	1.14 (0.71, 1.52)	0.94 (0.66, 1.35)	<0.01
FEV1/FVC (%)	N.A.	69.25 (50.35, 94.56)	53.34 (44.41, 71.51)	<0.01
FEV1 (L)	N.A.	1.15 (0.75, 1.53)	0.94 (0.66, 1.35)	<0.05
FVC (L)	N.A.	2.22 (1.65, 2.65)	1.90 (1.40, 2.33)	<0.05
Hospital stays (day)	N.A.	N.A.	10 (8, 14)	N.A.
CAT score	N.A.	N.A.	26 (21, 30)	N.A.
mMRC score	N.A.	N.A.	3 (2, 3)	N.A.
CCQ score	N.A.	N.A.	32 (27, 38)	N.A.
CRP (mg/L)	2.3 (0.6, 7.6)	11.5 (3.5, 33.9)	28.8 (8.2, 54.9)	<0.05
IL-6 (pg/mL)	2.3 (0.9, 6.5)	3.5 (0.8, 13.5)	6.0 (2.1, 21.3)	0.095
MCP-1 (pg/mL)	22.6 (11.3, 42.3)	54.5 (10.3, 98.5)	103.1 (72.1, 126.9)	<0.01
TNF-α (pg/mL)	18.9 (3.2, 33.8)	35.5 (12.3, 87.9)	64.4 (50.7, 109.2)	<0.01

Table 1. Demographic information and clinical characteristics. FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; N.A., not available.

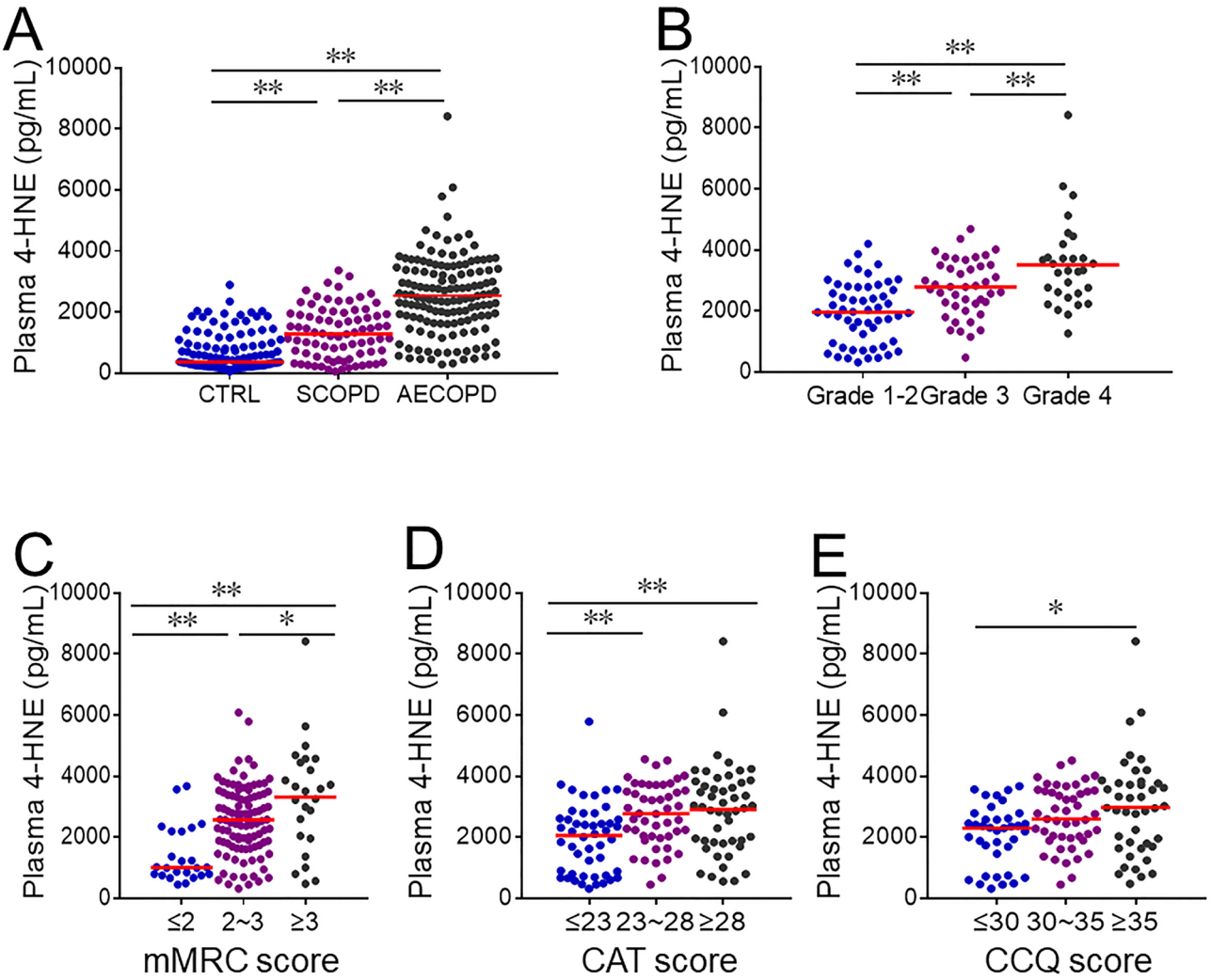

Fig. 1. Plasma 4-HNE concentrations in COPD patients and control subjects. Plasma 4-HNE was measured via ELISA and compared in different groups. (**A**) Plasma 4-HNE concentrations in the three groups ($n = 150$ for control subjects; $n = 150$ for AECOPD patients; $n = 80$ for SCOPD patients). (**B**) Plasma 4-HNE concentrations in AECOPD patients with different grades. (**C**) Plasma 4-HNE concentration in AECOPD patients with different mMRC scores. (**D**) Plasma 4-HNE concentrations in AECOPD patients with different CAT scores. (**E**) Plasma 4-HNE concentrations in AECOPD patients with different CCQ scores. $^{*}P < 0.05$, $^{**}P < 0.01$.

Variables	WBC	Neutrophil	Lymphocyte	Monocytes	Eosinophil	Basophil
r	-0.031	-0.020	-0.258	0.048	0.019	0.097
P	0.356	0.408	0.031	0.287	0.414	0.128
Variables	Uric acid	Urea nitrogen	Creatinine	ALT	AST	TBIL
r	-0.027	0.031	-0.035	0.272	0.261	0.249
P	0.374	0.360	0.341	0.022	0.030	0.040
Variables	DBIL	CKMB	LDH	cTnI	CK	D-Dimer
R	0.209	0.002	0.354	0.038	0.050	0.387
P	0.007	0.493	0.012	0.358	0.317	0.011
Variables	APTT	PT	BNP	PLT	PCT	FIB
r	0.160	0.114	-0.042	-0.085	0.331	0.235
P	0.243	0.087	0.313	0.160	0.043	0.045

Table 2. Associations between plasma 4-HNE and clinical characteristics in AECOPD patients.

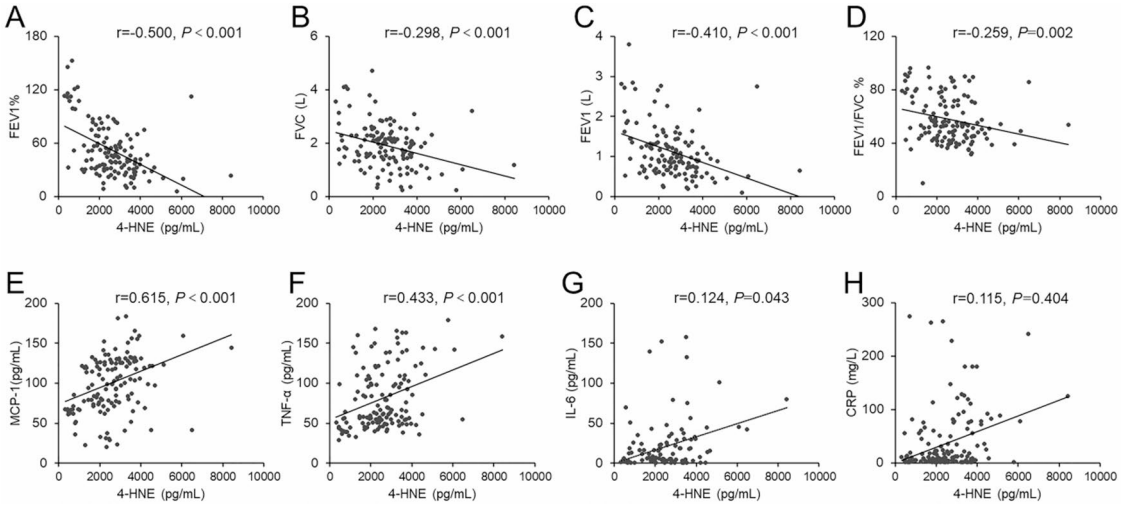

Fig. 2. Associations among plasma 4-HNE concentration, pulmonary function and inflammatory cytokines in AECOPD patients. (**A**) Associations between plasma 4-HNE concentration and FEV1% in AECOPD patients. (**B**) Association between plasma 4-HNE concentration and FVC in AECOPD patients. (**C**) Association between plasma 4-HNE concentration and FEV1 in AECOPD patients. (**D**) Association between plasma 4-HNE concentration and FEV1/FVC% in AECOPD patients. (**E**) Association between plasma 4-HNE concentration and MCP-1 concentration in AECOPD patients. (**F**) Association between plasma 4-HNE concentration and TNF-α level in AECOPD patients. (**G**) Association between plasma 4-HNE concentration and the IL-6 concentration in AECOPD patients. (**H**) Association between plasma 4-HNE concentration and CRP level in AECOPD patients.

	Univariable (β, 95% CI)	*P*	Multivariable (β, 95% CI) *	*P*
CAT	0.145 (-0.012, 0.365)	0.132	0.156 (0.038, 0.454)	0.663
CCQ	0.171 (0.018, 0.398)	0.041	0.146 (0.092, 0.435)	0.031
mMRC	0.106 (0.001, 0.121)	0.245	0.092 (0.100, 0.235)	0.336
FEV1%	-0.512 (-0.899, -0.018)	<0.001	-0.478 (-0.922, -0.026)	<0.001

Table 3. Association of plasma 4-HNE with severity in AECOPD patients. *Age, sex, BMI, comorbidities, and smoking status were adjusted.

patients. To control for confounding factors, age, sex, BMI, comorbidities, and smoking status were adjusted. Multivariate linear regression analysis was carried out. The results revealed that there was a positive correlation between plasma 4-HNE and CCQ score (β = 0.146, 95% CI: 0.092 ~ 0.435), and inverse correlation of plasma 4-HNE with FEV1% (β=-0.478, 95% CI: -0.922~-0.026) in AECOPD patients.

Association of plasma 4-HNE with hospital stay in COPD patients

We further compared the levels of plasma 4-HNE in AECOPD patients with different durations of hospital stay. Plasma 4-HNE concentrations were significantly higher in patients with ≥ 13 hospital days compared with ≤ 8 and 8 ~ 13 days (Fig. 3). As shown in Table 4, logistic regression analysis confirmed the odds ratio (OR) of hospital day was evidently increased in cases with ≥ 13 hospital days (OR = 1.331, 95% CI: 1.078 ~ 1.732). After adjusting for age, sex, BMI, comorbidities, and smoking status, plasma 4-HNE levels were still positively correlated with the risk of ≥ 13 days of hospital stay (OR = 1.298, 95% CI: 1.047 ~ 1.712) in AECOPD patients.

The ability of plasma 4-HNE to predict prognosis in COPD patients

The predictive capacities of plasma 4-HNE and common biomarkers for prognosis were analyzed through the receiver operating characteristic (ROC) area under the curve (AUC). As shown in Fig. 4A, the AUCs of AECOPD were as follows: 4-HNE, 0.847 (95% CI: 0.780 ~ 0.914); PCT, 0.476 (95% CI: 0.385 ~ 0.567); neutrophil count, 0.722 (95% CI: 0.642 ~ 0.802); IL-6, 0.622 (95% CI: 0.533 ~ 0.710); and CRP, 0.670 (95% CI: 0.585 ~ 0.756). The optimal cutoff value of plasma 4-HNE for AECOPD patients was 1223.88 pg/mL, with a specificity of 82.5% and a sensitivity of 76.9%. Moreover, the predictive powers for longer hospital stays in AECOPD patients were as follows: 4-HNE, 0.814 (95% CI: 0.718 ~ 0.910); PCT, 0.484 (95% CI: 0.341 ~ 0.628); neutrophil count, 0.544 (95% CI: 0.414 ~ 0.674); IL-6, 0.566 (95% CI: 0.432 ~ 0.699); and CRP, 0.558 (95% CI: 0.420 ~ 0.697) (Fig. 4B). The optimal cutoff concentration of plasma 4-HNE was 2729.10 pg/mL. The specificity was 54.5%, and the sensitivity was 95.7%.

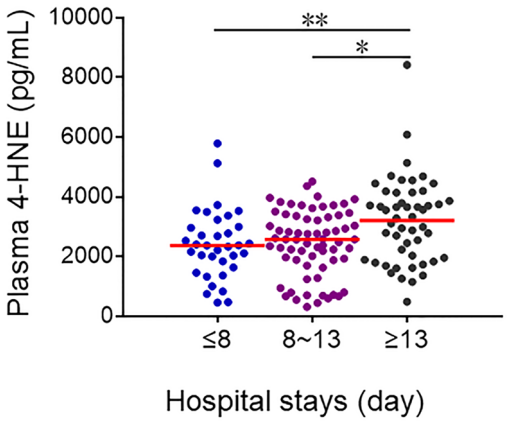

Fig. 3. The levels of plasma 4-HNE in AECOPD patients with different lengths of hospital stay. The levels of plasma 4-HNE in AECOPD patients with different hospital stays. *$P<0.05$, **$P<0.01$.

	Univariable (OR, 95% CI)	*P*	Multivariable (OR, 95% CI) *	*P*
Hospital stays (d)				
≤ 8	1	—	1	—
8 ~ 13	0.669 (0.365, 1.354)	0.879	1.221 (0.987, 1.652)	0.692
≥ 13	1.331 (1.078, 1.732)	0.021	1.298 (1.047, 1.712)	0.028

Table 4. Association of plasma 4-HNE with prognosis in AECOPD patients. *Age, sex, BMI, comorbidities, smoking status, and FEV1% were adjusted.

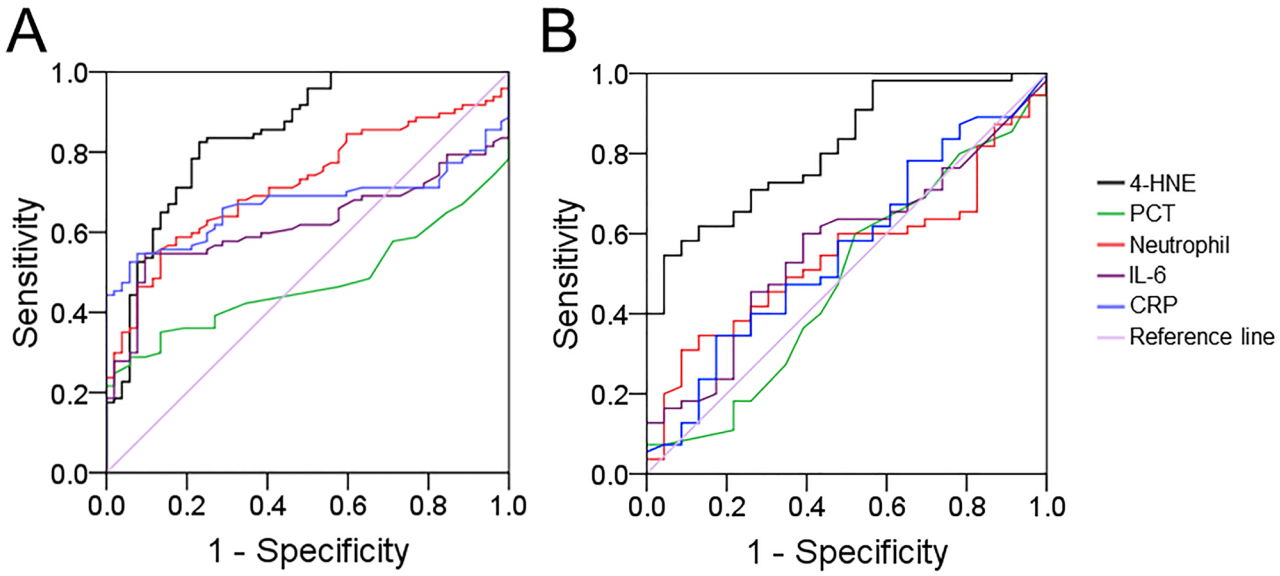

Fig. 4. The predictive power for AECOPD and length of hospital stay. The predictive power for AECOPD and hospital stay duration was analyzed through receiver operating characteristic curves for different predictive biomarkers at admission. (A) The predictive power of plasma 4-HNE, IL-6, CRP, neutrophil count and PCT for AECOPD was analyzed. (B) The predictive power of plasma 4-HNE, IL-6, CRP, neutrophil count and PCT for hospital stay was analyzed.

DISCUSSION

The purpose of this study was to estimate the relationships between plasma 4-HNE and severity and prognosis in AECOPD patients via a prospective cohort study. The findings of this study were as follows:[1] Plasma 4-HNE was increased in patients with AECOPD and SCOPD, particularly in patients with AECOPD[2]. Plasma 4-HNE

gradually increased as pulmonary function decreased in AECOPD patients[3]. Plasma 4-HNE was inversely correlated with pulmonary function in AECOPD patients[4]. Increased plasma 4-HNE elevated the length of hospital stay in AECOPD patients during hospitalization[5]. Compared with several common COPD biomarkers, plasma 4-HNE levels were better at predicting AECOPD and prolonged hospital stays.

An earlier study revealed that 4-HNE can upregulate the expression of transcription factors, such as nuclear factor-κB (NF-κB), which in turn regulates genes involved in cell proliferation and differentiation[37]. Previous studies have indicated that excessive NF-κB activation is closely correlated with many diseases, such as rheumatoid arthritis, cardiovascular and nervous system diseases[38–40]. In addition, 4-HNE can promote inflammation by stimulating the production of several inflammatory cytokines[41]. During the last decade, experimental evidence has indicated that 4-HNE is not only the product of oxidative stress but also a cell signaling molecule[42,43]. Previous results indicated that 4-HNE is increased in models of lipopolysaccharide-induced acute lung injury, bleomycin-evoked pulmonary fibrosis, and monocrotaline-induced pulmonary arterial hypertension[44–46]. Moreover, it is widely known that oxidative stress plays central roles in the occurrence and development of COPD[21]. Therefore, we speculate that 4-HNE may be involved in the pathogenesis of AECOPD. This study suggest that COPD patients have higher levels of plasma 4-HNE than healthy volunteers do, especially those with acute exacerbations. Pearson or Spearman correlative analyses found that plasma 4-HNE expression was closely associated with various clinical characteristics among AECOPD patients. In addition, linear regression analysis found plasma 4-HNE expression was positively related to the severity of AECOPD patients. So, we speculate that 4-HNE may be involved in the pathophysiology of AECOPD.

As shown in our previous studies, inflammation and oxidative stress are related to pulmonary function decline in COPD patients[29,47,48]. Increasing amounts of data have revealed that increased levels of inflammatory cytokines elevate the occurrence and development of COPD[49]. Moreover, an increasing number of studies have shown that redox imbalance and lipid peroxidation can serve as prognostic biomarkers in many diseases. An earlier retrospective cohort study suggested that serum 8-isoprostane and 8-hydroxydeoxyguanosine can predict the severity and prognosis of community-acquired pneumonia patients[19,50]. Serum malondialdehyde is positively correlated with adverse outcomes in patients with chronic heart failure[51]. The level of glutathione can reflect drug resistance and adverse effects in patients with lung cancer[52]. Some studies have shown that oxidative stress is one of the important causes of airway constriction and COPD[53]. Oxidative stress is a significant precursor of increased ROS in the human body[54]. ROS are produced by oxidative stress. It is correlated with lipid peroxidation and an imbalance in the redox system[14]. In fact, 4-HNE is also a biomarker of oxidative stress and lipid peroxidation. Moreover, we consider it to be one of the most powerful reactive aldehydes[24]. Therefore, the association between plasma 4-HNE and prognosis was evaluated in AECOPD patients.We found that the levels of plasma 4-HNE at admission were elevated in AECOPD patients with longer hospital stays, and were positively associated with the length of hospital stay in AECOPD patients. Additionally, the predictive power of plasma for AECOPD and hospital stay duration was greater than that of common biomarkers. This study demonstrated that the plasma 4-HNE at admission can predict the length of hospital stay among AECOPD patients.

Several studies have shown that increased 4-HNE may promote the progression of kidney and colon cancer[55,56]. In addition, 4-HNE can form adducts with enzymes in the electron transport chain complex, which promotes tumor metastasis[57]. 4-HNE or 4-HNE-protein adducts are elevated in some organs and tissues of diabetic patients and animal models of diabetes[58]. A recent study revealed that 4-HNE protein adducts are always found in vital organs and are particularly associated with inflammation, edema and tissue destruction in dead COVID-19 patients[59]. Because 4-HNE is increased in several diseases and disease complications, 4-HNE has been used as a therapeutic target in many diseases. ALDH2 (aldehyde dehydrogenase 2), an inhibitor of 4-HNE and a small molecule activator named Alda-1, can promote the production of ALDH2[60]. An earlier study showed that pretreatment of alveolar epithelial cells with Alda-1 can prevent pulmonary ischemia–reperfusion injury by reducing the production of 4-HNE[61]. Another study revealed that ARPE-19 cells exposed to quercetin display increased resistance to 4-HNE-mediated damage[62]. These data provide evidence that 4-HNE may be used as a therapeutic target for COPD in the future.

Although this study enhances the understanding of the role of 4-HNE in COPD, there are several limitations in this study. First, this was a single-center study with a small sample size. All selected samples were from a certain hospital, which inevitably introduces certain biases. Therefore, a larger sample from multiple centers is needed in the future. Second, this was a correlation analysis based on the hospital population, and the mechanism of 4-HNE elevation in AECOPD patients was unclear. Only animal experiments and cell experiments may help resolve this puzzle. Finally, 4-HNE is only measured in plasma via ELISA, and the concentrations of 4-HNE in lung tissues and bronchoalveolar lavage fluid of COPD patients are unknown.

Conclusion

In summary, this study analyzed the associations of plasma 4-HNE with the severity and prognosis of AECOPD patients. Our results revealed that plasma 4-HNE is elevated in COPD patients, especially in AECOPD patients, compared with control subjects. The plasma 4-HNE level increases with elevating severity in AECOPD patients. Additionally, plasma 4-HNE is inversely associated with pulmonary function in AECOPD patients. Higher plasma 4-HNE levels on admission elevates the risks of prolonging hospital stay and AECOPD patients. As substantial evidence shows, 4-HNE may play an important role in the pathophysiological process of COPD. Plasma 4-HNE may be a viable biomarker for predicting the severity and prognosis of AECOPD patients. Moreover, 4-HNE may also be a therapeutic target for treating AECOPD in future clinical work.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Lin Fu conceived the study; Lin Fu designed the study; Lin Fu, Dong-Mei Su, Chen Zhang, Meng-Die Li, Peng Cao performed the research; Lin Fu conducted the statistical analyses of all the data. Chen Zhang and Xiaoqiong Wang drafted the manuscript. All the authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.
The authors declare that they have no conflicts of interest.

Ethics declarations

This study was supported by the Ethics Committee of Anhui Medical University and met the principles expressed in the Declaration of Helsinki. All the COPD patients and controls agreed to participate in this study and signed the informed consent form by themselves or their authorized children.

Additional information

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