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Treatment of chronic obstructive pulmonary disease in patients with different fractional exhaled nitric oxide levels

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Abstract

Some patients with chronic obstructive pulmonary disease (COPD) have eosinophilic inflammation which may be evaluated via the measurement of fractional exhaled nitric oxide (FeNO) like asthma. The aim of this prospective study was to assess whether FeNO levels can be used to identify patients with COPD with eosinophilic inflammation who may respond to inhaled corticosteroid (ICS) therapy.

This study included patients (N = 112) with COPD (age >18 years) who were divided into 4 groups depending upon whether they had high (≥25 parts per billion [ppb]) or low (<25 ppb) pretreatment (baseline) FeNO and if they were treated with either ICS plus long-acting β-agonist (ICS + LABA) or a long-acting muscarinic antagonist (LAMA). The 4 groups were: high FeNO/ICS + LABA, high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA. Outcomes assessed included FeNO, COPD assessment test (CAT), and pulmonary function.

The high FeNO/ICS + LABA group had the greatest reduction from baseline in FeNO levels (−25.80 ppb ± 27.14) compared with the high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA groups (range, −4.45 to 1.31 ppb; $P < .001$). The high FeNO/ICS + LABA group also showed the greatest improvement in CAT (−7.20), which was statistically larger than the low FeNO/ICS + LABA and low FeNO/LAMA groups (−1.72 and −2.03, respectively). No difference in pulmonary function following treatment was observed across the 4 groups.

This study found that patients with high FeNO showed the greatest reduction in FeNO and improvement in CAT with ICS + LABA therapy, supporting the use of FeNO to identify patients who would benefit from ICS use.

Abbreviations: CAT = COPD assessment test, COPD = chronic obstructive pulmonary disease, FeNO = fractional exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, ICS = inhaled corticosteroid, IL = interleukin, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum mid-expiratory flow, ppb = parts per billion.

Keywords: chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, fractional exhaled nitric oxide, inhaled corticosteroid, inflammation, inhaled corticosteroids

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is poorly reversible and has an enhanced chronic inflammatory response.[1] COPD is one of the most prevalent noninfectious diseases worldwide and is anticipated to become the 3rd leading cause of death across the world by 2020.[1] The cost and health burden of COPD is high as it contributes to other comorbidities such as fractures, respiratory infections, osteoporosis, lung cancer, and cardiovascular disease.[1]

Airway inflammation in COPD is thought to be mainly characterized by CD8+ lymphocytes, neutrophils, and macrophages. However, some patients with COPD may have features of asthma, a condition called asthma COPD overlap syndrome, and subsequently have Th2-mediated airway eosinophilia-based inflammation; about 20% to 40% of patients with COPD have eosinophilic inflammation.[1] Th2-mediated airway inflammation can be evaluated through the measurement of fractional exhaled nitric oxide (FeNO).[2] Epithelial cells of the bronchial wall produce nitric oxide gas in response to interleukin (IL) 13 and IL4 through the STAT-6 pathway.[2] Several studies have found that FeNO levels are a strong predictor of the presence of eosinophilic inflammation in patients with COPD.[3,4] One study found that aggressive treatment of patients with COPD to minimize sputum eosinophilia may decrease the incidence of severe exacerbations and hospitalizations.[5] Measurement of FeNO using hand-held analyzers is a quick and easy method for measuring FeNO in clinical practice.

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The COPD is a heterogeneous disease and patients can have differing phenotypes. The different phenotypes can affect treatment response to therapy.[6,7] Prior studies have found that patients with sputum eosinophilia during an exacerbation may be more responsive to corticosteroid treatment than those without eosinophilia.[7] In addition, other investigators have shown that FeNO levels may also be predictive of corticosteroid and bronchodilator treatment response.[8,9]

Monotherapy with inhaled corticosteroids (ICSs) is not recommended in the treatment of COPD, instead it is recommended to be co-administered with a long-acting β-agonist (LABA).[1] ICS treatment can be costly and can increase the risk of certain complications such as cataracts, glaucoma, pneumonia, and osteoporosis. Hence, it would be of benefit if ICS therapy could be targeted to patients with COPD with Th-2-mediated inflammation who would have a greater likelihood of responding to ICS combination treatment.[3]

The purpose of the study was to evaluate if FeNO can be used to identify patients with COPD with eosinophilic inflammation who are more likely to respond to ICS + LABA therapy.

2. Methods

This prospective study was performed in accordance with the Declaration of Helsinki and complied with International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. The study was approved by Taipei Buddhist Tzu-Chi General Hospital's Institutional Review Board. All subjects gave their written informed consent.

2.1. Study population

Patients (>18 years of age) were recruited from the out-patient clinic of Taipei Buddhist Tzu-Chi General Hospital from July 2014 to June 2016. Included patients had clinical diagnosis of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 guidelines; patients had dyspnea, chronic cough, and/or sputum production, had history of exposure to risk factors for the disease, had a postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <70%.[1] Eligible patients were treatment naive, had never smoked or quit smoking >3 months from study start. Subjects with acute respiratory tract diseases, atopy, medical history of asthma, or other allergic diseases, such as allergic rhinitis, allergic conjunctivitis, and allergic dermatitis, were excluded.

2.2. Study design

The FeNO levels were measured using a hand-held analyzer (NIOX MINO; Aerocrine, Solna, Sweden) at a constant expiratory flow of 50 mL/s. The analyzers were calibrated according to the manufacturer's instructions. Exhaled gases were always collected prior to pulmonary function tests to avoid interference. Patients were treated with either ICS + LABA or long-acting muscarinic antagonist (LAMA). In addition, all patients received a short-acting β-agonist for rescue medication.[3] In this study design, our patients would not receive ICS, LABA, and LAMA triple treatment. Assignment of patients to ICS + LABA or LAMA therapy was based on random number table after grouping by FeNO levels. Thus finally the patients were divided into 4 groups: high FeNO (≥25 parts per billion [ppb]) treated with ICS + LABA, high FeNO treated with LAMA, low FeNO (<25 ppb) treated with ICS + LABA, and low FeNO treated with LAMA. The division of high and low FeNO was based on the American Thoracic Society Committee on interpretation of exhaled nitric oxide levels.[10]

Outcomes measured included FeNO, FVC, FVC% predicted, FEV1, FEV1% predicted, maximum midexpiratory flow (MMEF), and MMEF% predicted. Bronchodilator reversibility was defined as the change from baseline (prebronchodilator therapy) in FEV_1 or FVC 30 minutes after inhalation of 100 μg of Fenoterol. Severity of symptoms was evaluated with the COPD assessment test (CAT), as recommended in the GOLD 2013 guidelines. CAT t is used to evaluate the impact of COPD on the wellbeing and daily life of a patient.[1]

2.3. Statistical analysis

Mean and standard deviation (SD) are presented for continuous variables and counts and proportion are presented for categorical variables. The 4 patient groups were compared using analysis of variance in pre- and posttreatment values and the difference between pre- and posttherapy. If 4 groups were significantly different, a posthoc test using the Tukey method was performed. All statistical assessments were 2-tailed and considered significantly different as $P < .05$. All analyses were performed using R Core Team (2016).[11]

3. Results

A total of 112 patients were enrolled and grouped into 4 groups according to their pretreatment FeNO levels and treatment received. Demographics and baseline characteristics were similar across the 4 treatment groups (Table 1). The study had more males (86.0%) than females (14.6%), and more patients were in the low FeNO group than the high FeNO group. The median age for the entire study population was about 72 years and the majority (72.0%) were ex-smokers. The majority of patients (53.0%) had GOLD B stage of COPD and 73.0% were negative for bronchodilator test. Baseline characteristics of the low and high FeNO groups independent of treatment are summarized in Supplemental Table 1, http://links.lww.com/MD/C631.

Prior to therapy, FeNO, FVC, FEV_1, and FEV_1% predicted differed among the 4 groups (Table 2). Patients in the high FeNO/ICS + LABA group had significantly higher FeNO level compared to other 3 groups ($P < .001$). Patients in the low FeNO/ICS + LABA group had lower FEV_1, FEV_1% predicted, and FVC compared with the other 3 groups ($P \leq .029$).

Following therapy, FeNO and FEV_1 differed across the 4 groups (Table 3). Patients in the high FeNO groups had highest posttreatment FeNO compared with the low FeNO groups and this difference was significant compared with the 2 low FeNO groups ($P < .001$). Patients in the low FeNO/ICS + LABA group had the lowest FEV_1 compared with the other 3 groups, and this was statistically significant compared with patients in the low FeNO/LAMA group ($P = .036$). After adjusting for factors that were significantly different at baseline (i.e., FVC, FEV_1, and FEV_1% predicted) in the low FeNO group, no differenced were found between ICS + LABA and LAMA therapies ($P = .687$ for FVC, .205 for FEV_1, and .246 for FEV_1% predicted).

A significant change from baseline in FeNO (−25.80 ppb) was observed only in the group of patients with high baseline FeNO and who received ICS + LABA (Table 4). Improvement in CAT was observed in all groups except the low FeNO/ICS + LABA group. The patients in the high FeNO/ICS + LABA group had significantly greater improvement in CAT than the other 3

Table 1

Summary of demographic characteristics of the 4 groups (n = 112).

Variables	Total	High FeNO		Low FeNO		*P*-value
		ICS + LABA	LAMA	ICS + LABA	LAMA	
Demography						
Gender, n (%)						.923
Male	96 (85.7)	17 (85.0)	18 (90.0)	30 (83.3)	31 (86.1)	
Female	16 (14.3)	3 (15.0)	2 (10.0)	6 (16.7)	5 (13.9)	
Age, median (range)	71.98 ± 12.29	67.33 ± 12.62	74.62 ± 11.02	74.03 ± 10.19	71.04 ± 14.18	.172
BMI, median (range)	23.50 ± 3.74	22.17 ± 4.30	23.96 ± 3.31	23.80 ± 4.09	23.58 ± 3.21	.386
Smoking, n (%)						
Never	31 (27.7)	4 (20.0)	4 (20.0)	7 (19.4)	16 (44.4)	.059
Ex-smoker	81 (72.3)	16 (80)	16 (80)	29 (80.6)	20 (55.6)	
GOLD, n (%)						
A	24 (21.4)	3 (15.0)	4 (20.0)	6 (16.7)	11 (30.6)	.301
B	59 (52.7)	11 (55.0)	13 (65.0)	16 (44.4)	19 (52.8)	
C	6 (5.4)	0	1 (5.0)	4 (11.1)	1 (2.8)	
D	23 (20.5)	6 (30.0)	2 (10.0)	10 (27.8)	5 (13.9)	
Bronchodilator test, n (%)						
Positive	30 (26.8)	6 (30.0)	3 (15.0)	11 (30.6)	10 (27.8)	.615
Negative	82 (73.2)	14 (70.0)	17 (85.0)	25 (69.4)	26 (72.2)	

FeNO = fractional exhaled nitric oxide, GOLD = Global Initiative for Chronic Obstructive Lung Disease, ICS = inhaled corticosteroid, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist.

groups. Using the findings presented in Table 4, the cut-off for CAT improvement from baseline to 5 was established, and it could be determined whether baseline values influenced changes in CAT. In the high FeNO group receiving ICS + LABA, no differences were observed in baseline FeNO values between subjects with changes in CAT of ≤ 5 from baseline (n = 9) (43.22 ± 21.95) and those with a changes in CAT of >5 from baseline (n = 11) (61.73 ± 34.57) ($P = .182$).

The patients in the high FeNO/ICS + LABA group had the greatest improvement in pulmonary function from baseline compared with the other 3 groups, although this did not reach statistical significance ($P \geq .072$).

4. Discussion

The aim of this study was to assess whether baseline (pretreatment) FeNO can be used to identify patients who will respond to ICS + LABA therapy. The high FeNO/ICS + LABA group had the highest levels of FeNO at baseline, and was the only group to show a significant reduction (about −25.8%) from baseline in FeNO levels following therapy. This reduction was greater than the high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA groups (−4.45%, +1.31%, +0.5% change, respectively; $P < .001$). However, the levels of FeNO in the FeNO/ICS LABA group were still significantly higher than that in the 2 low FeNO groups. The high FeNO/ICS + LABA group showed the greatest improvement in CAT, which was statistically larger compared with the 2 groups with low baseline FeNO. No difference in pulmonary function was observed across the 4 groups. These finding indicate that FeNO can be used as a biomarker to identify patients with COPD who will respond to ICS + LABA treatment.

Our findings are consistent with other studies that found that FeNO levels may predict treatment response to ICS and bronchodilatory therapy.[8,9,12,13] Antus et al (2010) found that in patients with COPD (N = 58), who were hospitalized due to an exacerbation and treated with ICS and bronchodilators, a significant correlation between FeNO at admission and increase

Table 2

Summary of pretreatment FeNO, CAT, and pulmonary function test.

Variables*	Pretest				*P*-value
	High FeNO		Low FeNO		
	ICS + LABA	LAMA	ICS + LABA	LAMA	
FeNO, ppb	53.40 (40.09–66.71)	36.80 (31.43–42.17)†	14.25 (12.54–15.96)†	14.36 (12.65–16.07)†	**<.001**
CAT	20.85 (16.69–25.01)	15.05 (12.40–17.70)	16.11 (13.17–19.05)	14.19 (11.98–16.40)	.062
Pulmonary function test					
FVC, L	2.27 (1.94–2.60)	2.31 (2.02–2.60)	1.93 (1.75–2.11)	2.32 (2.10–2.54)‡	**.024**
FVC % predicted	77.95 (69.74–86.16)	81.35 (76.47–86.23)	72.42 (66.15–78.69)	78.50 (73.95–83.05)	.204
FEV_1, L	1.31 (1.09–1.53)	1.42 (1.18–1.66)	1.16 (1.02–1.30)	1.48 (1.32–1.64)‡	**.019**
FEV_1% predicted	57.30 (48.85–65.75)	64.50 (57.97–71.03)	54.86 (50.06–59.66)	64.08 (59.87–68.29)‡	**.029**
FEV_1/FVC	58.15 (52.51–63.79)	61.30 (56.58–66.02)	61.50 (56.36–66.64)	64.14 (61.18–67.10)	.305
MMEF, L/s	0.71 (0.53–0.89)	0.85 (0.67–1.03)	0.76 (0.56–0.96)	0.91 (0.75–1.07)	.394
MMEF % predicted	30.50 (23.03–37.97)	39.60 (32.45–46.75)	33.72 (27.47–39.97)	37.94 (33.06–42.82)	.267

CAT = COPD assessment test, FeNO = fractional exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ICS = inhaled corticosteroid, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum mid-expiratory flow, ppb = parts per billion.

* All values are mean (95% confidence interval).

† Posthoc Tukey test indicated findings were significantly different than the high FeNO and ICS + LABA group.

‡ Posthoc Tukey test indicated findings were significantly different than the low FeNO and ICS + LABA group.

Table 3

Summary of posttreatment FeNO, CAT, and pulmonary function tests.

	Posttest				
	High FeNO		Low FeNO		
Variables*	ICS + LABA	LAMA	ICS + LABA	LAMA	*P*-value
FeNO, ppb	27.60 (19.27–35.93)	32.35 (26.72–37.98)	15.56 (12.66–18.46)†	14.86 (12.19–17.53)†	**<.001**
CAT	13.65 (10.20–17.10)	12.15 (9.80–14.50)	14.39 (12.63–16.15)	12.17 (9.82–14.52)	.371
Pulmonary function test					
FVC, L	2.56 (2.31–2.81)	2.35 (2.04–2.66)	2.13 (1.95–2.31)	2.43 (2.21–2.65)	.055
FVC% predicted	88.85 (78.21–99.49)	83.45 (77.51–89.39)	80.11 (74.21–86.01)	82.28 (76.91–87.65)	.568
FEV_1, L	1.54 (1.30–1.78)	1.48 (1.23–1.73)	1.28 (1.14–1.42)	1.60 (1.44–1.76)‡	**.036**
FEV_1% predicted	66.85 (54.66–79.04)	68.20 (60.52–75.88)	61.28 (55.91–66.65)	68.39 (63.71–73.07)	.255
FEV_1/FVC	59.35 (53.25–65.45)	62.60 (57.46–67.74)	60.92 (55.80–66.04)	65.97 (62.91–69.03)	.169
MMEF, L/s	0.89 (0.65–1.13)	0.96 (0.72–1.20)	0.77 (0.61–0.93)	1.02 (0.88–1.16)	.161
MMEF% predicted	37.95 (27.03–48.87)	43.20 (35.50–50.90)	37.08 (29.98–44.18)	42.50 (37.48–47.52)	.562

CAT = COPD assessment test, FeNO = fractional exhaled nitric oxide, FEV = forced expiratory volume in 1 second, FVC = forced vital capacity, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum midexpiratory flow, ppb = parts per billion.

* All values are mean (95% confidence interval).

† Posthoc Tukey test indicated findings were significantly different than the high FeNO and ICS + LABA group.

‡ Posthoc Tukey test indicated findings were significantly different than the low FeNO and ICS + LABA group.

in FEV_1 following treatment ($r = 0.441$; $P < .001$); patients with higher FeNO levels at admission responded better to treatment.[8] They found that the best cut point for FeNO as a predictor for significant increase in FEV_1 was 26.8 ppb.[8] Kunisaki et al (2008) observed that among smokers with severe COPD (mean FEV_1, 1.07 L, 36% predicted) patients who responded to ICS treatment (fluticasone propionate 500 μg twice daily) had higher FeNO levels at baseline compared with nonresponders (46.5 ppb vs 25 ppb, $P = .028$).[9] Akamatsu et al (2011) investigated 14 patients with COPD treated with tiotropium plus flucticasone propionate plus salmeterol found that baseline FeNO >35 ppb and the presence of atopy were predictive of improvement in FEV_1 with ICS + LABA therapy.[12] Zietkowski et al (2005) evaluated the usefulness of FeNO in anticipating ICS response in patients (N = 47) with stable COPD.[13] They found FeNO levels were elevated in current and ex-smokers and that in both these groups ICS therapy resulted in a significant reduction in FeNO without significant changes in FEV_1 after 2 months of treatment.[13] Similar to Zietkowski et al, we found ICS + LABA treatment resulted in significant reduction in FeNO with little change in pulmonary function. The difference in findings between our study and that of Zietkowski et al compared with the other studies may reflect differences in patient populations and treatment regimens used.

Endogenous nitric oxide is a signaling molecular that is made by airway epithelium and inflammatory cells.[14] Nitric oxide plays an important role in regulating airway and vascular function.[15] Nitric oxide is produced by 3 isoforms of nitric oxide synthase and the activity of at least 1 isoform may be inhibited by corticosteroids in COPD.[15] The levels of FeNO in COPD appear to be influenced by several factors such as smoking status and severity of disease.[15] Increased levels of FeNO have been observed in patients during an exacerbation of COPD.[8] Also lower levels of FeNO were observed in ex-smokers and mild/moderate COPD.[15] Smoking may confound measurement of eosinophilic inflammation using FeNO as it may induce nitric oxide independent of inflammation. However, 1 study found a significant correlation between the levels of FeNO and sputum eosinophils regardless of smoking status in patients with COPD.[16] Increases in exercise tolerance due to pulmonary rehabilitation may also increase FeNO.[17]

Current guidelines for the management of COPD recommend limiting ICS use to patients with more severe disease and/or at risk

Table 4

Difference from baseline in FeNO, CAT, and pulmonary function test*.

	Difference				
	High FeNO		Low FeNO		
Variables	ICS + LABA	LAMA	ICS + LABA	LAMA	*P*-value
FeNO, ppb	−25.80 (−37.70, −13.90)	−4.45 (−9.02, 0.12)†	1.31 (−1.38, 4.00)†	0.50 (−1.73, 2.73)†	**<.001**
CAT	−7.20 (−9.94, −4.46)	−2.90 (−5.02, −0.78)	−1.72 (−3.99, 0.55)†	−2.03 (−3.89, −0.17)†	**.018**
Pulmonary function test					
FVC, L	0.29 (0.11, 0.47)	0.04 (−0.06, 0.14)	0.20 (0.06, 0.34)	0.11 (0.01, 0.21)	.072
FVC% predicted	10.90 (3.71, 18.09)	2.10 (−1.19, 5.39)	7.69 (2.85, 12.53)	3.78 (0.57, 6.99)	.093
FEV_1, L	0.23 (0.11, 0.35)	0.06 (−0.02, 0.14)	0.12 (0.06, 0.18)	0.11 (0.05, 0.17)	.199
FEV_1% predicted	9.55 (3.06, 16.04)	3.70 (−0.47, 7.87)	6.42 (3.09, 9.75)	4.31 (1.33, 7.29)	.402
FEV_1/FVC	1.20 (−1.17, 3.57)	1.30 (−1.29, 3.89)	−0.58 (−3.60, 2.44)	1.83 (−0.56, 4.22)	.673
MMEF, L/s	0.18 (0.06, 0.30)	0.12 (−0.02, 0.26)	0.00 (−0.12, 0.12)	0.10 (0.00, 0.20)	.266
MMEF% predicted	7.45 (1.67, 13.23)	3.60 (−1.75, 8.95)	3.36 (−2.25, 8.97)	4.56 (−0.09, 9.21)	.748

CAT = COPD assessment test, FeNO = fractional exhaled nitric oxide, FEV = forced expiratory volume in 1 second, FVC = forced vital capacity, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum midexpiratory flow, ppb = parts per billion.

* Difference was calculated as postvariable minus pre variables and represent mean (95% confidence interval).

† Posthoc Tukey test indicated findings were significantly different than the high FeNO and ICS + LABA group.

for an exacerbation.[1] ICS use is associated with several negative effects such as cataracts, glaucoma, pneumonia, and osteoporosis. Currently, there is inappropriate overuse of ICS in real-life practice, raising questions regarding the clinical benefit and long-term risk of ICS use, and the waste of health care resources.[7] Many patients being prescribed ICS do not meet the recommended criteria for ICS use.[18] It is estimated that ICS are used by >70% of patients with COPD and is given as initial therapy in >50% of newly diagnosed cases, usually in combination with a LABA.[20] A recent large randomized controlled study (N = 2485) designed to evaluate the effect of withdrawal ICS from background LABA therapy on treatment of COPD found that not all patients benefit from the inclusion of ICS in their treatment regimen.[6] They found only certain COPD phenotypes benefited from ICS therapy, particularly those with severe-to-very-severe COPD.[6] These findings highlight the need to identify biomarkers that can distinguish which patients with COPD may benefit the most from ICS use so as to help guide the management of the disease. Our findings indicate that high pretreatment FeNO levels may be a biomarker for patients who will respond to ICS + LABA therapy.

The present study has several limitations that must be considered. The study population was small and was performed in a single institution in Taiwan. Hence, it is not clear if the results would be translatable to other types of healthcare systems or geographic regions. Larger international studies are required to further assess the role of FeNO levels for indicating ICS treatment response in patients with COPD.

In conclusion, this study found that patients with COPD with high pretreatment FeNO respond better to ICS + LABA therapy, as evaluated by reduction in FeNO and improved CAT, than patients with high baseline FeNO not treated with an ICS or patients with low baseline FeNO treated with either ICS + LABA or LAMA. The results are consistent with FeNO being a biomarker that can be used to help identify patients with COPD in which ICS therapy may be beneficial.

Author contributions

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Wen-Lin Su: Data acquisition; Data analysis or interpretation; Critical manuscript revision

Chun-Yao Huang: Data acquisition; Critical manuscript revision

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