


RESEARCH

Open Access



# Developmental endothelial locus-1 as a potential biomarker for the incidence of acute exacerbation in patients with chronic obstructive pulmonary disease

Dong-Hyun Joo<sup>1†</sup>, Kyoung-Hee Lee<sup>1†</sup>, Chang-Hoon Lee<sup>1\*</sup> , Jisu Woo<sup>1</sup>, Jiyeon Kim<sup>1</sup>, Seung Ju Park<sup>2</sup>, Chin Kook Rhee<sup>3</sup>, Won-Yeon Lee<sup>4</sup>, Dongil Park<sup>5</sup>, Jae Seung Lee<sup>6</sup>, Ki-Suck Jung<sup>7</sup>, Kwang Ha Yoo<sup>8</sup> and Chul-Gyu Yoo<sup>1,9</sup>

## Abstract

**Background:** Despite the high disease burden of chronic obstructive pulmonary disease (COPD) and risk of acute COPD exacerbation, few COPD biomarkers are available. As developmental endothelial locus-1 (DEL-1) has been proposed to possess beneficial effects, including anti-inflammatory effects, we hypothesized that DEL-1 could be a blood biomarker for COPD.

**Objective:** To elucidate the role of plasma DEL-1 as a biomarker of COPD in terms of pathogenesis and for predicting acute exacerbation.

**Methods:** Cigarette smoke extract (CSE) or saline was intratracheally administered to wild-type (WT) and DEL-1 knockout (KO) C57BL/6 mice. Subsequently, lung sections were obtained to quantify the degree of emphysema using the mean linear intercept (MLI). Additionally, plasma DEL-1 levels were compared between COPD and non-COPD participants recruited in ongoing prospective cohorts. Using negative binomial regression analysis, the association between the plasma DEL-1 level and subsequent acute exacerbation risk was evaluated in patients with COPD.

**Results:** In the in vivo study, DEL-1 KO induced emphysema (KO saline vs. WT saline;  $P=0.003$ ) and augmented CSE-induced emphysema (KO CSE vs. WT CSE;  $P<0.001$ ) in 29 mice. Among 537 participants, patients with COPD presented plasma log (DEL-1) levels lower than non-COPD participants ( $P=0.04$ ), especially non-COPD never smokers ( $P=0.019$ ). During  $1.2 \pm 0.3$  years, patients with COPD in the lowest quartile of Log(DEL-1) demonstrated an increased risk of subsequent acute exacerbation, compared with those in the highest quartile of Log(DEL-1) (adjusted incidence rate ratio, 3.64; 95% confidence interval, 1.03–12.9).

**Conclusion:** Low DEL-1 levels are associated with COPD development and increased risk of subsequent COPD acute exacerbation. DEL-1 can be a useful biomarker in patients with COPD.

\*Correspondence: kauri670@empal.com

†Dong-Hyun Joo and Kyoung-Hee Lee contributed equally on this paper as co-primary authors

<sup>1</sup> Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, Republic of Korea

Full list of author information is available at the end of the article



**Keywords:** Chronic obstructive pulmonary disease, Developmental endothelial locus-1, Disease progression, Biomarkers, Animal disease models

## Background

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease, with a reported worldwide prevalence of 3.9% in 2017 [1]. Although COPD is a chronic disease, a substantial number of patients experience acute exacerbation [2]. Acute exacerbation is known to result in a reduced quality of life [3], disease progression [4], and even premature mortality. Globally, COPD was responsible for 5.7% of all-cause mortality in 2017 [1], projected to increase to 7.8% in 2030 [5]. Despite the importance of this disease, limited advances have been achieved in its treatment. Obstacles to advances in COPD therapeutics include unclear pathogenesis that needs to be comprehensively clarified [6], the complexity and heterogeneity of the disease [7], and a lack of biomarkers that can be easily determined. Although the forced expiratory volume in one second (FEV1) had long been used as an indicator of COPD severity in Global Initiative for Obstructive Lung Disease (GOLD) [8], FEV1 only weakly correlated with symptoms and health status [9]. Therefore, GOLD introduced ABCD system including COPD assessment test and prior history of acute exacerbation [10], and the needs for other biomarkers increased, which led to investigations of various biomarkers. As the difficulty in obtaining specimens such as sputum or bronchoalveolar lavage fluid hinder application, blood biomarkers have been of great interest recently. Indeed, COPD is not only characterized by airflow limitation but also by systemic manifestations [11]. A few blood biomarkers linked to systemic inflammation such as C-reactive protein (CRP), interleukins (ILs), fibrinogen and tumor necrosis factor (TNF)- $\alpha$  have been identified [12]. However, although these biomarkers are associated with COPD outcomes including acute exacerbation [12], the relationship between airway inflammation, that is the key pathogenesis in acute exacerbation, and systemic inflammation is unclear [13, 14]. There are other blood biomarkers, including surfactant protein D (SP-D) [15] and club cell protein-16 (CC-16) [16], associated with acute exacerbation, however, those have also limitations as reliable biomarkers due to conflicting results [17] and small size study [16].

Developmental endothelial locus-1 (DEL-1), also known as epidermal growth factor (EGF)-like repeats and discoidin I-like domains 3 (EDIL3), is an endogenous protein that is produced particularly in the brain and lungs, and secreted by various cells so that it can be easily measured in serum or plasma [18]. Reportedly, DEL-1

demonstrates anti-inflammatory effects by inhibiting neutrophil recruitment and promoting inflammation clearance [19–21]. Airway and systemic inflammation are principal mechanisms of acute exacerbation of COPD [22]. Furthermore, DEL-1 has inhibitory effects on endothelial cell apoptosis [23], as well as anti-fibrotic [24, 25], anti-aging [26], and anti-protease effects [27, 28], indicating that DEL-1 could have beneficial effects in COPD [28]. However, the majority of studies reporting the functions of DEL-1 were at the stage of mice or cells, and only a few studies investigated in humans the association between DEL-1 and humans diseases such as multiple sclerosis [29], periodontitis [30] and sepsis [31]. The effects of DEL-1 on COPD have not been studied in mice or humans. Therefore, we conducted the study in mice and humans to investigate whether DEL-1 could be a blood biomarker for the pathogenesis of COPD and for predicting acute exacerbation of COPD.

## Methods

### In vivo study

#### CSE preparation

Cigarette smoke extract (CSE) was prepared as previously described [32] and is detailed in Additional file 1.

#### Mice and intratracheal administration of CSE

Female 8-week-old C57BL/6 wild-type (WT) mice were purchased from Koatech Laboratory Animal Company (Pyeongtaek, Korea). DEL-1 knockout (KO) mice on a C57BL/6 genetic background were kindly donated by Dr. Eun Young Choi (Asan Medical Center, Seoul, Korea). C57BL/6 WT and DEL-1 KO mice were anesthetized and intratracheally administered saline or 100  $\mu$ L CSE. CSE was administered once a week for 8 weeks (WT saline, n=8; WT CSE, n=8; KO saline, n=5; KO CSE, n=8). To isolate the lungs, the mice were killed on the day after the last CSE instillation. Animal experiments were approved by the Institutional Animal Care and Use Committee (number 17-0134-C1A0(2)) of Seoul National University Hospital, Seoul, Korea.

#### Reverse transcriptase-PCR (RT-PCR)

Total RNA was isolated from different tissues of WT and DEL-1 KO C57BL/6 mice. Total RNA was isolated using a RNeasy kit (Qiagen, Hilden, Germany). cDNA was synthesized using the Reverse Transcription System (Promega, Madison, WI, USA). PCR Master Mix (Applied Biosystems, Carlsbad, CA, USA) was used for

amplification. The primers used in the study were as follows: mouse Del-1 primer (fwd: 5'-CCT GTG AGA TAA GCG AAG-3', rev: 5'-GAG CTC GGT GAG TAG ATG-3') and GAPDH (fwd: 5'-TCC CTC AAG ATT GTC AGC AAT G-3', rev: 5'-AGA TCC ACA ACG GAT ACA TTG G-3'). PCR conditions were as follows: initial denaturation at 94 °C for 2 min; 40 cycles were performed for the mRNA levels of DEL-1 and GAPDH, each cycle with 20 s of denaturation at 94 °C, 10 s of annealing at 60 °C, and 30 s of extension at 72 °C, with a final dwell at 72 °C for 5 min.

#### **Measurement of emphysema**

The mean linear intercept (MLI) was measured to quantify emphysema as previously described [33] and is detailed in Additional file 1. We compared MLIs between groups with analysis of variance.

#### **Cohort study**

##### **Study design and participants**

We conducted a cohort study to elucidate the role of DEL-1 as a blood biomarker in patients with COPD, including patients from the Korean COPD Subgroup Registry and Subtype Research (KOCOSS) (NCT02800499), an ongoing multicenter cohort study in South Korea. A patient with stable COPD was defined as a person with the post-bronchodilator FEV1/vital capacity (VC) < 0.70 who did not acute experience within 1 month. Those patients who were not followed up for at least 12 months, or who had no blood sample collected at baseline were excluded. Non-COPD participants were randomly selected from the Controls for Respiratory Diseases cohort (NCT03120481), which enrolled those who underwent health screening and consented to participate in the cohort. Inclusion criteria for the non-COPD group were as follows: pre-bronchodilator FEV1/FVC  $\geq$  0.7, and no history of chronic respiratory diseases. Never smokers and ever smokers were randomly included in a 1:1 ratio. Patients with insufficient blood samples were excluded. Written informed consent was obtained from all participants. The study was approved by the institutional review board of Seoul National University Hospital, Seoul, Korea (IRB no: 2007-029-1139).

##### **Measurements of DEL-1 and other variables**

For the COPD group, baseline characteristics including demographic factors, smoking history, acute exacerbation history in the past year, modified Medical Research Council (mMRC) grade, 6-min walk distance (6MWD), pulmonary function testing, and laboratory and radiologic findings were evaluated. The history of acute exacerbation and drug treatment were evaluated based on self-reported questionnaire by the study coordinator at

6 months and 12 months, and then annually. An acute exacerbation is defined as a condition that any worsening of cough, sputum, or dyspnea requires additional therapy with systemic corticosteroids or antibiotics, or hospitalization. For the non-COPD group, baseline demographic factors, smoking history, and pulmonary function testing were evaluated.

#### **Plasma DEL-1 measurement**

DEL-1 levels in humans plasma samples were measured using a commercially available humans EDIL3 DuoSet enzyme-linked immunosorbent assay (ELISA) kit (R&D System, Minneapolis, MN) according to the manufacturer's instructions.

#### **Statistical analysis**

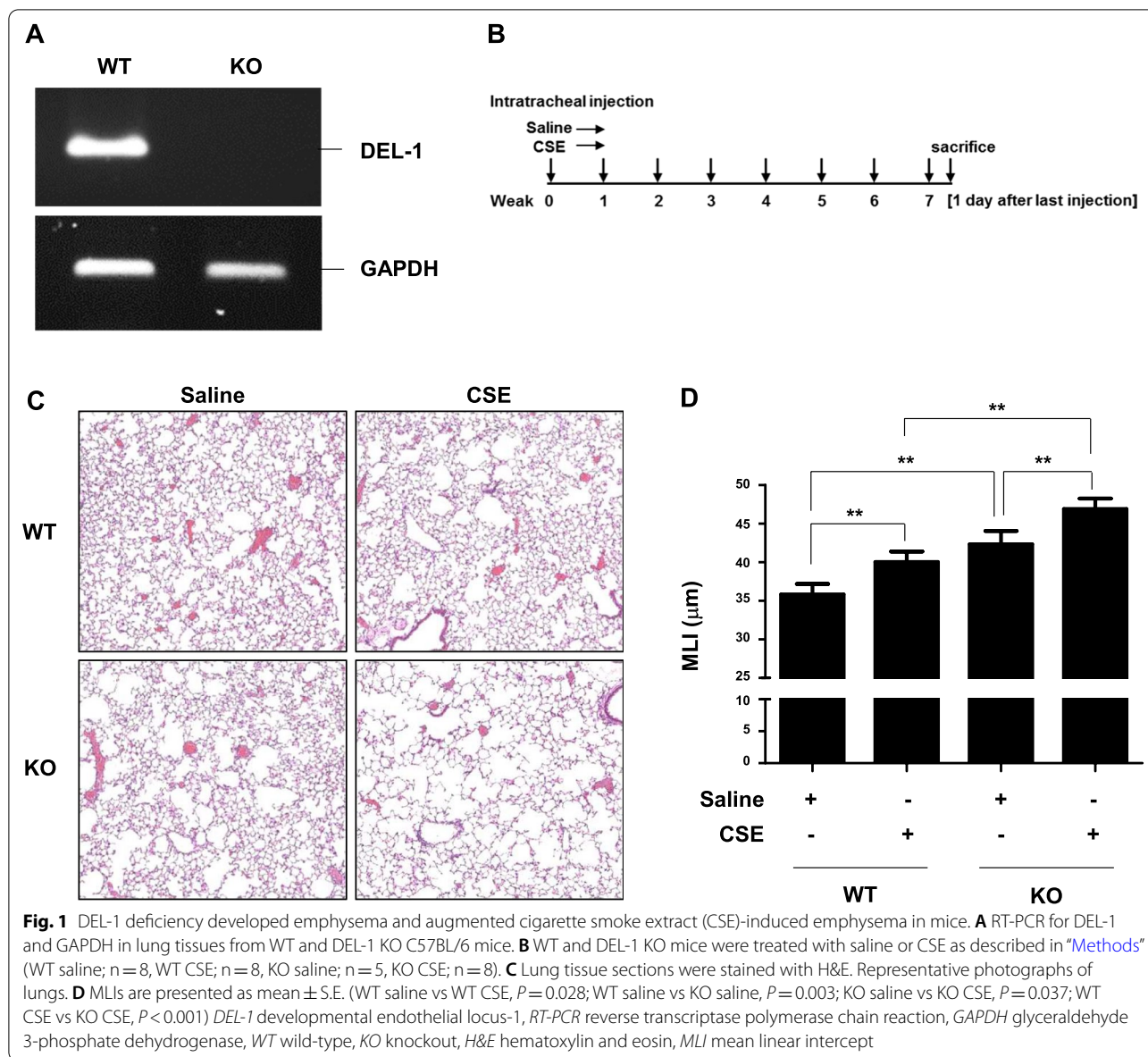
First, we compared the plasma concentration of DEL-1 between the COPD group and non-COPD group by a linear regression analysis adjusted by age and sex. If measurements were right-skewed, a log transformation was applied. Second, we investigated the association between plasma DEL-1 levels and outcomes in the COPD group. The main outcome was acute exacerbation rates, and a negative binomial regression model adjusted for confounders, including age, sex, acute exacerbation history in the past year, baseline post-bronchodilator FEV1 (% predicted), treatment drugs [inhaled corticosteroids (ICS), long-acting  $\beta$ 2-agonists (LABA), long-acting muscarinic agents (LAMA), phosphodiesterase-4 (PDE4) inhibitor] were used, and incidence rate ratios (IRR) with 95% confidence intervals (CIs) were estimated. All statistical analyses were performed using Stata 14.2 (Stata-Corp, College Station, TX, USA). A *P*-value < 0.05 was considered statistically significant.

## **Results**

### **In vivo study**

#### **DEL-1 deficiency resulted in emphysema development and augmented CSE-induced emphysema in mice**

We first evaluated the role of DEL-1 in the development of emphysema in mice following CSE treatment. DEL-1 KO was confirmed by RT-PCR (Fig. 1A). C57BL/6 WT and DEL-1 KO mice were intratracheally administered saline or CSE as described in the Methods section (Fig. 1B), and the severity of emphysema was determined by measuring MLI. DEL-1 KO mice demonstrated a higher MLI than WT mice, indicating that DEL-1 KO induced emphysema. CSE induced lung parenchymal destruction and led to emphysema, and DEL-1 KO augmented CSE-induced emphysema (Fig. 1C, D).



**Clinical study**

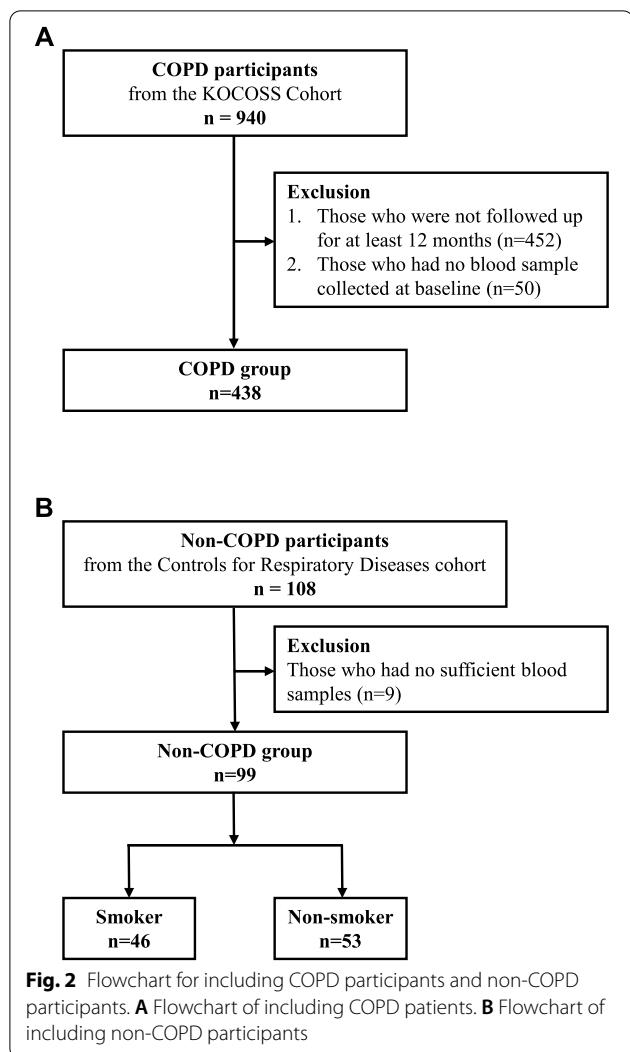
**Characteristics of the study population**

In total, 940 patients with COPD were eligible from the KOCOSS cohort. Among them, 452 participants who were not followed up for at least 12 months and 50 participants who had no blood sample collected at baseline were excluded. Finally, 438 COPD participants were categorized into the COPD group. Additionally, 108 non-COPD participants were initially recruited, and 9 participants without blood samples were excluded. Overall, 99 non-COPD participants were categorized into the non-COPD group (Fig. 2). The baseline characteristics of COPD patients and non-COPD participants are described in Table 1. The non-COPD group

was younger, had more females, and presented a better FEV1 than the COPD group. Among the non-COPD group, the ever-smoker group was older with more male participants than the never-smoker group. Each group demonstrated similar pre-bronchodilator FEV1 levels.

**Patients with COPD had lower plasma levels of DEL-1 compared with non-COPD never smokers**

Patients with COPD presented lower levels of DEL-1 than non-COPD participants ( $385.9 \pm 523.0$  vs.  $535.4 \pm 903$  pg/mL;  $P=0.03$ ). Furthermore, patients with COPD revealed lower levels of DEL-1 when compared with non-COPD never smokers, when age and sex were



adjusted ( $P=0.047$ ) (Fig. 3A). Log transformation of the DEL-1 value was performed as the distribution of measured DEL-1 was right-skewed. After log transformation of DEL-1, patients with COPD similarly showed lower levels of Log(DEL-1) than those without COPD ( $5.4 \pm 1.2$  vs.  $5.6 \pm 1.2$  pg/mL;  $P=0.04$ ). After adjusting for age and sex, patients with COPD also presented lower levels of Log(DEL-1) than non-COPD never smokers ( $P=0.019$ ) (Fig. 3B).

**Low plasma DEL-1 level was associated with increased risk of subsequent acute exacerbation in patients with COPD.**

During a mean  $1.2 \pm 0.3$  years follow-up period, 67 acute exacerbation events were reported among patients with COPD (incidence rate,  $0.15 \pm 0.75$  events per person-years). The lowest quartile of the Log(DEL-1) group (incidence rate, 0.36 events per person-year; 95% CI,

0.06–0.67) revealed a risk of subsequent acute exacerbations higher than the highest quartile group (incidence rate, 0.10 events per person-year; 95% CI, – 0.01–0.21). On adjusting the covariates, the lowest quartile group presented more than three times increased risk of acute exacerbations during the follow-up period when compared with the highest quartile group (IRR, 3.64; 95% CI, 1.03–12.9) (Fig. 4).

**Discussion**

In the present study, our findings demonstrated that the level of plasma DEL-1 in stable COPD patients was lower than that in non-COPD patients, with a low baseline DEL-1 level associated with a higher risk of subsequent acute exacerbation in the latter period in patients with COPD.

Although some patients with COPD do not experience acute exacerbations, other patients frequently do experience this complication. Acute COPD exacerbations reduce a patients’ quality of life [3], accelerate disease progression [4], and considerably increase healthcare costs [34]. As several patients with COPD do not report their acute exacerbation events to healthcare providers [35], the rate of acute exacerbation may be underestimated [36]. Thus, if a reliable and easily measurable biomarker to predict the subsequent incidence of acute exacerbation is identified, it would be extremely valuable in the management of patients with COPD.

Researchers have extensively explored biomarkers predicting acute COPD exacerbations and identified some biomarkers. The biomarkers of interest were systemic inflammatory biomarkers. Reportedly, ECLIPSE cohort researchers have measured six systemic inflammatory biomarkers in the peripheral blood of participants, including white blood cell count and CRP, IL-6, IL-8, fibrinogen, and TNF- $\alpha$  levels. They observed that those who presented persistent systemic inflammation were at a higher risk of all-cause mortality and more frequent acute exacerbations when compared with non-inflamed participants [12]. In participants of the Copenhagen City Heart Study, a serum CRP level >3 mg/L was associated with an increased risk of hospitalization and death due to COPD [37]. Furthermore, a high plasma fibrinogen level  $\geq 350$  mg/dL was associated with an increased risk of hospitalization owing to acute COPD exacerbation within 12 months and all-cause mortality within 36 months in pooled data from Atherosclerosis Risk in Communities Study (ARIC), Cardiovascular Health Study (CHS), and Evaluation of COPD longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study [38]. However, these systemic inflammatory biomarkers have limitations. The concentration of a blood biomarker might be influenced by prior acute exacerbation events

**Table 1** Baseline characteristics of COPD group and non-COPD group

Characteristics	COPD	Non-COPD		P-value	
	(n=438)	Total (n=99)	Ever smoker (n=46)		Never smoker (n=53)
Age (year)	69.0 ± 7.6	60.5 ± 4.8	61.4 ± 4.9	59.8 ± 4.6	p < 0.001
Sex (male)	394 (90.2%)	56 (56.6%)	44 (95.7%)	12 (22.6%)	p < 0.001
Pack-year	39.0 [24.0;50.0]	0.0 [0.0;17.9]	20.0 [10.0;34.5]	0.0 [0.0; 0.0]	p < 0.001
Current smoker	107 (24.4%)	8 (8.1%)			p < 0.001
Former smoker	278 (63.5%)	38 (38.4%)			p < 0.001
Never smoker	46 (10.5%)	53 (53.5%)			p < 0.001
Unknown	7 (1.6%)				
Pre-bronchodilator FEV1(% predicted)	65.0 [51.0;77.0]	102.0 [93.5;111.0]	101.0 [94.0;111.0]	104.0 [93.0;111.0]	p < 0.001
Post-bronchodilator FEV1(% predicted)	68.0 [54.0;80.0]				
Exacerbation history in past year	57.0 (13.0%)				
mMRC	1.14±0.82				
6MWD (meter)	439.0 [370.0;490.8]				
Lab finding					
WBC (× 10 <sup>3</sup> /mm <sup>3</sup> )	6.7 [5.8; 8.3]	4.8 [4.0;5.9]	5.2 [4.2; 6.0]	4.8 [3.9;5.6]	p < 0.001
Neutrophil (%)	58.4 [51.4;64.2]	55 [48.1;61.6]	57.1 [49.2;60.6]	53.3 [46.8;61.9]	p = 0.008
Lymphocyte (%)	29.2 [23.4;35.7]	34.3 [28.6;40.4]	33.6 [28.8;38.5]	35.6 [28.6;41.7]	p < 0.001
CRP (mg/dL)	0.8 [0.4; 1.9]				
Fibrinogen (mg/dL)	304.5 [256.5;347.0]				

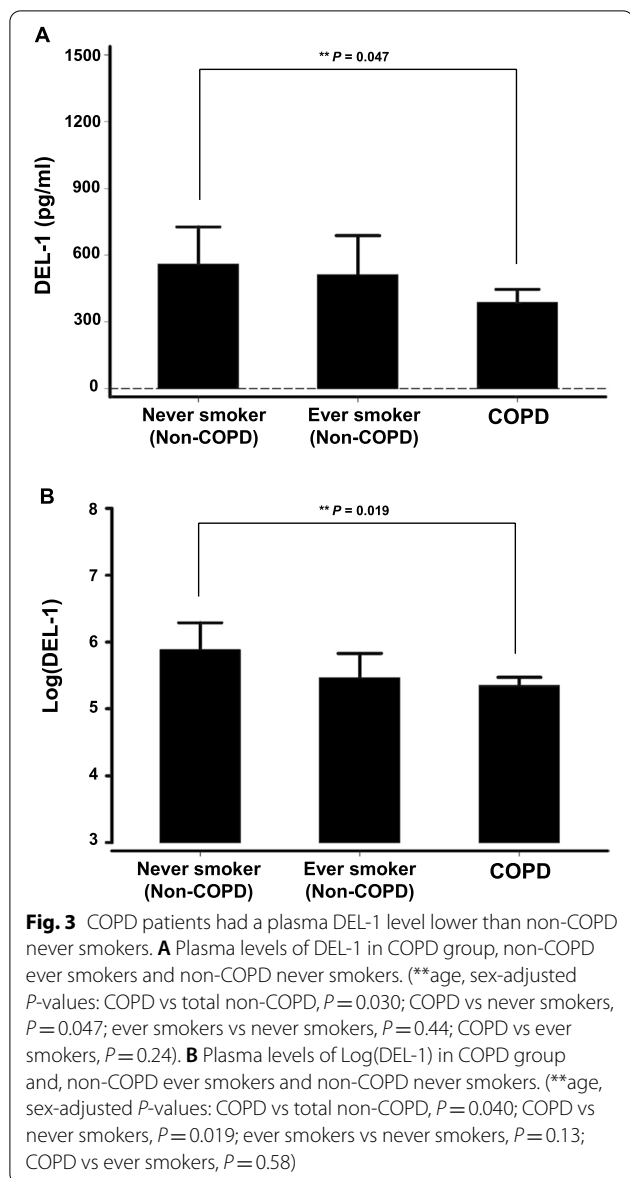
Data are presented as mean ± standard deviation, median [interquartile range], or frequency with percentage

mMRC modified Medical Round Council, 6MWD six-minute walk distance, WBC white blood cell, CRP c-reactive protein

that were similar to overwhelming systemic inflammation [36]. Additionally, although acute exacerbations originate in the airways, the relationship between airway and systemic inflammation remains unclear considering the poor correlation between sputum and blood biomarkers [13, 14]. Moreover, there are no drug candidates that target the direct reduction of systemic inflammatory biomarkers [39], although studies have reported that fibrinogen is reduced by p38 mitogen-activated protein kinase inhibitors [40]. In addition to systemic inflammation, other biomarkers have been identified, reportedly related to subsequent acute exacerbation risk. In the ECLIPSE cohort, a high serum surfactant protein D (SP-D) level > 175.4 ng/mL (greater than the 95th percentile of nonsmokers) has been associated with an increased risk of acute exacerbation within 12 months [15]. However, one study has revealed that SP-D levels are reportedly reduced in the bronchoalveolar lavage fluid of patients with COPD [17], which questions the usefulness of SP-D. Another study has reported that an increased

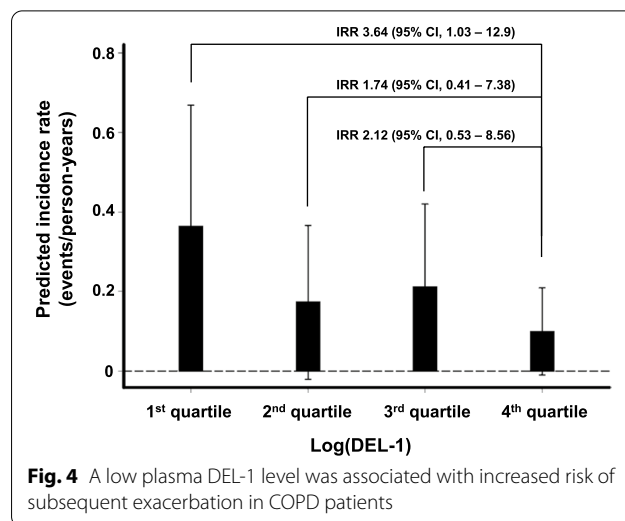
plasma level of CC-16 was reportedly associated with a decreased number of subsequent acute exacerbations during 6 months of follow-up; however, this study included only a small number (n=38) of participants [16]. Considering that these systemic biomarkers have limitations, efforts to identify new reliable biomarkers are warranted.

To our knowledge, the present study is the first to suggest DEL-1 as a novel blood biomarker for predicting subsequent acute exacerbations in patients with COPD. Although our study was unable to identify how DEL-1 decreases the risk of acute COPD exacerbations, several explanations could be considered. First, DEL-1 has anti-inflammatory properties. DEL-1 inhibits neutrophil recruitment by interrupting the binding of lymphocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) [19]. Furthermore, DEL-1 enhances macrophage efferocytosis and clearance of inflammation [20, 21]. Airway and systemic inflammation are principal mechanisms of acute



exacerbation of COPD, and DEL-1 can protect from acute exacerbations by decreasing inflammation [22]. Second, DEL-1 may protect against cardiovascular events by inhibiting inflammation [27]. Cardiovascular diseases increase the risk of acute COPD exacerbations [41]; additionally, acute COPD exacerbations increase the risk of subsequent cardiovascular events [42] that could worsen patient symptoms. Thus, DEL-1 could contribute to cardiovascular stability, leading to a decreased risk of COPD worsening.

Moreover, our study revealed that lower level of DEL-1 could contribute to the pathogenesis of COPD.



DEL-1 knockout resulted in the development and augmentation of emphysema in a mouse model. Furthermore, patients with COPD presented plasma DEL-1 levels lower than non-COPD controls ( $385.9 \pm 523.0$  vs  $535.4 \pm 903.2$  pg/mL; *P* = 0.03; Log(DEL-1),  $5.4 \pm 1.2$  vs  $5.6 \pm 1.2$  pg/mL; *P* = 0.04), especially non-COPD never smokers. (log (DEL-1), *P* = 0.019). As discussed above, DEL-1 demonstrates anti-inflammatory effects by inhibiting neutrophil recruitment, promoting macrophage efferocytosis, and clearance of inflammation. Persistent inflammation, in which neutrophils and macrophages are known contributors, has been regarded as the key factor in the pathogenesis of COPD [43]. Additionally, DEL-1 has inhibitory effects on endothelial cell apoptosis [23], along with anti-fibrotic [24, 25], anti-aging [26], and anti-protease effects [27, 28], suggesting that a reduced DEL-1 level can be related to the pathogenesis of COPD.

We acknowledge limitations. First, non-COPD participants were enrolled from another cohort, and were not matched to COPD patients. It could raise a concern for selection bias and confounding effects, although we adjusted age and sex as covariates for the comparison between groups. Second, although our cohort enrolled stable COPD patients who were not in acute exacerbation within one month, there might some participants, even though the number may be very small, who were not ‘stable’ at baseline considering a full recovery from acute exacerbation may not occur by months in a small number of patients [44]. A remaining acute exacerbation could affect the DEL-1 level. Third, DEL-1 was measured only at baseline in our study. As repeated measurement could provide additional clinical

implications, further studies are needed. Fourth, there could be another factors affecting DEL-1 levels. We did not perform subgroup analysis according to comorbidities, although it has been reported that DEL-1 could be decreased in some comorbid diseases such as inflammatory disorders [45]. Fifth, we did not evaluate the association between DEL-1 level and other variables including lung function and airway inflammation that are linked to COPD pathogenesis. To validate the role of DEL-1, further studies are needed.

## Conclusion

In conclusion, we demonstrated that low plasma DEL-1 levels are associated with COPD diagnosis and an increased risk of subsequent acute COPD exacerbation. Our results suggest that DEL-1 could be a good biomarker in patients with COPD. Considering these beneficial effects on COPD, DEL-1 can be further researched in the prevention and treatment of COPD.

## Abbreviations

COPD: Chronic obstructive pulmonary disease; DEL-1: Developmental endothelial locus-1; CSE: Cigarette smoke extract; WT: Wild-type; KO: Knock-out; MLI: Mean linear intercept; FEV1: Forced expiratory volume in one second; IRR: Incidence rate ratios; CI: Confidence interval.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-021-01878-7>.

**Additional file 1.** Supporting information on methods.

## Acknowledgements

We thank Prof. Triantafyllos Chavakis (Technische Universität Dresden, Germany) and Prof. Eun Young Choi (Asan Medical Center, Republic of Korea) for providing DEL-1 KO mice.

## Authors' contributions

All authors meet criteria for authorship recommended by the international Committee of Medical Journal Editors (ICMJE), contributed to data acquisition, data analysis, writing and reviewing manuscripts. All authors had complete access to the data in the study and agree to be accountable for all aspects of study including accuracy or integrity of data analysis, and have been given final approval of the version to be published. All authors read and approved the final manuscript.

## Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2019R1C1C1007918). This research was also supported by funds (2016ER670100, 2016ER670101, 2016ER670102 and 2018ER670100, 2018ER670101, 2018ER670102) from Research of Korea Centers for Disease Control and Prevention.

## Availability of data and materials

The data supporting our findings are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Animal experiments were approved by the Institutional Animal Care and Use Committee (number 17-0134-C1A0(2)) of Seoul National University Hospital, Seoul, Korea. Written informed consent was obtained from all participants. The cohort study was approved by the institutional review board of Seoul National University Hospital, Seoul, Korea (IRB no: 2007-029-1139).

### Consent for publication

Not required due to study design.

### Competing interests

All authors have no competing interest to declare.

### Author details

<sup>1</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul 03080, Republic of Korea. <sup>2</sup>Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju, Republic of Korea. <sup>3</sup>Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea. <sup>4</sup>Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea. <sup>5</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea. <sup>6</sup>Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. <sup>7</sup>Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University Medical School, Anyang, Republic of Korea. <sup>8</sup>Department of Internal Medicine, Division of Pulmonary and Allergy Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea. <sup>9</sup>Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

Received: 28 June 2021 Accepted: 24 October 2021

Published online: 20 November 2021

## References

- Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Abrams EM, Adedoyin RA, Adhikari TB, Advani SM, Agrawal A, Ahmadian E, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med*. 2020;8:585–96.
- Vinoli C, Vogelmeier CF. Exacerbations of COPD. *Eur Respir Rev*. 2018;27:170103.
- Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157:1418–22.
- Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57:847–52.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442.
- Agusti A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381:1248–56.
- Wedzicha JA. The heterogeneity of chronic obstructive pulmonary disease. *Thorax*. 2000;55:631–2.
- GOLD global initiative for chronic obstructive lung disease: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2009. [www.goldcopd.com](http://www.goldcopd.com).
- Jones PW. Health status and the spiral of decline. *COPD*. 2009;6:59–63.
- GOLD global initiative for chronic obstructive lung disease: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2021. [www.goldcopd.com](http://www.goldcopd.com).
- Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J*. 2009;33:1165–85.



12. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PMA, Wouters E, Crim C, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS ONE*. 2012;7: e37483.
13. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of "overspill" of inflammatory mediators from the lungs? Review of the evidence. *Thorax*. 2010;65:930–6.
14. Hurst JR, Wilkinson TM, Perera WR, Donaldson GC, Wedzicha JA. Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD. *Chest*. 2005;127:1219–26.
15. Lomas DA, Silverman EK, Edwards LD, Locantore NW, Miller BE, Horstman DH, Tal-Singer R. Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. *Eur Respir J*. 2009;34:95–102.
16. Labonté LE, Bourbeau J, Daskalopoulou SS, Zhang M, Coulombe P, Garland K, Bagloli CJ. Club cell-16 and RelB as novel determinants of arterial stiffness in exacerbating COPD patients. *PLoS ONE*. 2016;11: e0149974.
17. Winkler C, Atochina-Vasserman EN, Holz O, Beers MF, Erpenbeck VJ, Krug N, Roepcke S, Lauer G, Elmlinger M, Hohlfeld JM. Comprehensive characterisation of pulmonary and serum surfactant protein D in COPD. *Respir Res*. 2011;12:29.
18. Choi EY, Chavakis E, Czabanka MA, Langer HF, Fraemohs L, Economopoulou M, Kundu RK, Orlandi A, Zheng YY, Prieto DA, et al. Del-1, an endogenous leukocyte-endothelial adhesion inhibitor, limits inflammatory cell recruitment. *Science*. 2008;322:1101–4.
19. Choi EY. Inhibition of leukocyte adhesion by developmental endothelial locus-1 (del-1). *Immune Netw*. 2009;9:153–7.
20. Kourtzelis I, Li X, Mitroulis I, Grosser D, Kajikawa T, Wang B, Grzybek M, von Renesse J, Czogalla A, Troullinaki M, et al. DEL-1 promotes macrophage efferocytosis and clearance of inflammation. *Nat Immunol*. 2019;20:40–9.
21. Hanayama R, Tanaka M, Miwa K, Nagata S. Expression of developmental endothelial locus-1 in a subset of macrophages for engulfment of apoptotic cells. *J Immunol*. 2004;172:3876–82.
22. Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax*. 2006;61:250–8.
23. Ho HK, Jang JJ, Kaji S, Spektor G, Fong A, Yang P, Hu BS, Schatzman R, Quertermous T, Cooke JP. Developmental endothelial locus-1 (Del-1), a novel angiogenic protein: its role in ischemia. *Circulation*. 2004;109:1314–9.
24. Kim D-Y, Lee S-H, Fu Y, Jing F, Kim W-Y, Hong S-B, Song J-A, Choe H, Ryu HJ, Kim M, et al. Del-1, an endogenous inhibitor of TGF- $\beta$  activation, attenuates fibrosis. *Front Immunol*. 2020;11:68–68.
25. Kang YY, Kim DY, Lee SH, Choi EY. Deficiency of developmental endothelial locus-1 (Del-1) aggravates bleomycin-induced pulmonary fibrosis in mice. *Biochem Biophys Res Commun*. 2014;445:369–74.
26. Hajishengallis G. Aging and its impact on innate immunity and inflammation: implications for periodontitis. *J Oral Biosci*. 2014;56:30–7.
27. Kopaliani I, Failer T, Neuwirth A, Kourtzelis I, Subramanian P, Hajishengallis G, Chavakis T, Deussen A. Abstract 13671: Del-1 inhibits inflammation and protects from cardiovascular damage during hypertension. *Circulation*. 2019;140:A13671–A13671.
28. Chung KF, Adcock IM. Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *Eur Respir J*. 2008;31:1334–56.
29. Goris A, Sawcer S, Vandenbroeck K, Carton H, Billiau A, Setakis E, Compston A, Dubois B. New candidate loci for multiple sclerosis susceptibility revealed by a whole genome association screen in a Belgian population. *J Neuroimmunol*. 2003;143:65–9.
30. Folwaczny M, Karnesi E, Berger T, Paschos E. Clinical association between chronic periodontitis and the leukocyte extravasation inhibitors developmental endothelial locus-1 and pentraxin-3. *Eur J Oral Sci*. 2017;125:258–64.
31. Kim W-Y, Lee S-H, Kim D-Y, Ryu HJ, Chon GR, Park YY, Fu Y, Huh JW, Lim C-M, Koh Y, et al. Serum developmental endothelial locus-1 is associated with severity of sepsis in animals and humans. *Sci Rep*. 2019;9:13005.
32. Lee CH, Lee KH, Jang AH, Yoo CG. The impact of autophagy on the cigarette smoke extract-induced apoptosis of bronchial epithelial cells. *Tuberc Respir Dis (Seoul)*. 2017;80:83–9.
33. Lee KH, Lee CH, Jeong J, Jang AH, Yoo CG. Neutrophil elastase differentially regulates interleukin 8 (IL-8) and vascular endothelial growth factor (VEGF) production by cigarette smoke extract. *J Biol Chem*. 2015;290:28438–45.
34. Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson A, Prutz C, Ronmark E, Lundback B. The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med*. 2002;96:700–8.
35. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169:1298–303.
36. Donaldson GC, Wedzicha JA. Prediction of chronic obstructive pulmonary disease exacerbation frequency. Clinical parameters are still better than biomarkers. *Am J Respir Crit Care Med*. 2017;195:415–6.
37. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;175:250–5.
38. Mannino DM, Tal-Singer R, Lomas DA, Vestbo J, Graham Barr R, Tetzlaff K, Lowings M, Rennard SI, Snyder J, Goldman M, et al. Plasma fibrinogen as a biomarker for mortality and hospitalized exacerbations in people with COPD. *Chronic Obstr Pulm Dis*. 2015;2:23–34.
39. Moon JY, Leitao Filho FS, Shahangian K, Takiguchi H, Sin DD. Blood and sputum protein biomarkers for chronic obstructive pulmonary disease (COPD). *Expert Rev Proteomics*. 2018;15:923–35.
40. Lomas DA, Lipson DA, Miller BE, Willits L, Keene O, Barnacle H, Barnes NC, Tal-Singer R, Losmapimod Study I. An oral inhibitor of p38 MAP kinase reduces plasma fibrinogen in patients with chronic obstructive pulmonary disease. *J Clin Pharmacol*. 2012;52:416–24.
41. Westerik JA, Metting EI, van Boven JF, Tiersma W, Kocks JW, Schermer TR. Associations between chronic comorbidity and exacerbation risk in primary care patients with COPD. *Respir Res*. 2017;18:31.
42. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, Hartley BF, Martinez FJ, Newby DE, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med*. 2018;198:51–7.
43. Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation. *Int J Chron Obstruct Pulmon Dis*. 2011;6:413–21.
44. Wageck B, Cox NS, Holland AE. Recovery following acute exacerbations of chronic obstructive pulmonary disease—a review. *COPD*. 2019;16:93–103.
45. Hajishengallis G, Chavakis T. DEL-1-regulated immune plasticity and inflammatory disorders. *Trends Mol Med*. 2019;25:444–59.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.