High urinary desmosine is associated with long-term mortality in patients with COPD

Received: 6 Feb 2023
Accepted: 6 April 2023

To the Editor:

COPD is the third most frequent cause of death worldwide and its global burden is predicted to increase further. Accurate prediction of mortality is important because it helps identify patients for whom the implementation of therapeutic measures can improve outcomes. Although forced expiratory volume in 1 s (FEV_1) remains the most important indicator of the severity of airflow obstruction in COPD, its predictive value for mortality is weak when the FEV_1 value is >50% predicted [1]. Several other factors, including the severity of dyspnoea, resting hypoxaemia, exercise-induced desaturation, hyperinflation, low body mass index (BMI) and impaired exercise capacity have been identified as individual predictors of mortality in COPD [2, 3]. Meanwhile, several studies have explored the association between serum biomarkers and clinical outcomes in patients with COPD. A meta-analysis revealed that baseline levels of C-reactive protein and fibrinogen were related to the risk of premature death in stable patients with COPD [4]. The club cell secretory protein, which is associated with rapid lung function decline [5], was also found to be associated with mortality in the COPDGene cohort [6]. The degradation of elastin is an important feature of normal ageing and COPD [7]. Desmosine and isodesmosine (desmosines) are released as a result of elastin degradation and can be found in sputum, blood and urine [8]. Urinary desmosines have been proposed as a biomarker of emphysema severity in patients with COPD [9]. However, there are no reports of the relationship between urinary desmosines and mortality in patients with COPD.

To investigate the association between urinary desmosines and long-term mortality in patients with COPD, data from the Korean Obstructive Lung Disease (KOLD) cohort, recruited from the pulmonary clinics of 11 referring hospitals in South Korea between 2005 and 2015, were used. 180 patients were randomly selected, and their baseline levels of total urinary desmosines were measured. The study was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained from all the patients.

The baseline demographic and disease characteristics of the 180 patients who participated in the study were as follows: mean age 66.6 years; mean BMI 23.0 $kg \cdot m^{-2}$; mean smoking duration 48.1 pack-years; mean post-bronchodilator FEV_1 51.1% pred; and COPD severity 1.7% mild, 48.9% moderate, 42.8% severe and 6.7% very severe. The mean levels of urinary desmosines differed according to the severity of airflow limitation ($p<0.001$), and increased with the severity of airflow obstruction (figure 1a).

We classified the participants into four quartile subgroups based on urinary desmosine levels. The cut-off values of the quartiles were 2.95, 6.05 and 11.24 $ng \cdot mg^{-1}$ creatinine. The baseline BMI and diffusing capacity of the lung revealed significant differences between the four subgroups. Other baseline characteristics, such as Charlson comorbidity index, dyspnoea severity, airflow limitation and 6-min walk distance (6MWD), were also significantly different. No between-group differences were observed in age, smoking history, degree of hyperinflation, or St George's Respiratory Questionnaire score. The computed tomography emphysema indices tended to increase from the lowest to the high quartile groups, but did not reveal statistically significant differences among the four subgroups.

The mortality rates gradually increased from the lowest to the highest quartile subgroups of urinary desmosines, and significantly differed among the four subgroups during the 161-month (median 114 months)

Shareable abstract (@ERSpublications)
COPD patients with high baseline urinary desmosines demonstrated significantly higher mortality than those with lower urinary desmosines. High urinary desmosine is independently associated with an increased risk of long-term mortality in COPD patients. https://bit.ly/4015xZ9

Cite this article as: Kim C, Ko Y, Lee JS, *et al*. High urinary desmosine is associated with long-term mortality in patients with COPD. *ERJ Open Res* 2023; 9: 00078-2023 [DOI: 10.1183/23120541.00078-2023].

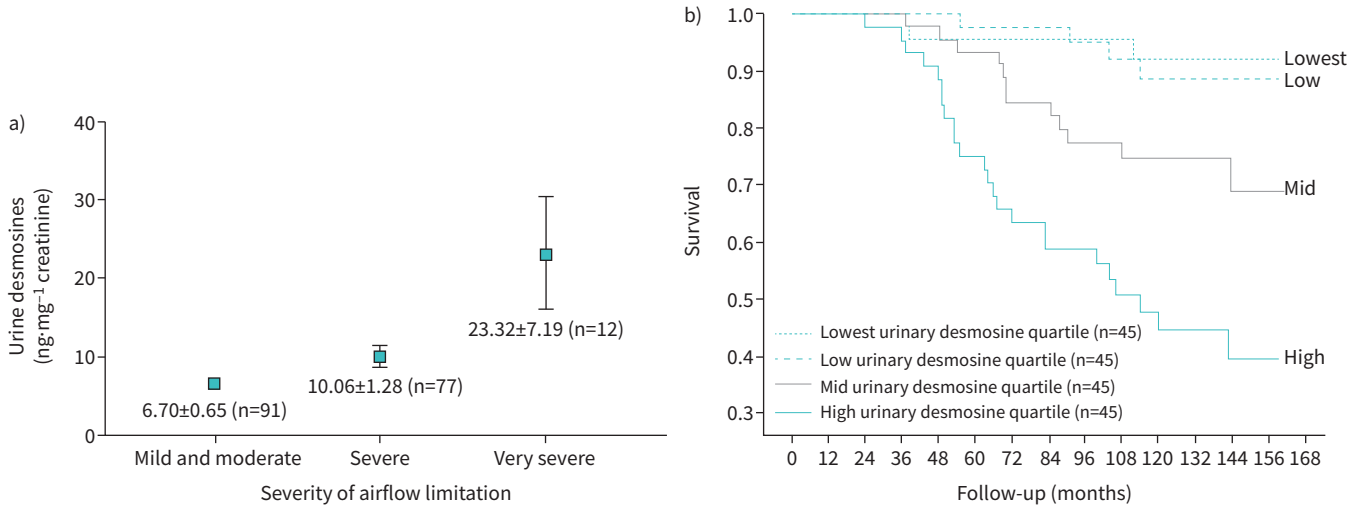

FIGURE 1 a) Means±SE of urinary desmosines according to the severity of airflow limitation (n=180). Only three patients showed mild airflow limitation and were included in the mild and moderate group. b) Survival analysis of the four quartile subgroups based on the levels of urinary desmosines using the Kaplan–Meier method (mean survival 108.5±7.4 months, 137.6±5.9 months, 152.6±3.6 months and 151.7±4.2 months, from highest to lowest quartile, respectively).

follow-up period (6.7%, 8.9%, 26.7% and 53.3%, from the lowest to highest quartile, respectively; p<0.001). Kaplan–Meier analyses revealed that patients with COPD with high levels of urinary desmosines survived for a significantly shorter duration than those with lower levels of urinary desmosines (mean survival 108.5±7.4 months, 137.6±5.9 months, 152.6±3.6 months and 151.7±4.2 months, from highest to lowest quartile; p<0.001) (figure 1b). The multivariate analysis using the Cox proportional hazards regression method (including age, Charlson comorbidity index, BMI, FEV_1, diffusing capacity of the lung and exercise capacity measured by 6MWD) revealed that the hazard ratios compared with the lowest quartile (reference) were 0.43 (95% CI 0.085–2.1984; p=0.312), 2.59 (95% CI 0.703–9.568; p=0.152) and 4.86 (95% CI 1.350–17.457; p=0.016), from lowest to highest quartile. The leading causes of death were respiratory conditions (n=20). Cancer was the second most common cause of death (n=9); lung cancer was the predominant cause of cancer-related death (n=5). Only two deaths were due to cardiovascular causes. All cardiovascular deaths occurred in the subgroup with high urinary desmosine levels.

To the best of our knowledge, there are no reports on the relationship between urinary desmosines and long-term mortality in patients with COPD. Indirect evidence was found in a recent study, which demonstrated that low vitamin K status was associated with increased elastin degradation (plasma matrix Gla protein and desmosine levels) and increased mortality in patients with COPD during >5 years of follow-up [10]. Another report on COPD and desmosines, mainly from the Evaluation of Chronic Obstructive Pulmonary Disease Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort analysis, showed that high levels of desmosines, although measured in plasma, were associated with poor survival, independent of several confounding factors [11]. However, no significant correlation was found between plasma desmosines and emphysema or emphysema progression [11]. The study suggested that circulating desmosines, which showed a positive prediction of mortality, but a poor correlation with emphysema, contributed more to the cardiovascular system than the lungs. In a recent study on bronchiectasis and mortality, in which patients were divided into four quantiles based on the concentrations of serum desmosines, similar to the present study, the authors suggested that serum desmosines were predictors of future mortality, particularly cardiovascular mortality in bronchiectasis [12]. In addition, there is emerging evidence concerning elastin degradation and vascular morbidities [13]. Therefore, circulating desmosines, in blood as well as urine, represent systemic elastin degradation, mainly from both the lungs and vascular walls, and may predict composite outcomes of mortality and vascular morbidities in patients with chronic pulmonary or vascular diseases. In future research, analysis of sputum desmosines might be helpful to differentiate the circulating desmosines from the lungs and vascular walls.

A strength of our study was the long follow-up period, which was sufficient for monitoring mortality. However, this study also had a limitation. Only a small number of patients died from clinically overt cardiovascular events, although all these events occurred in the high-desmosine subgroup. However, it is

difficult to accurately ascertain the causes of death in COPD cohorts, because many patients have multiple comorbid conditions. It is difficult to identify the correct event of an out-of-hospital death with breathlessness because of various possible causes, such as pneumonia, COPD exacerbation, cor pulmonale, pulmonary oedema due to cardiac ischaemia, decompensated heart failure and pulmonary embolism. Therefore, although the association between baseline urinary desmosines and subsequent mortality seems to be apparent in patients with COPD or bronchiectasis, cardiovascular and other comorbidities should be regularly monitored after enrolment.

In conclusion, the present study demonstrated that the level of urinary desmosines was a predictor of all-cause mortality in patients with COPD. Mortality rates gradually increased from the lowest to the high quartile subgroups of urinary desmosines. Patients with COPD in the high urinary desmosine group showed significantly poorer survival than those in other groups during a median 9.5 years of follow-up, and had an approximately five-fold increased risk of mortality. Further studies with urinary desmosines are warranted to thoroughly evaluate comorbidities at baseline and follow-up, and to clarify the possible causes of mortality.

Changhwan Kim[1,2,11], Yousang Ko[2,3,11], Jae Seung Lee[2,4], Chin Kook Rhee[2,5], Jin Hwa Lee[2,6], Ji-Yong Moon[2,7], Seong Yong Lim[2,8], Kwang Ha Yoo[2,9], Joon Beom Seo[2,10], Yeon-Mok Oh[2,4], Sang-Do Lee[2,4] and Yong Bum Park[2,3]

[1]Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Republic of Korea. [2]Clinical Research Center for Chronic Obstructive Airway Diseases, Seoul, Republic of Korea. [3]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea. [4]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. [5]Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea. [6]Department of Internal Medicine, Ewha Womans University Seoul Hospital, College of Medicine, Ewha Womans University, Seoul, Republic of Korea. [7]Division of Pulmonology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea. [8]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. [9]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea. [10]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. [11]These authors contributed equally.

Corresponding author: Yong Bum Park (bfspark2@gmail.com)

Provenance: Submitted article, peer reviewed.

Author contributions: C. Kim and Y. Ko contributed to the analysis and interpretation of the data, and the writing and reviewing of the manuscript. Y.B. Park contributed to the conception and design of the study, analysis and interpretation of the data, and review of the drafts of the manuscript. He had full access to all the data in the study and took responsibility for the integrity of the entirety of the work, from inception to publication. J.S. Lee, C.K. Rhee, J.H. Lee, J-Y. Moon, S.Y. Lim, K.H. Yoo, J.B. Seo, Y-M. Oh and S-D. Lee contributed to the enrolment of the cohort patients and review of the drafts of the manuscript. All authors approved the final version of the manuscript.

Conflict of interest: None declared.

Support statement: This work was supported by a research grant from the Jeju National University Hospital in 2021. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Celli BR. Predictors of mortality in COPD. *Respir Med* 2010; 104: 773–779.

2 Cote CG, Celli BR. Predictors of mortality in chronic obstructive pulmonary disease. *Clin Chest Med* 2007; 28: 515–524.

3 Kim C, Ko Y, Lee JS, *et al.* Predicting long-term mortality with two different criteria of exercise-induced desaturation in COPD. *Respir Med* 2021; 182: 106393.
4 Fermont JM, Masconi KL, Jensen MT, *et al.* Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis. *Thorax* 2019; 74: 439–446.
5 Park HY, Churg A, Wright JL, *et al.* Club cell protein 16 and disease progression in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188: 1413–1419.
6 Zemans RL, Jacobson S, Keene J, *et al.* Multiple biomarkers predict disease severity, progression and mortality in COPD. *Respir Res* 2017; 18: 117.
7 Huang JT, Bolton CE, Miller BE, *et al.* Age-dependent elastin degradation is enhanced in chronic obstructive pulmonary disease. *Eur Respir J* 2016; 48: 1215–1218.
8 Lindberg CA, Engström G, de Verdier MG, *et al.* Total desmosines in plasma and urine correlate with lung function. *Eur Respir J* 2012; 39: 839–845.
9 Kim C, Ko Y, Kim SH, *et al.* Urinary desmosine is associated with emphysema severity and frequent exacerbation in patients with COPD. *Respirology* 2018; 23: 176–181.
10 Piscaer I, van den Ouweland JMW, Vermeersch K, *et al.* Low vitamin K status is associated with increased elastin degradation in chronic obstructive pulmonary disease. *J Clin Med* 2019; 8: 1116.
11 Rabinovich RA, Miller BE, Wrobel K, *et al.* Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in COPD. *Eur Respir J* 2016; 47: 1365–1373.
12 Huang JT, Kuzmanova E, Dicker AJ, *et al.* Serum desmosine is associated with long-term all-cause and cardiovascular mortality in bronchiectasis. *Am J Respir Crit Care Med* 2020; 202: 897–899.
13 Iskandar Z, Patel S, Lancefield T, *et al.* Plasma desmosine, a biomarker of elastin degradation, predicts outcomes in coronary artery disease. *Eur Heart J* 2020; 41: Suppl. 2, 1351.