



# Endoscopic lung volume reduction with endobronchial valves in very low $D_{LCO}$ patients: results from the German Registry – Lungenemphysemregister e.V.

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## ABSTRACT

**Background:** Endoscopic lung volume reduction (ELVR) with valves has been suggested to be the key strategy for patients with severe emphysema and concomitant low diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ). However, robust evidence is still missing. We therefore aim to compare clinical outcomes in relation to  $D_{LCO}$  for patients treated with ELVR.

**Methods:** We assessed  $D_{LCO}$  at baseline and 3 months follow-up and compared pre- and postprocedural pulmonary function test, quality of life, exercise capacity and adverse events. This is a retrospective subanalysis of prospectively collected data from the German Lung Emphysema Registry.

**Results:** In total, 121 patients treated with ELVR were analysed. Thirty-four patients with a  $D_{LCO} \leq 20\%$  and 87 patients with a  $D_{LCO} > 20\%$  showed similar baseline characteristics. After ELVR, there was a decrease of residual volume (both  $p < 0.001$  to baseline) in both groups, and both demonstrated better quality of life ( $p < 0.01$  to baseline). Forced expiratory volume in 1 s ( $FEV_1$ ) improved significantly only in patients with a  $D_{LCO} > 20\%$  ( $p < 0.001$  to baseline). Exercise capacity remained almost unchanged in both groups ( $p = 0.3$ ). The most frequent complication for both groups was a pneumothorax ( $D_{LCO} \leq 20\%$ : 17.6% versus  $D_{LCO} > 20\%$ : 16.1%;  $p = 0.728$ ). However, there were no significant differences in other adverse events between both groups.

**Conclusions:** ELVR improves lung function as well as quality of life in patients with  $D_{LCO} > 20\%$  and  $D_{LCO} \leq 20\%$ . Adverse events did not differ between groups. Therefore, ELVR should be considered as a treatment option, even in patients with a very low  $D_{LCO}$ .



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**Endoscopic lung volume reduction with endobronchial valves can be safely performed in patients with a very low diffusing capacity of the lung ( $D_{LCO}$ ). Clinical effectiveness is comparable to patients with higher  $D_{LCO}$ .** <https://bit.ly/3cOgDK1>

**Cite this article as:** Lenga P, Ruwwe-Glösenkamp C, Grah C, *et al.* Endoscopic lung volume reduction with endobronchial valves in very low  $D_{LCO}$  patients: results from the German Registry – Lungenemphysemregister e.V. *ERJ Open Res* 2021; 7: 00449-2020 [<https://doi.org/10.1183/23120541.00449-2020>].



This study is registered at [www.drks.de](http://www.drks.de) with identifier number DRKS00021207. Individual deidentified patient data will be available upon reasonable request. The study protocol will be available. This will be immediately following publication. The data will be available to investigators whose proposed use of the data has been approved by an independent review committee for individual participant data meta-analysis. Proposals may be submitted up to 36 months following article publication.

Received: 30 June 2020 | Accepted after revision: 23 Sept 2020

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## Introduction

COPD is a highly prevalent disease worldwide, currently being among the top five causes of death [1]. In advanced disease, endoscopic lung volume reduction (ELVR) using endobronchial valves (EBV) has been shown to improve lung function, quality of life and exercise capacity for a subset of patients [2–10]. This subset consists mainly of patients suffering from severe emphysema and hyperinflation [11]. Further, endobronchial valves can only be used in candidates without evidence of collateral ventilation in adjacent targeted lung lobes [12, 13].

Analysis of the National Emphysema Treatment Trial (NETT), investigating the outcome of patients with severe emphysema undergoing surgical lung volume reduction, revealed a significantly higher mortality in patients with a preoperative diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ) of 20% or less of the predicted value [14]. Subsequently, this resulted in many of the clinical trials investigating the effectiveness of EBV treatment excluding patients with a  $D_{LCO}$  of <20% of the predicted value [3, 4, 15]. However, newer evidence suggests that lung volume reduction surgery in highly selected patients with a very low  $D_{LCO}$  might be safe in experienced centres [16].

Recently, a single-centre retrospective study suggested that endobronchial valve therapy in patients with a very low  $D_{LCO}$  does not confer an increased risk of adverse events when compared with a historical control group [17]. Clinical effectiveness, however, seemed to be smaller compared to patients with a higher  $D_{LCO}$ .

To further investigate the feasibility and effectiveness of endobronchial valve therapy in patients with very low  $D_{LCO}$ , we analysed data from the Lungenemphysemregister e.V (LE- Registry), which is a non-profit multicentre observational registry following patients after lung volume reduction in Germany. We compared incidences of adverse events and measures of clinical outcomes, as well as patient characteristics in the two groups conferring either a very low  $D_{LCO} \leq 20\%$  or a  $D_{LCO} > 20\%$ , respectively.

## Methods

### Study design and inclusion criteria

All clinical data for this retrospective analysis are based on pooled prospective data from the LE-Registry (<https://lungenemphysemregister.de/>). The LE-Registry is a national multicentre observational open-label study collecting clinical and imaging data exclusively for severe lung emphysema patients in Germany. The LE-Registry is a non-profit organisation founded by several German hospitals. Its main emphasis lies on collecting data of patient outcomes after surgical or endobronchial lung volume reduction, independent of any biotech/pharmaceutical companies. The ethics committee of the Charité Universitätsmedizin Berlin approved the collection of data (EA2/149/17). The study was registered with the German Clinical Trials Register (DRKS00021207). Each patient consented to participation. Patients were included in this specific study if they had been treated with endobronchial valves and they had documented  $D_{LCO}$  levels at baseline and 3 months follow-up. Patients were allocated into two groups: group 1:  $D_{LCO} \leq 20\%$ , group 2:  $D_{LCO} > 20\%$ . Data were available at 3 months follow-up for 26 out of 34 (76.5%) patients with a  $D_{LCO} \leq 20\%$  and for 65 out of 87 (74.7%) patients with a  $D_{LCO} > 20\%$ .

### Measurements

Between September 2017 and February 2020 121 patients after ELVR with EBV were included in the LE-Registry at eight emphysema centres in Germany. Inclusion criteria were: a proof of nicotine restriction over 3 months (carboxyhaemoglobin (CoHb) <2% or no cotinine levels in urine), motivation to participate

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in a patient mobility programme, a clinical assessment that dyspnoea was caused primarily by hyperinflation, 6-min walk distance (6MWD) <450 m, forced expiratory volume in 1 s (FEV<sub>1</sub>) <45% of predicted, residual volume (RV) >180% of predicted, total lung capacity (TLC) >100% of predicted, and absence of collateral ventilation in the target lobe assessed by Chartis® (Pulmonx, Redwood City, CA, USA) and/or by software-dependent analysis of fissure integrity (StratX platform; Pulmonx or VIDA Diagnostics, Coralville, IA, USA). Exclusion criteria were: inability to sign a consent form, significant pulmonary arterial pressure (sPAP >50 mmHg) or the omission of documentation of the  $D_{LCO}$  levels. This occurred in 15 cases. For all patients, final treatment strategies were determined in a local steering committee at each treatment site, consisting of members of the respective emphysema centres.

### Procedures

All bronchoscopic procedures were conducted according to guidelines [18–21]. The emphysema score was evaluated by software-based quantification of emphysema destruction at –950 Hounsfield units (StratX platform or VIDA Diagnostics). Homogeneous emphysema was defined as <15% difference in emphysema score between target and ipsilateral adjacent lobes [3, 22]. In the absence of collateral ventilation, 73.6% Zephyr® valve system (Pulmonx) and 26.4% Spiration valve system (Olympus, USA) were implanted. Patients were evaluated at baseline and 3 months follow-up for pulmonary function tests (FEV<sub>1</sub>, RV, TLC,  $D_{LCO}$ ), clinical condition (6MWD), quality of life (St. George's Respiratory Questionnaire (SGRQ)), Medical Research Council dyspnoea scale (mMRC) and for adverse events after ELVR.

Spirometry, body plethysmography and measurement of diffusion capacity were performed according to current standards [23–25]. Normal values for  $D_{LCO}$  were taken from the European Respiratory Society (ERS) formulas [26].

Patients were considered responders if the FEV<sub>1</sub>, RV, 6MWD, mMRC and SGRQ improved more than the minimal clinically important difference (MCID) after the implantation of endobronchial valves. We used the following MCID: improvement of FEV<sub>1</sub> of at least 10%, reduction of RV ≤0.43 L, increase of 6MWD of at least 26 m, reduction of mMRC of at least 1 point and reduction of SGRQ of at least 4 points as previously described [27–31].

### Statistical analysis

The Mann–Whitney U-test or Chi-squared test were used for comparison of the baseline characteristic data and the occurrence of adverse events between the  $D_{LCO}$  groups. The Chi-squared test was performed for the comparison of the MCID between  $D_{LCO}$  groups. The Mann–Whitney U-test was also performed for the comparison of lung function and quality of life data between the “delta” ( $\Delta$ )  $D_{LCO}$  groups. Delta was defined as the mean difference between the  $D_{LCO}$  group at baseline and at 3 months follow-up. Since all variables were normally distributed as examined with the Shapiro–Wilk test, all parameters are presented as means with standard deviation (SD). The relation between  $D_{LCO}$  and the improvement of FEV<sub>1</sub> at 3 months was tested by using the Pearson correlation. To investigate associations, we used linear regression analysis models with  $\Delta$ FEV<sub>1</sub> as the dependent variable and  $D_{LCO}$  levels as independent variables. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, Version 24.0.0.0 (IBM Corp., Armonk, NY, USA).

## Results

### Patients' baseline characteristics

We included 34 patients with  $D_{LCO} \leq 20\%$  and 87 patients with  $D_{LCO} > 20\%$  (table 1). The mean age was 65.5±6.8 years in the  $D_{LCO} < 20\%$  and 64.4±15.2 years in the  $D_{LCO} > 20\%$  groups (p=0.69). There was a predominance of female sex in the  $D_{LCO} \leq 20\%$  (58.8%) group compared to  $D_{LCO} > 20\%$  (37.2%; p=0.03). There was a significant difference between the groups in  $D_{LCO}$  at baseline ( $D_{LCO} \leq 20\%$ : 16.1±3.4 versus  $D_{LCO} > 20\%$ : 34.7±11.8; p<0.001). Regarding the emphysema score, no significant differences were found between the groups ( $D_{LCO} \leq 20\%$ : 42.9±13.3 versus  $D_{LCO} > 20\%$ : 45.8±10.7; p<0.31). No other significant differences between the groups were observed either for baseline data or for lung function, exercise capacity or the quality of life at baseline.

### Clinical outcome in relation to $D_{LCO}$ after ELVR

After ELVR, only patients with  $D_{LCO} \leq 20\%$  showed a significant increase in  $D_{LCO}$  from baseline to 3 months follow-up (16.1±3.4 to 22.0±5.7, p=0.003, table 2), while patients with  $D_{LCO} > 20\%$  remained almost unchanged (34.7±11.8 to 34.9±12.2, p=0.75). RV decreased significantly at 3 months follow-up from baseline in both groups (p=0.01 both to baseline). There was a similar increase in FEV<sub>1</sub> from baseline to 3 months follow-up in both patient groups, which was only significant for patients with a  $D_{LCO} > 20\%$ . Both groups showed a significant improvement in quality of life at 3 months follow-up, as measured with mMRC and SGRQ compared to baseline measurements (p<0.05 for all assessments to

TABLE 1 Baseline characteristics

	$D_{LCO} \leq 20\% \text{ pred}$	$D_{LCO} > 20\% \text{ pred}$	p-value
<b>Subjects n</b>	34	87	
<b>Age years</b>	65.5±6.8	64.4±15.2	0.69
<b>BMI kg·m<sup>-2</sup></b>	25.46±9.8	24.62±9.8	0.81
<b>Sex %</b>			<b>0.03</b>
Male	41.2	62.8	
Female	58.8	37.2	
<b>Comorbidities %</b>			
$\alpha_1$ -antitrypsin-deficiency	5.9	3.5	0.15
Cardiovascular disease	26.5	18.6	0.34
Pulmonary hypertension	8.8	9.3	0.94
Atrial fibrillation	5.9	8.1	0.67
Arterial hypertension	35.3	55.8	<b>0.04</b>
Osteoporosis	5.9	9.3	0.54
Diabetes mellitus type II	2.9	4.7	0.67
Lung cancer	0.0	1.2	0.17
Active tumours	0.0	2.3	0.53
Others	20.6	26.7	0.77
<b>Emphysema score in target lobe<sup>#</sup></b>	42.9±13.3	45.8±10.7	0.31
<b>Heterogeneity index between target and adjacent lobe<sup>#</sup></b>	22.7±9.6	21.0±12.5	0.45
<b>Lung function test at baseline</b>			
FEV <sub>1</sub> % pred	30.0±9.5	33.0±9.9	0.11
RV % pred	261.1±49.6	251.4±52.3	0.51
$D_{LCO}$ % pred	16.1±3.4	34.7±11.8	<b>&lt;0.001</b>
6MWD m	254.7±92.8	276.6±115.9	0.94
mMRC points	3.4±0.7	3.0±0.9	0.25
SGRQ points	60.7±12.0	59.6±11.9	0.98

Data are presented as mean±SD unless otherwise stated.  $D_{LCO}$ : diffusing capacity of the lung for carbon monoxide; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire. #: software automated quantification of emphysema destruction [−950 Hounsfield units]. Bold indicates statistical significance.

baseline). The 6MWD slightly increased at 3 months follow-up, irrespective of  $D_{LCO}$ , but was not statistically different compared to baseline (p=0.15). At 3 months follow-up there were no differences in the lung function parameters (FEV<sub>1</sub> and RV, exercise capacity (6MWD) or in quality of life (mMRC, SGRQ)) between both  $D_{LCO}$  groups.  $D_{LCO}$  in patients with an initially low  $D_{LCO}$  improved significantly, unlike in patients with higher  $D_{LCO}$  rates at 3 months follow-up (table 3).

TABLE 2 Comparison between diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ) groups from baseline to 3 months follow-up

	$D_{LCO} \leq 20\% \text{ pred}$			$D_{LCO} > 20\% \text{ pred}$		
	Baseline	3-month follow-up	p-value	Baseline	3-month follow-up	p-value
<b>Subjects n</b>	34	26		87	65	
<b><math>D_{LCO}</math> % pred</b>	16.1±3.4	22.0±5.7	<b>0.003</b>	34.7±11.8	34.9±12.2	0.75
<b>FEV<sub>1</sub> L</b>	0.8±0.3	0.9±0.4	0.09	0.9±0.3	1.01±0.1	<b>0.001</b>
<b>FEV<sub>1</sub> % pred</b>	30.0±9.5	33.3±9.8	0.08	33.0±9.9	36.84±12.0	<b>0.001</b>
<b>RV L</b>	5.9±1.1	5.5±1.7	<b>0.01</b>	5.6±1.9	4.93±1.4	<b>0.01</b>
<b>RV % pred</b>	261.1±49.6	246.0±73.3	<b>0.01</b>	251.4±52.3	211.51±52.0	<b>&lt;0.001</b>
<b>6MWD m</b>	254.7±92.8	305.4±117.2	0.15	276.6±115.9	296.00±128.2	0.15
<b>mMRC points</b>	3.4±0.7	3.0±0.8	<b>0.02</b>	3.0±0.9	2.72±1.0	<b>0.03</b>
<b>SGRQ points</b>	60.7±12.0	50.0±17.7	<b>0.049</b>	59.6±11.9	53.78±14.8	<b>0.04</b>

Data are presented as mean±SD unless otherwise stated. FEV<sub>1</sub>: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire. Bold indicates statistical significance.

TABLE 3 Change in lung function and clinical parameters at 3 months follow-up

	$D_{LCO} \leq 20\%$ pred	$D_{LCO} > 20\%$ pred	p-value
Subjects n	26	65	
$\Delta D_{LCO}$ kPa	0.35±0.86	0.03±1.10	0.04
$\Delta FEV_1$ L	0.17±0.42	0.11±0.25	0.70
$\Delta RV$ L	-0.5±0.9	-0.7±1.7	0.94
$\Delta 6MWD$ m	38.2±88.7	31.3±109.7	0.30
$\Delta mMRC$ points	-0.5±1.7	-0.4±0.9	0.83
$\Delta SGRQ$ points	-12.4±16.4	-6.0±11.5	0.29

Data are presented as mean±SD unless otherwise stated.  $D_{LCO}$ : diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; mMRC: Medical Research Council dyspnoea; SGRQ: St George's Respiratory Questionnaire.

Table 4 depicts the responders achieving an MCID in outcome measures. There were no significant differences in outcomes between patients with a  $D_{LCO} \leq 20\%$  and those with a  $D_{LCO} > 20\%$ .

There was no significant correlation between  $D_{LCO}$  levels and  $\Delta FEV_1$  (Pearson's  $R = -0.008$ ;  $p = 0.939$ , data not shown). After performing regression analysis models, there was no association between  $D_{LCO}$  and  $\Delta FEV_1$  at 3 months of follow-up ( $B = -0.04$ ;  $p = 0.678$ , data not shown).

#### Adverse events

There were no significant differences in complication rates between both groups (table 5). The most common complication was pneumothorax ( $D_{LCO} \leq 20\%$ : 23.1% versus  $D_{LCO} > 20\%$ : 21.5%;  $p = 0.73$ ). An acute exacerbation of COPD occurred in one patient (3.8%) in the  $D_{LCO} \leq 20\%$  group and in 13 patients (14.9%) in the  $D_{LCO} > 20\%$  group ( $p = 0.07$ ). In both cohorts, no deaths occurred until the 3-month follow-up. Three patients with a  $D_{LCO} > 20\%$  (4.6%) had to be admitted to an intensive care unit, compared to one patient in the  $D_{LCO} < 20\%$  group (3.8%). In the group with a  $D_{LCO} > 20\%$  three patients (4.6%) required mechanical ventilation. Postinterventional bleeding was present in one patient (1.5%), and pneumonia occurred in two patients (3.1%) compared to none in the group with a  $D_{LCO} \leq 20\%$ .

#### Discussion

Patients with a very low  $D_{LCO}$  played only a marginal role in previous prospective studies on treatment outcomes after EBV [3, 4, 15]. To our knowledge, we are the first to describe outcome results for patients undergoing treatment with endobronchial valves exclusively based on a large national cohort. One of the main results indicates that ELVR for patients with a very low  $D_{LCO}$  might be a safe therapy, since complication rates were substantially low and not a single death occurred in either group. Furthermore, we found a significant amelioration of quality of life as measured with the SGRQ and of lung function in patients with a very low  $D_{LCO}$ .

Hyperinflation of the lungs as a consequence of emphysema greatly diminishes exercise capacity [32]. In addition to inhaled bronchodilators, which are the current mainstay of treatment, only lung volume

TABLE 4 Comparison of minimal clinically important difference (MCID) for forced expiratory volume in 1 s (FEV<sub>1</sub>), residual volume (RV), 6-min walk distance (6MWD) and St George's Respiratory Questionnaire (SGRQ)

	$D_{LCO} \leq 20\%$ pred	$D_{LCO} > 20\%$ pred	p-value
Subjects n	26	65	
FEV <sub>1</sub> L, MCID $\geq +10\%$	7 (26.9)	13 (20.0)	0.744
RV L, MCID $\leq -0.43$ L	15 (57.7)	32 (49.2)	0.466
6MWD m, MCID $\geq +26$ m	14 (53.8)	26 (40.0)	0.620
mMRC points, MCID $\leq -1$ point	11 (42.3)	14 (21.5)	0.151
SGRQ points, MCID $\leq -4$ points	10 (38.5)	19 (29.2)	0.795

Data are presented as n [%] unless otherwise stated.  $D_{LCO}$ : diffusing capacity of the lung for carbon monoxide; mMRC: Medical Research Council dyspnoea.

TABLE 5 Adverse events after endobronchial implantation of valves in 3 months follow-up

Adverse event	$D_{LCO} \leq 20\%$ pred	$D_{LCO} > 20\%$ pred	p-value
<b>Subjects n</b>	26	65	
<b>ICU</b>	1 (3.8)	3 (4.6)	0.93
<b>Mechanical ventilation</b>	0.0	3 (4.6)	0.28
<b>Death</b>	0	0	
<b>Sepsis</b>	0	0	
<b>Bleeding</b>	0.0	1 (1.5)	0.54
<b>Pneumonia</b>	0.0	2 (3.1)	0.39
<b>AECOPD</b>	1 (3.8)	13 (20.0)	0.07
<b>Pneumothorax</b>	6 (23.1)	14 (21.5)	0.73

Data are presented as n (%) unless otherwise stated.  $D_{LCO}$ : diffusion capacity of the lung for carbon monoxide; ICU: intensive care unit; AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

reduction, either as a surgical or endobronchial technique, is available as an established treatment option to address hyperinflation in advanced COPD [33–37]. In the largest trial to date, examining the safety and effectiveness of surgical lung volume reduction, the NETT, subgroup analysis showed an increased mortality for patients undergoing surgery with a  $D_{LCO}$  of <20% of predicted [14]. This led to several trials examining the application of endobronchial valves to exclude patients with a very low  $D_{LCO}$  from treatment [3, 4, 15].

Little is known about safety and efficacy regarding implantation of valves in patients with very low  $D_{LCO}$ . While earlier data suggest the feasibility in patients with a very low  $FEV_1$  (<20% predicted) [38, 39], it is not known yet whether the same is true for a very low  $D_{LCO}$ .

Data collected for the current study show no statistically significant difference in outcomes for patients treated with EBV based on their  $D_{LCO}$  (tables 2 and 3). Both the >20% and  $\leq 20\%$   $D_{LCO}$  group, after EBV treatment, showed similar improvements of RV, decreased dyspnoea (mMRC) and increased life quality (SGRQ), while the 6MWD did not change significantly in either group, even though a trend towards improvement could be observed.  $FEV_1$  increased significantly only in the >20%  $D_{LCO}$  group, potentially caused by the lower number of patients included in the very low  $D_{LCO}$  group, thus reducing statistical power. Nevertheless, we did find that only patients with very low  $D_{LCO}$  showed a significant increase in  $D_{LCO}$  after ELVR at 3 months follow-up (table 3). This might seem surprising at first glance, since lung volume reduction per definition reduces the overall alveolar surface of a lung and therefore potentially aggravates an already low diffusing capacity. However, diffusing capacity in severe lung emphysema is determined through a combination of factors including, as already mentioned, decreased alveolar surface. Additionally, diffusing capacity causes changes in the pulmonary vasculature and, most significantly, ventilation–perfusion mismatches [40, 41]. Treatment with endobronchial valves decreases ventilation–perfusion mismatches in the lung, as shown with dual energy computed tomography of the lung, thus counteracting decreases in alveolar surface [42].

Table 1 shows an important strength of the study, namely that both groups were similar in most baseline characteristics, except for sex and rate of arterial hypertension. This may seem somewhat surprising, since  $D_{LCO}$  has been shown to correlate with several parameters of COPD severity, including  $FEV_1$  and lung density [43]. Thus, we would expect patients with a more severe disease phenotype at baseline in the very low  $D_{LCO}$  group. While a trend in terms of more severe emphysema, as measured with computed tomography quantification, and more hyperinflation, as measured with RV, can be observed, this is not statistically significant. One of the reasons for the relative homogeneity of the two groups at baseline is certainly the already highly selective process of choosing COPD patients for ELVR. All patients within the LE-Registry must fulfil restrictive criteria in terms of their baseline characteristics before being considered potential candidates for an intervention. Within this subset of patients with very severe emphysema,  $D_{LCO}$  might be perhaps less meaningful as an indicator of severity compared to milder forms of COPD.

In terms of efficacy, our data show similarly positive results as those published in previous prospective clinical trials [44]. In the LIBERATE study, the treatment group had a median reduction of RV of 490 mL, in the EMPROVE study RV reduction was 402 mL, while in our study there was a mean reduction of 540 mL in the very low  $D_{LCO}$  group, and 730 mL in the >20%  $D_{LCO}$  group [4, 9]. 6MWD increased by 38 m and 31 m, respectively, as compared to 13 m in the LIBERATE study and –4 m in the EMPROVE study, albeit there being no statistically significant difference between baseline and follow-up in our study.

This indicates reassuringly that outside of highly controlled conditions of randomised clinical trials, outcomes are similar in participating hospitals of the LE-Registry.

In addition to the positive efficacy outcomes in both  $D_{LCO}$  groups, the second main message of this study is that EBV treatment is safe even in patients with a very low  $D_{LCO}$ . There was not a single death in either group, in contrast to the results of the NETT trial, where patients with a very low  $D_{LCO}$  undergoing surgery were prone to adverse events and exhibited higher mortality rates [14].

Table 5 shows adverse events occurring during or after treatment in both groups. Reassuringly, adverse events did not differ significantly between the two groups and were overall low. Even though our study had presumably more severely ill patients by including those with a  $D_{LCO} < 20\%$ , rates of adverse events were not higher than those published in randomised controlled trials [44].

One of the main strengths of our study is the data originating from a multicentre, industry-independent registry. However, some limitations do exist. The included cohort of very low  $D_{LCO}$  patients is relatively small, even in this multicentre effort, potentially reflecting the hesitancy of physicians to treat patients with a very low  $D_{LCO}$  with EBV therapy. It is possible that the results of our current study will lead to more frequent treatment inclusions of this subgroup in the future. Another limitation of our study is that our recruited patients with a very low  $D_{LCO}$  generally had  $D_{LCO}$  levels between 10% and 20%, and much less often below 10%, which might underpower our effect size. Since patients with a  $D_{LCO}$  of  $< 20\%$  played only a marginal role in general in previously published studies, we believe that our findings could still be a meaningful tool in the decision-making process of clinicians.

Furthermore, our results showed improvements in the MCID for FEV<sub>1</sub>, RV, 6MWT and SGRQ at 3 months follow-up in both patient groups. However, these findings were partly lower than in randomised clinical trials. Perhaps a relatively high dropout rate of a quarter of patients during follow-up prevented more meaningful results in this regard. Since this is a registry, missing data are frequently inherent with this type of study. We strongly believe that there is a substantial need for further randomised trials expanding the evidence of that topic.

### Conclusion

There were significant improvements in hyperinflation, dyspnoea and quality of life in patients with a very low  $D_{LCO}$ . Additionally, we observed low complication rates and absence of mortality in both groups after EBV therapy. These findings stress the importance of when discussing treatment modalities for patients with a very low  $D_{LCO}$ , the implantation of valves should be considered, since it seems to be a safe and efficacious treatment tool. These findings might serve as a basis for the development of future research focusing on the clinical outcomes of patients with a very low  $D_{LCO}$  after ELVR.

Conflict of interest: P. Lenga has nothing to disclose. C. Ruwwe-Glösenkamp has nothing to disclose. C. Grah has nothing to disclose. J. Pfannschmidt has nothing to disclose. J. Rückert has nothing to disclose. S. Eggeling has nothing to disclose. S. Gläser reports personal fees from Boehringer Ingelheim, grants and personal fees from Novartis Pharma, and personal fees from Roche Pharma, Berlin Chemie, PneumRx, PulmonX, Actelion Pharma and Bayer Healthcare, outside the submitted work. B. Schmidt has nothing to disclose. P. Schneider has nothing to disclose. S. Kurz has nothing to disclose. G. Leschber has nothing to disclose. A. Gebhardt has nothing to disclose. B. Becke has nothing to disclose. O. Schega has nothing to disclose. J. Borchardt has nothing to disclose. R-H. Hübner reports personal fees and nonfinancial support from PulmonX outside the submitted work.

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