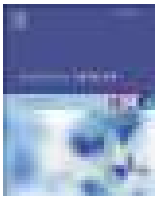
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Original Research



Survival in COPD patients treated with bronchoscopic lung volume reduction

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ABSTRACT

Background and objective: Severe COPD patients can significantly benefit from bronchoscopic lung volume reduction (BLVR) treatments with coils or endobronchial valves. However, the potential impact of BLVR on survival is less understood. Therefore, our aim was to investigate the survival rate in patients who are evaluated for BLVR treatment and whether there is a difference in survival rate between patients who undergo BLVR treatment and patients who do not.

Methods: We included patients with COPD who visited our hospital for a consultation evaluating their eligibility for BLVR treatment and who performed pulmonary function tests during this visit. Furthermore, vital status was verified.

Results: In total 1471 patients were included (63% female, mean age 61 years). A total of 531 patients (35%) died during follow-up and the median survival time of the total population was 2694 days (95% confidence interval (CI) 2462–2926) which is approximately 7.4 years. The median survival time of patients who were treated with BLVR was significantly longer compared to patients who were not treated with BLVR (3133 days versus 2503 days, $p < 0.001$), and BLVR was found to be an independent predictor of survival when adjusting for other survival-influencing factors such as age, gender or severity of disease.

Conclusions: Our results suggest that bronchoscopically reducing lung volume in patients with severe hyperinflation may lead to a survival benefit for a population with a severely reduced life expectancy.

1. Introduction

Bronchoscopic lung volume reduction (BLVR) with lung volume reduction coils or endobronchial valves (EBV) have become guideline treatments [1]. Both treatments are aimed to reduce hyperinflated lung volumes in Chronic Obstructive Pulmonary Disease (COPD), and by doing that, these treatments have shown significant benefit for patients in terms of improved pulmonary function, lung volumes, exercise capacity and quality of life [2]. However, not a lot is known about the impact of BLVR treatments on patient survival.

There are a handful of publications on survival after EBV treatment. First, in 19 EBV treated patients followed up to 10 year after treatment, it was shown that patients in whom lobar atelectasis was achieved after EBV treatment had a survival benefit compared to patients who did not [3,4]. This finding was confirmed in a larger cohort of 449 treated patients in whom successful lobar atelectasis was found to be associated with a survival benefit [5]. A fourth publication showed that the BODE index which is known as a predictor of survival improved after EBV treatment [6,7]. To our knowledge, there is only a single publication that has reported on long term survival after coil treatment, showing a 5 year follow-up in 45 patients, of whom 51% were still alive [8].

The above mentioned studies that investigated survival after BLVR generally have had small sample sizes, or only compared responders of the treatment with non-responders based on Residual Volume (RV) reduction or presence of lobar atelectasis. None of these studies compared the potential beneficial effect on survival with patients who did not undergo a BLVR treatment. Furthermore, not much is reported on the general survival rate in this specific group of severe COPD patients. Therefore, our aim was to investigate the survival rate in patients who are evaluated for BLVR treatment and to see whether there is a difference in survival rate between patients who undergo BLVR treatment and patients who do not.

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2. Methods

2.1. Study population

We included all patients with COPD who visited our hospital for a consultation evaluating their eligibility for BLVR treatment and who performed pulmonary function tests during this visit (spirometry and/or bodyplethysmography) between June 2006 and July 2019. Patients were referred to our hospital from physicians throughout the entire Netherlands.

Four hundred and fifty two (452) patients in this study were also included in the analysis previously reported on 1500 patients by Welling et al. [9]. However, for the current study we included patients who visited our hospital and only included measurements performed in our hospital and not from the referring hospital as was previously done by Welling et al. [9].

2.2. Study measurements

Vital status was verified with the Dutch government personal records database on April 3, 2021. During the consultation visit to our hospital, patients performed various measurements. Since August 2014, the number of tests extended and patients were asked to perform some additional tests and questionnaires for research purpose (COPD phenotypes study, clinical trials register: NCT04023409). The following measurements were performed: post-bronchodilator spirometry and bodyplethysmography according to the European Respiratory Society and/or American Thoracic Society guidelines [10,11], diffusion capacity, bioelectrical impedance analysis and chest computed tomography (CT)-scan. Quantitative CT analysis was performed using LungQ software (Thirona, Nijmegen, The Netherlands). The questionnaires included the St. Georges Respiratory Questionnaire (SGRQ), COPD assessment Test (CAT) [12,13] and a self-administered questionnaire about the presence of comorbidities. For all patients, we verified in their medical chart whether they were treated with BLVR using coils or EBVs. This research did not fall within the scope of the WMO (Medical Research involving human subjects act) but the COPD phenotypes study was approved by the medical ethical committee of our hospital and all patients gave written informed consent.

2.3. Statistical analyses

Differences between groups were tested with an independent sample T-test (in case of normal distributed data), Mann-Whitney *U* Test (non-normal distributed data) or a Chi-square test (categorical variables). Kaplan-Meier analyses were performed for survival analyses. Survival time was calculated from the date of the consultation visit to our hospital until date of death or the date of the verification with the Dutch government (April 2021). A log-rank test was performed to test whether there was a difference in survival between patients who underwent BLVR and who did not. Cox proportional-Hazards regression analyses were performed to investigate whether other factors univariately influenced survival and whether undergoing BLVR was an independent predictor of survival when adjusting for the other factors that influenced survival. All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM, New York, NY, USA) and p-values below 0.05 were considered statistically significant.

3. Results

3.1. Study population

A total of 1471 patients were included. For all patients the vital status could be verified. Patient demographics and clinical characteristics are shown in Table 1. Patients were predominantly female (63%), mean age of 61 years, 40 packyear smoking history, low FEV_1 (30%), hyperinflation with RV, 221% predicted, emphysema destruction score of 36.8% (−950 Hounsfield Units (HU)), and SGRQ total score of 59 units.

In total 483 patients (33%) underwent a BLVR treatment (73% with

Table 1
Patient characteristics of total group and differences between BLVR and non-BLVR groups.

	Total group (n = 1471)	*n (valid)*	BLVR group (n = 483)	non-BLVR group (n = 988)	p-value
Gender, *male (%)*	542 (37%)	*1471*	155 (32.1%)	387 (39.2%)	**0.008**§
Alpha-1 <0.9 g/L, *number (%)*	66 (8.3%)	*800*	18 (8.3%)	48 (8.2%)	1.00§
Age, *years*	61.0 ± 7.7	*1471*	60.1 ± 7.9	61.4 ± 7.6	**0.004**
Packyears, *years*	40 ± 19	*1347*	39 ± 18	40 ± 19	0.179
Exacerbations previous year, *number*	2.0 (0–15)	*951*	1 (0–12)	2 (0–15)	**<0.001**¶
Hospitalizations for an COPD exacerbation, *number*	0 (0–11)	*743*	0 (0–5)	0 (0–11)	0.068¶
FEV_1, % *of predicted*	30.3 ± 10.3	*1470*	27.2 ± 7.9	31.8 ± 10.9	**<0.001**
RV, % *of predicted*	221.2 ± 47.5	*1433*	236.8 ± 41.7	213.4 ± 48.4	**<0.001**
RV/TLC, *%*	60.9 ± 8.7	*1433*	63.4 ± 7.3	59.6 ± 9.1	**<0.001**
DLCO, *mmol/min*kPa*	2.54 (1.01–7.9)	*588*	2.57 (1.1–7.4)	2.52 (1.0–7.9)	0.162¶
$PaCO_2$, *kPa*	5.36 ± 0.78	*1273*	5.34 ± 0.75	5.37 ± 0.79	0.568
PaO_2, *kPa*	9.04 ± 1.26	*1271*	9.20 ± 1.22	8.95 ± 1.27	**0.001**
BMI, kg/m^2	24.2 ± 4.2	*1471*	23.8 ± 3.8	24.4 ± 4.4	**0.010**
Fat free mass, *index COPD*	15.6 ± 2.0	*878*	15.4 ± 1.8	15.7 ± 2.0	**0.036**
SGRQ, *total score*	58.9 ± 13.5	*980*	57.8 ± 12.7	59.2 ± 13.8	0.125
CAT, *total score*	22.4 ± 6.0	*966*	21.8 ± 5.6	22.6 ± 6.1	**0.049**
Emphysema score, *%*	36.8 ± 8.5	*934*	39.3 ± 7.7	35.6 ± 8.6	**<0.001**
Air trapping score, *%*	68.3 ± 8.9	*553*	71.8 ± 6.5	66.5 ± 9.4	**<0.001**
Pi10,*mm*	2.65 ± 0.31	*933*	2.63 ± 0.28	2.66 ± 0.32	0.222
Comorbidity7[a], *yes (%)*	614 (60%)	*1019*	184 (63.2%)	430 (59.1%)	0.229§
Comorbidity3[b], *yes (%)*	219 (22%)	*1019*	79 (27.1%)	140 (19.2%)	**0.007**§
Treated with BLVR, *number (%)*	483 (33%)	*1471*	NA	NA	
EBV/Coil, *number*	353/130				

Data are presented as number (%), mean ± standard deviation or median (range). Differences between groups were tested by an independent samples T-test, Mann-Whitney Test¶ or Chi-square test§. Significant values ($p < 0.05$) are depicted in bold.

N=Number, BLVR = bronchoscopic lung volume reduction, FEV_1 = forced expiratory volume in 1 s, RV = residual volume, TLC = total lung capacity, DLCO = diffusion capacity for carbon monoxide, $PaCO_2$ = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen, BMI = body mass index, COPD= Chronic obstructive pulmonary disease, SGRQ= St. Georges respiratory questionnaire, CAT= COPD assessment test, Pi10 = measure of airway wall thickness, mm = millimeter, EBV = endobronchial valves.

[a] Yes, when a patient has one or more of the following 7 comorbidities: cancer, diabetes mellitus, myocardial infarction, a percutaneous coronary intervention, heart failure, hypertension, loss of neurological function or stroke.

[b] Yes, when a patient has one or more of the following 3 comorbidities: myocardial infarction, a percutaneous coronary intervention or stroke.

EBV and 27% with coils). Table 1 also shows the differences between patients who were and who were not treated with BLVR. Patients in the BLVR group had significantly less COPD exacerbations, worse pulmonary function (lower forced expiratory volume in 1 s (FEV_1) and higher RV), higher PaO2, lower body mass index (BMI), and more emphysema and air trapping measured on CT-scan compared to patients who were not treated. Furthermore, the BLVR group had a higher percentage of females, were slightly younger and had more often one of the following three comorbid events in their medical history: myocardial infarction, a percutaneous coronary intervention, or stroke.

3.2. Survival and death

The minimum follow-up duration between the date of the consultation in our hospital and the vital status verification with the Dutch government was 633 days and the maximum 5401 days. In total 531 patients (35%) died during follow-up with a median time to death of 1077 days (range 2–4185) after the consultation. The median survival time of the total population was 2694 days (95% confidence interval (CI) 2462–2926) which is approximately 7.4 years (Fig. S1 online supplement).

3.3. BLVR and other factors influencing survival

In the BLVR group 165 patients (34%) died during follow-up. The median survival time of patients who were treated with BLVR was significantly longer compared to patients who were not treated with BLVR (3133 days (95%CI 2777–3489) versus 2503 days (95%CI 2281–2725), $p < 0.001$) (Fig. 1). There was no significant difference in median survival time between the patients who received coils or EBVs (3171 days versus 3133 days, respectively); See online supplement Figs. S2 and S3).

To determine whether BLVR treatment was an independent predictor of survival in this group we first assessed which other factors influenced survival. The other factors that significantly negatively influenced survival were male gender, higher age, higher number of packyears, higher number of hospitalizations for a COPD exacerbation, lower FEV_1, higher RV or RV/Total Lung Capacity(TLC)-ratio, lower DLCO, higher $PaCO_2$, lower PaO_2, lower BMI, lean weight or fat free mass index, higher percentage of emphysema, air trapping score or airway wall thickness measured on CT-scan and one of the following 3 comorbid events in the medical history: myocardial infarction, a percutaneous coronary intervention or stroke (Table 2).

It was not possible to include all the survival-influencing factors in one regression-model because not all patients performed all tests; consequently only a low number of patients would be included in this kind of model. Nevertheless, we included as many different factors as possible with the highest number of cases included. When adjusting for gender, age, packyears, FEV_1, RV/TLC, BMI, PaCO2, PaO2, emphysema destruction score, airway wall thickness and the presence of myocardial infarction, a percutaneous coronary intervention or stroke in medical history, not undergoing the BLVR treatment was an independent predictor of mortality (Hazard Ratio: 2.016 (95%CI: 1.455–2.793, $p < 0.001$) (Table 3).

4. Discussion

Our results showed that the median survival time for patients who are considered for BLVR treatment was approximately 7.4 years. Furthermore, the median survival time was significantly longer for patients treated with BLVR compared to patients who were not. The difference between these groups was 630 days, which is approximately 1.7 years. Furthermore, undergoing BLVR treatment was an independent predictor of survival when adjusted for other survival-influencing factors like age, gender, or disease severity.

Patients treated with BLVR had a median survival time of 3133 days (approximately 8.6 years) compared to 2503 days (approximately 6.9 years) for the non-treated group. The patient population included in this analysis is a highly selected population because all patients were referred to our institution for BLVR and invited for a consultation. Therefore, it is difficult to make a direct comparison to other severe COPD populations. The most comparable population is the NETT trial population, which consisted of patients who were eligible for lung volume reduction surgery (LVRS). In this group, the median survival time was approximately 6 years for the LVRS-group and approximately 5 years for the medical care control group (not receiving LVRS) [14].

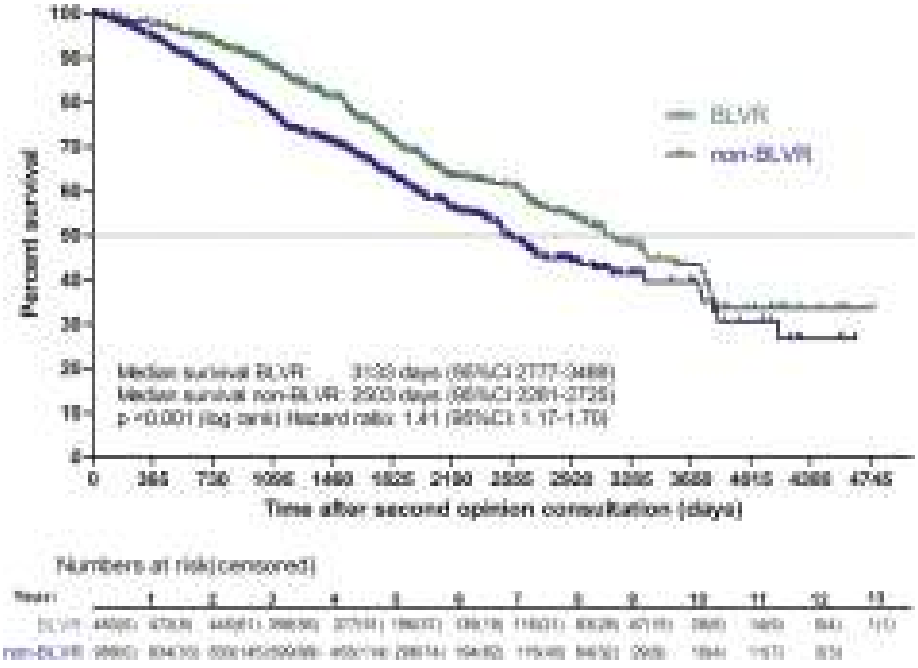


Fig. 1. Kaplan-Meier plot of survival of patients who underwent BLVR treatment and who did not. BLVR: patients who underwent a bronchoscopic lung volume reduction treatment. Non-BLVR: patients who did not undergo a bronchoscopic lung volume reduction treatment. 95%CI: 95% confidence interval.

Table 2
Results of univariate Cox-regression analyses to investigate the influence of the variable on mortality.

	Exp (B)	95%CI	p-value
Gender, *female*	0.704	0.593–0.835	**<0.001**
Alpha-1 <0.9 g/L?, *no*	1.725	0.912–3.264	0.094
Age, *years*	1.063	1.050–1.076	**<0.001**
Packyears, *years*	1.008	1.003–1.012	**0.001**
Exacerbations previous year, *number*	1.041	0.986–1.099	0.147
Hospitalizations for a COPD exacerbation, *number*	1.119	1.011–1.239	**0.029**
FEV_1, *percentage of predicted*	0.971	0.962–0.980	**<0.001**
RV, *percentage of predicted*	1.003	1.001–1.005	**0.001**
RV/TLC, *%*	1.043	1.032–1.053	**<0.001**
DLCO, *mmol/min*kPa*	0.708	0.600–0.834	**<0.001**
$PaCO_2$, *kPa*	1.416	1.274–1.574	**<0.001**
PaO_2, *kPa*	0.753	0.698–0.813	**<0.001**
BMI, kg/m^2	0.959	0.938–0.979	**<0.001**
Fat free mass, *index COPD*	0.905	0.844–0.972	**0.006**
Emphysema score, %	1.028	1.011–1.046	**<0.001**
Aitrapping score, %	1.049	1.022–1.076	**<0.001**
Pi10, *mm*	2.378	1.613–3.506	**<0.001**
Comorbidity7[a], yes (%)	1.135	0.887–1.453	0.314
Comorbidity3[b], yes (%)	1.332	1.018–1.744	**0.037**
Treated with EBV or Coils?, *no*	1.413	1.174–1.701	**<0.001**

Significant values ($p < 0.05$) are depicted in bold. 95%CI = 95% confidence interval.
FEV_1 = forced expiratory volume in 1 s, RV = residual volume, TLC = total lung capacity, DLCO = diffusion capacity for carbon monoxide, $PaCO_2$ = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen, BMI = body mass index, COPD= Chronic obstructive pulmonary disease, SGRQ= St. Georges respiratory questionnaire, CAT= COPD assessment test, Pi10 = measure of airway wall thickness, mm = millimeter, EBV = endobronchial valves.
[a] Yes, when a patient has one or more of the following 7 comorbidities: cancer, diabetes mellitus, myocardial infarction, a percutaneous coronary intervention, heart failure, hypertension, loss of neurological function or stroke.
[b] Yes, when a patient has one or more of the following 3 comorbidities: myocardial infarction, a percutaneous coronary intervention or stroke.

Table 3
Results of the Multivariate Cox-regression model (n = 838, 212 cases).

	HR (Exp(B))	95%CI	p-value
Treated with BLVR?, *no*	2.016	1.455–2.793	**<0.001**
Gender, *female*	0.712	0.513–0.988	**0.042**
Age, *years*	1.043	1.022–1.065	**<0.001**
Packyears, *years*	1.004	0.996–1.011	0.340
FEV_1, *liter*	0.580	0.233–1.443	0.241
RV/TLC, *%*	1.031	1.006–1.057	**0.014**
BMI, kg/m^2	0.930	0.894–0.968	**<0.001**
$PaCO_2$, *kPa*	1.072	0.847–1.357	0.563
PaO_2, *kPa*	0.847	0.742–0.966	**0.014**
Emphysema score, %	1.022	1.001–1.044	**0.039**
Pi10, *mm*	1.661	1.002–2.752	**0.049**
Comorbidity3**, *yes*	1.176	0.862–1.605	0.306

Method enter was performed, HR = hazard ratio, CI = confidence interval.
EBV = endobronchial valves, FEV_1 = forced expiratory volume in 1 s, RV = residual volume, TLC = total lung capacity, BMI = body mass index, $PaCO_2$ = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen, Pi10 = measure of airway wall thickness, mm = millimeter **Yes, when a patient has one or more of the following 3 comorbidities: myocardial infarction, a percutaneous coronary intervention procedure or stroke.

Furthermore, in large general cohorts of patients with (very) severe COPD the median survival time ranged between approximately 2.3 to 5.2 years for men, and between approximately 3.2 and > 8 years for women [15,16]. The median survival time in COPD patients after lung transplantation was found to be 6.3 and 9 years [17,18].

Our study differs from previously reported survival studies on BLVR in that we compared patients who underwent BLVR with patients who did not. The only other paper that compared patient selected for BLVR and not selected for BLVR is also from our hospital, and included some of the same patients [9]. However, it was limited to patients evaluated till 2014 and incorporated data of patient who were referred to but did not visit our hospital. We included all treated patients, regardless of whether they were responders or non-responders to the treatment and therefore the difference in survival when excluding the non-treatment-responders in our population could have been even larger. Even when considering that in the other studies, the responders based on the presence of a complete lobar atelectasis, consisted only of 26–45% of the total patients treated in those studies [3–5,8]. A pitfall of our study is that the non-treated group were not eligible for treatment (except for the small group that declined BLVR treatment themselves) which could have been reasons impacting survival. On the other hand, the group that was treated with BLVR had a significantly worse COPD functional disease status, as well as a higher degree of co-morbidity, which would probably negatively influence survival. Only the number of COPD exacerbations was higher in the non-BLVR group, which is known as a predictor of mortality. Furthermore, it would not have been ethical to withhold a known effective treatment from a group eligible for treatment for a long period to evaluate survival or other outcomes. The NETT trial, investigating LVRS, did include a control group for a long term follow up. After a median of 4.3 years they found that the mortality rate was significantly higher in the control group compared to the LVRS group, despite the increased early mortality secondary to the surgery [14]. These data from NETT also indicate that lung volume reduction positively influences survival in these patients.

Our results showed that BLVR treatment was an independent predictor of survival. The other independent predictors of survival were lower age, female gender, less hyperinflation or emphysema severity, higher BMI, higher PaO2 and less bronchial wall thickness measured on CT-scan. Of which most are known from literature [15,19–22]. We did not find a difference in median survival time between the two different BLVR techniques: coils or EBV treatment.

Besides the selected population and potential selection bias in our control group which included patients who were not eligible for BLVR, another limitation of our study is that the causes of death and also other medical events or treatments during the follow up period were unknown. This additional information could have provided a more in-depth analysis of mortality in this specific patient group. However, strengths of our study are the large sample size population for whom the vital status could be verified, and the targeted patient population with extended demographics and the long-term follow up.

In conclusion, our results together with the existing literature on both bronchoscopic and surgical lung volume reduction treatments show that reducing lung volume in patients with COPD and severe hyperinflation and reduced life expectancy may lead to a survival benefit.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

No funding was obtained for this study.

Summary at a glance

Bronchoscopically reducing lung volume in patients with severe hyperinflation can lead to a survival benefit for a population with a severely reduced life expectancy.

CRediT authorship contribution statement

Jorine E. Hartman: and. **Dirk-Jan Slebos:** designed the analysis,

wrote the first draft of the manuscript, and made revisions after feedback from co-authors. All the authors meet the definition of an author as stated by the International Committee of Medical Journal Editors, and all have seen and approved the final manuscript.

Declaration of competing interest

DJS reports: Grants or contracts from PulmonX Corp.,CA, USA and PneumRx/BTG, CA, USA (funding for clinical trials at local institute); support for attending meetings and/or travel from PulmonX Corp.,CA, USA and PneumRx/BTG, CA, USA; participation on a data safety monitoring board or advisory board as physician advisor from PulmonX Corp.,CA, USA and PneumRx/BTG, CA, USA. KK reports: payment or honoraria for lectures from PulmonX, Boehringer Ingelheim and Chiesi. All other autors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106825.

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