






## Endobronchial valves for persistent air leak all-cause mortality and financial impact: US trend from 2012–2016

Osama Mukhtar <sup>a</sup>, Mazin Khalid <sup>b</sup>, Binav Shrestha <sup>b</sup>, Oday Alhafdh <sup>a</sup>, Ramakanth Pata<sup>b</sup>, Manal Bakhiet <sup>b</sup>, Joseph Quist<sup>a</sup>, Danilo Enriquez<sup>a</sup>, Eugene Shostak<sup>c</sup> and Frances Schmidt<sup>a</sup>

<sup>a</sup>Pulmonary Division, Interfaith Medical Center, Brooklyn, NY, USA; <sup>b</sup>Department of Medicine, Interfaith Medical Center, Brooklyn, NY, USA; <sup>c</sup>Department of Cardiothoracic Surgery, Weill-Cornell Medicine, New York, NY, USA

### ABSTRACT

**Background:** Endobronchial valves (EBV) are considered an innovation in the management of the persistent air leak (PAL). They offer a minimally invasive alternative to the traditional approach of pleurodesis and surgical intervention. We examined trends in mortality, length of stay (LOS), and resources utilization in patients who underwent EBV placement for PAL in the US.

**Methods:** We utilized discharge data from the Nationwide Inpatient Sample (NIS) for five years (2012–2016). We included adults diagnosed with a pneumothorax who underwent EBV insertion at  $\geq 3$  days from the day of chest tube placement; or following invasive thoracic procedure. We analyzed all-cause mortality, LOS, and resources utilization in the study population.

**Results:** A total of 1,885 cases met our inclusion criteria. Patients were mostly middle-aged, males, whites, and had significant comorbidities. The average LOS was  $21.8 \pm 20.5$  days, the mean time for chest tube placement was  $3.8 \pm 5.9$  days, and the mean time for EBV insertion was  $10.5 \pm 10.3$  days. Pleurodesis was performed before and after EBV placement and in 9% and 6%, respectively.

**Conclusions:** Our study showed that the all-cause mortality rate fluctuated throughout the years at around 10%. Despite EBV being a minimally invasive alternative, its use has not trended up significantly during the study period. EBVs are also being used off-label in the US for spontaneous pneumothorax. This study shall provide more data to the scarce literature about EBV for PAL.

### ARTICLE HISTORY

Received 26 June 2019  
Accepted 27 September 2019

### KEYWORDS

Endobronchial valve;  
pneumothorax; persistent air  
leak; mortality; NIS database

## 1. Introduction

Pneumothorax (PTX) is the presence of air or gas within the pleural cavity. Persistent air leak (PAL) is defined as air bubbling within an underwater seal drain 48 hours or more after chest tube insertion for PTX. PAL is a challenging problem and comes with significant morbidity, mortality, and healthcare costs, typically due to prolonged hospitalization. Multiple treatment modalities are available, including chest tube with Heimlich valve, pleurodesis, autologous blood patch, surgical repair, Watanabe spigot, vascular occlusion coils, tracheobronchial stents, and Amplatzer occlusion devices [1].

Endobronchial valves (EBV) came to attention due to its minimally invasive approach and excellent results even in critically ill patients. Developed initially for bronchoscopic lung volume reduction (BLVR) in emphysema and hyperinflation, the Spiration intrabronchial valve system (Olympus respiratory, Redmond, WA, US) was first approved in 2006 under the Humanitarian Device Exemption (HDE) program by the US Food and Drug Administration (FDA) for PAL for more than 5 to 7 days after segmentectomy or lobectomy [2]. Here we

analyze mortality and financial impact of EBV for PAL in the USA.

## 2. Patients and methods

### 2.1. Data source

Our data source was discharge data from the Agency for Healthcare Research and Quality (AHRQ), National Inpatient Sample (NIS) for five consecutive years (2012 to 2016). The NIS is an extensive, publicly available, inpatient database for hospital discharges in the USA. It contains all-payer data from approximately 20% of nonfederal US hospitals. It encompasses more than 7 million unweighted discharges for each year. Each hospitalization can be transformed into an estimated count using discharge weights provided in the database to allow for calculation of the national estimates. The data include discharge-level records on demographics, diagnoses, procedures, length of hospital stay (LOS), and resource utilization. The NIS uses the *International Classification of Diseases, Clinical Modification*, 9<sup>th</sup>

revision (ICD-9-CM) before 1 October 2015, and 10<sup>th</sup> revision (ICD-10-CM) starting 1 October 2015. At least 25 diagnoses and 15 procedures are included for each hospitalization [3].

## 2.2. Patients selection

We queried the database for all adults (aged  $\geq 18$  years) who had an EBV insertion during hospitalization using ICD-9-CM and ICD-10-CM codes. We included those with PTX who had an EBV insertion at least 48 hours from the time of chest tube placement; or following an invasive thoracic procedure, in the absence of documentation of either PTX, or chest tube placement, or both. To increase our study cohort, we also included patients with documented post-operative or iatrogenic PTX on admission, who were transferred in for possible EBV placement, regardless of the time of EBV insertion. We excluded cases that were performed for research purposes using ICD-9-CM code: V707, and ICD-10-CM code: Z006.

## 2.3. Study measures and outcomes

We described baseline characteristics of the study cohort, including demographic data (age, gender, race), primary insurance provider, and comorbidities. We also reported hospital factors, including hospital size, hospital location, and teaching status. Finally, we analyzed each case to identify the reasons and timing of an EBV insertion and other related procedures such as chest tube placement and pleurodesis.

Our primary outcome was the trend in the utilization of EBV for PAL and all-cause inpatient mortality. Our secondary outcomes included LOS and resource utilization. The hospitalization costs and charges were also reported following adjusted for inflation using the data from the US Bureau of Labor Statistics.

## 2.4. Statistical analyses

We analyzed the data using Stata 15.1 for Windows (StataCorp, College Station, Texas, US), which allows for analysis using case weight to produce nationally representative estimates throughout the US. We reported study measures as mean  $\pm$  SD for continuous variables and as count and percentage for categorical variables. We performed statistical tests of significance to evaluate for between-group differences using Student's *t*-test for continuous variables and Person's  $\chi^2$  test for categorical variables. A two-tailed *p*-value  $\leq 0.05$  was considered statistically significant.

## 3. Results

We identified 2,040 cases of EBV placement (weighted for national estimate) during the study period from

2012 to 2016. Only 1,885 cases met our inclusion criteria (Table 1).

### 3.1. Baseline characteristics

The mean age in our study population was  $61.4 \pm 13.2$  years. Almost two-thirds of the patients were males (67%) and white (68%). The patients had significant comorbidities with an average Elixhauser's score of  $3.1 \pm 2.2$  and approximately 64% with a score  $\geq 3$ . Pulmonary disease was the most common

**Table 1.** Baseline characteristics of the study cohort.

Characteristics	n (%)
Total # of EBVs	
Unweighted	408
Weighted	2040
Total # of EBVs for PAL	
Unweighted	377
Weighted	1885
Age (years)	
Mean $\pm$ SD	61.4 $\pm$ 13.2
18–44	175 (9.3)
45–64	900 (47.7)
65–84	780 (41.4)
$\geq 85$	30 (1.6)
Gender	
Male	1270 (67.4)
Female	615 (32.6)
Race	
White	1280 (67.9)
Black	23 (1.2)
Hispanic	85 (4.5)
Asian or Pacific Islander	60 (3.2)
Unknown/others	437 (23.2)
Primary insurance provider	
Medicare	920 (48.8)
Medicaid	270 (14.3)
Private	575 (30.5)
Self-payer/others	120 (6.4)
Elixhauser's comorbidities score (points)	
Mean $\pm$ SD	3.1 $\pm$ 2.2
0	340 (18.0)
1–2	345 (18.3)
$\geq 3$	1200 (63.7)
Comorbidities	
Smoking	425 (22.5)
Hypertension	695 (36.9)
Diabetes	235 (12.5)
Congestive heart failure	155 (8.2)
Pulmonary disease	1055 (56.0)
Renal failure	130 (6.9)
Cancer	475 (25.2)
Hospital bed size	
Small	120 (6.4)
Medium	345 (18.3)
Large	1420 (75.3)
Hospital location	
Urban	1845 (97.9)
Rural	40 (2.1)
Hospital teaching status	
Teaching	1665 (88.3)
Non-teaching	220 (11.7)
Pneumothorax etiology	
Spontaneous	105 (5.8)
Iatrogenic/postoperative	495 (27.4)
Empyema with fistula	360 (19.9)
Others	845 (46.8)
Time to intervention	
Chest tube, Mean $\pm$ SD (days)	3.8 $\pm$ 5.9
Endobronchial valve, Mean $\pm$ SD (days)	10.5 $\pm$ 10.3
Pleurodesis before	160 (8.5)
Pleurodesis after	110 (5.8)

EBV, endobronchial valve; PAL, persistent air leak

comorbidity, observed in 56% of patients, followed by hypertension in 37% and cancer in 25%. Almost 23% were smokers. Most patients (75%) were treated in large hospitals, located in urban areas (98%). These hospitals were teaching hospitals in 88% of cases. Medicare was the primary insurance provider in approximately half of the patients (49%), private insurance in 31%, and Medicaid in 14%.

### 3.2. Indications for EBV placement

The most common documented reason for EBV placement was post-operative PTX (27%), followed by PTX complicating empyema with fistula (20%) and spontaneous PTX (6%). The remaining cases (47%) were documented as other pneumothorax/air leak (ICD-9-CM codes: 512.83, 512.84, 512.89; and ICD-10-CM codes: J93.81, J93.82, J93.83, J93.9). The mean time for chest tube placement was 3.8 ± 5.9 days, and the mean time for EBV insertion was 10.5 ± 10.3 days. Pleurodesis was performed before and after EBV placement and in 9% and 6%, respectively.

### 3.3. Trends and outcomes

The procedure was performed in 290 patients during 2012, increased gradually during 2013 and 2014, then plateaued during 2015 and 2016 at 430 cases per year. All-cause mortality fluctuated at around 10% during the study period but showed no statistically significant difference (*p*-value = 0.713). On the other hand, the LOS remained stable at about 21.8 + 20.5 days (*p*-value = 0.992). Table 2 and Figure 1 summarize trends in EBV over the study period.

## 4. Discussion

EBV is a small medical device that can be implanted in lobar, segmental, or subsegmental bronchi using a rigid or flexible bronchoscope. It is designed to have a unidirectional valve opening to help expel the air out from the affected bronchus. It is available in different sizes (5, 6, 7, and 9 mm). Four types of EBVs are reported in the literature, namely Zephyr one-way EBV (PulmonX Corp., US) [4]; Spiration valve system (Spiration, Inc., US) [5]; MedLung EBV (MedLung, Russia) [6]; and Endobronchial Miyazawa valve (Novatech, France) [7].

In the US, EBVs have been used mainly for the management of post-operative PAL and, in recent years, for BLVR in emphysema, especially for patients who are high-risk surgical candidates. Occasionally, they have been used in the management of MDR-TB to help improve the effectiveness of second-line chemotherapy or to facilitate weaning from extracorporeal membrane oxygenation (ECMO) in patients with acute respiratory distress syndrome (ARDS) and PAL

Table 2. Comparison of trends and outcome in EBV use.

	Total	2012	2013	2014	2015	2016	p Value
EBV	1,885	290	320	415	430	430	-
Mortality, n (%)	190 (10.0)	25 (8.6)	30 (9.4)	50 (12.0)	55 (12.8)	30 (7.0)	0.713
LOS, mean +SD, days	21.8 + 20.5	24.2 + 38.1	20.8 + 11.9	19.9 + 12.9	21.6 + 15.4	23.1 + 18.8	0.992
Total charges, median (IQR), USD	23,976 (11,544–49,302)	21,626 (10,478–44,503)	22,928 (11,027–47,240)	23,829 (11,502–48,946)	25,241 (12,188–51,748)	26,605 (12,847–54,338)	0.617
Total cost, median (IQR), USD	6,792 (3,559–13,244)	6,547 (3,450–12,778)	6,679 (3,489–13,054)	6,693 (3,506–13,071)	6,930 (3,631–13,492)	7,132 (3,733–13,816)	0.721

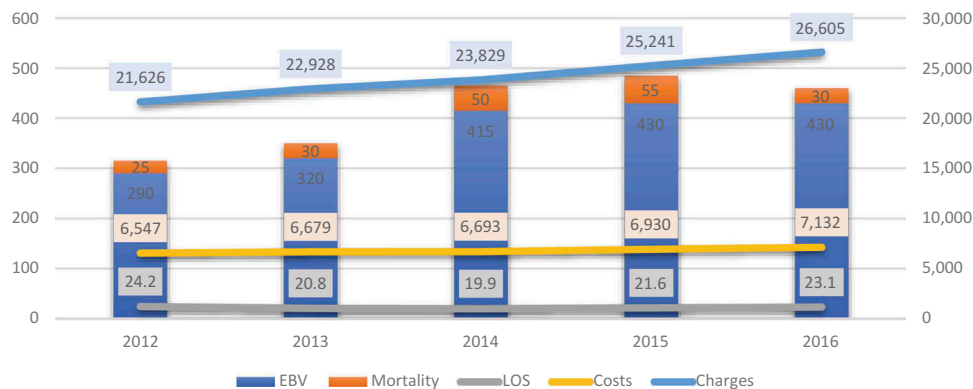


Figure 1. Trends and outcome in EBV use during study periods.

[6,8,9]. In Europe, they are also approved for the management of PAL in spontaneous PTX. In general, rigorous patient selection strategies must be strictly followed for the success of the EBV as it has severe implications in morbidity, mortality, and cost. EBV success requires evaluation for fissure completeness and collateral ventilation, quantification of air leak, and precise localization of the leak site; all have shown to have an impact on a successful outcome [10–14]. Failures are common, and the overall success rate was reported to be 22% in spontaneous PTX [15]. Detailed discussion about the patient selection, management and follow-up is a broad topic and beyond the scope of our study. Despite the current European approval, the FDA has not approved the use of EBV in spontaneous PTX in US and it remains off-label use. In our study, we identified about 6% of cases who had EBV inserted for treatment of PAL in spontaneous PTX.

PAL has higher morbidity, prolonged ICU stay, and complications, including pneumonia and pulmonary embolism [16]. The first successful use of EBV for PAL was described in 2006, and since then there have been numerous similar studies [17,18]. PAL has been defined inconsistently in the literature, but most studies label an ongoing air leak for 5 to 7 days despite constant drainage of the thoracic cavity as PAL [19–22]. This is consistent with our study where the mean time between chest tube insertion and EBV insertion was approximately 7 days. Following the EBV placement, 6% of the patient needed pleurodesis, which indicated EBV failure. On the other hand, 9% of patient who had pleurodesis needed EBV insertion. In our literature review, we could not find defined selection criteria that prioritize either procedure. A randomized head-to-head comparison might shed some light on the best algorithm for procedure selection in specific patient populations.

The cost-effectiveness of EBV is a topic of ongoing debate. A couple of studies have reported favorable long-term cost-effectiveness in the treatment of emphysema [23,24]. These findings were affirmed by LIBERATE trial – the first international multicenter,

randomized control trial of EBV in severe emphysema – which demonstrated lower healthcare costs through the use of EBV [25]. The highly selective nature for EBV makes it difficult to compare BLVR head-to-head with (lung volume reduction surgery (LVRS)). However, there is an ongoing study (CELEB trial) examining the effectiveness of these two techniques expected to be finalized by March 2020.

Podgaetz *et al.* in their retrospective analysis found the cost of EBV for PAL (defined as > 5 days) to be at a total of USD 13,900 until discharge, which is consistent with the upper limit of charges but substantially higher than the mean cost observed in our study period. Authors concluded that EBV is cost-effective if the predicted total duration of air leak is more than 8 days [22]. There has been variation in related healthcare costs reported by various authors, Dooms *et al.* estimated the direct cost of EBV deployment to be £6,970 per patient whereas Santini *et al.* reported mean cost of around £4,500 [26]. Fiorelli *et al.* adopted simplified model considering several variables: significant reduction of cost hospital stay (£10,283 ± 5,104 vs. £6,761 ± 1,823;  $p = 0.035$ ), pharmacy expenses (£126 ± 8.9 vs. £81.3 ± 19.6;  $p = 0.017$ ) when comparing before and after EBV implants with no significant difference in total costs (£10,411 ± 5,159 vs. £12,132 ± 1,857;  $p = 0.374$ ) [27]. Despite the differences among the health systems, the cost appeared to be relatively similar between the aforementioned trials and our cohort.

Mortality related to EBV is challenging to determine as most patients receiving EBV are patients with multiple comorbidities and thus unfit to undergo surgical interventions. Our study showed all-cause mortality of 7–12% during the study period without statistical significance in the variation. More studies are needed to examine the mortality rate and compare the outcomes in different cohorts.

EBV migration or expulsion, related infections, and post-deployment desaturation, in addition to its cost, are currently significant concerns related to EBV use [18,28,29]. Like any developing new field in medicine, EBV is surrounded by many unanswered

questions. For instance, after the deployment of EBV optimal timing for initiation of the pulmonary rehabilitation in patients undergoing BLVR or PAL is yet to be determined. Long-term implications, efficacy, and adverse events are yet to be unfolded. Furthermore, refractory patients, partial responders, and follow-up plans will hopefully be determined in the near future. Ongoing investigations are being conducted, e.g. SOLVE trial, addressing some of these issues [30].

## 5. Conclusion

This is the largest study of EBV for the management of PAL in the US. The mortality rate remained the same through the years, and the cost variation was not significant. Despite EBV being a less invasive alternative to surgery, its use has not trended up throughout the study period. Our study demonstrates reliable all-cause mortality and financial impact of EBV. This study shall provide more data to the scarce literature about EBV.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## ORCID

Osama Mukhtar  <http://orcid.org/0000-0002-0801-5253>  
 Mazin Khalid  <http://orcid.org/0000-0003-4868-4299>  
 Binav Shrestha  <http://orcid.org/0000-0002-6839-4726>  
 Oday Alhafdh  <http://orcid.org/0000-0003-2790-2437>  
 Manal Bakhiet  <http://orcid.org/0000-0002-7726-4587>

## References

- [1] Slade M. Management of pneumothorax and prolonged air leak. *Semin Respir Crit Care Med.* 2014 Dec;35(6):706–714. PubMed PMID: 25463161.
- [2] Giddings O, Kuhn J, Akulian J. Endobronchial valve placement for the treatment of bronchopleural fistula: a review of the current literature. *Curr Opin Pulm Med.* 2014 Jul;20(4):347–351. PubMed PMID: 24811833. .
- [3] The agency for healthcare research and quality - national inpatient sample (NIS). [cited 2019 May 10th]; Available from: <https://www.hcup-us.ahrq.gov/nisoverview.jsp>
- [4] Slebos D-J, Shah PL, Herth FJ, et al. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. *Respiration.* 2017;93(2):138–150.
- [5] Sterman D, Mehta A, Wood D, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration.* 2010;79(3):222–233.
- [6] Levin A, Sklyuev S, Felker I, et al. Endobronchial valve treatment of destructive multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2016;20(11):1539–1545.
- [7] Galluccio G, Lucantoni G, Surgery T. Bronchoscopic lung volume reduction for pulmonary emphysema: preliminary experience with a new NOVATECH® endobronchial silicone one-way valve. *Interact Cardiovasc Thorac Surg.* 2010;11(2):213–215.
- [8] Ghiani A, Hansen M, Tsitouras K, et al. Endobronchial one-way valve therapy facilitates weaning from extracorporeal membrane oxygenation in a patient with ARDS and persistent air leak. *Case Rep Crit Care.* 2018. p. 2018. doi:10.1155/2018/9736217. PMID: 30356361.
- [9] Kempainen RR, Pierson DJ, editors. Persistent air leaks in patients receiving mechanical ventilation. *Semin Respir Crit Care Med.* doi:10.1055/s-2001-18804. PMID: 16088712. .
- [10] Rathinam S, Bradley A, Cantlin T, et al. Thopaz portable suction systems in thoracic surgery: an end user assessment and feedback in a tertiary unit. *J Cardiothorac Surg.* 2011;6(1):59. doi:10.1186/1749-8090-6-59. PMID: 21510897 .
- [11] Ratliff JL, Hill JD, Tucker H, et al. Endobronchial control of bronchopleural fistulae. *Chest.* 1977;71(1):98–99.
- [12] Firlinger I, Stubenberger E, Müller MR, et al. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. *Ann Thorac Surg.* 2013;95(4):1243–1249. doi:10.1016/j.athoracsur.2012.12.036. PMID: 23434254.
- [13] Kheir F, Rivera E, Majid A, et al. An adolescent with dyspnea and cough. A case of congenital tracheal stenosis. *Am J Respir Crit Care Med.* 2017;196(7):e30–e31.
- [14] Majid A, Kheir F, Sierra-Ruiz M, et al. Assessment of fissure integrity in patients with intrabronchial valves for treatment of prolonged air leak. *Ann Thorac Surg.* 2019;107(2):407–411.
- [15] Yu W, Yu EL, Kwok H, et al. Endobronchial valve for treatment of persistent air leak complicating spontaneous pneumothorax. *Hong Kong Med J.* 2018;24(2):158–165. doi:10.12809/hkmj176823. PMID: 29622759.
- [16] Lois M, Noppen MJC. Bronchopleural fistulas: an overview of the problem with special focus on endoscopic management. *Chest.* 2005;128(6):3955–3965.
- [17] Feller-Kopman D, Bechara R, Garland R, et al. Use of a removable endobronchial valve for the treatment of bronchopleural fistula. *Chest.* 2006;130(1):273–275.
- [18] Ding M, Gao Y-D, Zeng X-T, et al. Endobronchial one-way valves for treatment of persistent air leaks: a systematic review. *Respir Res.* 2017 November 06;18(1):186. doi: 10.1186/s12931-017-0666-y. PMID: 29110704.
- [19] Varela G, Jiménez MF, Novoa N, et al. Estimating hospital costs attributable to prolonged air leak in pulmonary lobectomy. *Eur J Cardiothorac Surg.* 2005;27(2):329–333.doi:10.1016/j.ejcts.2004.11.005. PMID: 15691691.
- [20] Mathur R, Cullen J, Kinnear W, et al. Time course of resolution of persistent air leak in spontaneous pneumothorax. *Respir Med.* 1995;89(2):129–132.
- [21] Chee C, Abisheganaden J, Yeo J, et al. Persistent air-leak in spontaneous pneumothorax—clinical course and outcome. *Respir Med.* 1998;92(5):757–761.
- [22] Podgaetz E, Zamora F, Gibson H, et al. Intrabronchial valve treatment for prolonged air leak: can we justify the cost?. *Can Respir J.* 2016;2016. doi:10.1155/2016/2867547. PMID: 27445523.

- [23] Hartman JE, Klooster K, Groen H, et al. Cost effectiveness of endobronchial valve treatment in patients with severe emphysema compared to standard medical care. *Respirology*. 2018;23(9):835–841. doi:10.1111/resp.13295. PMID: 29575395.
- [24] Pietzsch JB, Garner A, Herth FJJR. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. *Respiration*. 2014;88(5):389–398.
- [25] Criner GJ, Sue R, Wright S, et al. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *Am J Respir Crit Care Med*. 2018;198(9):1151–1164.
- [26] Dooms CA, Decaluwe H, Yserbyt J, et al. Bronchial valve treatment for pulmonary air leak after anatomical lung resection for cancer. *Eur Respir J*. 2014;43(4):1142–1148.
- [27] Fann JJ, Berry GJ, Burdon T. The use of endobronchial valve device to eliminate air leak. *Respir Med*. 2006;100(8):1402–1406.
- [28] Fiorelli A, Reginelli A, Santini M, et al. Endobronchial valve migration: A “Whistle Blower”. *J Bronchol Interventional Pulmonol*. 2016;23(3):e24–e26.
- [29] Jenkins M, Vaughan P, Place D, et al. Endobronchial valve migration. *Eur J Cardiothorac Surg*. 2011;40(5):1258–1260.
- [30] Ingenito EP, Wood DE, Utz JP. Bronchoscopic lung volume reduction in severe emphysema. *Proc Am Thorac Soc*. 2008;5(4):454–460.