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Risk factors and outcomes of vocal cord paralysis after lung transplantation – a retrospective cohort study

Benjamin Seeliger[1], Nora Drick[1], Murat Avsar[2], Igor Tudorache[2], Tobias Welte[1,3], Jens Gottlieb[1,3] & Mark Greer[1,3]

1 Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany
2 Department of Cardiac, Thoracic, Transplantation, and Vascular Surgery, Hanover Medical School, Hanover, Germany
3 Biomedical Research in End-Stage and Obstructive Lung Disease (BREATH), German Centre for Lung Research (DZL), Hannover, Germany

Correspondence
Dr. Benjamin Seeliger MD, Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany.
Tel.: +49-(0)-511-532-3531; fax: +49-(0)-511-532-3353; e-mail: seeliger.benjamin@mh-hannover.de

SUMMARY

Vocal cord paralysis (VCP) may complicate thoracic surgery and is associated with increased morbidity and mortality. Among lung transplant (LTx) recipients, chronic pulmonary aspiration can contribute to chronic allograft dysfunction (CLAD). We herein assessed the unknown incidence and clinical impact of VCP in a large LTx cohort. All first-time bilateral LTx recipients, transplanted between January 2010 and June 2015 were included in a single-centre retrospective analysis. Bronchoscopy reports were assessed for VCP. Patients exhibiting VCP were compared to propensity score-matched negative controls regarding CLAD onset and graft survival and secondary end-points, including inpatient duration and complications; lower respiratory tract infections (LRTI) within 24 months. In total, 583/713 (82%) patients were included in the analysis. A total of 52 (8.9%) exhibited VCP, which was transient in 34/52 patients (65%), recovering after median 6 months (IQR 2–12). Compared to 268 controls, 3-year graft survival and CLAD-free survival were non-inferior in VCP [HR 0.74 (95% CI 0.35–1.57), and HR 0.74 (95% CI 0.39–1.41)] respectively. Duration of hospitalization was similar and no differences in LRTI rates or airway complications were observed. Lower pre-Tx BMI increased risk for VCP [HR 0.88 (95% CI 0.79–0.99)]. Overall, VCP did not adversely affect graft and CLAD-free survival and secondary outcomes including LRTIs and hospitalizations.

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Introduction

Lung transplantation (LTx) is now an established option for selected candidates with end-stage lung diseases, accounting for 4000 procedures worldwide annually [1]. Vocal cord paralysis (VCP) following recurrent laryngeal nerve injury is a known complication in cardiothoracic surgery and may also occur following LTx. VCP is associated with increased length of stay, risk of pneumonia and risk of ICU readmission [2–6]. It also causes recurrent aspiration [7]. Chronic aspiration in the context of gastroparesis and chronic gastroesophageal reflux, both common complications in LTx, has been repeatedly linked to the development of

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chronic allograft dysfunction syndrome (CLAD), the main limitation to long-term graft survival [8–11]. Undiagnosed VCP, which may be asymptomatic, may therefore impose significant risk to LTx recipients by facilitating aspiration [11,12].

Although most centres perform frequent postoperative endobronchial surveillance, no rigorous analysis of the incidence of VCP following LTx and its impact on clinical course has been published. Preliminary data have reported a prevalence of VCP in 23% of LTx recipients referred to speech therapy, but the true incidence remains to be determined [13]. Use of sedation and indeed intubation at time of bronchoscopy in some cases prevents VCP assessment. At our centre, bronchoscopy is routinely performed in the outpatient clinic without any sedation, allowing routine assessment of vocal cord function [14].

The aims of this study were to assess the prevalence of VCP following bilateral LTx and investigate its impact on clinical outcome as well as attempting to identify pretransplant risk factors for VCP.

Methods

Patient selection

Bronchoscopy reports from all patients undergoing a first bilateral LTx between January 2010 and June 2015 were retrospectively reviewed for documented VCP. The database extraction was performed in August 2017 to allow for a follow-up of ≥2 years. At our centre, bilateral LTx was performed using minimally invasive bilateral lung transplantation via two sequential anterolateral thoracotomies. All retrospective analyses were performed with approval of the local institutional review board. All patients provided written informed consent.

Exclusion criteria

Patients undergoing combined heart-lung-transplantation, single-lung transplantation or any retransplantation were excluded. Patients who never had vocal cord assessment, i.e. because of early ICU mortality, along with those not participating in regular bronchoscopy surveillance in our unit were excluded.

Vocal cord function assessment

Flexible surveillance bronchoscopy was performed at predefined intervals, beginning on the day of extubation and continuing at least weekly until discharge. Following discharge, all patients participated in structured surveillance, including repeated bronchoscopy at 1, 3 and 6 months post-LTx and half-yearly thereafter until 30 months post-LTx. Flexible bronchoscopy (Olympus, Tokyo, Japan; Type P180, Q180, T180) without sedation was performed using 3 ml nebulized 2% lidocaine solution in the nasopharynx, followed by sequential instillation of up to 10 ml 2% lidocaine via the bronchoscope working channel to vocal cords and proximal airways [14]. Vocal cord function was assessed and reported by experienced respiratory physicians prior to administering topical anaesthesia in every awake bronchoscopy. Vocal cord paralysis was defined as the inability to achieve vocal cord apposition during specified speech tones performed on command under videobronchoscopic visualization, regardless of degree of defect on at least two occasions. We opted for documentation at two occasions to minimize confounding vocal cord oedema or effects of topical anaesthesia which may be misinterpreted for paralysis. In the presence of VCP, the affected side was recorded, and subsequent bronchoscopies were evaluated for time interval to recovery if present. To evaluate for possible evidence of aspiration, peak percentage of lipid-laden macrophages by Sudan staining in bronchoalveolar fluid was analysed. Referral for fibreoptic swallow assessment (FEES) by an otorhinolaryngologist followed. FEES was performed by passing a flexible, fibreoptic endoscope transnasally into the pharynx and is always preceded by clinical assessment of swallowing [15].

VCP – symptoms and therapy

In symptomatic patients, speech and language therapy was initiated when hoarseness or dysphagia were present. When FEES was indicative of aspiration, swallow training was initiated. Quality of life was assessed at all attendances using the visual analogue scale. Patients with uncontrolled symptoms despite treatment were referred for surgical medialization or electrical stimulation at the discretion of the treating physician.

Primary outcomes – graft survival and CLAD occurrence

Graft survival was defined as the time to patient death or redo transplantation. Chronic allograft dysfunction (CLAD) was defined a persistent decrease in FEV_1 of at least 20% from baseline, persisting a minimum of 3 weeks in the absence of any other evident cause [16]. If present, time to onset as well as CLAD phenotype,

based on the proposed definitions by Verleden *et al.* [16], were documented.

Secondary outcomes

Length of initial ICU stay, along with duration of the entire postoperative hospitalization were calculated. Respiratory failure defined by need for reintubation during initial admission was noted.

After discharge, the number and duration of hospital admissions for any cause within the following year were recorded. Similarly, the number of lower respiratory tract infections (LRTI) with and without hospitalization in the first 2 years was recorded. In analogy to a previously published study, LRTI was defined as decrease in FEV_1 of $\geq$10% with suggestive symptoms (cough, malaise, new or progressive pulmonary infiltrate; new or worsening hypoxemia) [17]. Such constellations result routinely in a centre-based bronchoscopy or hospitalization, allowing identification of viral or bacterial pathogens. Clinical improvement following anti-infective therapy and exclusion of other causes such as graft rejection in the absence of an isolated pathogen was also considered as LRTI.

Number of bronchoscopies after initial discharge from hospital was noted and records were analysed for the occurrence of obstructive airway complications requiring intervention (i.e. stenting or argon-plasma-coagulation).

Quality of life was assessed at time of first presentation to the outpatient clinic by visual analogue scale ranging from 0 (worst) to 10 (best).

Risk factor assessment for developing VCP

To assess potential risk factors for VCP development, a multivariable logistic regression was used. Patients with evidence of pre-existing VCP demonstrated by assessment of pretransplant bronchoscopy records or spirometry flow-volume loops when bronchoscopy was not performed prior to transplantation were excluded from the risk factor analysis.

Statistical analysis

Continuous variables were graphically tested for normal-distribution and assessed using Mann–Whitney-*U* Test or *t*-test, as appropriate. Chi-square or Fisher's exact test was used as appropriate for categorical variables. Graft survival and CLAD-free survival was calculated using Kaplan–Meier estimator and utilized Log-Rank comparison between groups. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using the multivariable Cox regression analysis, controlling for gender, age at transplantation, BMI and underlying primary lung disease, since these are known confounders from the literature [9]. HRs for graft survival and onset of CLAD at 1, 3 and 5 years, were calculated by censoring event-free patients at the respective timepoints. Assumption of proportional hazards was confirmed using log (minus log) curves. Risk factors for VCP and categorical secondary outcomes were assessed using multivariable logistic regression with a case-number adjusted set of variables and univariable logistic regression respectively.

Potential risk factors included in the *ad hoc* analyses for VCP-risk factors were patient height, age, gender and BMI, ICU admission prior to LTx, need for intubation, tracheotomy or extracorporeal membrane oxygenation prior to LTx, duration of transplant surgery and whether LTx was performed out of hours, defined as surgery commencing between 6 pm and 5 am. Reported *P*-values are two-tailed, with $P < 0.05$ being considered statistically significant. Analysis was performed using STATA V13.1 (StataCorp LP, College Station, TX, USA) and GRAPHPAD PRISM V7.04 (GraphPad Software, San Diego, CA, USA).

Propensity score matching

To minimize confounder bias, propensity scores for VCP patients were matched to non-VCP using a 1:5 nearest neighbour model. Propensity scores were estimated using multivariable logistic regression modelling, accounting for patient sex, height, underlying lung pathology and age at LTx [9]. The balance of baseline characteristics used for the matching between VCP and comparators before and after PS matching was compared via standardized difference, expressed as a percentage of the pooled standard deviation [18,19]. As a sensitivity analysis of the matching, the primary outcomes of graft survival and CLAD were reanalysed using the entire (unmatched) cohort and controlling for the matching variables via multivariable Cox regression (Figs S1 and S2).

In the multivariable Cox regression model, propensity scores were entered as raw scores. Matching in the Cox regression model was accounted for by including a stratification-variable that divided patients with similar propensity scores into quintiles which was then used to estimate the overall HR [20].

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Results

Patient cohort

In total 713 LTx were performed. After excluding redo LTx, Heart-LTx and single-LTx (n = 80) and patients with follow-up at other centres (n = 27), bronchoscopy records of 606 patients (85%) were evaluated. Among these patients, 567/606 (94%) survived to hospital discharge. Of the 39 inpatient deaths, 23 (59%) were not evaluated for VCP because of continuous mechanical ventilation. Bronchoscopy records of the remaining 583 patients were finally assessed for VCP. In total 52 patients with VCP (8.9%) documented on ≥2 occasions were identified. Propensity score matching of the remaining 531 patients identified 268 suitable controls included in the final analysis (Fig. 1). Pretransplant diagnosis, age at transplantation and gender distribution was similar in both groups, with details and after matching provided in Table 1. Absolute standardized differences of the matching covariates before and after matching are reported in Fig. S3. Minimally invasive bilateral lung transplantation via two sequential anterolateral thoracotomies was performed in 317/320 patients (99%). Of the three patients undergoing clamshell procedures, one received a combined lung-liver transplantation and other two underwent concomitant coronary bypass grafting.

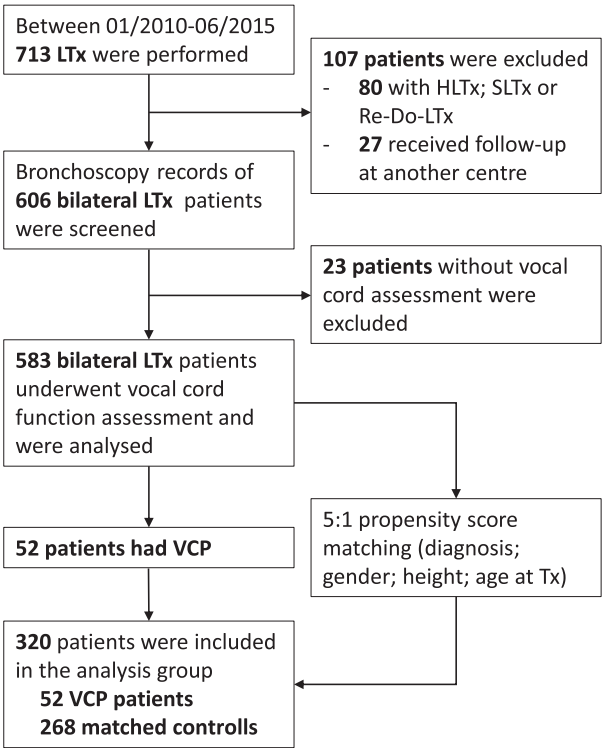


Figure 1 Study population. HLTx, heart-lung transplant; LTx, lung transplant; SLTx, single-lung transplant; VCP, vocal cord paralysis.

Incidence and characteristics of VCP

In 40/52 VCP patients (77%), unilateral involvement of the left vocal cord was noted, unilateral right-sided involvement was found in nine patients (17%), with three patients (6%) exhibiting bilateral involvement (Table 2).

Transient VCP was evident in 34/52 patients (65%), with recovery occurring after a median of 6 months (IQR 2–12). In the remaining 18 patients, persistent VCP after a median follow-up of 43 months (IQR 30.5–59.6) was noted.

Relevant symptoms were reported in 29/52 patients (56%), all of whom described hoarseness. Additional dysphagia was noted in 14/29 patients. Of these, nine patients (17% of VCP) underwent fibreoptic swallow assessments confirming aspiration. No difference in quality of life, assessed by visual analogue scale [7.3 (IQR 6.3–8.3) vs. 7.4 (IQR 6.4–8.2), P = 0.936] was evident between VCP patients and their matched controls. Twenty-six of the 29 symptomatic patients (90%) received treatment (speech therapy n = 26; swallow training n = 14; surgical medialization n = 1; electrical stimulation of recurrent laryngeal nerve n = 2). The remaining three patients not receiving treatment exhibited transient impairment with a median time to recovery of 1 month.

Graft survival

Median follow-up for the entire cohort was 41.5 months (IQR 27.7–56.5) (Fig. 2a). Among VCP patients, 10/52 grafts (19%) were lost because of nine deaths and one redo transplantation. This compared favourably to 80/268 lost grafts (30%) in the control group: 65 deaths and 15 redo transplants. Graft survival (VCP versus controls) at 1, 3 and 5 years was 96.2% vs. 93.7%, 84.3% vs. 78.6%, and 78.9% vs. 67.9% respectively. The adjusted HRs for graft loss at 3 and 5 years by Cox regression were 0.74 (95% CI 0.35–1.57, P = 0.430) and 0.61 (95% CI 0.31–1.2, P = 0.152). No significant differences at 3 years were observed even after stratifying VCP by recovery [adjusted HR for graft loss 0.36 (95% CI 0.06–2.27), P = 0.278] or presence of VCP symptoms [adjusted HR for graft loss 2.28 (95% CI 0.41–12.77), P = 0.350]. Only one VCP patient (2%) died prior to discharge, 97 days post-LTx.

Table 1. Baseline characteristics vocal cord paralysis and comparator group.

Characteristic	VCP (n = 52)	Non-VCP/comparators – unmatched (n = 531)	P	Non-VCP/comparators – matched (n = 268)	P
Patient demographics					
Male, n (%)	24 (46)	285 (53.7)	0.300	130 (49)	0.756
Age at LTx, years (IQR)	53 (43.8–58.2)	52 (39.3–58.5)	0.407	53 (43.4–59.1)	0.950
Height, cm (IQR)	170 (165–177)	171 (165–178)	0.703	170 (164–178)	0.928
BMI, kg/m^2 (IQR)	20.3 (18.1–22.7)	21.3 (19.1–23.9)	0.044	21.6 (19.3–23.8)	0.041
Diabetes mellitus, n (%)	10 (19)	96 (18)	0.855	46 (17)	0.720
Diagnosis, n (%)					
Emphysema	16 (31)	164 (31)	0.794	88 (33)	0.659
Fibrosis	13 (25)	161 (30)		83 (31)	
CF/bronchiectasis	12 (23)	123 (23)		55 (20)	
PH	4 (8)	37 (7)		21 (8)	
Other	7 (13)	46 (9)		21 (8)	

BMI, body mass index; CF, cystic fibrosis; LTx, lung transplant; PH, pulmonary hypertension.

Onset of chronic allograft dysfunction

Overall, 12 VCP patients (23%) developed CLAD compared to 88/268 controls (33%). Among the latter, CLAD occurred at a median 34 months (IQR 22–49), which was not significantly different to the median 40 months (IQR 29–60) post-LTx within the VCP group (Fig. 2b). One- and 3-year CLAD-free survival was 94% vs. 93% and 77% vs. 67.3% respectively. The respective adjusted HRs by multivariable Cox regression for developing CLAD at 1 and 3 years were 1.18 (95% CI 0.32–3.97), P = 0.851 and 0.74 (95% CI 0.39–1.41), P = 0.362. Persistent VCP-subtype did not significantly influence the likelihood of developing CLAD at 3 years [HR 0.97 (95% CI 0.29–3.21), P = 0.955] nor did presence of symptomatic VCP [adjusted HR 0.86 (95% CI 0.39–1.88), P = 0.708]. No differences in the incidence of the two CLAD phenotypes were evident. Three VCP patients (25%) fulfilled the criteria for the restrictive allograft syndrome, compared to 24/88 controls (27%; P = 0.868).

Postoperative hospitalization and outcomes

Vocal cord paralysis did not impact upon the length of ICU admission post-LTx [2 days (IQR 1–6) VCP group vs. 2 days (IQR 1–4) controls, P = 0.958] or on the total length of hospital stay [23 days (IQR 21–37.5) VCP group vs. 23 days (IQR 21–30) controls, P = 0.665]. VCP did not increase the risk of reintubation [unadjusted OR 1.1 (95% CI 0.48–2.52), P = 0.821].

Hospital readmission in the first year post-LTx

Median number of readmissions in the first year was equal in both groups: 1 (IQR 0–2). The cumulative duration of readmission was also similar at 3 days (IQR 0–13) in the VCP group vs. 2 days (IQR 0–17) among controls, P = 0.930.

Lower respiratory tract infections within the first 2 years following transplantation

The occurrence of lower respiratory tract infections [1 (IQR 0–2)]; and the number of LRTIs leading to hospital admission [0 (IQR 0–1)] were similar in both groups.

Obstructive airway complications and subsequent bronchoscopies

No difference in the incidence of obstructive airway complications requiring intervention was observed

Table 2. Characteristics of vocal cord paralysis in 52 patients following bilateral lung transplantation.

Finding, *n* (%)	All Patients with VCP (*n* = 52)
Affected side	
Left	40 (77)
Right	9 (17)
Bilateral	3 (6)
Recovery	34 (65)
Time to recovery, months (IQR)	6 (2–12)
Persistent VCP	18 (35)
Symptomatic	29 (56)
Dysphonia	29 (56)
Dysphagia	14 (23)
Evidence of aspiration of FEES	9 (17)
Treatment received	26 (50)

FEES, fibreoptic evaluation of swallowing.

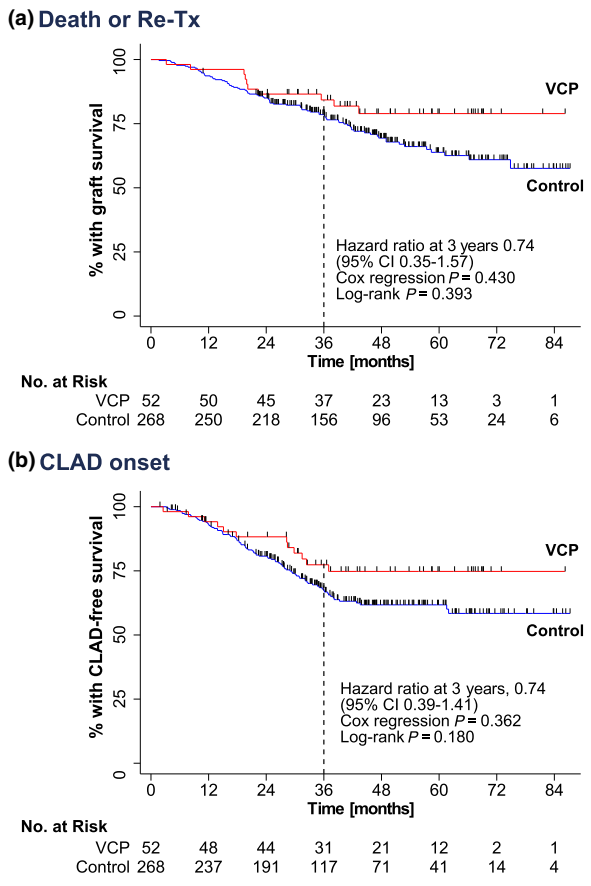


Figure 2 Kaplan–Meier curves comparing overall graft survival until death or redo transplantation (a) and survival free of chronic allograft dysfunction (b) between the vocal cord paralysis group and the control group. Adjusted hazard ratios are reported. Multivariable models for both graft survival and chronic allograft dysfunction include body mass index, sex, underlying lung pathology and age.

between groups (19% vs. 18%, $P = 0.872$). VCP additionally did not appear to increase risk for developing obstructive airway complications [unadjusted OR 1.06 (95% CI 0.50–2.27), $P = 0.872$]. The number of outpatient bronchoscopies performed postdischarge in the first 2 years was similar between groups [7 (IQR 6–9) VCP vs. 8 (IQR 6–10) controls, $P = 0.181$].

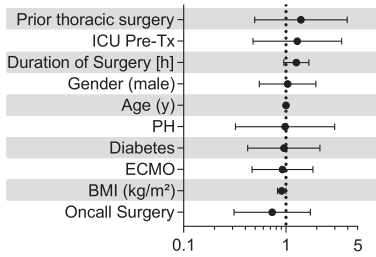
Lipid-laden macrophages, identified on Sudan staining were used as an indicato of endobronchial aspiration. The median peak percentage was similar in both groups at 1% (IQR 1–3) VCP vs. 1% (IQR 1–2) among controls, $P = 0.703$. In those patients demonstrating aspiration ($n = 9$) during fibreoptic swallow evaluation, the median peak percentage was 2 (IQR 1–5) compared to the remaining VCP patients without evidence of aspiration ($P = 0.50$).

Pulmonary function tests

The pulmonary function tests (indicated as percentage of predicted) were similar among the groups with no clinical meaningful differences. Forced expiratory volume in 1 s was 93% (IQR 82–104) in the VCP vs. 92% (75–109) in the comparator group ($P = 0.835$); forced vital capacity was 98.5% (IQR 85–116) vs. 102% (IQR 89–117; $P = 0.353$) and the mean expiratory flow at 25–75% was 90.5% (IQR 78–118) vs. 89% (IQR 63–117; $P = 0.243$).

Risk factors for developing postoperative VCP

Lower BMI was associated with increased risk for VCP with 9% per kg/m^2 [HR 0.91 (95% CI 0.82–0.99), $P = 0.049$; Fig. 3]. There was no influence by pretransplant setting (intensive care unit versus outpatient or regular ward) on development of VCP [HR 1.5 (95% CI 0.51–4.42)]. Within the entire cohort, only four patients were intubated prior to LTx, of whom 2 (50%) developed VCP. None of the perioperative parameters assessed proved significant in terms of developing VCP: LTx procedure duration [HR 1.26 (95% CI 0.98–1.07)]; or out of hours LTx [HR 0.66 (95% CI 0.27–1.61)]. Use of ECMO either pre- or peri-LTx had no apparent influence [HR 0.85 (95% CI 0.37–1.95)]. Diabetes mellitus present pre-LTx was not associated with occurrence of VCP [HR 1.15 (95% CI 0.54–2.49)]. Twenty-four patients (7.5%) received thoracic surgery prior to LTx (Thoracotomy $n = 9$; video-assisted thoracoscopic surgery $n = 12$ and sternotomy $n = 3$). Five of 52 patients who developed VCP (10%) underwent prior thoracotomy, but prior thoracic surgery was not a significant



Risk factor	No. at risk	Univariate HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Prior thoracic surgery	24	1.39 (0.5-3.9)	0.592	1.40 (0.5-4.0)	0.527
ICU Pre-Tx	28	1.46 (0.6-3.8)	0.440	1.29 (0.5-3.5)	0.618
Duration of Surgery [h]		1.26 (1.0-1.7)	0.108	-	-
Gender (male)	154	1.04 (0.5-2.0)	0.756	-	-
Age (y)		1.00 (1.0-1.0)	0.922	-	-
PH	25	0.98 (0.3-3.0)	0.972	-	-
Diabetes	56	1.15 (0.5-2.5)	0.720	0.95 (0.4-2.1)	0.907
ECMO	84	0.93 (0.5-1.8)	0.823	-	-
BMI (kg/m²)		0.91 (0.8-1.0)	0.030	0.91 (0.8-1.0)	0.049
Oncall Surgery	54	0.73 (0.3-1.7)	0.475	-	-

Figure 3 Pretransplant risk factors for occurrence of vocal cord paralysis following bilateral lung transplantation by univariate and multivariable logistic regression. No. at risk refers to the number of patients with the respective risk factor being present (out of all 320 patients). BMI, body mass index; CI, confidence interval; ECMO, extracorporeal membrane oxygenation peri- or preoperatively; HR, hazard ratio; PH, pulmonary hypertension.

risk factor on multivariate analysis [HR 1.40 (0.5–3.9), $P = 0.527$].

Discussion

To our knowledge, this is the first study directly assessing vocal cord paralysis following lung transplantation. The key findings of this study are that VCP occurs relatively frequently, affecting 8.1% of recipients. Despite obvious concerns regarding an increased endobronchial aspiration risk, we could not establish meaningful adverse effects of VCP on clinical outcome.

The only other published report addressing vocal cord dysfunction in LTx recipients focused on clinical dysphonia after transplantation, revealing an incidence of 23% in 78/337 patients. Further investigation revealed vocal cord dysfunction in 18/337 (5.3%) [13]. This initially appears lower than in our cohort, but it should be noted that not all patients in our study exhibited clinical symptoms. Indeed, given that almost half of our patients were asymptomatic, it is conceivable that the incidence reported by Meszarich *et al.* was underestimated. Screening of symptomatic patients is clinically indicated and thus across the literature, all patients with VCP identified were also symptomatic, rendering the reported incidence rates of between 0.7% and 23% incomparable to our cohort, where every patient was assessed regardless of symptoms [12,21–24].

Given the known associations between gastroesophageal reflux and development of CLAD, it was hypothesized that VCP play an independent contributory role [8,9,13,25]. Surprisingly, only 9/52 (17%) patients affected had actual evidence of aspiration on fibreoptic swallow assessment. This along with the fact that 65% of VCP patients demonstrated confirmed recovery of vocal cord function at median 6 months may explain the lack of influence of VCP on CLAD development. Similarly, the maximum percentage of Sudan-positive cells in the bronchoalveolar lavage fluid did not vary meaningfully between VCP patients with and without confirmed endobronchial aspiration, although the sensitivity of this as a reliable marker remains questionable [26]. Further stratifying survival by persistence of VCP, the persistent VCP curve approached that of controls, but there remained no statistically significant difference between the groups.

The incidence of lower respiratory tract infections within 2 years of LTx was similar in both groups. In a cohort undergoing a thoracic aortic procedure with postoperative VCP, a strikingly high incidence of pneumonia (58% vs. 17% of matched controls) was reported [3]. We could not find a similarly increased risk in our cohort, but the postoperative regimens especially regarding antiinfective prophylaxis are incomparable in LTx recipients.

Regarding specific risk factors for VCP, previous studies have identified duration of intubation, diabetes mellitus and specific thoracic procedures such as implantation of ventricular assist devices and aortic arch repair [2,21,22,27]. The contribution of the minimally invasive surgical approach used at our centre to VCP development cannot be assessed in this study and comparative data from centres using primarily the clamshell technique is currently lacking. It could be argued that our results regarding diabetes mellitus as a risk for VCP, do not dispute current data. Although not statistically significant, prevalence of diabetes was low at 18% in our cohort compared to 38% reported by Taenaka *et al.* [2].

The finding that lower BMI may increase the risk for VCP is novel, have not been previously reported. It is worth reemphasizing that BMI across the entire cohort was lower than average (21.4 kg/m^2). It is also worth reemphasizing that CF and non-CF bronchiectasis patients were over-represented in the cohort. This is important not only because they accounted for the lowest

BMIs in the cohort but also they were smaller in stature and the most likely patients to require piecemeal resection of the native lung because of adhesions or previous thoracic surgery. Perhaps more surprisingly, were the low BMIs among fibrosis patients affected, suggesting increased frailty and again the possibility of chest wall adherence of the native lung. The true clinical significance of this findings remains to be further evaluated.

In other cardiothoracic procedures, VCP has been associated with early intensive care postoperative morbidity and mortality [2–6]. Of the 35 ICU deaths during the observation period, two-thirds (n = 23) died intubated on mechanical ventilation, where VCP was inconsequential regarding outcome. Of the 12 remaining off-ventilator deaths during the index admission, all underwent VCP assessment with just one patient having VCP.

The results of this investigation may be limited by the biases of hidden covariates and inexact matching, especially since the relatively small number of VCP patients limits exploration of more variables in statistical models [19] Although matching reduced the absolute standardized differences over the matching covariates, difference was still above 10% in one of the four matching covariates (Fig. S3). However, the main results were unaltered when comparing VCP patients to the unmatched cohort of 531 patients (Fig. S1).

In conclusion, our analysis revealed that vocal cord paralysis occurred in approximately 1:12 bilateral LTx recipients, approximately half of whom were asymptomatic. In almost two-thirds of patients affected, recovery within the first year is possible. Despite its frequency, VCP resulted in demonstrable endobronchial aspiration in only a small fraction of patients. No adverse effects on CLAD-free or graft survival were observed, although the impact of VCP recognition and treatment cannot be ascertained. Formal screening and evaluation of VCP should be encouraged, particularly in the presence of clinical symptoms such as dysphonia and dysphagia to facilitate initiation of appropriate treatment. Additional data on the benefit of therapy in asymptomatic patients remain to be gathered.

Authorship

BS: participated in research design, writing of the paper, performance of the research and data analysis. ND: participated in writing of the paper, performance of the research and data analysis. MA: participated in editing of the paper and data analysis. IT: participated in editing of the paper and data analysis. TW: participated in editing of the paper and data analysis. JG: participated in research design, writing of the paper. MG: participated in research design, writing of the paper, performance of the research and data analysis.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier curves comparing overall graft survival until death or Re-do transplantation (a) and survival free of chronic allograft dysfunction (b) between the VCP group and the *unmatched* control group. Adjusted hazard ratios (HR) are reported. Multivariable models for both graft survival and chronic allograft dysfunction include body mass index, sex, underlying lung pathology and age.

Figure S2. Forest plot for the subgroup analyses for all covariates used in the multivariable Cox regression models for graft-loss at 3 years (a) and onset of chronic allograft dysfunction (b).

Figure S3. Absolute standardized differences before (blue dots) and after (red triangles) propensity score matching between patients with vocal cord paralysis or controls.

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