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High Incidence of Diaphragmatic Dysfunction after Lung Transplantation: Results of a Prospective Observational Study

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Abstract:	- Background: Diaphragmatic dysfunction is common after cardiothoracic surgery, but few studies report its incidence and consequences after lung transplantation. We aimed to estimate the incidence of diaphragmatic dysfunction using ultrasound in lung transplant patients up to three months postoperatively and evaluated the impact on clinical outcomes. - Methods: This was a single-centre prospective observational cohort study of 27 lung transplant recipients using diaphragmatic ultrasound preoperatively, at one day, one week, one month, and three months postoperatively. Diaphragmatic dysfunction was defined as excursion <10mm in men and <9mm in women during quiet breathing. Clinical outcomes measured included duration of mechanical ventilation, length of stay (LOS) in Intensive Care (ICU), and hospital LOS. - Results: 62% of recipients experienced new, postoperative diaphragmatic dysfunction, but the prevalence fell to 22% at three months. No differences in clinical outcomes were found between those with diaphragmatic dysfunction compared to those without. Patients who experienced diaphragmatic dysfunction at one day postoperatively were younger and had a lower BMI than those who did not. - Conclusions: Diaphragmatic dysfunction is common after lung transplant, improves significantly within three months, and did not impact negatively on duration of mechanical ventilation, LOS in ICU or hospital, or discharge destination.

Table 1. Patient characteristics

Variables	Total
Number of patients	27
Age, years	58 (43-61)
Male	13 (48%)
BMI, kg/m^2	23.1 (18.5-27.7)
Primary Diagnosis	
- Cystic fibrosis	4 (15%)
- Chronic obstructive pulmonary disease	6 (22%)
- Pulmonary fibrosis	8 (30%)
- Other	9 (33%)
Transplant Type	
- Right Single Lung	1 (4%)
- Left Single Lung	1 (4%)
- Bilateral Lung	22 (81%)
- Combined Organ	3 (11%)
Incision Type	
- Clamshell	8 (30%)
- Bilat anterior thoracotomies	15 (56%)
- Sternotomy	2 (7%)
- Unilateral thoracotomy	2 (7%)
CPB time, mins	205 (187-233)
ECMO time, days	0
Duration of Mechanical Ventilation, hours	22.3 (12.7-38.9)
ICU length of stay, hours	141.7 (53-162)
Hospital length of stay, days	25.4 (13-35)
Discharge Destination	
- Home	19 (70%)
- Inpatient Rehabilitation Facility	6 (22%)
- Deceased	2 (7%)

Legend:

Continuous variables reported as median (interquartile range); percentage data shown as n (%).

Abbreviations: BMI; body mass index; CPB, cardio-pulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

HIGH INCIDENCE OF DIAPHRAGMATIC DYSFUNCTION AFTER LUNG TRANSPLANTATION:

RESULTS OF A PROSPECTIVE OBSERVATIONAL STUDY

Running Head: Diaphragmatic Dysfunction after Lung Transplantation

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ABSTRACT

- **Background:** Diaphragmatic dysfunction is common after cardiothoracic surgery, but few studies report its incidence and consequences after lung transplantation. We aimed to estimate the incidence of diaphragmatic dysfunction using ultrasound in lung transplant patients up to three months postoperatively and evaluated the impact on clinical outcomes.
- **Methods:** This was a single-centre prospective observational cohort study of 27 lung transplant recipients using diaphragmatic ultrasound preoperatively, at one day, one week, one month, and three months postoperatively. Diaphragmatic dysfunction was defined as excursion <10mm in men and <9mm in women during quiet breathing. Clinical outcomes measured included duration of mechanical ventilation, length of stay (LOS) in Intensive Care (ICU), and hospital LOS.
- **Results:** 62% of recipients experienced new, postoperative diaphragmatic dysfunction, but the prevalence fell to 22% at three months. No differences in clinical outcomes were found between those with diaphragmatic dysfunction compared to those without. Patients who experienced diaphragmatic dysfunction at one day postoperatively were younger and had a lower BMI than those who did not.
- **Conclusions:** Diaphragmatic dysfunction is common after lung transplant, improves significantly within three months, and did not impact negatively on duration of mechanical ventilation, LOS in ICU or hospital, or discharge destination.

Key words: diaphragmatic dysfunction, ultrasound, lung transplantation, intensive care

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INTRODUCTION

Diaphragmatic dysfunction is a well-known complication after cardiac [1-5] and thoracic surgery [1, 6, 7], but very few studies have documented its incidence and consequences after lung transplantation. Previous research has demonstrated that patients with diaphragmatic dysfunction frequently require increased duration of mechanical ventilation [1, 2, 5, 8, 9], longer length of stay in Intensive Care [1, 3, 5, 10] and in hospital [3]. The incidence of diaphragmatic dysfunction could be as high as 41% after bilateral lung transplantation [6]; however, it is likely that the incidence in the acute postoperative period has been underestimated. This is because previous research has been conducted retrospectively [1, 3], used diagnostic methods which cannot be readily applied in the acute postoperative phase (such as nerve conduction studies or fluoroscopy) [6], or investigated at discharge from hospital [11]. Dorffner and colleagues [8] were the first group to prospectively evaluate diaphragmatic function in heart and lung transplant recipients within three hours after extubation using bedside ultrasound; however, the ultrasound assessment method they used (diaphragm mobility during forced nasal inspiration) has not been standardised as an index of diaphragmatic dysfunction.

Ultrasound is emerging as the modality of choice to examine diaphragm function because it is non-invasive, devoid of radiation, readily available at the bedside, and relatively fast and easy to use [12, 13]. Measuring diaphragm excursion by M-mode ultrasonography has high intra- and inter-observer reproducibility [2, 14, 15] and has been shown to be as accurate as fluoroscopy for detecting diaphragmatic dysfunction in patients after cardiac surgery [16]. In addition, there is a significant reduction in the mean time between clinical suspicion and diagnostic testing [16]. Point-of-care ultrasound, therefore, has the potential to be a clinically valuable tool for investigating the incidence, time course, and impact of diaphragmatic dysfunction after lung transplantation.

The primary aim of this study, therefore, was to estimate the incidence of diaphragmatic dysfunction by comparing pre- and postoperative diaphragmatic function in lung transplant patients using point-of-care ultrasound. In addition, this study aimed to examine the time course of diaphragmatic

dysfunction persistence up to three months postoperatively, to demonstrate the inter-rater reliability of taking ultrasound measurements in retrospect, to determine the influence of baseline characteristics and perioperative variables on the development of diaphragmatic dysfunction, and to evaluate the impact of diaphragmatic dysfunction on clinical outcomes.

MATERIALS AND METHODS

This study was a prospective, observational cohort study conducted at a single-centre, heart and lung transplantation unit at a tertiary hospital in Sydney, Australia. Approval to conduct this study was granted by the St Vincent's Hospital Health Research Ethics Committee (HREC/14/SVH/203) and the study was registered with the Australian New Zealand Clinical Trials Registry ACTRN12615001371583. The principles of the Declaration of Helsinki formulated by the World Medical Association, the Declaration of Istanbul, and the ISHLT Statement of Transplant Ethics have been adhered to. Written informed consent was obtained from eligible participants on the lung transplant waiting list.

Patients

Potential lung transplant recipients were identified from the active lung transplant waiting list between February 2016 and December 2017 and approached for enrolment when they attended their routine heart-lung clinic outpatient appointments. Patients were enrolled into the study if they were >18 years of age, on the active waiting list for lung transplant, and able to provide written informed consent. Patients were excluded if they were currently on a mandatory mode of mechanical ventilation, had known diaphragmatic dysfunction from another aetiology, were unable to maintain the position required for optimum imaging, body habitus prevented optimum imaging, or had a prior history of lung transplantation.

Study Protocol

Ultrasonographic assessment of both hemidiaphragms was conducted preoperatively, then one day after transplant in the Intensive Care Unit (ICU), one week after transplant in hospital, one month, and three months after transplant, either in the hospital or in the outpatient Heart-Lung Clinic (Figure 1). For each postoperative assessment the following preconditions needed to be met: Glasgow Coma Scale [17] score ≥ 14, extubated or on a spontaneous ventilator mode with fraction of inspired oxygen < 50% and positive end-expiratory pressure ≤ 5 cm H_2O and tolerates disconnection from ventilator for ultrasound imaging, haemodynamic stability without significant vasopressor use, no suspected or ongoing sepsis or decompensated cardiac failure.

Our primary outcome measure was the presence of ultrasonographic diaphragmatic dysfunction defined as diaphragmatic excursion < 9mm for women or < 10mm for men during quiet breathing. Demographic and other data were collected preoperatively from the medical record including patient age, sex, body mass index (BMI), and primary diagnosis for lung transplant. Intraoperative variables considered as possible predictors for diaphragmatic dysfunction included the type of transplant received, type of incision used and time on cardiopulmonary bypass. Postoperative clinical outcome measures assessed were the duration of mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), length of stay in intensive care, length of stay in hospital, and discharge destination (Table 1) which was obtained retrospectively from the patient's medical record and/or from the hospital's transplant record database.

Ultrasonography

Ultrasonographic assessments were performed by one investigator (E.C.), a physiotherapist trained in lung and diaphragmatic ultrasound assessments with completion of a course accredited by the Australasian Society for Ultrasound in Medicine, followed by mentored bedside training with senior author G.N. We chose to measure diaphragm excursion during quiet breathing because this has previously been validated as an index of diaphragmatic dysfunction in critically ill [15] and surgical

patients [2, 7, 18]. Measures of diaphragmatic excursion were obtained using the methods previously described by Boussuges et al. [14] as these methods have reported high intra- and inter-rater reliability. Ultrasonographic examinations were conducted using either the FujiFilm SonoSite M-Turbo (Fujifilm, Bothell, WA, USA) or GE Healthcare Venue 50 (GE Healthcare Australia, NSW, Australia) point-of-care ultrasound machines. All still images were recorded on a computer for subsequent analysis using Image J software (Rasband, W.S., Image J, U.S. National Institutes of Health, Bethesda, Marylands, USA. https://imagej.nih.gov/ij/, 1997-2018). To evaluate accuracy, all images were independently analysed by E.C. and N.M. to test inter-rater reliability.

Examinations were performed with the patient in the semi-recumbent position, with head up 30-45 degrees. An anterior, subcostal, horizontal probe position was chosen, placing a low frequency curvilinear probe between the anterior and mid-axillary lines (Venue 50 4C 2.5-6MHz or SonoSite C60xi 5-2MHz transducer). B-Mode was used to select the exploration line of each hemidiaphragm using the liver as an acoustic window on the right and the spleen on the left [13, 14]. The transducer was angled medially, cranially, and dorsally to visualise the posterior third of the hemidiaphragm [14, 19]. The diaphragm inspiratory amplitudes (excursions) were measured from M-mode sonography, placing the ultrasound beam as perpendicular as possible to each hemidiaphragm [12]. The amplitude of excursion was measured on the vertical axis of the tracing from the end of expiration to the end of inspiration as marked on the ultrasound image (Figure 2). Measures were averaged from up to three breath cycles and then repeated by a blind assessor (N.M.) for reliability analyses.

Statistical Analysis

A sample size of 25 was selected based on an expected prevalence of 40% to enable the evaluation of at least 10 patients with diaphragmatic dysfunction. Statistical analysis was conducted using SPSS Statistics for Windows, Version 25.0 (IBM, USA) and SAS (SAS/STAT 15.1, SAS Institute, Cary, NC, USA). Continuous data were presented as median (interquartile range). Categorical data were presented as frequency (percent). For univariate analyses, the chi-squared test was used to test for differences between categorical variables, and the Mann-Whitney U test was used to compare

continuous variables between groups (*i.e.*, those patients with diaphragmatic dysfunction vs those without diaphragmatic dysfunction). A two-tailed p-value < 0.05 was considered statistically significant.

To estimate the change in diaphragm excursion over time (treated categorically as pre-operative; one day, one week, one month, and 3 months post-operatively), we used a linear mixed model (with unstructured covariance structure to account for repeated measures). Inter-observer repeatability was tested using intraclass correlation coefficient (Shrout and Feliss 1979, ICC(3, k)). Some patients had missing study data, for analyses of change in excursion over time we have assumed missing-at-random (from maximum likelihood in the mixed model), and for univariate analyses listwise-deletion was used.

RESULTS

Participants

During the study period, 127 patients were screened for eligibility from the lung transplant waiting list. Of these, 52 patients met all inclusion criteria and were available at the preoperative assessment clinic during the enrolment period. 27 of these enrolled patients received a lung transplant during the study period and were included in the study (Figure 3). The first postoperative assessment was conducted between one and three days after surgery, as soon as the desired postoperative preconditions were met as outlined in the study protocol section. All study patients were extubated by the third day after surgery, however, five patients had a total ventilation time greater than 72 hours as they were subsequently reintubated.

Incidence and Time Course of Diaphragmatic Dysfunction

The prevalence of diaphragmatic dysfunction at each time point is presented in Table 2. Preoperatively, three of the 27 study patients had diaphragmatic dysfunction. These three patients were excluded from the postoperative incidence calculation at day one after transplant but were included in all other analyses. The incidence of new postoperative diaphragmatic dysfunction

observed at one day after transplant, was 62% (12 patients, excluding the 3 patients with preoperative dysfunction). The prevalence of diaphragmatic dysfunction changed over time, and by three months, only 22% (5 patients) had persistent diaphragmatic dysfunction. The other patients identified as having diaphragmatic dysfunction showed recovery of diaphragmatic function back to normal values, including two of the three patients with preoperative diaphragmatic dysfunction.

Diaphragm excursion measures at each time point for left and right hemidiaphragms are shown in Figure 4. Mixed model analysis showed left and right hemidiaphragm excursion was significantly reduced at one day after transplant (left mean difference 0.5cm, 95% CI 0.21 – 0.8cm, $p = 0.002$; right mean difference 0.86cm, 95% CI 0.5 – 1.23cm, $p < 0.0001$) and one month after transplant (left mean difference 0.44cm, 95% CI 0.15 – 0.74, $p = 0.005$; and right mean difference 0.78cm, 95% CI 0.41 – 1.16, $p = 0.0002$) compared to preoperative excursion. By three months, the amount of excursion for both hemidiaphragms was significantly better than excursion measured at one day after transplant (left mean difference 0.34cm, 95% CI 0.04 – 0.063, $p = 0.028$; and right mean difference 0.43cm, 95% CI 0.12 – 0.73, $p = 0.008$). For the right hemidiaphragm, excursion at three months was still significantly lower than preoperative excursion (mean difference 0.44cm, 95% CI 0.05 – 0.83, $p = 0.027$), however, left hemidiaphragm excursion was not significantly different to the preoperative measurement (mean difference 0.17cm, 95% CI 0.12 – 0.45, $p = 0.24$) suggesting almost complete recovery. See Supplementary Tables S1 and S2.

Ultrasound Measures Reproducibility

All the ultrasound measures taken using Image J software were independently assessed by two investigators (E.C. and N.M.) to determine accuracy. The intraclass correlation coefficient between the two assessors was calculated for every patient at each time point (preoperative; one day, one week, one month, and three months postoperatively). There was excellent concordance between the two assessors ranging from 0.931-0.978, demonstrating a high agreement rate between both observers (see Supplementary Table S3).

Influence of Diaphragmatic Dysfunction on Postoperative Clinical Outcomes

Patients with and without diaphragmatic dysfunction at one day post-transplant were compared with regard to the duration of mechanical ventilation, need for and duration of ECMO, their length of stay in intensive care, their length of stay in hospital and their discharge destination. There was no significant difference in clinical outcomes for those with or without diaphragmatic dysfunction at one day post-transplant (Table 3). Five patients with persistent diaphragmatic dysfunction at three months post-transplant were compared to those without diaphragmatic dysfunction for the same clinical outcomes (Table 4) but there was no significant difference in clinical outcomes.

Relationship between Perioperative Variables and development of Diaphragmatic Dysfunction

As seen in Table 3, patients who experienced diaphragmatic dysfunction at one day after surgery were younger in age (median [IQR]; 55 [30;58] vs. 61 [58;62], p=0.043) and had a lower BMI (19.03 [17.85;22.72] vs. 24.46 [23.08;31.45], p=0.026) than those who did not. This difference was not seen at three months post-transplant, and no other perioperative variables were statistically different between those patients with or without diaphragmatic dysfunction at one day or three months post-transplant.

DISCUSSION

This is the first prospective study to report that the incidence of postoperative diaphragmatic dysfunction one day after lung transplant is 62%. By three months after transplant, the prevalence of diaphragmatic dysfunction was only 22%, suggesting that most patients recovered. The high incidence we observed at one day post-transplant is supported by the findings from Spadaro et al. [7] in their study of diaphragmatic function after video-assisted thorascopic and thoracotomy surgery for resection of pulmonary neoplasm, where 62% of patients experienced diaphragmatic dysfunction on the operated side one day postoperatively. This high incidence of diaphragmatic dysfunction in the

early postoperative period has not been reported previously because until now the utility of M-mode ultrasound during quiet breathing has not applied in this cohort.

It has been assumed previously that surgical injury of the diaphragm or the phrenic nerve are the main causes of postoperative diaphragmatic dysfunction; however, diaphragmatic fatigue due to altered postoperative respiratory mechanics may also play an important role in its pathogenesis [7]. If the prevalence of diaphragmatic dysfunction were related to surgical trauma or complexity, patients with longer cardiopulmonary bypass time might have a higher incidence of postoperative diaphragmatic dysfunction; however, this was not the case. Likewise, there was no difference in the development of postoperative diaphragmatic dysfunction according to primary diagnosis for transplant. This is contrary to the expectation that patients with fibrotic lung disease might have more pleural adhesions leading to prolonged and difficult explantation of the native lungs, therefore increasing risk of surgical damage to the diaphragm or phrenic nerve.

There was a significant recovery of diaphragm function between one month and three months postoperatively which is in accord with prior findings. LoMauro et al. [11] in a prospective study of 30 bilateral lung transplant patients, reported that diaphragmatic dysfunction was present at discharge from hospital and persisted for 3-6 months after surgery but returned to normal function by 12 months.

In contrast to the findings of other studies [1, 8], the presence of diaphragmatic dysfunction in this study did not have a negative impact on the duration of mechanical ventilation, length of stay in ICU, or length of stay in hospital. However, our findings are supported by LoMauro et al. [11] who described the signs of diaphragmatic dysfunction as “sub-clinical”. That is, almost all their patients had signs of

diaphragmatic dysfunction at hospital discharge despite having an uneventful clinical course and good results on spirometry and the 6-Minute Walk Test.

The main strength of our study is that all of the patients were studied prospectively to find the true postoperative incidence of diaphragmatic dysfunction at one day post-transplant, with follow up over three months to observe the natural history and prevalence of diaphragmatic dysfunction. Another strength of the study is that we examined both hemidiaphragms whereas, most other studies have only examined the right hemidiaphragm. High agreement was demonstrated between both observers in their measurements of diaphragmatic excursion during quiet breathing. This suggests that measures of diaphragmatic excursion during quiet breathing can be viewed in retrospect to save time at the bedside, with a high inter-rater reliability.

There were, however, several limitations to the study. First, data acquisition was not always possible due factors outlined in Figure 3 including scheduling conflicts and inability to obtain a satisfactory image of the hemidiaphragm. For the right hemidiaphragm, 11% (15/135 assessments) of data were missed compared with 26% (35/135 assessments) for the left hemidiaphragm. If neither diaphragm was able to be imaged for an assessment, this was reported in Figure 3. In many ultrasonographic assessments it was difficult to obtain a satisfactory acoustic window which resulted in poor quality images. For the right hemidiaphragm we were unable to obtain a satisfactory image on three occasions, one explained by the presence of subcutaneous emphysema. For the left hemidiaphragm we were unable to obtain a satisfactory image on 23 occasions (oedema in one case, subcutaneous emphysema in two and unknown reasons in 20). Difficulty visualising the left hemidiaphragm has also been reported by other authors [13] for which reason other investigators have only examined the right hemidiaphragm [11].

Second, this study evaluated the impact of diaphragmatic dysfunction upon several common clinical outcomes (e.g., hospital length of stay); however, we did not assess the impact of diaphragmatic dysfunction on postoperative pulmonary function (e.g., spirometry), the development of postoperative pulmonary complications, or need for non-invasive ventilation, physical function, or quality of life measures. In our study cohort, there was no relationship between the presence of diaphragmatic dysfunction and the clinical outcomes we examined. It is possible however, that diaphragmatic dysfunction had an influence on other clinical outcomes we did not study.

Third, the presence and severity of postoperative pain, and the use of postoperative opioid analgesics, are potential, albeit unmeasured confounders of postoperative diaphragmatic function in this cohort. These, or other unmeasured variables may explain why several patients had worse diaphragmatic function at Month 1 compared to Week 1.

In summary our study shows that the incidence of diaphragmatic dysfunction after lung transplantation is high in the acute postoperative period but improves markedly by three months postoperatively. Further still, when comparing patients with diaphragmatic dysfunction to those without diaphragmatic dysfunction, we did not detect a significant difference in the postoperative clinical outcomes examined, or any of the predictive perioperative variables. The incidence of persistent diaphragmatic dysfunction was approximately 22% but we do not know its impact on long-term functional outcome, research into which may provide valuable insights of clinical importance.

AUTHOR CONTRIBUTIONS

EC was involved in the trial design, data collection, trial management and manuscript writing. GN was involved in the trial design, data collection and data monitoring. NM was involved in data collection. SS was involved in the trial conception and design. AG was involved in trial design, acquisition of funding and manuscript writing. SE and KR performed the data analyses. DK was

involved in data analyses and manuscript writing. All authors were involved in revising the manuscript. All authors read and approved the final manuscript.

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FINANCIAL DISCLOSURE STATEMENT

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or any other conflicts of interest to disclose.

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Table 2. Prevalence of diaphragmatic dysfunction during quiet breathing

	Pre-op	Day 1	Week 1	Month 1	Month 3
Isolated Right	4% (1/27)	24% (5/21)*	15% (3/20)	17% (4/24)	14% (3/22)
Isolated Left	4% (1/24)	35% (6/17)*	6% (1/17)	25% (5/20)	6% (1/17)
Bilateral	4%(1/24)	12% (2/17)*	24% (4/17)	19% (4/21)	6% (1/18)
Total	**11% (3/27)**	**62% (13/21)***	**38% (8/21)**	**52% (13/25)**	**22% (5/23)**

Legend:

*Data removed for patients with preoperative diaphragmatic dysfunction.

Data for Week 1, Month 1 and Month 3 includes the patients who had preoperative diaphragmatic dysfunction.

Table 3. Characteristics of patients with and without diaphragmatic dysfunction at one day post lung transplantation

Variables	DD at Day 1	No-DD at Day 1	*p*-value
No. of patients	15	7	
Age, years	55 (30-58)	61 (58-62)	0.043*
BMI, kg/m^2	19.03 (17.85-22.72)	24.46 (23.08-31.45)	0.026*
Male	7 (47%)	4 (57%)	1.000^
Primary Diagnosis			0.623^
- Cystic fibrosis	3 (20%)	1 (11%)	
- COPD	4 (27%)	2 (22%)	
- Pulmonary fibrosis	1 (7%)	0	
- Other	6 (40%)	4	
Transplant Type			1.000^
- Single Lung	0	0	
- Bilateral Lung	13 (87%)	7 (100%)	
- Combined Organ	2 (13%)	0	
Incision Type			0.448^
- Clamshell	3 (20%)	4 (57%)	
- Bilat anterior thoracotomies	11 (73%)	3 (43%)	
- Sternotomy	1 (7%)	0	
- Unilateral thoracotomy	0	0	
CPB time, mins	210 (189-246)	201 (194-233)	0.641*
ECMO time, days	0 (0-0)	0 (0-0)	1.000*
Duration of Mechanical Ventilation, hours	22.5 (12.6-38.9)	21.1 (12.7-33)	0.891*
ICU length of stay, hours	94.9 (52.9-141.2)	72.2 (45.5 – 162)	0.837*
Hospital length of stay, days	16 (13-32)	26 (15-36)	0.522*
Discharge Destination			0.071^
- Home	12 (80%)	3 (43%)	
- Inpatient Rehabilitation	3 (20%)	2 (29%)	
- Deceased	0	2 (29%)	

Legend:

Continuous variables reported as median (interquartile range); percentage data shown as n (%).

*Compared using Mann-Whitney U test. ^Compared using Chi-squared test.

Abbreviations: DD, diaphragmatic dysfunction; BMI; body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardio-pulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Table 4. Characteristics of patients with and without diaphragmatic dysfunction at 3 months post lung transplantation

Variables	DD at Month 3	No-DD at Month 3	*p*-value
No. of patients	5	15	
Age, years	56 (38-61.5)	57 (30-63)	0.917*
Male	3 (60%)	8 (40%)	1.00^
Body Mass Index, kg/m^2	19.23 (17.7-28.4)	22.72 (18.12-26.69)	0.440*
Primary Diagnosis			0.902^
- Cystic Fibrosis	1 (20%)	3 (20%)	
- COPD	2 (40%)	2 (13%)	
- Pulmonary Fibrosis	1 (20%)	5 (33%)	
- Other	1 (20%)	5 (33%)	
Transplant Type			1.000^
- Single Lung	0	2 (13%)	
- Bilateral Lung	5 (100%)	11(73%)	
- Combined Organ	0	2 (13%)	
Incision Type			1.000^
- Clamshell	2 (40%)	4 (27%)	
- Bilat anterior thoracotomies	3 (60%)	8 (53%)	
- Sternotomy	0	1 (7%)	
- Unilateral thoracotomy	0	2 (13%)	
CPB time, mins	194 (174-214)	227 (189-246)	0.136*
ECMO time, days	0 (0-0)	0 (0-0)	1.000*
Duration of Mechanical Ventilation, hours	19.37 (6.4-30.7)	21.08 (12.62-33.5)	0.486*
ICU length of stay, hours	60.82 (51.54-106.71)	94.68 (39.88-137)	0.800*
Hospital length of stay, days	32 (14-48.5)	16 (13-32)	0.317*
Discharge Destination			0.677^
- Home	3 (60%)	1 (7%)	
- Inpatient Rehab Facility	2 (40%)	11 (73%)	
- Deceased	0	3 (20%)	

Legend:

Continuous variables reported as median (interquartile range); percentage data shown as n (%).

*Compared using Mann-Whitney U test. ^Compared using Chi-squared test.

Abbreviations: DD, diaphragmatic dysfunction; BMI; body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardio-pulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Figure 1. Study protocol timeline

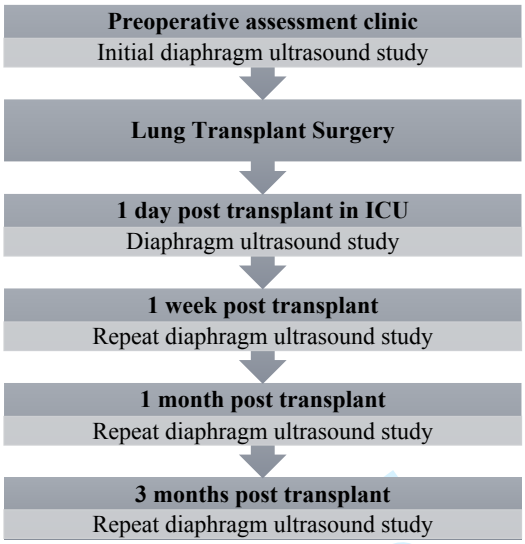


Figure 2. Ultrasound image (A) image in two-dimensional B-Mode, the curved white line depicts the right hemidiaphragm (B) image in motion M-Mode where the height of the curve from the end of expiration to the end of inspiration represents the amount of diaphragmatic excursion.

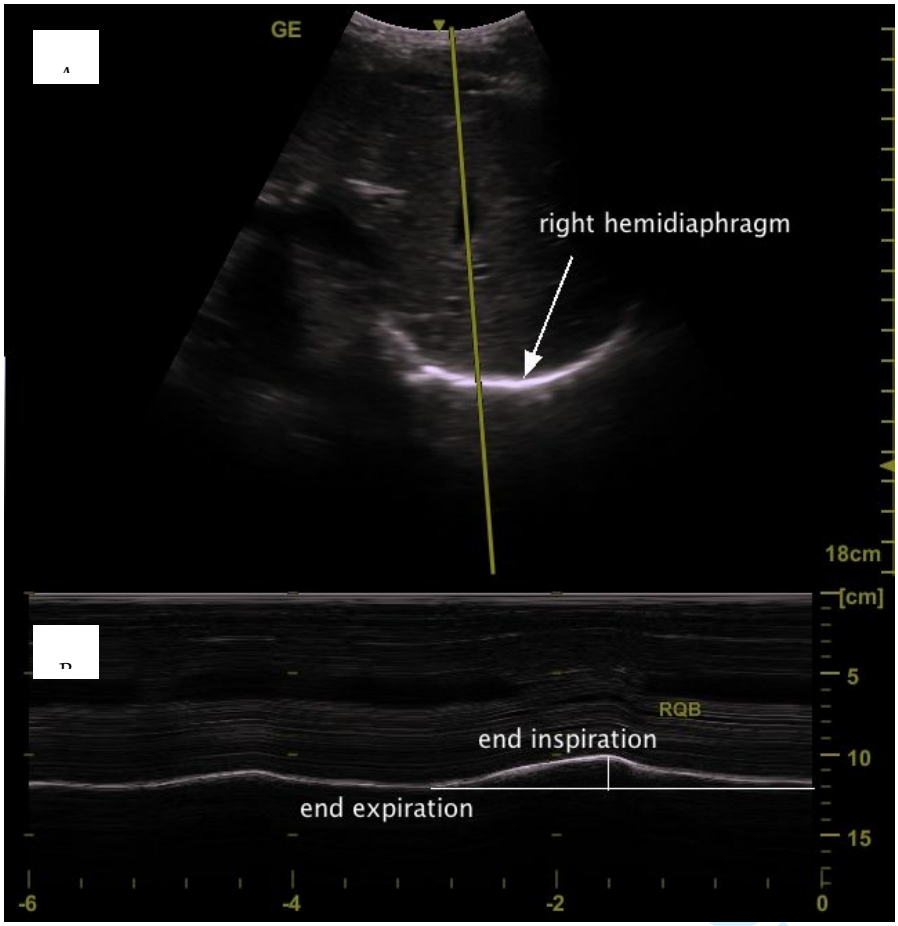


Figure 3. Patient flow diagram

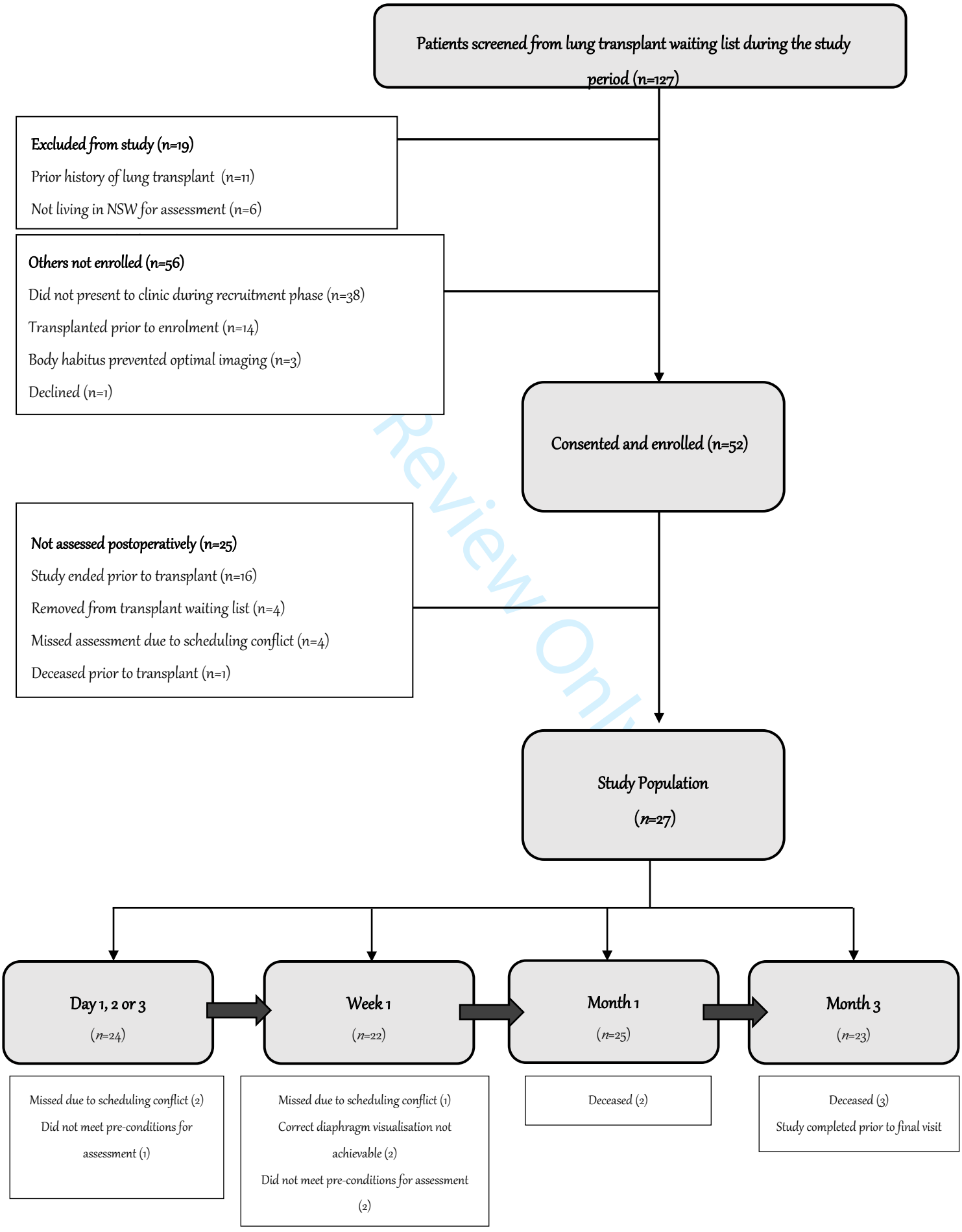
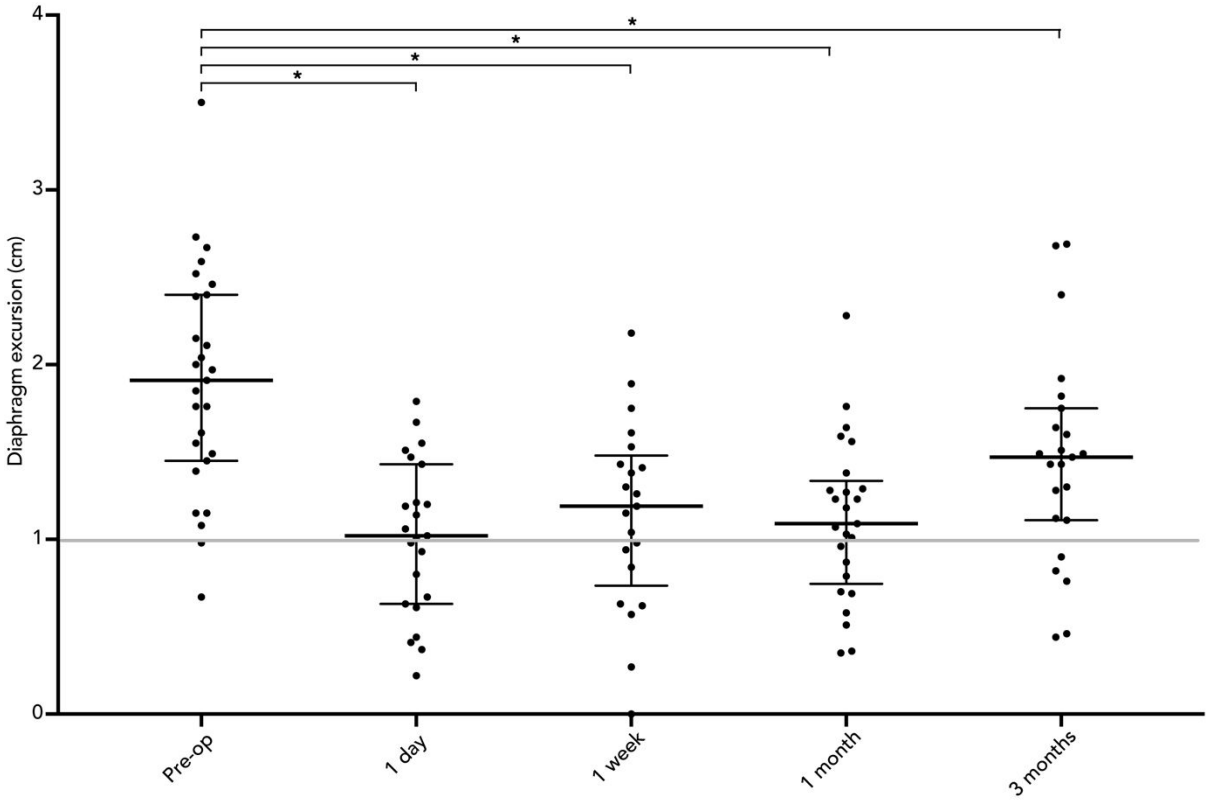
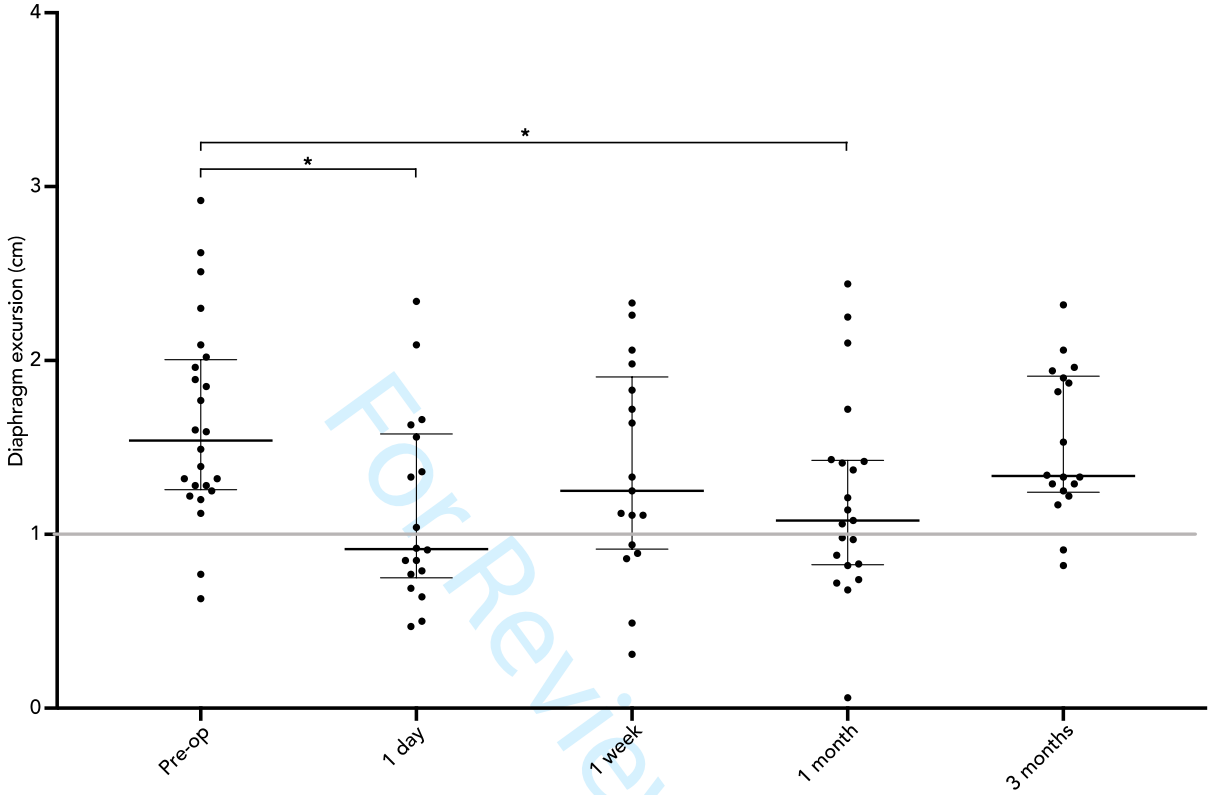


Figure 4. Hemidiaphragm excursion in cm during quiet breathing over time (A) Individual data (small filled circles) for right hemidiaphragm excursion. Group medians are represented by bold black lines and the whiskers represent interquartile ranges. *Significant difference ($P < 0.05$) from baseline. (B) Individual data (small filled circles) for left hemidiaphragm excursion. Group medians are represented by bold black lines and the whiskers represent interquartile ranges. *Significant difference ($P < 0.05$) from baseline.

(A)



(B)



SUPPLEMENTARY APPENDIX MATERIAL

HIGH INCIDENCE OF DIAPHRAGMATIC DYSFUNCTION AFTER LUNG TRANSPLANTATION:

RESULTS OF A PROSPECTIVE OBSERVATIONAL STUDY

Elise Crothers, BASc[a,b], David Kennedy, PT, BA, BS, MSci, PhD[b], Sam Emmanuel[c], Nikki Molan, MD, BASc[d], Sean Scott[e], Kris Rogers, PhD MBiostats[b,f], Allan R Glanville, MBBS,MD,FRACP[g], George Ntoumenopoulos, PhD[a]

TABLES

Supplementary Table S1. Estimated change in diaphragmatic excursion from study baseline (preoperative measurement)

Supplementary Table S2. Estimated change in diaphragmatic excursion between each time point

Supplementary Table S3. Inter-rater reliability

Supplementary Table S1. Estimated change in diaphragmatic excursion from study baseline (preoperative measurement)

Time	RQB (95% CI)	p - value	LQB (95% CI)	p - value
Pre Op	Reference		Reference	
Day 1	-0.86 (-1.23; -0.5)	<0.0001	-0.5 (-0.8; -0.21)	0.0016
Week 1	-0.77 (-1.17; -0.38)	0.0005	-0.27 (-0.65; 0.11)	0.1593
Month 1	-0.78 (-1.16; -0.41)	0.0002	-0.44 (-0.74; -0.15)	0.0052
Month 3	-0.44 (-0.83; -0.05)	0.272	-0.17 (-0.45; 0.12)	0.2388

Legend:
Abbreviations: RQB, right hemidiaphragm quiet breathing; LQB, left hemidiaphragm quiet breathing

Supplementary Table S2. Estimated change in diaphragmatic excursion between each time point

Reference	Time	RQB (95% CI)	p - value	LQB (95% CI)	p - value
Day 1	Week 1	-0.09 (-0.3; 0.12)	0.386	-0.23 (-0.43; -0.03)	0.0242
Day 1	Month 1	-0.08 (-0.26; 0.1)	0.3544	-0.06 (-0.33; 0.12)	0.6666
Day 1	Month 3	-0.43 (-0.73; -0.12)	0.0084	-0.34 (-0.63; -0.04)	0.0277
Week 1	Month 1	0.01 (-0.23; 0.25)	0.9337	0.18 (-0.12; 0.47)	0.2309
Week 1	Month 3	-0.34 (-0.64; -0.03)	0.0332	-0.12 (-0.4; 0.2)	0.4864
Month 1	Month 3	-0.35 (-0.59; -0.1)	0.0069	-0.28 (-0.57; 0.01)	0.06

Legend:
Abbreviations: RQB, right hemidiaphragm quiet breathing; LQB, left hemidiaphragm quiet breathing

Supplementary Table S3. Inter-rater reliability

RQB Measures	Intraclass Correlation Coefficient	95% Confidence Interval Lower Bound	Upper Bound	Significance
Pre Op	0.942	0.770	0.949	< 0.001
Day 1	0.931	0.838	0.971	< 0.001
Week 1	0.964	0.912	0.986	< 0.001
Month 1	0.967	0.925	0.986	< 0.001
Month 3	0.967	0.923	0.986	< 0.001

LQB Measures	Intraclass Correlation Coefficient	95% Confidence Interval Lower Bound	Upper Bound	Significance
Pre Op	0.936	0.852	0.972	< 0.001
Day 1	0.978	0.942	0.992	< 0.001
Week 1	0.963	0.897	0.986	< 0.001
Month 1	0.978	0.945	0.991	< 0.001
Month 3	0.917	0.779	0.969	< 0.001

Legend:
Abbreviations: RQB, right hemidiaphragm quiet breathing; LQB, left hemidiaphragm quiet breathing