Two Single Lung Transplantations from one Donor: Lung Twinning in the LAS Era

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Abstract

Objectives

The implementation of the Lung Allocation Score (LAS) in the Eurotransplant international collaborative framework decreased waiting list mortality, but organ shortage remains a significant problem. Transplantation of two single lungs from one donor into two recipients (lung twinning) may decrease waiting list mortality. We sought to analyze if this strategy can lead to an acceptable intermediate-term outcome.

Methods

Since the LAS-implementation we performed 32 paired single-lung transplantations from 16 postmortal donors. Data and outcome were analyzed retrospectively comparing recipients receiving the first lung (first twins) with recipients receiving the second lung (second twins), left versus right transplantation and restrictive versus obstructive disease.

Results

Survival at one year was 81% and 54% at five years. Veno-venous ECMO had been successfully used as bridge-to-transplant in three patients with ECMO-explantation immediately after surgery. Bronchial anastomotic complications were not observed in any patient. First twins and second twins exhibited similar survival ($p = 0.82$) despite higher LAS in first twins (median 45 versus 34, $p < 0.001$) and longer cold ischemic time in second twins (280 ± 83 vs. 478 ± 125, $p < 0.001$). Survival of left and right transplantation was similar ($p = 0.45$) with similar best post-transplant FEV1 (68 ± 15% versus 62 ± 14%, $p = 0.26$). Survival was similar in restrictive and obstructive disease ($p = 0.28$) with better post-transplant FEV1 (70 ± 15% versus 57 ± 11%, $p = 0.02$) in restrictive disease.

Conclusions

Performing two single-lung transplantations from one donor can be performed safely with encouraging intermediate-term outcome and good functional capacity. Lung twinning maximizes the donor pool and may help to overcome severe organ shortage.

Introduction

Since the Lung Allocation Score (LAS) was introduced in Germany in 2011 a decreased number of deaths among patients on the waiting list could be documented.(1) Nevertheless death on the waiting list remains a clinical challenge due to severe organ shortage since only 10–30% of donor lungs are judged suitable for transplantation.(2) Extended donor criteria have been suggested to overcome this dilemma

and have become clinical reality in daily practice.(3) The clinical value of ex-vivo-lung perfusion for marginal donors remains to be defined, yet.(4)

In our center we have followed a simple and cost-effective alternative. We have consistently performed single-lung transplantations (sLTx) for patients with pulmonary fibrosis since 1995. Moreover we have tried to perform sLTx in patients with COPD/emphysema once hyperinflation of the remaining native lung was prevented with prior lung volume reduction. When a single lung was allocated for a fibrosis patient with higher LAS, the remaining donor lung was frequently allocated to our center for a COPD-patient with lower LAS. With this strategy we have created a cohort of lung twins, i.e. single-lung-recipients from the same donor.(5) Such approach expands the donor pool and may reduce waiting list mortality. The drawback of such strategy is that the second organ is exposed to prolonged ischemic time with increased risk of ischemia/reperfusion injury and primary graft failure.(2) In the current investigation we report our medium-term results with “lung twinning”.

Methods

Between January 2012 and December 2023, a total of 205 LTx (sLTx n = 117, double LTx n = 88) were performed in our center. All sLTx (n = 32) from the same donor (n = 16) were included in the current retrospective investigation. Follow-up was performed by our transplant outpatient clinics. Data collection for the current retrospective investigation was approved by the Saarland University Medical Center Transplantation Ethics Committee before data collection. All patients had signed informed consent for data collection and analysis before admission on the transplant waiting list. The study was conducted in compliance with the Declaration of Helsinki.

Statistical Analysis: Data were expressed as mean ± standard deviation unless otherwise specified. Statistical analysis was performed using standard software (SigmaStat, Systat). Normal distribution was assessed using the Kolmogorov-Smirnov-test. Comparisons were perfomed between groups (normally distributed continuous data: t-test, non-normally distributed continuous data: Mann-Whitney-U-rank-test, discrete data: Fisher´s exact test). Kaplan-Meier-analyses of survival were also calculated using standard software (Prism, Graphpad) - the log-rank test was used to compare the survival distributions.

Results

Underlying disease was classified as restrictive (n = 18 / 56%) or obstructive (n = 12 / 38%) lung disease (Table 1: Demographic data and postoperative outcome). Two patients with prior sLTx bronchiolitis obliterans syndrome (BOS 6%) underwent sLTx of the native contralateral lung. Sex was distributed equally (male n = 16, female n = 16) among recipients—recipient age ranged from 38 to 67 years (mean 58 ± 7 years).

A high LAS (> 50) was present in 6 patients, median LAS was 38 (range 31–92). Three patients required veno-venous ECMO-support as bridge-to-transplant (5, 51 and 75 days, awake ECMO n = 2).

All donor lungs were cadaveric organs from donors within the Eurotransplant cooperation. Donor age was 48 ± 16 years, donor TLC was 6.2 ± 1.2 L, mean ventilation time was 5 ± 4 days, median C-reactive protein (CRP) was 120 ± 74 mg/L, and mean Horovitz index (pO2/FiO2) was 415 ± 88 mmHg. Ten donors had a history of smoking, 8 donors had abnormal bronchoscopy findings (inflammation, pus, aspiration). The first implantation was always performed for the patient with the higher LAS. Ischemic time was significantly longer for the second lung (280 ± 83 vs. 478 ± 125, p < 0.001).

Post-transplant survival was 81% at one year and 54% at five years. Survival was similar compared with 45 standard sLTx, which had been performed in our center in the same time period (p = 0.71; Fig. 1). One BOS-patient died in hospital due to aspiration pneumonia. Median follow-up of the 31 remaining recipients was 42 months. Thirteen recipients died during the follow-up (pneumonia/sepsis n = 8, pulmonary embolism n = 1, lung cancer of native fibosis lung n = 2, acute rejection n = 1, stroke n = 1; Table 1: Demographic data and postoperative outcome). Surveillance bronchoscopy did not show any bronchial anastomotic complication such as dehiscence or stenosis.

Subgroup analysis first twin versus second twin:

Age was distributed similarly in recipients receiving the first lung (first twin) and patients receiving the second lung (56 ± 8 versus 60 ± 5, p = 0.11). First twin recipients had higher LAS (median 45 versus 34, p < 0.001) and had predominantely ILD (n = 13 / 81%). Cold ischemic time was longer in second twins (280 ± 83 vs. 478 ± 125, p < 0.001) Survival was similar in both goups (1-year-survival: 81 versus 81%, 5-year-survival: 57 versus 50%, p = 0.82; Fig. 2). Best postoperative FEV1 was similar in both groups (68 ± 14% versus 62 ± 15, p = 0.26). Eight surviving first lung recipients are in CLAD stage 0 – one patient has CLAD stage I. Five of nine surviving second lung recipients have no or mild (CLAD stage 0: n = 4, CLAD stage I: n = 1), while four patients have significant CLAD (CLAD stage II: n = 2, CLAD stage III: n = 2).

Subgroup analysis left sLTx versus right sLTx:

Recipients receiving a left sided graft tended to be younger (56 ± 6 versus 60 ± 5, p = 0.06) and had a higher LAS (median 45 versus 34, p = 0.03). Underlying disease in left sLTx-recipients was predominantely restrictive (n = 13 / 81%). Survival tended to be superior in left lung allogrfat recipients after one year, but was similar in both goups in the further follow-up (1-year-survival: 94 versus 69%, 5-year-survival: 58 versus 50%, p = 0.45; Fig. 3). Best post-transplant FEV1 was similar in both subgroups (left sLTx: 68 ± 14% versus right sLTx: 62 ± 14%, p = 0.26). Eight recipients of the surviving recipients of a left lung allograft have no or mild CLAD (CLAD stage 0: n = 6, CLAD stage I: n = 2), while one patient has CLAD stage III. Six of nine surviving recipients of a right lung allograft hav no CLAD, while two patients have advanced CLAD (stage II: n = 1, stage III: n = 1).

Subgroup analysis restrictive versus obstructive lung disease:

Age was distributed similarly in recipients with restrictive and obstructive disease (61 ± 5 versus 56 ± 9, p = 0.10). Recipients with restrictive lung disease had a higher LAS (median 45 versus 34, p < 0.001). Survival tended to be superior in the group with obstructive lung disease (1-year-survival: 92 versus 83%, 5-year-survival: 70 versus 49%, p = 0.28; Fig. 4). Post-transplant FEV1 was superior in recipients with restrictive lung disease (70 ± 15% versus 57 ± 11%, p = 0.02). Five of 9 surviving COPD-patients exhibit no or mild CLAD (no CLAD: n = 4; CLAD stage I: n = 1), while 4 COPD-patients have advanced CLAD (CLAD stage II: n = 2; CLAD stage III: n = 2). All fibrosis-patients have no or mild CLAD (CLAD stage 0: n = 8, CLAD stage I: n = 1).

Discussion

Double lung transplantation (dLTx) is associated with a better postoperative functional capacity when compared with sLTx.(6, 7) However, a clear survival benefit conferred by dLTx has not unequivocally been documented.(7, 8) Can we therefore offer dLTx to all recipients? Or should we rather perform sLTx whenever possible in face of severe organ shortage and associated waiting list mortality?

Single center studies and registry-based studies have reported periprocedural and long-term outcomes after sLTX and dLTx. However, no prospective randomized trials have ever been performed to clearly document the individual merit of both procedures. Nevertheless 75% of lung transplantations are nowadays performed as dLTx.(9)

Pulmonary fibrosis is as restrictive pulmonary disease is frequently associated with secondary pulmonary hypertension. SLTx for pulmonary fibrosis will therefore lead to preferred ventilation of the graft and preferred perfusion of the graft resulting in an optimal ventilation perfusion match. Accordingly sLTX was considered to be an optimal procedure for fibrosis.(10) Meyers reported the first larger cohort of recipients with pulmonary fibrosis and did not observe a survival difference for sLTx vs. dLTx.(11) In a more recent analysis with pooled data from the United Network for Organ Sharing (UNOS) database a better graft survival was documented with dLTx for recipients with pulmonary fibrosis.(12) In contrast a current study based on pooled data of the Scientific Registry of Transplant Recipients employed propensity score matching to compare sLTX and dLTx. Long-term-survival up to ten years was similar in both groups (n = 466 in each group). A trend towards reduced rate of posttransplant renal failure and reduced hospital length of stay was observed in sLTx-recipients. (13)

SLTX for patients with COPD / emphysema is usually technically simple and rarely requires cardiopulmonary bypass. However, air trapping in the native lung may cause mediastinal shift and impaired ventilation-perfusion match. Thus volume reduction of the contralateral lung has been suggested to overcome this clinical dilemma.(10) If used with this precautions sLTx may lead to satisfactory long-term results, particularly for the elderly recipient. Thabut used the ISHLT database to analyse recipients between 1987 and 2007 worldwide. He documented a survival benefit of dLTx for recipients < 60 years.(14) The study by Schaffer et al. mentioned above, which employed the UNOS database, did not find a survival difference between sLTx and dLTx for COPD-patients.(12)

The LAS-system was implemented in the USA in 2005 and in 2011 in Germany. With this allocation model decreasing mortality on the waiting list was observed in both countries.(1, 15). While in Germany up to every fifth patient died on the waiting list before the advent of the LAS-system, mortality was reduced since then by 25%.(1) Nevertheless death on the waiting list is still an issue. A recent analysis based on the UNOS database documented that in only 43% of donors for sLTx, both lungs were used.(16) Thus centers should rethink their individual donor profiles. While an earlier analysis shed a critical light on lung splitting and sLTx (17), a very recent editorial by Ramos identified a decreased risk for death on the waiting list when patients with COPD or fibrosis were listed for sLTx without a compromised posttransplant outcome.(9)

Lung twinning, i.e. two sLTx from one lung donor, was first reported by Haydock in a multi-center-study.(18) This strategy may help to overcome donor lung shortage, but exposes the second donor lung to prolonged ischemic time since both single lung transplantation may only rarely be performed at the same time in different operating rooms by different teams in the same transplant center. Prolonged cold ischemia may in turn lead to ischemia/reperfusion injury. Improvements in lung preservation, surgical technique and perioperative care have helped to reduce the reduce the incidence of ischemia/reperfusion induced primary graft failure from 30–15% or less. Nevertheless ischemia/reperfusion injury remains a significant cause of early morbidity and mortality after lung transplantation.

Does the lung twinning concept turn the second twin (i.e. the low-risk patient with lower LAS) into a high-risk patient due to increased risk of ischemia/reperfusion injury? Sommers analyzed differences between lung twin pairs in the Pittsburgh transplant program and observed impaired early graft function associated with left-single-lung-recipients, pulmonary hypertension and cardiopulmonary bypass.(19) In contrast, Glanville documented that prolonged ischemia for the second lung did not induce early graft dysfunction.(20) Snell reported the largest single-center-experience of lung twinning with 38 pairs of recipients.(21) This Australian group did not observe different outcomes between first and second twins. However this group reported an inferior intermediate outcome of left-single-lung-recipients - primarily related to increased mortality from airway complications.(21) These observations were supported by Smits from Eurotransplant, who analyzed the outcome of 90 lung twin pairs operated in 16 European centers.(5) In this analysis more fatal complications were observed in recipients receiving a left-sided sLTx. Outcome was particularly worse if the retrieval center was different from the transplanting center (1-year-survival: right sLTx 92% / left sLTx 62%, p = 0.04).

Our results with lung twinning support the findings of prior studies that lung twinning can be performed safely despite of prolonged ischemic time for the second lung. Survival of our twin cohort was similar when compared with all standard sLTx, which had been performed in the same era. Our data document that also challenging transplantations in high-LAS patients (n = 6) or ECMO (n = 3) may be performed in this context without survival difference between first twin (high-risk-patient) and second twin (low-risk patient). Intermediate-term outcomes are comparable with outcomes in the ISHLT registry. Of interest, no survival difference was observed for left versus right sLTx in our patient cohort. Maybe this finding could

be attributed to the fact that all retrievals were performed by our center and no airway complications were observed.

We conclude that stringent use of sLTX - i.e. (almost) always for pulmonary fibrosis and if suitable for COPD - may expand the donor pool and allows lung twinning. Such concept can lead to encouraging intermediate-term outcomes and may help to further reduce waiting list mortality in the LAS-era.

Table 1: Demographic data and postoperative outcome

Figure 1: Kaplan-Meyer survival analysis: whole cohort

Figure 2: Kaplan-Meyer survival analysis: first twin versus second twin

Figure 3: Kaplan-Meyer survival analysis: restrictive versus obstructive disease

Figure 4: Kaplan-Meyer survival analysis: left versus right single lung transplantation.

Table 1
Demographic data and postoperative outcome

Twin Pair No.	Age	Sex	Disease type	LAS	Allocation	sLTx type	Outcome	Best FEV1 (%)	CLAD Stage
1	59	f	REST	55	regular	left	alive 107 mo	72	0
	50	f	BOS	43	regular	right	died 4 d postop (sepsis)		
2	62	f	REST	49	regular	left	alive 84 mo	72	0
	63	f	OBST	36	regular	right	died 6 mo postop (sepsis)		
3	56	m	REST	90	regular	right	died 11 mo postop (sepsis)	50	0
	53	m	REST	34	ext all	left	alive 84 mo	70	
4	45	m	REST	88	regular	left	died 70 mo postop (rejection)	79	0
	59	m	OBST	38	rescue	right	alive 75 mo	58	1
5	63	m	REST	40	regular	right	alive 65 mo	90	0
	50	m	OBST	32	regular	left	alive 65 mo	53	3
6	52	m	REST	44	regular	left	died 40 mo postop (stroke)	89	0
	61	m	OBST	34	ext all	right	alive 63 mo	63	2
7	63	m	REST	67	regular	left	alive 61 mo	89	0
	64	m	OBST	32	ext all	right	died 39 mo postop (sepsis)	73	0
8	53	m	BOS	43	regular	right	died 2 mo postop (sepsis)	98	0
	61	m	REST	38	regular	left	died 42 mo postop (lung cancer in native fibrosis lung)		
9	54	f	REST	61	regular	left	died 42 mo postop (pneumonia)	59	0
	64	f	OBST	33	regular	right	alive 58 mo	65	0
10	38	m	REST	92	regular	left	alive 56 mo	65	0
	56	m	OBST	34	rescue	right	alive 56 mo	61	0

Twin Pair No.	Age	Sex	Disease type	LAS	Allocation	sLTx type	Outcome	Best FEV1 (%)	CLAD Stage
11	55	m	REST	38	regular	left	died 48 mo postop (lung cancer in native fibrosis lung)	52	0
	56	m	REST	34	rescue	right		57	0
							died 6 mo postop (pulmonary embolism)		
12	61	f	OBST	34	ext all	left	alive 53 mo	54	0
	66	f	OBST	31	rescue	right	died 47 mo postop (CLAD)	62	3
13	61	f	OBST	33	regular	left	alive 39 mo	59	0
	64	f	OBST	34	regular	right	alive 39 mo	52	0
14	67	m	REST	46	regular	left	died 15 mo postop (COVID)	53	0
	63	f	OBST	40	regular	right	alive 33 mo	69	
15	38	f	REST	46	regular	left	alive 16 mo	60	0
	61	f	REST	34	regular	right	alive 16 mo	73	0
16	62	f	REST	37	ext all	left	died 5 mo postop (sepsis)	30	3
	57	f	OBST	33	ext all	right	alive 14 mo		

(REST: restrictive lung disease, OBST: obstructive lung disease, BOS: bronchiolitis obliterans syndrome, ext all: extended allocation, CLAD: chronic lung allograft dysfunction)

Declarations

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Contributions

F. Langer: conception and design of the study, data collection and analysis, writing of the manuscript. P. Lepper, B. Weingard, P. Aliyev, R. Bals and H. Wilkens: patient care, revision of the manuscript. All authors read and approved the final manuscript for publication.

Clinical Trials

This research is not a clinical trial. Thus no registration details will be provided.

Ethics Declaration

The study was conducted in compliance with the Declaration of Helsinki. All patients had signed informed consent for data collection and analysis before admission on the transplant waiting list. Data collection for the current retrospective investigation was approved by the Saarland University Medical Center Transplantation Ethics Committee before data collection.

Availability of Data

All clinical data can be accessed in the institutional lung transplant database.

Competing Interests

R. Bals serves as Editor-in Chief of the journal.

References

1. Gottlieb J, Smits J, Schramm R, Langer F, Buhl R, Witt C, et al. Lung Transplantation in Germany Since the Introduction of the Lung Allocation Score. Dtsch Arztebl Int. 2017;114(11):179–85.
2. de Perrot M, Liu M, Waddell TK, Keshavjee S. Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med. 2003;167(4):490–511.
3. Smits JM, van der Bij W, Van Raemdonck D, de Vries E, Rahmel A, Laufer G, et al. Defining an extended criteria donor lung: an empirical approach based on the Eurotransplant experience. Transpl Int. 2011;24(4):393–400.
4. Warnecke G, Van Raemdonck D, Smith MA, Massard G, Kukreja J, Rea F, et al. Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. Lancet Respir Med. 2018;6(5):357–67.
5. Smits JM, Melman S, Mertens BJ, Laufer G, Persijn GG, Van Raemdonck D, et al. The Eurotransplant Study on Twin Lung Transplants (ESOTWIN): 90 paired single-lung transplants from the same donor. Transplantation. 2003;76(11):1604–8.

6. Bavaria JE, Kotloff R, Palevsky H, Rosengard B, Roberts JR, Wahl PM, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg. 1997;113(3):520–7. discussion 8.
7. Subramanian MP, Meyers BF. Bilateral versus single lung transplantation: are two lungs better than one? J Thorac Dis. 2018;10(7):4588–601.
8. Aryal S, Nathan SD. Single vs. bilateral lung transplantation: when and why. Curr Opin Organ Transplant. 2018;23(3):316–23.
9. Ramos KJ, Harhay MO, Mulligan MS. Which Shall I Choose? Lung Transplantation Listing Preference for Individuals with Interstitial Lung Disease and Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2019;16(2):193–5.
10. Cooper JD. The history of surgical procedures for emphysema. Ann Thorac Surg. 1997;63(2):312–9.
11. Meyers BF, Lynch JP, Trulock EP, Guthrie T, Cooper JD, Patterson GA. Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis: a ten-year institutional experience. J Thorac Cardiovasc Surg. 2000;120(1):99–107.
12. Schaffer JM, Singh SK, Reitz BA, Zamanian RT, Mallidi HR. Single- vs double-lung transplantation in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis since the implementation of lung allocation based on medical need. JAMA. 2015;313(9):936–48.
13. Ranganath NK, Malas J, Phillips KG, Lesko MB, Smith DE, Angel LF, et al. Single and Double Lung Transplantation Have Equivalent Survival for Idiopathic Pulmonary Fibrosis. Ann Thorac Surg. 2020;109(1):211–7.
14. Thabut G, Christie JD, Ravaud P, Castier Y, Brugiere O, Fournier M, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet. 2008;371(9614):744–51.
15. Yusen RD, Shearon TH, Qian Y, Kotloff R, Barr ML, Sweet S, et al. Lung transplantation in the United States, 1999–2008. Am J Transplant. 2010;10(4 Pt 2):1047–68.
16. Speicher PJ, Ganapathi AM, Englum BR, Gulack BC, Osho AA, Hirji SA, et al. Single-lung transplantation in the United States: what happens to the other lung? J Heart Lung Transplant. 2015;34(1):36–42.
17. Anyanwu AC, Rogers CA, Murday AJ. Does splitting the lung block into two single lung grafts equate to doubling the societal benefit from bilateral lung donors? Comparisons between two single versus one bilateral lung transplant. UK Cardiothoracic Transplant Audit Steering Group. Transpl Int. 2000;13(Suppl 1):201–2.
18. Haydock DA, Low DE, Trulock EP, Kaiser LR, Pasque MK, Molmenti E, et al. Pulmonary twinning procedure: use of lungs from one donor for single-lung transplantation in two recipients. Ann Thorac Surg. 1992;54(6):1189–92.
19. Sommers KE, Griffith BP, Hardesty RL, Keenan RJ. Early lung allograft function in twin recipients from the same donor: risk factor analysis. Ann Thorac Surg. 1996;62(3):784–90.

20. Glanville AR, Marshman D, Keogh A, Macdonald P, Larbalestier R, Kaan A, et al. Outcome in paired recipients of single lung transplants from the same donor. J Heart Lung Transplant. 1995;14(5):878–82.
21. Snell GI, Shiraishi T, Griffiths A, Levvey B, Kotsimbos T, Esmore DS, et al. Outcomes from paired single-lung transplants from the same donor. J Heart Lung Transplant. 2000;19(11):1056–62.

Figures

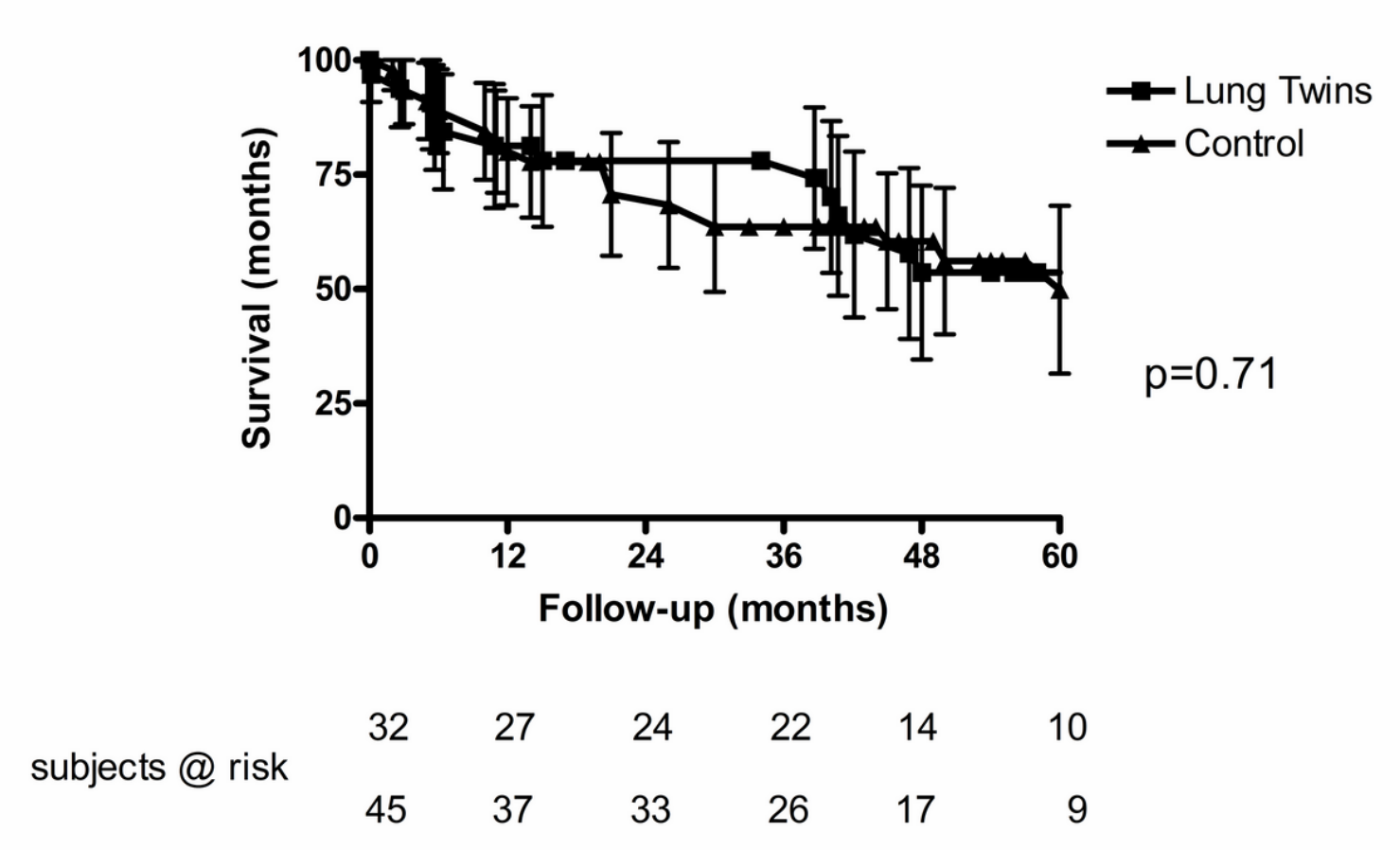

Figure 1

Kaplan-Meyer survival analysis: whole cohort

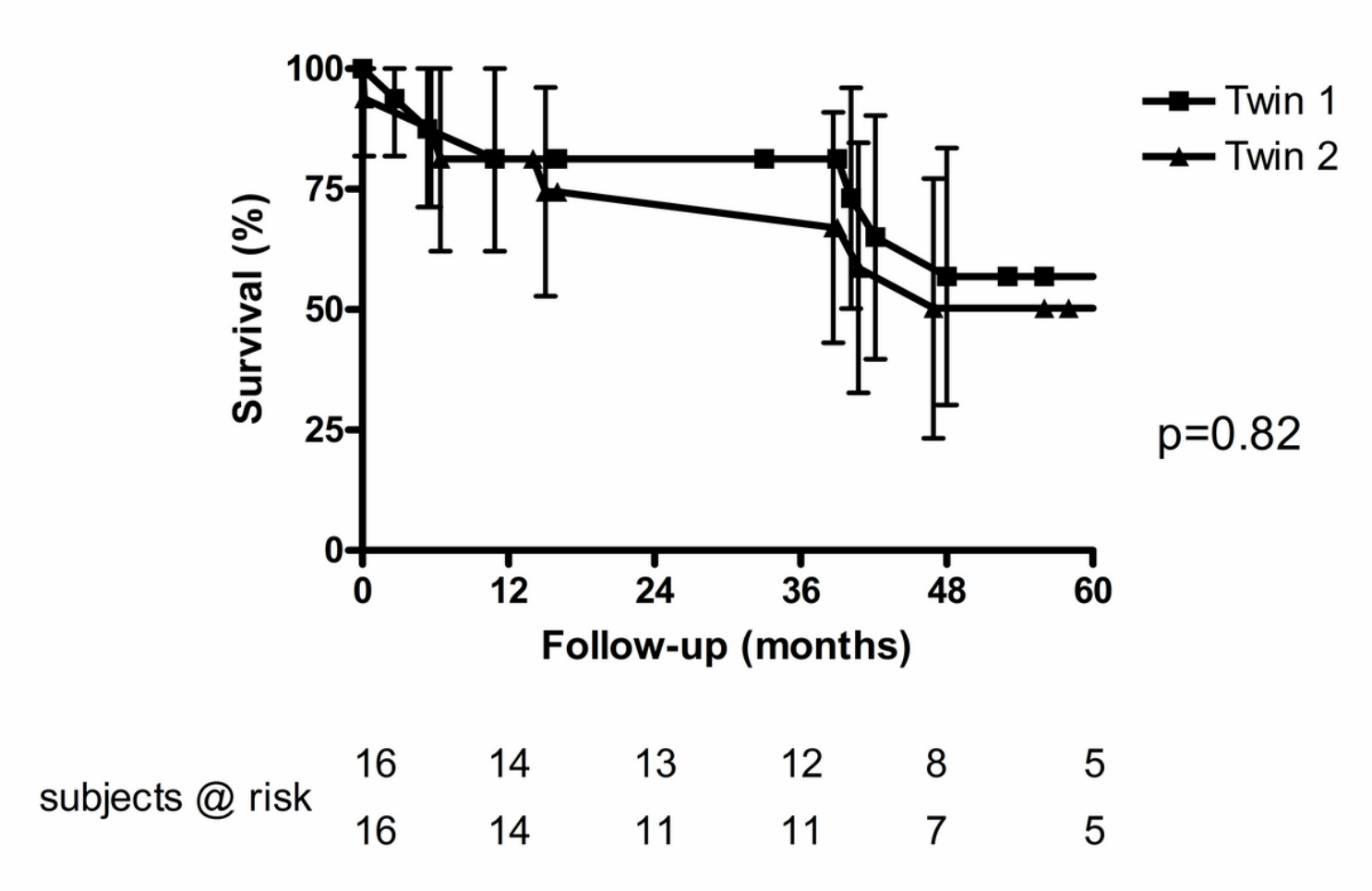

Figure 2

Kaplan-Meyer survival analysis: first twin versus second twin

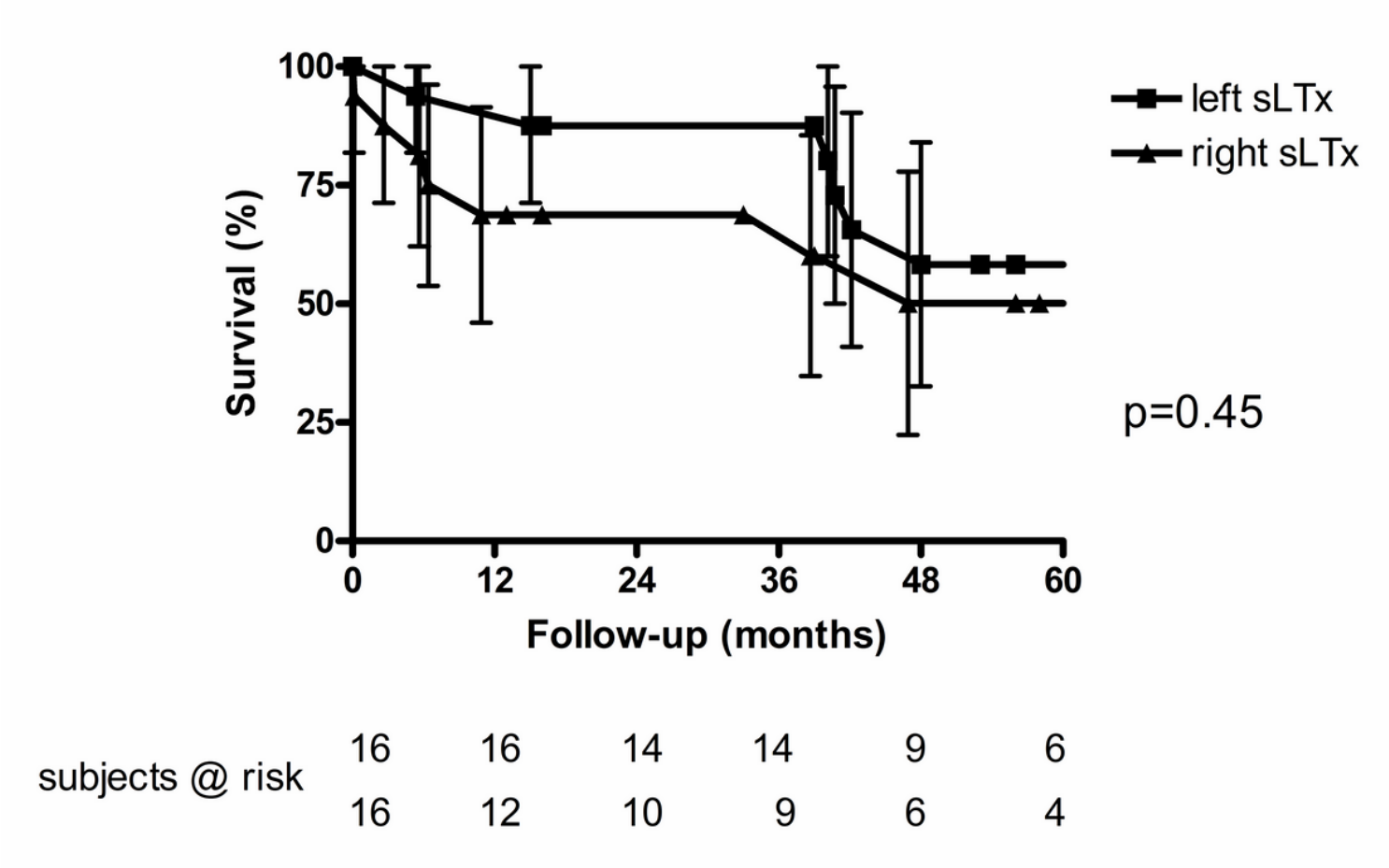

Figure 3

Kaplan-Meyer survival analysis: restrictive versus obstructive disease

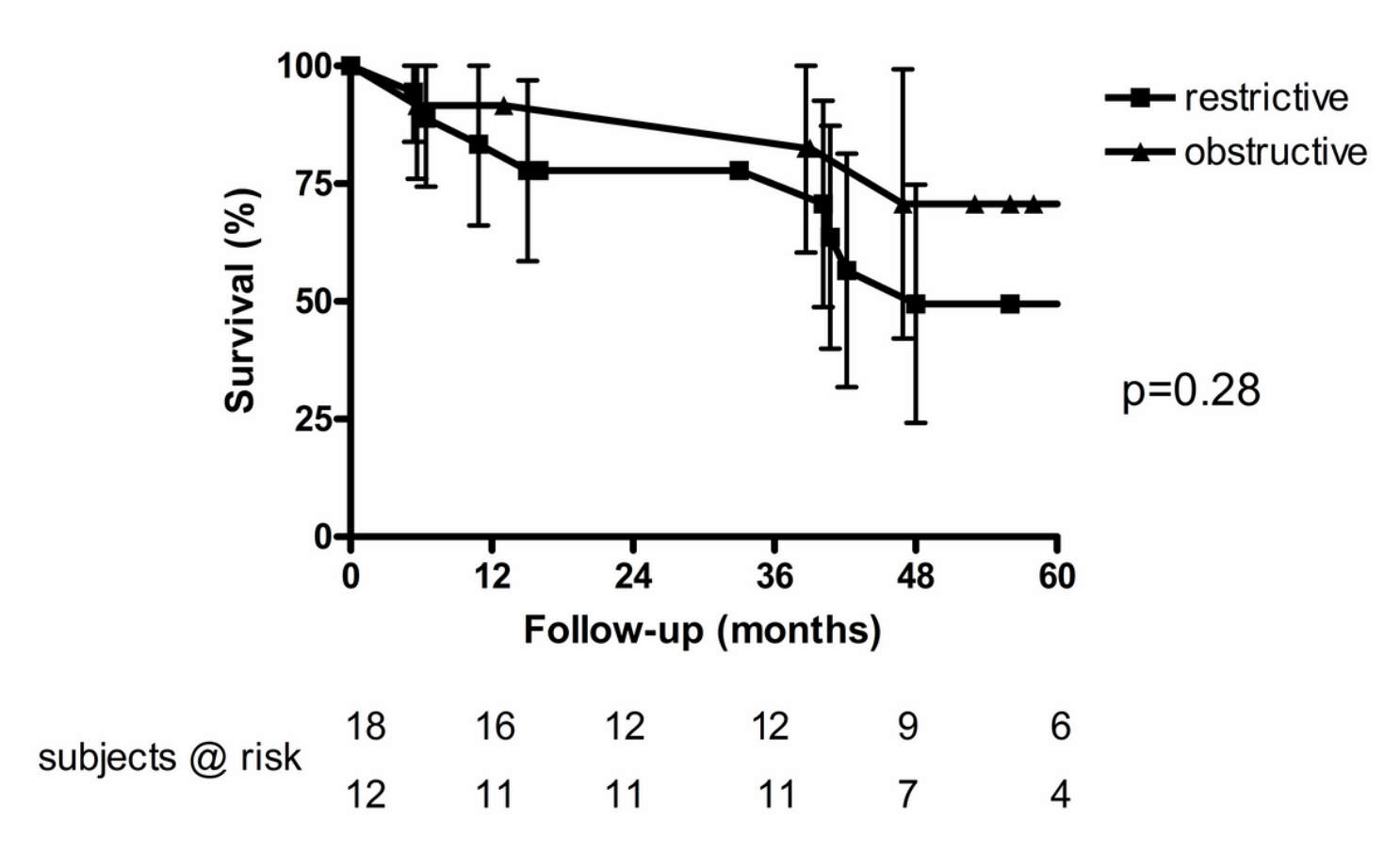

Figure 4

Kaplan-Meyer survival analysis: left versus right single lung transplantation.