

Incidence and risk factors of anastomotic complications after lung transplantation

Agathe Delbove¹, Thomas Senage, Pierre Gazengel, Adrien Tissot, Philippe Lacoste, Laurent Cellerin, Christian Perigaud, Isabelle Danner-Boucher, Arnaud Cavailles, Thierry Lepoivre, Antoine Mugniot, Johanna Nicolet, Delphine Horeau-Langlard, Nicolas Groleau, Yannick Fedun, Bertrand Rozec, Antoine Magnan, Jean-Christian Roussel and François-Xavier Blanc

Abstract

Background: Anastomotic complications are common after lung transplantation (1.4–33% of cases) and still associated with a high morbi-mortality.

Methods: The current study is a monocenter retrospective analysis of symptomatic anastomotic complications (SAC) occurring after lung transplantation between 2010 and 2016, using the macroscopic, diameter, and suture (M-D-S) classification from consensus of French experts in bronchoscopy. The objectives were to determine incidence from surgery, risk factors, and impact of survival of SAC. We defined SAC as M-D-S abnormalities (stenosis $\geq 50\%$ or dehiscence) requiring bronchoscopic or surgical interventions.

Results: A total of 121 patients were included. SAC occurred in 26.5% of patients ($n=32$), divided in symptomatic stenosis for 23.7% ($n=29$), and symptomatic dehiscence in 2.5% ($n=3$). In multivariate analysis, donor bacterial lung infection [HR 2.08 (1.04–4.17), $p=0.04$] and age above 50 years [HR 3.26 (1.04–10.26), $p=0.04$] were associated with SAC occurrence. Cystic fibrosis etiology was associated with better survival on Kaplan–Meier curve ($p<0.001$). SAC [HR 2.15 (1.07–4.32), $p=0.03$] was independently associated with worst survival. The 29 symptomatic patients because of stenosis required endoscopic procedure, of whom 16 patients needed bronchial stent placement. Four patients underwent surgery: three patients because of dehiscence and one because of severe bilateral stenosis (re-transplantation).

Discussion: SAC occurred in 26.5% of patients. Donor lung infection was the only alterable identified factors. The increase rate of SAC in older patients above 50 years of age encourages in regular endoscopic monitoring.

Keywords: airway complications, lung transplantation, risk factors, symptomatic anastomotic complications

Received: 14 April 2022; revised manuscript accepted: 14 June 2022.

Introduction

Despite remarkable improvement in surgical techniques and post-operative intensive care unit management, lung transplantation is still associated with significant mortality and morbidity related to infections, rejection episodes, or surgical complications. Among the latter, anastomotic complications are defined by any injuries involving bronchial anastomoses, such as ischemia or bronchial anastomotic necrosis, stenosis (stricture, malacia, or

granulomas), and dehiscence. Bronchial arteries are necessarily sectioned during surgical procedure. However, 2–4 weeks are needed for revascularization and the sole retrograde circulation from the low pressure arterial pulmonary regimen allows healing of anastomoses at the initial stage.¹ Complex surgical strategies of arterial reimplantation have been proposed, but their benefit correlates with prolonged graft ischemic time, known to be deleterious.²

Ther Adv Respir Dis

2022, Vol. 16: 1–10

DOI: 10.1177/
17534666221110354

© The Author(s), 2022.

Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Agathe Delbove
Service de Pneumologie,
L'institut du thorax,
Boulevard Jacques Monod,
CHU Nantes, hôpital G. et
R. Laennec, 44 093 Nantes
cedex 1, France.

Current address: Service de
Réanimation polyvalente,
Centre Hospitalier
Bretagne Atlantique, 20,
Boulevard du Général
Maurice Guillaudot, 56 017
Vannes Cedex, France.
[agathe.delbove@ch-
bretagne-atlantique.fr](mailto:agathe.delbove@ch-bretagne-atlantique.fr)

Thomas Senage
Service de chirurgie
thoracique et
cardiovasculaire, CHU
Nantes, Nantes, France
INSERM UMR
1246-SPHERE, Nantes
University, Tours
University, Nantes, France

Pierre Gazengel
Service de pneumologie,
L'institut du thorax, CHU
Nantes, Nantes, France

Service de transplantation,
Clinique chirurgicale Marie
Lannelongue, Le Plessis
Robinson, France

Adrien Tissot
Laurent Cellerin
Isabelle Danner-Boucher
Arnaud Cavailles
**Delphine Horeau-
Langlard**
François-Xavier Blanc

Service de pneumologie,
L'institut du thorax, CHU
Nantes, Nantes, France

Philippe Lacoste
Christian Perigaud
Antoine Mugniot
Jean-Christian Roussel
Service de chirurgie
thoracique et
cardiovasculaire, CHU
Nantes, Nantes, France

Thierry Lepoivre
INSERM UMR
1246-SPHERE, Nantes
University, Tours
University, Nantes, France

Johanna Nicolet

Nicolas Groleau

Bertrand Rozec

Service de réanimation
chirurgicale thoracique
et cardiovasculaire, CHU
Nantes, Nantes, France

Yannick Fedun

Service de réanimation
polyvalente, Centre
Hospitalier Bretagne
Atlantique, Vannes, France

Antoine Magnan

Service de pneumologie,
l'institut du thorax, CHU
Nantes, Nantes, France

Service de Pneumologie,
Hôpital Foch, Suresnes,
France

Studies reporting anastomotic complications are heterogeneous with a wide variation of incidence due to the absence of consensual classification. Depending on authors, anastomotic complications occur from 1.4% to 33% of lung transplantations with a mortality ranging from 2% to 4%.³⁻⁶ Couraud *et al.*⁷ were the first to propose a classification for anastomotic complications but they focused on bronchial anastomotic necrotic lesions. Other classifications were not precise enough regarding the localization of anastomotic complications or the description of multiple complications.¹ In 2013, a consensus of French experts in bronchoscopy established a classification for anastomotic complications, aiming to be simple, applicable, and efficient.³ The macroscopic, diameter, and suture classification (M-D-S) describes most of the possible complications and localizations (suture, extend to lobar or beyond). In the available literature, this classification has only been used in Yserbyt *et al.*⁶ study, whereas most of French lung transplant centers routinely use it.

Several risk factors of anastomotic complications after lung transplantation have already been identified in previous studies, such as donor conditions, initial disease, surgical technique, immunosuppressive therapy, right-sided anastomoses, infections, and comorbidities.^{6,8-10} Nevertheless, few preventive strategies can be proposed because most of these risk factors are not alterable. Curative therapeutic options include medical treatment (immunosuppressive change, antibiotics), bronchoscopic intervention (dilatation, bronchial stent placement), and surgical intervention.

The objectives of the study were to determine the incidence of symptomatic anastomotic complications (SACs) in lung-transplanted patients and to identify risk factors to develop each complication with the help of regular M-D-S scoring.

Material and methods

Design and population

The current study is a monocenter retrospective analysis. Patients were eligible if lung-transplanted adults followed in Nantes University Hospital, France, between January 1, 2010 and December 31, 2016. We excluded heart-lung transplantations and deaths that occurred within the first 30 days after lung transplantation and patients opposed to participation.

Outcomes

The main outcome of this study was the time between surgery and SAC occurrence. SAC were defined as M-D-S abnormalities (stenosis $D2 \geq 33\%$ or dehiscence $\geq S1$) requiring bronchoscopic or surgical interventions because of dyspnea, handicapping cough, forced expiratory volume in 1 s (FEV1) decline, or recurrent infection.

Secondary outcomes were as follows:

- Time between surgery and patient death
- To determine the incidence of severe endoscopic complications and provide the rate of worst anastomoses endoscopic scoring for each M-D-S and each bronchus (left or right) classification in the population
- To investigate the risk factors associated with SAC
- To describe SAC management.

Data collection

Donor. Epidemiologic data were collected: age, sex, weight, height, tobacco history, intensive care unit length of stay, and respiratory infections.

Recipient. Medical history was retrieved from hospital medical reports: age, sex, underlying disease, nutritional parameters, bacterial or fungal colonization before lung transplantation.

Graft follow-up. Surgical information, total graft ischemic time, intensive care unit length of stay, and organ dysfunctions were collected. Post-transplant complications and their treatments were collected: infections, immunosuppressive regimen, diabetes, allograft dysfunction, and anastomotic complications.

Donor infection was based on anonymous biomedicine agency file when the following criteria were present: purulent respiratory secretions associated with identified bacteria and compatible radiological findings on computed tomography (CT)-scan.

Recipient colonization was defined by bacterial or fungal identification more than two times a year (3 months apart) without active infection.

Graft infection was defined by isolation of bacteria or fungi associated with clinical (cough, secretions, fever $> 38.5^\circ\text{C}$), biological (leukocytes

elevation > 12 G/l), or radiological signs (alveolar infiltrates, condensations, nodes) of infection needing treatment.

M-D-S classification definition and rules of scoring

We collected bronchoscopy reports (text and pictures if available) at regular times: day 1, day 7 (± 1 day), day 14 (± 2 days), day 30 (± 7 days), 3 months (± 1 month), 6 months (± 2 months), and 12 months (± 3 months) after lung transplantation. Two independent physicians scored each anastomoses according to the bronchoscopy reports in M-D-S classification, routinely used in our department since 2014.³ Score 0 corresponds to normal score (normal anastomose scored M0D0S0). The detailed classification is provided in the Supplemental Material. In case of discordant classification between the two bronchoscopists, the anastomoses were re-sorted until mutual agreement.

We chose to define severe anastomotic complications as follows, regarding usual evolution of these endoscopic aspects toward symptoms:

- Severe bronchial anastomotic necrosis as M3c or M3d (named \geq M3c) scoring;
- Stenosis D2 \geq 33% to exclude malacia and mild stenosis $<$ 33%;
- Dehiscence \geq S1 (S0 being normal).

Survival was evaluated by June 1, 2018.

Data analysis

Quantitative data are expressed as median \pm interquartile range. Nonparametric two-sided tests, such as the Fisher's exact test and the Mann-Whitney U test, were used as appropriate. A p -value less than or equal to 0.05 was considered significant.

The analyses of long-term outcomes were performed with the use of the Kaplan-Meier estimator. A first selection of covariates was performed with the log-rank test ($p < 0.20$). Then, a Cox model was estimated with a backward procedure performed manually variable by variable with the use of a Wald test ($p < 0.05$). This procedure allows the identification of possible confounding factors (variation of regression coefficients $> 20\%$). Hazards proportionality was checked by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals. Time-dependent coefficients were used for

nonproportional covariates. In the analysis of time to death, SAC were considered as time-dependent covariates with the use of an extended Cox model.

The following preoperative data were considered as possible correlates of SAC or patient death: donor ages (years), donor gender, mechanical ventilation duration of donor (days), donor PaO₂/FiO₂ ratio before explantation, donor bacterial lung infection, recipient age (years), recipient gender, recipient transplant etiology, recipient body mass index, recipient fungal and bacterial colonization, recipient FEV1 at 1 year, recipient diabetes, tracheostomy, recipient mechanical ventilation (days), thymoglobulin induction, and recipient preoperative cardiopulmonary bypass.

Statistical analyses were performed with the use of version 4.0.3 of R software.

Results

SAC characteristics

From 2010 to 2016, 145 patients were transplanted in our institution. Death within 30 days post transplantation were excluded (no one was attributed to anastomotic complication). Overall, 121 patients (237 anastomoses) were included (Figure 1).

SAC occurred 32 patients (26.5%) concerning 44/237 (18.5%) anastomoses (15 localized on the left side and 29 on the right side).

The worst endoscopic evaluation for each side is described in Table 1, associated with the complication rate of each staging. Bronchial anastomotic necrosis \geq M3c occurred in 46.2% of patients (56/121), of whom 53.6% (30/56) induced a symptomatic complication (stenosis or dehiscence). Stenosis occurred in 47/121 patients, and the symptomatic stenosis \geq D2 in 23.7% (29/121) [endoscopic stenosis \geq D2 in 38.0% (46/121)] and symptomatic dehiscence \geq S1 in 2.5% (3/121) of them [endoscopic dehiscence \geq S1 in 7.4% (9/121)].

Patients with and without SAC are described in Table 2. The median donor age was 46 (31–55) years, with 53% males. Donors had tobacco-smoking history in 31%, with median mechanical ventilation duration of 2 (1–3) days and a PaO₂/FiO₂ ratio of 414 (365–467) before explantation. A lung infection was identified in 37% of donors

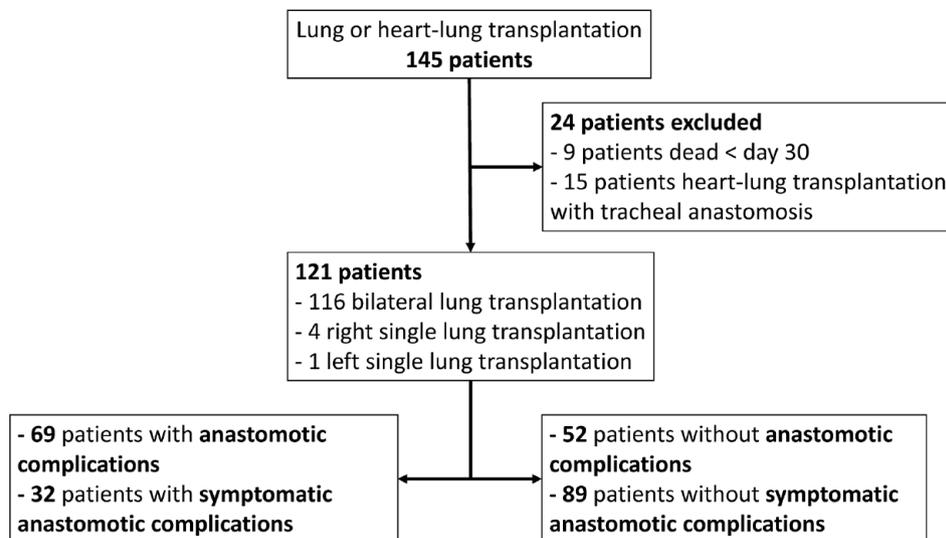


Figure 1. Flowchart of patients screened during the study period, excluded and finally included, with the repartition of patients with and without SAC.

(among the main pathogens found: 20% *Streptococcus spp.*, 35% *Staphylococcus aureus*, 9% *Pseudomonas aeruginosa*; and 20% polymicrobial). Recipients had a median age of 38 (28–50) years, with 54.5% males. Median body mass index was 19.2 (17.6–21.9) kg/m². Underlying respiratory disease was cystic fibrosis in 50%, lung fibrosis in 13%, chronic obstructive pulmonary disease (COPD) in 11%, alpha-1 antitrypsin deficiency in 12%, and others in 14% (bronchiectasis, pulmonary hypertension, and rare lung diseases). Immunosuppressive induction was systematic, using thymoglobulin in 63%. Surgical technique was homogeneous with continuous suture with non-absorbable material, termino-terminal anastomoses, minimizing the length of the donor bronchus. Neither tissue-covered anastomosis nor bronchial revascularization was performed. Cold ischemic time was similar in both groups [539 (428–610)].

Risk factors of SAC

In multivariate analysis, donor bacterial lung infection [HR 2.08 (1.04–4.17), $p=0.04$] and age above 50 years [HR 3.26 (1.04–10.26), $p=0.04$] were associated with SAC occurrence (see Table 3).

Survival

Cystic fibrosis etiology was associated with a better survival (Figure 2). In multivariate analysis,

SAC was associated with a twofold increased risk of death [HR 2.15 (1.07–4.32), $p=0.03$] (see Table 4).

Management of SAC

Stenosis. The 29 patients developed symptomatic stenosis \geq D2 in median delay of 90 days (30–90). Nine patients had a single treatment: three had endoscopic desobstruction and six balloon dilatation. The remaining patients required combined therapy: 4 had endoscopic desobstruction associated with balloon dilatation, 16 had either desobstruction or balloon dilatation followed by bronchial stent placement. Endoscopy desobstruction was performed either with argon laser (eight patients), either electrocauterization (two patients) or forceps biopsy (three patients). Median time for prosthesis insertion was 6 (\pm 4) months post lung transplantation. One patient with severe bilateral stenosis was re-transplanted 2 years after the first lung transplantation.

Dehiscence. Nine patients had dehiscences (three of them bilateral), but only three of them (2.5%) were symptomatic and primitive. Three dehiscences evolved favorably: one spontaneously (ended as a diverticulum), one with pleural drainage (accidental bronchial placement of a nasogastric tube), and one with surgery (anastomoses wrapping).

Three other dehiscences were dilatation procedure-induced leading to two fatal gaseous embolisms and one fatal hemoptysis.

The remaining three patients underwent surgery (two for anastomosis wrapping and one for anastomoses resection). Two of them had post-operative fatal hemoptysis and one had large bilateral dehiscence that would require a heart-lung transplantation that was decided against by medico-surgical staff because of altered condition.

Discussion

To our knowledge, this study is the first to use a systematic bronchoscopic evaluation to evaluate SAC incidence after lung transplantation, using the M-D-S classification. We report 26.5% of SAC ($n=32$), 23.8% symptomatic stenosis \geq D2 requiring endoscopic procedure ($n=29$), and 2.5% primitive and symptomatic dehiscence \geq S1 ($n=3$) requiring surgery in our patients. Of note, a total of nine patients suffering from dehiscence, three experienced spontaneous resolution, three were secondary to stenosis dilatation procedure, and three were the primitive and symptomatic described above. All anastomotic complications leading to death were attributed to dehiscences.

There is still a wide variation of these rates in the literature, mainly due to the absence of consensus. Awori Hayanga *et al.*⁴ reported a low rate of 1.4%, but they did not precisely define anastomotic complications and their data were extracted from a national register (potentially reporting the most severe complications only). In a study conducted between 2005 and 2013, that is, before the publication of the M-D-S, Yserbyt *et al.*⁶ described 11% of anastomotic complications, but no clear definition was provided. Olland *et al.*¹¹ reported 20% of anastomotic complications after lung transplantation and Cho *et al.*⁵ reported 28% of early and 16% of delayed anastomotic complications in their cohorts.

Based on our data, we identified several risk factors of anastomotic complications after lung transplantation. Among them, donor bacterial lung infection [HR 2.08 (1.04–4.17), $p=0.04$] is

Table 1. Occurrence of worst endoscopic scoring of anastomoses on M-D-S classification in the study population.

M-D-S stage	Left (N= 117)		Right (N= 120)	
	N (%)	Complication rate, %	N (%)	Complication rate, %
M: macroscopic aspect				
M0	2 (2)	0	2 (2)	0
M2a	1 (1)	0	0 (0)	NA
M3a	58 (50)	7	48 (40)	13
M3b	27 (23)	11	32 (27)	13
M3c	28 (24)	21	38 (32)	47
M3d	1 (1)	100	0 (0)	NA
D: diameter				
D0	81 (69)	0	91 (76)	0
D1	3 (3)	0	2 (2)	50
D1a	1 (1)	0	4 (3)	50
D2a	22 (19)	23	9 (7)	67
D2b	1 (1)	0	4 (3)	50
D2d	1 (1)	0	0 (0)	NA
D3a	7 (6)	43	9 (7)	67
D3b	0 (0)	NA	3 (2)	100
D3d	1 (1)	100	6 (5)	100
S: sutures (dehiscence)				
S0	113 (97)	0	112 (93)	0
S1	1 (1)	100	2 (2)	50
S1e	0 (0)	NA	3 (2)	67
S1f	1 (1)	100	2 (2)	100
S2e	1 (1)	100	0 (0)	NA
S3e	0 (0)	NA	1 (1)	100
S3f	1 (1)	100	0 (0)	NA

NA, not applicable.

There were 116 bilateral lung transplantations and 5 single lung transplantations (4 right and 1 left single lung transplantations). M1, D1b, D1c, D2c, D3c, and S2f stages are not shown because no patient was concerned by these stages. For M-D-S classification detail, see on the "Method" section.

Table 2. Baseline characteristics according to groups.

	All patients (N= 121)	Without SAC (N=89)	With SAC (N=32)
Donor			
Age, years	46 (31–55)	46 (31–54)	51 (32–60)
Sex, male, N (%)	64 (53)	50 (56)	14 (43)
Mechanical ventilation duration of donor, days	2 (1–3)	2 (2–3)	2 (1–3)
PaO ₂ /FiO ₂ ratio	411 (365–467)	414 (368–467)	403 (357–463)
Bacterial lung infection, N (%)	45 (37)	28 (31)	17 (53)
Recipient			
Age, years	38 (28–50)	34 (21)	46 (37–52)
Male, N (%)	66 (55)	50 (56)	16 (50)
Non-cystic fibrosis, N (%)	60 (50)	35 (39)	25 (72)
BMI, kg/m ²	19.2 (17.6–21.9)	18.7 (17.4–20.7)	21.3 (18.4–24.0)
HLA antibody, N (%)	21 (17)	15 (17)	6 (19)
Fungal colonization, N (%)	67 (55)	59 (66)	8 (25)
<i>Aspergillus</i> , N (%)	65 (54)	58 (65)	7 (21)
Bacterial colonization, N (%)	76 (63)	67 (75)	9 (28)
<i>Pseudomonas aeruginosa</i> , N (%)	65 (54)	58 (65)	7 (22)
<i>Staphylococcus aureus</i> , N (%)	42 (35)	39 (44)	3 (9)
<i>Gram-negative bacillus</i> , N (%)	36 (30)	31 (35)	5 (16)
Graft			
TLC mismatch > 1 l, N (%)	20 (17)	16 (18)	4 (13)
Thymoglobulin induction, N (%)	76 (63)	51 (57)	25 (78)
Cold ischemic time, min (N=87)	539 (428–610)	546 (450–616)	472 (420–539)
Preoperative bypass and intraoperative ECMO, N (%) (N= 104)	76 (63)	53 (68)	23 (88)
PGD all grade, n (%)	23 (19)	14 (16)	9 (28)
Intensive care length of stay, days	25 (17–43)	25 (16–42)	30 (21–52)
Mechanical ventilation, days	3 (1–38)	2 (1–27)	14 (1–45)
Tracheostomy, N (%)	37 (31)	24 (27)	13 (40)
Post-operative ECMO, N (%)	14 (12)	6 (7)	8 (25)
Bacterial lung infection, N (%)	112 (93)	83 (93)	29 (91)

(Continued)

Table 2. (Continued)

	All patients (N=121)	Without SAC (N=89)	With SAC (N=32)
Invasive fungal infection, N (%)	9 (7)	5 (6)	4 (13)
Diabetes, N (%)	79 (65)	65 (73)	14 (43)
Steroids M1, (mg/kg) (N=104)	0.72 [0.63–0.80]	0.73 [0.64–0.81]	0.67 [0.61–0.74]
Steroids M6, (mg/kg) (N=110)	0.40 [0.33–0.50]	0.41 [0.34–0.51]	0.38 [0.31–0.42]
Acute AMR, n (%)	19 (16)	13 (15)	6 (19)
Acute CMR, n (%)	16 (13)	12 (13)	4 (13)
FEV1 at 1 year, theoretic %	73 (60–89)	79 (65–93)	59 (47–68)

AMR, antibody-mediated rejection; BMI, body mass index; CMR, cellular-mediated rejection; ECMO, extra corporal membrane oxygenation; FEV1, forced expiratory volume in 1 s; HLA, human leukocytes antigen; PGD, primary graft dysfunction; SAC, symptomatic anastomotic complication; TLC, total lung capacity. Quantitative data are provided as median [interquartile range].

an interesting risk factor since being the only alterable one. To manage that, *ex vivo* lung perfusion could help physicians to better identify atelectasis *versus* pneumonia in donor when CT-scan is confusing and could save time needed for bacteriological bronchoscopic results. We started to use this procedure in 2018 in our center, that is, after the end of this study. In case of confirmed pneumonia, physicians could decide to stop procedure if pneumonia gets worse during the *ex vivo* lung perfusion. Of note, no study ever reported this risk factor.¹ We can hypothesize that donor lung infection induces local inflammation that alters and delays healing of bronchial mucosa and worsens ischemia. Older recipient age (>50 *versus* <30 years) [HR 3.26 (1.04–10.26), $p=0.04$] and non-cystic fibrosis etiology (Kaplan–Meier survival curves without SAC, $p<0.001$) were two other factors associated with a higher risk of SAC. Despite of numerous comorbidities (nutritional status, bacterial and fungal colonization),¹² cystic fibrosis was not a risk factors of SAC, probably because of the younger age of patients and their better vascularization which probably play a key role in anastomosis healing. Non-cystic fibrosis group includes several etiologies, mostly COPD, emphysema, and pulmonary fibrosis, which have already been identified as an ‘at-risk’ group: they are older with altered vascularization, especially in previous smokers patients.¹¹

In our study, surgical technique was homogeneous, using termino-terminal anastomosis without

Table 3. Risk factors of SAC (multivariate analysis).

Donor bacterial lung infection	2.08 [1.04–4.17]; 0.04
Thymoglobulin induction	2.24 [0.97–5.20]; 0.06
Recipient age (ref < 30 years)	
30–50	2.96 [1.00–8.82]; 0.05
>50	3.26 [1.04–10.26]; 0.04

Hazard ratio is presented as: HR [confidence interval 95%]; p -value.

recovery strategy or bronchial reimplantation, as recommended.¹³ We used non-absorbable material, as opposed to Weder *et al.*,¹⁴ who observed no significant dehiscence in a cohort of 441 anastomosis. Cold ischemic time was not associated with a higher risk of SAC, as previously described.^{1,4,6}

Few studies reported the impact of SAC on survival. Our study found that SAC occurrence was independently (adjusted on BMI, donor and recipient ages) associated with a twofold increased risk of death [HR 2.15 (1.07–4.32)]. In a retrospective analysis of 94 anastomotic complication in 48 patients, Murthy *et al.* reported an equivalent early survival in patients with treated complication compared with patient without anastomotic complication (80 *versus* 82%, $p=0.9$) but worse late survival at 4 years (27 *versus* 60%, $p=0.03$). To the opposite, patients with an untreated complication had a

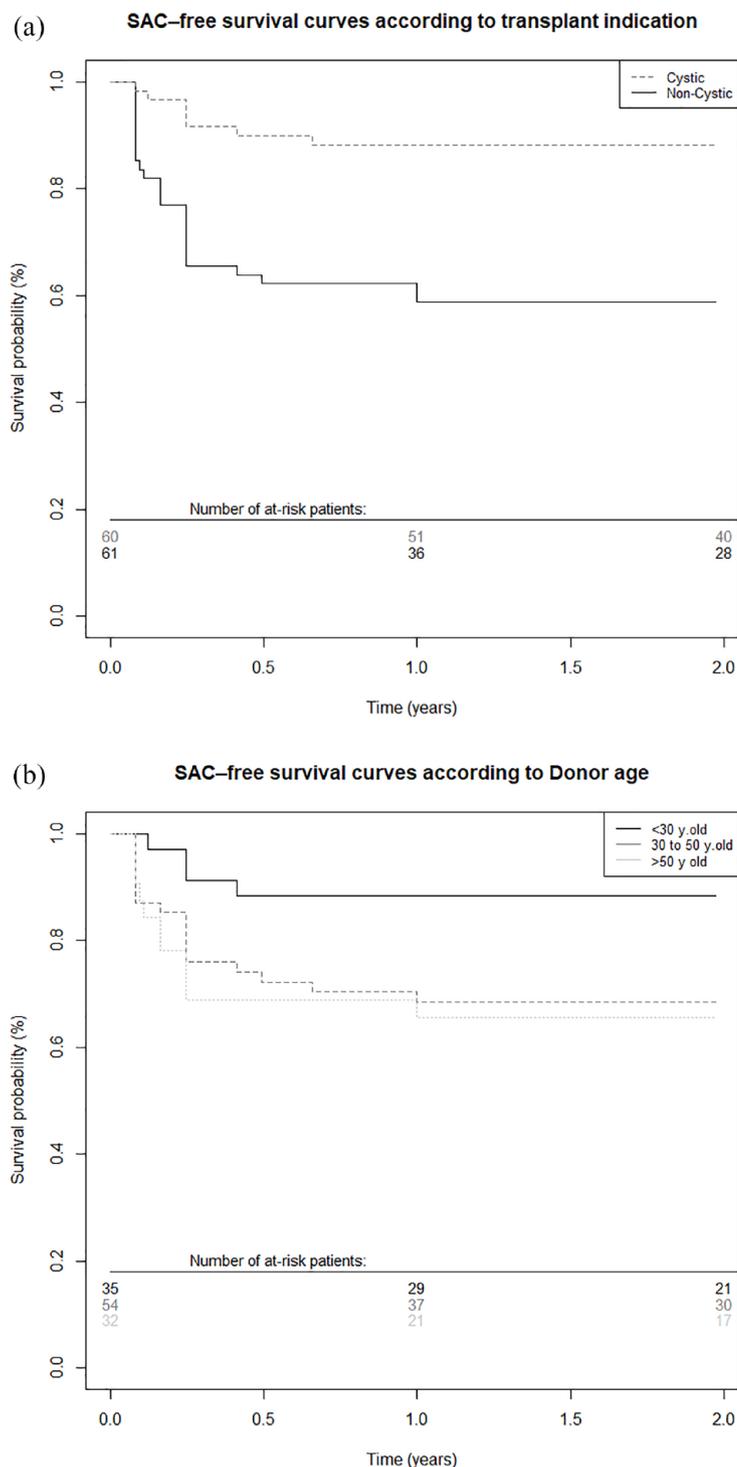


Figure 2. Survival without SAC depending on (a) graft etiology and (b) recipient age.

worse early survival (66.2 versus 82%, $p=0.004$) without difference in late survival.¹⁵ We can

hypothesize dehiscence provided early mortality and stenosis delayed survival impact.

In our study, all SAC were treated, whereas Yserbyt *et al.*⁶ reported that only 25% of their anastomotic complications were actively treated. Among untreated anastomotic complications, they observed only 7% of secondary degradation and 7% of altered functional respiratory test. From our point of view, mechanical complications, such as lung infections, dyspnea because of the reduced bronchial diameter, and atelectasis, justify early intensive treatment to prevent side effects of chronic infections, such as bronchiectasis.

Our study is limited by its retrospective nature, leading to missing data. Another limitation is its reproducibility because of a high proportion of cystic fibrosis patients and the frequent thymoglobulin induction that was used in our center even without prior immunization. For bronchoscopy classification, twofold independent reading was performed, with an examination of non-conformity and new readings for agreement. The International Society for Heart and Lung Transplantation (ISHLT) classification was published during our study.¹ Because our team, as with all French ones, was familiar with the M-D-S classification for years, we refrained from using a new classification that could have induced incorrect a posteriori coding in our inexperienced group. We precisely defined anastomotic complications with M-D-S classification and distinguished the symptomatic ones, which is often missing in most studies. Each parameter was well described and analyzed to give an overview of anastomotic complications.

Conclusion

SAC still occurred in 26.5% ($n=32$) of patients after lung transplantation. We report twofold increased risk of death in patients with SAC. Donor bacterial lung infection, non-cystic fibrosis etiology, and older recipient age were associated with an increased risk of SAC. Based on these findings, careful evaluation of potential donor lung infection and endoscopic monitoring, especially in older recipient, are needed.

Survival presented as Kaplan–Meier curve, $p<0.001$.

Table 4. Multivariate analysis for survival.

SAC	2.15 [1.07–4.32]; 0.03
BMI (ref 18–25 kg/m ²)	
<18	0.93 [0.42–2.08]; 0.87
>25	0.95 [0.34–2.69]; 0.93
Donor age (ref < 30 years)	
30–50	1.44 [0.54–3.94]; 0.47
>50	1.94 [0.77–4.89]; 0.16
Recipient age (ref < 30 years)	
30–50	0.57 [1.25–1.31]; 0.19
>50	1.10 [0.42–2.82]; 0.85
BMI, body mass index. Hazard ratio is presented as: HR [confidence interval 95%]; <i>p</i> -value.	

Declarations

Ethics approval and consent to participate

The study was approved by our local hospital ethic committee (*Groupe Nantais d’Ethique dans le Domaine de la Santé – 12.02.18*) and by the institutional review board (N°2018-20) of the French-speaking respiratory medicine society (*Société de Pneumologie de Langue Française*), according to the French legislation. All living patients received oral and written information about the study and its objectives, and were aware to the possibility to oppose to inclusion.

Consent for publication

All authors accepted the final version.

Author contributions

Agathe Delbove: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

Thomas Senage: Formal analysis; Methodology; Writing – review & editing.

Pierre Gazengel: Conceptualization; Data curation; Investigation; Writing – review & editing.

Adrien Tissot: Writing – review & editing.

Philippe Lacoste: Writing – review & editing.

Laurent Cellerin: Data curation; Writing – review & editing.

Christian Perigaud: Validation; Writing – review & editing.

Isabelle Danner-Boucher: Validation; Writing – review & editing.

Arnaud Cavailles: Validation; Writing – review & editing.

Thierry Lepoivre: Supervision; Validation; Writing – review & editing.

Antoine Mugniot: Validation; Writing – review & editing.

Johanna Nicolet: Validation; Writing – review & editing.

Delphine Horeau-Langlard: Validation; Writing – review & editing.

Nicolas Groleau: Validation; Writing – review & editing.

Yannick Fedun: Validation; Writing – review & editing.

Bertrand Rozec: Validation; Writing – review & editing.

Antoine Magnan: Validation; Writing – review & editing.

Jean-Christian Roussel: Validation; Writing – review & editing.

François-Xavier Blanc: Formal analysis; Methodology; Supervision; Validation; Writing – review & editing.

Acknowledgements

The authors thank Mrs Aurore Foureau (Lung O₂ cluster for research, Nantes) for helping in designing and writing the study protocol and Mrs Alison Mc Lean, Medical Librarian at Vannes hospital, for proofreading the English version.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: B.R. reports grants and personal fees outside the submitted work. Other authors: none.

Availability of data and materials

On request, data and material could be available.

ORCID iD

Agathe Delbove  <https://orcid.org/0000-0003-0170-9508>

Supplemental material

Supplemental material for this article is available online.

References

1. Crespo MM, McCarthy DP, Hopkins PM, *et al.* ISHLT consensus statement on adult and pediatric airway complications after lung transplantation: definitions, grading system, and therapeutics. *J Heart Lung Transplant* 2018; 37: 548–563.
2. Pettersson GB, Karam K, Thuita L, *et al.* Comparative study of bronchial artery revascularization in lung transplantation. *J Thorac Cardiovasc Surg* 2013; 146: 894–900.
3. Dutau H, Vandemoortele T, Laroumagne S, *et al.* A new endoscopic standardized grading system for macroscopic central airway complications following lung transplantation: the MDS classification. *Eur J Cardiothorac Surg* 2014; 45: e33–e38.
4. Awori Hayanga JW, Aboagye JK, Shigemura N, *et al.* Airway complications after lung transplantation: contemporary survival and outcomes. *J Heart Lung Transplant* 2016; 35: 1206–1211.
5. Cho EN, Haam SJ, Kim SY, *et al.* Anastomotic airway complications after lung transplantation. *Yonsei Med J* 2015; 56: 1372–1378.
6. Yserbyt J, Dooms C, Vos R, *et al.* Anastomotic airway complications after lung transplantation: risk factors, treatment modalities and outcome—a single-centre experience. *Eur J Cardiothorac Surg* 2016; 49: e1–e8.
7. Couraud L, Nashef SA, Nicolini P, *et al.* Classification of airway anastomotic healing. *Eur J Cardiothorac Surg* 1992; 6: 496–497.
8. Alvarez A, Algar J, Santos F, *et al.* Airway complications after lung transplantation: a review of 151 anastomoses. *Eur J Cardiothorac Surg* 2001; 19: 381–387.
9. Murthy SC, Gildea TR and Machuzak MS. Anastomotic airway complications after lung transplantation. *Curr Opin Organ Transplant* 2010; 15: 582–587.
10. Nunley DR, Gal AA, Vega JD, *et al.* Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. *Chest* 2002; 122: 1185–1191.
11. Olland A, Reeb J, Puyraveau M, *et al.* Bronchial complications after lung transplantation are associated with primary lung graft dysfunction and surgical technique. *J Heart Lung Transplant* 2017; 36: 157–165.
12. Villanueva G, Marceniuk G, Murphy M, *et al.* Diagnosis and management of cystic fibrosis: summary of NICE guidance. *Br Med J* 2017; j4574.
13. Anile M, Diso D, Rendina EA, *et al.* Airway anastomosis for lung transplantation. *J Thorac Dis* 2016; 8(Suppl. 2): S197–S203.
14. Weder W, Inci I, Korom S, *et al.* Airway complications after lung transplantation: risk factors, prevention and outcome. *Eur J Cardiothorac Surg* 2009; 35: 293–298; discussion 298.
15. Murthy SC, Blackstone EH, Gildea TR, *et al.* Impact of anastomotic airway complications after lung transplantation. *Ann Thorac Surg* 2007; 84: 401–409, 409.e1–409.e4.