Incidence, management and outcome of respiratory syncytial virus infection in adult lung transplant recipients: a 9-year retrospective multicentre study

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ABSTRACT

Objectives. To analyze functional outcome parameters according to antimicrobial treatments after respiratory syncytial virus (RSV)-confirmed infection in adult lung transplant recipients.

Methods. A 9-year retrospective multicenter cohort study (2011-2019) included adult lung transplant recipients with RSV-confirmed infection. The first endpoint determined new allograft dysfunction (acute graft rejection, chronic lung allograft dysfunction [CLAD]) 3 months after infection. Then, baseline and 3-months post-infection forced expiratory volume in 1-second (FEV1) values were compared according to antimicrobial treatments. Univariate logistic regression analysis was used.

Results. RSV infection was confirmed in 77/424 lung transplant recipients (estimated incidence of 0.025 per patient/year, 95% [confidence interval] CI [0.018;0.036]). At 3 months, 22 (28.8%) recipients developed allograft dysfunction: 10 (13%) possible CLAD, 6 (7.9%) acute rejection and 6 (7.9%) CLAD. Recipients with the lowest pre-infection FEV1 had a greater risk of developing pneumonia (1.5 [IQR, 1.1-1.9] *versus* 2.2 [1.5-2.4] L/s; *P*=0.003) and a higher odds of receiving antibiotics (1.6 [IQR, 1.3-2.3] *vs* 2.3 [1.9-2.5] L/s; *P*=0.017; Odd ratio [OR] 0.52 95%CI [0.27;0.99]). In comparison with tracheobronchitis/bronchiolitis, VRS-induced pneumonia led more frequently to hospitalization (22 [91.7%] *vs* 29 [58.0%]; *P*=0.003) and ICU admission (8 [33.3%] *vs* 0 [0%]; $P<10^{-3}$). For ribavirin-treated recipients (n=19, 24.7%) and azithromycin prophylaxis (n=39, 50.6%), 3-month FEV1 values were not different from untreated recipients. The overall mortality was 2.5% at 1 month, 5.3% at 6 months, unrelated to RSV.

Conclusions. At 3 months after RSV-confirmed infection, 22 (28.8%) recipients had new allograft dysfunction. Ribavirin treatment and azithromycin prophylaxis did not prevent FEV1 decline.

INTRODUCTION

Lung transplantation is the only effective treatment for patients with end-stage lung disease associated with a rather poor median recipient survival of 5.8 years [1,2]. Post-transplant lung allograft failure is the major cause of fatal outcome [3]. The range of pathological processes in the allograft that lead to a durable deterioration of lung function beyond three months post-transplant is now termed chronic lung allograft dysfunction (CLAD). This includes a spectrum of manifestations ranging from bronchiolitis obliterans syndrome (BOS) to restrictive allograft syndrome (RAS) defined by a decline in measurable forced expiratory volume in 1-second (FEV1) from the reference baseline value [4]. Annual incidence of BOS is estimated to be 9% and affects more than 50% of lung transplant recipients who survive beyond 5 years [5]. Approximately 75% of recipients who develop BOS die from respiratory failure within five years after diagnosis [5].

Community-acquired respiratory virus infections are associated with the development of CLAD [6-12]. In a recent retrospective cohort of 250 lung transplant recipients, community-acquired respiratory virus infections were independently associated with CLAD (adjusted hazard ratio, HR [95% CI]) 1.9 [1.1–3.5], P=0.03) [6]. Another observational cohort study that prospectively followed 563 recipients with 245 CARV infection episodes found that viral pneumonia independently increased the risk of CLAD (HR 3.94 95%CI [1.97, 7.90], P< 0.01) [7].

Among the genus *Pneumovirus*, respiratory syncytial virus (RSV) is responsible for bronchiolitis in infants but is known to be relatively infrequent after lung transplantation [13,14]. There are discrepancies regarding the outcome of lung transplant graft after RSV infection. Studies have reported insignificant negative impact on FEV1 after RSV-confirmed infection in comparison with baseline FEV1 [15-17]. Nonetheless, severe complications are described such as enhancement of allograft failure and the development of BOS [18,19]. A

study has reported 13 BOS onset or progression, among which five (38%) recipients had RSV infection within 6 months prior to BOS [19]. Case-fatality rate due to RSV infection in the lung transplant setting has been reported to range from 10 to 20% [18,19]. Ribavirin therapy for RSV infection is controversial and its toxicity is a concern. Recent guidelines have recommended oral or aerosolized ribavirin with adjunctive corticosteroids and intravenous immunoglobulins in RSV-infected lung transplant recipients (weak to moderate evidence) [20].

To gain further insights into RSV infection in the lung transplant setting, the outcome of recipients who developed RSV-confirmed infection was investigated with regards to the development of CLAD according to antimicrobial strategies.

PATIENTS AND METHODS

Study design and patient population. A retrospective, multicenter cohort study was conducted among adult (≥ 18 year-old) lung transplant recipients transplanted for end-stage lung disease at three French tertiary-care university hospitals (Paris, Hôpital Marie Lannelongue; Lyon, Centre Hospitalier Lyon-Est; Bordeaux, Hôpital Haut-Levêque) between January 2011 and July 2019. Case recipients eligible for inclusion were those who had RSV positive polymerase chain reaction (PCR) or immunofluorescence assay results from a least one respiratory tract sample [21]. For further details on microbiological diagnosis assessment, refer to supplemental digital content. Sampling for detection of respiratory viral infections was only performed in symptomatic recipients, as no standardized routine screening was active during the study period. When administrated, ribavirin was delivered either by aerosol or oral route. Pre-existing azithromycin prophylaxis was systematically investigated in the form of 250 mg capsule formulation taken three times a week started at least a month before RSV-confirmed infection.

Upper and lower respiratory tract infections were defined according to the International Society for Heart & Lung Transplantation (ISHLT) criteria [21]. RSV-confirmed infections were classified as non- or poorly symptomatic, tracheobronchitis/bronchiolitis, or pneumonia. The following patient characteristics were collected: demographics; underlying pulmonary diseases; comorbidities; pulmonary function testing; respiratory bacterial co-infection(s); immunologic status; clinical and radiologic features; immunosuppressive treatment and dose of corticosteroid therapy; initiation and duration of anti-infectious treatment regimen; outcome. Because of the retrospective observational nature of the study, the need for informed consent was waived by the ethics committee of the Lyon teaching hospitals (*Comité d'Ethique*, *Hospices Civils de Lyon*, approval number 19-117).

Definitions of lung allograft dysfunction. Acute rejection was defined as a biopsy of lung tissue demonstrating injuries as defined by the ISHLT guidelines [22]. BOS was defined as a substantial and persistent decline (≥ 20%) in measurable forced expiratory volume in 1-second (FEV1) from the reference baseline value, associated with airflow obstruction marker. The baseline value was computed as the mean of the best two post-operative FEV1 measurements taken more than 3 weeks apart [4]. The latest pre-infection FEV1 was the last measurement recorded within 3 months prior to RSV infection. Possible CLAD was defined as a 10 to 20% FEV1 decline from baseline (formerly stage BOS 0-p). Definite CLAD was defined as an irreversible ≥ 20% decline in FEV1 at 3 months and beyond compared to the reference baseline value [3,4].

Endpoints. The primary endpoint was to determine new occurrences of lung allograft dysfunction three months after RSV-confirmed infection as well as factors associated with the use of ribavirin and the co-prescription of antibiotics and their influence on FEV1. Secondary endpoints were: the assessment of annual incidence and seasonal distribution RSV-confirmed infection among the lung transplant population; clinical presentations and factors associated

with RSV tracheobronchitis/bronchiolitis or pneumonia; the need for hospitalization or intensive care unit (ICU) admission; and the overall outcome.

Statistical analysis. Descriptive data were used to estimate the frequencies of the study variables, expressed as count (percentage, %) for dichotomous variables and as medians (interquartile range [IQR]) for continuous values. The number of missing values was excluded from the denominator. Non-parametric statistical methods Fisher's exact test, $\chi 2$ test, and Mann-Whitney U test were used to compare groups, where appropriate. Evolution over time of dichotomous and continuous variables was assessed using the McNemar and Wilcoxon matched-pairs signed rank tests, respectively. Determinants of the main study endpoints were determined using a univariate logistic regression, expressed as odds ratios (OR) with 95% confidence intervals (95%CI). The incidence of hospitalization due to RSV-confirmed infection was estimated per patient/year within the temporal window of three full years after transplantation for patients transplanted after 2011. A value of $P < 0.05$ was considered significant. All analyses were performed using SPSS software version 24.0 (SPSS, Chicago, IL).

RESULTS

Epidemiology of RSV-confirmed infection and characteristics of lung transplant recipients with RSV-confirmed infection

From 2011 to 2019, the cohort of lung transplant recipients in the three centers increased from 381 to 805 patients for a total of 424 new procedures. Among them, 77 recipients developed an RSV-confirmed infection requiring 57 (74%) hospitalizations. Monthly distribution of RSV infection cases in lung transplant recipients peaked in January (Figure S1 of supplementary material). The overall incidence of RSV-confirmed infection was estimated at 0.025 per patient/year [95%CI 0.018;0.036] and that of RSV-related hospitalization at 0.020 per patient/year [95%CI 0.013;0.029]. Incidence of RSV-related hospitalization did not

significantly differ between the first (0.025 per patient/year, [95%CI 0.015;0.041]) and second year (0.014 per patient/year, [95%CI 0.007;0.028]) following transplantation. RSV-confirmed infection incidence drastically dropped to 0.002 per patient/year [95%CI 0.001;0.008] in the third year after lung transplantation.

Median age at infection was 45.1 years [IQR, 34-53.9] and the sex ratio M/F was 0.83 (Table 1). Median time from lung transplantation to RSV-confirmed infection was 28.7 months [IQR, 10.3-62.8]. Of note, in addition to their rejection therapy, 39/77 (50.6%) recipients received azithromycin prophylaxis. Although RSV was the only infectious agent identified in a majority of cases (54.5%, n=42/77), this was significantly more frequently the case in tracheobronchitis/bronchiolitis (62.0%, n=31/50) than in pneumonia (37.5%, n=9/24; *P*=0.048). The proportion of recipients hospitalized was significantly higher in the pneumonia subset (22/24 [91.7%] *versus* 29/50 [58.0%]; *P*=0.003), which accounted for all ICU admissions ~~and~~ for mechanical ventilation supports (8/24 [33.3%] *vs* 0/50 [0%]; $P<10^{-3}$) (Table 2). The median follow-up time was 37 months [IQR, 19-65]. The overall mortality was 2.5% (n=2/76) at 30 days and 5.3% (n=4/76) at 6 months post RSV-confirmed infection, and none of these deaths were directly attributable to RSV.

Lung allograft dysfunction after RSV-confirmed infection

Recipients who developed pneumonia had significantly lower FEV1 values compared to recipients who developed RSV tracheobronchitis/bronchiolitis at baseline (1.8 [IQR, 1.4-2.2] L/s *vs* 2.4 [IQR, 1.8-2.6]; *P*=0.021) and at the latest pre-RSV measurements (1.5 [IQR, 1.1-1.9] *vs* 2.2 [1.5-2.4]; *P*=0.003, Table 2). Prior to RSV-confirmed infection, 46/76 (60.5%) acute rejections and 13/77 (16.9%) CLAD were documented. Three months after RSV-confirmed infection, 6/76 (7.9%) new acute rejections and 6/76 (7.9%) CLAD (5 BOS and 1 RAS) were recorded but none of them were among the previously documented CLAD (Table 2). Of note, 10/77 (13.0%) additional recipients qualified for possible CLAD. The association

between RSV-confirmed infection and CLAD was addressed by comparing different values of FEV1 over time. When comparing the FEV1 baseline values (2.3 [IQR, 1.6-2.6] L/s) to the FEV1 values measured 3 months post-RSV infection (2.0 [IQR, 1.5-2.5]), the latter were significantly lower (P< .0001; Figure 1A) corresponding to a median net loss of 7.3% [IQR, -0.9--20.4]. No significant difference was found when comparing the latest pre-RSV infection FEV1 value (2.0 [IQR, 1.4-2.4]) to the FEV1 value measured at 3 months post-RSV infection (-0.6% [IQR, -5.2-+9.1], P=0.56; Figure 1A). In summary, at 3 months after RSV-confirmed infection, 22 (28.5%) recipients had some degree of new lung dysfunction classified as possible CLAD (13%), acute rejection (7.9%, n=6/76), and CLAD (7.9%).

Antimicrobial treatments during RSV-confirmed infection

At 3 months post-infection, the FEV1 values of ribavirin-treated and -untreated recipients were not different (2.2 [1.7-2.4] *vs* 1.9 [1.4-2.5] L/s; P=0.34; Figure 1B). Ribavirin administration did not influence short-term outcomes such as hospital length of stay (9.5 [IQR, 7-10] *vs* 7 [3-14.5] days; P=0.139), and ICU admission for mechanical ventilation requirement (2/19 [10.5%] *vs* 6/58 [10.3%]; P=1.000). Recipients with respiratory bacterial co-infection were significantly less likely to receive ribavirin (4/19 [21.1%] *vs* 31/58 [53.4%]; OR 0.23, 95%CI [0.07;0.78], P=0.019) and more likely to receive antibiotics (31/52 [59.6%] *vs* 4/25 [16.0%]; OR 7.75, 95%CI [2.3;25.8], P=0.001). Recipients having the lowest FEV1 values before RSV-confirmed infection were more likely to receive antibiotics (1.6 [IQR, 1.3-2.3] *vs* 2.3 [1.9-2.5] L/s; OR 0.52, 95%CI [0.27;0.99], P=0.045; Table 3). Three-month FEV1 values were significantly lower in antibiotic treated recipients than in the untreated ones (1.7 [IQR, 1.3-2.4] *vs* 2.2 [1.9-2.8] L/s; P= 0.013; Figure 1B), with no significant difference regarding their loss compare to baseline (-8.6% [IQR, -21.0--2.9] *vs* -4.4% [IQR, -12.8-+0.9]; P=1.000). In recipients receiving azithromycin for BOS prevention, 3-month FEV1 values were not different in azithromycin-treated (2.0 [IQR, 1.4-2.4] L/s) and -untreated (2.0 [1.5-

2.7] L/s) recipients in comparison to baseline (*P*=0.37; Figure 1C). Azithromycin prophylaxis was associated with significantly less bacterial co-infections (n=14/39 [35.9%] *vs* 21/38 [55.3%]; *P*=0.023).

DISCUSSION

In a cohort of 77 lung transplant recipients with RSV-confirmed infection, nearly 30% of recipients developed some degree of new lung allograft dysfunction at 3 months post-RSV infection, including 7.9% of acute rejections and 7.9% of CLAD. Curative ribavirin and preventive azithromycin did not influence functional outcome parameters. It appears that the poorer the functional status at baseline, the greater the risk of developing pneumonia, and the higher the association with antibiotic co-prescription.

The present study confirms the low incidence of RSV infection after lung transplantation (0.025 per patient/year [95%CI 0.018;0.036]) in the era of widely available PCR testing. Interestingly, most cases occurred during the second year or beyond, certainly reflecting higher protection measures applied to and by recipients during the first year after transplantation.

There is concern that community-acquired respiratory virus infections can trigger local alloimmune responses and result in a durable negative impact on lung function [23]. Recent studies suggest that the inflammatory infiltrates noted on biopsy specimens during acute rejection are mostly antiviral response effectors in the process of clearing the infection [17]. Accordingly, studies have suggested the lack of impact of RSV infection on FEV1 after lung transplantation; of note, all recipients received anti-inflammatory corticosteroids and/or immunoglobulins in addition of ribavirin treatment. In our study, nearly half of recipients received steroid therapy at the time of infection and 5/77 recipients received immunoglobulins. Although we observed a decline in 3-month FEV1 compared to baseline, we consider difficult to draw definite conclusion with regards to the raw negative impact of

RSV. Most recipients of our study developed RSV infection rather late (median of 28 months post-transplant) implying that FEV1 might have considerably changed in the interval. Although biased by numerous missing values and temporal heterogeneity, this is suggested by the lack of difference between the latest pre-infection and the 3-month FEV1 values. Thus, we strongly subscribe to the necessity of monitoring FEV1 at least every 6 months [3], or more frequently in case of progressive FEV1 decline. This is of particular importance when considering that recipients with the poorest lung function have higher odds of developing pneumonia, ICU admission and ventilation support.

Prophylactic azithromycin has been demonstrated to significantly reduce the overall prevalence of BOS in a randomized clinical trial [4,24]. In the pediatric setting, two studies, which included a total of 281 participants, compared azithromycin with placebo in children < 2 years diagnosed with RSV bronchiolitis. Both studies found no significant difference for length of hospital stay, duration of oxygen requirement, and readmission [25,26].

Bacterial co-infections is highlighted herein and has been described previously. A nested case-control analysis performed in a lung transplant recipient cohort (n=98) monitored for respiratory virus infections (n=10 RSV infections), showed that *Pseudomonas aeruginosa* was significantly associated with lower respiratory tract infections (HR [95%CI] 8.54 [1.54;47.4], $P< 0.01$) [27]. Another retrospective study that documented 89 RSV-confirmed pneumonia across various adult settings found 27 bacterial super-infections with *Streptococcus pneumonia* (9.3%), *Haemophilus influenza*, *Staphylococcus aureus*, *P. aeruginosa*, and *Moraxella catarrhalis* [28]. The authors concluded that no major epidemiological difference was observed compared to post-influenza pneumonia.

The present study has limitations. Data should be interpreted with caution because of the retrospective nature of the study and the absence of a control group. It is possible that the collected data misestimate true RSV-related morbidity and mortality, particularly among

recipients who did not seek medical attention for minor respiratory symptoms. A quantitative PCR assay follow-up could have been of more value for detecting RSV in respiratory specimens and evaluating the efficacy of antiviral therapy. There were no definite criteria for prescribing ribavirin, initiated at the discretion of physicians, thus resulting in analyzing outcome parameters in a non-controlled manner. Weak consistency in antimicrobial treatment decision-making likely reflects differences among physician management strategies. Treatment duration and outcome criteria were not standardized, which prevented a more precise assessment of treatment efficacy. Finally, to avoid over-interpreting the current data, no multivariable model analysis was performed due to the lack of a RSV-uninfected control cohort comparator, as well as insufficient power.

At 3 months after RSV-confirmed infection, 28.8% of new allograft dysfunction was observed in a retrospective cohort of 77 lung transplant recipients with a proportion of 7.9% acute rejections and 7.9% CLAD. Recipients with the lowest FEV1 at baseline were at higher risk of developing pneumonia and more likely to receive antibiotics. Ribavirin curative treatment and azithromycin prophylaxis did not prevent FEV1 decline after RSV-confirmed infection.

AUTHORSHIP STATEMENTS

HT contributed to study conception and design, acquisition of the data, interpretation of the data, drafted the manuscript and approved the final version; MB contributed to acquisition of the data and approved the final version; FV and JSC carried out the statistical analysis, participated in the revision of the manuscript for important intellectual content, and approved the final version; JSC, AG, MEL provided RSV case list as members of the virology laboratories. They participated in the revision of the manuscript for important intellectual content, and approved the final version; FP, AS, EB, JLP substantially contributed to acquisition of the data, revision of the manuscript for important intellectual content, and

approved the final version; FA is the project initiator, contributed to study conception and design, drafted the manuscript, and approved the final version. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the manuscript. Production of this manuscript did not require writing assistance.

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TABLES

Table 1. Lung transplant recipient characteristics

n=77	
Demographics	
age, years, median [IQR]	45.1 [34-53.9]
male, n (%)	35 (45.5)
Pulmonary and transplant-related characteristics, n (%)	
Underlying pulmonary diseases	
interstitial lung disease	21 (27.3)
pulmonary hypertension	19 (24.7)
COPD/emphysema	16 (20.8)
cystic fibrosis	15 (19.5)
others	6 (7.8)
Type of lung transplantation	
double-lung	53 (68.8)
single-lung	16 (20.8)
cardiothoracic	8 (10.4)
Immunomodulatory therapies within the previous year	
biotherapies (anti-CD20, anti-TNF-α)	3 (3.9)
azithromycin	39 (50.6)
Immunosuppressive drug regimen	
tacrolimus or everolimus and MMF	58 (75.3)
[a]high-dose CST therapy	35 (45.5)
[b]maintenance CST therapy	36 (46.8)
Post-transplant complications, n (%)	
chronic renal failure (GFR < 40 mL/min)	12 (15.6)
any cardiac disease requiring specific treatment	14 (18.2)
diabetes mellitus	10 (13)
Time from transplantation to RSV infection, months, median [IQR]	28.7 [10.3-62.8]
Infection type, n (%)	
tracheobronchitis/bronchiolitis	50 (65)
pneumonia	24 (31.2)
non-symptomatic or poorly symptomatic URTI	3 (3.8)
RSV-related hospitalization	57 (70.1)
length of hospital stay, days	7 (4-13)
ICU admission, n (%)	9 (11.7)
length of ICU stay, days	7 (6.5-12)
mechanical ventilation, n (%)	8 (10.4)
vasoactive drug requirement, n (%)	3 (3.9)
[c]**Neutropenia**	1 (1.4)
[d]**Lymphocytopenia**	27 (38)
Antiviral treatment, n (%)	
[e]ribavirin	19 (24.7)
palivizumab infusion	3 (3.9)
IVIG infusion	2 (2.6)
Overall mortality (6 months), n (%)	4 (5.3)
death within 30 days after RSV infection	2 (2.5)
RSV-related death	0

[a]High dose corticosteroid therapy ≥ 1 mg/kg > 21 days or ≥ 10 mg/day > 3 months.

[b]Maintenance corticosteroid therapy < 10 mg/day.

[c]Neutropenia was defined as polymorphonuclear neutrophils < 0.5 G/L at inclusion. Information available for only 71 recipients.

[d]Lymphocytopenia was defined as absolute lymphocyte count < 1 G/L at inclusion. Information available for only 71 recipients.

[e]Administered for at least 48 hours.

Abbreviations: COPD, chronic obstructive pulmonary disease; CST, corticosteroid; GFR, glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; IS, immunosuppressive; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; URTI, upper respiratory tract infection.

Table 2. Characteristics of recipients according to respiratory syncytial virus-confirmed infection type

	Tracheobronchitis n=50	Pneumonia n=24	*P-value*
Demographics			
age at transplantation, years, median [IQR]	40.8 (30.5-52.7)	47.7 (41.1-56.6)	0.076
CST therapy, n (%)			
[#]high-dose	25 (50)	8 (33.3)	0.17
[§]maintenance	22 (44)	13 (54.2)	0.41
Time since transplantation, months, median [IQR]	24.5 [11.9-55.6]	41.1 [8.6-94.7]	0.48
RSV as only documentation, n (%)	31 (62)	9 (37.5)	**0.048**
Respiratory bacterial co-infection at RSV-confirmed infection, n (%)	21 (42)	13 (54.2)	0.32
Non-fermenting Gram negative bacteria	11 (50)	6 (46.2)	0.82
Respiratory fungal co-infection at RSV-confirmed infection, n (%)	13 (26)	5 (20.8)	0.62
Respiratory viral co-infection at RSV-confirmed infection, n (%)	6 (12)	4 (16.7)	0.72
C-reactive protein at RSV infection, mg/L, n (%)			
< 50	19 (42.2)	11 (47.8)	0.66
50-100	2 (4.4)	5 (21.7)	**0.039**
> 100	4 (8.9)	5 (21.7)	0.25
RSV-related hospitalization	29 (58)	22 (91.7)	**0.003**
ICU admission	0	8 (33.3)	**< 0.0003**
Antiviral therapy, n (%)			
ribavirin	11 (22)	8 (33.3)	0.29
palivizumab or IVIG infusions	2 (4)	4 (16.7)	0.08
Antibiotic treatment during RSV infection	31 (62)	20 (83.3)	0.1
FEV1, L/sec, median [IQR]			
[*]baseline value (2 best values)	2.4 [1.8-2.6]	1.8 [1.4-2.2]	**0.021**
latest pre-RSV infection value	2.2 [1.5-2.4]	1.5 [1.1-1.9]	**0.003**
at RSV infection	1.9 [1.5-2.3]	1.2 [1-1.6]	**0.023**
at 3 months post-RSV infection	2.2 [1.6-2.7]	1.7 [1.3-1.9]	**0.015**
FEV1 loss *vs.* baseline values, % [IQR]	-5.8 [-15-0]	-15.9 [-26.7- -6.4]	0.2
FEV1 loss *vs.* latest value, % [IQR]	0 [-0.1- -0.1]	0 [0- -0.1]	0.95
New or worsening graft dysfunction at 3 months			
acute rejection	5 (10)	1 (4.2)	0.65
CLAD compared to baseline FEV1	5 (10)	1 (14.3)	0.31
CLAD compared to pre-infection FEV1	3 (7.5)	0 (0)	0.5

[#]High dose corticosteroid therapy ≥ 1 mg/kg > 21 days

[§]Maintenance corticosteroid therapy < 10 mg/day

[*]Baseline value is defined by the mean of the best two post-operative FEV1 measurements taken more than three weeks apart.

403 Abbreviations: CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CST,
404 corticosteroid; FEV1, forced expiratory volume in 1-second; ICU, intensive care unit; IQR,
405 interquartile range; IVIG, intravenous immunoglobulins; RSV, respiratory syncytial virus.

406 **Table 3. Comparison of treated and untreated recipients**

n, %	**Ribavirin-treated (n=19)/ untreated (n= 58)**	**OR [95% CI]**	***P-value***	**Antibiotic therapy (n= 52)/ no antibiotic therapy (n=25)**	**OR [95% CI]**	***P-value***
Latest pre-infection FEV1, L/sec, median [IQR]	2.1 [1.7-2.3]/1.9 [1.4-2.5]	1.08 [0.55-2.13]	0.5	1.6 [1.3-2.3]/2.3 [1.9-2.5]	0.52 [0.27-0.99]	**0.045**
RSV as only documentation	14 (73.7)/28 (48.3)	3 [0.95-9.4]	**0.06**	23 (44.2)/19 (76)	0.25 [0.08-0.73]	**0.011**
Respiratory bacterial co-infection at RSV-confirmed infection	4 (21.1)/31 (53.4)	0.23 [0.07-0.78]	**0.019**	31 (59.6)/4 (16)	7.75 [2.3-25.8]	**0.001**
Ribavirin treatment	/	/	/	9 (17.3)/10 (40)	0.31 [0.11-0.92]	**0.035**
Antibiotic treatment upon RSV-confirmed infection	9 (47.4)/43 (74.1)	0.31 [0.1-0.82]	**0.035**	/	/	/
Type of RSV-confirmed infection						
Tracheobronchitis/bronchiolitis	11 (57.9)/39 (67.2)	0.67 [0.23-1.9]	0.46	31 (59.6)/19 (76)	0.46 [0.16-1.36]	0.16
Pneumonia	8 (42.1)/16 (27.6)	1.9 [0.65-5.6]	0.24	20 (38.5)/4 (16)	3.28 [0.98-10.9]	0.054

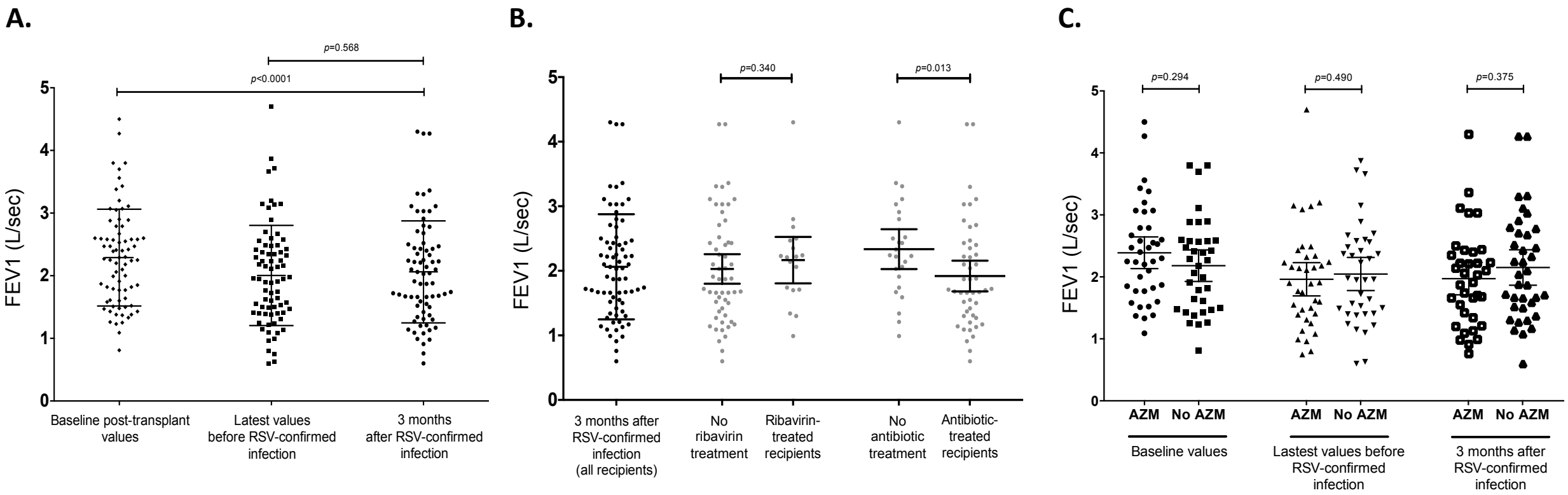
407

408 Abbreviations: FEV1, forced expiratory volume in 1-second; IQR, interquartile range; RSV, respiratory syncytial virus.

FIGURES LEGENDS

Figure 1. Panel A: values of forced expiratory volume in 1-second before and 3 months after respiratory syncytial virus-confirmed infection. Panel B: values of forced expiratory volume in 1-second before and 3 months after respiratory syncytial virus-confirmed infection according to ribavirin or antibiotic treatment. Panel C: changes over time of forced expiratory volume in 1-second values according to long-term azithromycin prophylaxis.

Abbreviations: AZM, azithromycin; FEV1, forced expiratory volume in 1-second; RSV, respiratory syncytial virus.


A.
p=0.568
p<0.0001
FEV1 (L/sec)
0
1
2
3
4
5
Baseline post-transplant values
Latest values before RSV-confirmed infection
3 months after RSV-confirmed infection
B.
p=0.340
p=0.013
FEV1 (L/sec)
3 months after RSV-confirmed infection (all recipients)
No ribavirin treatment
Ribavirin-treated recipients
No antibiotic treatment
Antibiotic-treated recipients
C.
p=0.294
p=0.490
p=0.375
FEV1 (L/sec)
AZM
No AZM
Baseline values
Lastest values before RSV-confirmed infection
3 months after RSV-confirmed infection