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Rhinovirus and Other Respiratory Viruses Exert Different Effects on Lung Allograft Function That Are Not Mediated Through Acute Rejection

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Abstract

Background—Community acquired respiratory virus (CARV) infections in lung transplant recipients (LTR) have been associated with adverse outcomes, including acute rejection (AR) and decline in allograft function, in some but not all studies.

Methods—Spirometry and transbronchial biopsy results of LTR diagnosed with CARV infection over a 2-year period were extracted from clinical records. Primary outcomes, studied at 1-2.5 months post-infection, were: (1) incidence of biopsy-proven AR (grade>A0) and (2) allograft function, defined by forced expiratory volume in 1 second (FEV_1). A reference group of biopsies (n=526) collected during the study period established the baseline incidence of AR. Rhinovirus (RV) and non-rhinovirus (non-RV) infections were analyzed as subgroups.

Results—87 cases of CARV infection were identified in 59 subjects. Incidences of AR were similar in the post-CARV and reference groups, and did not differ significantly after RV vs non-RV infection. Allograft function declined significantly after non-RV infection, but not after RV infection.

Conclusions—In LTR, CARV infections other than RV are associated with allograft dysfunction at 1-2.5 months after infection. However, CARVs do not appear associated with AR at this time point. The impact of specific CARVs on lung allografts, including the development of chronic allograft rejection, merits further study.

Keywords

Lung transplantation; graft rejection; adenoviridae infections; influenza; paramyxoviridae infections; picornaviridae infections

Introduction

Community acquired respiratory virus (CARV) infections are increasingly appreciated as a potential cause of significant morbidity and mortality in lung transplant (LTx) recipients.[1]

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CARV infections have been associated with both acute lung allograft rejection (AR),[2] and chronic rejection (also known as bronchiolitis obliterans syndrome [BOS]).[1-4] CARV infections are postulated to create an inflammatory environment in the lung allograft that promotes allorecognition and an exaggerated injury response.[5-8]

Studies examining short and long term outcomes after CARV infection in LTx recipients have been mixed. Some,[2,3] but not all[1,9-11] have established an association between CARV infections and risk of subsequent AR. Further, CARV infection has been associated with the development of BOS; however estimates of BOS incidence after CARV infection vary widely, ranging from 5% to greater than 60%.[12]

Notably, different CARVs may exert different effects on allograft function. Respiratory syncytial virus (RSV), for example, has been associated with devastating declines in lung allograft function in some, though not all, case series.[13,14] In contrast, studies of rhinovirus infection in LTx recipients suggest that asymptomatic lower respiratory tract infection is not uncommon,[15] although chronic rhinovirus infection may be associated with chronic allograft dysfunction.[16,17] Differences in study design, definitions of outcomes (AR and/or BOS), and analytic approaches, however, limit our ability to draw more robust conclusions regarding the impact of CARV infections on allograft function.[12]

In response to the published literature, as well as anecdotal experience at our center, we developed a surveillance protocol for AR and allograft dysfunction early after CARV infection. In this study, we sought to determine whether CARV infections are associated with AR and allograft dysfunction shortly (1-2 months) after infection by employing a strict definition of AR and data from our structured post-CARV allograft surveillance protocol.

Patients and Methods

Study Population

All single-, bilateral-, and heart-lung transplant recipients diagnosed with a new CARV infection at the University of California, San Francisco (UCSF) between June 1st 2009 (the date of implementation of the post-CARV surveillance protocol) and May 31st 2011 were analyzed. Patients who underwent re-transplantation were excluded from the time of re-transplant onward. CARV infections were identified by searching an electronic clinical database for positive CARV assays. Demographic, clinical, spirometric and treatment data were collected from medical records.

Allograft Surveillance

Routine lung allograft surveillance at our center includes spirometry, high-resolution computed tomography of the chest (HRCT), and bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies performed on post-transplant day 14, and months 1, 2, 3, 6 12, 18, and 24. Annual surveillance HRCT and spirometry are continued thereafter. Spirometry, HRCT, and bronchoscopy are additionally performed when clinically indicated.

Diagnosis of CARV Infection

LTx recipients exhibiting symptoms of respiratory infection are evaluated for CARV infection by testing nasal swab specimen, expectorated sputum or BAL fluid. Bronchoscopy is performed at the discretion of the treating transplant pulmonologist. Specimens are first tested by the direct fluorescence antigen (DFA) method for the following viruses: influenza A and B, parainfluenza virus (PIV) 1-3, adenovirus and respiratory syncytial virus (RSV). A negative DFA test triggers testing of the specimen by a polymerase chain reaction (PCR) assay (Respiratory Viral Panel, Viracor, Lee's Summit, MO) that detects the following

viruses: RSV A, RSV B, influenza A, influenza A subtype H1, influenza A subtype H3, influenza B, PIV 1-3, human metapneumovirus (hMPV), rhinovirus, and adenovirus. The collection date of the CARV-positive specimen is designated as the date of CARV infection.

In addition to testing patients with clinically-suspected CARV infection, all BAL specimens, including those obtained during surveillance bronchoscopy, are screened for CARVs by the method described above.

Post-CARV Surveillance

The post-CARV surveillance protocol is implemented when a new CARV infection is diagnosed. New CARV infection is defined as a positive DFA or PCR, as described above. Some patients have multiple positive PCR assays for the same virus over a period of greater than 30 days without an intercurrent negative assay. These cases are considered prolonged viral shedding rather than new infections, a phenomenon that has been previously described.[2,17] The post-CARV surveillance protocol is only implemented once after the initial diagnosis of CARV infection, not for subsequent positive assays.

Spirometry, HRCT, and bronchoscopy with transbronchial biopsies are performed by protocol 1-2 months after the diagnosis of CARV infection. If no abnormalities are identified, patients return to the routine surveillance schedule described. While this post-CARV infection surveillance protocol serves as a guideline for all cases of CARV infection in LTx recipients, treating transplant pulmonologists are permitted to deviate from the protocol as clinically appropriate. A graphical representation of this surveillance protocol is shown in Figure 1.

Because of studies suggesting a benefit in reducing the potential risk of acute rejection or BOS following CARV infection,[18] we routinely treat LTx recipients with the following regimen of augmented corticosteroids when a CARV infection is diagnosed: oral prednisone at 60mg daily for 3 days, followed by a 2-week taper back to the patient's baseline prednisone dose. For some LTx recipients manifesting severe allograft dysfunction or concurrent allograft rejection at the time of CARV infection, larger doses of corticosteroids are administered. LTx recipients diagnosed with influenza are treated with appropriate anti-influenza agents; those diagnosed with RSV infection are treated according to a clinical protocol that includes aerosolized ribavirin (6 grams inhaled daily for 5-7days), high-dose intravenous methylprednisolone (250mg daily for 3 days), and intravenous immunoglobulin (500mg/kg every other day for 4 doses).

Outcome Measures

We studied two primary outcomes after CARV infection: the incidence of AR, and the change in allograft function. AR was defined by the presence of peri-vascular lymphocytic infiltrates in a transbronchial biopsy specimen obtained during post-CARV surveillance bronchoscopy, corresponding to any ISHLT score of >A0.[19] Change in allograft function was defined as the difference in forced expiratory volume in 1 second (FEV_1) from baseline to the FEV_1 obtained for post-CARV surveillance.

Secondary outcomes included (1) the incidence of AR grade ≥A2;[19] (2) the incidence of lymphocytic bronchiolitis (LB) in post-CARV surveillance protocol biopsies (defined as the presence of a monocytic peri-bronchiolar infiltrate, corresponding to any ISHLT score of >B0);[19] and (3) the proportion of patients in whom FEV_1 declined by ≥20% following CARV infection.

A single expert pulmonary pathologist evaluated all biopsy specimens. Baseline FEV_1 was defined as the most recent FEV_1 value obtained at least 30 days prior to the diagnosis of CARV infection.

For this study, we extended the surveillance period specified in our clinical post-CARV surveillance protocol up to 2.5 months after infection. This was done in order to include a small number of cases that completed post-CARV surveillance with a small (2 week) delay from the institutional protocol.

Because prior literature suggested virus-specific effects on lung allografts, outcomes were assessed both among all cases of CARV infection, and in two *a priori* subgroups: rhinovirus (RV) and non-rhinovirus (non-RV) infections. Simultaneous infections with RV and another CARV were included in the non-RV group. No additional *a priori* or *post-hoc* analyses were performed.

To establish a baseline incidence of AR and LB in our overall lung transplant population, we identified a reference group. This group consisted of all transbronchial biopsies obtained during the study period, excluding those collected for post-CARV surveillance. 526 biopsies were included in this reference group, which we defined as “non-CARV” biopsies.

Analytic Approach

Changes in FEV_1 were analyzed by paired *t* test. Proportions were compared by Fisher's exact test or chi-square test, as appropriate. 95% confidence intervals for proportions were calculated by the modified Wald method. Numbers of biopsies performed in each group were compared by the Mann-Whitney test. p-values <0.05 were considered significant. Since acute rejection occurs most frequently in the first year following transplant, we performed a secondary analysis of acute rejection (grade >A0) in post-CARV infection and reference transbronchial biopsies stratified at one-year post-lung transplant. Analyses were performed using Prism 5 software (GraphPad Software, La Jolla, CA).

Results

Over 2 years, 59 lung transplant recipients were diagnosed with at least 1 new CARV infection. Subjects were 39% female, had a mean age of 53±13 years, and 97% had received bilateral lung allografts (Table 1). 87 new CARV infections were diagnosed in this cohort (Table 2). 72 (83%) infections were diagnosed by BAL, 13 (15%) by nasal swab, and 2 (2%) by expectorated sputum. The high rate of diagnosis by BAL reflects our low threshold to perform diagnostic bronchoscopy in LTx recipients with respiratory symptoms. 23 subjects (39%) were diagnosed with 2 or more distinct CARV infections during the study period. The time from transplant to CARV infection varied widely, although most subjects were >1 year post-transplant at the time of infection (median 581 days, interquartile range: 184-1242). During the two-year study period, the post-CARV group trended towards undergoing more bronchoscopies that included transbronchial biopsies (median 4, interquartile range: 2-6) for any indication than the reference group (n=96 subjects) (median: 3, interquartile range: 2-5) (p=0.07).

RV was the most frequently detected CARV, accounting for 55 of the 87 infections (63%) (Table 2). In 64 cases (74%), the corticosteroid dose was augmented at the time CARV infection was diagnosed. 3 subjects died during the post-CARV surveillance period; none of the deaths were attributable to either CARV infection or complications of the surveillance protocol.

Histopathologic Outcomes

Of the 87 cases of CARV infection, 45 were followed up with transbronchial biopsies, obtained during the specified surveillance period, that yielded adequate tissue for the pathologic scoring of AR. Biopsies were inadequate in 2 cases, and were deferred at the discretion of the treating pulmonologist in 37 cases. 3 patients died before undergoing biopsy. 15 of the biopsies were obtained during the first year after transplant, while 30 were obtained after the first year.

The incidence of acute rejection (AR) was similar in the post-CARV and reference groups. The incidence of AR (>A0) in the post-CARV group was 8.9% (95% confidence interval [CI]: 3.0-21.3%, [Table 3]). This was similar to the incidence in the non-CARV reference group (13.1%; 95%CI: 10.5-16.3%; p=0.64). Further, the incidence of AR grade ≥A2 was 4.4% (95%CI: 0.4-15.7%) in the post-CARV group, and was similar to the incidence in the reference group (4.9%; 95%CI: 3.4-7.2%; p=1.0). No cases of A4 rejection were diagnosed in either group. The incidence of LB was 15.6% (95%CI 7.4-29.1%) in the post-CARV group and 11.0% (95%CI: 8.6-14.0%) in the reference group (p=0.3) (Table 3). All cases of LB in the post-CARV group were grade B1R.

In subgroup analyses, point estimates for the incidence of >A0 AR, ≥A2 AR, and LB were all higher in the non-RV group compared to the RV group, although none achieved statistical significance (Table 3).

4 cases of acute rejection were identified following CARV infection (Table 4). In 3 of these cases, CARV infection was diagnosed >1 year after transplant. Also, 3 of 4 patients had been treated with augmented corticosteroids at the time infection was diagnosed. The untreated case was ultimately diagnosed with grade A1 acute rejection.

The incidence of AR obtained during the first year after transplant in the reference group (13.2%; 95%CI 10.0-17.3%; biopsy n=333) was similar to that obtained after the first year (13.0%; 95%CI 8.9-18.5%; biopsy n= 193) (p=1.0). Results were similar for the incidence of AR grade ≥A2 (≤1 year: 5.7%; 95%CI 3.6-8.8%; >1 year 3.6%; 95%CI 1.6-7.4%) (p=0.4).

Spirometric Outcomes

Complete spirometric data were available for 62 cases (71%). Reasons for missing data included CARV infection too proximal to lung transplantation to have a pre-infection baseline spirometry (n=7), death before post-infection spirometry (n=3) and failure to obtain spirometry after CARV infection within the defined surveillance period (n=15).

Overall, CARV infection was associated with a trend towards poorer allograft function (baseline FEV_1 2.34±0.70L vs 2.19±0.79L after CARV infection; p=0.07) (Table 5). Significantly poorer allograft function was observed in the non-RV group after CARV infection (baseline FEV_1 2.28±0.75L vs 2.08±0.74L after CARV infection; p=0.047). This effect was not seen in the RV group (baseline FEV_1 2.38±0.68L vs 2.27±0.83L after CARV infection; p=0.38).

In 9 cases (14%), FEV_1 decreased by >20% from baseline (Table 5). In 5 of these cases, the decline in FEV_1 followed a rhinovirus infection, and in 4 followed other infections (RSV, adenovirus, and co-infection of RV with either influenza A or hMPV). No AR was observed in the 5 cases that had adequate biopsy tissue for AR scoring.

Discussion

In this study, we found that among lung transplant (LTx) recipients, community acquired respiratory virus (CARV) infections, other than rhinovirus (RV) infections, are associated with allograft dysfunction as assessed by spirometry. Further, it appears that our cohort of LTx recipients, who were predominantly treated with augmented corticosteroids at the time of CARV infection, was not at higher risk for acute rejection (AR) following such infections. The incidence of acute rejection after CARV infection was low at 9%, equivalent to the incidence seen in a reference group of LTx recipients not infected with CARV. Further, the incidence of grade ≥A2 AR (a threshold many institutions, including ours, use to augment immunosuppression) was low following CARV-infection and similar to the incidence in the reference group. Taken together, these findings suggest that non-RV CARV infections can lead to poorer allograft function through a mechanism other than inciting AR. Our findings support a previous study that identified an association between CARV infection and the subsequent development of BOS, independent of AR.[1]

Our study builds upon a small but growing literature examining the effects of CARV infections on lung allograft function. Multiple studies have shown that LTx recipients may experience a decline in FEV_1 shortly after CARV infections.[3,5,8-10,13,20,21] Our study expands upon these findings by identifying different effects of RV compared to other CARVs on FEV_1. This finding is of particular relevance because RV is a commonly identified viral pathogen in this population.[2,3,10]

To date, studies of the impact of CARV infection on the subsequent development of AR are mixed.[1-3,9-11] A recent meta-analysis did not find an association between respiratory viral infections and AR, although the number of studies analyzed was small (n=4).[12] Different definitions of AR employed by researchers may be one potential explanation for the inconsistent findings. For example, a recent study identified an association between CARV infection and AR.[2] This study, however, utilized a composite definition of AR that included either histopathologic or spirometric changes. Another recent study that defined AR based solely on histopathology did not demonstrate such an association.[10] Our study, employing a strict definition of AR based on histopathology, suggests that the risk of AR following CARV infection is low. Further, because allograft dysfunction assessed by spirometry following CARV infection does not appear to be mediated through AR, composite definitions of AR may overestimate its true incidence following CARV infection.

We found a lower incidence of AR after CARV infection than previously reported.[1-3,10] Several explanations are possible. First, there may be no actual association between CARV infection and AR. Second, augmentation of corticosteroids in our subjects at the time of CARV infection diagnosis may have prevented subsequent AR. Lastly, while biopsies in our study were all interpreted by a single expert pulmonary pathologist, high inter-observer variability in the diagnosis of AR could lead to different results between centers.[22]

Our study has several strengths. A major strength is that our study population was managed according to a clinical protocol that included routine surveillance for AR and allograft dysfunction following CARV infection. Also, we defined AR strictly based on consensus ISHLT histopathologic guidelines. As discussed above, by separately analyzing AR and allograft function, we were able to distinguish between impacts on these two outcomes. Lastly, by defining *a priori* subgroups of viral infections, we demonstrated differential effects of different CARVs on allograft function. These strengths allow our study to help clarify areas where prior studies reached contradictory results.

Our study also faces limitations. First, deviations from the surveillance protocol by treating pulmonologists who deferred transbronchial biopsies occurred in 43% of cases. The most

frequent reason for forgoing biopsy was a low suspicion for AR. Since clinically significant rejection frequently manifests with symptoms and/or radiographic and spirometric abnormalities,[23-26] we suspect that our results are biased towards overestimating the true incidence of AR after CARV infection. Second, our study assessed short-term outcomes. Longer-term impacts of RV and non-RV CARV infection may differ from the short-term, and we cannot draw conclusions about BOS, which is an important long-term outcome. Third, while our medical records did not reliably distinguish symptomatic from asymptomatic CARV infection, outcomes may differ by symptomatology. Asymptomatic carriage of CARVs is rare in the general population,[27,28] but the effect of immunosuppression on the development of CARV infection symptoms is unknown. Therefore, extrapolating from the general population to LTx recipients may not be valid. Indeed, the available evidence in LTx recipients suggests that asymptomatic viral carriage may be more common with some viruses, particularly RV, than with others,[2,15,29] which may help to explain the difference in allograft function between the RV and non-RV subgroups in our study. Fourth, within the non-RV CARV group, different viruses may exert different effects on lung allografts. Our modest sample size makes further comment on this possibility purely speculative. Fifth, we cannot exclude the possibility that patients were treated for CARV infection outside of our center and, therefore not identified in our review. This possibility is unlikely, however, since patients and referring providers receive extensive education to immediately contact our transplant center with respiratory concerns and, in particular, respiratory viral syndromes. Additionally, any modifications to immunosuppression are managed directly by our transplant pulmonologists for the life of our transplant recipients.

In conclusion, infections with community acquired respiratory viruses other than rhinovirus are associated with early allograft dysfunction in lung transplant recipients. Notably, this dysfunction does not appear to be mediated through an increased incidence of acute rejection. In total, our findings suggest a direction for future study may be to examine the impact of specific respiratory viruses on allograft function via pathways distinct from acute rejection.

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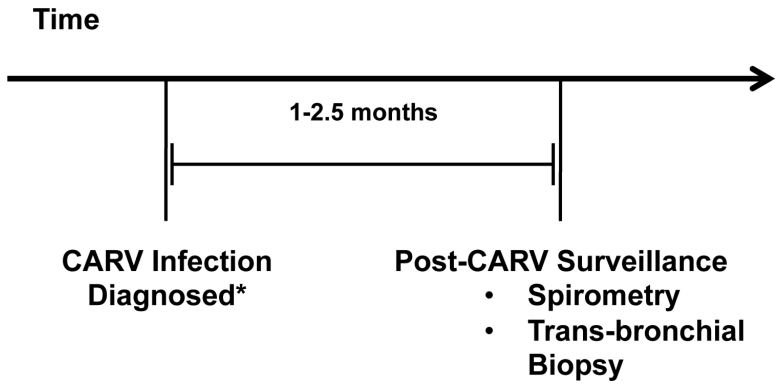

Figure 1.

Post-community-acquired respiratory virus (CARV) infection surveillance protocol for lung transplant recipients. *Diagnosis of CARV infection was defined as identification of a CARV in a respiratory specimen (nasal swab, expectorated sputum, or bronchoalveolar lavage fluid) by either DFA or PCR methods, irrespective of patient symptoms. Post-CARV surveillance consisted of spirometry and trans-bronchial biopsy, performed per protocol during a surveillance window that extended from 1-2.5 months after diagnosis of CARV infection.

Table 1

Demographic information of lung transplant recipients diagnosed with community acquired respiratory virus (CARV) infections.

Total	**59**
Male	36 (61)
Age at Time of CARV Infection, Years	53 ±13
Type of Transplant	
Single	2 (3)
Bilateral	54 (92)
Heart/Lung	3 (5)
Indication for Transplantation*	
IPF	20 (34)
COPD	10 (17)
CF	6 (10)
HP	6 (10)
PAH	5 (8)
Other[a]	12 (20)

Data presented as mean ±SD or n(%)

*IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; PAH, pulmonary arterial hypertension; HP, hypersensitivity pneumonitis.

[a]Other (each $n \leq 2$): idiopathic bronchiolitis, acute interstitial pneumonitis, alpha-1 antitrypsin deficiency, pulmonary alveolar proteinosis, Eisenmenger syndrome, bronchoalveolar carcinoma, and pulmonary fibrosis related to scleroderma, rheumatoid arthritis, or polymyositis.

Table 2

Characteristics of community acquired respiratory virus (CARV) infection cases.

Virus	
All	87 (100)
Rhinovirus	55 (63.2)
Parainfluenza	9 (10.3)
Influenza A	7 (8.0)
Metapneumovirus	4 (4.6)
Respiratory syncytial virus	6 (6.9)
Adenovirus	2 (2.3)
Rhinovirus + Metapneumovirus	3 (3.4)
Rhinovirus + Influenza	1 (1.1)
Infections per Patient	
Mean	1.5 ±0.7
Range	1 - 4
Time From Transplant to Infection, Days	
Mean	872 ±911
Median (25^{th}, 75^{th} percentiles)	581 (182, 1244)
Range	2 - 5239
Steroid Treatment For CARV Infection	64 (74)

Data presented as mean ±SD, or *n* (%)

Table 3

Acute rejection and lymphocytic bronchiolitis after community acquired respiratory virus (CARV) infection.

Pathologic Grading*	Post-CARV Infection (*n*=45)	Non-CARV Reference Group (*n*=526)	p value	RV Subgroup (*n*=28)	Non-RV Subgroup (*n*=17)	p value
A1-A4	4 (8.9)	69 (13.1)	0.64	2 (7.1)	2 (11.8)	0.62
≥ A2	2 (4.4)	26 (4.9)	1.0	0 (0)	2 (11.8)	0.14
LB**	7 (15.6)	58 (11.0)	0.33	3 (10.7)	4 (23.5)	0.40

Data presented as *n*(%)

RV = rhinovirus. “Non-RV” subgroup includes co-infections with rhinovirus and another CARV. “Non-CARV Reference Group” includes all biopsies taken from lung transplant recipients during the study period excluding those taken for post-CARV surveillance.

*Grading of transbronchial biopsies according to ISHLT criteria.[19]

**LB= lymphocytic bronchiolitis

Table 4

Characteristics of 4 cases of acute rejection after community acquired respiratory virus (CARV) infection.

Case	Sex	Age at Virus Dx	Virus Detected	Days Post-Transplant at Virus Dx	Steroids*	Days Btwn Viral Dx and Biopsy	Path. Score	Days Btwn Viral Dx and Spirometry	% Change in FEV_1
1	F	31	Influenza A	2046	Yes	28	A2 B1R	57	-12.9%
2	F	60	RSV	681	Yes	33	A2 B1R	73	-12.5%
3	M	54	Rhinovirus	585	Yes	43	A1 B1R	38	-14.4%
4	F	65	Rhinovirus	96	No	34	A1 B0	33	+11.0%

* Indicates whether the corticosteroid dose was increased after CARV infection. % Change in FEV1 is the change in FEV1 between baseline and post- CARV infection values.

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Table 5

Change in spirometrically assessed allograft function before and after community acquired respiratory virus (CARV) infection.

	Baseline FEV_1	Post-Infection FEV_1	%Change in FEV_1 (Baseline vs. Post)	p value (Baseline vs. Post)	> 20% FEV_1 Decline
All CARVs (*n*=62)	2.34 ±0.70	2.19 ±0.79	-6.4%	0.07	9 (14.1)
RV Subgroup (*n*=36)	2.38 ±0.68	2.27 ±0.83	-4.6%	0.37	5 (13.9)
Non-RV Subgroup (*n*=26)	2.28 ±0.75	2.08 ±0.74	-8.8%	0.047	4 (15.4)

Data presented as mean ±SD, or *n*(%).

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