Survival After Lung Transplant for Cystic Fibrosis in Italy: A Single Center Experience With 20 Years of Follow-up

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ABSTRACT

Objectives. Lung transplantation is currently the only treatment for end-stage respiratory failure in patients with cystic fibrosis (CF). In this study we retrospectively analyzed our experience since the start of the transplantation program in 1996 with focus on survival analysis.

Methods. All patients with CF who underwent lung transplant at our center were included (1996–2016). Survival analysis after lung transplant was performed using the Kaplan-Meier estimate, comparing by sex and by 4 eras (1996–2000, 2001–2005, 2006–2010, and 2011–2016).

Results. In a 20-year period, 243 patients with CF were listed for lung transplant; 123 patients (61 male, 62 female) underwent transplant, and 85 died while waiting for donor organs. The mean (SD) and median age at transplant was 27.7 (8.7) years and 26.9 years (range, 9.1 – 52.1 years), respectively. Mean (SD) forced expiratory volume in the first second was 27.6 (9.7)% predicted; 115 patients (92.0%) were pancreatic insufficient, and 43 patients (34.0%) had CF-related diabetes. Removing patients with CF who died within the first 3 postoperative months, the mean (SD) and median survival after transplant were 8.2 (5.7) years and 7.5 years (range, 3 months-20 years), respectively. Overall post–lung transplant 1-year survival was 93.6%, 5-year survival was 71.4%, 10-year survival was 53.6%, 15-year survival was 36.7%, and 20-year survival was 31.6%. We found no difference in survival between sex ($P = .22$) and among the 4 eras ($P = .56$).

Conclusions. Survival after lung transplant in our single center is similar to international data.

CYSTIC fibrosis (CF) is the most common life-threatening inherited disease among the white population. CF usually involves the lungs, the pancreas, and the liver [1]. The respiratory manifestations are characterized by progressive development of bronchiectasis and chronic airway infection with both gram-positive and gram-negative, often multiresistant organisms [1]. Despite new medical therapies that have delayed the progression of lung disease with consequent improvement of life expectancy, lung transplant is currently the only treatment for end-stage respiratory failure in patients with CF [2]. In Italy, a country with 60 million inhabitants, CF is a rare disease with 5000 patients in the whole population, and a calculated birth incidence of 1 of 4000 with wide variation among regions [3].

According to recent International Society for Heart and Lung Transplantation Registry data, CF represents the third most common indication for lung transplant, and

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encouraging post-transplant outcome has been reported worldwide [4–6]. In Italy, a national program for bilateral sequential lung transplant in patients with CF started in 1996, and the regional center in Rome was the pilot center. Although previous Italian results were published several years ago, to date, recent surveys from national CF registry reports are lacking. To our knowledge, an Italian overview of experience of bilateral sequential lung transplantation over a 20-year period has not been published [7–9].

In this study, we analyzed retrospectively our experience since the beginning, focusing on survival analysis.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort study assessing patients who received transplants at our institution from 1996–2016 with follow-up through December 2016. We reviewed the CF transplant local database and all patient charts. We assessed all recipients with CF, including adult and pediatric cases, undergoing lung transplant. For further comparison, the time period of this analysis was divided into 4 discrete eras to enable the assessment of changes in survival over time. Era 1 was defined as January 1, 1996, to December 31, 2000. Era 2 was defined as January 1, 2001, to December 31, 2005. Era 3 was defined as January 1, 2006, to December 31, 2010, and era 4 was defined as January 1, 2011, to December 31, 2016.

Selection Criteria

Patients with CF with a history of increasing frequency of hospitalization, forced expiratory volume in the first second <30% predicted, declining exercise tolerance, oxygen therapy, and difficulty in maintaining weight were assessed for transplant. Inclusion and exclusion criteria for lung transplant were in line with the international guidelines over time [10,11]. Recipients and donors were matched according to the ABO-system, measured and calculated total lung capacity, and height.

Immunosuppression

Our immunosuppressive protocol included prednisone, cyclosporine (CSA) or tacrolimus (FK506), or sirolimus and azathioprine, adjusted according to renal function, leucocytes, and platelet count. During these 20 years of follow-up, CSA was started at the end of lung transplant and otherwise 24 hours after transplant as a continuous infusion at the dose of 2 mg/kg/d. As soon as the patient was able to tolerate enteral feeding, CSA was converted orally twice daily (10 mg/kg/d). Patients who did not tolerate CSA or had chronic rejection received FK506 at the starting dose of 0.2 mg/kg/d. For patients who had chronic renal insufficiency, CSA and FK506 were replaced with sirolimus at the dose to maintain a blood level of 10 to 20 ng/mL.

To stabilize plasma levels, CSA and FK506 were given in combination with erythromycin twice daily at doses ranging from 400 mg to 600 mg. Azathioprine was started before entrance in the operating room and continued after surgery at the dose of 2 mg/kg/d.

Methylprednisolone was administered perioperatively and for the first 3 postoperative days at the dose of 125 mg intravenously 3 times a day and subsequently tapered to prednisone 0.5mg/kg/d (maximum dose 25 mg/d).

Antibiotics

Patients were treated according to the resistance pattern of the microorganisms colonizing the patient before transplant and to donor bronchoalveolar lavage cultures at the time of organ harvesting. All patients were treated for *Pseudomonas aeruginosa* infection prior to transplant. Antimicrobial therapy was carried on for at least 14 days and adjusted according to microbial findings in bronchoalveolar lavage fluid. Permanent prophylaxis after transplant against *Pneumocystis jirovecii* infection included sulfamethoxazole-trimethoprim. For the postoperative cytomegalovirus prophylaxis, we used ganciclovir (10 mg/kg/d) for 3 weeks followed by oral treatment for 3 months. Fungal infections were treated on a case by case basis without prophylaxis.

Ethical Considerations

The study was conducted in accordance with the Helsinki declaration. All patients gave consent prior to surgery to have their data collected in CF and transplant registries for care management and research purposes.

Statistical Analysis

A descriptive analysis of CF transplant population was first carried out using simple descriptive statistics (mean, median, proportions). Post-transplant survival was measured from the date of the first lung transplant to date of death or the last recorded visit on December 31, 2016. The probably of surviving 1, 5, 10, 15, and 20 years post transplant was calculated using the Kaplan-Meier method. Comparison by era was tested using the log-rank test. Results were considered statistically significant when the 2-sided P value was <.05. Statistical analyses were performed using the Stata Statistical Software: Release 12 (StataCorp LP, College Station, Tex, United States).

RESULTS

From 1996 to December 31, 2016, a total of 243 patients with CF were accepted for transplant in our CF center. We performed bilateral sequential lung transplant in 123 patients (61 men and 62 women); the mean (SD) and median age at transplant were 27.7 (8.7) years and 26.9 years (range, 9.1–52.1 years), respectively (Table 1). A total of 85 patients with CF (median age, 23.8 years; range, 10–40 years) died on the waiting list. Mean (SD) and median time on the waiting list among recipients was 12.7 (11.7) months and 8.6 months (range, 0–51.5 months), respectively. Most candidates were in fair nutritional status with mean body mass index of 18.34 kg/m^2 (range, 12.64–27.14 kg/m^2). Ninety-two percent of the recipients had pancreatic insufficiency with weak evidence of difference between men and women ($P = .05$); 34% had CF-related diabetes. Pretransplant mean forced expiratory volume in the first second was 27.7% predicted (range, 6.0%-64.0%). All patients were in oxygen therapy. Six recipients were colonized with *Burkholderia cepacia* complex.

Among 77 deaths after transplant (41 women, 53.2% of all deaths) identified in the hospital database between 1996 and 2016, the mean (SD) and median age at death was 31.0 (10.2) years and 30.4 years (range, 10.4–64.8 years), respectively. The death occurred at the same age in women

Table 1. Demographic Characteristics and Pulmonary Function of Cystic Fibrosis Patients Before Lung Transplant

Characteristics	All (n = 123)	Men (n = 61)	Women (n = 62)
Age, mean (SD), y	27.7 (8.7)	27.4 (8.6)	27.9 (8.9)
BMI	18.3 (3.0)	18.6 (3.1)	18.1 (2.8)
Pseudomonas aeruginosa infection, %	86.5	87.5	85.6
Staphylococcus aureus infection, %	62.0	62.5	61.5
Burkholderia cepacia complex infection, %	4.8	4.8	4.7
Pancreatic insufficiency, No. (%)	115 (92.0)	60 (97.0)*	55 (87.0)
Diabetes CF-related, No. (%)	43 (34)	20 (32.0)	23 (36.0)
Lung function			
FEV_1, mean (SD), L	0.85 (0.3)	0.88 (0.4)	0.81 (0.2)
FEV_1, mean (SD), % of predicted	27.7 (9.8)	26.4 (9.5)	29.0 (9.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV_1, forced expiratory volume in 1 second.
*$P < .05$, differences between CF men and CF women.

(mean [SD], 30.9 [10.8] years) vs men (mean [SD], 31.1 [9.6] years; $P = .9$). Causes of death after lung transplant are presented in Fig 1. During the first 3 months after transplant, death was mostly related to technical (surgical and airway) complications; chronic lung allograft dysfunction (CLAD) and infections were the most frequent causes of death occurring after the first year.

When we divided the whole period into 4 eras, we observed that the number of transplants performed decreased over time. Specifically, 42 patients with CF received lung transplants in the first quinquennium, 21 in the second one, 27 in the third one, and 33 in the last one ($P < .001$; Fig 2A). We observed that in the last quinquennium, 12 patients with CF had urgent transplant operations. The overall median waiting time increased over time with 3.9 months in the first era, 15.6 months in the second era, 12.5 in the third era, and 17.4 months in the fourth era ($P < .001$; Fig 2B). There was no significant difference for lung function and nutritional status recorded at the time of transplant among the 4 eras ($P = .72$ and $P = .56$, respectively). We observed that the mean age at surgery was significantly different among the 4 eras ($P < .001$), increasing from 25.2 years in the first era to 33.1 years in the last one.

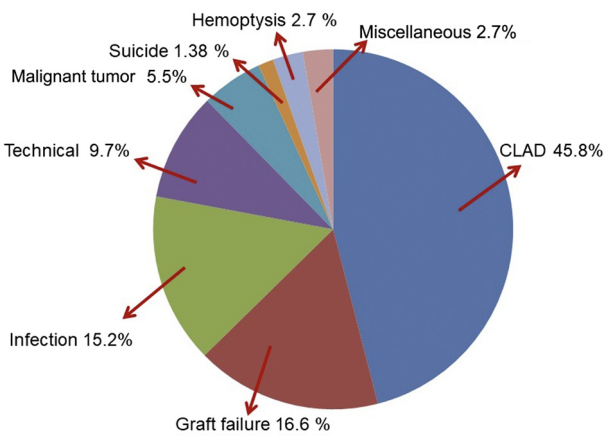

Fig 1. Specific causes of death in cystic fibrosis patients who died after receiving lung transplant. CLAD, chronic lung allograft dysfunction.

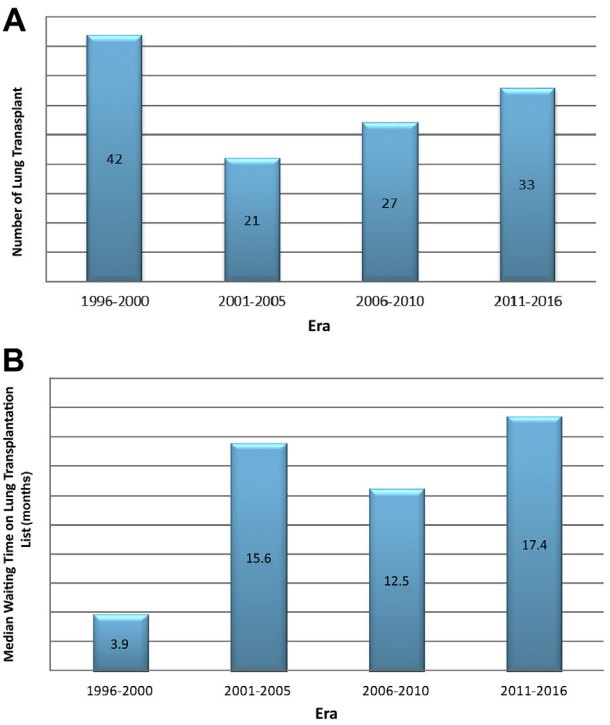

Fig 2. **(A)** Number of lung transplants performed in our center after having divided the whole period of 20-year follow-up into 4 eras, $P < .001$. **(B)** Overall mean waiting time on transplantation list of cystic fibrosis population after having divided the whole period of 20-year follow-up into 4 eras, $P < .001$.

We assessed the impact of preoperative infection with certain multiresistant bacteria considered as a relative contraindication for lung transplant. There were 6 patients with CF with *B. cepacia* complex infection. The patient with *Burkholderia pyrrocinia* (*B. cepacia* Genomovar IX) infection has previously been reported [12]. In the *B. cepacia* complex group there were 3 deaths. Two patients died of *B. cepacia* sepsis after 4 days and after 6 months, respectively; 1 patient died after 3 months from primary graft failure and infectious complications. Two patients were 15 years and 14 years post transplant.

Removing patients with CF who died within the first 3 postoperative months from the analysis, overall post–lung transplant 1-year survival was 93.6%, 5-year survival was 71.4%, 10-year survival was 53.6%, 15-year survival was 36.7%, and 20-year survival was 31.6%. The mean (SD) and median survival after transplant were 8.2 (5.7) years and 7.5 years (range, 3 months-20 years), respectively (Fig 3A).

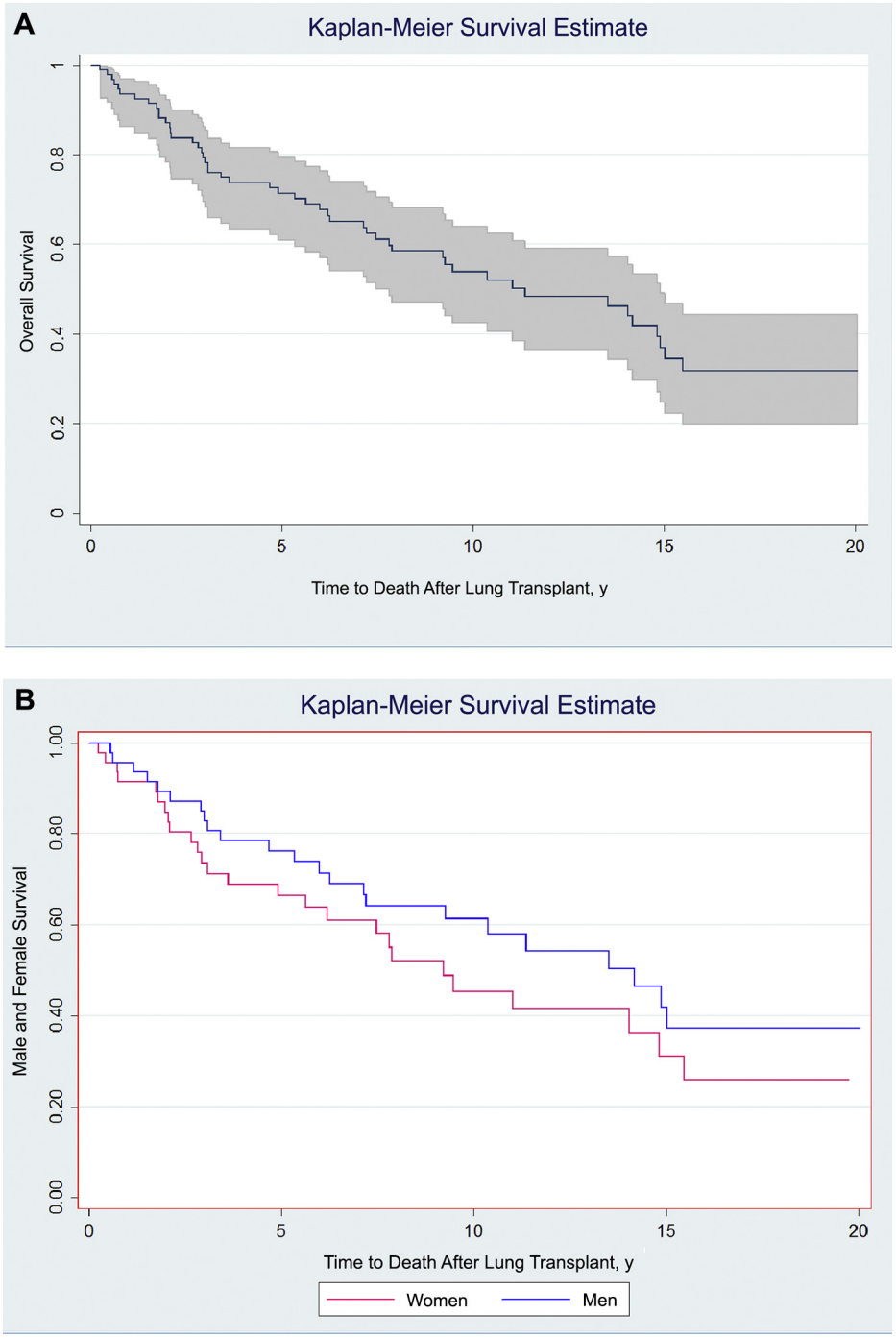

Fig 3. Survival after lung transplant in patients with cystic fibrosis (CF) after removed patients who died within the first 3 postoperative months. **(A)** Overall survival; **(B)** Male and female survival, $P = .22$. Blue line CF men, pink line CF women.

We did not find sex difference in survival ($P = .22$; Fig 3B). In addition, we found no difference in survival among the 4 eras ($P = .56$; Fig 4).

DISCUSSION

This is the first Italian 20-year follow-up report describing an overall picture of survival and outcomes of a single-center experience with lung transplant for CF. Survival after lung transplant in our center is good and comparable with international data.

Lung transplant is a well-established life-extending treatment for patients with end-stage CF. The median age of survival in patients with CF who receive transplants has steadily increased over the last 2 decades [13]. Globally the 10-year CF liver transplant survival from 1990–2013 was

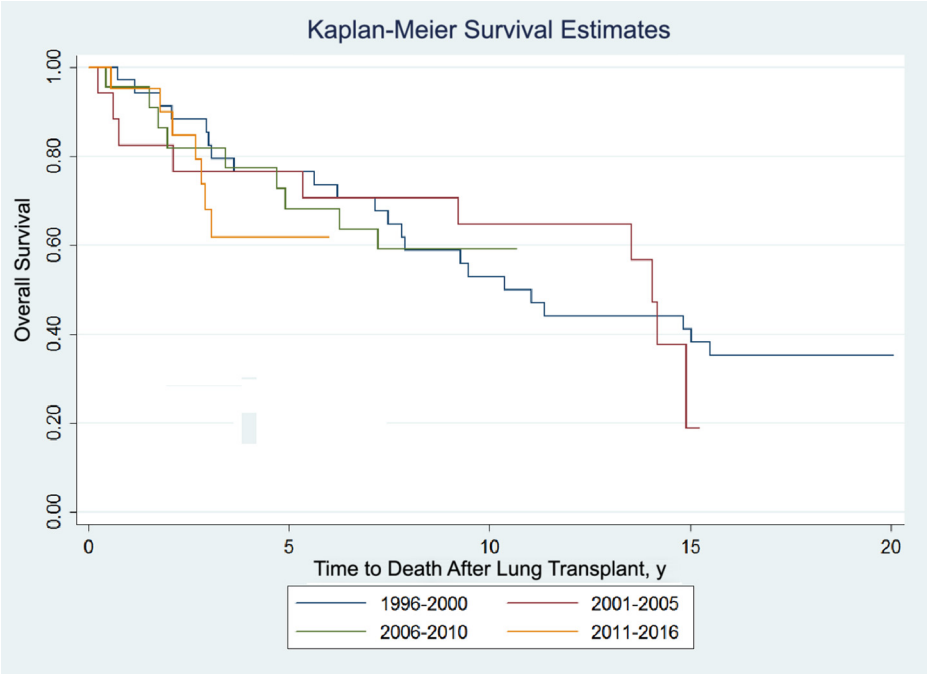

Fig 4. Overall post–lung transplant 5-year, 10-year, 15-year, and 20-year survival of the cystic fibrosis population from 1996–2016.

45.0%, with higher survival of 50.0% reported in the Canadian CF registry and 62.4% reported in Sweden [5,13,14]. Our study shows a 10-year survival of 53.6% perfectly in line with these highest reports. Also, no differences were found for overall post-transplant 1-year and 5-year survival between our center and European and American centers. Specifically, survival in our Italian center increased in the same manner as in these CF centers. One-year and 5-year survival was 88.0% and 72.0% in Switzerland, 86.4% and 73.7% in Sweden, 87.8% and 66.7% in Canada, and 93.6% and 71.4% in our single CF center, respectively [5,6,13]. Moreover, based on contemporary data from the last 20 years, transplant recipients who underwent bilateral lung transplant had median survival of 7.1 years [15]. The median age of survival in our Italian single center reflects the international reports, even if it is slightly lower compared with some European CF reports [5]. However, the interesting data highlighted in this report is that we observed an Italian trend for survival over the past 20 years similar to global published reports for the first time [15].

When we focused the outcomes in the different time periods, we observed that the number of transplants decreased over time, and the median waiting time in our center significantly increased from the first era to the last era (3.9 vs 17.4 months). In this preliminary report, we can only provide some potential reasons. In Italy, lungs are allocated within a donor service area managed by 1 of 3 organ procurement regional organizations. Each organization allocates organs to its transplantation centers following a rotation scheme. The transplantation centers allocate lungs to their nonurgent listed patients based on clinical assessment. In addition, the Italian allocation system includes a national emergency program that collects, in a single national list, patients who require extracorporeal support. Priority for lung allocation was given to those with the longest time on the emergency transplant wait list. Over the past 10 years, the number of Italian transplantation centers has risen compared with 1996 when the regional center in Rome was the pilot center. As a result of population trends and scarcity of available donors, our lung transplant waiting list was steadily growing. Recently, the Italian Cystic Fibrosis Registry reports that during 2011–2014, 135 patients (median age, 32.5 years) received a double lung transplant, and national median waiting time was 11 months [3]. The median waiting time in our single center during the mentioned period was 17.4 months, significantly higher compared with the published Italian data. Given the inherent unpredictability of actual organ allocation for any specific patient, patients with CF were exposed to the risk of urgent transplant surgery, especially in the last quinquennium, requiring extracorporeal membrane oxygenation while waiting for lung transplant and developing pulmonary hypertension [16]. We recognize that further analysis is needed to identify the multifactorial mechanisms that might have contributed both to increase the waiting times and to reduce the numbers of CF transplants at our center. Armed with this data, we suggest that the complete centralization of the lung procurement, the implementation of a single national waiting list for nonurgent patients, and the introduction of the Lung Allocation Score (LAS) are items that should be discussed in Italy shortly. International data reported that a paradigm shift in lung allocation occurred when an LAS was approved [17]. Since the implementation of the LAS, substantial declines

in the duration of time on the wait list and improved wait list mortality have been observed [18,19].

In this study we report that the mean age at lung transplant was 25.2 years in the first era, with a progressive significant increase in the last era reaching 33.1 years. This result is in line with the international data reporting a median age at lung transplant of about 30 years [12–15]. Despite CF survival steadily increasing over the last 2 decades [2], lung transplant for progressive respiratory failure is still the only available therapy at a relative young age. However, the expected median age at transplant seems to increase over time with prospects of further improvement because of research in areas such as gene therapy, targeted correctors, and modifiers of CF transmembrane conductance regulator channel function [20–22].

The available data reporting the 20-year evolution in the pattern of mortality in our CF lung transplants showed that, in general, CLAD remains the single biggest issue, followed by infection and technical problems. We are in line with the literature, reporting CLAD as a very common problem, which causes approximately 50% of all deaths in the first 10 years [15]. Differences in infectious complications as cause of mortality were found between our data and the last French report (15.2% vs. 28.3%, respectively) [23]. Further analysis of our data will be able to give an overview of postoperative bacterial, mycotic and viral infections including *Pneumocystis jirovecii* and cytomegalovirus. In our clinical practice erythromycin was included in the immunosuppressive treatment, stabilizing CSA or FK506 plasma levels using lower drug quantity. If this regimen was or was not one of the reasons for lower infections observed in our center, this is a step for further analysis. In preliminary analysis, we decided to group together the few patients who harbored *B. cepacia* (Genomovar-III) in the survival analysis. The data should be interpreted with caution, but we consider the results encouraging enough to continue considering these patients to be discussed by the liver transplant multidisciplinary team. We highlight the importance that patients and families should be carefully informed of the increased risk of post-transplant complications. The *B. cepacia* group did not receive induction therapy with antithymocyte globulin, and 30% of them are alive more than 10 years after transplant.

We recognize that the present study has some limitations. We did not include any correlation with the donation process and characteristics. Second, this study did not analyze surgery procedures or perioperative complications. Finally, we did not investigate if there was a change in the overall lung transplant volume in our center or if there is a change in the proportion of recipients with other diagnoses.

In conclusion, survival after lung transplant in our center is good and comparable with international data. We believe that in the future, in our country, an increased donor pool, a revision of the organ allocation system, and timely listing might be able to improve our results. Our statistical analysis will continue with the focus to highlight pretransplant clinical factors associated with post-transplant survival and to quantify the risk of specific factors associated with death after transplant (ie, age, nutritional status, and sex). Armed with these data, clinicians can formulate new strategies to increase the existing experience of transplant with CF.

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