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Factors associated with pulmonary infection in kidney and kidney-pancreas transplant recipients: a case-control study

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ABSTRACT

Objective: To evaluate the etiology of and factors associated with pulmonary infection in kidney and kidney-pancreas transplant recipients. Methods: This was a single-center case-control study conducted between December of 2017 and March of 2020 at a referral center for kidney transplantation in the city of Belo Horizonte, Brazil. The case:control ratio was 1:1.8. Cases included kidney or kidney-pancreas transplant recipients hospitalized with pulmonary infection. Controls included kidney or kidney-pancreas transplant recipients without pulmonary infection and matched to cases for sex, age group, and donor type (living or deceased). Results: A total of 197 patients were included in the study. Of those, 70 were cases and 127 were controls. The mean age was 55 years (for cases) and 53 years (for controls), with a predominance of males. Corticosteroid use, bronchiectasis, and being overweight were associated with pulmonary infection risk in the multivariate logistic regression model. The most common etiologic agent of infection was cytomegalovirus (in 14.3% of the cases), followed by Mycobacterium tuberculosis (in 10%), Histoplasma capsulatum (in 7.1%), and Pseudomonas aeruginosa (in 7.1%). Conclusions: Corticosteroid use, bronchiectasis, and being overweight appear to be risk factors for pulmonary infection in kidney/kidney-pancreas transplant recipients, endemic mycoses being prevalent in this population. Appropriate planning and follow-up play an important role in identifying kidney and kidney-pancreas transplant recipients at risk of pulmonary infection.

Keywords: Kidney transplantation; Immunosuppression therapy; Pneumonia.

INTRODUCTION

Over the past few years there has been an increase in the development of public health policies for solid organ transplantation in Brazil, especially kidney and kidney-pancreas transplantation. The Brazilian National Transplant System acts by coordinating and regulating the transplantation program in the country.⁽¹⁾ In patients with stage 5 chronic kidney disease, kidney transplantation improves quality of life and reduces mortality when compared with renal replacement therapy.^(2,3) However, health complications, particularly respiratory complications, are common because of continuous immunosuppression (triple therapy with steroids, calcineurin inhibitors, and antiproliferative agents in most cases) to avoid immune rejection. Patients undergoing deceased-donor kidney transplantation have a higher risk of developing pulmonary infectious complications in the post-transplant period.^(4,5)

Brazil has distinct characteristics regarding the prevalence of infections in kidney transplant recipients. This is possibly due to environmental exposure and the population profile, which is different from the population profiles in North America and Europe. Studies conducted in Brazil and investigating invasive fungal diseases have shown an increased prevalence of cryptococcosis and histoplasmosis in the country. There is currently a lack of data regarding pulmonary infectious complications in kidney transplant recipients in Brazil; the epidemiological features of pulmonary infectious complications in this population; and the relationship between infectious events and the intrinsic characteristics of this population.(4-7)

The objective of the present study was to evaluate the etiology of and factors associated with pulmonary infection in patients undergoing kidney or kidneypancreas transplantation at a referral center for kidney transplantation in the state of Minas Gerais, Brazil.

METHODS

This was a single-center case-control study conducted between December of 2017 and March of 2020 at Hospital Felício Rocho, a general hospital that is a referral center for kidney transplantation in the city of Belo Horizonte, Brazil. The hospital specializes in minimally invasive and highly complex procedures such as robotic, neurological, cardiac, and transplant surgeries, and provides care to patients in the public and private health care systems.

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Cases and controls were matched for sex, age group (18-24 years, 25-34 years, 35-44 years, 45-54 years, and 55-64 years), and donor type (living or deceased). The case:control ratio was 1:1.8. Cases included kidney or kidney-pancreas transplant recipients ≥ 18 years of age hospitalized with suspected pulmonary parenchymal infection, characterized by one or more of the following: fever (body temperature > 38.0°C) or hypothermia (body temperature of $< 36.0^{\circ}$ C), acute cough, purulent sputum, chest discomfort, or dyspnea in association with pulmonary opacities of infectious etiology on chest HRCT scans or identification of infectious agents by serological methods; direct identification of infectious agents in pulmonary or lung biopsy specimens (transbronchial biopsy or surgical lung biopsy specimens); or identification of infectious agents by indirect methods, such as assays for cell-surface or cell-wall antigens and molecular biology tests. All cases were considered incident cases (i.e., new cases). Controls included kidney or kidney-pancreas transplant recipients without respiratory symptoms or pulmonary opacities of infectious etiology, having undergone transplantation within three months after the cases and being recruited in an outpatient follow-up setting.

For cases and controls, the exclusion criteria were withdrawal of participation in the study and incomplete medical records. Because of the population profile, the study sample was a convenience sample, with no sample size calculation being performed.

The following patient data were collected: age; sex; occupation; transplant type; place of residence; donor type (living or deceased); transplant date; BMI; pre-transplant dialysis duration; post-transplant antimicrobial prophylaxis; previous pulmonary infections; pre-transplant tuberculin skin test results; diagnosis of diabetes mellitus; smoking status; diagnosis of lung disease prior to transplantation; etiology of kidney disease; cardiovascular disease; current or previous neoplastic disease; recurrent urinary tract infections; immunosuppressive regimen (calcineurin inhibitors, mammalian target of rapamycin inhibitors, antiproliferative agents, and corticosteroids); cytomegalovirus infection status (in case patients); pulse therapy with methylprednisolone and/or use of antilymphocyte antibodies in the post-transplant period; and prior diagnosis of humoral or cellular rejection. In addition to the aforementioned patient data, the following chest HRCT findings were collected: ground-glass opacities, consolidation, pleural effusion, nodules/micronodules, and cavitation.

BAL and transbronchial biopsy were performed by fiberoptic bronchoscopy. BAL fluid and transbronchial biopsy samples underwent the following: Gram staining; total and differential cell counts; cytometry; bacterial culture; antimicrobial susceptibility testing; microscopy for *Pneumocystis jirovecii*; and sputum smear microscopy for AFB, fungi, and parasites. Cultures for mycobacteria and fungi were also performed, as were detection of galactomannan in BAL fluid and PCR for cytomegalovirus. All transbronchial biopsy samples underwent pathological examination for identification of etiologic agents.

Surgical lung biopsy by video-assisted thoracoscopy under general anesthesia was considered in cases in which the etiologic agent could not be identified. All decisions regarding the diagnostic workup and treatment of the patients included in the present study were made by the team of attending physicians.

Ethical aspects

All of the study participants gave written informed consent. The study project was approved by the Research Ethics Committees of the *Hospital Felício Rocho* Health Sciences Center and the Federal University of Minas Gerais (CAAE no. 88306218.5.0000.5125). All patients were treated in accordance with current guidelines for the management of infectious diseases.

Statistical analysis

Data were presented as absolute and relative frequencies, and as mean ± standard deviation or median (interquartile range) for quantitative variables, which were tested for normality by means of the Kolmogorov-Smirnov test. Variables with a non-normal distribution were compared by means of the Mann-Whitney test, and variables with normal distribution were compared by means of the Student's t-test. In order to compare independent categorical variables and to assess associations between qualitative variables, the nonparametric chi-square test was used. Fisher's exact test was used for variables with a value of less than five. All of the variables showing p < 0.20 in the univariate analysis were included in the stepwise multivariate logistic regression model. For all tests, the level of significance was set at a two-sided value of $p \leq 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 197 patients were included in the present study. Of those, 70 were included as cases and 127 were included as controls. Table 1 shows the main characteristics of the study population.

Cases and controls were similar in terms of the proportions of respiratory comorbidities, cardiovascular comorbidities, neoplasms, and recurrent urinary tract infections. The BMI was significantly lower in cases than in controls (p = 0.013). As can be seen in Table 1, bronchiectasis was the only comorbidity that was significantly more prevalent in cases than in controls (12.9% vs. 2.4%; OR = 6.1; 95% CI, 1.6-23.2; p = 0.003). With regard to the use of immunosuppressants, there were no significant differences between cases and controls, the exception being corticosteroid use, which was significantly more common in cases than in controls (95.7% vs. 83.7%; OR = 4.4; 95% CI, 1.3-15.4; p = 0.012). As can be seen in Table 2, there was no significant difference between the two groups



of patients regarding the use of other drugs for organ rejection prevention.

The variables age, BMI, smoking, calcineurin inhibitors, corticosteroids, methylprednisolone, use of antilymphocyte antibodies, and bronchiectasis were included in the multivariate logistic regression model (Table 3). In the final model, the variables BMI, use of corticosteroids, and bronchiectasis had a joint effect with the outcome of respiratory infection. An overweight individual was found to be 2.21 times more likely to have a respiratory infection than an individual with a normal BMI. An individual who used corticosteroids was found to be 4.22 times more likely to have a respiratory infection than an individual who did not. An individual with bronchiectasis was found to be 7.01 times more likely to have a respiratory infection than an individual without it.

As can be seen in Table 4, the most common etiologic agent of infection was cytomegalovirus (in 14.3% of the cases), followed by *Mycobacterium tuberculosis* (in 10%), *Histoplasma capsulatum* (in 7.1%), and *Pseudomonas aeruginosa* (in 7.1%). The etiologic

agent remained unidentified in one third of the cases. As can be seen in Table 5, the most common chest HRCT findings were ground-glass opacities (in 50% of the cases), followed by consolidation (in 48.6%) and nodules (in 45.7%).

DISCUSSION

This was a single-center case-control study including 70 cases and 127 controls and conducted between December of 2017 and March of 2020. Cases and controls were matched for demographic variables related to the post-transplant period. All comparisons were homogeneous and included age and mean dialysis duration in the pre-transplant period. With regard to general characteristics, males predominated in both groups, a finding that is consistent with those of a meta-analysis conducted in Brazil and investigating patients with stage 5 chronic kidney disease.⁽⁸⁾ When the etiology cannot be determined by accurate methods, diagnosis is commonly delayed.^(9,10)

The variables age, BMI, smoking, calcineurin inhibitors, corticosteroids, methylprednisolone, use

| Table 1. General characteristics of cases and controls | s, as well as comorbidities found in both groups.ª |
|--|--|
|--|--|

| Variable | Group | | | OR | 95% CI | р |
|--|--------------|--------------|-------------|------|-----------|---------|
| | Case | Control | Total | | | |
| | (n = 70) | (n = 127) | (N = 197) | | | |
| Age, years | 55 (44-63) | 53 (43-59) | | | | 0.139* |
| Pre-transplant dialysis duration, months | 60 (19.5-84) | 44.5 (32-72) | | | | 0.846* |
| Sex | | | | | | |
| Female | 28 (40%) | 46 (36.2%) | 74 (37.6%) | | | 0.600** |
| Male | 42 (60%) | 81 (63.8%) | 123 (62.4%) | | | |
| BMI | | | | | | |
| Underweight | 10 (14.3%) | 5 (3.9%) | 15 (7.6%) | 0.52 | 0.27-0.98 | 0.013** |
| Normal | 40 (57.1%) | 62 (48.8%) | 102 (51.8%) | | | |
| Overweight | 14 (20%) | 41 (32.3%) | 55 (27.9%) | | | |
| Obese | 6 (8.6%) | 19 (15%) | 25 (12.7%) | | | |
| Transplant type | | | | | | |
| Kidney | 63 | 113 | 176 | | | |
| Kidney-pancreas | 7 | 14 | 21 | | | |
| Donor type | | | | | | |
| Deceased | 56 (80%) | 107 (84.3%) | 163 (82.7%) | | | 0.575** |
| Living | 14 (20%) | 20 (15.8%) | 34 (17.3%) | | | |
| Smoking | 21 (30%) | 24 (18.9%) | 45 (22.8%) | | | 0.076** |
| Comorbidities | | | | | | |
| COPD | 2 (2.9%) | 1 (0.8%) | 3 (1.5%) | | | 0.256** |
| Bronchiectasis | 9 (12.9%) | 3 (2.4%) | 12 (6.1%) | 6.1 | 1.6-23.2 | 0.003** |
| Pulmonary arterial hypertension | 2 (2.9%) | 3 (2.4%) | 5 (2.5%) | | | 1.000** |
| Asthma | 3 (4.3%) | 4 (3.1%) | 7 (3.6%) | | | 0.701** |
| Diabetes mellitus | 25 (35.7%) | 55 (43.3%) | 80 (40.6%) | | | 0.299* |
| Hypertension | 55 (78.6%) | 106 (83.5%) | 161 (81.7%) | | | 0.395* |
| Coronary artery disease | 7 (10%) | 12 (9.4%) | 19 (9.6%) | | | 0.900* |
| Heart failure | 11 (15.7%) | 19 (15%) | 30 (15.2%) | | | 0.888* |
| Dyslipidemia | 20 (28.6%) | 43 (33.9%) | 63 (32%) | | | 0.466 |
| Cancer | 5 (7.1%) | 9 (7.1%) | 14 (7.1%) | | | 1.000* |
| Recurrent urinary tract infection | 11 (15.7%) | 17 (13.4%) | 28 (14.2%) | | | 0.654** |

^aData presented as n, n (%), or median (IQR). *Chi-square test. **Fisher's exact test.



Table 2. Immunosuppressants and pulse therapy used in cases and controls.^a

| | Gr | Group | | | | |
|---------------------------------------|------------|-------------|-------------|-----|----------|-------|
| Variable | Case | Control | | OR | 95% CI | p* |
| | (n = 70) | (n = 127) | (N = 197) | | | |
| Calcineurin inhibitors | | | | | | |
| No | 16 (22.9%) | 18 (14.2%) | 34 (17.3%) | | | |
| Yes | 54 (77.1%) | 109 (85.8%) | 163 (82.7%) | | | 0.123 |
| Antiproliferative agents | | | | | | |
| No | 10 (14.3%) | 21 (16.5%) | 31 (15.7%) | | | |
| Yes | 60 (85.7%) | 106 (83.5%) | 166 (84.3%) | | | 0.678 |
| Corticosteroids | | | | | | |
| No | 3 (4.3%) | 21 (16.5%) | 24 (12.2%) | | | |
| Yes | 67 (95.7%) | 106 (83.5%) | 173 (87.8%) | 4.4 | 1.3-15.4 | 0.012 |
| Inhibitors of mTOR | | | | | | |
| No | 52 (74.3%) | 94 (74%) | 146 (74.1%) | | | |
| Yes | 18 (25.7%) | 33 (26%) | 51 (25.9%) | | | 0.967 |
| Pulse therapy with methylprednisolone | | | | | | |
| No | 59 (84.3%) | 116 (91.3%) | 175 (88.8%) | | | |
| Yes | 11 (15.7%) | 11 (8.7%) | 22 (11.2%) | | | 0.158 |
| Use of antilymphocyte antibodies | | | | | | |
| No | 63 (90%) | 123 (96.9%) | 186 (94.4%) | | | |
| Yes | 7 (10%) | 4 (3.1%) | 11 (5.6%) | | | 0.056 |

mTOR: mammalian target of rapamycin. ^aData presented as n (%). *Chi-square test.

Table 3. Final multivariate logistic regression model for the respiratory infection outcome.*

| Variable | β | SE | Wald | df | р | OR | 95 % | 6 CI |
|-----------------|--------|-------|-------|----|-------|------|-------------|--------|
| | | | | | | | Lower | Higher |
| Corticosteroids | 1.439 | 0.667 | 4.652 | 1 | 0.031 | 4.22 | 1.14 | 15.60 |
| Bronchiectasis | 1.947 | 0.717 | 7.380 | 1 | 0.007 | 7.01 | 1.72 | 28.56 |
| BMI | | | | | | | | |
| Normal | | | 9.253 | 2 | 0.010 | | | |
| Underweight | -0.884 | 0.600 | 2.170 | 1 | 0.141 | 0.41 | 0.13 | 1.34 |
| Overweight | 0.791 | 0.347 | 5.199 | 1 | 0.023 | 2.21 | 1.12 | 4.35 |

of antilymphocyte antibodies, and bronchiectasis showed p < 0.20 in the univariate analysis and were therefore included in the multivariate logistic regression model, which showed that BMI, corticosteroid use for immunosuppression, bronchiectasis, and being overweight were risk factors for pulmonary infection in kidney/kidney-pancreas transplant recipients, having a joint effect with the outcome of respiratory infection.

With regard to nutritional status (as assessed by the BMI), an overweight individual was found to be 2.21 times more likely to have a respiratory infection than an individual with a normal BMI. Studies examining the negative impact of poor nutrition on the risk of infection have shown that immune disorders such as leukopenia and decreased CD4+ lymphocyte count and antibodies directed to opsonization of encapsulated bacteria can increase the risk of infections.^(11,12)

With regard to donor type, there was no significant difference between cases and controls, deceased donors having predominated. In a previously published metaanalysis, receiving a transplant from a deceased donor was found to be an independent risk factor for pulmonary infection in cases of prolonged organ ischemia.⁽¹²⁾ In the present study, corticosteroid use was associated with pulmonary infection occurrence. Our multivariate logistic regression model showed that individuals using corticosteroids were 4.22 times more likely to have a respiratory infection. No positive association was found between the use of antilymphocyte antibodies and pulmonary infections (p = 0.056). This is probably due to the size of the study sample. In any case, the use of polyclonal antibodies against human lymphoid tissue in pulse therapy regimens for acute rejection must be highlighted, because of lymphopenia in the spleen and thymus.⁽¹³⁻¹⁶⁾

Corticosteroids have numerous therapeutic effects, part of them not yet understood, which involve blocking the expression of genes responsible for cytokine synthesis (IL-1, IL-2, IL-3, IL-6, and TNF-a).⁽¹⁴⁻¹⁶⁾ In general terms, the use of corticosteroids in kidney transplant recipients may be associated with a higher risk of complications of an infectious nature. Nonetheless, it is of note that ours is a peculiar study population and this was a single-center study, the number of cases therefore being limited. In addition, we were unable to determine the mean dose of corticosteroids used



| Table 4. | Etiologic | agents | of | infection | in | case | patients |
|-----------|-----------|--------|----|-----------|----|------|----------|
| (n = 70). | | | | | | | |

| Etiologic agent | n (%) |
|--|-----------|
| Aspergillus fumigatus | 2 (2.9) |
| Gram-negative bacilli | 2 (2.9) |
| Cytomegalovirus | 10 (14.3) |
| Gram-positive cocci in pairs | 1 (1.4) |
| Cryptococcus neoformans | 3 (4.3) |
| Eikenella corrodens | 1 (1.4) |
| Enterobacter cloacae | 1 (1.4) |
| Escherichia coli | 1 (1.4) |
| Histoplasma capsulatum | 5 (7.1) |
| Influenza virus | 1 (1.4) |
| Klebsiella pneumoniae | 1 (1.4) |
| Klebsiella pneumoniae/Moraxella catarrhalis | 1 (1.4) |
| Leishmania braziliensis | 1 (1.4) |
| Mycobacterium tuberculosis | 7 (10) |
| Unidentified | 21 (30) |
| Paracoccidioides brasiliensis | 3 (4.3) |
| Pneumocystis jirovecii | 2 (2.9) |
| Pseudomonas aeruginosa | 5 (7.1) |
| Streptococcus agalactiae/Pseudomonas aeruginosa | 1 (1.4) |
| Streptococcus pneumoniae | 1 (1.4) |
| Total | 70 (100) |

Table 5. Chest HRCT findings in case patients (n = 70).

| Chest HRCT finding | n (%) |
|------------------------|-----------|
| Ground-glass opacities | 35 (50) |
| Nodules | 32 (45.7) |
| Cavitation | 7 (10) |
| Consolidation | 34 (48.6) |
| Pleural effusion | 11 (15.7) |

by the patients. The use of lower doses (2.5-5 mg/ day) could reduce undesirable side effects and not increase the immunological risk.⁽¹⁷⁾

Of the comorbidities evaluated in this study, only bronchiectasis was associated with the occurrence of infection. Our multivariate logistic regression model showed that an individual with bronchiectasis was 7.01 times more likely to have a respiratory infection. Bronchiectasis is a chronic respiratory disease whose clinical manifestations include cough, sputum production, and bronchial infections, and whose radiological features include abnormal and permanent dilation of the bronchi. This means that bronchiectasis is a structural lung disease in which recurrent bronchopulmonary infections constitute the main complication. This can explain the association between bronchiectasis and immunosuppression as a risk factor for respiratory infections.^(18,19)

With regard to chest HRCT findings, ground-glass opacities predominated in the case patients in the present study, being found in approximately 50%. The differential diagnosis is extensive, requiring an in-depth knowledge of the patient history of diseases and patient immunosuppression status, and can be closely associated with infectious conditions.⁽²⁰⁻²²⁾ With regard to the etiologic agents of infection, fungal agents were highly prevalent in the study population, being found in 21.4%. Cytomegalovirus was also prevalent, being found in 14.3%. These findings reinforce the need for an etiologic diagnosis for optimal clinical outcomes in this group of patients.

The present study has limitations. First, it was a single-center study, meaning that the number of case patients was limited. Second, regional differences could prevent the generalization of the results. Third, information regarding patient exposure and identified etiologic factors was obtained after the infection, being the main limiting factor of the study.

The present study is unique in the regional context, involving a population of kidney/kidney-pancreas transplant recipients with respiratory infections. The study can contribute to improving early identification of kidney and kidney-pancreas transplant recipients especially susceptible to lower respiratory tract infections.

AUTHOR CONTRIBUTIONS

LMF, VN, and RAC: study design; data analysis; and reviewing of the manuscript. LROG and CMS: data analysis and reviewing of the manuscript. ADS, DRE, and BPP: reviewing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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