Risk factors for lung diseases after renal transplantation

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Background: Lung diseases are one of the major causes of morbidity and mortality after renal transplantation. The aim of the study is to define the risk factors for infectious and noninfectious pulmonary complications in kidney transplant patients. **Materials and Methods:** We prospectively studied 267 patients after renal transplantation. The kidney recipients were followed-up for the development of pulmonary complications for a period of 7 years. Different noninvasive and invasive diagnostic tests were used in cases suspected of lung disease. **Results:** The risk factors associated with the development of pulmonary complications were diabetes mellitus (odds ratio [OR] = 4.60; $P = 0.001$), arterial hypertension (OR = 1.95; $P = 0.015$), living related donor (OR = 2.69; $P = 0.004$), therapy for acute graft rejection (OR = 2.06; $P = 0.038$), immunosuppressive regimens that includes mycophenolate (OR = 2.40; $P = 0.011$), azathioprine (OR = 2.25; $P = 0.023$), and tacrolimus (OR = 1.83; $P = 0.041$). The only factor associated with the lower risk of complications was a positive serology test for Cytomegalovirus of the recipient before transplantation (OR = 0.1412; $P = 0.001$). **Conclusion:** The risk factors can be used to identify patients at increased risk for posttransplant lung diseases. Monitoring of higher-risk patients allow timely diagnosis and early adequate treatment and can reduce the morbidity and mortality after renal transplantation.

Key words: Kidney transplantation, pulmonary complications, recipient, risk factors

INTRODUCTION

Kidney transplantation procedures are the most common organ transplantation surgeries: About 60% of all cases. Pulmonary complications take an important place in the prognosis of kidney transplant patients. According to medical literature data, their frequency varies. The main part of complications is due to pulmonary infections, although their development following renal transplantation is the lowest, compared to patients with other organ transplants.[1,2] Immunosuppression after transplantation creates a higher risk of infection. Due to the different drug use and dosage regimens the spectrum of infection varies over time. The 1st month after transplantation is influenced predominantly by nosocomial bacterial infections. The second posttransplant period (from 1 to 6 months) is characterized by the development of opportunistic pathogens as a result of the maximum sustained immunosuppression. Beyond 6 months (late posttransplant period), the allograft function is usually stable, and the immunosuppression level is reduced. The main infections are due to common community-acquired pathogens. The risk of viral and opportunistic infections is high only in patients treated for chronic rejection or recurrent episodes of acute rejection.[3] Noninfectious complications after renal transplantation include atelectasis, pulmonary edema, pulmonary thromboembolic events, and posttransplant malignancy.

Risk factors associated with the development of pulmonary complications are not yet fully understood. They can occur as a result of the mechanical ventilation performed during the surgery, the presence of arteriovenous fistulas, ureteric stents, and because of delayed graft function.[4-8] Diabetes mellitus and the

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type of the dialysis treatment before the operation and the posttransplantation immunosuppressive therapy have also been related to heightened risks of pulmonary infections in kidney transplant patients.[9-15]

The aim of this study is to define the risk factors for infectious and noninfectious pulmonary complications in kidney transplant patients.

MATERIALS AND METHODS

Study population

This is a prospective study of 267 patients who have undergone renal transplantation. They were randomly selected from among all renal transplant patients who were obligatory monitored after an operation in the only Bulgarian Clinical Center of Nephrology and Transplantation, "Alexandrovska" University Hospital, Sofia. The recipients were followed up for the development of lung diseases from May 2007 to November 2014. The protocols conformed to the guidelines of the 1975 Helsinki Declaration and were approved by the Ethics Committee of Medical University, Sofia (protocol no 44-2246). All patients gave their written informed consent to participate. The initial demographic, clinical, and pretransplant laboratory data were collected from medical charts at patient entry into the study. The kidney recipients included in the study were above 18 years of age, with normal lung function and without a history of chronic pulmonary diseases before transplantation. Patients with known oncology diseases or with graft failure needing dialysis were excluded. All patients underwent immunosuppressive therapy, according to the generally accepted treatment regimens.[16-18]

Testing procedures

During the study period, the patients were monitored for the onset of clinical signs and symptoms suspected of lung diseases (high temperature, cough, sputum, chest pain, shortness of breath, or wheezing). In these cases, the recipients were clinically examined. Hematological and biochemical analysis of blood, microbiological tests of sputum, blood and urine were carried out. In all patients electrocardiography, spirometry, and arterial blood gases analysis, pulse oxymetry, posteroanterior radiography of the lungs and heart and echocardiography were performed. High-resolution computer tomography of the thorax was performed in 29 cases and fiber-optic bronchoscopy with bronchoalveolar lavage — in 32 cases with the unclear diagnosis. Analyzes of pleural effusion were done in eight cases. Cytological or histological examinations of the material from the bronchial mucosa or the lung parenchyma were all examined.

The immunological methods — enzyme-linked immune spot assay for the diagnosis of active tuberculosis (T-SPOT-TB;

Oxford Immunotec Ltd, Oxford, UK) and the real-time polymerase chain reaction amplification for cytomegalovirus (CMV) detection (REALQUALITY RQ-CMV, AB Analitica, Italy) were used. Trained laboratory technicians from the clinic of immunology performed and interpreted all assays according to manufacturers' recommendations.

The diagnoses of lung diseases were based on clinical signs, abnormal diagnostic test results, and chest X-ray abnormalities.

Statistical methods

The statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). A variational analysis of the quantitative variables was used, as well as the Chi-square test and Fisher's exact test, the method of Kolmogorov-Smirnov, and the method of Mann-Whitney. Logistic regression analysis was applied to identify clinical variables significantly associated with the occurrence of pulmonary complications. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Of all, 267 kidney recipients were followed up during the study period. The age of the patients was 40.57 ± 12.299 years. The male-to-female ratio was 172/95 (64.4% men and 35.6% women). The mean time of dialysis before transplantation was 34.93 ± 31.803 months. Living related donors were used in 60 (22.5%) of the transplantations, living unrelated donors in 105 (39.3%) and kidneys from cadaver donors were used in 66 (24.7%) of the transplantations. The early postoperative period was complicated in 66 (24.7%) of the cases.

Of all 267 monitored kidney recipients, 97 (36.3%) developed pulmonary complications throughout the duration of the study. 81 of those 97 patients had pneumonia, 5 patients developed mycotic infections, and 5 patients developed pulmonary tuberculosis. 4 kidney recipients were diagnosed with pulmonary thromboembolism and 2 patients with lung tumors.

The comparisons of the main demographic data between the PC+ and PC− groups are shown in Table 1. There was no significant difference between the two groups according to age, sex, smoking status, type, and length of dialysis treatment before transplantation ($P > 0.05$ for all).

The frequency of concomitant arterial hypertension and diabetes mellitus was significantly higher in the group with pulmonary complications than in the PC− group ($P < 0.05$ for both).

The primary kidney conditions that had led to an end-

stage renal disease (ESRD) in the patients who developed pulmonary complications and in the other group — without complications — are presented in Table 2. The causes that had led to ESRD were similar in the two groups ($P > 0.05$ for all).

Eighty-five (39.7%) of the recipients in PC− group were with positive serological status for CMV before transplantation vs. 12 (22.6%) in PC+ group ($P = 0.025$). There was no significant difference between two groups according to the CMV-serological status of the donors prior to operation ($P = 0.367$).

The immunosuppressive agents used in both patient groups, determined by the development of pulmonary complications, are shown in Table 3. There were significant differences between the PC+ and the PC− group when comparing the use of mycophenolate ($P = 0.009$), azathioprine ($P = 0.025$) and tacrolimus ($P = 0.05$) in the immunosuppressive treatment schemes.

Complications of the early postoperative period were established in 23 recipients of the PC+ group and in 44 recipients in the PC− group ($P = 0.770$). Treatment of acute rejection was provided in 20 (20.6%) of the cases with pulmonary complications versus 19 (11.2%) of the kidney transplant patients without lung diseases ($P = 0.047$).

The factors associated with a higher likelihood of developing posttransplant lung diseases are presented in Table 4.

DISCUSSION

Pulmonary complications after kidney transplantation usually occurs in 5-24% of the patients, but according to some authors, the incidence can reach up to 37%.[19,20] In our study, 267 posttransplantation patients were monitored, and 36.3% of them (97 patients) developed various infectious and noninfectious pulmonary complications. The frequency of registered pulmonary complications in this study is higher, compared to data reported in most publications. At the same time, our results are almost identical to those published by Edelstein *et al.* who found a 37% frequency of pulmonary complications in 110 kidney transplant patients.[20] The higher frequency of registered pulmonary complications in our study is most probably due to our active subject-specific research within the patients, involved in the analysis. The data was collected from a single transplantation center, and it was obtained through a prospective analysis.

Our data shows no correlation between sex ($P = 0.288$) and age ($P = 0.301$) and the development of pulmonary complications. The results are similar to those published

Table 1: Demographics of groups with and without pulmonary complications

Characteristic	PC− (n = 170) (%)	PC+ (n = 97) (%)	P
Age years±SD	40.01±12.410	41.56±12.101	0.301
Male	105 (61.8)	67 (69.1)	0.288
Current smokers	41 (24.1)	18 (18.6)	0.358
Ex-smokers	14 (8.2)	7 (7.2)	0.818
Dialysis before transplantation months±SD	33.90±30.223	35.52±32.743	0.694
Hemodialysis	151	85	0.843
Peritoneal dialysis	11	5	0.792
Without dialysis	8	7	0.416
Arterial hypertension	97 (57.1)	70 (72.2)	0.018*
Diabetes mellitus	7 (4.1)	16 (16.5)	0.001*

*P value with statistic significant difference. Data are given as mean (SD) or n (%). Statistical analysis: Chi-square test, Fisher's exact test, method of Mann-Whitney U-test. PC− = Patients without pulmonary complications; PC+ = Patients with pulmonary complications; SD = Standard deviation

Table 2: Type of kidney disease as a reason for transplantation in patients with pulmonary complications

Kidney disease	PC+ (n = 97) (%)	PC− (n = 170) (%)	P
Glomerulonephritis	59 (60.8)	92 (54.1)	0.307
Pyelonephritis	13 (13.4)	33 (19.4)	0.241
Unknown	7 (7.2)	4 (2.4)	0.104
Renal polycystosis	6 (6.2)	11 (6.5)	1.000
Congenital renal anomalies	6 (6.2)	21 (12.4)	0.140
Renal involvement in systemic diseases	6 (6.2)	9 (5.3)	0.786

Data are given as n (%). Statistical analysis: Chi-square test, Fisher's exact test. PC− = Patients without pulmonary complications; PC+ = Patients with pulmonary complications

Table 3: Immunosuppression of both groups

Drugs	PC+ (n = 97) (%)	PC− (n = 170) (%)	P
Prednisolone	92 (94.8)	167 (98.2)	0.144
Mycophenolate	84 (86.6)	124 (72.9)	0.009*
Azathioprine	12 (12.4)	41 (24.1)	0.025*
Cyclosporine A	65 (67.0)	105 (61.8)	0.429
Tacrolimus	21 (21.6)	57 (33.5)	0.05*
Everolimus	2 (2.1)	2 (1.2)	0.623
Sirolimus	5 (5.2)	7 (4.1)	0.762
Monoclonal antibodies	6 (6.2)	16 (9.4)	0.642

*P value with a statistic significant difference. Data are given as n (%). Statistical analysis: Chi-square test, Fisher's exact test. PC− = Patients without pulmonary complications; PC+ = Patients with pulmonary complications

by Sarnak and Jaber and contradict those by Souse *et al.*[21,22]

The primary kidney condition which has led to an ESRD is not a factor responsible for the developing of pulmonary complications. The collected results do not show the statistical significant difference between the two groups of patients and their primary kidney condition ($P = 0.110$).

Table 4: Risk factors for posttransplant lung diseases

Risk factor	OR	95% CI	P
Living related donor	2.69	1.39-5.23	0.004
Arterial hypertension	1.95	1.14-3.34	0.015
Diabetes mellitus	4.60	1.82-11.63	0.001
Mycophenolate	2.40	1.22-4.71	0.011
Azathioprine	2.25	1.12-4.53	0.023
Tacrolimus	1.83	1.02-3.26	0.041
Treatment of acute rejection	2.06	1.04-4.10	0.038
Positive CMV-serostatus of the recipients prior to transplantation	0.1412	0.0719-0.2773	0.001

Statistical method: Logistic regression analysis. CMV = Cytomegalovirus; OR = Odds ratio; CI = Confidence interval

The duration and the type of predialysis treatment cannot be considered as the factors responsible for developing pulmonary complications ($P > 0.05$). The results are in contradiction to those published by Passalacqua *et al*. Their findings point to a heightened frequency of infectious complications in patients that have peritoneal dialysis in comparison to patients that have hemodialysis for a period of 30 days after the operation. These differences are reversible, and after the discontinuation of the dialysis the risk of developing complications becomes equal for both groups of patients.[10] The lack of correlation of our results is probably due to the fact that the number of patients who had peritoneal dialysis was far lower (13 patients — 4.87%).

A study of 1 676 kidney transplant patients showed that the risk of developing infectious complications when receiving an organ from a living related donor stands at 1.93 times (odds ratio [OR] = 1.93).[22] According to the results that we collected, the living related donor increases the risk of developing pulmonary complications 2.69 times (OR = 2.69; $P = 0.004$), which is slightly higher, compared to the results achieved by other researchers. At the same time, we cannot confirm the medical literature data that the risk of developing infectious pulmonary complications is heightened in cases where the donor is a cadaver.[22]

Our data does not recognize possible complications of the early postoperative period and the delayed graft function as factors related to a heightened risk of pulmonary complications ($P > 0.05$). These results differ from those published by other authors who claim that the delayed graft function is a risk factor for developing infectious complications.[4,5] Their data is obtained from a much bigger base of postkidney transplantation patients from more than one center and has a retrospective character. The results gathered by us are based on the data obtained from the patients of one center, and the conducted monitoring was with a prospective character. Probably this is the reason the two results do not match.

Immunosuppressants are used to prevent rejection after transplantation suppress both humoral and T-cell-mediated immunity. They have a different mechanism of action and interact with many cells. Glucocorticoids affect multiple leukocyte cell lines, including T- and B-cells, macrophages, granulocytes, and monocytes. The calcineurin inhibitors cyclosporine and tacrolimus inhibit T-cell activation by binding to intracellular immunophilins. The antimetabolite agents such as mycophenolate and azathioprine inhibit deoxyribonucleic acid and ribonucleic acid production. Sirolimus and everolimus are rapamycin inhibitors. T-cell specific antibodies used for prevention and treatment of rejection episodes can be poly- or monoclonal.[23]

Several earlier studies have reported the role of immunosuppressants in the development of infectious and noninfectious pulmonary complications.[24,25] According to our data, the use of mycophenolate, azatioprine or tacrolimus in the immunosuppressive treatment schemes increase the risk of pulmonary, mainly infectious, complications. Mycophenolate increases the risk of developing pulmonary complications 2.40 times (OR = 2.40; $P = 0.011$), azatioprine 2.25 times (OR = 2.25; $P = 0.023$) and tacrolimus - 1.83 times (OR = 1.83; $P = 0.041$). Our results are close to those published by Sousa *et al*.[22] It is well known that corticosteroids can increase the risk of pulmonary complications. We were unable to statistically calculate this risk in our study because Prednisolon is broadly used in immunosuppression schemes of our patients-more than 90% in both groups — with and without pulmonary complications.

Acute rejection episodes require the use of medications that will suppress them. In the study published by Sousa *et al*. monoclonal anti-bodies are shown to increase the risk of developing infectious complications 3.75 times (OR = 3.75) and the polyclonal anti-bodies — 5.43 times (OR = 5.43).[22] According to our results, the therapy administered due to the occurrence of acute rejection of the graft increases the risk of developing pulmonary complications 2.06 times (OR = 2.06; $P = 0.038$).

The role of donor's and recipient's serological CMV status in developing pulmonary complications has been well documented. Bando *et al*. monitored 250 lung transplantation patients and established that the CMV-serostatus difference between the donor and the recipient before the transplantation (in the cases of a CMV-positive donor and a CMV-negative recipient) is a factor increasing the frequency of infections, different from CMV at a later stage of the postoperative period.[26] Tveit *et al*. wrote about a correlation between the positive CMV serology status of the recipient and the development of pneumonia.[27] Our study does not recognize the CMV serological status of the donor as a risk factor for developing pulmonary

complications (*P* > 0.05). At the same time, in the group that did not develop pulmonary complications, the frequency of CMV-serologically positive recipients before transplantation was significantly higher (39.7%) than that in the group that developed pulmonary complications (22.6%). Our results differ from those published by some other authors.[27,28] These are most probably the cases in which the positive recipients have received an organ from a negative donor.[26,29] Another explanation may be the close monitoring and prophylaxis of the CMV-positive recipients after the operation. According to our data, the positive CMV serological status of the recipients before the kidney transplantation is associated with a lower risk of pulmonary complications (OR = 0.1412; *P* = 0.001).

The data that we collected confirmed the role of arterial hypertension and diabetes mellitus as factors related to the development of lung diseases.[12,30-32] Our results show that diabetes mellitus increases the risk of developing pulmonary complications 4.60 times (OR = 4.60; *P* = 0.001). The patients with arterial hypertension are 1.95 times (OR = 1.95; *P* = 0.015) more likely to develop pulmonary complications as opposed to patients without arterial hypertension.

CONCLUSION

The living related donor, the arterial hypertension and the diabetes mellitus, the involvement of mycophenolate, azathioprine, or tacrolimus in the immunosuppressive treatment, as well as the therapy of acute rejection increase the probability of pulmonary complications. Recognizing these factors can give the opportunity to isolate groups of high-risk patients, which can undergo a strict monitoring in order to prevent posttransplant lung diseases. This leads to a general decrease of morbidity and mortality in the group of kidney transplant patients.

Conflicts of interest
There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

VP contributed to the conception and design of the work, performed data collection and analysis, drafted the manuscript, performed significant revisions, approved the final version of the manuscript, and agreed to all aspects of the work. DP contributed to the conception of the work, revised the draft, approved the final version of the manuscript, and agreed to all aspects of the work. DG contributed to the conception and design of the work, performed data collection, drafted the manuscript, performed significant revisions, approved the final version of the manuscript, and agreed to all aspects of the work. OG contributed to the design of the work, performed significant revisions, approved the final version of the manuscript, and agreed to all aspects of the work.

DSP contributed to the conception of the work, revised the draft, approved the final version of the manuscript, and agreed to all aspects of the work.

DKG contributed to the conception and design of the work, performed data collection, drafted the manuscript, performed significant revisions, approved the final version of the manuscript, and agreed to all aspects of the work.

OBG contributed to the design of the work, performed significant revisions, approved the final version of the manuscript, and agreed to all aspects of the work.

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