ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pneumonia and in-hospital mortality after renal transplantation

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SUMMARY

Introduction/Objective Pneumonias remain one of the most frequent reasons for morbidity and mortality in the group of kidney recipients.

The objective of the study was to define the factors associated with a higher risk for in-hospital mortality from pneumonia after renal transplantations.

Methods A total of 124 patients with kidney transplants hospitalized with pneumonia for the period of nine years were studied. Different noninvasive and invasive diagnostic tests were used.

Results Forty-one of the patients died as a result of pneumonia or related complications during their hospital stay. The factors associated with the increased risk for in-hospital mortality were as follows: the development of pneumonia during the early postoperative period (during the first month after surgery) (HR = 2.027; p = 0.025) or between the first and sixth month after surgery (HR = 2.303; p = 0.026), dyspnoea (HR = 2.184; p = 0.007) and hypoxemia (HR = 2.261; p = 0.003). The presence of bilateral infiltrates (HR = 2.482; p = 0.001), failure of initial antibiotic therapy (HR = 3.548; p < 0.001), intubation and mechanical ventilation (HR = 4.635; p < 0.001) also increased the risk for the fatal outcome.

Conclusion Knowing the prognostic factors associated with the increased risk for in-hospital fatal outcome from pneumonia after renal transplantation makes it possible to differentiate the high-risk group of renal recipients who require early etiological diagnosis and strict control of the condition, in order to reduce the mortality from pulmonary infections in the group.

Keywords: pneumonia; mortality; recipient; transplantation, solid organ, renal

INTRODUCTION

The solid transplantation, as a treatment method of the final stage of organ insufficiency, has become increasingly significant in recent years. Renal transplantation (RT) is the most frequently performed organ transplant, accounting for approximately 60% of all cases. Of particular significance for the prognosis of the survival rate and the mortality among renal transplant recipients are pulmonary complications. According to different data in the literature, the frequency of post-RT pulmonary complications varies 5-37%. Most complications are caused by pulmonary infections, although their development after renal transplants is the lowest, compared to patients with other organ transplants (frequency of 8-16% and mortality rate of 5-8% per annum) [1, 2, 3].

The risk of infection after transplantation changes in time, especially with the modification of the therapy, and it varies depending on the immunosuppressive agents used. There are various therapeutic schemes, differing by drug interactions, side effects, as well as the risk of developing infections [4]. As a result of their inhibiting effects, the immunosuppressive drugs affect the endogenic barrier of the lungs against the penetration of infectious pathogens [4]. The immunosuppressive therapy, used after surgery, defines three sub-periods in the posttransplantation period, where different infectious agents causing pulmonary complications are prevalent – the first month after the operation, from the first to the sixth month after the transplantation, and late post-transplant period (more than six months after the surgery) [5, 6].

The main challenge when providing care for patients after transplantation is to choose the optimal immunosuppression, ensuring the balance between the prevention of rejection reactions and the minimization of the risk of infection [7]. This can be achieved with a strict monitoring of the immunosuppressive medications [8]. Nevertheless, pneumonias remain one of the most frequent reasons for morbidity and mortality in this group of patients [9, 10].

The aim of this study is to define the factors associated with a higher risk for in-hospital mortality from pneumonia after renal transplantations.

METHODS

Patients

A total of 124 post-RT patients diagnosed with pneumonia were included in the study. They were admitted to the Clinic of pulmonology



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of the Alexandrovska University Multiprofile Hospital for Active Treatment over a period of nine years. All the patients gave their written informed consent to participate. The protocols conformed to the guidelines of the 1975 Helsinki Declaration. All the patients had renal transplantation and were at least 18 years of age. Patients with mental disturbances or proven oncological diseases, including pulmonary neoplasms, were excluded from the study. The exclusion criteria were chronic pulmonary diseases like asthma and chronic obstructive pulmonary disease or dysfunctional graft with developed terminal renal insufficiency, and chronic hemodialysis treatment. A history of pulmonary tuberculosis successfully treated in the past did form part of the eligibility criteria. In cases of a second or subsequent pulmonary complication, only the first complication, registered for the respective patient, was used for the needs of the study and the data analysis.

Methods

Detailed medical history was prepared for each patient, and all the patients underwent complete clinical examination. When the criteria responsible for the development of pneumonia were present, the patients were hospitalized for treatment at the clinic. During the hospitalization period, the pulmonary and cardiac statuses were followed-up on a daily basis, along with a control of the vital signs - arterial pressure, pulse and respiration rate, body temperature, and 24-hour quantity of urine. The following hematological and biochemical blood tests were performed: complete blood count with differential leukocyte count, erythrocytes sedimentation rate, C-reactive protein (CRP), creatinine, urea, aspartate aminotransferase, alanine aminotransferase, potassium, sodium, chlorides, blood glucose, fibrinogen. The tests of all the patients also included electrocardiography and arterial blood gases (ABGs) analysis (equipment used - RapidLab 248; Siemens Healthineers, Erlangen, Germany). Spirometry and in some cases diffusion capacity analysis (equipment used - Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) were performed in accordance with the requirements of the American Thoracic Society / European Respiratory Society Guidelines (Miller 2005). Microbiological tests of sputum, pleural effusion liquid or broncho-alveolar lavage, and of blood for aerobic and anaerobic microorganisms, fungi, and Mycobacterium tuberculosis were done. We used Realquality RQ-CMV standard kits by AB Analitica s.r.l., Padova, Italy, for the identification and quantitative determination of the Cytomegalovirus deoxyribonucleic acid. Posteroanterior radiography of all the patients was performed. In cases of diagnostic difficulties, high resolution computer tomography of the thorax was performed (device used - Aquilion 64-multi-slice, Toshiba Medical Systems Corporation, Otawara, Japan; following Vitrea 2 protocol of Vital Images, Minnetonka, MN, USA). Some of the patients underwent fiberoptic bronchoscopy with bronchoalveolar lavage, catheter-biopsy, and - if necessary -fibre-clamp biopsy (BF 1T30, Olympus Corporation, Tokyo, Japan). Cytological or histological examinations

of the material from the bronchial mucosa or the lung parenchyma were all examined.

Statistical analysis

The statistical data processing was carried out using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The adopted level of significance, eliminating the null hypothesis, was p < 0.05. The statistical analyses included a variational analysis of the quantitative variables - median, standard deviation, standard error of the median, and 95% confidence interval of the median, frequency analysis of qualitative variables, graphics. The χ^2 test and the Fisher's exact test were used for establishing the dependency between two qualitative variables, and the Kolmogorov-Smirnov and the Mann-Whitney methods for testing the normality of distribution of the quantitative variables. Quantitative indicators were assessed using a receiver operating characteristic (ROC) analysis. The probability ratio was calculated using logistic regression analysis, and the establishment of the effects of various factors and the risk estimation were carried out based on the Cox regression, using Kaplan-Meier survival curves.

RESULTS

A total of 124 kidney recipients with pneumonia were included in the study. The mean age of the patients was 41.23 ± 13.46 years. The male-to-female ratio was 78/46 (62.9% men and 37.1% women). According to the outcome of pneumonia, the patients were divided into two groups. In the first group, which was pneumonia (+), there were 83 patients recovered from pneumonia. The other 41 recipients in pneumonia (–) group died as a result of the pneumonia or related complications during their hospitalization. There was no significant difference between the two groups according to main demographic data – age, sex, smoking status, type and length of dialysis treatment before transplantation, immunosuppressive agents used in both patient groups, concomitant diseases (p > 0.05 for all).

In the pneumonia (+) group, three patients became ill during the first postoperative month, 36 patients between the first and sixth month after the transplantation, and 44 patients in the late post-transplantation period (more than six months after surgery). In the pneumonia (-) group, six patients became ill during the first postoperative period, 27 patients became ill between the first and sixth month after the transplantation, and eight patients in the late post-transplantation period. There is a statistically significant dependence between the period of development of pneumonia and the outcome of the disease (p < 0.001).

The effect of the period during which pneumonia occurs on the survival rate of the patients is shown in Figure 1.

The main clinical symptoms are similar in both groups (p > 0.05). The only statistically significant difference in clinical features between the two groups is the presence of dyspnoea at admission (p = 0.033). This symptom occured more frequently in the pneumonia (–) group.

The major hematological and biochemical parameters are shown in Table 1. Statistical differences between their values in the groups of patients according to the outcome of pneumonia were observed for CRP and lymphocytes. The calculated ROC curve for CRP is shown in Figure 2. The area below the curve is 0.702 (95% CI, 0.584–0.819), p = 0.003.



Figure 1. Kaplan–Meier plot – effect of the period after the transplant on the survival rate in patients with pneumonia

Table 1. Comparison of the hematological and biochemical parameters between the two groups

Laboratory indicator	Median ± SD Pneumonia (+)	Median ± SD Pneumonia (–)	р
CRP	54.60 ± 77.285	94.32 ± 94.100	0.026*
Erythrocytes	51.19 ± 31.688	55.30 ± 26.913	0.530
Leukocytes	9.175 ± 4.6359	9.656 ± 4.3531	0.583
Neutrophils	10.072 ± 11.8294	15.200 ± 21.3843	0.069
Lymphocytes	2.573 ± 3.8850	1.535 ± 2.5872	0.026*
Monocytes	0.965 ± 1.9900	0.777 ± 0.8372	0.301
Eosinophils	0.164 ± 0.4307	0.126 ± 0.1667	1.000
Basophils	1.02 ± 0.136	1.04 ± 0.192	1.000
Thrombocytes	266.59 ± 103.618	236.01 ± 132.407	0.062
Hemoglobin	117.00 ± 23.261	111.22 ± 18.331	0.442
Fibrinogen	5.1842 ± 1.66059	5.9019 ± 1.92601	0.559
Creatinine	205.94 ± 165.943	270.69 ± 210.343	0.321
Albumin	33.75 ± 1.03	32.00 ± 0.96	1.000

CRP – C-reactive protein *Statistically significant



Figure 2. ROC curve of CRP as a predictor of the fatal outcome of pneumonia

The ABGs analysis shows that at admission 38 patients (45.78%) of those that subsequently recovered and 35 (85.37%) of the subsequently deceased patients had hypoxemia (p = 0.001). Figure 3 shows the ROC curve for PaO₂ in the ABGs at admission. The area below the curve is 0.703 (95% CI, 0.591–0.815), p = 0.003.

The ABGs analysis, performed on the third day of the treatment, revealed hypoxemia in 23 (27.71%) of the subsequently recovered and in 39 (95.12%) of the subsequently deceased patients (p < 0.001). Figure 4 shows the ROC analysis comparing both groups, based on the outcome of the disease and the PaO₂ values, obtained from the ABGs analysis on the third day of the treatment. The area below the curve is 0.884 (95% CI, 0.814–0.955), p < 0.001.

There was a statistically significant difference in the localization of the X-ray alterations between the two groups (p < 0.001). The predominant radiological findings in the pneumonia (–) group were bilateral changes. They increased the risk of fatal outcome (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

A failure of the antibiotic treatment administered and a need to re-evaluate it was determined in 21 (25.3%) recipients in the pneumonia (+) group and in 38 (92.68%) patients in the pneumonia (–) group. The two groups differ statistically (p < 0.001) (Figure 5).

In the pneumonia (–) group, three (7.31%) recipients were subjected to non-invasive ventilation (NIV) and 31 (75.61%) to invasive ventilation. In the pneumonia (+) group, seven (8.43%) patients were subjected to NIV, and two (2.41%) to invasive ventilation (p < 0.001). The effect of the need for intubation and mechanical ventilation



Figure 3. ROC curve of PaO, on the first day, as a lethality predictor



Figure 4. ROC curve of PaO, on the third day, as a lethality predictor



Figure 5. Effect of adjusting the antibiotics therapy on the survival rate of pneumonia patients



Figure 6. Effect of mechanical ventilation on the survival rate of pneumonia patients

r			
Indicator	HR	95% CI	р
1st month after renal transplantation	2.027	1.092–3.761	0.025
1–6 months after renal transplantation	2.303	1.104–4.803	0.026
Dyspnoea	2.184	1.239–3.849	0.007
Hypoxemia	2.261	1.314–3.890	0.003
Bilateral radiological changes	2.480	1.439–4.279	0.001
Failure of initial antibiotic therapy	3.548	2.418-5.205	< 0.001
Intubation and mechanical ventilation	4.635	2.276–9.437	< 0.001
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Table 2. Indicators for the assessment of the fatal outcome risks

HR – hazard ratio

on the survival rate of pneumonia patients is shown in Figure 6.

The risk factors for an in-hospital fatal outcome of pneumonia in patients after renal transplantation are shown in detail in Table 2.

DISCUSSION

The frequency of pneumonia, reported after RT varies 2.9–30%, as these are the lowest rates, compared to other organ transplantations [11, 12]. According to our results,

the mortality rate resulting from pneumonia is 33.06%. The available literature provides inconsistent data on the mortality of pulmonary infections. Some authors report a rate of 15-20% [13]. Other studies show mortality rates of 21-35%, as there are certain differences between the mortality from pneumonia, acquired in public (8%), and Hospital-acquired (nosocomial) cases (58%) [14, 15]. There is a statistically significant dependency between the period of the development of the pulmonary infection and the outcome of the disease (p < 0.001). The pneumonia outcome depends on the amount of time which passes after the transplantation before the infection develops [16]. The mortality rate is higher among patients who acquire pneumonia in the early post-transplantation period, i.e. between one and six months after surgery. The development of pneumonia during the early postoperative period (during the first month) increases the lethal outcome risk 2.027-fold (HR = 2.027; 95% CI, 1.092-3.761; p = 0.025). The development of pneumonia one to six months after surgery increases the risk of an unfavorable outcome 2.303fold (HR = 2.303; 95% CI, 1.104–4.803; p = 0.026). At the same time, most of the successfully treated patients developed pneumonia in the late post-transplantation period.

Clinical symptoms of pneumonia do not differ from those in immunocompetent patients. The prevailing complaints of patients with the fatal outcome were dyspnoea. A statistically significant dependency between the outcome of pneumonia and the presence of dyspnoea at admission was determined (p = 0.033). The dyspnoea increases the risk of the unfavorable outcome 2.184-fold (HR = 2.184; 95% CI, 1.239–3.849; p = 0.007).

The analysis of the laboratory indicators revealed typical changes in infection markers, also observed in immunocompetent patients with pneumonia – increased CRP, leukocytosis with neutrophilia, lymphopenia, monocytosis. Also observed were slight anemic syndrome and increased levels of creatinine and fibrinogen. Statistically significant differences between the values of the laboratory results in the groups of patients, according to the pneumonia outcome, were observed only for CRP and lymphocytes. The analysis of the CRP ROC curve showed that CRP at 44mcg/L reveals the highest sensitivity (74.1%) and specificity (70.4%) as a fatal outcome predictor. In multivariate analysis, Diadar et al. [17] also found that high CRP is associated with significant risk for death from pneumonia.

Patients with post-RT pneumonia show increased rates of hypoxemia. At the same time, low levels of PaO_2 on admission or in the course of treatment are a risk factor for the fatal outcome of pneumonia [18]. Our results show that the ABGs analysis at admission revealed hypoxemia in 85.37% of the patients who subsequently died (p = 0.001). The PaO₂ values below the normal range increase the risk of the fatal outcome 2.261 times (HR = 2.261; 95% CI, 1.314–3.890; p = 0.003). According to the ROC analysis, the PaO₂ level of 64.7 mmHg has both the highest sensitivity and specificity (63%) as a predictor of the fatal outcome. If PaO₂ is observed dynamically, hypoxemia was determined in 95.12% of the deceased patients (p < 0.001) on the third day of the treatment. The analysis of the ROC curve on the third day of the treatment showed the PaO_2 value of 60.8 mmHg with very high sensitivity (79.6%) and specificity (81.5%) as a predictor of the fatal outcome. These results coincide with the manuals prepared to date, in which PaO_2 values below 60 mmHg are considered a risk factor for the fatal outcome of pneumonia.

Several previous studies showed that multilobar radiographic pulmonary infiltrates were significantly associated with mortality [19, 20]. In our study, X-ray changes have diverse localization, as the presence of bilateral infiltrates increase the risk of the fatal outcome 2.482 times (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

The early initiation of the treatment with appropriate antibiotics is of great importance for the outcome of pneumonia after RT. In the case of therapy failure, risk of mortality increases significantly [21, 22, 23].

According our results, a failure of the originally started antibiotics treatment and its subsequent re-evaluation in the course of treatment was observed in 92.68% of the patients in the pneumonia (–) group (p < 0.001). The need for adjusting the antibiotics therapy increases the risk of the fatal outcome 3.548-fold (HR = 3.548; 95% CI, 2.418–5.205; p < 0.001).

Due to the occurring complications in the course of pneumonia, some patients had to undergo NIV or invasive ventilation. Mechanical ventilation increases the risk of the fatal outcome in patients with pneumonia. This fact has been confirmed by numerous studies carried out previously [15, 24, 25]. Prolonged mechanical ventilation is mentioned in a number of publications as the main risk factor for the development of nosocomial pneumonias [14, 15]. At the same time, in recent years, a significant volume of data has been accumulated on the role of the NIV in the treatment of acute respiratory insufficiency in immunosuppressed patients [26]. A randomized study by Antonelli et al. [27], involving 25 patients post RT, showed that NIV, due to hypoxemic respiratory failure, significantly reduced mortality rates (p = 0.05). Hilbert et al. [28] reported a lower rate of use of intubations (46% compared to 77%) and lower mortality rate (50% compared to 81%) $(p \le 0.05 \text{ for both})$ among immunocompromised patients with acute respiratory failure and NIV, compared to those observed in conventional treatment [28].

The results of our study are similar to the previous publications. We have established a statistically significant

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correlation between the outcome of the disease and the type of ventilation administered (p < 0.001). The group of the recovered patients is dominated by those with non-invasive ventilation – seven kidney recipients (8.43%). In the pneumonia (–) group, 31 (75.61%) patients had been intubated and mechanical invasive ventilation had been administered to them. The need for intubation and mechanical ventilation increases the risk of the fatal outcome 4.635 times (HR = 4.635; 95% CI, 2.276–9.437; p < 0.001). Most patients on NIV recovered. At the same time, NIV is not statistically significant for the outcome of the disease. The results are probably due to the small number of patients treated with NIV.

The markers of inflammation, hypoxemia, and hypocapnea from the ABGs analysis, as well as the bilateral infiltration changes, shown by the radiological tests of the lungs, may be used as predictors for the outcome of the disease and the occurrence of complications. The need for re-evaluation of the antibiotics treatment in the course of the disease is an independent risk factor for the development of complications and the fatal outcome. That fact may be used when determining the high-risk groups of renal recipients with pneumonia, requiring increased attention and strict control in the course of treatment.

Our study has not determined any factors associated with increased risk of developing pneumonia. No comorbidities which may have an aggravating effect on the course of pneumonia have been taken into account. No long-term evaluation of the survival rate after pneumonia in this group of patients has been made. We studied only in-hospital death and did not analyze the mortality thereafter.

CONCLUSION

Based on the results that we have obtained, it is possible to prepare an algorithm with prognostic factors associated with a more severe course of pulmonary infections and an increased risk of the occurrence of complications and the fatal outcome. This makes it possible to differentiate a high-risk group of patients requiring early etiological diagnosis or strict control of the condition, in order to reduce the mortality from pneumonia after a renal transplantation.

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Упала плућа и болничка смртност после трансплантације бубрега

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САЖЕТАК

Увод/Циљ Пнеумоније су један од најчешћих разлога морбидитета и морталитета код прималаца бубрега.

Циљ овог рада је био да дефинише факторе повезане са већим ризиком од морталитета од упале плућа у болници после пресађивања бубрега.

Методе Анализирана су 124 болесника са пнеумонијом и пресађеним бубрегом хоспитализована у периоду од девет година. Коришћени су различити неинвазивни и инвазивни дијагностички тестови.

Резултати Због пнеумоније или сродних компликација умро је 41 болесник током боравка у болници. Фактори повезани са повећаним ризиком од морталитета у болници били су следећи: развој пнеумоније током раног постоперативног периода (до првог месеца) (*HR* = 2,027; *p* = 0,025) или од пр-

вог до шестог месеца после операције (HR = 2,303; p = 0,026), диспнеја (HR = 2,184; p = 0,007) и хипоксемија (HR = 2,261; p = 0,003). Присуство билатералних инфилтрата (HR = 2,482; p = 0,001), неуспех почетне антибиотске терапије (HR = 3,548; p < 0,001), трахеална интубација и механичка вентилација (HR = 4,635; p < 0,001) такође су повећавали ризик од смртног исхода.

Закључак Познавање прогностичких фактора повезаних са повећаним ризиком од смртног исхода од пнеумоније у болници после трансплантације бубрега пружа могућност одређивања групе болесника високог ризика, која захтева рану етиолошку дијагнозу и строгу контролу стања да би се смањила смртност од плућних инфекција код прималаца бубрега. Кључне речи: пнеумонија; смртност; прималац; трансплантација, солидни орган, бубрег