Acute respiratory distress syndrome in renal transplant patients with pneumonia

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Abstract: *Objective:* To establish the frequency of Acute Respiratory Distress Syndrome in kidney transplant patients with pneumonia and to define the risk factors associated with its development. *Material and Methods:* 81 kidney transplant patients hospitalized with pneumonia for the period of three years were studied. All the recipients were observed for the development of Acute Respiratory Distress Syndrome. Different noninvasive and invasive diagnostic tests were used. *Results:* 15 of the patients with pneumonia developed ARDS. The factors associated with increased risk for the development of Acute Respiratory Distress Syndrome included pneumonia in 1-6 month after transplantation, increased level of C – reactive protein, Cytomegalovirus-infection, bilateral lung infiltrates and failure of initial antibiotic therapy. *Conclusions:* The risk factors can be used to identify patients with pneumonia at increased risk for development of Acute Respiratory Distress Syndrome. Strict monitoring of high-risk patients can reduce the morbidity and mortality after renal transplantation.

Keywords: Recipient, Transplantation, Pneumonia, ARDS

1. Introduction

Acute respiratory failure is one of the most common complications in patients with pulmonary infiltrates and suppressed immune system. It is usually associated with high mortality, and it is a main reason for admission to the intensive care unit of these patients [1, 2].

Acute Respiratory Distress Syndrome (ARDS) is a fast progressing form of acute respiratory failure, usually characterized by hypoxemia and a noncardiogenic pulmonary edema. The syndrome is associated with severe damaging of the alveolar-capillary membrane that has a partially clear pathological mechanism. Roentgenological changes occur in both lungs. One of the main causes of ARDS development after kidney transplantation is pulmonary infections [3]. The treatment of ARDS requires the patient to be admitted to an intensive care unit, and to be ventilator supported with non-invasive or invasive mechanical ventilation [4 - 8]. The development of ARDS has a high mortality rate. Within the general population that rate stands at 50%, while in kidney transplant patients with

ARDS it may reach 100% [9, 10].

The aim of this study is to evaluate the frequency of ARDS in kidney transplant patients with pneumonia, and to define the risk factors related to its development.

2. Material and Methods

2.1. Patients

Table 1. Demographic data

Age years	40.59±12.4 (18-61)
-Male	53 (65.4%)
-Female	28 (34.6%)
Dialysis before transplantation (months)	33.25±30.898
-Living related donor	26 (32.1%)
-Living unrelated donor	33 (40.7%)
-Deceased donor	22 (27.2%)
Complicated early postoperative period	18 (22.2%)

81 kidney transplant recipients with pneumonia were enrolled in the study. All patients provided written informed

consent to participate. The protocols conformed to the guidelines of the 1975 Helsinki Declaration. Patients younger than 18 years of age, patients with concomitant chronic respiratory diseases (COPD, asthma, emphysema, chronic bronchitis or active tuberculosis) and all types of neoplasm were excluded from the study. All enrolled kidney transplant recipients were monitored for the development of ARDS during the treatment period. The diagnosis of ARDS was based on the Berlin definition [11]. All recipients received combination of two or three drugs used for immunosuppressive therapy prior to admission to the hospital. Basic demographic data are shown in Table 1. 52 (64.2%) of the recipients were with hypoxemia at the time of hospital admission. There were no patients diagnosed with ARDS at this time.

2.2. Testing Procedures

Medical history and physical examination were performed in all of the cases. Hematological and biochemical blood analysis, microbiological tests of sputum, blood and bronchoalveolar lavage were performed. Electrocardiography, spirometry and arterial blood gases analysis, pulse oximetry, posteroanterior radiography of the lungs and heart, echocardiography were performed in all patients. High resolution computer tomography of the thorax (HRCT) was done in 24 (29.6%) cases. The indications of HRCT are 1) high clinical suspicion of pulmonary infection with normal or dubious chest radiography and 2) exclusion of alternative diagnoses. Depending on the localization of roentgenological changes, pneumonia is divided into unilateral – left or right and bilateral – affected both lungs.

Fiberoptic bronchoscopy (FOB) was performed in 28 (34.6%) cases. The indications for FOB include microbiological diagnosis in patients with no sputum production or lack of improvement within 3 days of initial antibiotic therapy.

Immunological methods, including enzyme-linked immunospot (ELISPOT), enzyme-linked immunosorbent assay (ELISA) for the analyses of Cytomegalovirus (CMV) IgM and IgG anti-bodies, and the Real Time polymerase chain reaction amplification for Cytomegalovirus detection, were used.

2.3. Statistical Analysis

We used SPSS version 14 to analyze the data. 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. Evaluation of the quantitative parameters was done with a ROC-analysis. Logistic regression analyses, Cox-regression with the formation of curves of survivability in accordance with the Kaplan-Meier method were used. A value of $P \leq 0.05$ was considered statistically significant.

3. Results

Throughout the course of the study, 15 of the patients affected by pneumonia developed ARDS. There is a statistically significant difference between the groups with ARDS, and without ARDS in the postoperative period of the pneumonia onset ($p=0.012$). In the early postoperative period (0-1 month) two (33.33%) out of 6 patients developed ARDS. In the 1 to 6 months period – 11 (28.95%) out of 38 pneumonia patients developed ARDS. In the late postoperative period only 2 (5.41%) of all 37 pneumonia patients developed ARDS.

The analysis of the laboratory results of the patients in ARDS and non – ARDS group are shown in Table 2.

Table 2. Laboratory parameters in non – ARDS and ARDS patients.

Laboratory parameter	Mean $\pm$ SD non- ARDS (n=66)	Mean $\pm$ SD ARDS (n=15)	P
CRP mg/l	31.26 $\pm$ 46.45	107.23 $\pm$ 98.69	0.020*
Erythrocytes $10^{12}/L$	4.27 $\pm$ 0.58	4.02 $\pm$ 0.44	0.260
Leukocytes $\times 10^9/L$	8.84 $\pm$ 3.50	9.87 $\pm$ 5.41	0.998
Neutrophils $10^9/l$	7.59 $\pm$ 3.47	16.29 $\pm$ 21.62	0.897
Lymphocytes $10^9/l$	2.03 $\pm$ 1.32	2.44 $\pm$ 4.92	0.364
Monocytes $10^9/l$	0.53 $\pm$ 0.39	1.31 $\pm$ 2.35	0.478
Eosinophils $10^9/l$	0.18 $\pm$ 0.48	0.12 $\pm$ 0.16	0.154
Basophils $10^9/l$	1.02 $\pm$ 0.15	1.03 $\pm$ 0.16	0.986
Thrombocytes $10^9/L$	242.88 $\pm$ 80.73	270.96 $\pm$ 141.29	0.642
Hemoglobin g/L	116.93 $\pm$ 24.50	113.08 $\pm$ 18.57	0.780
Creatinine mkmol/l	219.99 $\pm$ 183.90	235.64 $\pm$ 184.51	0.762
Fibrinogen g/l	4.67 $\pm$ 1.45	6.26 $\pm$ 1.75	0.503
BUN mmol/L	7.25 $\pm$ 5.42	7.33 $\pm$ 5.83	0.975

* - p-value with statistic significant difference

Figure 1. ROC curve of CRP for development of ARDS

The difference in the mean levels of C-reactive protein (CRP) between these groups was significant ($p=0.020$). The heightened values of CRP (normal values < 5 mg/L) increase the probability of developing ARDS. The calculated ROC- curve is shown in Figure 1. The area under the curve is 0.674 (95% CI 0.539-0.808), $p=0.037$. There is no statistically significant difference regarding other laboratory parameters.

The analysis of the arterial blood gases of the patients in ARDS and non – ARDS group at the time of hospital

admission is shown in Table 3. There is not statistically significant difference between arterial blood gases in the two groups. At the time of hospital admission 36 (54.5%) of the patients in the non-ARDS group had hypoxemia versus 12 (80%) of the patients with ARDS ($p=0.086$).

Table 3. Arterial blood gases analysis in non – ARDS and ARDS patients at the time of hospital admission.

	Non-ARDS (n=66)	ARDS (n=15)	P
pH	7.39(7.30-7.49)	7.40(7.37-7.44)	0.691
PaO ₂ mmHg	66.53(31.60-106.30)	59.08(46.16-79.50)	0.077
PaCO ₂ mmHg	34.39(28.7-42.4)	34.36(27.4-44.0)	0.989
HCO ₃ mEq/L	23.1(22.1-24.4)	22.2(20.9-24.8)	0.351
BE mmol/L	0.57(-5.8-8.2)	-0.42(-6.0-4.3)	0.492

PaO₂ – partial pressure of arterial oxygen; PaCO₂ – partial pressure of arterial carbon dioxide; HCO₃ – arterial blood bicarbonate; BE – base excess

Figure 2 represents the ROC- curve of the values of the partial pressure of arterial oxygen (PaO₂). The area under the curve is 0.678 (95% CI 0.553-0.802), $p=0.032$.

Figure 2. ROC-curve of PaO₂ mmHg on the first day.

The analysis of the arterial blood gases of the patients in ARDS and non – ARDS group on the third day of treatment is shown in Table 4. The difference in mean value of PaO₂ between these groups was significant ($p=0.001$). 30 (46.3%) of the patients in the non – ARDS group and all 15 (100%) patients in the ARDS – group had hypoxemia ($p<0.001$).

Table 4. Arterial blood gases analysis in non – ARDS and ARDS patients on third day.

	non – ARDS (n=66)	ARDS (n=15)	P
pH	7.38 (7.34 – 7.44)	7.37 (7.33 – 7.40)	0.604
PaO ₂ mmHg	68.90 (29.20 – 92.40)	50.69 (33.50 – 68.20)	0.001*
PaCO ₂ mmHg	36.57 (33.20 – 44.0)	34.77 (29.70 – 42.40)	0.066
HCO ₃ mEq/L	22.4 (21.9 – 24.0)	22.7 (21.0 – 26.8)	0.710
BE mmol/L	0.14 (-2.1 – 2.7)	-0.86 (-2.8 – 1.2)	0.122

PaO₂ – partial pressure of arterial oxygen; PaCO₂ – partial pressure of arterial carbon dioxide; HCO₃ – arterial blood bicarbonate; BE – base excess; * - p - value with statistic significant difference

Figure 3 represents the ROC- curve of the values of PaO₂ on the third day. The area under the curve is 0.786 (95% CI 0.688-0.884), $p=0.001$.

There is a statistically significant correlation between the development of ARDS and the presence of CMV-infection ($p=0.016$). Five of the non – ARDS patients and 5 patients with ARDS were with active CMV infection (9.1% vs. 33.3%).

Figure 3. ROC-curve of PaO₂ mmHg on the third day.

The localization of the roentgenological changes at the time of hospital admission differs significantly between ARDS and non – ARDS groups ($p=0.007$). There was a predominance of bilateral pneumonia (in 80% of the cases) in the group of patients who developed ARDS.

In 26 (39.39%) of the patients without ARDS and in 14 (93.33%) of the patients with ARDS a change in the antibiotic therapy was needed due to failure of the initial treatment ($p<0.001$).

The factors which increase the probability of ARDS development are presented in Table 5.

Table 5. Risk factors for ARDS.

Factor	OR	95% CI	P
1-6 month after transplantation	7.130	1.457-34.895	0.015
Increased level of CRP	1.471	1.021-2.120	0.039
CMV-infection	7.700	1.892-31.344	0.004
Bilateral lung infiltrates	1.826	1.230-2.710	0.003
Failure of initial antibiotic therapy	21.538	2.669-173.784	0.004

4. Discussion

ARDS often occurs as a complication of pneumonia in kidney transplant patients [12 - 17]. The risk factors for its development include pneumonia in 1-6 month after transplantation, increased level of C- reactive protein, Cytomegalovirus-infection, bilateral lung infiltrates and failure of initial antibiotic therapy. The pathogenesis of ARDS in these patients is characterized by severe diffuse damage to the alveolar–capillary membrane as a result of

the infection. Some of the alveoli get filled with liquids, while others collapse and thus there is a sharp disturbance of the ventilation/perfusion ratio with a mosaic nature [18 - 20]. In a study conducted by Shorr et al. 42 190 kidney transplant patients in the USA were observed. 86 of those cases (0.2%) developed ARDS, while the estimated incidence of ARDS within the general population was 51 cases per 100 000 per year. The incidence of ARDS in kidney transplant patients was significantly higher than that in the general population of the USA ($p < 0.05$). The study showed that factors such as the demographic characteristics, transplantation indications, comorbidity, the antigen compatibility, the CMV-serostatus and the development of transplant rejection do not correlate with the development of ARDS [9]. Sun et al. analyzed 486 patients that had received a kidney from a cadaver, and 21 of them developed ARDS [10]. From our results, during the treatment period, ARDS developed in 15 of the patients with pneumonia (19%). Our results concerning the incidence of ARDS are significantly higher due to the specificity of patient's cohort included in this study. We calculated the incidence of ARDS only for the patients with pneumonia.

The time of developed pulmonary infections after the operation is crucial to the development of ARDS [21 - 23]. According to our data, the development of pneumonia during the second postoperative period (1 to 6 months) increases the risk of ARDS 7.13 times ($OR = 7.13$; 95% CI 1.457 – 34.895; $P = 0.015$). Our results come close to those collected by Sun et al. In their study, 18 of the ARDS cases developed within the second or third month of the postoperative period [10]. Gui et al. found that ARDS caused by pneumonia usually occurred 3-6 months after transplantation [24].

The laboratory results of the patients with both pneumonia and development of ARDS do not differ significantly when compared to those collected from the patients without ARDS. The only exception is CRP as it is statistically higher in the group suffering from ARDS ($p < 0.05$). The CRP increased as a result of lung injury and as a systemic inflammatory response [24 - 31]. If the CRP increases with one unit upper than maximum reference level, the risk for developing ARDS increases 1.475 times ($OR = 1.471$; 95% CI 1.021 – 20.120; $P = 0.039$). CRP values of 45.95 mg/L are with both the highest sensitivity - 73.3% and specificity – 65.2%. A more detailed monitoring of the patients is required in CRP values above this point. This will further improve early diagnosis of ARDS.

Hypoxemia at the time of hospital admission increases the risk of ARDS [32, 33]. Values of PaO_2 of 59.70 mmHg are both with the highest sensitivity – 74.2% and specificity- 66.7% as a prognostic indicator for ARDS development.

On the third day of treatment, arterial blood gases tests showed a prevalence of hypoxemia in patients who would develop ARDS ($p < 0.001$). The PaO_2 values of 58.45 mmHg on the third day of hospitalization can predict with

high probability ARDS development (sensitivity- 74.2%, specificity- 73.3%).

There is a correlation between the development of ARDS and the presence of CMV-infection [34 - 38]. The presence of CMV-infection increases the risk for ARDS 7.7 times ($OR = 7.7$; 95% CI 1.892 – 31.344; $P = 0.004$). The results come close to those collected by Shorr et al. In their study, 9.1% of the cases of CMV-serologically negative recipient/CMV-serologically positive donor developed ARDS [9].

The severity of the lung injury and the localization of the roentgenological changes in pneumonia patients play a certain role in the development of ARDS [39, 40]. The presence of bilateral roentgenological changes with inflammatory character at the time of hospital admission increases the risk of ARDS development 1.826 times ($OR = 1.826$; 95% CI 1.826 – 2.710; $P = 0.003$).

The initial antibiotic treatment failure increases the risk of ARDS [41 - 46]. According to our data initial antibiotic failure is associated with 21.538 times ($OR = 21.538$; 95% CI 2.669 – 173.784; $P = 0.004$) higher risk of ARDS development.

5. Conclusion

ARDS is one of the main complications of pneumonia in kidney transplant recipients. In our study, risk factors for the development of ARDS are: pneumonia in 1- 6 month after transplantation, increased level of C – reactive protein, bilateral lung infiltrates, CMV – infection and failure of initial antibiotic therapy. Recognition of risk factors would help prevention or early treatment of ARDS. That would lead to a general decrease of morbidity and mortality in the group of patients after renal transplantation.

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