Krasnalhia Lívia Soares de Abreu[1], Geraldo Bezerra da Silva Junior[1,2], Thalita Diógenes Muniz[1], Adller Gonçalves Costa Barreto[1], Rafael Siqueira Athayde Lima[3], Marcelo Alcântara Holanda[4], Eanes Delgado Barros Pereira[1], Alexandre Braga Libório[2], Elizabeth de Francesco Daher[1]

Acute kidney injury in critically ill patients with lung disease: kidney-lung crosstalk

Lesão renal aguda em pacientes com doença pulmonar: interação rim-pulmão

1. Department of Internal Medicine, Faculdade de Medicina, Universidade Federal do Ceará - UFC - Fortaleza (CE), Brazil.
2. Faculdade de Medicina, Health Sciences Center, Universidade de Fortaleza - UNIFOR - Fortaleza (CE), Brazil.
3. Department of Internal Medicine, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo - USP - Ribeirão Preto (SP), Brazil.
4. Respiratory Intensive Care Unit, Hospital de Messejana - Fortaleza (CE), Brazil.

ABSTRACT

Objective: To examine the factors associated with acute kidney injury and outcome in patients with lung disease.

Methods: A prospective study was conducted with 100 consecutive patients admitted to a respiratory intensive care unit in Fortaleza (CE), Brazil. The risk factors for acute kidney injury and mortality were investigated in a group of patients with lung diseases.

Results: The mean age of the study population was 57 years, and 50% were male. The incidence of acute kidney injury was higher in patients with PaO2/ $FiO_2 \leq 200$ mmHg (54% versus 23.7%; p=0.02). Death was observed in 40 cases and the rate of mortality of the acute kidney injury group was higher (62.8% versus 27.6%; p=0.01). The independent factor that was found to be associated with acute kidney injury was $PaO_2/FiO_2 \leq 200$ mmHg (p=0.01), and the independent risk factors for death were PEEP at admission (OR: 3.6; 95%CI: 1.3-9.6; p=0.009) and need for hemodialysis (OR: 7.9; 95%CI: 2.2-28.3; p=0.001).

Conclusion: There was a higher mortality rate in the acute kidney injury group. Increased mortality was associated with mechanical ventilation, high PEEP, urea and need for dialysis. Further studies must be performed to better establish the relationship between kidney and lung injury and its impact on patient outcome.

Keywords: Acute kidney injury; Respiratory insufficiency; Lung diseases; Prognosis; Mortality; Risk factors

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in critically ill patients and its incidence has been increasing.(1) AKI occurs in approximately 36 to 67% of patients admitted to intensive care units (ICUs). AKI is associated with increased mortality,(1,2) and even small increases in serum creatinine are associated with an increased risk of death.(2,3) The causes of AKI in the ICU are frequently "multi-factorial", and in most cases, AKI develops from a combination of hypovolemia, sepsis, nephrotoxins, and hemodynamic perturbations.(1)

Recent studies have demonstrated that AKI impacts the function of other organs, which is associated with increased mortality.(2) Patients with AKI have an increased risk for developing sepsis, respiratory insufficiency, hemorrhage and central nervous system dysfunction.(2) Experimental studies have demonstrated that ischemic AKI leads to an increase in circulating cytokines, chemokines and activated leucocytes, resulting in the infiltration of cells into a number of different organ systems, including the lungs, heart and central nervous

This study was conducted at the Hospital de Messejana - Fortaleza (CE), Brazil.

Conflicts of interest: None.

Submitted on February 9, 2013
Accepted on June 18, 2013

Corresponding author:
Elizabeth De Francesco Daher
Rua Vicente Linhares, 1.198
Zip code: 60135-270 - Fortaleza (CE), Brazil
E-mail: ef.daher@uol.com.br, geraldobezerrajr@yahoo.com.br

DOI: 10.5935/0103-507X.20130024

system.[4-6] The association between AKI and the need for mechanical ventilation (MV) has been demonstrated in past studies, suggesting a possible link between AKI and lung involvement.[3,7]

AKI can increase pulmonary vascular permeability and downregulate ion channels critical for fluid absorption in the lungs, leading to pulmonary inflammation, hemorrhage, septal edema and apoptosis.[8]

The occurrence of lung injury can also affect the kidneys and ventilator-induced lung injury is the most studied example of the lung-kidney interaction.[8] MV causes hemodynamic abnormalities, which can, in turn, affect renal perfusion by reducing cardiac output and stimulating hormonal and sympathetic pathways.[9]

The aim of this study was to examine the risk factors associated with AKI and outcome in patients with lung disease.

METHODS

Study subjects

A prospective study was conducted on all consecutive patients admitted to the respiratory ICU of Hospital de Messejana, Fortaleza city, northeast of Brazil, in the period between May and December 2009. The study protocol was reviewed and approved by the Committees of Ethics of the Hospital de Messejana, and signed informed consent was obtained from all patients or their legal representative, as appropriate.

The inclusion criteria were all patients with primary lung disease admitted to the ICU in the study period who required mechanical or noninvasive ventilation. Patients with acute lung injury (ALI) from non-pulmonary origin were not included. Patients under MV were considered to be invasively ventilated. The exclusion criteria were patients with preexisting chronic kidney disease (CKD), arterial hypertension, diabetes mellitus and other co-morbidities that could chronically affect renal function.

Parameters

The patients' demographic and clinical characteristics, such as age, gender, cause of pulmonary disease that led to ICU admission, length of hospital stay, need for MV and 24-hour urinary volume, were recorded. The laboratory data collected at admission, including urea, creatinine, hemoglobin, positive-end expiratory pressure (PEEP), arterial carbon dioxide tension ($PaCO_2$) and arterial oxygen tension/fractional inspired oxygen ratio (PaO_2/FiO_2), were analyzed. The hospital mortality data were also evaluated.

Definitions

The patients were classified according to the RIFLE criteria ("Risk", "Injury", "Failure", "Loss" and "End-stage renal disease") based on the creatinine criteria because most patients did not have their urinary volumes recorded in their medical charts.[10] Baseline creatinine was taken to be the value at the moment of hospital admission or the lowest creatinine level before admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) was used as the gold-standard severity score.[11] Oliguria was defined as urinary volume <400 mL/day despite appropriate fluid replacement.

Patient groups

The risk factors for AKI and mortality were investigated in a group of critically ill pulmonary patients. The factors associated with AKI and death were investigated through univariate and multivariate analyses. The glomerular filtration rate (GFR) was estimated through the MDRD (Modification of Diet in Renal Disease) formula, as previously described.[12] We also compared the GFR of the surviving patients at hospital discharge, using 60 mL/min/1.73 m^2 as the cutoff.

Statistical analyses

Statistical analyses were performed with the programs Statistics Package for the Social Science (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Epi-Info 6.04b (Centers for Disease Control and Prevention, Atlanta, GA, USA) and consisted of univariate and multivariate analyses. The comparisons between the two groups of patients were conducted using Student *t* test, Fischer exact test, Mann Whitney test and chi-square test, as appropriate. A logistic regression model was built for quantitative variables, and association measures were calculated (adjusted odds ratio - OR), with a confidence interval of 95% (95%CI). Multiple logistic regression analysis was used to identify the independent variables used as indicators of the predictors of mortality (dependent variable). The variables were chosen from the univariate model and entered into separate models using the stepwise method. Only those of statistical significance ($p<0.05$) were included in the final regression model. These models were built taking into account the problems of confounding factors and co-linearity. The following variables were entered into the model in the first block: PEEP, APACHE, need for MV and urea. The following variables were entered into the model in the second block: hemodialysis, urinary volume and GFR. For the investigation of independent risk factors for

AKI, a multivariate analysis was performed. This analysis included the factors that presented a significance level <20% in the univariate analysis (Mann-Whitney and chi-square tests). Values below 5% (p<0.05) were considered statistically significant.

RESULTS

A total of 100 patients were included in the study. The mean age of the study population was 57.2±18.3 years, and 50% were male. The causes of pulmonary disease that led to hospital admission were pulmonary infection (54%), chronic obstructive pulmonary disease (24%), lung neoplasm (9%), pulmonary tuberculosis (7%) and others (6%). AKI, as defined by the RIFLE criteria, was found in 30 cases (30%) at the moment of ICU admission and in 35 cases during ICU stay (35%). The patients were classified as "Risk" (34%), "Injury" (18%) and "Failure" (48%). There was no association between RIFLE classification and the study parameters.

There was no difference in age between patients with and without AKI (59.0±18.3 versus 56.2±18.4 years; p=0.47). There was also no difference in ICU stay between these two groups of patients (10.6±9.9 versus 8.5±6.6 days; p=0.26).

A total of 86 patients (86%) required mechanical ventilation, and the remaining cases used noninvasive ventilation. There was no significant association between the need for MV and AKI. MV was necessary for 32 patients with AKI (91.4%) and for 54 non-AKI patients (83%; p=0.32). There was a significant association between PaO_2/FiO_2 at admission and AKI. There were 12 patients with PaO_2/FiO_2 ≤200 mmHg, among which the AKI incidence was 54% at admission. In contrast, patients with PaO_2/FiO_2 >200 mmHg had an AKI incidence of only 23.7%. This difference was statistically significant (p=0.02). The mean PEEP at admission was similar in patients with and without AKI (6.8±2.4 versus 6.3±2.1; p=0.28), and the levels of hemoglobin were lower among AKI patients (8.8±2.6 versus 10.2±2.6 g/dL; p=0.001). The APACHE II score was higher among AKI patients (24±8.1 versus 20±10; p=0.04). The use of vasoactive drugs was not more frequent in patients with AKI, but sepsis was more frequent in patients with AKI (48.5% versus 20%; p=0.005). A comparison of the patients with and without AKI is shown in table 1.

Death occurred in 40 cases (40%). Patients with AKI had a mortality of 62.8%, which was higher than the mortality of non-AKI patients (27.6%; p=0.01). The comparison of survivors and nonsurvivors showed that nonsurvivors had a higher frequency of MV requirement, a higher PEEP at admission, an elevated urea level at admission and a higher APACHE II score and required dialysis more often (Table 2). The use of vasoactive drugs, as well as sepsis, was more frequent among nonsurvivors (72.5% versus 1.6%; p=0.0001). The following independent risk factors were associated with death: PEEP at admission (OR: 3.6; 95%CI: 1.3-9.6; p=0.009) and need for hemodialysis (OR: 7.9, 95%CI: 2.2-28.3; p=0.001). The risk factors for AKI and death, as analyzed by logistic regression, are shown in tables 3 and 4.

The sensitivity of RIFLE and APACHE II classifications in predicting mortality were shown by the areas under the curve of 0.64 (p=0.01) and 0.62 (p=0.03), respectively, as illustrated in figure 1.

Table 1 - The comparison of critically ill patients with lung disease according to the occurrence of acute kidney injury

	AKI (N=35)	Non-AKI (N=65)	p value
Age (years)	59.0±18.3	56.2±18.4	0.47
Gender			
Male	19 (54)	31 (48)	0.67
Female	16 (46%)	34 (52)	
Pulmonary disease			
Infection	20 (57.1)	34 (52.3)	0.67
CPOD	6 (17.1)	18 (27.6)	0.32
Neoplasm	4 (11.4)	5 (7.6)	0.71
Tuberculosis	4 (11.4)	3 (4.6)	0.23
ICU length of stay (days)	10.6±9.9	8.5±6.6	0.26
Use of vasoactive drugs during ICU stay	18 (51.4)	40 (61.5)	0.72
Sepsis	17 (48.5)	13 (20)	0.005
Need for mechanical ventilation	32 (91.4)	54 (83)	0.32
$PEEP_{adm}$ (cmH2O)	6.8±2.4	6.3±2.1	0.28
$PaCO_{2\ adm}$ (mmHg)	44±15	51±18	0.05
$PaO_2/FiO_{2\ adm}$ (mmHg)	200±135	322±215	0.01
PaO_2/FiO_2≤200 mmHg	20 (57.1)	17 (26.1)	0.02
Hb_{adm} (g/dL)	8.8±2.6	10.2±2.6	0.01
Ur_{adm} (mg/dL)	74.4±44.8	59.4±37.7	0.07
Cr_{adm} (mg/dL)	1.8±1.6	1.0±0.5	0.0003
GFR_{adm} (mL/min)	60±39	87±45	0.003
Urinay volume $(mL/day)_{adm}$	293±35	1025±369	0.0001
APACHE II	24±8.1	20±10	0.04
Death	22 (62.8)	18 (27.6)	0.01

AKI - acute kidney injury; CPOD - chronic obstructive pulmonary disease; ICU - intensive care unit; PEEP - positive-end expiratory pressure; $PaCO_2$ - arterial carbon dioxide tension; PaO_2 - arterial oxygen tension; FiO_2 - fractional inspired oxygen ratio; Hb - hemoglobin; Ur - urea; Cr - creatinine; GFR - glomerular filtration rate (MDRD); APACHE II - Acute Physiology and Chronic Health Evaluation II. *Student t* test and Fisher's exact test were used for analysis and significance was set at p<0.05. The results are expressed as numbers (%) and median±SD.

Table 2 - The comparison of critically ill patients with lung disease according to the occurrence of death

	Survivors (N=60)	Non-survivors (N=40)	p value
Age (years)	54.9±18.3	60.6±18.1	0.13
Gender			
Male	30 (50)	20 (50)	1.0
Female	30 (50)	20 (50)	
ICU length of stay (days)	9.7±7.0	8.7±9.2	0.56
Use of vasoactive drugs	22 (36.6)	36 (90)	0.008
Sepsis	1 (1.6)	29 (72.5)	0.0001
Need for mechanical ventilation	47 (78.3)	39 (97.5)	0.001
$PEEP_{adm}$ (cmH_2O)	5.8±1.7	7.2±2.5	0.009
$PaCO_{2adm}$ (mmHg)	46±13	51±22	0.23
PaO_2/FiO_{2adm} (mmHg)	310±211	232±171	0.05
PaO_2/FiO_2 ≤200 mmHg	7 (11.6)	5 (12.5)	1.0
Hb_{adm} (g/dL)	10±2.5	9.2±2.8	0.08
Ur_{adm} (mg/dL)	55.9±35.5	78.2±44.9	0.01
Cr_{adm} (mg/dL)	1.3±1.2	1.4±0.9	0.53
GFR_{adm} (mL/min)	81±48	62±35	0.03
APACHE II	20±10	24±9.6	0.04
Urinary volume (mL/day)	595±42	350±43	0.0001
Hemodialysis	5 (8.3)	15 (37.5)	0.001

ICU - intensive care unit; PEEP - positive-end expiratory pressure; $PaCO_2$ - arterial carbon dioxide tension; PaO_2 - arterial oxygen tension; FiO_2 - fractional inspired oxygen ratio; Hb - hemoglobin; Ur - urea; Cr - creatinine; GFR - glomerular filtration rate (MDRD); APACHE II - Acute Physiology and Chronic Health Evaluation II. The *Student t* test and Fisher's exact test were used for analysis and significance was set at $p<0.05$. The results are expressed as numbers (%) and median±SD.

Table 3 - Risk factors for acute kidney injury and death in critically ill patients with lung disease, as determined by univariate analysis

	OR	95%CI	p value
Risk factors for AKI			
Hemoglobin <8	3.12	1.18-8.25	0.02
APACHE >20	5.27	2.05-13.5	0.01
PaO_2/FiO_2≤200 mmHg	3.48	1.47-8.24	0.005
Risk factors for death			
PEEP>5 cmH_2O	2.08	1.31-9.70	0.01
Hemodialysis need	6.41	1.74-23.5	0.005
Need for mechanical ventilation	10.7	1.35-86.1	0.01

OR - odds ratio; 95%CI - 95% confidence interval; AKI - acute kidney injury; APACHE - acute physiology and chronic health evaluation; PaO_2 - arterial oxygen tension; FiO_2 - fractional inspired oxygen ratio; PEEP - positive-end expiratory pressure.

Table 4 - Risk factors for acute kidney injury and death in critically ill patients with lung disease, as determined by multivariate analysis

	OR	95%CI	p value
Risk factors for AKI			
PaO_2/FiO_2 ≤200 mmHg	2.9	1.4-7.9	0.03
Hemoglobin <8	4.7	1.3-12.6	0.01
APACHE >20	5.23	1.5-14.8	0.02
Risk factors for death			
PEEP	3.6	1.3-9.6	0.009
Hemodialysis need	7.9	2.2-28.3	0.001

OR - odds ratio; 95% CI - 95% confidence interval; PaO_2 - arterial oxygen tension; FiO_2 - fractional inspired oxygen ratio; APACHE - Acute Physiology and Chronic Health Evaluation; PEEP - positive-end expiratory pressure; AKI - acute kidney injury.

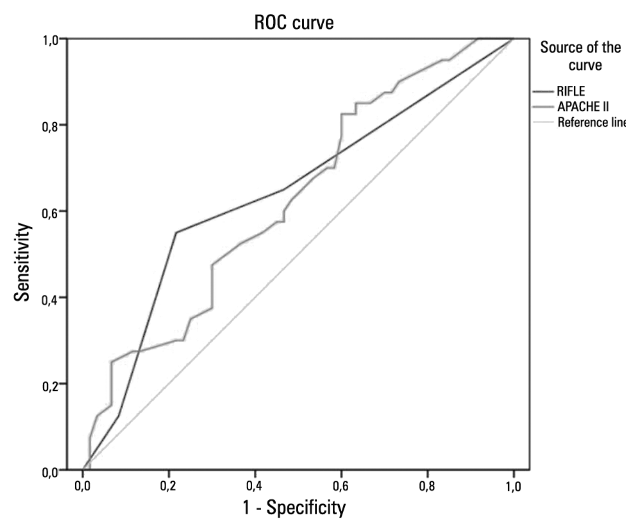

Figure 1 - The sensitivity of the RIFLE and APACHE II classifications in predicting mortality in patients with acute kidney injury and lung disease (AUC=0.64, p=0.01; AUC=0.62, p=0.03, respectively).

DISCUSSION

The kidney and lungs are the two organs that are most frequently involved in the so-called multi-organ failure syndrome. Additionally, there is some evidence that kidney failure can adversely affect pulmonary function and that pulmonary injury can lead to AKI.[9] Volume overload, which may occur during renal impairment, may increase pulmonary capillary hydrostatic pressure. Cytokines play a major role in the initiation and progression of both AKI and ALI and appear to be the prime factors mediating the local and systemic effects of kidney injury.[13] Here, we found important associations between kidney and lung disease among critically ill patients with pulmonary disease.

In the present study, AKI, as defined by the RIFLE criteria, was found in 30% of cases at the moment of ICU admission and in 35% cases during ICU stay. This result is in accordance with previous studies in which the RIFLE criteria was validated.[14] In our cohort, the patients with AKI were of similar age to those without AKI, and their age was similar to the findings reported by other studies conducted in our region.[7,15,16] The ICU length of stay was similar in patients with and without AKI, most likely due to the severity of pulmonary disease in both groups.

Mechanical ventilation was instituted for 86% of the studied cases, and there was no significant association between the need for MV and AKI. There was, however, a significant association between PaO_2/FiO_2 at admission and AKI, evidencing the impact of AKI in lung function. An independent risk factor associated with AKI was $PaO_2/FiO_2 \leq 200$ mmHg. Positive pressure ventilation alters venous return, cardiac preload, pulmonary vascular resistance and cardiac afterload. Accordingly, a decrease in several parameters of renal function, including GFR, renal blood flow and free water clearance, has been noted during positive pressure ventilation.(17) Blood gas changes induced by ALI/ARDS can also adversely affect renal hemodynamics and function. Severe hypoxemia and hypercapnia have been demonstrated to reduce renal blood flow due to increased renal vascular resistance related to the activation of vasoactive factors, including angiotensin II and endothelin, and a decrease in nitric oxide, which stimulate noradrenaline release and induce vasoconstriction, respectively.(18) In our cohort, the patients with AKI were more severely ill than those without AKI, as evidenced by a higher APACHE II score. This could have an impact on lung function.

Vieira et al.(19) reported that the median duration of MV, length of ICU stay and ICU mortality rate were longer in AKI patients compared with non-AKI patients. In the present study, there was no significant difference in the length of ICU stay between patients with and without AKI. In the present study, the patients with AKI had a mean duration of hospital stay of 10.6 days, compared to 8.5 days among those without AKI. This difference was not statistically significant. Similar results were also found for the frequency of MV requirement.

AKI-associated mortality remains high, ranging from 50 to 60%, despite the advances in critical care. This may be explained by the use of more aggressive medical and surgical interventions in an aging population.(2) In our cohort, the mortality rate was higher among patients with AKI (62.8%) and was significantly higher than in patients without AKI (27.6%). Previous studies have described AKI, as well as respiratory insufficiency, as independent risk factors for death in critically ill patients.(7,20) It is known that ALI and the consequent hypoxemia, hypercapnia and MV that arise from it worsens renal hemodynamics. This could have increased mortality among the studied cases.(18)

Death occurred in 40% of cases. The comparison of survivors and nonsurvivors showed that nonsurvivors had a higher frequency of MV requirement, higher PEEP at admission and higher urea levels at admission and required dialysis more often. The independent risk factors associated with death were PEEP at admission and need for hemodialysis. High values of PEEP are known to decrease the urinary flow rate, urinary sodium excretion and creatinine clearance.(18) It is currently accepted that much of the increased risk of death during AKI is actually due to extrarenal complications that are usually related to distant organ dysfunction.(21) As such, ALI and AKI synergistically worsen the outcome of critically ill patients.(22) In a study of patients with severe AKI who required dialysis, Chertow et al.(23) found a markedly higher mortality rate in patients who needed MV (81%). Both RIFLE and APACHE II were not good predictors of mortality, as shown in the ROC curve (AUC was under 0.7).

AKI is associated with a high risk for developing CKD.(24,25) Recent studies have shown that patients admitted with AKI are frequently discharged with decreased GFR and later develop CKD. In a study of 187 patients with acute tubular necrosis without previous kidney disease, Liaño et al.(26) showed that after a median follow-up of 7.2 years, 81% of patients had normal renal function. In a study of 206 ICU patients with AKI, 96 (46%) remained alive after 90 days. Of these patients, 89 (94%) had data after 3 years, 32 (35%) had CKD from disease onset and 25 (28%) developed CKD following the AKI episode.(25)

The exact mechanisms by which AKI can become CKD and its risk factors are still poorly understood. In a study of 131 CKD patients who developed dialysis-requiring AKI, Lee et al.(27) showed that 21 (16%) successfully withdrew from acute dialysis. The factors associated with dialysis withdrawal were larger kidney size (OR=1.755; p=0.018), lower predialysis creatinine (OR=0.722; p=0.002), and non-diabetes (OR=0.271; p=0.037). All patients in the non-withdrawal group remained on chronic dialysis after 5 years and 8 of 21 (38%) patients in the withdrawal group developed end-stage renal disease.

This study has some limitations. Due to the small number of patients included in the study, the power of the statistical analysis may have been compromised. As such, it is possible that other risk factors that were not identified here may also be involved in the interactions between the kidney and lung in critically ill patients. It is also possible that other variables that were missed could have influenced the occurrence of AKI and outcome.

CONCLUSIONS

The present study found a higher mortality rate in the acute kidney injury group. However, there was no association between the need for mechanical ventilation and acute kidney injury. The independent factor associated with acute kidney injury was $PaO_2/FiO_2 \leq 200$ mmHg. Increased mortality was associated with mechanical ventilation, high PEEP, urea and need for dialysis. Further studies must be performed to better establish the relationship between kidney and lung injury and its impact on patient outcome.

ACKNOWLEDGEMENTS

We are very grateful to the team of physicians, nurses and medical students at the Hospital de Messejana for the assistance provided to the patients.

RESUMO

Objetivo: Investigar os fatores associados à lesão renal aguda e o prognóstico em pacientes com doença pulmonar.

Métodos: Foi realizado estudo prospectivo com cem pacientes consecutivos admitidos em uma unidade de terapia intensiva respiratória em Fortaleza (CE). Foram investigados fatores de risco para lesão renal aguda e mortalidade em um grupo de pacientes com doenças pulmonares.

Resultados: A média de idade foi de 57 anos, sendo 50% do gênero masculino. A incidência de lesão renal aguda foi maior nos pacientes com $PaO_2/FiO_2 \leq 200$ mmHg (54% *versus* 23,7%; p=0,02). O óbito ocorreu em 40 casos. A mortalidade no grupo com lesão *renal* aguda foi maior (62,8% *versus* 27,6%; p=0,01). A relação $PaO_2/FiO_2 \leq 200$ mmHg foi fator independente associado à lesão renal aguda (p=0,01); PEEP na admissão (OR: 3,6; IC95%: 1,3-9,6; p=0,009) e necessidade de hemodiálise (OR: 7,9; IC95%: 2,2-28,3; p=0,001) foram fatores de risco independentes para óbito.

Conclusão: Houve maior mortalidade no grupo com lesão renal aguda. Mortalidade aumentada foi associada com ventilação mecânica, PEEP alta, ureia e necessidade de diálise. Estudos futuros devem ser realizados para melhor estabelecer as inter-relações entre lesão renal e pulmonar e seu impacto no prognóstico.

Descritores: Lesão renal aguda; Insuficiência respiratória; Pneumopatias; Prognóstico; Mortalidade; Fatores de risco

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