ORIGINAL ARTICLES

Acute Renal Failure in Lung Transplantation: Incidence, Correlation With Subsequent Kidney Disease, and Prognostic Value

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Objective: We studied the incidence of postoperative renal failure and its association with mortality in lung transplant patients in our hospital classified according to the severity of renal failure in the immediate postoperative period, and at 30 days, 6 months, and 1 year after transplantation.

Material and methods: For the period March 1997 through January 2006, 144 lung transplants were performed in our hospital. Six patients were lost to follow-up. Patients were assigned to 1 of the 5 Chronic Kidney Disease (CKD) classes according to the glomerular filtration rate on admission to the intensive care unit, and at 1 month, 6 months, and 12 months. Descriptive statistics were calculated for the sample. The relationship between the CKD classification and mortality was analyzed by calculating the odds ratio with a logistic regression model. The correlation between CKD classification on admission and at 1 month, 6 months, and 1 year after transplantation was analyzed using the Spearman correlation coefficient.

Results: Of the 144 patients analyzed, 52 patients were in CKD class 1, 63 in class 2, 19 in class 3, 2 in class 4, and 2 in class 5, according to the glomerular filtration rate. The correlation between mortality at 1 month and CKD classification on admission was not statistically significant (odds ratio, 1.11; 95% confidence interval, 0.42-3.11; *P*=.82) among patients with normal kidney function (CKD class 1) and those with some degree of renal failure (CKD classes 2-5). There was no correlation between CKD classification on admission and CKD classification at 1 month, 6 months, and 1 year although a significant positive correlation was found between CKD classification at 1 month and CKD classes at 6 months and 1 year.

Conclusions: We did not find any association between 1-month mortality and the degree of renal failure in the immediate postoperative period in lung transplant patients. There was a positive correlation between the degree of kidney failure at month and that observed 6 and 12 months after the procedure.

Key words: *Lung transplantation. Acute renal failure. Correlation. Mortality.*

Insuficiencia renal y trasplante pulmonar: incidencia, correlación con patología renal posterior y valor pronóstico

Objetivo: Presentamos un análisis de incidencia de disfunción renal y mortalidad de los pacientes a quienes se practicó un trasplante pulmonar en nuestro centro según el grado de insuficiencia renal que desarrollaron en el postoperatorio inmediato, a los 30 días, a los 6 meses y al año de realizado el trasplante.

Material y métodos: Durante el período definido (de marzo de 1997 a enero de 2006) se realizaron 144 trasplantes de pulmón en nuestro centro. Hubo 6 pérdidas en el seguimiento de los pacientes. Se clasificó a los pacientes en 5 grupos dependiendo del valor del filtrado glomerular en el momento de ingreso en la unidad de cuidados intensivos, al mes, a los 6 y 12 meses de realizado el trasplante, según la clasificación Chronic Kidney Disease (CKD). Se realizó un análisis estadístico descriptivo de la muestra. Se estudió la relación entre el CKD y la mortalidad, medida como *odds ratios*, mediante regresión logística. Se realizó un análisis de correlación entre el CKD al ingresar, al mes, a los 6 meses y al año de realizado el trasplante mediante el coeficiente de correlación de Spearman.

Resultados: De los 144 pacientes analizados, se clasificó, atendiendo al filtrado glomerular, a 52 en el grupo I, a 63 en el grupo II, a 19 en el III, a 2 en el IV y a otros 2 en el V. La asociación entre mortalidad al mes y CKD al ingresar no evidenció significación estadística (*odds ratio* = 1,11; intervalo de confianza del 95%, 0,42-3,11; p = 0,82) entre los pacientes con función renal normal (CKD 1) y aquéllos con algún grado de insuficiencia renal (CKD 2-5). No se encontró correlación entre el CKD al ingreso y el CKD al mes, a los 6 meses y al año. Sin embargo, se halló una correlación positiva (significativa) entre el CKD al mes y el CKD a los 6 meses y al año.

Conclusiones: No encontramos diferencias de asociación con la mortalidad al mes atendiendo al grado de insuficiencia renal en el postoperatorio inmediato de los pacientes con trasplante de pulmón. Existe una correlación positiva entre el grado de insuficiencia renal al mes y el observado a los 6 y 12 meses de realizado el trasplante.

Palabras clave: *Trasplante pulmonar. Insuficiencia renal aguda. Correlación. Mortalidad.*

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Introduction

Lung transplantation is indicated in patients with progressive lung disease when pharmacotherapies and other alternatives have failed and when the patients' clinical condition is deteriorating rapidly.[1] However, transplantation is not devoid of major complications in the short, medium, and long term.[2-6] Constant attention has been paid to factors predictive of mortality, such as the perfusion solutions used, the nutritional status of the recipients, and oxygenation in the early postoperative period, with a view to identifying risk factors and improving the outcomes.[7-11] It is known that, after lung transplantation, a significant percentage of patients will develop chronic renal failure, a condition that has often been attributed to the toxic effect of the calcineurin inhibitors used.[12-15] However, the incidence of acute renal failure and its effect on survival in the immediate postoperative period, and the subsequent changes in renal function, are not well characterized.

Several factors may contribute to the high incidence of acute renal failure in lung transplant recipients in the immediate postoperative period. First, it is known that patients with respiratory failure suffer hemodynamic instability of varying severity. This instability might be responsible for renal hypoperfusion, thereby favoring the development of renal failure. Second, the use of diuretics to manage pulmonary edema might also reduce circulating blood volume and so aggravate renal hypoperfusion.[15,16]

Although several authors have studied the effects of the hemodynamic status of the recipient before transplantation and the influence of this status on the postoperative glomerular filtration rate (GFR), few have investigated the role of acute renal failure in these patients.[15,17]

We undertook an analysis of the incidence of acute renal failure in the immediate postoperative period in patients receiving lung transplants in our center. We also studied the association with mortality of such failure according to severity. In addition, an analysis was performed of the correlation between the Chronic Kidney Disease (CKD) classification[18] on admission and 1 month, 6 months, and 1 year after the transplant procedure.

Material and Methods

All patients who underwent lung transplantation at the Hospital Universitario Marqués de Valdecilla in Santander, Spain, between March 1997 and January 2006 were included in the study. Clinical findings, laboratory data, and outcomes were reviewed from the patient records taken from the hospital database. Likewise, data on the transplanted organ taken from the hospital's transplant records were also reviewed.

Serum creatinine concentrations were obtained within 24 hours of transplantation—that is, while the patients were in the intensive care unit (ICU)—and 1 month, 6 months, and 12 months after the procedure. The GFR was estimated using the simplified Modification of Diet in Renal Disease formula. Patients were assigned to 1 of 5 CKD classes[18] according to their GFR (Table 1) on admission and 1 month, 6 months, and 1 year after the procedure. Hemofiltration was recorded if it had been performed in the first 72 hours after admission.

TABLE 1
Degree of Renal Failure According to the Chronic Kidney Disease (CKD) Classification

Class	GFR, mL/min/1.73 m^2	Description
1	>90	Normal renal function
2	60-89	Mild decrease in renal function
3	30-59	Moderate decrease in renal function
4	15-29	Severe decrease in renal function
5	<15	Very severe decrease in renal function

Abbreviation: GFR, glomerular filtration rate.

Statistical Analysis

Descriptive statistics were calculated for the sample. The results were presented in the form of numbers and percentages for categoric variables and as means (SD) for continuous ones. Means were compared using the *t* test or analysis of variance; proportions were compared with the χ^2 test or the Fisher exact test. The relationship between CKD classification on admission and mortality at 1 month was investigated using the odds ratio (OR) calculated from a logistic regression analysis. The relationship between CKD classification at 6 months and mortality at 1 year was investigated in the same way.

The correlations between CKD classification on admission and 1 month, 6 months, and 1 year after transplantation were analyzed using the Spearman correlation coefficient.

Results

From March 1997 through January 2006, 144 lung transplant procedures were performed in the transplant unit of the Hospital Universitario Marqués de Valdecilla. Six patients were lost to follow-up because not all the data required for analysis could be obtained from the retrospective search in the patient records.

These 144 transplant procedures were performed in 141 patients. The mean (SD) age of the recipients was 52 (11.7) years (median, 55 years; 25th and 75th percentiles, 48 and 60 years, respectively). Seventy percent of the 144 recipients were men and 30% were women. Transplantation was indicated for pulmonary emphysema in 36%, idiopathic pulmonary fibrosis in 31%, cystic fibrosis in 4%, primary pulmonary hypertension in 3%, retransplantation in 1%, and α_1-antitrypsin deficiency in 9%; transplantation was performed for other reasons in 15% of the patients. A double-lung transplant was performed in 92 patients and a single-lung procedure was done in 52. The mean age of the donors was 37 (13) years, 65% were men, and the ratio of PaO_2 to mean fraction of inspired oxygen was 464 (75) mm Hg. The mean duration of the surgical procedure was 364 (12) minutes. The 2 main lung preservation solutions used were Eurocollins solution (in 41%) and Perfadex solution (in 59%). On admission to the ICU after the transplant procedure, the mean systolic blood pressure was 113 (22) mm Hg (median, 110 mm Hg) and the mean diastolic blood pressure was 62 (14) mm Hg (median, 60 mm Hg). The mean systolic pulmonary artery pressure was 35 (11) mm Hg

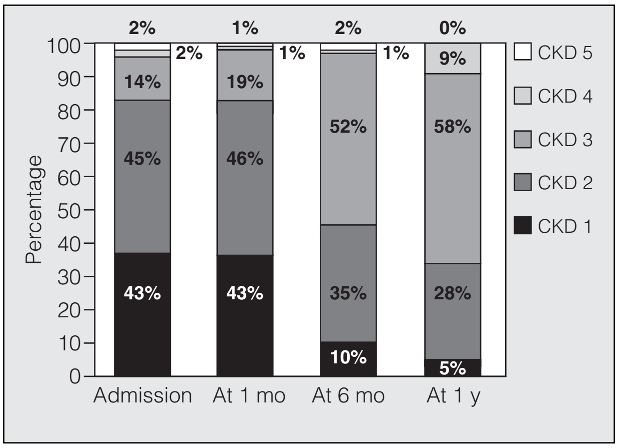

Figure 1. Distribution of patients according to degree of renal failure on admission and 1 month, 6 months, and 1 year after transplantation. CKD indicates Chronic Kidney Disease classes.

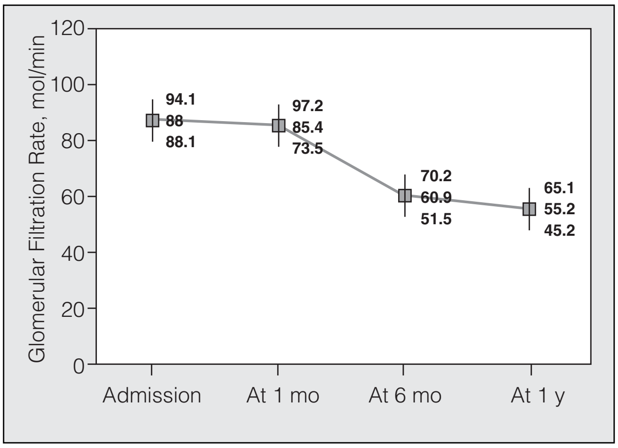

Figure 2. Changes in glomerular filtration rates in lung transplant recipients during the first year after the procedure.

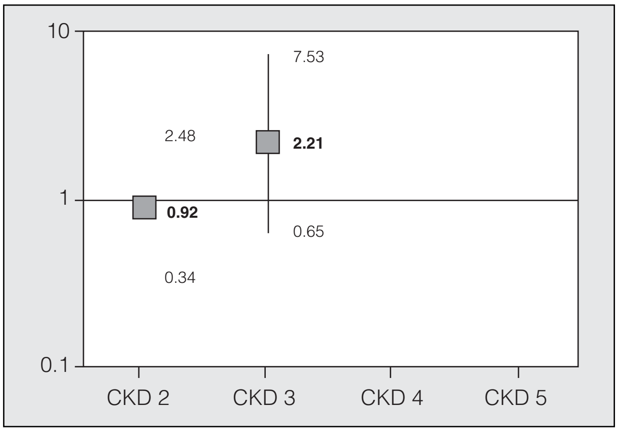

Figure 3. Association between Chronic Kidney Disease (CKD) classification in the immediate postoperative period and 30-day mortality reflected by the odds ratio calculated from a logistic regression analysis taking patients in CKD class 1 as the reference group.

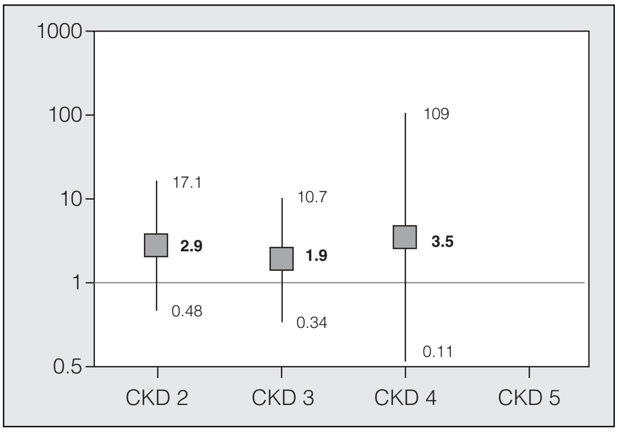

Figure 4. Association between Chronic Kidney Disease (CKD) classification at 6 months after the procedure and mortality at 1 year measured with the odds ratio calculated from a logistic regression analysis taking patients in CKD class 1 as the reference group.

and the mean diastolic pulmonary artery pressure was 19 (7) mm Hg. The mean concentration of serum creatinine in the first 24 hours was 0.98 (0.33) mg/dL. Some sort of continuous renal replacement therapy was used in 11% of the patients in the first 72 hours.

Table 2 shows the CKD classification of the patients on admission along with their main characteristics.

Patient follow-up during the first year after transplantation revealed a progressive decline in GFR (Figure 1). The decline during the first 6 months was 4.5 mL/min/mo compared to 1 mL/min/mo in the second half of the first year (Figure 2).

The association between CKD class and mortality at 30 days was studied using the OR calculated from a logistic regression analysis and taking the patients in CKD class 1 as the reference group (Figure 3). Patients with renal failure (CKD classes 2-5) were also grouped together and the association between renal failure and 30-day mortality was analyzed, taking patients with no renal failure (CKD class 1) in the immediate postoperative period as the reference group. An OR of 1.11 was thus obtained (95% confidence interval, 0.42-3.11; *P*=.82). Similarly, the association between CKD classification 6 months after the procedure and mortality at 1 year was studied (Figure 4).

The cause of death was classified into 5 categories: *a)* sepsis, septic shock, multiorgan failure; *b)* chronic respiratory failure or bronchiolitis obliterans; *c)* primary graft failure (early); *d)* cardiac events; and *e)* others. No differences were found in the distribution of causes of death between the 5 CKD classes (Table 2).

The Spearman correlation coefficients between CKD classification on admission and at 1 month, 6 months, and 1 year after transplantation are shown in Table 3.

There was a clear trend for patients who developed more severe renal failure (lower GFR) to have longer ICU stays and be connected to mechanical ventilation for longer periods, although the differences were not quite statistically significant (*P*=.07 and *P*=.06, respectively).

Of the 144 patients, 16 (11%) received continuous renal replacement therapy. The indication for such therapy was not always deterioration in renal function. In 31% of the patients, it was used to force a larger negative water balance

TABLE 2
Main Patient Characteristics by Degree of Renal Failure According to the Chronic Kidney Disease (CKD) Classification on Admissiona

	CKD 1 (n=52)	CKD 2 (n=63)	CKD 3 (n=19)	CKD 4 (n=2)	CKD 5 (n=2)	*P*[b]
Mean age, y	52 (13)	53 (9)	57.7 (5)	56 (12.7)	46 (19.8)	.44
Men	67% (n=35)	73% (n=46)	58% (n=11)	50% (n=1)	100% (n=2)	.58
ECC	4% (n=2)	11% (n=7)	16% (n=3)	100% (n=2)	50% (n=1) 0	
MAP	79.6 (19.5)	77.7 (14.25)	76 (11.15)	67.5 (17.6)	85.8 (17.6)	.71
Reperfusion edema	25% (n=13)	36% (n=23)	52% (n=10)	0%	0%	.13
CsA groupc	52% (n=27)	54% (n=34)	73% (n=14)	50% (n=1)	(n=50%)	.57
Cause of death at 30 d/at 1 y						NS
Sepsis/MOF	44% (n=4)/52% (n=10)	50% (n=5)/45% (n=10)	50% (n=3)/54.5% (n=6)	–/–	–/–	
Bronchiolitis obliterans	–/5% (n=1)	–/4.5% (n=10)	–/–	–/–	–/–	
IPF	–/–	30% (n=3)/18% (n=4)	17% (n=1)/9% (n=1)	–/–	–/–	
CRA	33% (n=3)/16% (n=3)	10% (n=1)/9% (n=2)	17% (n=1)/18% (n=2)	100% (n=1)/100% (n=1)	–/–	
Cancer	–/5% (n=1)	–/4.5% (n=1)	–/–	–/–	–/–	
Other/not reported	22% (n=2)/21% (n=4)	10% (n=1)/18% (n=4)	17% (n=1)/18% (n=2)	–/–	–/100% (n=1)	
Disease						NS
COPD/emphysema	22 (42%)	25 (39%)	4 (21%)	0 (0%)	0 (0%)	
Pulmonary fibrosis	13 (25%)	18 (28%)	9 (47%)	2 (100%)	0 (0%)	
PCF	4 (8%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	
PPHT	1 (2%)	2 (3%)	0 (0%)	0 (0%)	1 (50%)	
α_1-ATD	6 (11%)	5 (8%)	3 (16%)	0 (0%)	1 (50%)	
Other	6 (11%)	13 (20%)	2 (10%)	0 (0%)	0 (0%)	
Duration of first lung ischemia	239 (47)	237 (56)	248 (44)	312	269 (22)	.727
Second lung ischemia duration	326 (59)	346 (57)	336 (75)	345	327 (46)	.422
Hours of mechanical ventilation	111 (256)	180 (300)	172 (212)	1080	625 (643)	.06
Duration of ICU stay, d	7 (4)	13 (19)	14 (17)	43	27 (25)	.007

[a]Results are shown as mean (SD), absolute number (percentage), or percentage (number of patients).
[b]Analysis of variance and χ^2 or Fisher exact test.
[c]Use of cyclosporine vs tacrolimus as a calcineurin inhibitor.
Abbreviations: α_1-ATD, α_1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; CRA, cardiorespiratory arrest; CsA, cyclosporine A; ECC, extracorporeal circulation; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; MAP, mean arterial pressure; MOF, multiorgan failure; NS, not significant; PCF, pancreatic cystic fibrosis; PPHT, primary pulmonary hypertension.

TABLE 3
Spearman Correlation Coefficients Between Chronic Kidney Disease (CKD) Classification on Admission and 1 Month, 6 Months, and 1 Year After Transplantation

CKD	CKD			
	On Admission	1 Month	6 Months	1 Year
On admission				
Correlation coefficient	1	0.142	0.155	0.040
P		.139	.149	.726
1 Month				
Correlation coefficient		1	0.378[a]	0.255[b]
P			<.001	.022
6 months				
Correlation coefficient			1	0.526[a]
P				<.001
1 Year				
Correlation coefficient				1
P				–

[a]Significant correlation at .01 level. [b]Significant correlation at .05 level.

due to the presence of reperfusion edema. In total, 81% of the patients who underwent renal replacement therapy died within 1 month of the procedure. The relative risk of death was 5.91 (95% confidence interval, 4.06-34.50) among patients who received hemofiltration.

Discussion

There is no general agreement on a definition for acute renal failure. Recently, a consensus statement was published based on the criteria known as RIFLE (risk, injury, failure, loss, and endstage kidney disease criteria), by which renal failure is classified in part by changes in serum creatinine and in part by changes in GFR.[18] Given that we could not determine the GFR before transplantation, the patients were classified and studied by assessing the GFR in the first 24 hours of admission to the ICU, and 1, 6, and 12 months after the lung transplant procedure.

We should also point out that serum creatinine and/or urea do not always truly reflect the functional status of the kidneys. The GFR can decrease by as much as 50% without creatinine elevations occurring because increased tubular secretion can compensate for loss of filtration. On other occasions, urea and creatinine are elevated for reasons other than renal failure (eg, gastrointestinal bleeding, corticosteroid administration, tetracycline and/or cephalosporin use, increased protein intake, administration of amino acids, and hypercatabolic and febrile conditions). However, in all cases, there is a decrease in GFR.[19,20]

In our group of lung transplant recipients, the incidence of acute renal failure of any degree was 59% in the immediate postoperative period. Few studies analyzing acute renal failure in these patients in the immediate postoperative period can be found in the literature. Recently, Rocha et al[17] presented the findings of a retrospective analysis of a group of 296 patients. In their study, the incidence of development of acute renal failure—56%—was similar to that found in ours —59%. Here we should emphasize that, whereas Rocha et al used RIFLE-1 criteria for defining and classifying the patients, we used GFR recorded in the first 24 hours. This could lead to a loss of specificity when diagnosing acute renal failure in our patients given that individuals with normal renal function will be correctly diagnosed less often.

Our patients showed a progressive decline in GFR during the year of follow-up. This decline could be divided into 2 phases with a sharper decrease during the first half of the first year (4.5 mL/min/mo) than during the second half (1 mL/min/mo). Broekroelofs et al[21] studied this sharper decline in renal function in the first 6 months in 57 patients, finding that the decrease in renal function in the first period depended on the underlying lung disease prior to transplantation. Thus, cystic fibrosis was the disease associated with the sharpest decline in the 6-month period after the procedure, whereas those transplant recipients who had pulmonary hypertension were the group with the best preserved GFRs. Those authors suggested that the principle explanations for this difference were the larger doses of cyclosporine and the greater use of nephrotoxic antibiotics in patients with cystic fibrosis. Indeed, when we stratify our patients by the indication for transplantation and look at their distribution according to CKD classification (Figure 5), we see that all patients with cystic fibrosis were in CKD class 5 at 1 year after the procedure. This finding is consistent with the aforementioned study of Broekroelofs et al, although the number of patients with cystic fibrosis who received a lung transplant in our series was small. Our analysis also shows that patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis were mainly in CKD classes 1 and 2 in the immediate postoperative period, consistent with the findings of Rocha et al.[17] Finally, the patients who underwent the procedure for COPD or emphysema were those who had the best preserved their renal function 1 year after the procedure (Figure 5).

Our analysis failed to reveal a correlation between degree of renal failure on admission to the ICU and after 1 month, 6 months, and 1 year of follow-up of GFR in our patients. However, there was a positive correlation between the different degrees of renal failure at 1 month and CKD at 6 months and 1 year. Broekroelofs et al[21] did in fact find a correlation between changes in GFR during the first month (pretransplant reference value) and the absolute value of GFR at 24 months after the procedure. The main difference between our findings and theirs lies in the fact that they analyzed changes in GFR and the fact that those authors did not classify their patients according to degree of renal failure as we did.

The survival analysis in the study of Rocha et al[17] showed that patients who developed acute renal failure had a greater probability of delayed withdrawal of mechanical ventilation, prolonged hospital stay, and higher early mortality. The main difference in this respect compared to our study lies in the fact that those authors assessed renal failure in the first 2 weeks after the procedure whereas we did so in the first 24 hours. Our findings on the delay in withdrawal of mechanical ventilation and longer stay in the ICU are

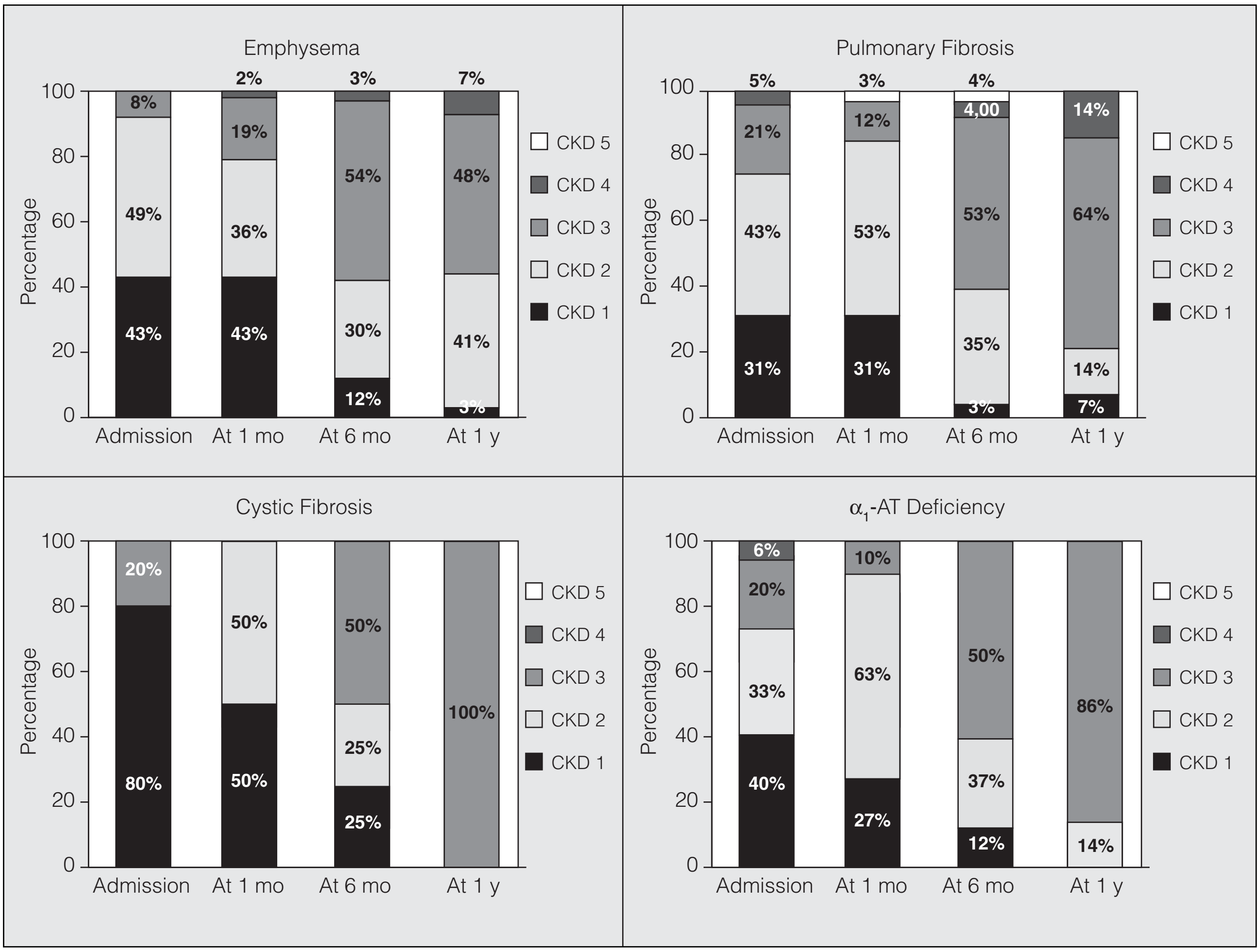

Figure 5. Distribution of patients according to the Chronic Kidney Disease (CKD) classification in the first year after transplantation, stratified by disease for which the transplant procedure was indicated. α_1-AT indicates α_1-antitrypsin.

consistent with theirs; however, we believe that it might be harder to control the water balance in the patients who develop renal failure than in those who do not. With a positive water balance (fluid retention), patients would have more water in the bloodstream. In combination with low oncotic pressure (usually in malnourished patients and those with protein depletion or hypoalbuminemia), this could also increase the amount of extravascular lung water present. Such a process could hinder adequate oxygenation and delay withdrawal of mechanical ventilation. However, this explanation would only be valid when renal failure occurred before respiratory failure. In short, unlike other studies, which analyzed chronic renal failure in lung transplant recipients in terms of use immunodepressants,[16,17,21] we assessed acute renal failure in the immediate postoperative period. The few studies published that analyze this aspect focus mainly on associated morbidity. Therefore, we can conclude that acute renal failure in these patients in the postoperative period is common, but it does not correlate with degrees of chronic renal failure in the first year after transplantation. Recipients who develop moderate acute renal failure (CKD class 3) tended to present a stronger association with mortality 1 month after the procedure than those who did not develop any failure, although this finding was not statistically significant. A progressive 2-phase loss in renal function—greater in the first 6 months after the intervention—was observed. The greater degree of chronic renal failure after 6 months was associated with a greater risk of death 1 year after the procedure.

Finally, when acute renal failure in the immediate postoperative period required renal replacement therapy, the association with mortality became stronger. The incidence of patients requiring dialysis in the series studied by Rocha et al[17] was 8% compared to 11% in our series. This difference could be explained by the fact that we assessed renal replacement therapy even when it was not indicated for acute renal failure. On this point it remains unclear, though, whether the use of renal replacement therapy had a direct effect on mortality or whether it was simply a marker of disease severity. Theoretically, appropriate use of these techniques improves control of water volume, electrolyte imbalance, and acid-base balance and so should decrease mortality due to acute renal failure.

This does not, however, appear to be the case. When analyzed with adjustment for different postoperative comorbidities and complications, the use of renal replacement therapy increased mortality in the ICU.[22]

Finally, we should mention the limitations of the present study. In addition to the criterion used for studying and comparing renal function of patients at a specific moment, our study has 2 important limitations. First, our sample was taken from a single transplant center, was retrospective, and covered a period of 9 years. This period therefore does not capture changes in clinical practice, such as the different immunosuppression protocols or changes that might occur in surgical techniques. Second, valuable information was lost in the analysis of different risk factors, such as use of inotropic agents during the intervention or the hemodynamic status during surgery. However, we were able to account for use of unscheduled extracorporeal circulation, hemodynamic status on admission to the ICU, and administration of inotropic agents in the immediate postoperative period.

We believe that further studies with greater statistical power should be done to confirm our findings.

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