

Prevalence of Chronic Renal Dysfunction in Maintenance Kidney, Liver, Heart, and Lung Transplant Recipients - ICEBERG Study

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Abstract

Background: *Early detection of chronic renal dysfunction after organ transplantation is essential to delay the progression of kidney disease, but uniform diagnostic criteria are not well established. We sought to compare the prevalence of chronic renal dysfunction according to different diagnostic criteria in maintenance kidney, liver, heart, and lung transplant patients.*

Methods: *A retrospective, cross-sectional, multicenter study was conducted in transplant units in Spain. We analyzed 1,617 kidney (n = 869), liver (n = 395), heart (n = 244), and lung (n = 109) transplant patients, with ≥ 2 years of evolution. Chronic renal dysfunction was defined according to physician's clinical criteria and objective laboratory criteria (serum creatinine ≥ 2 mg/dl and/or estimated glomerular filtration rate < 60 ml/min/1.73 m²).*

Results: *67.2% of patients were male and the mean (standard deviation) age of the population was 48.5 (12.5) years. Posttransplantation follow-up was 7.6 (4.6) years. Chronic renal dysfunction was diagnosed in 36.7% of patients (95% CI: 34.4-39.0) according to clinical criteria, and in 65.2% (95% CI: 62.9-67.5) according to objective criteria (70.2% kidney, 50.4% liver, 65.6% heart, and 78.9% lung transplants; p < 0.0001). There was fair-to-moderate agreement (Kappa coefficient: 0.45) between both diagnostic methods; 46.3% of patients without clinical diagnosis of chronic renal dysfunction had objective diagnosis. Renal biopsies were performed almost exclusively in kidney transplant patients with chronic renal dysfunction (29.8%).*

Conclusions: *Due to the lack of consensus on the definition of chronic renal dysfunction, there is a significant underestimation of the clinical diagnosis by physicians. Eight years*

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after transplantation, chronic renal dysfunction affected 65% of patients. The use of estimated glomerular filtration rate to diagnose chronic renal dysfunction would allow an earlier detection and better therapeutic approach. (Trends in Transplant. 2013;7:59-66)

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Key words

Chronic renal dysfunction. Diagnosis. Prevalence. Solid-organ transplantation.

Introduction

Chronic renal dysfunction (CRD) is a frequent complication in nonrenal solid-organ transplantation, associated with increased morbidity and premature mortality. Overall, the occurrence of CRD after nonrenal organ transplantation is associated with a four- to fivefold increase in mortality¹. In kidney transplantation, CRD also remains the leading cause of allograft failure among kidney transplant recipients².

Serum creatinine remains as one of the most established methods for estimating renal function in daily practice³. However, serum creatinine is a delayed marker of renal dysfunction and values within normal range can correspond to significantly decreased levels of glomerular filtration rate (GFR)⁴. Thus, a number of creatinine-based formulae, which take into account some nonrenal independent factors influencing renal impairment, have been developed for estimating the GFR⁵.

The present study aimed to compare the prevalence of CRD according to different diagnostic criteria (physician's clinical criteria vs. objective laboratory criteria) in maintenance kidney, liver, heart, and lung transplant recipients. A secondary objective was to evaluate to what extent the clinical diagnosis of CRD led to a change in immunosuppressive therapy in these patients.

Methods

We present a pooled analysis of four retrospective, cross-sectional, multicenter ICEBERG studies, conducted in 92 organ transplant outpatient units (52 kidney, 21 liver, 13 heart, and six lung transplant units) in Spain, which included recipients of a kidney⁶, liver, heart, or lung transplant between 2007 and 2011. A consecutive sampling was performed following initiation of each ICEBERG study at each site.

The study population for our analysis included 1,617 patients aged 18 years or older at the study visit who received a kidney (n = 869), liver (n = 395), heart (n = 244), or lung (n = 109) transplant at least two years before inclusion. Multiorgan transplant recipients or patients on dialysis were excluded.

The four ICEBERG studies were conducted in accordance with the Declaration of Helsinki (2000), and the respective protocols were approved by the ethics committees of all participating institutions. Signed informed consent was obtained from all patients prior to their inclusion.

Chronic renal dysfunction was recorded according to physician's clinical criteria (the physician was specifically asked, through a yes/no dichotomy, if clinical diagnosis of CRD had been established) and, alternatively, based on objective laboratory criteria (serum

Table 1. Demographics, anthropometrics, and clinical characteristics of 1,617 organ transplant recipients

Characteristic	Kidney (n = 869)	Liver (n = 395)	Heart (n = 244)	Lung (n = 109)	Total (n = 1,617)	P-value
Age at transplant (years), mean (SD)	45.8 (13.0)	52.5 (9.8)	51.2 (12.1)	48.9 (12.7)	48.5 (12.5)	< 0.0001
Gender (male), n (%)	534 (61.5)	284 (71.9)	197 (80.7)	71 (65.1)	1,086 (67.2)	< 0.0001
Time since transplantation (years):						
mean (SD)	8.2 (5.1)	6.9 (3.9)	7.7 (4.0)	5.0 (2.4)	7.6 (4.6)	< 0.0001
BMI (kg/m ²):						
mean ± SD	26.8 (4.7)	26.8 (4.6)	27.7 (4.9)	25.4 (4.8)	26.9 (4.8)	0.0003
Induction therapy (yes), n (%)	314 (36.1)	65 (16.5)	171 (70.1)	26 (23.9)	576 (35.6)	< 0.0001
Type of induction therapy, n (%)*:						
Anti-CD25	166 (52.9)	51 (78.5)	57 (33.3)	22 (84.6)	296 (51.4)	< 0.0001
OKT3	20 (6.4)	1 (1.5)	84 (49.1)	0 (0.0)	105 (18.2)	
Thymoglobulin	128 (40.8)	13 (20.0)	30 (17.5)	1 (3.9)	172 (29.9)	
immunosuppressive treatment at discharge, n (%):						
Monotherapy	3 (0.4)	33 (8.4)	1 (0.4)	2 (1.8)	39 (2.4)	< 0.0001
Combination therapy	866 (99.7)	331 (83.8)	243 (99.6)	107 (98.2)	1,547 (95.7)	
Combination therapy at discharge, n (%)†:						
CNI-based	693 (80.0)	108 (32.6)	223 (91.8)	87 (81.3)	1,111 (71.8)	< 0.0001
mTOR inhibitor-based	36 (4.2)	1 (0.3)	6 (2.5)	1 (0.9)	44 (2.8)	
Others	137 (15.8)	222 (67.1)	14 (5.8)	19 (17.8)	392 (25.3)	

Patients lacking data: age at transplantation (21 kidney); gender (1 kidney); time since transplantation (1 liver); body mass index (20 kidney, 13 liver, 8 heart); induction therapy (16 kidney, 1 liver, 1 heart); type of induction therapy (3 lung); immunosuppressive treatment at discharge (31 liver).

*Percentages with respect to the total number of patients on induction therapy.

†Percentages with respect to the total number of patients on combination therapy.

BMI: body mass index; CNI: calcineurin inhibitor; mTOR: mammalian target of rapamycin.

creatinine at time of clinical diagnosis of CRD ≥ 2 mg/dl and/or estimated GFR [eGFR] < 60 ml/min/1.73 m²). For patients without a physician's clinical diagnosis of CRD, we considered serum creatinine at the study visit to estimate GFR. Objective laboratory criteria set the cutoff point for serum creatinine at ≥ 2 mg/dl and/or eGFR < 60 ml/min/1.73 m² according to National Kidney Foundation guidelines⁷. Glomerular filtration rate was estimated using Modification of Diet in Renal Disease (MDRD)-4 equation⁸.

Qualitative and quantitative variables were analyzed by the Chi-square or Fisher's exact tests and the Kruskal-Wallis test, respectively.

Concordance between physician-based clinical and objective diagnosis of CRD was evaluated using the Kappa index. A p-value < 0.05 was considered significant. Statistical analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC).

Results

A total of 1,617 patients were included in the analysis. Table 1 shows the main characteristics of the study population. Two-thirds of patients were male (80.7% among heart transplant recipients; $p < 0.0001$), with a mean age of 48.5 (12.5) years at transplantation,

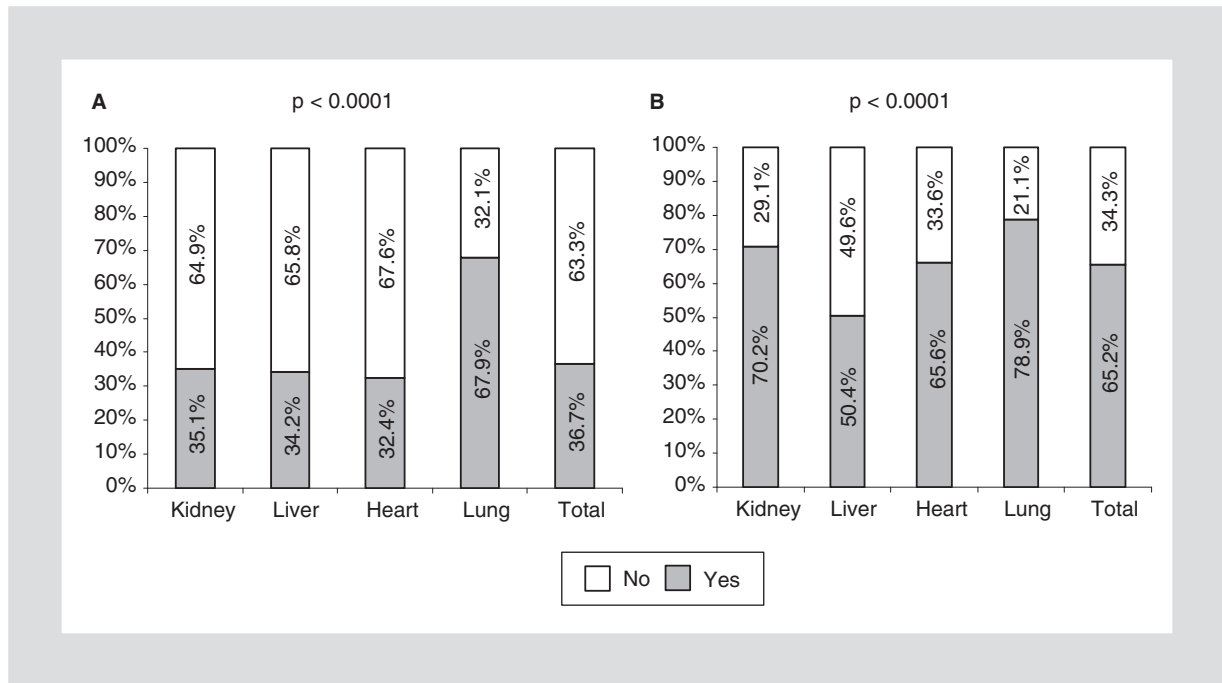


Figure 1. Prevalence of chronic renal dysfunction based on physician's clinical criteria (A) and objective laboratory criteria (serum creatinine ≥ 2 mg/dl and/or estimated glomerular filtration rate < 60 ml/min/1.73 m²) (B) in a total of 1,617 solid-organ transplant recipients: kidney (n = 869), liver (n = 395), heart (n = 244), or lung (n = 109) transplant recipients.

with kidney and liver transplant recipients being slightly younger and older than the others, respectively ($p < 0.0001$). Mean time post-transplantation was 7.6 (4.6) years (minimum two years and maximum 32 years). According to the transplanted organ, posttransplant time was longer in kidney transplant recipients, followed by heart and liver transplants ($p < 0.0001$). Nearly 62% of patients were overweight or obese (ranging from 50.5 to 65.6% for lung and heart transplant recipients, respectively; $p < 0.0001$). Antibody induction therapy was used in 35.6% of patients (16.5% liver vs. 70.1% heart transplant recipients; $p < 0.0001$), mainly anti-CD25 for lung and liver transplants, and OKT3 for heart transplants ($p < 0.0001$). Thymoglobulin accounted for 40.8% of the induction therapies among kidney transplant recipients. At the time of discharge, the most commonly used immunosuppressants were calcineurin inhibitors (CNI), administered in combination with other immunosuppressive treatments (71.8% of combination therapies).

Chronic renal dysfunction was diagnosed based on physician's clinical criteria in 593 out of 1,617 patients (36.7%; 95% CI: 34.4-39.0) whereas, according to objective laboratory criteria, CRD was diagnosed in 1,055 patients (65.2%; 95% CI: 62.9-67.5) (Fig. 1). All 1,055 patients showed eGFR < 60 ml/min/1.73 m² in whom creatinine levels were ≥ 2 mg/dl in 355 (33.6%) or < 2 mg/dl in 693 (65.7%) patients.

Diagnosis of CRD based on physician's clinical criteria was the highest among lung transplant recipients (67.9%) and was lower for kidney (35.1%), liver (34.2%), and heart transplants (32.4%), while CRD diagnosis based on objective laboratory criteria ranged from 50.4 to 78.9% for liver and lung transplants, respectively ($p < 0.0001$ for both) (Fig. 1).

When examining the concordance between physician's clinical criteria and objective laboratory criteria, there was fair-to-moderate agreement between the clinical

Table 2. Renal biopsies performed, renoprotective treatment introduced, and changes in immunosuppressive therapy after clinical diagnosis of chronic renal dysfunction in 593 organ transplant recipients

Variable	Kidney (n = 305)	Liver (n = 135)	Heart (n = 79)	Lung (n = 74)	Total (n = 593)	P-value
Renal biopsy (yes), n (%)	91 (29.8)	2 (1.5)	0 (0.0)	0 (0.0)	93 (15.7)	< 0.0001
Renoprotective treatment (yes), n (%):	108 (35.4)	39 (28.9)	13 (16.5)	9 (12.2)	169 (28.5)	< 0.0001
Changes in immunosuppressive therapy (yes), n (%)	132 (43.3)	121 (89.6)	37 (46.8)	58 (78.4)	348 (58.7)	< 0.0001
Type of change, n (%)*:						
CNI reduction without any other change	51 (38.6)	37 (30.6)	21 (56.8)	20 (34.5)	129 (37.1)	0.0003
CNI reduction/withdrawal + MPA (MMF/MPS) modification	47 (35.6)	59 (48.8)	8 (21.6)	14 (24.1)	128 (36.8)	
CNI reduction/withdrawal + mTOR inhibitor introduction	34 (25.8)	16 (13.2)	8 (21.6)	6 (10.3)	64 (18.4)	
Other changes	0 (0.0)	9 (7.4)	0 (0.0)	3 (5.2)	12 (3.5)	

Patients lacking data: renal biopsy (4 kidney, 3 lung); renoprotective treatment (6 kidney, 1 heart); changes in immunosuppressive therapy (39 kidney, 4 heart, 1 lung); type of change (15 lung).

*Percentages with respect to the total number of patients with changes in immunosuppressive therapy.

CNI: calcineurin inhibitor; MPA: mycophenolic acid (mycophenolate mofetil [MMF], mycophenolate sodium [MPS]); mTOR: mammalian target of rapamycin.

criteria and objective laboratory diagnostic methods (Kappa coefficient: 0.45 [95% CI: 0.42-0.49]; 46.3% of patients without clinical diagnosis of CRD had objective diagnosis based on eGFR.

Following a physician’s clinical diagnosis of CRD, renal biopsies were performed almost exclusively in kidney transplant recipients (29.8%; $p < 0.0001$). In addition, renoprotective treatment (angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARB]) was introduced in 28.5% of patients with CRD (ranging from 12.2 to 35.4% for lung and kidney transplant recipients, respectively; $p < 0.0001$) (Table 2).

At the time of a physician’s clinical CRD diagnosis, the immunosuppressive regimen was modified in 58.7% of patients, mostly liver (89.6%) and lung (78.4%) transplant recipients ($p < 0.0001$). The main changes were based on a reduction or withdrawal of CNI therapy (37.1% CNI reduction without any other change, being significantly more frequent [56.8%] among heart transplants [$p = 0.0003$]). Besides, modifications to mycophenolic acid (MPA) therapy or introduction of mammalian

target of rapamycin (mTOR) inhibitors were carried out in 36.8% (21.6% heart vs. 48.8% liver transplant recipients; $p = 0.0003$) and 18.4% (10.3% lung vs. 25.8% kidney transplant recipients; $p = 0.0003$) of patients with CRD in whom changes in immunosuppressive therapy were undertaken, respectively (Table 2).

Discussion

In our study, CRD emerged as a common posttransplant complication either in recipients of renal or nonrenal transplants, with a prevalence ranging from 32.4 to 78.9% depending on the organ involved and the criteria applied, which is consistent with previous evidences that had already found CRD to be a frequent long-term complication after solid-organ transplantation⁹⁻¹².

Early recognition of renal dysfunction following any solid-organ transplantation is essential to establish a therapeutic strategy aimed to delay or avoid the progression to end-stage renal disease^{6,12-14}. However, the main finding of this pooled analysis is that

CRD was significantly underdiagnosed when applying physicians' criteria. Almost half of patients without clinical diagnosis of CRD had objective diagnosis based on the estimation of GFR using the MDRD-4 equation⁸. Our results indicate that physicians frequently rely only on the less sensitive measure of increased serum creatinine concentration as a screening test for clinical diagnosis of renal dysfunction in daily clinical practice, although a more precise tool for detecting early renal dysfunction can be obtained estimating the GFR through creatinine-based equations^{15,16}.

Despite the fact that the etiology of chronic kidney disease in transplant recipients may be multifactorial, CNI-associated nephrotoxicity significantly contributes to the development of renal dysfunction over time, either in nonrenal or renal transplant recipients¹⁷, even though recent studies have downplayed the importance of CNI nephrotoxicity in late graft failure^{18,19}.

Interestingly, lung transplant recipients showed double the prevalence of clinical diagnosis of CRD compared to liver, heart and renal transplantation, who all together showed very close frequencies. In addition, the difference between the prevalence of CRD based on clinical or objective criteria was lower in lung transplant recipients. These findings suggest that monitoring of renal function in daily clinical practice is more accurate in lung transplantation, a procedure that usually dictates the need for augmented CNI dosing versus other solid-organ transplants. On the other hand, CRD was less common in liver transplant recipients, who are generally treated with lower CNI concentrations than recipients of other solid organs such as heart or lung²⁰. In any case, CNI minimization protocols or CNI withdrawals and conversion to MPA or mTOR-based immunosuppressive regimens have been shown to improve renal function in kidney^{21,22}, liver²³, heart^{24,25}, and lung^{26,27} transplant patients. In our study, the

reduction or withdrawal of CNI therapy was performed in nearly 54% of recipients with clinical diagnosis of CRD, whereas MPA modifications and mTOR inhibitor introduction were carried out in approximately 22 and 11% of patients with clinical diagnosis of CRD, respectively.

Although the beneficial effect of ACE inhibitors or ARB in kidney transplant recipients is not yet well established^{28,29}, their introduction may be beneficial in solid-organ transplantation due to their potential to preserve or improve renal function through renin-angiotensin system blockade^{20,30,31}. However, the introduction of renoprotective treatment after clinical diagnosis of CRD was moderately low (only 29% of patients) in routine clinical practice. Besides, determinations of proteinuria were only undertaken in 56% of patients with clinical diagnosis of CRD, and renal biopsies to confirm renal dysfunction were performed almost exclusively in kidney transplant recipients with clinical criteria of CRD (30%).

The current study has several strengths. The large sample size, with consecutive sampling procedure, is representative of daily clinical practice regarding solid-organ transplant populations in Spain. On the other hand, the study design was retrospective and therefore subject to patient selection bias and inaccurate data collection. Moreover, the use of an abbreviated MDRD equation for GFR estimation, albeit recommended to monitor GFR in kidney³² and heart¹⁵ transplant recipients, carries some limitations depending on the population sample^{33,34}. Finally, we did not collect data about CNI dosing and once the clinical diagnosis of CRD was established we could not assess whether the changes in immunosuppressive therapy had any effects on renal function.

In summary, our study confirms that CRD is a common condition following solid-

organ transplantation (eight years after transplantation CRD affected 65% of kidney, liver, heart, or lung transplant patients), and that there is a noteworthy underestimation of the clinical diagnosis by physicians due to the lack of consensus on the definition of CRD in daily clinical practice. The use of objective criteria, such as eGFR, to diagnose CRD would allow an earlier detection of renal dysfunction and better therapeutic strategy.

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Appendix

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