

Epidemiology of Chronic Kidney Disease in Renal Transplantation

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Abstract

Kidney Disease: Improving Global Outcomes (KDIGO) recommends considering all kidney transplant recipients to have chronic kidney disease irrespective of glomerular filtration rate and the presence or absence of kidney damage. Furthermore, between 60 and 75% of renal transplant recipients have an estimated glomerular filtration rate lower than 60 ml/min/1.73m² and the majority of them are in stage 3, with a glomerular filtration rate between 30 and 59 ml/min/1.73m². Moreover, graft function declines at a rate of 0.5 to 2.2 ml/min/1.73m² per year. But, this declining rate is lower than that observed in non-renal transplant patients. The incidence of some complications, such as anemia, calcium phosphate metabolism disorders, and hypertriglyceridemia, increases as chronic kidney disease stage progresses. The adequacy of treatment of chronic kidney disease complications when compared with non-transplant patients is controversial and there are data supporting that care is poorer or similar to that given to non-transplant patients. Graft dysfunction or function decline at an early posttransplant date are associated with poor graft outcomes. In the general population, graft dysfunction is a cardiovascular risk factor. Cardiovascular events and patient mortality are increased in renal transplant recipients compared with the general population. An important percentage of renal transplant recipients have chronic kidney disease and increased cardiovascular risk that suggests the existence of a link between graft function and increased cardiovascular events. Graft function is generally measured by the Cockcroft-Gault clearance and by the glomerular filtration rate calculated by the abbreviated equation of the Modification of Diet in Renal Disease study. The accuracy of these equations in the measurement of glomerular filtration rate has been questioned as well as in the evaluation of chronic kidney disease progression as they can over- or underestimate the rate of glomerular filtration decline. More precise evaluation of glomerular filtration rate is difficult to perform in routine clinical practice and, until more precise methods are developed, the guideline recommendations are a useful tool, which will probably improve the management of renal transplant recipients in the long-term follow-up. (Trends in Transplant. 2010;4:19-28)

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Key words

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Introduction

The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative Advisory Board (K/DOQI) developed clinical practice guidelines to define chronic kidney disease (CKD) and to classify stages of progression of kidney disease. They classified five stages of CKD according to the level of graft function. Chronic kidney disease was defined as kidney damage or glomerular filtration rate (GFR) $< 60 \text{ ml/min/1.73m}^2$ for three months or more, irrespective of cause¹. Concerning renal transplant recipients, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended that kidney transplant recipients should be considered to have CKD, irrespective of GFR or the presence or absence of markers of renal failure². This statement was supported by the Lisbon conference, where workers considered that there were no reasons to exclude transplanted CKD patients from the staging guidelines proposed by NKF-K/DOQI and modified by KDIGO³ based on the results of two reports^{4,5}. More recent works with higher numbers of patients have confirmed that most of the renal transplant recipients have CKD stage 3 and beyond^{6,7}. Moreover, progression of CKD was associated with an increasing number of CKD-related complications that are difficult to keep within the targets recommended.

The purpose of the present work was to review the methods of assessment of graft function, to investigate the incidence and rate of progression of CKD, and to evaluate the impact of CKD stages on cardiovascular risk

factors, the feasibility of achieving recommended targets, and the effects of CKD on cardiovascular events in renal transplant recipients.

Measurement of glomerular filtration rate

Glomerular filtration rate (GFR) is considered the best overall index of renal function in health and disease, and monitoring its changes can delineate progression of kidney disease. Direct measures of GFR, such as renal clearance of inulin or renal clearance of [¹²⁵I]iothalamate, are considered the gold standard for assessing kidney function. But these techniques are rarely applied in routine clinical practice because they are not readily available. Serum creatinine concentration and creatinine clearance using 24-hour urine collection have been routinely used in the assessment of GFR. But serum creatinine (Scr) is not an acute index of GFR, and 24-hour creatinine clearance needs to collect timed urine accurately. Consequently, several equations to predict GFR and creatinine clearance from Scr have been developed and used in many studies. The K/DOQI clinical practice guidelines recommend the Cockcroft-Gault equation using Scr, age, weight, and sex and the abbreviated Modification of Diet in Renal Disease (MDRD) equation using four variables; Scr, age, sex, and race¹. Stage classification of CKD was performed using these equations in the evaluation of kidney function (Table 1). As the equations underestimate GFR in persons without CKD who have a high-normal

Table 1. Stages of chronic kidney disease (K/DOQI guidelines¹)

Stage	Description	GFR (ml/min/1.73m ²)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

GFR: glomerular filtration rate; K/DOQI: Kidney Disease Outcomes Quality Initiative.

Scr level and consequently overestimate the prevalence of a reduced GFR in non-selected populations, the accuracy and the utility of these equations have been questioned^{8,9}. In addition, the measurement of Scr concentration is subject to error due to assay calibration bias or imprecision. However, the guidelines considered that despite the limited precision of these equations in the evaluation of GFR, they provide a basis for classification of CKD, detection of substantial progression, and planning treatment strategies¹.

In renal transplant recipients, Scr levels have been used in the estimation of graft function. But, as in the general population, biological and therapeutic conditions can affect Scr concentration, and estimation equations of GFR that include variables such as age, sex, and race could be more informative. Cockcroft-Gault equation, abbreviated MDRD equation, and Nankivell formula are the most widely used estimation equations of GFR in transplant recipients. Several studies in which estimated GFR calculated by several equations was compared with GFR measured by more precise methods have shown the poor predictive performance of renal function equations in renal transplant recipients¹⁰⁻¹². For stages 2 and 4, less than 50% of estimated GFR was correctly classified by Cockcroft-Gault and MDRD equations with respect to inulin clearance¹¹. Recently, Bosma, et al.¹³

have investigated the suitability of nine equations to monitor renal function over time in a large population of kidney transplant recipients using iothalamate GFR as reference measurement. The predictive performance of renal function equations was poor or modest; MDRD and Jelliffe-2 were the best predictors of GFR.

It has been suggested that serum cystatin C, a low molecular weight protein, is a better marker of GFR than Scr. Several prediction equations have been derived from pediatric and adult patients to estimate GFR from the serum cystatin C concentration, but the best equation has not been definitively established. So, White, et al.¹⁴ have compared four GFR equations based on serum cystatin C with the Nankivell and abbreviated MDRD equations using the plasma clearance of radiolabeled diethylenetriaminepentaacetic acid as the reference method. In this study, cystatin C equations, Filler and Le Bricon, were more accurate at predicting GFR than traditional creatinine-based equations. Other authors, using the same reference method, have found other cystatin C-based equations, Hoek and Larsson, as the most precise¹⁵. It seems clear that we still do not have an easy and accurate measurement of GFR in renal transplant recipients, and Scr levels and estimated GFR should be used with caution and more reliable methods of GFR measurement have to be developed.

Table 2. Prevalence of chronic kidney disease in selected studies (estimated glomerular filtration rate < 60 ml/min/1.73m²)

Author	(n)	Time of the study	Method of GFR measurement	Mean GFR ml/min/1.73m ²	% of recipients with GFR < 60 ml/min/1.73m ²
Karthikeyan, et al. ⁴ 2003	459	7.7 years	eMDRD	48.2	75.0
Djamali, et al. ¹⁶ 2003	890	8.5 years	eCCR	69.0	38.9
Marcén, et al. ⁵ 2005	447	1 year	eMDRD	54.5	64.1
Ansell, et al. ⁶ 2007	9,542	6.4 years; median	eMDRD	45.7; median	76.3
Gera, et al. ¹⁷ 2007	684	1 year	iothalamate eMDRD eCCR eMayo	54.7 51.7 65.8 62.0	62.0
Kukla, et al. ¹⁸ 2008	431	6.7 years	eMDRD	50.8	79.0
Marcén, et al. ⁷ 2009	2,160	8.7 years	eMDRD	50.6	69.7

GFR: glomerular filtration rate; eCCR: Cockcroft-Gault creatinine clearance; eGFR: estimated glomerular filtration rate; eMDRD: estimated glomerular filtration rate by the abbreviated Modification of Diet in Renal Disease equation; eMayo: estimated glomerular filtration rate by the Mayo equation.

Prevalence and risk factors for chronic kidney disease

According to KDIGO guidelines, all renal transplant recipients have to be considered as having CKD irrespective of GFR. An estimated GFR < 60 ml/min/1.73m² is present in 64-76% of renal transplant recipients (Table 2). These differences among the series are possibly due to the equation used to estimate graft function and the characteristics of the population included in the study (recipient and donor age, type of donor, etc.^{4-6,17}). At one year posttransplantation, more than 60% had a GFR < 60 ml/min/1.73m² (CKD stage 3-5). It is important to point to that there were only 2% differences in the percentage of recipients with CKD when GFR was estimated by the MDRD equation⁵, or measured by a more precise method such as iothalamate clearance¹⁷. Furthermore, the highest percentage of patients were in stage 3 (55-65%). In long-term follow-up, there were no significant differences in the CKD stage distribution at one, five, and 10 years after transplantation (Fig. 1).

Graft function is affected by several variables. Data from the United Network for Organ Sharing (UNOS) database have shown that recipient (younger age, black race), donor (older age, female sex, black race), and graft (delayed graft function, HLA mismatches, acute rejection) were the variables associated with increased risk of renal dysfunction and these variables are the same as those associated with long-term graft failure¹⁹.

Chronic kidney disease progression

Chronic kidney disease is frequently a progressive disease. In patients with native kidney disease, GFR declines progressively over time, with mean annual rates of decline between 0 and 12.6 ml/min. A slow decline in GFR is also present in some renal transplant recipients (Table 3). Cohort studies have shown that about 50% of recipients lost kidney function, while the rest showed improvement or stabilization²⁰. Declining graft function was not affected by the absolute level of

Table 3. Progression of chronic kidney disease in selected studies

Author	(n)	Length of the study	Method of eGFR	Mean eGFR at starting point ml/min/1.73m ²	Progression ml/min/1.73m ² per year
Gill, et al. ²⁰ 2003	40,963	5.7 years	eMDRD	49.6 ± 15.4	-1.66 ± 6.5
Gourishankar, et al. ²¹ 2003	495	10 years	eCCR		-1.4 ± 0.5
Djamali, et al. ¹⁶ 2003	890	8.5 years	eCCR	69.0 ± 22	-1.90 ± 4.7
Bosma, et al. ¹³ 2005	798	1 to 4 years	lothalamate eMDRD eJelliffe2	55.0 ± 18.0	-1.9 ± 15.1 -0.5 ± 10.9 -1.9 ± 9.8
Gera, et al. ¹⁷ 2007	360	3.0 years	lothalamate eCCR eMDRD eMayo		-1.06 ± 5.29 0.31 ± 5.55 1.43 ± 4.52 -0.66 ± 5.35
Kukla, et al. ¹⁸ 2008	431	6.7 years	eCCR eMDRD	69.7 ± 1.0 50.8 ± 0.7	-2.2 ± 0.3 -1.4 ± 0.2

eCCR: Cockcroft-Gault creatinine clearance; eGFR: estimated glomerular filtration rate; eMDRD: estimated glomerular filtration rate by the abbreviated Modification of Diet in Renal Disease equation; eJelliffe2: estimated glomerular filtration rate by the Jelliffe equation; eMayo: estimated glomerular filtration rate by the Mayo equation.

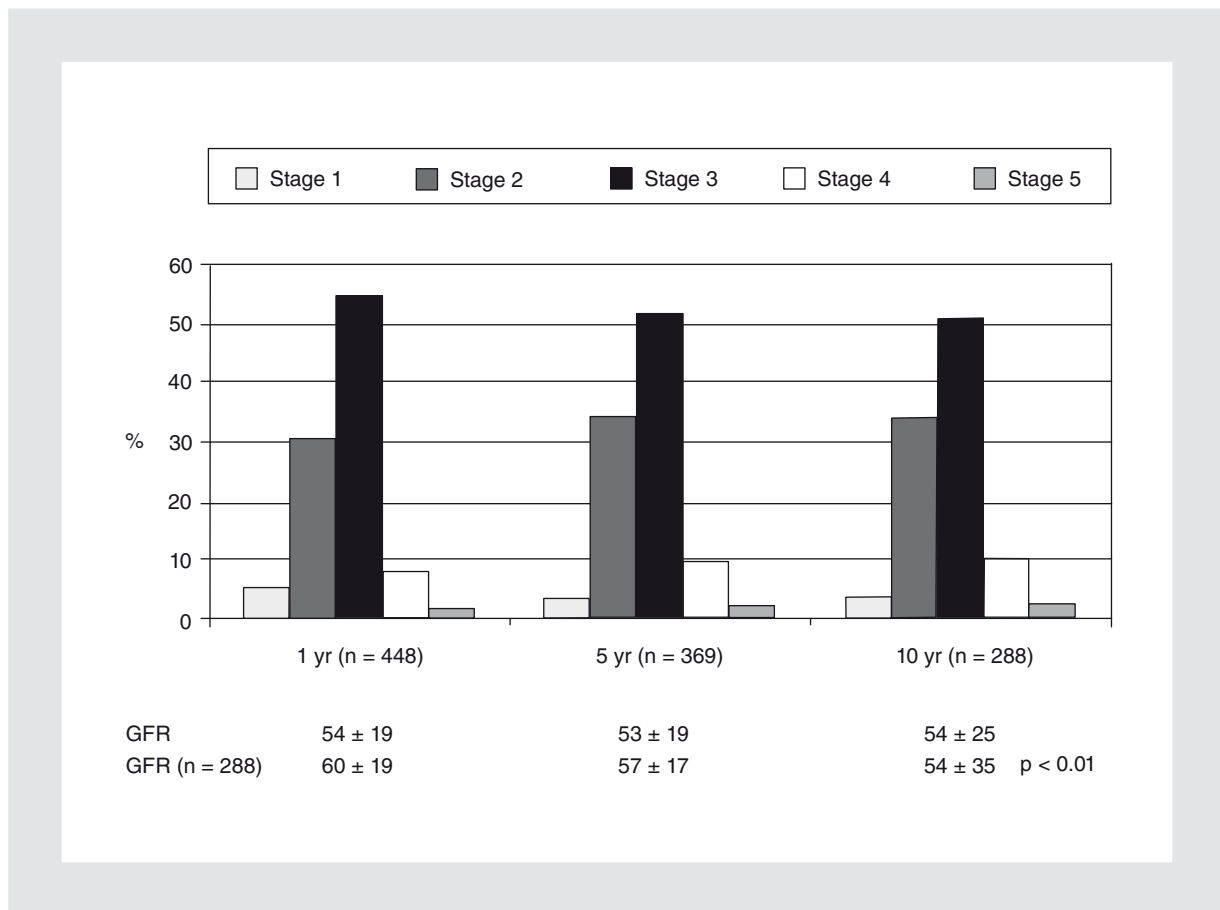


Figure 1. Distribution of chronic kidney disease stages and evolution of estimated glomerular filtration rate at one, five and 10 years follow-up in 488 recipients from Hospital Ramón y Cajal. GFR: glomerular filtration rate.

GFR, and there was no accelerated loss of function at low GFR levels²¹. Kidney grafts with reduced function can remain stable over time. When comparing outcomes and rates of progression between renal transplant recipients and non-transplanted patients after staging both populations according to K/DOQI classification, the rate of creatinine clearance decline was faster in non-transplanted patients than in transplant recipients, independently of the level of kidney function¹⁶. In addition, the annual percentage of patients with progression was lower and the half-life, defined as the median time when 50% of patients had progressed from one stage to the next, was longer in renal transplant recipients than in non-transplant patients¹⁸. But, renal transplant recipients are at risk of immunologic and nonimmunologic injuries at any time after transplantation that could make the kidney function decline more unpredictable. The influence of immunosuppression on CKD progression has seldom been analyzed. In registry studies, tacrolimus and mycophenolate mofetil (MMF) were the immunosuppressive agents associated with the most favorable effects on rates of change in allograft function²². Some data suggest an improvement in the rate of decline in allograft function in the last years^{21,23}, which may be due to new immunosuppressive regimens or to other treatment strategies.

All the previous studies have assessed the CKD progression based on Cockcroft-Gault or on estimated GFR calculated by the abbreviated MDRD equation. However, as previously stated, estimated GFR is not an accurate measurement of GFR and consequently the changes of graft function over time will not be as precise as they should be. When compared with iothalamate clearance, all models, including Cockcroft-Gault and abbreviated MDRD, overestimated the rate of GFR decline¹⁰. However, when iothalamate GFR was compared with estimated GFR in 684 kidney allograft recipients followed for at least three

years, the estimated GFR slope, calculated by the abbreviated MDRD equation, underestimated the number of patients with declining graft function¹⁷.

Chronic kidney disease stages and complications

One of the objectives of the K/DOQI clinical practice guidelines was to investigate the association of the level of GFR with complications of CKD to determine the stage when complications appear. The prevalence of most complications, including anemia, hypertension, high triglyceride levels, hypocalcemia, and hyperphosphatemia, and the average number of complications per patient increased as CKD stage progressed⁴⁻⁷. Moreover, most patients with CKD complications were not adequately treated. Achieving the recommended targets of the different CKD complications is not easy, as the number of complications and severity as well as the number of medications administered increases as renal function declines (Fig. 2).

Anemia, defined by a serum hemoglobin < 11 mg/dl, was present in 6.5% in stage 3T and around 50% in stage 5T and erythropoiesis-stimulating agents were used in 4.4 to 68% of recipients, respectively^{4,7}. Hypertension, defined by a systolic blood pressure > 130 mm Hg or a diastolic blood pressure > 80 mm Hg, was almost universal. In some series, about 90-100% of recipients had high blood pressure despite 100% of recipients being on antihypertensive therapy. Dyslipidemias are also common in renal transplant recipients. High total or LDL-cholesterol serum levels have been observed in more than 50% of recipients and around 50% were on statin therapy⁷. Cholesterol serum levels did not increase with CKD stages, but that could be related to treatment with statins. However, the proportion of patients with suboptimal triglyceride control increased as graft function

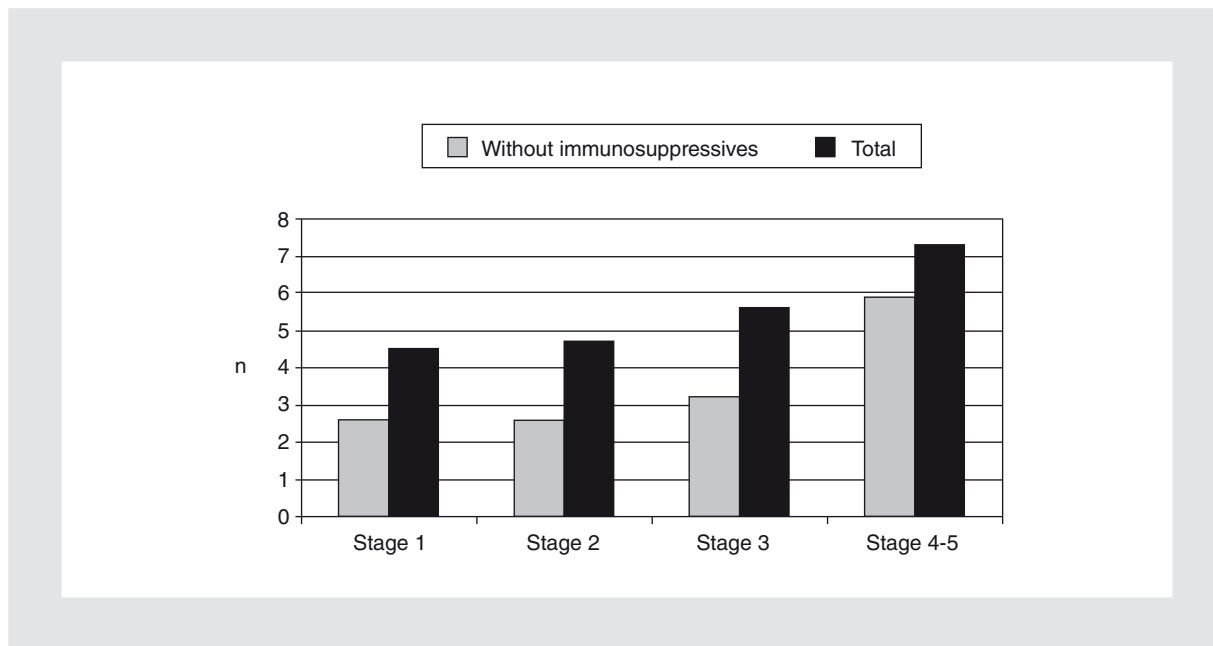


Figure 2. Number of different medications administered to patients at each chronic kidney disease stage (Anova; $p = 0.000$) (from Marcén, et al.⁵).

deteriorated⁴. The clinical guidelines recommend treating hypertension and dyslipidemias until reaching the targets.

Data concerning hyperparathyroidism are controversial. Karthikeyan, et al.⁴ did not find an association between hyperparathyroidism and CKD stage, but in other studies the intact parathyroid hormone levels progressively increased with declining GFR^{6,7}. It is important to point out that calcium-phosphate disorders are not within the scope of many units caring for renal transplant recipients, and systematic measurements of parathyroid hormone are only performed in 30-50% of patients^{6,7}. The adequacy of CKD complication treatment when compared with non-transplant patients with CKD has been evaluated in a small number of studies. Some authors have found that the management of transplant recipients differed in the treatment of anemia, with more transplant patients not receiving erythropoietin therapy, in lipid control with more patients with serum cholesterol and triglyceride levels above the

recommended ranges, and in the percentage of patients with proteinuria on angiotensin-converting enzyme inhibitors, which was lower in transplant recipients^{24,25}. Data from our own unit have shown that renal transplant recipients received similar care to non-transplant patients, and in both groups there were some parameters far from the recommended targets²⁶.

There is some evidence that control of blood pressure could preserve graft function and improve patient outcomes²⁷. Moreover, treatment with statins could reduce cardiac death and the incidence of myocardial infarction²⁸. Among the management strategies, the reduction/conversion from calcineurin inhibitors (CNI) to another immunosuppressive regimen could play an important role. There are several control trials in which the CNI was converted either to MMF^{29,30} or to sirolimus³¹. It appears that CNI withdrawal is safe and could be an alternative to graft function deterioration. However, both medications (MMF and sirolimus)

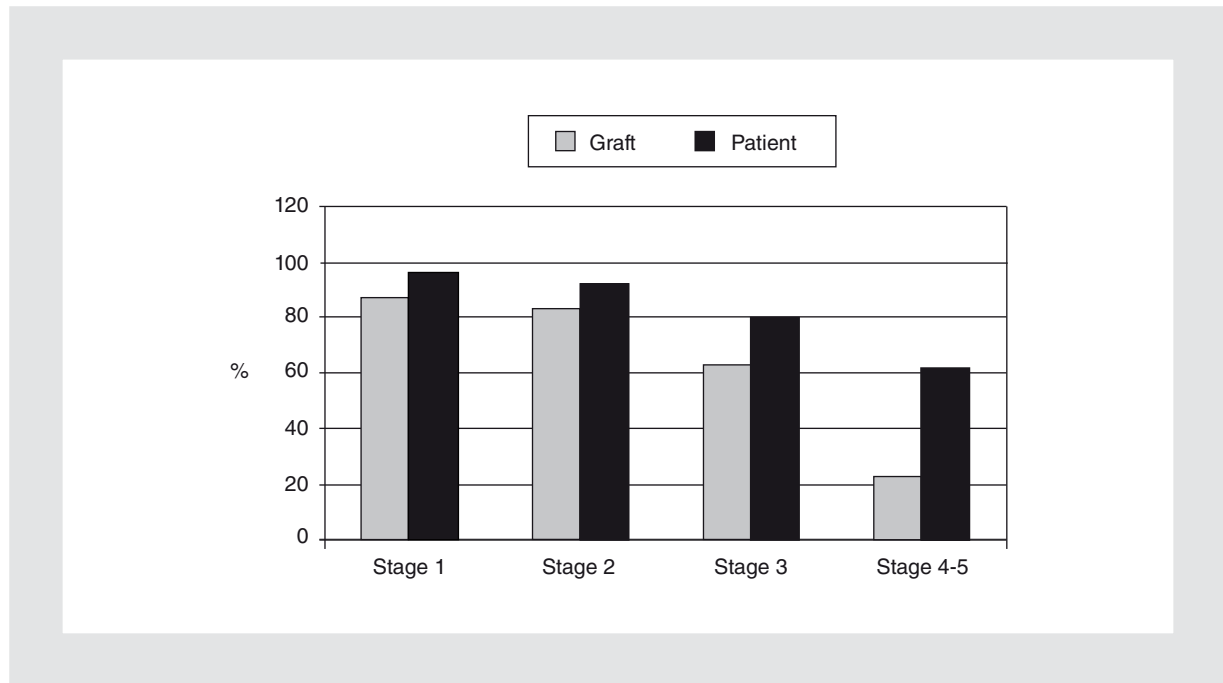


Figure 3. Patient and graft survival at 10 years according to chronic kidney disease stages, the differences in both cases were statistically significant (log-rank test, $p < 0.001$) (from Marcén, et al.⁵).

have important adverse effects that preclude their generalized administration and the follow-up of the patients is too short for drawing definitive conclusions.

Chronic kidney disease and clinical outcomes

Graft function at early follow-up is today the best indicator for predicting outcomes, and several estimations of graft function have been used. Serum creatinine at one year, increases in Scr from six months to one year, change in estimated GFR level measured by the slope of least-squares regression, or the occurrence of a 25% decline in estimated GFR were associated with long-term graft survival^{32,33}. The CKD stage at one year after transplantation was also a predictor of graft outcomes⁵. In the general population, renal dysfunction measured by estimated GFR has appeared as a cardiovascular risk factor³⁴. As was established before, an

important percentage of renal transplant recipients have CKD and these patients die from premature cardiovascular disease, which suggests the existence of a link between graft function and increased cardiovascular events. There are data supporting this relationship. Meier-Kriesche, et al.³⁵ have shown an independent association between renal dysfunction at one year posttransplantation and cardiovascular mortality, and a Scr > than 1.5 mg/dl was the threshold value above which there was an increase in the endpoint incidences. The Assessment of Lescol in Renal Transplantation (ALERT) trial has established baseline graft dysfunction as a risk factor for mortality and cardiac complications and the threshold was around a Scr of 2.3 mg/dl³⁶. There are no data in which cardiovascular events increased as estimated GFR declined or CKD stages progressed. But it is likely that cardiovascular risk will increase as traditional and nontraditional risk factors increase in prevalence and severity as graft function deteriorates (Fig. 3).

Conclusions

Most renal transplantation recipients have an estimated GFR below 60 ml/min/1.73m². But the most commonly used methods to estimate GFR lack accuracy and may underestimate or overestimate the percentage of patients with declining graft function. However, KDIGO clinical guidelines have permitted the stage classification of CKD patients. Stage progression increased the number of complications and the need for treatment. Moreover, graft dysfunction and declining graft function were associated with poor graft and patient outcomes. Despite their limitations, estimated GFR and CKD stage classification can be useful tools in the clinical setting.

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