ORIGINAL ARTICLE

Prognostic Value of Glomerular Filtration Rate 1 Year After Heart Transplantation

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Introduction and objectives. The development of renal failure is one of the most important problems after heart transplantation (HT), but the wide range of definitions means that estimates of its prevalence vary considerably. Furthermore, its impact on mortality has not been adequately studied. The objective was to investigate the relationship between the glomerular filtration rate (GFR) 1 year after transplantation and mortality during follow-up.

Methods. The GFR was determined in 316 patients still living 1 year after transplantation using the abbreviated Modification of Diet in Renal Disease Study formula. Patients were divided into three groups according to GFR (i.e. <30, 30–59 and ≥60 mL/min per 1.73 m^2) and pretransplant variables and rejection and infection rates within the first year were analyzed. The association between GFR at 1 year and mortality during follow-up was evaluated and reasons for the association were examined.

Results. There was no difference in the number of rejections or infections in the first year between the three groups. During a mean follow-up period of 6.3 years, 74% of patients with a GFR <30 mL/min per 1.73 m^2 died, compared with 24% and 30% of those with a GFR ≥60 and 30–59 mL/min per 1.73 m^2, respectively. Survival analysis (i.e. Cox regression analysis) demonstrated a significant difference between patients with a GFR <30 mL/min per 1.73 m^2 and other patients (P<.001). A very low GFR at 1 year was the only independent predictor that remained statistically significant on multivariate analysis (hazard ratio =2.87; 95% confidence interval, 1.52–5.41).

Conclusions. Severe renal dysfunction at 1 year was an independent predictor of long-term all-cause mortality in heart transplant patients.

Key words: *Glomerular filtration rate. Renal dysfunction. Mortality. Heart transplantation.*

Valor pronóstico de la tasa de filtración glomerular al año del trasplante cardiaco

Introducción y objetivos. Uno de los problemas más relevantes tras el trasplante cardiaco es el desarrollo de insuficiencia renal. La heterogeneidad en su definición hace que la estimación de su prevalencia sea variable. Por otro lado, su impacto en la mortalidad no ha sido suficientemente estudiado. El objetivo fue evaluar la relación entre la tasa de filtración glomerular al año (TFG) y la mortalidad en el seguimiento.

Métodos. Se analizó la TFG de 316 pacientes vivos al año del trasplante mediante la fórmula abreviada Modification of Diet in Renal Disease Study. Se clasificaron en tres grupos según su TFG (< 30, 30-59 y ≥ 60 ml/min/1,73 m^2, respectivamente) y se analizaron variables antes del trasplante, tasa de rechazo e infección durante el primer año. Se evaluó la relación entre la TFG al año y la mortalidad en el seguimiento y se revisaron sus causas.

Resultados. No hubo diferencias en el número de rechazos ni infecciones durante el primer año en los tres grupos. En el seguimiento medio (6,3 años) falleció el 74% de los pacientes con TFG < 30, frente al 24% y al 30% de aquellos con TFG ≥ 60 y 30-59, respectivamente. El análisis de supervivencia (regresión de Cox) mostró diferencias estadísticamente significativas entre aquellos con TFG < 30 y el resto (p < 0,001). La TFG gravemente disminuida al año se mantuvo como el único predictor independiente en el análisis multivariable (*hazard ratio* = 2,87; intervalo de confianza del 95%, 1,52-5,41).

Conclusiones. La disfunción grave de la función renal al año es un predictor independiente de mortalidad por todas las causas a largo plazo en el paciente con trasplante cardiaco.

Palabras clave: *Filtración glomerular. Disfunción renal. Mortalidad. Trasplante cardiaco.*

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ABBREVIATIONS

GFR: glomerular filtration rate

INTRODUCTION

Heart transplant is indicated for the treatment of severe, highly symptomatic heart failure in the absence of other medical or surgical options. It is associated with 1-, 5-, and 10-year survival rates of 90%, 70%, and 50%, respectively.[1] Nevertheless, it is not exempt from problems due to rejection and, in particular, side effects associated with immunosuppressive drugs (infections, tumors, chronic rejection, diabetes mellitus, hypertension, dyslipidemia, and renal disease).[1] One of the main adverse effects of calcineurin inhibitors is nephrotoxicity, which can be progressive and have prognostic implications.[2,3]

Estimates of the prevalence of chronic renal dysfunction following solid organ transplants vary as a result of differences in the definitions used. When defined as a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2, the 5-year risk of chronic renal dysfunction is 16% for lung transplants, 18% for liver transplants, and 21% for intestinal transplants.[4] Although no large-scale studies have been performed in heart transplant patients, the 5-year risk has been estimated at 11%.[4] As observed for heart failure,[5-9] renal dysfunction has been identified as an independent predictor of mortality in lung, liver, and intestinal transplants.[4] Preliminary studies involving small numbers of patients have also suggested that it could be predictive of mortality in heart transplant patients.[4,9,10]

In this study, we addressed the hypothesis that renal failure 1 year after heart transplant could identify a subgroup of patients at high risk of subsequent complications and, therefore, death. The main study objective was to assess the relationship between GFR at 1 year and death during follow-up.

METHODS

Patients

A total of 434 heart transplant patients were consecutively recruited at our hospital between January 1, 1994 and December 31, 2008. Patients were excluded if heart transplantation was performed in combination with other organ transplants (29), if they were undergoing repeat transplantation (10), if they were classified as pediatric patients (14), or if they died during the first year of follow-up (65). Following application of the exclusion criteria, a total of 316 patients were included in the study.

The study was approved by the Institutional Review Board and all patients provided signed informed consent to inclusion in the study.

Analysis of Renal Function

Serum creatinine was used to calculate the GFR according to the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation.[11] According to this equation, GFR = 186 × age–0.203 × serum creatinine$^{-1.154}$ (× 0.742 in women and × 0.21 in African Americans) mL/min/1.73 m^2. This method has been validated for the estimation of GFR in patients with renal dysfunction following heart transplantation; it has the advantage of being both rapid and simple compared with other more complex measures such as those based on inulin.[12,13] Renal function was analyzed repeatedly throughout the year following heart transplant. When creatinine level at 1 year was inconsistent with the profile observed over the course of the year (sudden elevations or reductions without apparent cause), the measurement was repeated.

Patients were grouped according to renal dysfunction using the classification from the Kidney Disease Outcomes Quality Initiative guidelines of the US National Kidney Foundation (NKF-KDOQI), which stratifies patients according to GFR <30, 30 to 59, or ≥60 mL/min/1.73 m^2.

Variables Analyzed

For each of the 3 subgroups defined according to renal dysfunction, baseline variables prior to transplant (demographic variables, cardiovascular risk factors, and functional status) were analyzed along with immunosuppressive therapy, rejection, and infections at 1 year. Characteristics were compared among the 3 subgroups, and their association with death during follow-up was analyzed.

Immunosuppressive Therapy

All patients included in the study received induction therapy immediately following transplant and triple maintenance therapy comprising a calcineurin inhibitor (ciclosporin or tacrolimus), an antiproliferative drug (mycophenolate mofetil or azathioprine) and corticosteroids. The plasma trough concentrations during the first 6 months were 200-300 ng/mL for ciclosporin and 10 to 15 ng/mL for tacrolimus. After the first 6 months, the values were between 100 and 200 ng/mL for ciclosporin and between 5 and 10 ng/mL for tacrolimus. There were

TABLE 1. **Clinical Profile Immediately Prior to Transplant**

	GFR≥60 (n=135)	GFR 30-59 (n=158)	GFR<30 (n=23)	*P*
Age, mean (SD), y[a]	47 (12)	53 (9)	57 (5)	<.0001
Men	116 (86%)	137 (87%)	19 (83%)	.87
Weight, kg	73 (14)	74 (13)	74 (9)	.68
Height, cm	168 (8)	166 (7)	16 (8)	.16
Hypertensiona	41 (30%)	57 (36%)	14 (60%)	.02
Diabetes mellitus	21 (16%)	34 (22%)	7 (30%)	.16
Hypercholesterolemiaa	51 (37%)	80 (51%)	8 (34%)	.05
Smoking	79 (59%)	91 (58%)	14 (61%)	.97
Ischemic heart diseasea	49 (36%)	81 (51%)	10 (43%)	.037
LVEF, %	22 (10)	21 (10)	19 (5)	.46
Creatinine, mg/dL[a]	1.06 (0.3)	1.21 (0.32)	1.33 (0.42)	<.0001
mPAP, mm Hg	34 (11)	32 (10)	30 (6)	.16
Urgent heart transplant	32 (23%)	31 (20%)	3 (15%)	.43
Inotropic therapy	36 (26%)	39 (25%)	3 (15%)	.37
Ischemia time, min	150 (49)	148 (52)	146 (56)	.9

GFR indicates glomerular filtration rate; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure.
Values are shown as n (%) or mean (SD).
[a]*P*<.05

no planned changes in the dose of mycophenolate mofetil (2 g/d) or azathioprine (2 mg/kg/d). The corticosteroid used was deflazacort. The target dose at the end of the first month was 30 mg/d, followed by progressive reduction to a dose of 6 mg/d without a withdrawal protocol.

Statistical Analysis

Discrete variables were expressed as percentages and continuous variables as means (SD); data were normally distributed (Kolmogorov-Smirnov test, *P*>.05). Univariate analysis was performed by χ^2 and *t* tests. Survival analysis was performed using Kaplan-Meier curves and the log-rank test. Multivariate analysis was undertaken by Cox regression. Significant variables from the univariate analysis were included. The cutoff for statistical significance was set at *P*<.05. Statistical analyses were performed using SPSS version 15.0.

RESULTS

Glomerular Filtration Rate

Of the 316 patients included in the study, 23 (7.3%) displayed a severe reduction in renal function (GFR <30 mL/min/1.73 m^2) and 158 (50%) showed a moderate reduction (30-59 mL/min/1.73 m^2) at 1 year.

Clinical Profile of Patients at the Time of Transplant

Table 1 shows the baseline characteristics of the study population immediately prior to transplant. Patients with severely reduced GFR at 1 year were older, more hypertensive, and more hypercholesterolemic. They also had higher serum creatinine prior to transplant and the most common underlying condition was ischemic heart disease.

Clinical Characteristics at 1 Year

Among patients with worse GFR, a greater percentage received induction therapy with muromonab-CD3 than with IL-2 inhibitors. Transplant patients treated with mycophenolate mofetil had a better GFR at 1 year than those who had received azathioprine. There were no differences in the rate of rejection. There was a trend towards a greater number of infections in the subgroup of patients with greater deterioration of renal function (Table 2).

Glomerular Filtration Rate and Mortality

Mean follow-up was 6 (3) years. A total of 97 (30.7%) patients died during follow-up. The mean GFR in patients who died compared with those who survived was 53.8 versus 60.8 mL/min/1.73 m^2 (*P*=.006).

Comparison of the 3 groups (<30, 30-59, and ≥60) revealed that mortality was higher in patients who had a worse GFR: 23.7% in patients with a GFR ≥ 60 mL/min/1.73 m^2, 30.3% in those with a GFR of 30-59 mL/min/1.73 m^2, and 73.9% in those with a GFR <30 mL/min/1.73 m^2 (*P*<.0001). Kaplan-Meier analysis revealed a statistically significant difference in survival of patients with severely diminished renal function compared with those in whom renal function was conserved or only moderately diminished (Figure 1).

TABLE 2. **Clinical Characteristics of Patients During the First Year of Follow-up**

	GFR≥60 (n=135)	GFR 30-59 (n=158)	GFR<30 (n=23)	*P*
Induction therapy				<.0001
ALG/ATG	0	2 (1%)	1 (4%)	
OKT3	53 (40%)	93 (59%)	17 (74%)	
anti-IL-2	82 (60%)	63 (40%)	5 (22%)	
Ciclosporin	115 (85%)	144 (91%)	22 (95%)	.15
Tacrolimus	19 (15%)	14 (9%)	1 (5%)	.21
MM[a]	82 (60%)	63 (40%)	4 (17%)	<.0001
Azathioprinea	50 (37%)	89 (56%)	18 (72%)	<.0001
Rejections in the first year	1.12 (1%)	1.3 (1.2%)	1.4 (1.2%)	.28
Infections in the first year[b]	0.6 (0.8%)	0.8 (1%)	1 (1%)	.09

ALG indicates anti-lymphocyte globulin; anti-IL-2, interleukin-2 inhibitors; ATG, anti-thymocyte globulin; MM, mycophenolate mofetil; OKT3, muromunab CD3.
Data are shown as n (%).
[a]*P*<.05.
[b]*P*<.1.

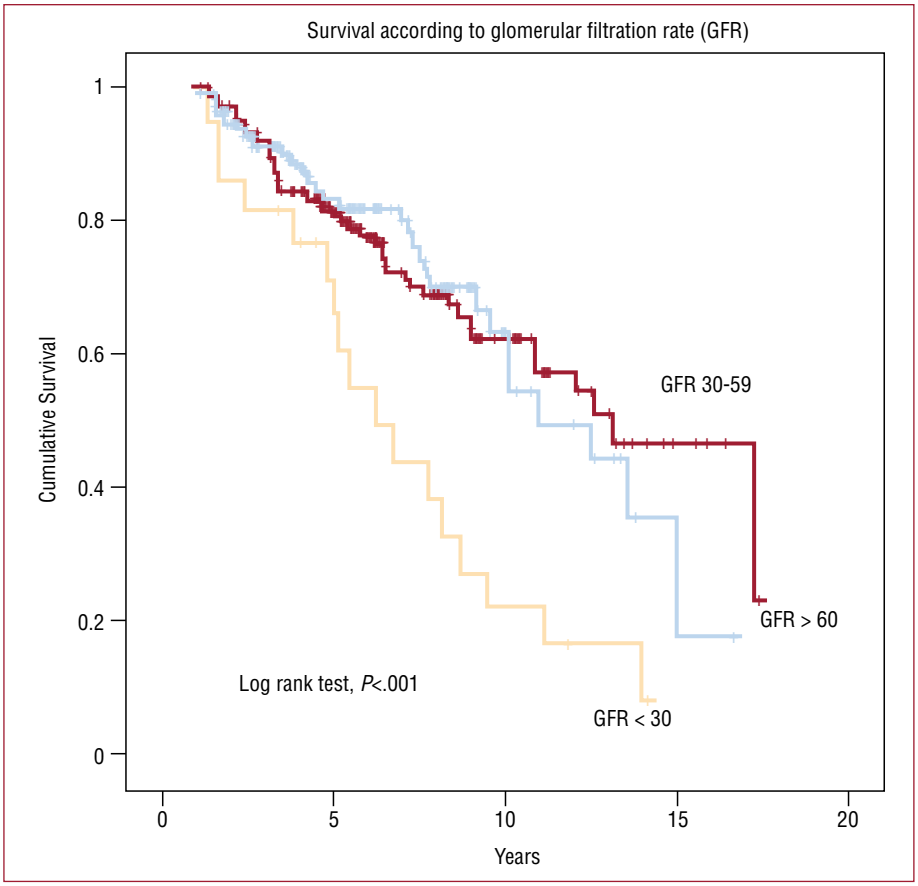

Figure 1. Survival according to glomerular filtration rate (GFR) (≥60, 30-59, <30 mL/min/1.73 m^2) at 1 year. Patients with worse GFR at 1 year show worse survival than those in whom GFR is conserved or moderately reduced (log-rank test, *P*<.001).

In the Cox regression analysis, only GFR <30 mL/min/1.73 m^2 remained an independent predictor of mortality (hazard ratio =2.87; 95% confidence interval, 1.52-5.41; *P*=.01) (Table 3).

Causes of Death

Of the 97 deaths recorded (30.7% of the study population), the main cause was rejection of the

TABLE 3. **Multivariate Analysis of All-Cause Mortality**

Risk Factor	Hazard Ratio	95%CI	*P*
Hypertension prior to transplant[a]	1.44	0.93-2.21	.09
Baseline creatinine	1.31	0.67-2.61	.41
Inotropic therapy	0.87	0.48-1.46	.54
Mycophenolate mofetil	2.06	0.27-15.24	.59
Azatioprina	0.9	0.11-8.22	.98
TFG < 30 ml/min/1,73 m^2[b]	2.87	1.52-5.41	.01

ICI indicates confidence interval; GFR, glomerular filtration rate.
[a]*P*<.1.
[b]*P*<.05.

TABLE 4. **Causes of Death**

Cause of Death	All Patients	GFR≥60	GFR 30-59	GFR<30	*P*
Rejection	32 (10%)	11 (3%)	16 (5%)	5 (1.5%)	.13
Cardiovascular	17 (5%)	4 (1.2%)	11 (3%)	2 (1%)	.24
Tumor	16 (5%)	9 (3%)	5 (1.5%)	2 (1%)	.28
Infection	15 (4%)	5 (1.5%)	7 (2%)	3 (1%)	.14
Othera	17 (5%)	3 (1%)	9 (3%)	5 (1.5%)	<.001

TGFR indicates glomerular filtration rate.
Data are shown as n (%).
[a]P<.05.

transplanted organ (10%) followed by cardiovascular events (5%), tumors (5%), and infections (4%). Analysis of the relationship between GFR and mortality due to specific causes is shown in Table 4.

DISCUSSION

Heart transplant is the treatment of choice for severe heart failure. Although improvements have been made in the rate of survival, the procedure is still associated with complications, in particular renal failure. The differences in the definitions applied make renal failure difficult to study, and its effect on mortality is poorly understood. The aim of this study was to analyze the relationship between GFR at 1 year after heart transplant and death during follow-up. Among the 316 heart transplant patients included in the study, 7.3% had a GFR <30 and 50% had GFR between 30 and 59 mL/min/1.73 m^2 at 1 year. Patients with a GFR <30 mL/min/1.73 m^2 at 1 year displayed worse survival than those in whom the GFR was less diminished.

Hamour et al[14] described a biphasic profile for the development of renal dysfunction following transplant. During the first few months, they observed a rapid reduction in GFR, which stabilized at 1 year and then displayed a slow but continuous deterioration. Thus, 1 year appears to be the optimal time point at which to assess GFR prior to the onset of a slow deterioration, given its stability and the fact that it is likely to be a reliable indicator of renal reserve. In our study, 7% and 50% of heart transplant patients displayed severe or moderate reduction in GFR (<30 and 30-59 mL/min/1.73 m^2, respectively) at 1 year. The frequency of renal dysfunction in heart transplant patients varies according to the criteria applied. Al Aly et al[15] reported that only 4.2% of patients in their study had a GFR <29 mL/min/1.73 m^2 at 5 years, whereas in our study higher rates were obtained at only 1 year of follow-up. Ojo et al[4] reported a rate close to 2% at 1 year. Nevertheless, Arora et al[9] reported rates very similar to those obtained in our study. Thus, although the percentage of patients with a severely reduced GFR varies in different studies,[16,17] the continued deterioration of GFR is a constant observation in the literature.

The clinical profile of our population prior to transplant shows that patients with a worse GFR at 1 year were older, more hypertensive, and had higher pretransplant creatinine levels. Other studies have reported very similar baseline differences.[9] Although the univariate analysis showed an association between hypertension and mortality, the relationship was no longer statistically significant in the multivariate analysis.

Patients received induction therapy and were then treated with a calcineurin inhibitor, a proliferation inhibitor, and a corticosteroid. In our study, there were baseline differences in the induction therapy chosen; these were not associated, however, with an increase in mortality. There are few reports in the literature on the effects of different induction therapies on renal function following heart transplant. Some studies have suggested that prolonging treatment with anti-CD25 monoclonal antibodies and delaying the introduction of calcineurin inhibitors can help to preserve renal function in those patients who display reduced GFR at the time of transplant.[18-20]

Although there were baseline differences in the choice of proliferation inhibitor, these were not associated with mortality in the multivariate analysis. Despite these differences, there were no significant differences in the number of rejections or infections during the first year. No differences were observed in terms of the calcineurin inhibitor (ciclosporin or tacrolimus) chosen between the different groups. In any case, according to protocols used in our patients, C0 values for calcineurin inhibitors were homogeneous. Deleterious effects of calcineurin inhibitors have been reported in numerous studies, in both heart transplant patients and patients receiving other solid organ transplants, and it represents one of the principal risk factors for renal failure following transplant.[2,21-23] A multicenter study has shown that adjusting the dose of the

calcineurin inhibitor and increasing that of the less nephrotoxic drug (mycophenolate mofetil) helps to preserve renal function without increasing the number of rejections.[24] The ELITE-SYMPHONY study in renal transplant patients showed that a regimen of daclizumab, mycophenolate mofetil, and corticosteroids combined with low doses of tacrolimus can have beneficial effects on renal function, survival of the transplanted organ, and the rate of rejection when compared with low doses of ciclosporin, low doses of sirolimus, or conventional doses of ciclosporin without induction therapy.[25]

Death during follow-up was close to 31% and reached 74% in patients with a GFR <30 mL/min/1.73 m^2 at 1 year, compared with 25% and 30% in the other groups. Arora et al[9] reported very similar results, with slightly lower mortality (54%) for the group with GFR <30 mL/min/1.73 m^2 and a mean follow-up of 7.4 years. In that study, however, the difference was also statistically significant for the group with a GFR of 30-59 mL/min/1.73 m^2. Ojo et al[4] described a similar effect on mortality for all types of non-renal solid organ transplant (lung, heart-lung, intestine, and liver), although the length of follow-up was shorter (mean of 42 months). In our study, although various factors were associated with mortality in the univariate analysis, only GFR <30 mL/min/1.73 m^2 remained predictive in the multivariate analysis. There are various possible explanations for this strong association. Firstly, renal function is associated with various cardiovascular risk factors, such as age, diabetes mellitus,[26] and anemia.[10] It also presents difficulties for immunosuppressive therapy and sometimes makes it necessary to substitute a calcineurin inhibitor with an m-TOR inhibitor[27,28] or reduce the intensity of immunosuppression. Finally, renal dysfunction has a direct effect on mortality and is an independent predictor of death.[4,9,29,30]

There were various causes of death and none were found to be predominant. Deaths due to organ rejection, cardiovascular events, tumors, or infections were evenly distributed among the groups. These observations are also consistent with the findings of Arora et al.[9] In that study, the main cause of death was cardiovascular events (sudden death and death due to vascular disease of the transplanted heart), but this was closely followed by other causes of death, as seen in our study.

A number of factors are noteworthy in our study. Firstly, renal dysfunction was assessed according to GFR and NKF-KDOQI classification. Therefore, the problem of heterogeneity in the definition of renal dysfunction is avoided and the results reflect the true prevalence, which may be underestimated if defined on the basis of creatinine levels.[31] In addition, few studies of heart transplant patients have assessed the relationship between prognosis and renal dysfunction defined according to GFR. Finally, our study demonstrated the significant clinical impact of renal failure on survival. In our opinion, GFR should be calculated in all heart transplant patients, as it is easily determined and has major prognostic implications. Furthermore, measures should be taken to prevent deterioration of renal function during follow-up.

Despite the patient group being restricted to a single hospital, all were treated similarly according to the criteria of the Consensus Conference of Spanish Heart Transplant Groups.[32] Therefore, the results can be extrapolated to all Spanish heart transplant groups and, probably, to hospitals in other countries.

In terms of the limitations of the study, estimation of GFR by the abbreviated MDRD equation may appear to be less reliable than other procedures; however, it has been validated in heart transplant patients by comparison with direct GFR measurement methods.[12,13] Our results are based exclusively on GFR and proteinuria was not systematically analyzed. Furthermore, the choice of some immunosuppressive drugs as induction and maintenance therapy may be obsolete in the light of recent clinical trials. However, it should be remembered that our study included patients who underwent heart transplant as early as 1994, with more than 10 years of follow-up. The possible limitation of measuring GFR at 1 year is justified by the attempt to limit bias generated by early mortality, mainly due to primary failure of the transplanted organ. Furthermore, creatinine concentrations can oscillate early after heart transplant as a result of a number of factors. We therefore feel that assessment of GFR during the period of greatest clinical stability is most appropriate given that the aim is to analyze long-term mortality.

CONCLUSIONS

Severe renal dysfunction defined as GFR <30 mL/min/1.73 m^2 1 year after heart transplant is an independent of medium-term to long-term all-cause mortality.

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