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Original Article

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Clinical profile and post-transplant anaemia in renal transplant recipients restarting dialysis after a failed graft: changing trends between 2001 and 2009

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Abstract

Background. The aim of this study was to compare the clinical profile, outcome and the prevalence and management of anaemia between two cohorts of renal transplant patients with graft failure restarting dialysis in 2001 and 2009.

Methods. Cross-sectional, observational, retrospective and multicentre study of 397 patients in the 2001 cohort and 222 in the 2009 cohort. Data were recorded at 0, 3, 6, 9 and 12 months before the onset of dialysis resumption and during the first 90 days after restarting dialysis (mortality and hospital admission).

Results. Patients in the 2009 cohort were older at the time of inclusion in the study and transplantation, and restarted dialysis therapy with a significantly better glomerular filtration rate. In both cohorts, there was a rapid deterioration of renal function with statistically significant differences in serum creatinine and glomerular filtration rate between the monthly intervals −12 and 0. The mean haemoglobin value at −12 months was 11.6 g/dL [7.2 mmol/L] in the 2001 cohort when compared with 12.3 g/dL [7.6 mmol/L] in the 2009 cohort, and at the time of restarting dialysis 9.6 g/dL [6.0 mmol/L] versus 10.6 g/dL [6.6 mmol/L]. The percentage of patients treated with erythropoiesis-stimulating agents, at any time during the 12 months before readmission to dialysis, increased significantly from 61.5% in the 2001 cohort to 96% in the 2009 cohort. There were no significant differences between the 2001 and 2009 cohorts in mortality rate (8.8 versus 9.0%) or hospital admission (31.5 versus 31.1%) during the study time.

Conclusions. At restarting dialysis, the proportion of patients with anaemia (and its severity) due to progressive graft nephropathy decreased over the past 8 years, increasing significantly the percentage of patients treated with erythropoietin. Differences in morbimortality after dialysis resumption were not observed, this is probably due to an increase in the age of donors and recipients.

Keywords: anaemia/epidemiology; dialysis; erythropoiesis stimulating agents; graft survival; kidney transplantation

Introduction

Interest in late renal transplant (RT) graft loss has increased substantially in recent years as it has become evident that improvement in long-term graft survival is still limited by cardiovascular events with functioning grafts and chronic allograft injury, which results in an annual graft loss rate of 3–5% [1]. In fact, RT failure is a leading cause of end-stage renal disease (ESRD) and represents a major reason for resumption of renal replacement therapy [2,3]. Patients with graft failure are readmitted to dialysis treatment, and account for 4–10% of the patients starting dialysis therapy each year [4]. It has been shown that the number of patients readmitted on dialysis therapy after a failed graft has increased in recent years. Before starting dialysis, these patients are re-exposed to the complications of chronic renal failure but there are no specific guidelines for their treatment. The Kidney Disease Quality Initiative Advisory Board clinical practice guidelines [5] given for non-transplant chronic kidney disease patients have been recommended for ameliorating their clinical situation and the rate of progression of graft failure. The point of dialysis reinitiation and dialysis modality are currently in debate [6]. On

the other hand, patients with chronic renal failure due to graft failure have a poorer renal function at the time of dialysis reinitiation, and a more profound anaemia [7]. Additionally, patients starting dialysis with late RT failure are at an increased risk of complications and have strikingly higher mortality rates than non-transplanted dialysis patients [8].

Post-transplant anaemia is a common complication (~60%) among kidney recipients in the early post-transplant period as well as in the long term (between 20 and 40%), and is mostly associated with decreased graft function [1, 9, 10, 11]. Other contributing factors apart from allograft dysfunction include the type of immunosuppression (i.e. mycophenolatemofetil, azathioprine, sirolimus and evorolimus), antiviral agents, infections, chronic iron deficiency and use of hypotensive agents, such as angiotensin system blockers [10]. Anaemia may lead to ventricular hypertrophy and congestive heart failure, which may contribute to higher cardiovascular morbidity and mortality [12, 13]. Recent data have suggested strong associations of anaemia with graft failure and mortality in kidney transplant patients [14–16]. Moreover, adequate management of anaemia may slow the decline of renal function [17].

However, the impact of post-transplant anaemia on kidney recipient outcomes is sparsely reported. The aim of this multicentre study was to assess changes in the clinical profile and the prevalence and management of

Table 1. Characteristics of the study population and comparison of the two cohorts

Characteristic	2001 Cohort (*n* = 397)	2009 Cohort (*n* = 222)	P-value
Sex (% men)	235/162 (59.2%)	131/91 (59.0%)	0.504
Age, years, mean ± SD (range)			
At the time of inclusion in the study	48.0 ± 13.3 (18–78)	55.9 ± 13.8 (19–82)	<0.001
At the time of transplantation	41.0 ± 14.1 (11–71)	45.9 ± 14.4 (11–76)	<0.001
Cause of chronic renal failure, *n*(%)			
Chronic glomerulonephritis	150 (37.8)	63 (28.4)	<0.001
Diabetic nephropathy	10 (2.5)	20 (9.0)	<0.001
Renal vascular disease	31 (7.8)	12 (5.4)	<0.001
Tubulointerstitial nephritis	73 (18.4)	23 (10.4)	<0.001
Polycystic kidney disease	26 (6.5)	19 (8.5)	<0.001
Hereditary renal disease	16 (4.0)	8 (3.6)	<0.001
Other/unknown	91 (23.0)	77 (34.7)	<0.001
Hepatitis C virus infection, *n* (%)	112 (28.2)	35 (15.8)	<0.001
Cardiovascular co-morbidity, *n* (%)[a]			
Hypertension	70 (17.6)	21 (9.5)	0.006
Ischaemic heart disease	21 (5.3)	7 (3.2)	0.313
Acute myocardial infarction	5 (1.3)	5 (2.3)	0.342
Arrhythmia	20 (5.0)	6 (2.7)	0.211
Heart failure	74 (18.6)	35 (15.8)	0.381
Stroke	7 (1.8)	4 (1.8)	1.000
Peripheral vascular disease	4 (1.0)	4 (1.8)	0.466
Pulmonary embolism	0 (–)	3 (1.4)	0.046
Non-cardiovascular morbidity, *n* (%)[a]			
Chronic obstructive pulmonary disease	2 (0.5)	2 (0.9)	0.621
Dyslipidaemia	36 (9.1)	12 (5.4)	0.118
Post-transplant diabetes	14 (3.5)	2 (0.9)	0.063
Hepatitis	13 (3.3)	3 (1.4)	0.191
Diagnosis of malignancy	16 (4.0)	10 (4.5)	0.835
Infection, acute or chronic	87 (21.9)	61 (27.5)	0.133
Haemorrhage, acute or chronic	32 (8.1)	15 (6.8)	0.552
Blood transfusion	70 (17.6)	28 (12.6)	0.109
Surgical procedure	44 (11.1)	26 (11.7)	0.793
Transplant-related data			
Donor age, years, mean ± SD	43.0 ± 18.2	46.9 ± 18.5	0.017
Time from RT to restarting dialysis (months) (mean ± SD)	83.6 ± 52.3	102.9 ± 64.04	<0.001
Number of transplantation, *n* (%)			
First	319 (80.4)	185 (83.3)	0.159
Second	58 (14.6)	32 (14.4)	0.159
Third and subsequent	7 (1.7)	4 (1.8)	0.159
Not available	13 (3.3)	1 (0.5)	0.159
Nephrectomy, *n* (%)	44 (11.1)	30 (13.5)	0.369
Cause of graft failure, *n* (%)			
Chronic graft failure	318 (80.1)	167 (75.2)	0.563
Drug toxicity	6 (1.5)	4 (1.8)	0.563
Obstructive uropathy	7 (1.8)	4 (1.8)	0.563
Late acute rejection	10 (2.5)	8 (3.6)	0.563
Relapse of underlying renal disease	26 (6.5)	13 (5.9)	0.563
Other	30 (7.6)	26 (11.7)	0.563
Type of dialysis, *n* (%)			
Haemodialysis	376 (94.7)	209 (94.1)	0.854
Peritoneal dialysis	21 (5.3)	13 (5.9)	0.854
Type of access, *n* (%)			
Arteriovenous fistula	301 (75.8)	151 (68.0)	0.037
Catheter	58 (14.6)	53 (23.9)	0.037
Peritoneal access	21 (5.3)	11 (5.0)	0.037
Not recorded	17 (4.3)	7 (3.2)	0.037

[a]Conditions developed during the 12 months prior to starting dialysis treatment.

post-transplant anaemia between two cohorts of RT recipients with graft failure restarting dialysis in 2001 and 2009. Secondly, we analysed changes in ratios of morbidity and mortality between the 2001 and 2009 cohorts after restarting dialysis.

Materials and methods

This was a cross-sectional, observational, retrospective multicentre study, which was conducted at 15 nephrology and kidney transplant units, and 20 acute care university-affiliated hospitals throughout Spain. The study was carried out according to routine daily practice. The study population consisted of RT recipients who presented progressive loss of graft function and had to be readmitted on dialysis therapy independently of the time elapsed from transplantation. Inclusion criteria were as follows: 18 years of age or older, functioning graft for at least 1 year, chronic deterioration of allograft function after RT, data of serum haemoglobin levels in the patient's medical record for the previous 12 months with regard to readmission to dialysis therapy and during at least 90 days after restarting dialysis, and signed informed consent form. Patients in whom serum haemoglobin data were not consistently registered in the medical records or those who did not provide informed consent as well as multiorgans transplant were excluded and those whose charts were incomplete or unavailable.

The primary objective of the study was to assess changes in the prevalence and management of post-transplant anaemia as well as renal function-related variables of RT patients with graft failure restarting dialysis. To this purpose, two cohorts of RT patients with graft failure were compared. The first cohort included patients restarting dialysis during 1999–2000 and the second cohort included patients restarting dialysis during 2007–08. The secondary objective of the study was the description of the clinical profile of these patients, including clinical risk factors for graft loss and clinical course during the first 90 days after resumption of dialysis treatment. Patients included in the first cohort were recruited from 20 centres between September and December 2001, and patients included in the second cohort were recruited from 15 centres between April and October 2009. All patients or their legal representatives (if a patient has died) gave written informed consent to participate in the study and to use data from the medical records.

For each patient, the following variables were recorded: demographics (age and sex), aetiology of chronic renal failure, RT-related data, management of post-transplant anaemia excluding the early postoperative period, associated co-morbidities developed during the 12 months before dialysis treatment and outcome (hospital admission and death) during the first 90 days after restarting dialysis. Moreover, clinical, laboratory data, immunosuppressive regimen and management of anaemia were recorded at 3-month intervals during the 12-month period before readmission to dialysis treatment (0, −1, −3, −6, −9 and −12).

Anaemia was defined as a haemoglobin concentration <12 g/dL [7.4 mmol/L] in adult women and <13 g/dL [8.1 mmol/L] in adult men [18]. A cut-off value of serum haemoglobin of 11 g/dL [6.8 mmol/L] triggered treatment with erythropoiesis-stimulating agents (ESA) according to clinical practice [19, 20]. Hypertension was defined as blood pressure ≥ 140/90 mm Hg. The glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease (MDRD)-4 formula. A decline in renal graft function was defined as an unexplained rise of 25% in serum creatinine clearance compared with baseline.

Student's *t*-test or the Wilcoxon signed-rank test was used for the comparison of haemoglobin levels at the onset of dialysis and for each study period before readmission to dialysis therapy. Differences in morbidity and mortality according to the presence of anaemia and renal function data (serum creatinine, GFR and creatinine clearance) were also analysed. We used multivariable logistic regression to assess the association of clinical factors and outcomes in both cohorts. Also, all the patients were followed up until 3 months after graft loss date. Death at third month was analysed as the dependent variable and age >55 years at the time of inclusion, previous diabetes diagnosis, hepatitis C virus (HCV) infection, hypertension, serum haemoglobin level at Month 0, renal function as serum creatinine at Month 0 and use of ESAs were entered in the model as independent variables. The SPSS program, versions 8.0 and 13.0 were used to analyse data of the 2001 and 2009 cohorts, respectively. Statistical significance was set at $P < 0.05$.

Results

A total of 397 patients were included in the 2001 cohort and 222 in the 2009 cohort. The distribution of variables in both cohorts is shown in Table 1. There were no significant differences except for age at the time of inclusion in the study and at the time of transplantation (younger patients in the 2001 cohort) (Figure 1), causes of renal failure, HCV infection, pulmonary embolism, donor age, time from renal transplantation to restarting dialysis and peritoneal access. Chronic glomerulonephritis was the most common cause of ESRD. RT-related data are also shown in Table 1. Donors were also younger in the 2001 cohort than in the 2009 cohort (Figure 1). The mean time from RT to restarting dialysis was 103.0 months in 2009 and 83.6 months in 2001.

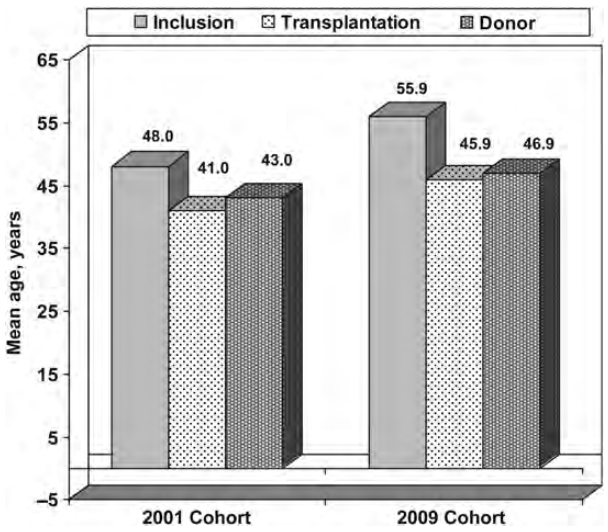

Fig. 1. The mean age of recipients and donors in the two study cohorts.

Table 2. Clinical characteristics and laboratory data on readmission to dialysis therapy

Cohort year	Age, years mean (range)	Timing	Glomerular filtration rate, mL/min/1.73m^2 mean (95% CI)	Serum creatinine mg/dL mean (95% CI)	Haemoglobin g/dL mean (95% CI)	Anaemia[a] % patients	Treatment with ESA % patients	Treatment with iron % patients
2001	48.0 (18–78)	−12	25.18 (23.71–26.65)	3.19 [288.0 µmol/L] (3.04–3.33 [268.7–394.4 µmol/L])	11.57 [7.2 mmol/L] (11.36–11.78 [7.1–7.3 mmol/L])	70.5	14.1	21.2
		0	9.91 (9.12–10.70)	6.85 [605.54 µmol/L] (6.63–7.07 [586.1–625.0 µmol/L])	9.59 [6.0 mmol/L] (9.40–9.77 [5.8–6.1 mmol/L])	94.9	55.4	44.5
		−12 vs. 0	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
2009	55.9 (19–81)	−12	28.63 (26.71–30.55)	2.76 [244.0 µmol/L] (2.61–2.91 [230.1–257.2 µmol/L])	12.35 [7.7 mmol/L] (12.15–12.55 [7.5–7.8 mmol/L])	54.9	61.3	35.6
		0	13.26 (11.5 3–15.00)	5.58 [493.3 µmol/L] (5.27–5.88 [465.7–519.8 µmol/L])	10.64 [6.6 mmol/L] (10.43–10.85 [6.5–6.7 mmol/L])	86.8	86.5	48.2
		−12 vs. 0	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001

[a]<12 g/dL in women <13 g/dL in men.

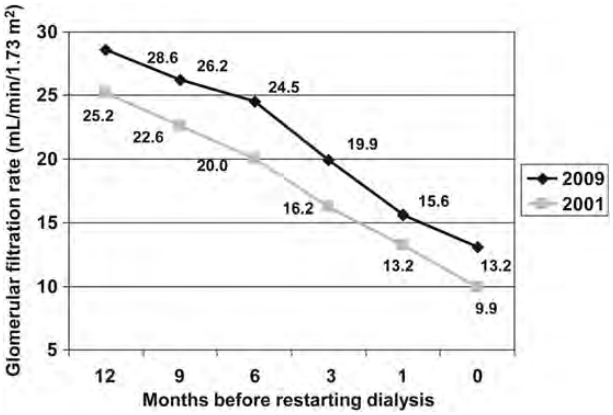

Fig. 2. Comparison of GFR using the MDRD-4 equation in the study cohorts of 2001 and 2009 over 1 year before readmission to dialysis therapy (P < 0.01).

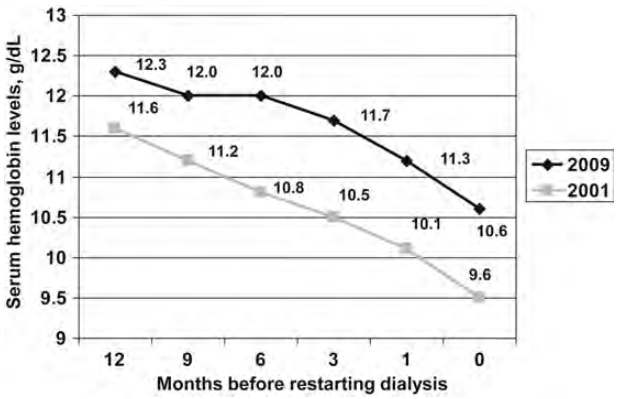

Fig. 3. Serum haemoglobin levels during the 12 months before resumption of dialysis and at the time of restarting dialysis in the 2009 and 2001 cohorts (P < 0.001 for the comparison of Month −12 to Month 0 for each cohort).

Changes in renal function, mean haemoglobin levels and percentage of patients treated with ESAs in the study population are shown in Table 2. Patients in the 2009 cohort restarted dialysis therapy with a significantly better GFR than those in the 2001 cohort (1 year before resumption of dialysis 28.6 versus 25.2 mL/min/1.73 m^2, P < 0.009; on readmission to dialysis therapy 13.3 versus 9.9 mL/min/1.73 m^2, P < 0.009) (Figure 2). In both cohorts, however, there was a rapid deterioration of allograft function within the last months prior to reinitiating dialysis therapy, with statistically significant differences in serum creatinine and GFR between the monthly intervals −12 and 0 (Table 2).

The percentage of patients with allograft dysfunction-related anaemia as well as its severity decreased over the past 8 years. The prevalence of anaemia at any time during the 12 months before readmission to dialysis therapy was 99% in the 2001 cohort and 97% in the 2009 cohort. For instance, the percentage of patients with anaemia in the 2009 cohort increased from 54.9% at Month −12 to 86.8% on resumption of dialysis, and 11.7% required blood transfusion at any time during the year prior to dialysis. Iron supplementation was administered to 54.7% of patients at any time during the 12 months before readmission to dialysis in the 2001 cohort and to 59.5% in the 2009 cohort.

The mean haemoglobin value at 12 months before readmission to dialysis was 11.6 g/dL [7.2 mmol/L] in the 2001 cohort when compared with 12.3 g/dL [7.6 mmol/L] in the 2009 cohort. Likewise, at the time of restarting dialysis, haemoglobin levels were 9.6 g/dL [6.0 mmol/L] and 10.6 g/dL [6.6 mmol/L], respectively (Figure 3). However, in both cohorts, decreases in serum haemoglobin from Month −12 to Month 0 were statistically significant (P < 0.001) (2009 cohort, 12.3 versus 10.6 g/dL [7.6 versus 6.6 mmol/L]; 2001 cohort 11.6 versus 9.6 g/dL [7.2 versus 6.0 mmol/L]). On the other hand, the percentage of patients treated with ESAs at any time during the 12 months before readmission to dialysis therapy increased significantly from 61.5% in the 2001 cohort to 90.1% in the 2009 cohort (P < 0.001) (Figure 4). In the 2001 cohort, mean serum haemoglobin levels were similar in patients treated with erythropoietin than in those untreated (Figure 5).

The relationship between the percentage of patients with important anaemia (defined as serum haemoglobin ≤11 g/dL [6.8 mmol/L]) and the immunosuppressive regimens for the 2001 and 2009 cohorts is shown in Table 3. Overall, the percentage of patients with anaemia for the three more frequent immunosuppressive combinations was lower in the 2009 cohort either at Month -12 than at time 0 upon restarting dialysis.

Morbidity and mortality

As shown in Table 4, morbimortality data in both cohorts were similar. There were no significant differences between the 2001 and 2009 cohorts in the mortality rate (8.8 versus 9.0%) or the percentage of patients requiring hospital admission (31.5 versus 31.2%) during the first days after resumption of dialysis therapy. The distribution of causes of death was also similar in the 2001 and 2009 cohorts, with cardiac causes as the most common (35.3 and 30%, respectively) followed by infection (20 and 17.6%), malignancies (15 and 14.7%) and acute cerebrovascular event (5 and 5.9%). Sudden death occurred in 17.6% of cases in the 2009 cohort but in none of the 2001 cohort. A subgroup analysis of morbidity and mortality according to renal function (serum creatinine concentration categorized as ≤2 mg/dL [176.8 µmol/L] versus >2 mg/dL [176.8 µmol/L]) and serum haemoglobin level (categorized as ≤11 g/dL [6.8 mmol/L] versus >11 g/dL [6.8 mmol/L]) did not show significant differences at any of the −12 to 0 months intervals either in the 2001 or the 2009 cohorts.

Results of logistic regression analyses are shown in Tables 5 and 6. Table 5 shows that morbimortality was the same for 2009 and 2001 despite the fact that the 2001 cohort was a population with an expected higher disease load (higher age at the time of inclusion or at the time of transplantation and longer interval between transplantation and restarting dialysis). Adjusted by the effect of the remaining variables, population in the 2009 cohort also appears to present a lower percentage of first transplantations. A decrease in HCV infection from 2001 to 2009 was noted. Table 6 shows significant differences with better levels of haemoglobin and renal function in the 2009 cohort at the time of restarting dialysis despite differences in morbimortality when compared with the 2001 cohort and a probable higher disease load.

As shown in Table 7, age >55 years was the main variable related to death at 3 Months, whereas a higher haemoglobin level at Month 0 and the use of ESAs reduced the risk.

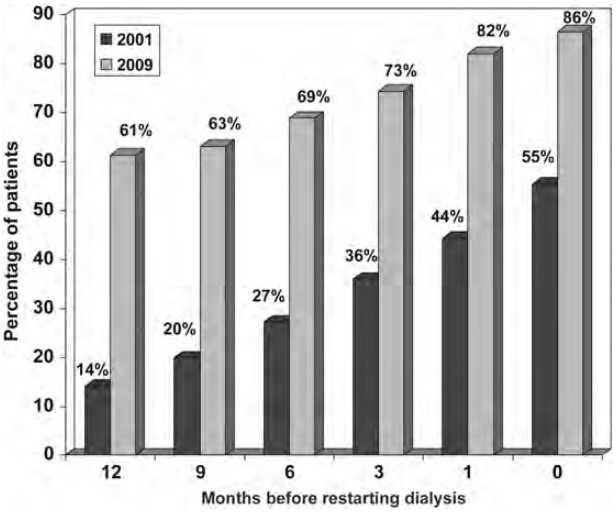

Fig. 4. Treatment with ESA in the study population.

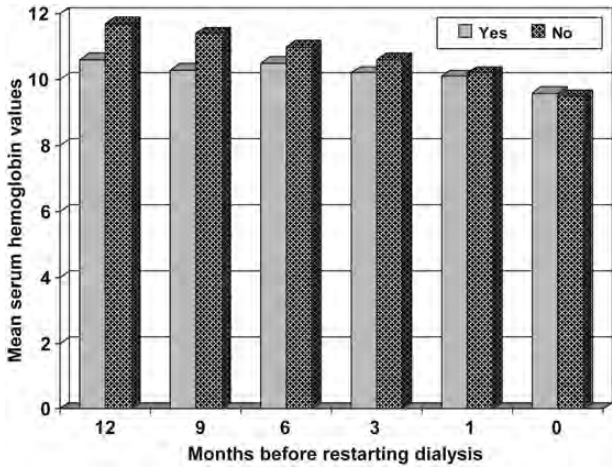

Fig. 5. Mean serum haemoglobin levels in patients treated (yes) and untreated (no) with erythropoietin during the 12 months before resumption of dialysis were similar (2001 cohort).

Table 4. Morbidity and mortality data in the two study cohorts

	2001 Cohort (*n* = 397)	2009 Cohort (*n* = 222)	P-value
Deaths during first 90 days after transplantation, *n* (%)	35 (8.8)	20 (9.0)	0.504
Hospital admission during the first 90 days after transplantation, *n* (%)	125 (31.5)	69 (31.19)	0.928
Hospital admission during the first 90 days after transplantation (excluding patients who died), *n* (%)	101 (25.4)	57 (25.7)	0.998
Cardiovascular morbidity (excluding hypertension) during the 12 months before dialysis treatment, *n* (%)	96 (24.2)	52 (23.4)	0.845
Hospital admission and/or cardiovascular morbidity (excluding hypertension) during the 12 months before dialysis treatment *n* (%)	171 (43.1)	44.6 (23.4)	0.736

Table 3. Differences in the percentage of patients with the serum haemoglobin level ≤11 g/dL [6.8 mmol/L] according to post-transplant immunosuppressive regimen between the 2001 and 2009 cohorts

	2001 Cohort		2009 Cohort	
Immunosuppressive combination	Month −12 (%)	Month 0 (%)	Month −12 (%)	Month 0 (%)
Everolimus, tacrolimus, mycophenolate mofetil	8/18 (44.4)	24/27 (88.9)	13/55 (23.6)	29/43 (67.4)
Everolimus, cyclosporine, mycophenolate mofetil	38/74 (51.4)	54/66 (81.8)	5/38 (13.2)	15/28 (53.6)
Everolimus, cyclosporine, azathioprine	22/72 (30.6)	19/25 (76)	3/6 (50)	2/5 (40)

Table 5. Logistic regression analysis: profile of patients in the 2001 and 2009 cohorts (without including haemoglobin or renal function)

	Age at the time of inclusion[a]			Age at the time of transplantation[a]		
	Odds ratio[b]	95% CI	P-value	Odds ratio[b]	95% CI	P-value
Cardiovascular morbidity developed during the 12 months before dialysis	0.666	0.413–1.073	0.095	0.724	0.452–1.160	0.180
Non-cardiovascular morbidity developed during the 12 months before dialysis	1.179	0.798–1.744	0.408	1.180	0.802–1.735	0.400
Hospital admission during the first 90 days after transplantation	0.970	0.636–1.479	0.888	0.979	0.646–1.484	0.920
Death during the first 90 days after transplantation	0.675	0.347–1.316	0.249	0.730	0.378–1.410	0.348
HCV infection	0.354	0.213–0.588	0.001	0.359	0.218–0.592	0.001
Diabetes post-transplantation	1.514	0.907–2.526	0.112	1.574	0.949–2.611	0.079
Age of the donor	1.003	0.990–1.015	0.678	1.006	0.994–1.018	0.324
Time from transplantation to restarting dialysis	1.008	1.004–1.012	0.001	1.012	1.008–1.015	0.001
Age at the time of inclusion	1.054	1.035–1.072	0.001			
Age at the time of transplantation				1.041	1.023–1.059	0.001
Second or successive transplants	2.020	1.192–3.424	0.009	1.876	1.116–3.154	0.018

[a]Due to the association between age at inclusion and age at the time of transplantation, two models were adjusted: one considering age at the time of inclusion and another considering age at the time of transplantation.
[b]Odds ratios adjusted by the remaining variables (OR > 1 means higher probability to belong to the 2009 cohort; OR < 1 means higher probability to belong to the 2001 cohort).

Table 6. Logistic regression analysis for the comparison of the 2001 and 2009 cohorts including haemoglobin level and renal function at starting dialysis

	Odds ratio[a]	95% CI	P-value
Cardiovascular morbidity developed during the 12 months before dialysis	0.744	0.442–1.255	0.268
Non-cardiovascular morbidity developed during the 12 months before dialysis	1.080	0.702–1.659	0.727
Hospital admission during the first 90 days after transplantation	0.942	0.595–1.493	0.801
Death during the first 90 days after transplantation	0.655	0.308–1.391	0.271
HCV infection	0.334	0.192–0.580	0.001
Diabetes post-transplantation	1.392	0.810–2.393	0.231
Age of the donor	1.001	0.988–1.015	0.855
Time from transplantation to restarting dialysis	1.008	1.004–1.012	0.001
Age at the time of inclusion	1.055	1.035–1.075	0.001
Second or successive transplants	2.457	1.379–4.376	0.002
Serum haemoglobin level at Month 0	1.336	1.179–1.513	0.001
Renal function at Month 0	1.034	1.006–1.063	0.018

[a]Odds ratios adjusted by the remaining variables (OR >1 means higher probability to belong to the 2009 cohort; OR <1 means higher probability to belong to the 2001 cohort).

Table 7. Risk factor for death at 3 months

Risk factor	Odds ratio (95% CI)	P-value
Age over 55 years (yes)	2.967 (1.559–5.645)	0.001
Diabetes mellitus (yes)	1.264 (0.340–4.702)	0.727
HCV infection (yes)	0.932 (0.453–1.917)	0.849
Hypertension (yes)	1.108 (0.489–2.513)	0.806
Haemoglobin (g/dL)[a]	0.822 (0.687–0.984)	0.032
Creatinine (mg/dL)[b]	0.882 (0.761–1.021)	0.093
ESA	0.525 (0.285–0.970)	0.040

[a]For each 1 g/dL haemoglobin or 0.6206 mmol/L haemoglobin, the risk increases 0.822.
[b]For each 1 mg/dL creatinine or 88.40 µmol/L creatinine, the risk increases 0.882.

Discussion

RT is the optimal mode of replacement therapy in most patients with ESRD. Although there has been progressive improvement in short-term patient and graft survival rates in the modern immunosuppressant era, in the longer term, there is a persistent graft loss of 2–5% annually. This attrition is due in part to death with a functioning graft, but in most series, the most common cause of graft loss is chronic allograft failure [21]. The mean allograft half-time in Spain is 14 years (time when 50% of the grafts are lost excluding the graft loss within the first year) [22]. Readmission to dialysis therapy in these patients is associated with a higher morbidity and mortality [23, 24], particularly within the first 90 days of restarting dialysis [25, 26] and is notably higher than that found in patients admitted to dialysis therapy for the first time.

On the other hand, the presence of anaemia in the context of RT is a common feature [27], with a clear association between haemoglobin levels, renal function and cardiovascular complications [28]. Given the clinical relevance of these data, the present observational retrospective study was conducted to assess changes in the prevalence and management of anaemia in RT patients with graft loss requiring readmission to dialysis therapy based on a comparison of two cohorts of patients attended in clinical practice with an interval of 8 years (2001 and 2009).

With improved and early allograft survival, chronic allograft nephropathy has become the dominant cause of kidney transplant failure [29]. The present results show that in patients with chronic graft nephropathy, there is a rapid deterioration of renal function in the last months prior to requiring resumption of dialysis treatment. In both cohorts, statistically significant differences in serum creatinine levels and GFR were found between values at −12 months and upon reinitiating dialysis. In agreement with other studies [17, 30–32], the prevalence of anaemia was high but there was a decrease over the 8-year study period, with a mean haemoglobin value of 11.6 g/dL [7.2 mmol/L] in 2001 versus 12.3 g/dL [7.6 mmol/L] in 2009 at −12 months and 9.6 g/dL [6.0 mmol/L] in 2001 versus 10.6 g/dL [6.6 mmol/L] in 2009 at the time of restarting dialysis. A recent study carried out in Spain has shown that failed transplant

patients start dialysis with more severe anaemia than patients entering dialysis for the first time. Twelve months later, both groups present a similar clinical condition with the exception of residual kidney function, higher in failed native kidney patients [33].

Taken together, these findings suggest a better clinical management of kidney transplant recipients in recent years compared with previous periods despite a higher donor and recipient age as well as a higher proportion of diabetes in the 2009 cohort. As a result, the percentage of patients treated with an ESA at any time during the 12 months before readmission to dialysis therapy increased significantly between 2001 and 2009. The fact that morbidity and mortality rates were similar between both cohorts supports this argument.

The present results should be interpreted taking into account some limitations of the study. One important limitation is the intrinsic design of the study. As has been the case of other studies in this area, our data were collected retrospectively. Unlike most previous studies, however, we have examined differences in two kidney transplant population cohorts to ascertain changes in the impact of anaemia on the long-term outcome of kidney transplant recipients. Moreover, differences in the clinical profile of patients with chronic progressive graft dysfunction during the previous year before readmission to dialysis therapy have not been evaluated in previous reports. Although a centre effect may be present, we have compared the total cohort data in relation to coincident centres and there were no statistically significant differences suggesting bias by centre (data not shown). The fact that we have no data to calculate the evolution of the erythropoietin resistance index in the cohort from 2009 is a weakness of the study. Other limitations of the study include the lack of data on donor-specific antibodies, delayed graft function and long-term outcome.

Finally, although patients with chronic renal failure due to graft failure had a poorer renal function at the time entering dialysis and a more profound anaemia [7], the management of anaemia to achieve haemoglobin target is similar among European countries [27, 34].

In conclusion, the percentage of patients with anaemia (and its severity due to progressive chronic graft nephropathy) 1 year before and at the time of restarting dialysis has decreased over the past 8 years, increasing significantly the percentage of patients treated with ESAs.

Authors' contributions

M.A., J.M.C., D.H. and J.S.P. provided the conception and design of the study, analysis and interpretation of data, and gave final approval of the version to be submitted.

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