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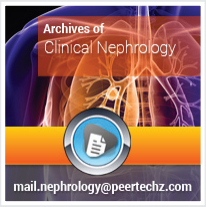

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Research Article

Epidemiological and clinical implications in Kidney Transplantation of occult Hepatitis C virus infection

Abstract

Occult Hepatitis C virus (HCV) infection (OCI) is characterized by the presence of HCV-RNA in liver or in peripheral blood mononuclear cells (PBMC) in the absence of serological markers. HCV infection in kidney transplant (KT) recipients is associated with lower patient and graft survival. However, the relationship between KT outcome and OCI is unknown. Our aim was to determine in KT recipients the prevalence, risk factors for OCI, and its prognostic implications. We tested 149 adults KT recipients for the presence of OCI. HCV-RNA was tested by a RT-PCR in PBMC and in 2 ml of plasma after ultracentrifugation. OCI was positive in 21 patients (14.1%). Previous blood transfusion was a risk factor for acquiring OCI (p=0.044). Although there were no statistical differences in clinical complications post-KT and in the immunosuppression, graft and patient survival were worse in the OCI positive group (p=0.02 and p=0.04, respectively). In summary, there was a high prevalence of OCI in our KT population with previous blood transfusion as the main risk factor. Long-term graft and patient survival were reduced as compared to OCI negative recipients although the contribution of particular co-morbidities did not reach statistical significance.

Abreviations

ATG: Antitymocite Immunoglobulin; CKD: Chronic Kidney Disease; DGF: Delayed Graft Function; HCV: Hepatitis C virus; HCV: RNA: Hepatitis C virus-Ribonucleic Acid; HIV: Human Immunodeficiency Virus; IMGN: Immune Mediated Glomerulonephritis; KT: Kidney Transplantation; mTOR: Mammalian Target of Rapamycine; NC: Non Coding; NODAT: New Onset Diabetes After Transplantation; OCI: Occult HCV Infection; PBMC: Peripheral Blood Mononuclear Cells; PTLD: Post-Transplant Lymphoproliferative Disease; RT-PCR: Real Time Reverse Transcription;

Introduction

Chronic hepatitis C virus (HCV) infection has been recognized as an important health problem in kidney transplant (KT) recipients, with a significantly higher prevalence than in general population [1]. The survival rate for HCV-infected KT recipients is better than that for HCV-infected hemodialysis patients on transplant waiting lists [2]. However, in KT recipients, HCV infection (often acquired because of dialysis treatment) is associated with liver disease and is an independent risk factor for graft loss, chronic rejection, transplant glomerulopathy, post-transplant diabetes and HCV- associated glomerulonephritis [3]. The increased risk of death in HCV-infected renal allograft recipients has been attributed to cardiovascular mortality, linked someway to the insulin resistance and high risk of new onset diabetes after transplantation (NODAT) rather than the progressive of HCV- related liver disease [4]. Determining the best immunosuppressive regimen after KT in the presence of HCV infection remains challenging as it has significant consequences on HCV replication and disease [5].

Occult HCV infection (OCI) is characterized by the presence of HCV-RNA in liver or peripheral blood mononuclear cells (PBMC) in the absence of serological markers [6]. OCI may also be diagnosed by concentrating 2 ml of serum by ultracentrifugation followed by HCV-RNA detection by real-time PCR [7]. Our group has found a high prevalence of OCI in hemodialysis patients [8] and also in patients with primary and secondary glomerular nephropathies [9]. In both groups the presence of OCI was associated with a worse outcome including a potential role in the progression of the renal disease. To our knowledge, there is only one study reporting a low prevalence of OCI in KT recipients [10]. Thus, we aimed to determine the prevalence as well as the epidemiological and clinical implications of OCI in a Spanish population of KT recipients. In addition, we also studied the possible association of OCI with renal graft function, development of NODAT and cancer, opportunistic infections, kidney rejection and graft and patient survival

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Material and Methods

Patients

This prospective study included 149 patients attending a Nephrology consulting due to functioning KT, at different stages. All patients had to be anti-HCV and serum HCV-RNA negative as well as hepatitis B surface antigen and anti-HIV negative by routine commercial tests. We did not use HCV positive donor as in our center these are reserved for HCV infected recipients.

All patients had to be followed up after KT for a period longer than one year, and their vital prognostic had to be unaffected by any known process. Over 2015 and 2016, 149 adults, non-selected patients, were recruited. The study was approved by the Ethic Committee of the Hospital and was conducted according to the Declaration of Helsinki. Each patient gave a written informed consent and afterwards was tested for OCI. All the participants were followed-up as recommended by the European Best Practice Guidelines for renal transplantation [11]. Recommendations for prevention and treatment about infections, cardiovascular risk (obesity, smoking, hiperlipidaemia NODAT, hypertension) or cancer development (skin, solid organ and PTLD) were strictly followed. A follow-up period of (119.8 ±77 months) was used to explore kidney function stability, needs of immunosuppression and the incidence of complications related with KT outcome. The last 24 months of this follow-up allowed the observation of all patients after OCI testing to explore its role on graft and patient survival.

Type and time on dialysis, previous blood transfusions, surgical procedures, household contacts and partners diagnosed of HCV infection, as the presence of tattoo or piercing were recorded as potential risk factors for HCV infection. The acute and chronic rejection had to be confirmed by a kidney graft biopsy. The delayed graft function (DGF) was defined as the need for dialysis the first week post-KT. The presence of NODAT was defined as the requirement of oral antidiabetics or insulin for a minimum period of 30 days post-KT. Opportunistic infections were registered in KT recipients, as well as infections due to organisms with microbiological resistance. The time until the loss of the graft was calculated from the date of the KT until the date of graft loss. The patient's survival was calculated from the KT until the date of death.

Methods

HCV- RNA detection in PBMC and in plasma samples: PBMC and plasma were isolated from anticoagulated blood by Biocoll (Biochrom, Berlin, Germany) density gradient centrifugation. Plasma was aliquoted and stored at -30ºC. PBMC were washed three times in phosphate-buffered saline and stored in RNAlater solution (Ambion, Austin, TX) at -30ºC.

Total RNA from PBMC was isolated with SV Total RNA Isolation System (Promega, Madison, WI). After precipitation, pellets were dissolved in diethyl-pyrocarbonate-treated water and RNA concentration was determined by spectrophotometry. In addition, 2 ml of plasma were ultracentrifuged over a 10% sucrose cushion at 100,000 xg for 17 h at 4ºC. The pellet was dissolved in 250 ml of TE buffer (Tris-HCl 10 mmol/l, EDTA 10 mmol/l; pH 7.5) and, total RNA was isolated with Trizol LS Reagent (Invitrogen, Carlsbad, CA.), precipitated, and the pellet dissolved in diethyl-pyrocarbonate-treated water.

Amplification of the HCV-RNA 5' noncoding (NC) region was performed by quantitative real-time reverse transcription (RT)-PCR with fluorescence resonance energy transfer probes. Two microliters of total RNA isolated from 2 ml of ultracentrifuged plasma, or 0.5 µg of total RNA from PBMC were retrotranscribed and amplified in a single tube reaction containing RNA reaction mix (LightCycler Master Hybprobe, Roche Diagnostics, Mannheim, Germany), The conditions of this RT-PCR have been previously described [12-16]. A standard curve constructed with 10-fold dilutions of a synthetic HCV-RNA was used for quantification. The lower limit of HCV-RNA detection of the assay was 10 IU/ml (mean threshold cycle [Ct], 39.32) with a lower limit of quantification of 100 IU/ml (mean Ct, 35.64), as determined by testing serial dilutions of HCV-RNA positive serum sample, in which HCV-RNA quantification was previously assessed by an HCV test (Cobas TaqMan, Roche Diagnostics).

HCV-RNA detection was performed by laboratory personnel who were blinded to the clinical status of the patients. Each PCR run included a maximum number of 10 samples along with negative controls (repeatedly HCV-RNA negative sera and PBMC samples) and reagent blanks in which total RNA was replaced with PCR-grade water. Negative controls and blanks were processed with the samples and accompanied them through the entire PCR process. As positive controls, HCV-RNA positive sera and PBMC from patients with chronic HCV infection were used. The guidelines of Kwok and Higuchi [12], were strictly observed for avoiding contaminations. To further confirm OCI results, positive samples and randomly selected negative ones were tested again on different days by another person who was blinded to previous results.

Statistical analysis

The data were processed by a database in the program SPSS version 20, for its statistical treatment. For the description of continuous quantitative variables, the mean was used together with the standard deviation. Qualitative variables were described by absolute and relative frequencies expressed as a percentage. The comparisons between continuous quantitative variables between the two independent groups were performed primarily using a non-parametric (Mann-Whitney U Test) technique. For the analysis of frequencies between qualitative variables, the chi-square test or Fisher's exact test was used when possible. The analysis of the temporal evolution between moments of the quantitative variables was performed in paired form, by the Wilcoxon signed rank test. A Kaplan-Meier method and log-rank test were used to calculate kidney graft and patient survival. A P value <0.05 indicated statistical significance.

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Results

Of the 149 KT receptors studied, 20 tested positive for the presence of HCV RNA in PBMC with an average concentration of 1727.35 copies per µg of total RNA (range 347-6810). HCV RNA was detected in the plasma after the ultracentrifugation of 2 ml of plasma in another patient at a concentration of 872 copies per ml of plasma. Positive results were obtained in different runs on different days, excluding intersample cross-contamination and the retesting of positive and negative samples in a blind fashion by different operators, confirmed the results. Therefore, we found a prevalence of occult HCV infection of 21/149 (14.1%); these patients had viral RNA detectable in PBMC or in plasma after ultracentrifugation despite the absence of anti-HCV antibodies.

When comparing demographic and clinical features (12 months after KT) of the patients according to their OCI status (Table 1) it was found that previous history of blood transfusion was significantly higher (p=0.044) in the OCI group (18; 94.7%) than in the negative one (91; 71.7 %), (odds ratio=7.121; 95% confidence interval: 0.916-55.332).

At this first year of post KT follow-up, renal function and proteinuria were similar in both groups although plasma creatinine and proteinuria in the OCI positive group were mildly lower (1.44 ± 0.86 (mg/dl); 0.30 ± 0.30 (g/24h)) than in the OCI negative group (1.58 ± 0.49 (mg/dl); 0.42 ± 0.65 (g/24h)). However, at the end of the whole follow-up period (119.8 ± 77 months), renal function tended to decline faster and proteinuria values were higher in the OCI positive group (1.93 ± 1.05 (mg/dl); 0.86 ± 1.14 (g/24h)), than in the OCI negative group, (1.74 ± 0.80 (mg/dl); 0.62 ± 1.38 (g/24h)), although these differences did not reach statistical significance (p=0.44 and 0.77).

Type of immunosuppression at induction therapy and once stabilized at the time of the study, did not differ between OCI positive and negative group (Table 2).

Clinical complications post-KT were similar in both group of patients (Table 3).

Graft loss occurred in 5/149 (3.3%) patients, being 2 of them OCI positive (Table 2). In 3 of these 5 patients (60%), transplant glomerulopathy was the cause of returning to dialysis programme (one patient was OCI positive). In the remaining 2 cases, it was due to development of myeloma multiple (patient with OCI) and pelvic cancer (OCI negative). During the follow-up, it was recorded a total of 7/149 (4.7%) exitus. In the group of patients with OCI there was a trend of more deaths (3/21; 14.3%) than in negative ones (4/128; 3.1%) but without statistical difference (p=0.06) (Table 3). In the

Table 1: Demographic, epidemiological, clinical and analytical parameters of the patients at the study.

	Occult negative HCV infection (N = 128)	Occult positive HCV infection (N=21)	Significance	Odds ratio	95% Confidence interval
Age (years; mean ± SD)	52.73 ± 14.43	55.19 ± 14.03	0.386		
Male (n; %)	83; 64.8	12; 57.1	0.625	0.723	0.283-1.845
Time on dialysis programme (months; mean ± SD)	31.10 ± 21.13	25,55 ± 18,97	0.585		
Time of follow up after renal transplantation (months; mean ± SD)	120 ± 78.56	118.52± 68.6	0.475		
Serum creatinine (mg/dl; mean ± SD)	1.58 ± 0.49	1.44 ± 0.86	0.096		
Proteinuria (gr/24h; mean ± SD)	0.42 ± 0.65	0.30 ± 0.30	0.247		
Risk factors for HCV infection: (n;%)					
Type of dialysis			0.520	N/A	N/A
Hemodialysis	52; 43.7	10; 55.6			
Peritoneal dialysis	44; 37	6; 33			
None	3; 2.5	0; 0			
Both	20; 16.8	2; 11.1			
Previous Blood Transfusion	91; 71.7	18; 94.7	0.044	7,127	0.916-55332
Household HCV contact	0; 0	0; 0	0	N/A	N/A
Tatoo/drogadiction	11 ;12.8	4; 25	0.247	2,273	0.622-8.310
HBV infection	19; 15.7	5; 27.8	0.199	2,065	0.659-6.467
Etiology of renal disease (n;%)			0.081	N/A	N/A
Glomerular nephropathy	37; 29.8	1; 4.8			
Hereditary nephropathy	35; 28.2	4 ;19			
Systemic nephropathy	14 ; 11.3	5; 23.8			
Tubulointersticial nephropathy	22; 17.7	5 ; 23.8			
Diabetic nephropathy	16 ; 12.9	6 ;28.6			

HCV: Hepatitis C virus; HBV: Hepatitis B virus; SD: standart desviation; N/A: Not available.

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OCI positive group deaths were due to urinary tract cancer, myeloma, and one of sudden death, while in the OCI negative group causes were urinary tract neoplasia, cervix and lung cancer and septicaemia. Therefore, neoplasia was the first cause of death in both groups.

With respect to the outcome of renal transplantation, in terms of graft and patient survival at (9.98 ± 6.41 years) (Figure 1), it was found that OCI patients had significant greater loss of

Table 2: Immunosuppression according to occult HCV infection.

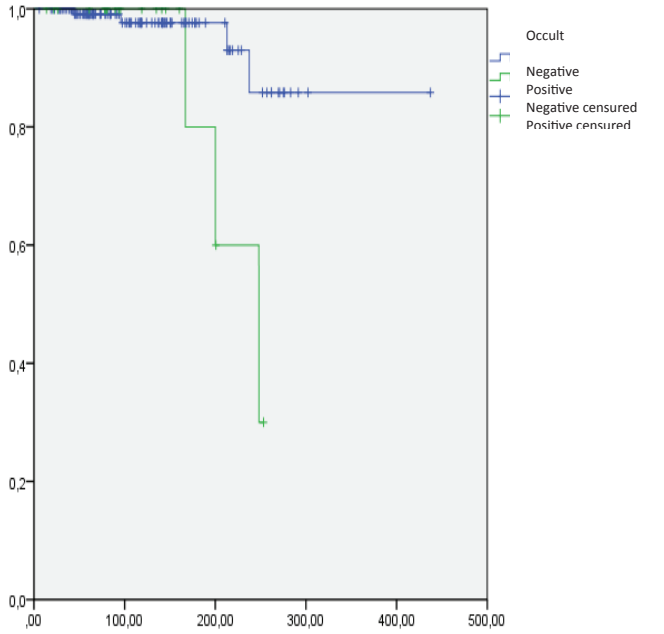
	Occult negative HCV infection	Occult positive HCV infection	Significance	Odds ratio	95% Confidence
	(n=129)	(n=21)			interval
Mycophenolate mofetil (n; %)	99; 79,2	18; 85.7	0.767	1,576	0.431-5.761
mTOR (n; %)	22; 17.6	2; 9.5	0.529	0.493	0.107-2.271
ATG (n; %)	42; 49.4	7; 46.7	1	0.896	0.298-2.691
Basiliximab (n; %)	28; 32.9	6; 40	0.572	1,357	0.439-4.192
Calcineurinic inhibitor (n; %)			0.639	N/A	N/A
Tacrolimus	94, 75.2	17; 81			
Cyclosporin	17; 13,6	2; 9.5			
None	14; 11,2	2; 9.5			
Steroids (n; %)	89;71.8	14; 66.7	0.613	0.787	0.293-2.112

HCV: Hepatitis C virus; mTOR: mammalian Target of Rapamycine; ATG: antitymocite immunoglobulin; N/A: Not available.

Table 3: Clinical complications post renal transplantation according to negative/positive occult HCV infection.

	Occult negative HCV	Occult positive HCV	Significance	Odds ratio	95% Confidence
	infection (n=128)	infection (n=21)			interval
DGF (n; %)	17; 13.5	2; 9.5	1	0.675	0.144-3.161
Acute rejection (n; %)	13;10.3	2; 9.5	0.603	N/A	N/A
Opportunistic infection (n;%)	46; 36.5	7; 33.3	1	0.870	0.327-2.310
NODAT (n; %)	29;22.65	6;28.57	0.384	2,129	0.834-5.433
Cancer (n;%)	24; 18.9	7; 33.3	0.151	2,146	0.781-5.893
Chronic rejection (n; %)	5; 3.9	2; 9.5	0.257	2,589	0.469-14.310
Myocardial infartion (n;%)	14; 11	4; 19	0.289	1,899	0.559-6.449
Cerebrovascular ischemia (n;%)	4; 3.1	1; 4.8	0.540	1,538	0.163-14.467
Graft loss (n;%)	3; 2.4	2; 9.5	0.147	4,351	0.682-27.760
Deaths (n;%)	4; 3.1	3; 14.3	0.06	5,125	1.059-24.796

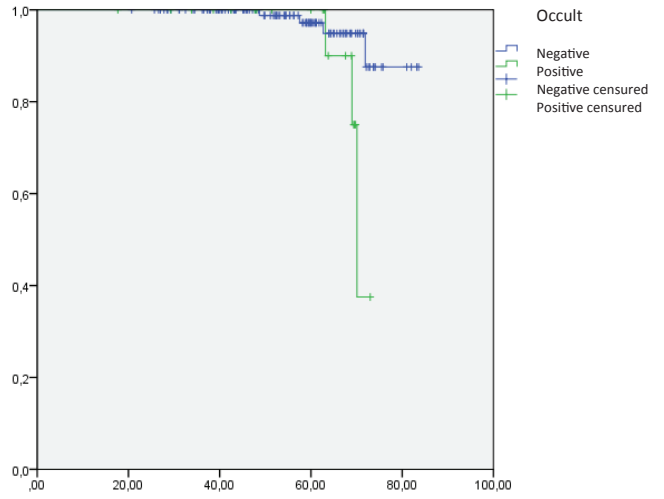
Acute and chronic rejection had to be confirmed by a renal allograft biopsy. Delayed graft function (DGF) was defined as need of dialysis. New-onset diabetes after transplantation (NODAT) was defined as the requirement of oral antidiabetics or insulin for a minimum period post-KT (often 30 days). Common infections in solid organ transplant recipients as well as infections due to organisms with microbiological resistance were recorded.
N/A: Not available.



Time to allograft loss was calculated from KT until the date of allograft loss.

OCI positive patients had significant greater loss of the graft (2; 9.5%) vs OCI OO negative ones (3; 2.4%),
p=0.02.

Figure 1A: Kaplan-Meier plot for Graft survival according to OCI recipients. (Months).



The patient's survival was calculated from the KT until the date of death.

OCI positive patients had significant less survival (3; 14,3% deaths) than negative ones (4; 3,1%), p=0.04.

Figure 1B: Kaplan-Meier plot for patient survival according to OCI recipients (Years).

the graft (2; 9.5%) (p= 0.02) and patient (3; 14.3%) (p= 0.04,) than negative ones (3; 2.4% vs 4; 3.1%) respectively.

There was a recipient in the OCI negative group with an extremely long-term graft survival (432 moths). Statistical analysis was repeated excluding this patient and statistical significances were still confirmed (p=0.02 and p=0.04).

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Discussion

The prevalence of positive occult HCV in patients with KT in our study was 14.1%, as evidenced by the detection of HCV RNA in PBMC or plasma after a lower ultracentrifugation than that found in patients on hemodialysis (45%) and IMGN (38%) and more than in patients with diabetic nephropathy (8%) [8,9,13]. The prevalence of HCV infection in KT is quite variable depending on the geographical areas. One study reported a progressive and marked decrease in the prevalence of HCV infection among kidney transplant recipients in Spain from 29.5% in 1990 to 10% in 1998 [15].

Baid and Agrawal [10], found a low prevalence of positive occult HCV infection 2/398 (0.5%) in patients with KT. They performed a 30-month longitudinal follow-up of the 3 patients with occult HCV infection, and there was no clinical or virological evidence of HCV infection. This contrasts with our results in which we observed worse outcome of renal function, perhaps due to a longer follow-up period.

The difference found in the prevalence of occult HCV in both studies can be explained by the difference in prevalence of HCV in the general population in Spain (2%) and in Germany (0.3%).

In the retrospective Spanish epidemiological study (GEHEP) of HCV, which covered the period 2000-2015, the most frequent route of transmission among 10,441 patients for whom data were available was parenteral (58.7%), followed by unknown origin (38, 6%) and sexually transmitted [16]. According to this study, we found that prior blood transfusion was the main risk factor for the acquisition of positive occult HCV. In this sense, occult HCV infection has been described in progress among 50% of the blood donors who tested positive for the HCV core-specific antibody and were negative for anti-HCV and HCV RNA in routine screening in a study of forty two donations (2.1%) [16] (The study was in 2007 blood donors negative for anti HCV and HCV RNA in routine screening, of which 42 were positive for anti-HCV. Three of these 42 donors (7.1%) had occult HCV infection. In another recent study in China that included blood samples from blood donors that were anti-HCV negative and in which it was determined in PBMC, a prevalence of 2.2% was found [17].

The effect of HCV infection on the risk of acute rejection is controversial [7]. It has been reported that the rate of acute rejection in patients with HCV infection is 14.5% over a 20-year period [18]. Immunosuppressive drugs have various effects on viremia. [19-21]. We did not identify statistical differences between both groups in immunosuppression strategies in graft survival or of the patient, and the neoplasm in the positive occult HCV group was related to CKD, and not to immunosuppressive medication [22].

Recipients of organ transplants with an existing active HCV infection have a higher frequency of life-threatening infections after surgery compared to recipients without HCV infection [14,22]. We did not find differences in the two groups according to the result of the occult HCV infection.

In KT, NODAT is an important cause of post-transplant morbidity and mortality [23]. The incidence is quite variable according to its definition, which varies between 2% and 53%. The prevalence of NODAT has increased [24,25]. The cause is multifactorial and infection by HCV has been implicated in the pathogenesis. We did not find differences in the immunosuppression administered between the two groups, but the positive occult HCV infection tended to have more NODAT. KT recipients with HCV have a reduced chance of survival compared to transplant recipients without HCV infection. The mortality rate at HCV positive receptors was approximately 3 times higher than that of non-infected recipients (12; 1% versus 3.7%) [3]. The increased risk of death in renal allograft recipients infected with HCV has been attributed to cardiovascular mortality. We also did not find differences in cardiovascular events (myocardial infartion or cerebrovascular ischemia) and neoplasia was the first cause of death in our study.

In the positive occult HCV group deaths were due to cancer of the urinary tract and myeloma, related to CKD, and in urinary tract neoplasms of occult negative HCV group, cancer of the cervix, related to CKD and lung cancer related to immunodeficiency, according to Stewart et al [22] and septicemia. In our group, the 5-year survival rate of patients is 90% and so, the number of not included dead patients is limited and in no case their cause of death was due to a liver problem.

We did not have any hepatocellular carcinoma. Post-transplant lymphoproliferative disorder and multiple myeloma have been associated with HCV infection [26,27], and we have also found a high prevalence of monoclonal gammopathy in diabetic nephropathy patients with positive occult HCV patients [14]. In a recent meta-analysis by Yuying Li, HCV increased the risk of multiple myeloma in countries with a high prevalence of HCV [28]. It has been also reported by Hashem A. et al a prevalence of 24,5% of OCI in patients diagnosed of multiple myeloma compared to a 3 % OCI in a control group (p=0.01) suggesting association of OCI and multiple myeloma [29]. Besides, Farahani M. et al have also detected a prevalence of 1.9% of OCI in patients who suffer lymphoproliferative disorders [30].

Limitations of the study

Given the difficulty in recruiting patients for this study, this study can present statistical power problems due to a limited sample size especially when there is stratification. For example, in the comparison between positive and negative OCI and presence of cancer we have a power of 25.5% or a beta error of 74.4%. In another study [10], the prevalence of the occult hepatitis C virus was low, which corroborates the difficulty in recruiting a sufficient sample size. For all these reasons, we believe that the difficulty in obtaining a sufficiently powerful study in this field should be taken into account.

In conclusion, in patients with KT there is a lower prevalence (14.1%) of occult positive HCV compared to the prevalence in patients with immune -mediated glomerulonephritis (39%) or hemodialysis (45%). Blood transfusion prior to KT was the

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main risk factor for acquiring occult HCV infection. The long-term survival of the graft and patients of OCI positive receptors were diminished compared to that of OCI negative receptors, although the contribution of particular comorbidities did not reach statistical significance. In the group with positive occult HCV, however, the progression of kidney disease tended to be faster. We did not identify statistical differences between both groups in immunosuppressive strategies and it seems not to affect OCI.

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