Impact of hepatitis B and C on kidney transplantation outcome in Romania

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Abstract

Introduction. HBV and HCV infections are a major health problem worldwide. Long term impact of both HBV and HCV infections on ESRD patients undergoing renal transplantation is controversial [2]. Amongst these patients, chronic liver disease represents a major health problem which might influence the renal graft rejection. Immunosuppressive therapy of renal transplanted patients has been proven to have a major role in decreasing the viral replication but the problem of morbidity and mortality amongst the transplanted patients with liver disease caused by HBV and HCV is still a significant one [5].
Materials and methods. The purpose of this study is to evaluate the impact of HBV and HCV infections on morbidity and mortality amongst renal transplanted patients which are chronically infected with hepatitis viruses between 2010- 2015.
Results. Survival rate as we have seen at 12, 24, 36, 48, 60 months was 93%, 91%, 88%, 83% and 77%, respectively. The median of age at the time of renal transplantation varied from 33 years to 47 years (P=0.003). Post-transplant survival rate was significantly different among the studied groups of patients (P<0.001).
Conclusions. Renal transplanted population age at the moment of transplantation and the HBV and HCV viral replication status of the patients represent independent prognostic factors for patients' survival. HCV infection shows lower risk for both renal graft rejection and mortality compared to HBV, while HBV-HCV co-infection rejection and mortality rates are higher. But the risk of graft rejection and mortality in HCV infected patients is significantly higher than in uninfected persons.

Keywords: HBV, HCV, infection, kidney, liver, morbidity, mortality, rejection, transplantation

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Introduction

HBV and HCV infections are a major health problem worldwide. This intensively studied subject also involves the population suffering from end-stage renal disease (ESRD). Renal transplantation, identified as the best renal function replacement therapy, was confronted to the problems HBV and HCV infections caused among patients with renal graft [1].

Long term impact of both HBV and HCV infections on ESRD patients undergoing renal transplantation is controversial [2]. Amongst these patients, chronic liver disease represent a major health problem which might influence the renal graft rejection and patients' survival, despite the science evolution regarding the diagnosis and treatment of chronic hepatitis [3].

Immunosuppressive therapy of renal transplanted patients has been proven to have a major role in decreasing the viral replication. This result is obvious when administering Cyclosporine to HCV infected patients [4]. But, although this effect is utterly debated by scientists and researchers and new therapies are applied to hepatitis virus infected patients, even with promising results from anti-HBV vaccination, the problem of morbidity and mortality amongst the transplanted patients with liver disease caused by HBV and HCV is still a significant one [5].

Materials and methods

Patients

This study's purpose is to evaluate the impact of HBV and HCV infections on morbidity and mortality amongst renal transplanted patients which are chronically infected with hepatitis viruses. I have used registered and reported data from the Romanian Renal Register for all the 437 transplanted patients between 2010- 2015. The main criteria to be admitted in this prospective study was to be a beneficiary of a renal graft from a live donor or a cadaveric donor.

Patients enlisted on the renal transplant waiting list were tested before the transplantation for: HBV and HCV using a chemiluminescent microparticle immunoassay (Abbott Architect i2000 - Abbott Diagnostics, Abbott Park, IL, USA), HLA genotyping for donor match with PCR (Invitrogen by Life Technologies), as well as for liver and renal functions (serum creatinine, cholesterol, triglycerides) by colorimetric and turbidimetric methods (Thermo Konelab Prime 60). All these parameters, along with the identification of the viral load (COBAS TaqMan 48Roche real-time PCR analyzer) of the infected patients, were determined before the transplantation and at 3 months after the surgical procedure.

The patients were divided into 4 groups depending on the type of virus. The first group (Group I) is made of patients infected with HBV, the second group (Group II) consists of patients infected with HCV and the patients with both HBV and HCV infection form the third group (Group III). Group IV is represented by transplanted patients with serological negative results for both hepatitis viruses.

Statistical analysis

Categorical variables are presented as percentages, and comparisons were performed with the χ^2 test. Continuous variables are displayed as median with 95% confidence interval (95% CI), according to their non-Gaussian distribution (Shapiro-Wilk test).

Survival analyses were conducted with Kaplan-Meier method, and the log-rank test was used for comparisons. The relationship between viral status and the composite endpoint was evaluated using multivariate Cox proportional hazard (CPH) models at 3 and 6 months. Logarithmic transformation of the variables was performed in order to satisfy the assumption of normality. A $p \leq 0.05$ was considered statistically significant. Analyse-it (Analyse-it Software, Ltd., Leeds, UK) and SPSS (SPSS Inc., Chicago, IL, USA) software were used to analyze the data.

Results

Of the 437 patients who met the study inclusion criteria, 56 had chronic HBV infection, 31 were HCV positive and 13 were infected with both HBV and HCV.

The median age at the time of renal transplantation varied from 33 years in Group III to 36 years in Group I and 47 years for Group II. In Group IV it was observed that the median age was 37 years, same as in the total population of kidney transplanted patients (P=0.003).

In the studied population it was found that 63% of kidney grafts were taken from living donors, most often relatives, while 37% were taken from cadaveric donors. Similar to the case of gender distribution, where men account for 62% of all transplants, the results are statistically insignificant.

Statistical analysis describes a population of patients proposed for renal replacement therapy through renal transplant graft were patients primary kidney disease was glomerulonephritis (47%), followed by tubulointerstitial nephritis (9%), diabetic nephropathy (6%) and hereditary nephropathy (5 %) (Table I).

Table I. Population characteristics

	Total	VHB positive	VHC positive	VHB&VHC positive	Negative VHB&VHC	P
Number	437	56 Group I	31 Group II	13 Group III	337 Group IV	
Age (years)	37 (36-39)	36 (31-40)	47 (39-52)	33 (26-38)	37 (36-39)	0.003
Male gender (%)	62	70	58	69	61	0.5
Preemptive KTx (%)	19	21	13	15	19	0.7
Living donor (%)	63	59	52	69	64	0.5
Primary renal disease (%) Glomerulonephritis Diabetic nephropathy Hereditary nephropathy Tubulointerstitial nephritis Other NA	 47 6 5 9 4 29	 45 5 5 5 2 38	 45 10 3 13 3 26	 31 - - 31 - 38	 48 6 5 8 4 29	0.4
HLA match (%)	41.0 (41.0-41.0)	41 (40-50)	41 (40-50)	41 (40-50)	41.0 (41.0-41.0)	0.6
Serum creatinine (mg/dL) 3 months 6 months	 1.40 (1.34-1.45) 1.50 (1.40-1.55)	 1.53 (1.30-1.80) 1.50 (1.40-2.00)	 1.32 (1.10-1.70) 1.40 (1.20-1.90)	 2.00 (1.10-4.70) 2.75 (2.20-5.90)	 1.40 (1.30-1.40) 1.48 (1.40-1.60)	 0.1 0.01
Total serum protein (g/dL) 3 months 6 months	 6.4 (6.1-6.5) 6.5 (6.3-6.5)	 6.1 (5.8-6.5) 6.5 (6.3-6.8)	 6.4 (6.1-6.7) 6.4 (5.4-6.9)	 6.7 (6.0-7.2) 6.5 (5.2-7.3)	 6.4 (6.1-6.7) 6.5 (6.3-6.5)	 0.4 0.9
Total serum albumin (g/dL) 3 months 6 months	 3.8 (3.7-3.9) 3.8 (3.7-3.8)	 4.0 (3.9-4.3) 4.0 (3.9-4.1)	 4.3 (3.9-4.4) 3.9 (3.4-4.1)	 3.6 (3.0-4.4) 3.4 (3.4-4.0)	 4.0 (3.9-4.0) 4.0 (3.9-4.0)	 0.2 0.1
Total serum cholesterol (mg/dL) 3 months 6 months	 185 (183-192) 184 (178-189)	 190 (183-201) 200 (182-215)	 183 (162-196) 169 (140-188)	 190 (183-201) 199.5 (169-248)	 184 (180-192) 184 (177-189)	 0.4 0.01
Serum triglycerides (mg/dL) 3 months 6 months	 130 (126-137) 138.5 (128-145)	 134.9 (115-148) 140.7 (114-158)	 128.6 (103.1-151) 144 (98.7-166)	 130 (110-181) 147.5 (122-191.9)	 128 (125-139.8) 137.8 (126-145)	 0.9 0.8
TGO (U/L) 3 months 6 months	 20 (20-21) 19 (19-20)	 20 (19-22) 20 (19-22)	 20 (15-25) 19 (15-21)	 21 (17-42) 20.5 (17-31)	 20 (20-21) 19 (18-20)	 0.07 0.2
TGP (U/L) 3 months 6 months	 25 (23-27) 22 (21-24)	 24 (21-28) 24 (21-28)	 27 (17-32) 24 (19-28)	 27 (16-50) 31 (19-39)	 24 (22-27) 21 (20-24)	 0.7 0.2
Transplant rejection (%)	11	14	13	31	9	0.06
Mortality (%)	3	6	6	23	2	0.05
Composite endpoint (%)	14	20	19	54	11	<0.001

Analyzing composite end point consisting of transplant rejection combined with death, we watched survival rate and we have seen that survival at 12, 24, 36, 48, 60 months was 93%, 91%, 88%, 83% and 77%, respectively (Fig. 1).

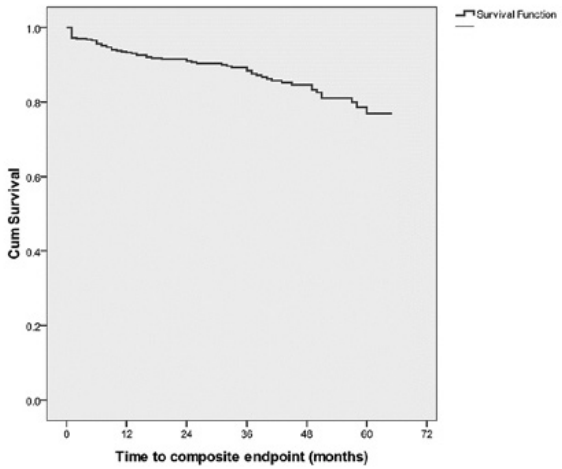


Fig. 1. Graft survivals at 5 years, Composite endpoint (death+transplant rejection)

Post-transplant survival rate was significantly different among the studied groups of patients. Increased mortality was noticed amongst HBV and HCV coinfected patients (Group III, 54%), followed by the group of patients with HBV infection (Group I, 20%) and the HCV positive (Group II, 19%). Among the control group (Group IV) renal transplant rejection and mortality rate was the lowest (11%); P<.001 (Fig. 2).

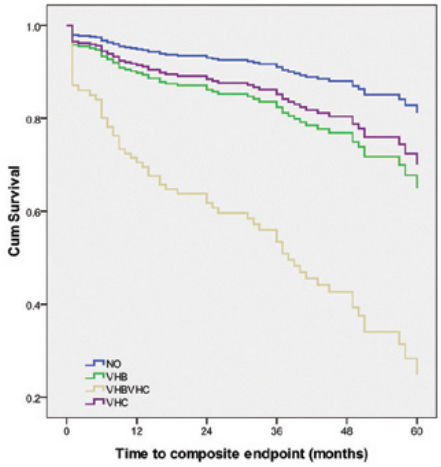


Fig. 2. Graft survivals at 5 years, Composite endpoint (death+transplant rejection) in HBsAg positive patients, in anti-HCV–positive patients, in HBsAg positive and anti-HCV positive patients, and in non-infected patients.

Using multivariate analysis, there were significant differences in the evolution of serum creatinine and total serum cholesterol in the second patients evaluation post-transplant, respectively at six months. It was found that the evolutions of these parameters are independent of each other. Thus median serum creatinine value for Group III (HBV+HCV) was higher than the previous six-month evaluation and in the same time higher than in the other three groups analyzed (P=0.01). The median of measured values of total serum cholesterol at six months was greater than the one calculated at three months post-transplant for Group I (HBV) and it was higher than in Groups II, III and IV (P =0.01).

Table II. Evolution of patientsat 3 months post-transplant

	B	HR (95% CI)	P
Hepatitis vs. non infected			<0.001
HBV	0.93	2.53 (1.27-5.02)	0.008
HCV	0.49	1.64 (0.68-3.95)	0.2
HBV&HCV	1.95	7.04 (3.10-16.01)	<0.001
BKV vs. non infected	0.98	2.68 (0.91-7.90)	0.07
Serum creatinine at 3 months	0.21	1.24 (1.14-1.34)	<0.001
HLA match	-8.14	0.00 (0.00-0.01)	<0.001
Variables entered at step 1: age, gender, primary renal disease, HLA match, Hepatitis infection status, preemptive transplantation, serum creatinine, serum total protein, serum albumin, serum cholesterol, serum triglycerides, TGO, TGP, BKV infection, CMV infection.			

Table III. Evolution of patients at 6 months post-transplant

	B	HR (95% CI)	P
Hepatitis vs. non infected			<0.001
HBV	0.74	2.10 (1.03-4.27)	0.04
HCV	0.12	1.13 (0.39-3.21)	0.8
HBV&HCV	1.68	5.39 (2.24-12.92)	<0.001
Serum creatinine at 6 months	0.27	1.31 (1.21-1.41)	<0.001
Total serum protein	-0.22	0.79 (0.61-1.03)	0.09
HLA match	-6.5	0.00 (0.00-0.07)	0.001
Variables entered at step 1: age, gender, primary renal disease, HLA match, Hepatitis infection status, preemptive transplantation, serum creatinine, serum total protein, serum albumin, serum cholesterol, serum triglycerides, TGO, TGP, BKV infection, CMV infection.			

Conclusions

After the analysis we can conclude that in the renal transplanted population age at the moment of transplantation and the HBV and HCV viral replication status of the patients represent independent prognostic factors for patients' survival.

HCV infection shows lower risk for both renal graft rejection and mortality compared to HBV and HBV-HCV co-infection where rejection and mortality rates are

higher. But the risk of graft rejection and mortality in HCV infected patients are significantly higher than in uninfected persons.

Another aspect that draws attention is achieving the end point. This is not influenced by gender distribution even if the male patients percentage was 70% in Group I and 69% in Group III, groups were kidney rejection rates were the highest.

Renal graft rejection combined with death were significant for the groups of HBV positive patients. This leads to the conclusion that any form of HBV infection, alone or combined with HCV, will determine a worse prognosis compared to the rest of transplanted patients.

Liver biopsy before renal transplantation and kidney-liver combined transplantation would still increase life expectancy and decrease renal rejection rate among the transplanted patients with chronic HBV and HCV infection.

Acknowledgement. This paper received financial support thanks to the "Program of Excellence in doctoral and postdoctoral research in multidisciplinary chronic diseases", number POSDRU/159/1.5/S/133377, project co-financed by the European Social Fund through the Sectorial Operational Programme Human Resources Development (SOPHRD) 2007-2013.

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