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Control of replication of hepatitis B and C virus improves patient and graft survival in kidney transplantation

Short title: Better prognosis in kidney recipients without HCV/HBV replication

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Abbreviations:

- DAA: Direct Antiviral Agent
- ESDR: End Stage Renal Disease
- HBV: Hepatitis B Virus
- HCV: Hepatitis C Virus
- KTR: Kidney Transplant Recipients

- NA: Nucleos(t)ide Analog
- RT: Renal Transplantation
- SVR: Sustained Virological Response

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ABSTRACT

Background and aim: Before antiviral therapy, kidney transplant recipients infected with hepatitis B (HBV) and C (HCV) virus had a poor outcome. Since the 90s, nucleos(t)ide analogues have been widely used in HBV infected patients, while interferon-based therapy was rarely used in HCV infected patients. The aim was to update the impact of HBV and HCV on patient and graft survival, according the viral replication

Methods: Analyze the French national database CRISTAL: 31433 kidney transplant recipients including 575, 1060 and 29798 with a chronic hepatitis B, C and non-infected, respectively

Results: Ten-year survival was lower in HCV (71.3%) than in HBV (81.2%, $p=0.0004$) or non-infected kidney transplant recipients (82.7%, $p<0.0001$). Ten-year kidney graft survival was lower in HCV (50.6%) than in HBV (62.3%, $p<0.0001$) or non-infected patients (64.7%, $p<0.0001$). A random analysis of the medical records of 184 HBV and 504 HCV patients showed a control of viral replication in 94% and 35% of cases, respectively. Ten-year patient and graft survival in patients with detectable HCV RNA was lower than in their matching controls. Conversely, HCV patients with undetectable HCV RNA had higher ten-year survival than their matched controls without significant differences in graft survival.

Conclusions: Chronic HBV infection does not impact ten-year patient and kidney graft survival thanks to control of viral replication, with nucleos(t)ide analogues. In HCV kidney transplant recipients, patients with detectable RNA had the poorer outcome whereas outcome of those with undetectable RNA is at least as good as non infected patients. Thus, direct anti-virals should be systematically offered to HCV-infected patients.

Key-words: kidney transplant recipients; chronic hepatitis C; chronic hepatitis B; prognosis

Lay summary: Outcome of kidney transplant KTR with viral suppression is at least as good as non-infected KTR whereas KTR with viral replication had the poorer outcome.

Antiviral therapy should be systematically proposed to HBV- and/or HCV-infected kidney recipients or candidates to renal transplantation in order to prevent the deleterious hepatic and extra-hepatic impact of chronic viral replication. Recent access to direct antiviral agents in HCV patients with renal dysfunction provides exciting perspectives.

INTRODUCTION

Renal transplantation (RT) is the best treatment of patients with end stage renal disease (ESRD) because of a significant survival benefit as compared to patients who remain on hemodialysis¹. Although the prevalence of Hepatitis B virus (HBV) and C virus (HCV) infection in patients with ESRD has significantly declined over time, it remains at least 4-times higher than in the general population^{2, 3}. Chronic HCV or HBV infection can result in chronic liver disease, cirrhosis, and hepatocellular carcinoma⁴⁻⁶ and increase the risk of chronic kidney disease⁷⁻¹⁰. Before the use of antiviral therapy, HBV and HCV infection were associated with a poor outcome in kidney transplant recipients (KTR)¹¹⁻¹⁴. This poorer outcome has been reported in untreated patients¹¹⁻¹⁴. With the development of new treatments against viral hepatitis, an update of data in large cohorts of KTR with long-term follow-up is warranted.

HBV treatment has improved in the last 2 decades¹⁵⁻¹⁷. The probability of undetectability HBV DNA upon therapy has increased from the use of first generation (lamivudine or adefovir)¹⁸⁻²⁰ treatment to the second generation analogs (tenofovir or entecavir)^{21, 22}. Most HBV kidney transplant recipients have received this safe long-term treatment with analogs before and continue long after RT. However, the impact of viral replication on RT remains somewhat controversial²³. Additional studies in HBV-infected RT are needed with longer follow-up, larger sample populations, and prospective designs to provide accurate evaluation. During the same period, in HCV KTR, interferon based regimens were contraindicated due to the high risk of transplant rejection. KDIGO recommendations were to treat patients on hemodialysis²⁴, but interferon-based regimens were associated with a low efficacy²⁵ and poor tolerance in ESRD patients²⁵⁻²⁸. Since 2017, the updated KDIGO and international guidelines recommend extensive use of the new direct anti-viral agents (DAAs) because of their good efficacy and safety^{29, 30}.

The aims of the present study were to update on the influence of HBV and HCV on patient and graft survival and to assess the prognostic influence of viral replication in a large prospective French database of KTR.

METHODS

Study Conduct

Both scientific Committees from the ANRS (in charge of the research on viral hepatitis) and the ABM (Agence de Biomédecine in charge of graft allocation), two French governmental agencies, approved the study. The CNIL (Commission Nationale de l'Informatique et des Libertés), the French government agency in charge of the authorization for the use of database, allowed the CRHU of Lille to analyze these data on December, 28th 2012 (authorization number: 912384).

Data collection and variables

From January 1993 to December 2010 data were extracted from CRISTAL, a national database begun in 1993 and administered by the ABM that prospectively collects data on all organ transplant recipients in France along with their outcomes and donor characteristics. Recipient and donor data are entered into the CRISTAL registry by transplant and procurement centers, respectively. Recipient deaths are reported prospectively. The study was performed in accordance with the French law indicating that research studies based on the national registry CRISTAL are part of transplant assessment activity and do not require institutional review board approval. Data are entered into the register by each center. Data collection is mandatory. Variables potentially associated with outcomes were analyzed. Demographic and clinical data were collected at the time of transplantation and annually thereafter. The following variables were analyzed: gender of donors and recipients, age of

recipients and donor, duration of dialysis, duration of cold ischemia, underlying nephropathy, year of transplantation, screening of HBsAg, and anti-HCV. Only adult KTR (i.e age ≥ 18 years) were included.

Random checking of viral replication in infected HBV and HCV recipients

We randomly selected 191 HBV and 511 HCV KTR cases to assess the control of viral replication among the centers with high yearly transplant activities from the CRISTAL database. These numbers were calculated on the basis of the following assumptions: a) for HBV cases, we expected 70% of patients with control viral replication, a relative precision of 20% in the estimation of this rate (corresponding to a width of 95% confidence interval) and 25% with unavailable virological data. b) for HCV KTR cases, we expected 20% of patients with control viral replication, a relative precision of 40% in the estimation of this rate and 25% with unavailable virological data. Between 2014 and 2015, research assistants visited the centers of selected recipients to analyze recipients' medical records and recorded in case report forms the following information: results of quantification of HBV DNA viral and/or HCV RNA, antiviral therapy ("yes" or "no"), the type of regimen in treated patients, data for diagnosis of cirrhosis such as histological data and/or results of Fibrotest® and Fibroscan®. HBV replication was considered to be controlled in HBV KTR if DNA $< 20\,000$ units during follow-up, based on the definition proposed by the EASL Clinical Practice Guidelines published in 2012 to consider antiviral therapy or classify patients as inactive carriers¹⁵. RNA was classified as undetectable in HCV patients in two cases: a/ spontaneous HCV clearance defined as anti-HCV antibodies and negative HCV RNA; b/ sustained virological response defined as undetectable HCV RNA 24 weeks after the end of antiviral therapy in treated patients.

Case-Control Study of HCV recipients with available HCV RNA data

For each HCV KTR with detectable or undetectable HCV RNA (cases), we randomly selected one to four matched controls from the 29797 non-infected RT patients, with the following matching criteria: gender, age of recipients ± 5 years, duration of dialysis in quartiles calculated for the overall population (<40, 41 to 82, 83 to 206, ≥ 207 months), quartiles of duration of cold ischemia (<15.8, 15.8 to 20.4, 20.5 to 28.4, ≥ 28.5 hours) and year of transplantation ± 5 years. The control groups were randomly matched to case groups using the global optimal matching algorithm.

Endpoints

The primary endpoint was ten-year overall survival and the secondary endpoint was ten-year graft survival. Overall survival was defined as the time from the date of renal transplantation to the date of death from any cause. Patients with repeat renal transplants were also treated as censored cases at the time of the second renal transplant. Graft survival was defined as the time from the date of renal transplantation to the date of graft loss or death from any cause. Graft loss was defined as the need for permanent dialysis or repeat transplantation.

For both overall- and graft-survivals, patients with no information at ten years were treated as censored cases at the date of the last follow-up and events that occurred after the ten-year follow-up period were not included in analysis.

Statistical analysis

Quantitative variables were expressed as means (standard deviations) or medians (interquartile range) and categorical variables were expressed in numbers and percentages.

10-year overall and graft survivals were estimated using the Kaplan-Meier method.

Main baseline characteristics were compared in the overall cohort (n=31433 adult KTR) according to viral status (non-infected, HBs Ag positive or anti-HCV positive) using the Chi-Square test, one-way analysis of variance or Kruskal-Wallis test, as appropriate. Comparisons

in overall and graft survivals were obtained in relation to viral status using the log-rank test. To identify independent predictors of ten-year overall and graft survivals, we performed univariate and multivariate Cox proportional hazards regression models by including viral status and other main baseline characteristics (gender, age of recipients and donors, duration of dialysis, duration of cold ischemia, and year of transplantation). For each candidate predictor, the proportional hazards assumption was assessed by examining Schoenfeld residuals plots. The log-linearity assumption for continuous predictors was assessed by examining Martingale residual plots. Since the log-linearity assumption for the age of recipients and donors was satisfied after including both linear and quadratic terms, the effect of both ages was modelled using a polynomial function. All candidate predictors associated with survival at a level of significance of $p < 0.10$ were included in the multivariate Cox regression models. We derived hazard ratios (HRs) from Cox regression models as effect size measures with the 95% confidence intervals (CIs).

The percentage of patients treated by antiviral therapy and the percentage of responders to antiviral therapy were compared from random samples of available viral data from HBV and HCV KTR between HBV patients with viral replication and HCV patients with detectable RNA using the Chi-square test.

Finally, comparisons of overall and graft-survivals between HCV KTR and their matched non-infected controls were performed separately based on detectable HCV RNA using Cox regression models with the robust sandwich variable estimate to take into account the matched sets.

Statistical testing was performed at the 2-tailed α -level of 0.05. Data were analyzed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

Between January 1993 and December 2010, 32,249 KTR were entered into the Cristal database, and 816 who were < 18 years old were excluded from the study (figure 1). A total of 31,433 adult KTR (19,580 men and 11,853 women) were included with a median age, duration of dialysis, and cold ischemia of 49.4 years, 28.1 months, and 18.8 hours, respectively. Patients were grouped according to virological status (table 1): 575 HBV KTR (HBs antigen positive) (1.83%), 1,060 HCV KTR (anti-HCV positive) (3.37%), and 29,798 non-infected patients (without anti-HCV antibodies or HBs antigen) (94.8%). The 3 groups differed significantly for sex ratio, age, duration of dialysis and cold ischemia, year of transplantation, and causes of underlying nephropathy (table 1). The prevalence of HBV decreased after 2003 (the median year of transplantation) from 2.26% to 1.4% ($p < 0.0001$), while the prevalence of HCV remained stable (3.38% vs 3.36%).

Ten-year patient survival (primary outcome)

Ten-year patient survival in HCV KTR (71.3%, 95% CI: 67.5-75.2%) was significantly lower than in the HBV KTR (81.2%, 95% CI: 77.1-85.2%, $p = 0.0004$) and non-infected (82.7%, 95% CI: 82.1-83.2%, $p < 0.0001$) groups (figure 2a). There was no difference in ten-year survival between the HBV and non-infected groups ($p = 0.6$). In multivariate analysis, male sex, age of KTR, duration of dialysis, anti-HCV antibodies, age of donor, duration of cold ischemia, and year of transplantation were independently associated with mortality at ten years (table 2). The proportion of liver-related deaths were significantly higher in HBV (6.85%, $p = 0.01$) and HCV (7.29%, $p < 0.0001$) KTR than in non-infected KTR (2.33%).

Ten-year graft survival (secondary outcome)

Ten-year graft survival in HCV KTR (50.6%, 95% CI: 46.8-54.4%) was significantly lower than in the HBV (62.3%, 95% CI: 57.6-67%, $p < 0.0001$) or non-infected (64.7%, 95% CI: 64-

65.4%, $p < 0.0001$) groups (figure 2b). There was no difference in ten-year survival between HBV and non-infected groups ($p = 0.7$). In multivariate analysis, male sex, age of recipient, duration of dialysis, anti-HCV antibodies, age of donor, duration of cold ischemia, and the year of transplantation were independently associated with graft loss at ten years (table 3).

Random checking of viral replication in infected HBV and HCV recipients

Virological data were available in 167 out of 191 medical records from HBV KTR patients (87.4%). Viral replication was controlled in 157 out of 167 HBV KTR (94%), including 21 inactive carriers and 136 treated with NAs. In the ten HBV KTR with viral replication, three were not treated and seven insufficiently controlled by antiviral therapy.

Virological data were available in 441 out of 511 medical records from HCV KTR patients (86.3%) (figure 1). HCV RNA was undetectable in 155 out of 441 HCV KTR (35%), including 75 with spontaneous HCV clearance and 80 with a SVR after antiviral therapy. HCV RNA was detectable in 286 out of 441 HCV KTR (64.9%), including 140 untreated patients and 146 non-responders to antiviral therapy. In patients with viral hepatitis who were candidates for antiviral therapy (i.e. with viral replication before initiation of antiviral therapy), HBV KTR were more frequently treated than HCV KTR (85.6% (143/167) vs 61.7% (226/366), $p < 0.0001$) with greater success (95.8% (137/143) vs 35.4% (80/226), $p < 0.0001$). Using the cut off of 2000 IU/ml, the percentage of patients with control of viral replication was lower but not so different than the percentage of patients with control of viral replication using the cutoff of 20 000 IU: 83% vs 94%. The proportion of liver-related deaths among all deaths in HCV KTR patients was 0% in HCV KTR with undetectable RNA and 8.93% in HCV KTR with detectable RNA. A sensitivity analysis was performed in patients with fibrosis assessment. Assessment of fibrosis was available in 374 out of 702 (53.2%) medical records of infected patients: 93 out of 191 (48.7%) of HBV KTR and 281 out of 511

(55%) HCV KTR. Assessment of liver fibrosis was performed in 293 (78.3%) cases with histological analysis, in 12 (3.2%) with Fibrotest and in 69 (18.4%) with liver stiffness. Diagnosis of cirrhosis was based on histological analysis or according to cut-offs of non-invasive methods indicating the diagnosis of cirrhosis (0.74 for Fibrotest and 14.6 KPa for Fibroscan). There were no significant differences between patients with fibrosis assessment and those without fibrosis assessment in terms of: male sex (67% vs. 62.6%), virological status (21.5% HBV and 78.5% HCV vs. 24.7% HBV and 75.3% HCV), duration of dialysis (76.8 vs. 87.9 months), duration of cold ischemia (20 vs 20.8 hours) age of donors (44 vs. 45.1 years), patient (78.9% vs 73.8%) and graft (57.1% vs 52%) survival. Infected patients with fibrosis assessment were younger than those without fibrosis assessment (46.9 vs. 49.1 years, $p=0.01$). In infected KTR patients with fibrosis evaluation, 29 (7.8%) were classified as cirrhotic and 345 (92.2%) as non-cirrhotic. Ten-year patient survival in cirrhotic (16.4%, 95% CI: 0-36.2%) was significantly lower than in non-cirrhotic (84.7%, 95% CI: 79.6-89.9%, $p<0.0001$) with an HR of 7.30 (95% CI 2.3-23.3). Ten-year graft survival in cirrhotic (12%, 95% CI: 0-27%) was also lower than in non-cirrhotic (61%, 95% CI: 54.5-67.6%, $p<0.0001$) with an HR of 3.24 (95% CI: 1.5-6.9). The proportion of liver-related deaths was higher in infected KTR with cirrhosis than in infected KTR without cirrhosis: 64.7% vs 1.8%, $p<0.0001$. In non-cirrhotic infected patients, ten-year patient survival in KTR with viral replication (79.9%, 95% CI: 72.1-87.6%) was lower than in those without viral replication (89.4%, 95% CI: 81.8-96.9%, $p=0.02$) with an HR of 2.5 (95% CI: 1.3-4.9). Ten-year graft survival in KTR with viral replication (54.1%, 95% CI: 45.1-63.1%) was also lower than in those without viral replication (70.4%, 95% CI: 60.5- 80.2%, $p=0.02$) with an HR of 1.69 (95% CI:1.1-2.6).

Case-control study

Use of the global optimal algorithm resulted in the random selection of 935 matched non-infected controls for 263 HCV KTR with detectable RNA and 482 matched non-infected controls for 137 HCV KTR with undetectable RNA. The global optimal algorithm could not identify matched controls for 23 HCV with detectable RNA and 18 HCV with undetectable RNA. The baseline characteristics of the two cases–control studies of HCV KTR (detectable and undetectable RNA) are provided in supplementary tables 1 and 2. Ten-year patient survival in HCV KTR with detectable RNA (66.1%, 95% CI: 61.1-77.1%) was significantly lower than in their matching non-infected controls (81.5%, 95% CI: 78.1-84.9%, $p=0.003$) with an HR of 1.61 (95%CI, 1.18-2.21) (figure 3a). Ten-year graft survival in HCV KTR with detectable RNA (45.7%, 95% CI: 38.2-53.2%) was significantly lower than in their matching non-infected controls (59.2%, 95% CI: 55.3-63.1%, $p=0.01$) with an HR of 1.31 (95% CI, 1.06-1.61) (figure 3b). Ten-year patient survival in HCV KTR with undetectable RNA (86.5%, 95% CI: 77.8-95.3%) was significantly higher than in their matching non-infected controls (77.9%, 95% CI: 72.5-83.4%, $p=0.04$) with an HR of 0.50 (95% CI, 0.25 to 0.98) (figure 4a). Ten-year graft survival in HCV KTR with undetectable RNA (63.8%, 95% CI: 52.8-74%) was not significantly different than in their matching non-infected controls (61.5%, 95% CI: 55.7-67.3%, $p=0.3$) with an HR of 0.84 (0.57 to 1.22) (figure 4b). In HCV KTR, we conducted a post-hoc secondary analysis adjusted for diabetes as primary cause of end-stage renal disease (table 1) and for smoking (31.5% of former or current smokers) showing that the deleterious effect of HCV replication remained significant on 10-year patient (HR 2.3, 95% CI: 1.11-4.8, $p=0.03$) and graft survival (HR 1.63, 95%CI:1.04-2.54, $p=0.03$).

DISCUSSION

This study evidences that HBV chronic infection, which had previously a negative impact on patient and survival in KT, no longer influences ten-year patient or graft survival due to the

control of viral replication in 90% of cases, related to the extensive use of nucleos(t)ides analogues^{16, 17}. By contrast, HCV chronic infection still negatively impact ten-year patient and graft survival, while this negative influence of HCV is removed by sustained viral suppression, since no longer observed in KTR with undetectable HCV RNA. The present results suggest, in line with the international and KDIGO guidelines, that antiviral therapy should be systematically proposed to HBV- and/or HCV-infected kidney recipients or RT candidates to prevent the deleterious hepatic and extra-hepatic impact of chronic viral replication^{29, 30}.

In this study of 31,433 French patients with renal transplantation performed between 1993 and 2010, the prevalence of HBV and HCV chronic infection was 1.8 % and 3.37 %, respectively. HBV prevalence decreases from 2.26% before 2003 to 1.4% thereafter; the HCV prevalence remains stable at approximately 3.4%. These prevalences of HCV and HBV are significantly lower than the 30% and 15% reported in our 2 studies of cohorts transplanted before 1990^{12, 13}. This decrease is related to universal hygienic precautions in hemodialysis units and systematic anti-HBV vaccination in patients with end-stage renal disease. However, the current prevalence of both infection in patients with CKD, including KTR, is still higher compared to the general population.

In the sensitivity analysis restricted to infected patients with available assessment of fibrosis, cirrhotic infected patients had the worst outcome and the value of controlling viral replication was confirmed even in patients with less severe liver injury. However, the results of this sensitivity analysis should be treated with caution because of the limited sample size of the cohort of patients with available evaluation of fibrosis, the a posteriori analysis, the important variability in the delay to perform the assessment of fibrosis according to the date of transplantation and the risk of inflated false positive (Type I) errors because of multiplicity of comparison. We did not adjust for multiple comparison given the exploratory nature of this

sensitivity analysis restricted to patients with fibrosis assessment. Therefore we couldn't exclude false positive findings.

Before the era of NAs, HBV KTR ten-year patient and graft survival was the worst¹³. In the present study, there was no significant difference in patient and graft survival between HBV and non-infected KTR, thanks to the extensive use of NAs¹⁸⁻²¹, as shown by the random checking of recipient's medical records. Thus, these data support the benefit of NAs in HBV KTR.

By opposition with HBV, HCV continues to negatively influence KTR. These results are similar to those observed more than 20 years ago^{12, 13}. However, to further clarify this observation, we checked a large number of patient files to classify KTR according to viral replication. KTR with undetectable RNA had higher ten-year patient survival and similar ten-year graft survival than non-infected. Conversely, the case-control study clearly shows that KTR with detectable RNA have lower ten-year patient and graft survivals than non-infected. These data strongly support the control of viral replication in HCV KTR as the best approach to improve patient and graft survivals. It should be emphasized that the applicability of anti-viral treatment was limited during the era of interferon-based regimens. The use of several DAA regimens in CKD patients including KTR with renal impairment represents major progress that will allow extensive use of antiviral therapy in RT candidates and KTR patients with HCV¹⁴. HCV therapies with DAAs are being constantly improved. Three DAAs combination have been approved in dialyzed patients or in patients with ESRD³¹⁻³⁴. Only the new combination of glecaprevir and pibrentasvir has shown pan-genotypic HCV activity achieved SVR rate of more than 95%³⁴ with negligible renal excretion. Other DAA regimens may be used in KTR patients when the glomerular filtration rate is > 30 ml/mn^{35, 36}. DAA treatment should be systematically proposed before and after RT in KTR with HCV replication.

Future studies are needed to confirm what has been previously reported in high-risk population for HCV (intravenous drugs user and men who have sex with men), namely whether systematic anti-viral treatment can decrease or even eliminate the incidence of viral hepatitis in dialysis patients and KTR. An European initiative for HCV elimination (European Hepatology –EASL- and Nephrology association -ERA/EDTA) proposed a program for “micro-elimination” of HCV in CKD patients.

The limit of this study was the absence of data concerning the anti-viral treatment and its efficacy on the viral replication in all patients collected in the Cristal database. We try to overcome this limit by performing a case-control study in which virological data and anti-viral therapies were collected, by research assistance who analyze recipients’ medical records. In conclusion, HBV and HCV KTR without viral replication have similar patient and graft survivals than non-infected patients. Recent access to DAA regimens in HCV patients with renal dysfunction provides exciting perspectives.

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Legends of the tables :

Table 1. Clinical characteristics according to virological status

Table 2. Multivariate Analysis of Factors Associated with 10-year patient mortality in overall cohort

Table 3. Multivariate analysis of factors associated with 10-year graft failure in overall cohort

Supplementary Table 1. Results of case–control comparisons of undetectable HCV RNA patients and their randomly selected matched controls

Supplementary Table 2: Results of case–control comparisons of detectable HCV RNA patients and their randomly selected matched controls

Figure legends:

Figure 1. Flow chart of the study: 32,249 KTR were entered into the Cristal database; 816 who were < 18 years old were excluded from the study. A total of 31,433 adult KTR were included.

Figure 2a. Ten-year patient survival in HCV, HBV and non-infected KTR were estimated using the Kaplan-Meier method.

Figure 2b. Ten-year graft survival in HCV, HBV and non-infected KTR were estimated using the Kaplan-Meier method.

Figure 3a. Ten-year patient survival in HCV KTR with viral replication (detectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method.

Figure 3b. Ten-year graft survival in HCV KTR with viral replication (detectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method

Figure 4a. Ten-year patient survival in HCV KTR without viral replication (undetectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method.

Figure 4b. Ten-year graft survival in HCV KTR without viral replication (undetectable RNA) and in their matching non-infected controls were estimated using the Kaplan-Meier method

Table 1. Clinical characteristics according to virological status

	Virological status			<i>P Value</i>
	Positive HBs Ag	Positive anti-HCV	Negative HBs Ag and negative anti-HCV	
Number of patients	575	1060	29798	
Male sex, n (%)	420 (73.0)	656 (61.9)	18503 (62.1)	<0.0001
Age of recipients, mean (SD), years	45.9 (11.8)	48.5 (11.3)	48.4 (13.7)	<0.0001
Duration of dialysis, median (IQR), months	51.1 (25.8 to 111.4)	78.8 (37.2 to 188.3)	27.0 (14.5 to 50.9)	<0.0001
Duration of Cold ischemia, median (IQR), hours	20.0 (15.3 to 28)	20.0 (14.9 to 26.5)	18.8 (14.4 to 24.7)	<0.0001
Age of donors, mean (SD), years	44.3 (14.1)	44.4 (15.4)	45.2 (15.9)	0.13
Year of transplantation, median (IQR)	2001 (1996 to 2006)	2003 (1999 to 2007)	2004 (1999 to 2007)	<0.0001
Underlying nephropathy, n (%)				
Chronic glomerulonephritis	160 (27.8%)	291 (27.4%)	8079 (27.1%)	
Chronic interstitial nephropathy	40 (7%)	121 (11.4%)	2947 (9.9%)	
Genetic or congenital	97 (16.9%)	185 (17.5%)	5897 (19.8%)	
Undetermined and miscellaneous causes ^a	255 (44.3%)	390 (36.8%)	10865 (36.5%)	
Diabetes	23 (4%)	73 (6.9%)	2010 (6.7%)	

Values are number (%) unless otherwise indicated.

^aincluding mainly hypertensive nephropathy in addition others causes.

Abbreviations: IQR=Interquartile range

Table 2. Multivariate Analysis of Factors Associated with 10-year patient mortality in overall cohort

Factors	Univariate analysis		Multivariate analysis^a	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male sex, n (%)	1.21 (1.12 to 1.29)	<0.0001	1.20 (1.11 to 1.29)	<0.0001
Age of recipients (per 10 years increase)	1.74 (1.69 to 1.79)	<0.0001	1.67 (1.61 to 1.74)	<0.0001
Duration of dialysis (per 1 SD log increase)	1.27 (1.22 to 1.31)	<0.0001	1.26 (1.21 to 1.31)	<0.0001
Viral status, n (%)		<0.0001		0.0005
Non infected	1.00 (ref.)	-	1.00 (ref.)	-
Ag HBs positive	1.06 (0.84 to 1.33)	0.62	1.00 (0.78 to 1.27)	1.00
Anti-HCV-positive antibodies	1.69 (1.46 to 1.95)	<0.0001	1.38 (1.17 to 1.63)	<0.0001
Age of donors (per 10 years increase)	1.33 (1.29 to 1.36)	<0.0001	1.11 (1.07 to 1.14)	<0.0001
Duration of cold ischemia (per 1 SD log increase)	1.20 (1.15 to 1.25)	<0.0001	1.07 (1.01 to 1.14)	0.008
Year of transplantation (per 5-year increase)	1.07 (1.03 to 1.11)	<0.0001	0.90 (0.85 to 0.94)	<0.0001

^a calculated from a multivariable cox's regression model on the basis of the 26276 patients with non-missing data.

Abbreviations: CI=confidence interval; HR=hazard ratio; SD=standard deviation

Table 3. Multivariate analysis of factors associated with 10-year graft failure in overall cohort

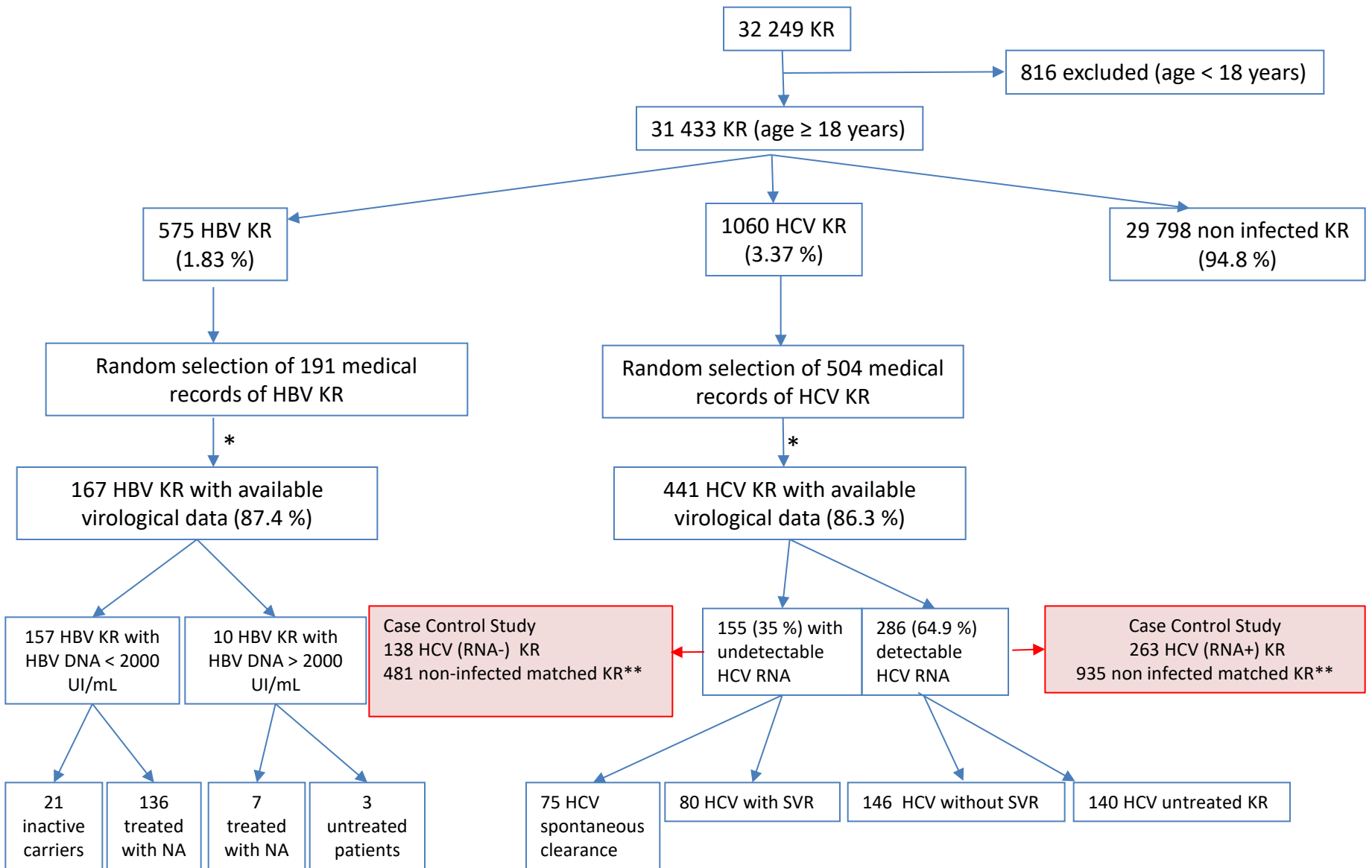
Factors	Univariate analysis		Multivariate analysis ^a	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male sex, n (%)	1.05 (1.00 to 1.10)	0.030	1.06 (1.00 to 1.11)	0.024
Age of recipients (per 10-year increase)		<0.0001 ^b		<0.0001 ^b
Linear term	1.85 (1.67 to 2.04)	<0.0001	1.82 (1.63-2.04)	<0.0001
Quadratic term	1.08 (1.07 to 1.10)	<0.0001	1.07 (1.06 to 1.09)	<0.0001
Duration of Dialysis (per 1 SD log increase)	1.18 (1.15 to 1.21)	<0.0001	1.17 (1.14 to 1.20)	<0.0001
Viral Status, n (%)		<0.0001		<0.0001
Non infected	1.00 (ref.)	-	1.00 (ref.)	-
Ag HBs positive	1.03 (0.88 to 1.20)	0.68	0.93 (0.79 to 1.10)	0.38
Anti-HCV-positive antibodies	1.49 (1.34 to 1.65)	<0.0001	1.30 (1.16 to 1.45)	<0.0001
Age of donors (per 10 years increase)		<0.0001 ^b		<0.0001 ^b
Linear term	1.15 (1.07 to 1.23)	<0.0001	1.02 (0.94 to 1.10)	0.66
Quadratic term	1.04 (1.02 to 1.05)	<0.0001	1.02 (1.01 to 1.03)	<0.0001
Duration of cold ischemia (per 1 SD log increase)	1.19 (1.15 to 1.22)	<0.0001	1.13 (1.09 to 1.17)	<0.0001
Year of transplantation (per 5-year increase)	1.01 (0.98 to 1.03)	0.42	0.91 (0.88 to 0.94)	<0.0001

^a calculated from a multivariable cox's regression model on the basis of the 26276 patients with non-missing data.

^b global effect including the linear and quadratic terms

Abbreviations: CI=confidence interval; HR=hazard ratio; SD=standard deviation

Figure 1: Flow chart of the study



* research assistants visited the centers of selected recipients to analyze recipients' medical records

** Controls from the 29797 non-infected RT patients were matched on gender, age of recipients, duration of dialysis, duration of cold ischemia, year of transplantation

Figure 2a: 10-Year patient survival according to Virological status

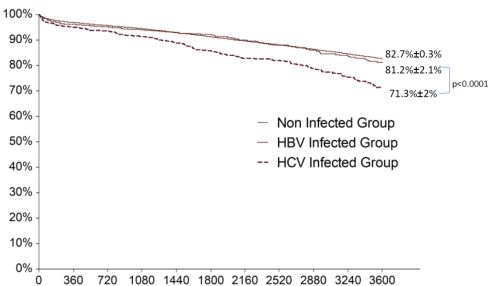


Figure 2b: 10-Year graft survival according to Virological status

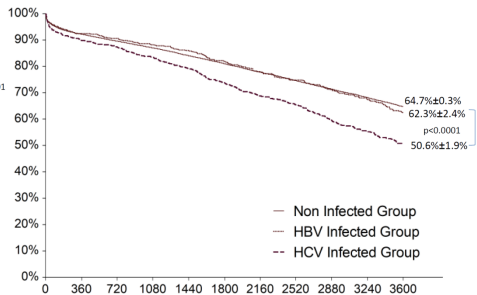


Figure 3a: 10-Year patient survival of HCV RNA patients with detectable RNA and their matched non-infected controls

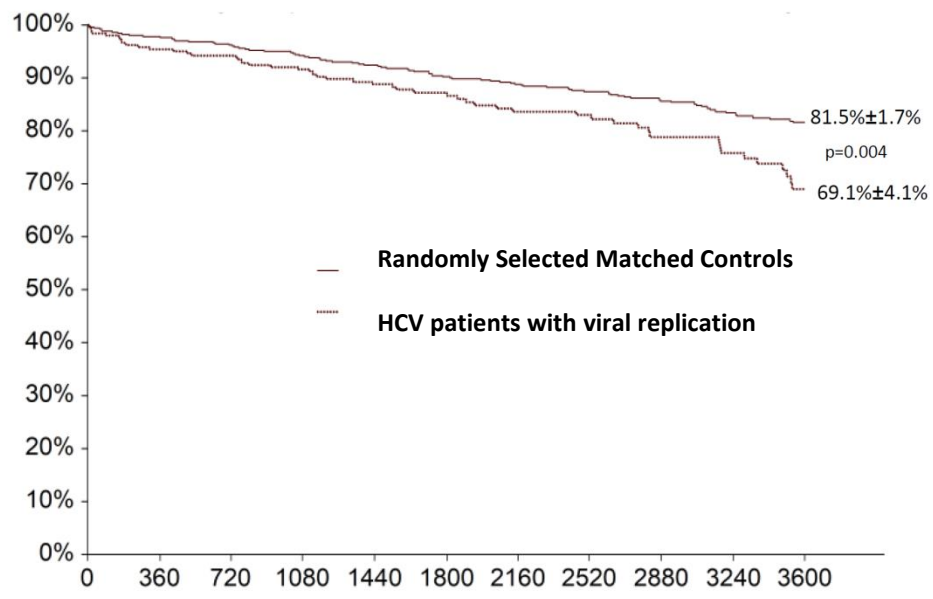


Figure 3b: 10-Year graft survival of HCV RNA patients with detectable RNA and their matched non-infected controls

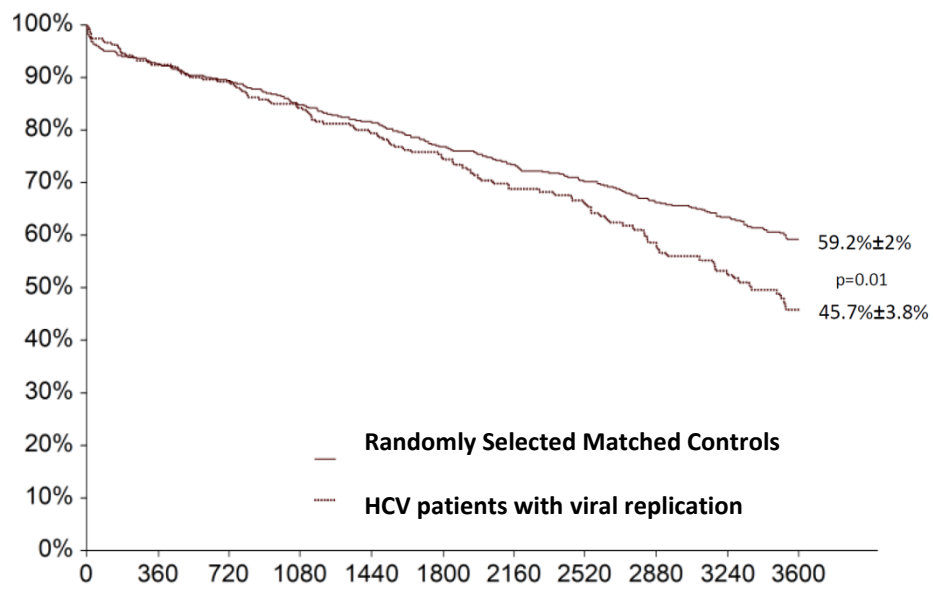
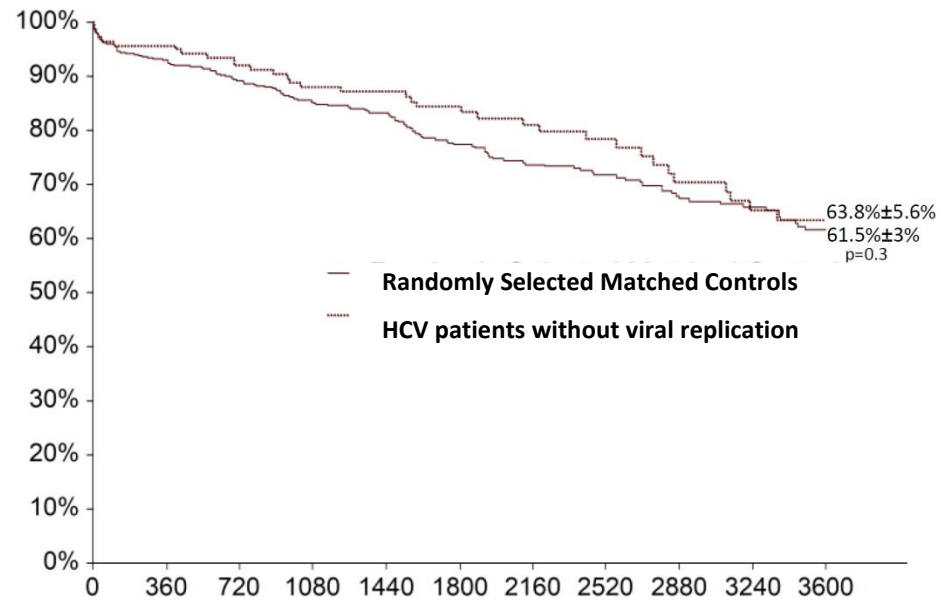
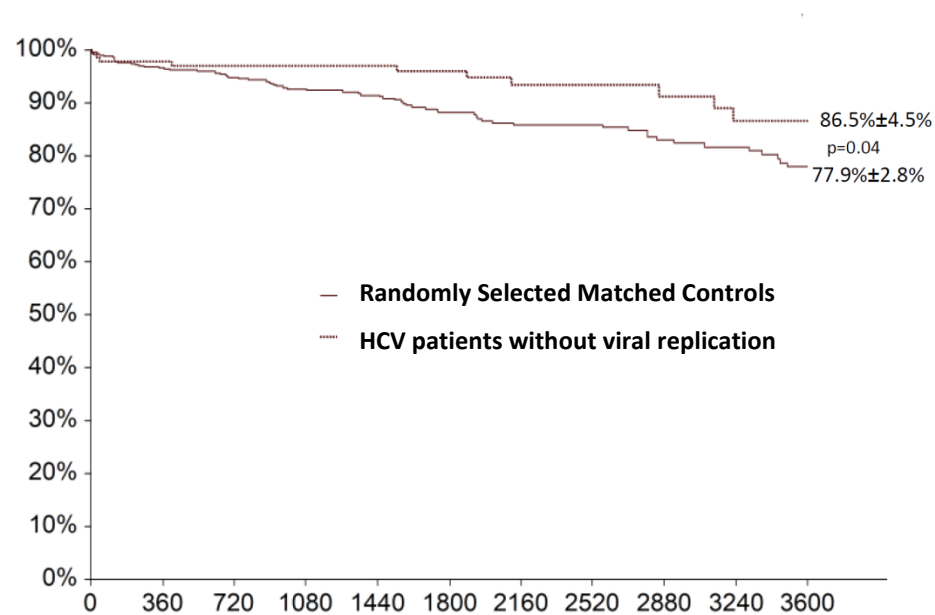
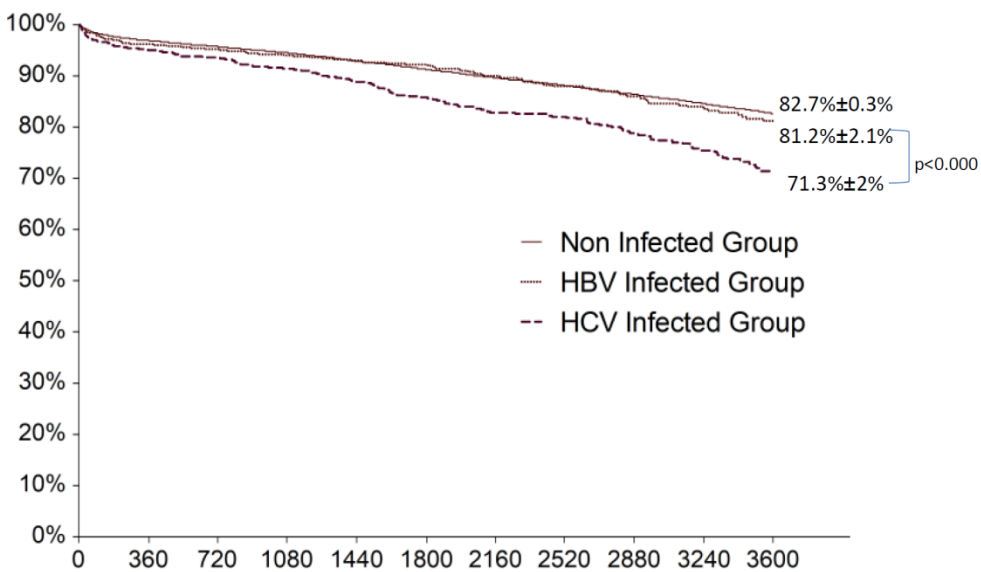


Figure 4a: 10-Year patient survival of HCV RNA patients with undetectable RNA and their matched non-infected controls and **Figure 4b: 10-Year graft survival of HCV RNA patients with undetectable RNA and their matched non-infected controls**



10-Year patient survival according to Virological status



10-Year graft survival according to Virological status

