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Elderly Recipients of Hepatitis C Positive Renal Allografts Can Quickly Develop Liver Disease

Tanya R. Flohr, M.D.[*,1], **Hugo Bonatti, M.D.**[†], **Tjasa Hranjec, M.D.**[*], **Doug S. Keith, M.D.**[‡], **Peter I. Lobo, M.D.**[‡], **Sean C. Kumer, M.D.**[*], **Timothy M. Schmitt, M.D.**[*], **Robert G. Sawyer, M.D.**[*], **Timothy L. Pruett, M.D.**[§], **John P. Roberts, M.D.**[¶], and **Kenneth L. Brayman, M.D., Ph.D.**[*]

[*]Department of Surgery, University of Virginia Health System, Charlottesville, Virginia

[†]Department of Surgery, Vanderbilt University, Nashville, Tennessee

[‡]Department of Medicine, Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia

[§]Department of Surgery, University of Minnesota, Minneapolis, Minnesota

[¶]Department of Surgery, University of California San Francisco, San Francisco, California

Abstract

Our institution explored using allografts from donors with Hepatitis C virus (HCV) for elderly renal transplantation (RT). Thirteen HCV− elderly recipients were transplanted with HCV+ allografts (eD+/R−) between January 2003 and April 2009. Ninety HCV− elderly recipients of HCV− allografts (eD−/R−), eight HCV+ recipients of HCV+ allografts (D+/R+) and thirteen HCV + recipients of HCV− allografts (D−/R+) were also transplanted. Median follow-up was 1.5 (range 0.8–5) years. Seven eD+/R− developed a positive HCV viral load and six had elevated liver transaminases with evidence of hepatitis on biopsy. Overall, eD+/R− survival was 46% while the eD−/R− survival was 85% ($P = 0.003$). Seven eD+/R− died during follow-up. Causes included multi-organ failure and sepsis ($n = 4$), cancer ($n = 1$), failure-to-thrive ($n = 1$) and surgical complications ($n = 1$). One eD+/R− died from causes directly related to HCV infection. In conclusion, multiple eD+/R− quickly developed HCV-related liver disease and infections were a frequent cause of morbidity and mortality.

Keywords

kidney transplant; elderly; end-stage renal disease; infectious diseases; hepatitis C; HCV

INTRODUCTION

The elderly are the fastest growing population of end-stage renal disease (ESRD) patients [1]. Dialysis for this population is poor treatment option with first year mortality 1.6- to 2.5 fold higher compared with younger patients [1, 2]. The surgical option of renal transplantation (RT) for elderly ESRD patients has a well-established survival advantage with a >40% lower overall risk of mortality compared with age-matched waitlist candidates

[1]To whom correspondence and reprint requests should be addressed at Department of Surgery, Division of Transplantation, University of Virginia Health System, P.O. Box 800709, Charlottesville, VA 22908-0709. trf7b@virginia.edu..

on dialysis [3]. After RT, elderly recipients have a 10 y life expectancy compared with only 6 y for dialysis patients of the same age [4].

Currently, more than 13,000 candidates >65 y are on the RT waitlist; this number has increased 2.3-fold between 1999 and 2004 [5]. The lack of suitable organs, longer wait-times, and worsening co-morbidities are great impedances forcing the use of non-standard allo-grafts, such as those from donors with positive Hepatitis C (HCV) serology. The deceased donor HCV prevalence is 1.08% to 12% worldwide [6–9].

Abbott *et al.* observed in all (HCV+ and HCV−) RT-waitlist patients (mean age 47.6 ± 13.8 y), receipt of an allograft from a donor with HCV+ serology was associated with increased mortality compared with an allograft from a donor with negative HCV serology. For all potential recipients, RT with an allograft from an HCV+ donor was, however, independently associated with improved survival compared with those remaining on the RT waitlist [10]. The adverse effects of these allografts, specifically from cirrhosis, were thought to be diminished because of the long duration between viral transmission and liver disease sequelae [11]. Death secondary to hepatic disease was only observed in 8% to 28% of RT recipients of allografts from HCV+ donors surviving more than 5 y [12]. Others have demonstrated that the natural history of HCV is very different depending on age at infection, and is particularly accelerated in those of older age [13, 14]. These studies and the multiple studies correlating increased donor age with rapid fibrosis progression in liver transplantation (LT) recipients suggest the elderly liver is more susceptible to HCV-related disease [15–20].

In this review, we report our institution's experience with 13 elderly (≥60 y) patients with negative pre-RT HCV serology who received an allograft from a HCV+ donor (eD+/R−). The cohort was compared with a control group of elderly primary RT recipients with negative pre-RT HCV serology receiving an allograft from a HCV− donor (eD−/R−). The cohort was also compared with all adult (≤18 y) deceased donor allograft recipients with positive pre-RT HCV serology (D+/R+ and D−/R+ respectively). Organ Procurement and Transplantation Network (OPTN) data including deceased donor RTs performed from 2003 through 2007 were also analyzed for the number of eD+/R− recipients, patients, and graft survival. The goals of this retrospective review were to (1) compare the patient and graft outcomes for eD+/R− and control groups, and (2) describe the progression of HCV-related liver disease (clinical and histologic) in these unique RT recipients.

MATERIALS AND METHODS

Patients and Transplants

From January 2003 to April 2009, 611 patients underwent RT at the University of Virginia, including 160 elderly patients with negative pre-RT HCV serology. One hundred three elderly RT recipients received a deceased donor allograft including 13 eD+/R− and 90 eD−/R−. The eD+/R− outcomes were also compared with all recipients with positive HCV serology, pre-RT, including those receiving an allograft from a HCV+ deceased donor (D+/R+, $n = 8$) and those receiving an allograft from a HCV− deceased donor (D−/R+, $n = 13$). The University of Virginia Institutional Review Board granted permission for the retrospective review of all RT recipients' charts during the study period (protocol #14045).

Pre-RT Counseling and Evaluation

All potential elderly RT recipients underwent counseling regarding potential allograft sources. Recipients were informed of the increased morbidity and mortality of acquiring HCV from a HCV+ donor. If agreed upon by the recipient, informed consent was obtained for the use of these allografts. All potential RT recipients had HCV serology testing

performed pre-RT. Pre-RT HCV serology status was determined using an enzyme linked immunosorbent assay (ELISA) (Abbott Laboratories, Abbott Park, IL) per the Centers of Disease Control recommendations. All recipients underwent a complete physical, psychological, social examination pre-RT. Elderly patients underwent a more intense evaluation of mental status, liver, vascular, pulmonary, and cardiac function (echocardiography, stress test, thallium scintigraphy, and coronary angiography). Exclusion of pending malignancies was confirmed with multiple imaging techniques.

Donor HCV Status

All donors included were tested for HCV serology prior to procurement using an ELISA (Abbott Laboratories) per the Centers of Disease Control and Food and Drug Administration recommendations. The 11 donors included in the eD+/R− group were considered HCV+ based on positive HCV serology testing. HCV RNA nucleic acid testing (NAT) was not routinely performed by the organ procurement organizations for donors with positive HCV serology testing. Given the interest of this study, HCV RNA NAT was performed using donor sera (COBAS AmpliScreen HCV test; Roche Molecular Systems, Pleasanton, CA) after transplantation was complete for the most recent three eD+/R− RT performed. Donor sera specimens collected earlier were not available for HCV RNA NAT.

Perioperative Management and Immunosuppression

Deceased donor procurement and recipient surgical procedure were performed according to standard techniques. All study recipients received anti-thymocyte globulin (ATG) induction: intraoperatively (1 mg/kg) prior to reperfusion and post-RT d 1 and 2 (1.5 mg/kg). Methylprednisolone was given intraoperatively (500 mg) and then tapered to a maintenance dose by post-RT d 5 (20 mg). Recipients were tapered to low dose prednisone: 10 mg/d, 7.5 mg/d, and 5 mg/d at 1, 3, and 6 mo, respectively. Tacrolimus (TAC) was initiated on post-RT d 1 and slowly increased to maintain trough levels (6–10 ng/mL for the first 3 mo and 4–8 ng/mL thereafter). For recipients with delayed graft function (DGF), TAC was started after 3 to 5 d post-RT when serum creatinine levels normalized. Some received mycophenolate-mofetil (MMF) (1–2 g/d) or enteric coated mycophenolic acid (1440 mg/d).

HCV-Related Liver Disease Assessment

Recipients were evaluated for liver disease based on physical exam findings, not protocol. Liver function tests (LFTs) were monitored at routine evaluations. If indicated, recipients were assessed with liver ultrasound and needle biopsy. Modified Ishak score was determined by an experienced liver pathologist to describe the extent of liver fibrosis [21].

HCV viral load (VL) and serology were not routinely assessed post-RT. If evaluated, HCV serology was determined as previously described in pre-RT evaluation. VL was determined using recipient serum samples. Viral RNA was extracted using the MagNA Pure LC instrument (Roche Applied Science, Pleasanton, CA). Amplification of HCV viral RNA was accomplished with reverse transcriptase polymerase chain reaction (RT-PCR) using analyte specific reagents and COBAS TaqMan 48 analyzer (Roche Applied Science, Pleasanton, CA). The detection range of HCV was 50 to 5 million international units per milliliter (IU/mL).

Complications and Treatment

DGF was defined as the need for dialysis within 2 wk of RT. Graft function was evaluated at the end of the study or at recipients' death with serum creatinine and need for dialysis. Acute rejection was defined as a >20% rise in creatinine in the absence of infection, ureteral stenosis, or any other etiology. All suspected cases of rejection were confirmed by histologic

examination of core biopsy specimens using Banff criteria before anti-rejection treatment was initiated. First and second acute cellular rejection (ACR) episodes were treated with bolused steroids (1250 mg, three doses). Steroid resistant ACR was treated with ATG (1.5 mg/kg/daily for 3 d). Rituximab (375 mg/m^2) in combination with intravenous immunoglobulin (IVIG) and whole plasma exchange was used for antibody mediated rejection (AHR).

Post-RT infections were evaluated including urinary tract infections (UTI), surgical site infections (SSI), respiratory infections, sepsis, endocarditis, orthopedic infections, *Clostridium difficile* associated colitis (C. *difficile*), CMV, herpes simplex virus (HSV), and BK virus (BK) associated diseases. Other infections were grouped separately. Surgical complications evaluated included hemorrhage, lymphocele, hernia, ureteral complications, and renal artery stenosis. Other post-RT complications evaluated included cardiac, respiratory, biliary, hematologic, vascular, and oncologic complications.

OPTN Data Collection

OPTN data for primary deceased donor RTs performed 2003–2007 in recipients with negative HCV serology were evaluated. Adult (≥18 y) and elderly (≥60 y) recipients of allografts from HCV+ donors(aD+/R− and eD+/R−, respectively) were compared with recipients allografts from HCV− donors (aD−/R− and eD−/R−, respectively) for patient and graft survival. Causes of death were also evaluated.

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Statistical Analysis

Statistical analysis was performed using SAS StatView 9.1 program (Cary, NC). Data were expressed as percentages, median values (ranges) or means ± standard deviations when appropriate. A Student's *t*-test, two-way analysis of variance, and Mann-Whitney U test for single variable evaluation for repeated measurements were used when appropriate. Additionally, x^2, Wilcoxon sign rank test (continuous variables), and Fisher exact test (categorical variables) for intergroup comparisons were used if appropriate. Patient and graft survival was calculated for both study and control patients using the Kaplan-Meier method with log rank statistics. A P value < 0.05 was considered statistically significant.

RESULTS

Demographics

The eD+/R− renal disease, years on hemodialysis, and pre-RT co-morbidities are listed (Table 1). The eD+/R− and control groups' demographics and out-comes are listed (Tables 2 and 3). Twelve of 13 eD+/R− and all eD−/R− were primary RT recipients. Of the additional comparison groups, six of eight D+/R+ and 12 of 17 D−/R+ were primary RT recipients. The D−/R+ group also included five previous LT recipients.

Donor Characteristics

The thirteen eD+/R− donors included nine males with medan donor age 49 (range 21–53) y. The causes of death were various (intracranial hemorrhages $n = 7$, closed head injuries $n = 2$, anoxia $n = 2$, motor vehicle collisions $n = 2$). Median cold ischemia time was 24:29 (range

15:00–37:08) h. Median distance from which the 13 allografts were obtained was 549 (range 0–5649) miles with one allograft acquired from Hawaii.

Recipient HCV Pre-RT

None of the eD+/R− patients had received anti-viral therapy or had their VL assessed before RT. Prior to RT, all D+/R+ patients had positive VL detected. One D+/R+ patient received an incomplete course of pegylated interferon, which resulted in no VL change. Six D−/R+ patients were treated with pegylated interferon and ribavirin prior to RT resulting in a negative VL in two patients prior to and after RT. Two D−/R+ patients were HCV positive by serology but had no detectable VL prior to and after RT.

Patient Survival

Seven eD+/R− died during the study period. Five (62%) died within 1 y post-RT: sepsis (n = 3), multi-organ failure (n = 1), and failure-to-thrive (n = 1). The later deaths were from surgical complication (n = 1). and oropharyngeal cancer recurrence (n = 1). Overall and median days survived was significantly less for eD+/R−compared with each control group. Patient survival was calculated for both eD+/R−and eD−/R−using Kaplan-Meier survival analysis (Fig. 1A). The analysis revealed survival curves that crossed with survival for eD+/R− better initially. This early survival improve ment was not statistically significant compared with eD−/R− (P = 0.465). Patient survival was calculated for eD+/R−, D+/R+, and D−/R+ using Kaplan-Meier survival analysis (Fig. 1B).

Graft Function and Survival

DGF requiring dialysis was not significantly different between eD+/R− and control groups. Both ed+/R− with DGF revovered graft function within one month. All eD−/R− patients with DGF recovered graft function within three months post-RT. The number of grafts lost in eD+/R− was similar to control groups. The Kaplan Meier plots of graft survival are shown (Fig. 2A and B). Creatinine at most recent assessment for all groups was also similar.

HCV-Related Liver Disease

Five eD+/R− had no HCV detectable VL. One eD+/R− was never tested and died without signs of HCV-related disease. The course of liver disease for the seven eD+/R− with positive VL is depicted (Fig. 3). Three had positive VL within one month post-RT. HCV serology was tested once post-RT in six of 13 eD+/R− at a median of 3.5 (range 1–14) mo post-RT and for all six recipients was found to be negative. When NAT was performed in addition to assessing donor HCV serology, the testing results correlated with the development of a positive VL for the recipient. For the last three RT performed, NAT was completed revealing a positive donor (the source of two allografts) and a negative donor (the source of a single allograft). The associated three eD+/R− recipients developed a positive VL, positive VL, and negative VL, respectively.

Six eD+/R− were found to have abnormal LFTs, ranging from mild and quickly resolved transaminitis to severe elevations (Table 4). By the mo 5 post-RT, the six eD+/R− with positive VL and abnormal LFTs were found to have significant increases in total bilirubin, alkaline phosphatase, alanine transaminases, and aspartate transaminases compared with their LFTs at RT. Four of the seven eD+/R− with positive VL had liver biopsies performed revealing various stages of hepatitis. Three were found to have stage 1–3 fibrosis progression within 1–2 years, with one recipient having reversal of portal venous blood flow on ultrasound.

Four eD+/R− with HCV-related liver disease were transplanted using two pairs of donor allografts. For the first allograft pair, the two eD+/R− had multiple problems related to their

HCV disease including chole-static hepatitis and evidence of cirrhosis and portal hypertension. One of these recipients died from causes directly related to HCV hepatitis. Prior to death, the recipient was treated for AHR and subsequently developed sepsis, a positive VL, and transaminitis. At autopsy, this recipient had evidence of cholestatic hepatitis, portal inflammation, and hepatic steatosis. Recipients of the other allograft pair had elevated LFTs, positive VLs, and acute hepatitis on liver biopsy. One of these recipients did receive pegylated interferon and ribavirin with a response in VL (10^7 to 10^4 IU/ mL). Both recipients are deceased (multi-organ failure and failure-to-thrive) within 1 y post-RT.

Immunologic Complications

The number of eD+/R− treated with TAC, MMF, and prednisone was similar to control groups. The eD+/R− experienced similar numbers of rejection episodes compared with all control groups. Three eD+/R− were diagnosed with rejection (ACR $n = 1$, AHR $n = 1$, and both $n = 1$). All three eD+/R− (43%) with rejection episodes died during the study period; only one has a positive VL. The recipient diagnosed with only ACR (Banff 1A) was never treated and died 3 y later from cancer recurrence with graft function. Both recipients with AHR were treated with rituximab. They both died shortly after rejection treatment from sepsis. Only four of the 22 (18%) deceased eD−/R− were ever diagnosed with acute rejection.

Other Complications

Post-RT complications experienced by eD+/R− are listed (Table 5). Infectious complications occurred more often in eD+/R−compared with eD+/R− ($P = 0.006$). No difference in infection rate was seen comparing the eD+/R− to D+/R+ and D−/R+. Multiple infections also occurred at a greater frequency in the eD+/R−compared with the eD−/R−. Five of the seven deceased eD+/R− (71%) and seven of 22 deceased eD−/R− (32%) had multiple infections.

No difference in surgical complications was noted between eD+/R− and control groups. The most common surgical complication encountered in eD+/R− was lymphoceles, which were drained with laparoscopy ($n = 1$) and open laparotomy ($n = 2$). Six cardiac complications occurred in the eD+/R− : myocardial infarction, ($n = 3$), congestive heart failure, ($n = 2$), and coronary artery disease requiring coronary arterial bypass grafting, ($n = 1$). Two of the myocardial infarctions occurred in septic eD+/R−. Cardiac complications occurred more frequently in eD+/R− than eD−/R−, however, no difference was seen comparing eD+/R− to D+/R+ and D−/R+. Other complications are listed (Table 3).

The median body mass index (BMI) for the eD+/R− group was 25 (range 21–38). Four eD+/R− patients were obese with a BMI > 30. Two obese eD+/R− are deceased and two obese eD+/R− survived. No difference in BMI was noted between the surviving and deceased eD+/R− patients. The BMI was no different between those eD+/R− patients with and without immunologic, infectious, and surgical complications ($P = 0.61$, 0.32, and 0.17, respectively).

OPTN Data Results

A total of 32,900 primary deceased donor RTs were performed from January 2003 through December 2007, including 127 adult (≥18 y) D+/R− (0.4%) and 32,773 adult D−/R− (99.6%). Median age for 127 adult D+/R− was 55 (range 20–78) y. Patient and graft survival for 1 y is shown (Table 6). Cause of death was reported for 23 adult D+/R− with infectious causes being the most common followed by cardiovascular complications (26.1% and 17.4%, respectively). For the 3488 adult D−/R−, cardiovascular complications were the most common cause of death, followed by infectious causes (21.5% and 16.7%, respectively).

A total of 37 eD+/R− and 10,488 eD−/R− were transplanted with deceased donor allografts during the same period. Median age of the eD+/R− was 67 (range 61–78) y. Patient and graft survival at 1y is shown (Table 6). Cause of death was reported for ten eD+/R− with infectious causes being the most frequent (30%). The most common cause of death for 1041 eD−/R− reported was cardiovascular causes (21.6%), followed by infectious causes (16.7%).

DISCUSSION

These eD+/R− were unlikely to have received a standard allograft before dying. Alternative sources, such as allografts from HCV+ donors, were thought to provide these elderly recipients the best chance for RT. Unfortunately, the overall and 1 y survival associated with the receipt of an allograft from HCV+ donor (46% and 58%, respectively), compared with a HCV− donor, was significantly worse. These results were considerably worse than the USRDS reported elderly RT cadaveric allograft recipients 1 y survival (60–64 and ≥65 years; 91.4% and 89.5%, respectively) [1].

Our results were noticeably discordant compared with Pereira *et al*. While the study included renal and extrarenal transplants, the survival associated with the receipt of an allograft from an HCV+ donor was found to be similar to a control cohort of transplantations performed with allografts from HCV− donors (31% *versus* 33% overall survival, $P < 0.01$). Additional differences exist between the studies, including the age of the recipients and the length of follow-up. The recipients included in the referenced study were considerably younger (median 40 y of age) and were followed for a longer period of time (median 42 mo) [22].

More importantly, our results were worse than 1 y survival for age-matched ESRD patients on dialysis (60–64, 65–69, and ≥70 y; 82.5%, 78.6%, and 71.0% respectively) [1]. We did find the OPTN 1 y survival for eD+/R− recipients to be 83%. This was more comparable to the survival reported for those age-matched patients on dialysis but the OPTN patients were few and outcomes were under-reported (only 10 of 37). Our findings, consistent with other findings, show that receipt of an allograft from a HCV+ donor by elderly ESRD patients offered no survival benefit compared with remaining on dialysis [10, 12].

The four allografts lost in eD+/R− group were lost during multi-organ failure. While the percentage of allografts lost in eD+/R− was not statistically different compared with control groups, the cause of graft loss was different. Control recipients lost graft function secondary to chronic allograft nephropathy. Others have reported no increased graft loss associated with the receipt of an allograft from an HCV+ donor [9].

HCV-liver disease affected six eD+/R− (46%) who developed acute hepatitis defined as a detectable VL with elevated LFTs. The number of recipients developing a positive VL was less than reported in other studies of transplants with allografts from HCV+ donors (96%), however, the percentage of patients developing an acute hepatitis was similar (55%) [22]. Acute hepatitis occurred more frequently in the eD+/R− group than in immunocompetent individuals potentially due to the size of the inoculation [23]. Those with a positive VL developed viremia within 4 mo post-RT, suggesting an incubation time similar to immunocompetent individuals [24]. None of the recipients found to have viremia spontaneously cleared the virus. HCV liver disease, specifically cholestatic hepatitis, was the direct cause of only one death.

The eD+/R− appear very prone to cirrhosis development. Three eD+/R− developed fibrosis progression (stages 1–3) approximately 12 mo post-RT. The natural course of HCV-related fibrosis in immunocompetent patients with chronic HCV is 0.13 stages per year with cirrhosis development in approximately 30 y [25]. The natural history of HCV is accelerated

with older age. Age > 50 y was an independent risk factor for a 67% increased fibrosis progression rate [26]. In studies of HCV+ LT recipients, allografts from older donors have up to an 8-fold higher risk of severe fibrosis compared with allografts from younger donors [13–15, 17, 18, 20]. Recipients of liver allografts from donors > 50 y had fibrosis progression of 2.7 stages per year and developed cirrhosis from HCV sequelae shortly beyond 2 y of transplantation [18]. Some of the eD+/R− in this study developed fibrosis as quickly.

We were unable to determine if immunosuppressives were specifically responsible for the severity of HCV liver disease experienced given the small sample size and that most recipients were treated with the same induction and maintenance regimen. Only one eD+/R− with acute hepatitis was treated for rejection. This recipient did develop cholestatic hepatitis quickly after AHR treatment. Variables independently associated with cirrhosis development in HCV+ LT recipients included ATG induction and maintenance with tacrolimus, however, another independent study did not show any increased risk of fibrosis with either and extrapolating these results to our eD+/R− is difficult [13, 14]. Some investigators advocate+the use of cyclophilins, such as cyclosporine A (CsA), for immunosuppression because of the inhibition of HCV replication in hepatocytes *in vitro* [27, 28].

Our eD+/R− were probably excessively immunosuppressed considering their significantly higher incidences of infections and their persistently negative anti-HCV serology. Our protocol of immunosuppression for eD+/R− did not take into consideration their potential HCV and was no different than control recipients. Our rationale for the protocol was the high rate of rejection our elderly recipients have experienced previously (25%, not reported). Yet multiple researchers suggest elderly RT recipients are less likely than their younger counterparts to develop rejection arguing for decreased immunosuppression [29–31]. The frequency and severity of infections in the eD+/R− recipients was of concern. Thirty percent of eD+/R− died after developing sepsis or multi-organ failure and increased age likely compounded their susceptibility [32, 33].

Others suggest a role for concomitant HCV increasing vulnerability to infections. El-Serag *et al*. found an association between HCV and opportunistic infection, even in the absence of clinically overt liver disease [34]. With regards to infectious risks, transplant recipients with HCV are known to be vulnerable to over-immunosuppression. Roth *et al*. and Singh *et al*. both found in RT and LT recipients respectively, a higher infection rate in those recipients with HCV [35, 36]. In another study of HCV+ RT recipients with post-RT hepatic dysfunction and chronic hepatitis, 79% of deaths were attributed to sepsis. The age of the RT recipients in the study was considerably less than our population, suggesting an added immune dysfunction related specifically to HCV and not just age [37]. Treating physicians have attempted to make adjustments to the immunosuppressive regimen for transplant recipients with HCV [10, 38–40]. Physicians caring for eD+/R−, and transplant recipients with HCV, in general, need to be aware of the increased risk of infectious-related death.

Not all eD+/R− developed liver disease. It is possible that donors associated with eD+/R− who never developed a positive VL, cleared their HCV infection prior to organ procurement, and the risk associated with using their allografts is equivalent to HCV− donors. NAT of the donor tissue would have helped to reveal their infection status. For the few donors with NAT performed, the results correlated positively with recipients VL status.

Interestingly, eD+/R− tested for HCV serology were all found to be negative. Negative HCV serology might be expected for those recipients tested soon after RT or rejection diagnosis considering recent induction or treatment. However, two eD+/R− with no

rejection episodes and a positive VL had negative HCV serology when tested 1 y after RT. These findings confirm the impaired immune response of the RT recipient, possibly exaggerated by age. The negative serology also demonstrates the permissivity of HCV and continual adaptive ability to evade the immune response. Future D+/R− should be followed for HCV-related disease by evaluating viral load.

Surgical complications in the eD+/R− were limited with exception of lymphoceles which occurred at a rate higher than reported previously [41–43]. No study exists correlating age with lymphoceles. The high incidence seen in this study might indicate some association with age. Cardiac complications were also more frequent in eD+/R−. The increased frequency could be explained by the age difference or the multi-organ failure often experienced in the setting of sepsis by the eD+/R−.

The small number of eD+/R− is a limitation of this study. Despite the small number of eD+/R− included, we can conclude the use of allografts from HCV+ donors should have been reserved for those recipients with preexisting HCV. Emphasis should be placed on the fact that the outcome for RT recipients with pre-existing HCV (D+/R+) in our study was superior compared with eD+/R− (survival, 87.5% *versus* 46.1%, $P = 0.07$). As shown by others, D+/R+ are unlikely to develop acute liver issues in the setting of their chronic infection [44, 45]. While the risk of death associated with liver disease in the eD+/R− was not excessive, the likeli-hood of the recipient having severe postoperative complications leading to mortality was high. These observations confirm that HCV+ allografts should only be used for HCV+ recipients until there is a better understanding of the mechanism of HCV immunosuppression. Additionally, the population of elderly transplant recipients are likely to be more vulnerable to HCV and transplant sequelae. This conclusion possibly explains the difference in survival findings between this study and Pereira *et al.* [22]. Renal allografts from HCV+ donors are not acceptable for RT in elderly recipients.

The eD+/R− susceptibility to serious infection is also to be expected. Less aggressive immunosuppression regimens and minimal rejection treatments would potentially be more appropriate for the elderly in general and allow for better use of non-standard allografts. Even though there exists limited time for organ assessment at procurement, probable HCV+ donors should be evaluated for HCV VL. Lastly, recipients HCV+ allografts should be monitored regularly for signs of liver disease and HCV VL.

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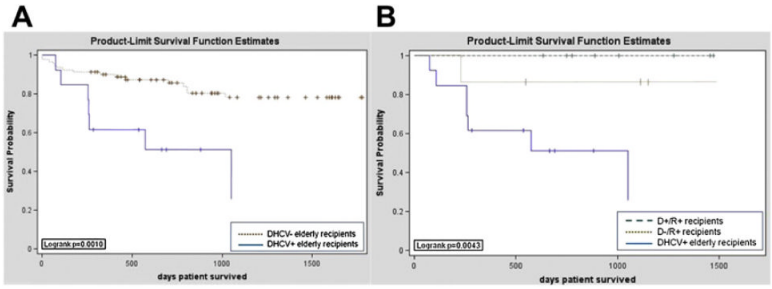

FIG. 1.

Kaplan Meir plot showing patient survival for (A) eD+/R− recipients compared with eD−/R − recipients and (B) eD+/R− recipients compared with D+/R+ and D−/R+ recipients.

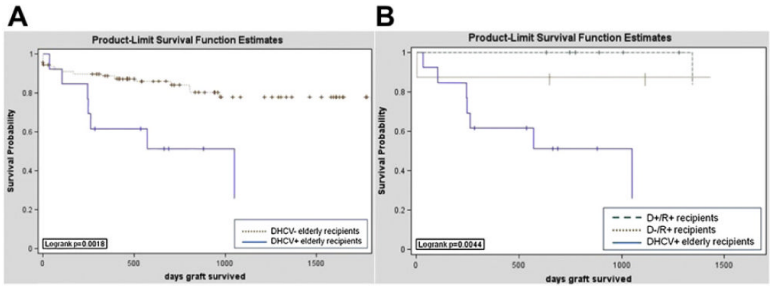

FIG. 2.

Kaplan Meier plot showing graft survival for (A) eD+/R− recipients compared with eD−/R− recipients and (B) eD+/R− recipients compared with D+/R+ and D−/R+ recipients.

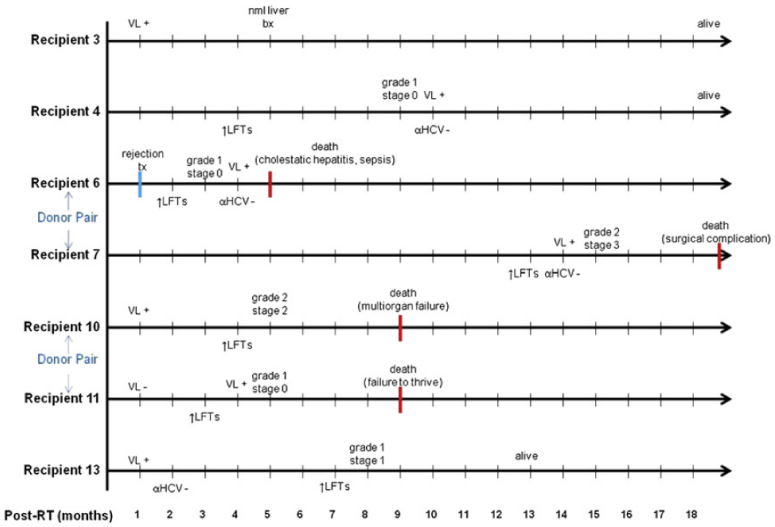

FIG. 3.

Course of liver disease in eD+/R− recipients with positive VL post-RT.

TABLE 1

eD+/R− Recipients Pre-RT

Patient	Age	Gender	BMI at RT	Renal disease	Dialysis (y)	Co-morbidities
1	73	F	23.8	Wegner's	3	Pericarditis
2	61	M	24.7	DM, HTN	3	HBV, CAD, PVD s/p amputations
3	65	F	33.9	DM, HTN	3	CAD, BMI > 30, hypotension
4	72	M	28.4	DM, HTN	7	CAD
5	78	M	23.0	HTN	1	Skin CA, carotid body tumor
6	71	F	38.3	DM, HTN	3	TIA, *C. diff,* BMI > 30
7	72	M	34.7	HTN	2	CHF, afib, CAD, BMI > 30
8	61	F	35.0	DM, HTN	3+	CAD s/p MI, PVD s/p amputation, osteomyelitis, thyroid and breast tumors, BMI > 30, *C. diff*
9	74	M	25.1	IgA nephropathy	5	Oral pharyngeal CA, TIA, CAD s/p CABG, CHF
10	69	M	26.5	Pyelonephritis	Intermittent	Bladder CA s/p ileal conduit, Crohn's disease
11	73	M	24.3	DM	1	DM, HTN
12	73	M	21.1	PCKD	2.5	HTN, gout
13	60	M	22.4	Bright's disease	1.5	Previous RT, DM, HTN, CVA, skin CA, seizures

BMI = body mass index; HTN = hypertension; DM = type II diabetes mellitus; CA = cancer; CAD = coronary artery disease; PVD = peripheral vascular disease; afib = atrial fibrillation; *C. diff= Clostridium difficile* colitis; CHF = congestive heart failure; MI = myocardial infarction; PCKD = polycystic kidney disease; HBV = Hepatitis B virus; TIA = transient ischemic attack; CVA = cerebrovascular accident.

TABLE 2

eD+/R− and eD−/R− Recipients' Outcomes

	Variable	eD+/R− (*n* = 13)	eD−/R− (*n* = 90)	*P* value
Demographics	Median age (range) y	72 (60–78)	65 (60–77)	0.028
	Males	69.2%	63.3%	0.766
	Survival	46.1%	82.3%	0.008
	D survived (range)	537 (77–2275)	821 (0–2522)	0.032
	Median follow-up d (range)	666 (284–2299)	1122 (271–2522)	0.121
Graft Function	DGF	15.4%	24.4%	0.728
	Grafts lost	30.8%	20.0%	0.468
	D graft survived (range)	537 (35–2275)	735 (0–2362)	0.086
	Recent creatinine (range) mg/dL	1.4 (0.7–4.7)	1.5 (0.5–10.9)	0.721
Immunologic Complications	Any rejection episode	23.0%	17.8%	0.703
	ACR	15.4%	14.4%	>0.999
	AHR	15.4%	6.7%	0.266
	Both ACR and AHR	7.7%	3.3%	0.422
	Any infection	92.3%	51.1%	0.006
	Multiple infections	53.9%	20.0%	0.014
Other Complications	Surgical complications	38.5%	33.3%	0.759
	Cardiac complications	46.2%	11.1%	0.005
	Squamous cell cancer	0.0%	4.4%	>0.999
	Other cancers	15.4%	4.4%	0.165
Maintenance Immunosuppression	TAC	100.0%	88.9%	0.354
	MMF	69.0%	66.7%	>0.999
	Pred	100.0%	92.2%	0.592

TABLE 3

eD+/R−, D+/R+ and D−/R+ Recipients' Outcomes

	Variable	eD+/R− (*n* = 13)	D+/R+ (*n* = 8)	D−/R+ (*n* = 13)	*P* value
Demographics	Median age (range) y	72 (60–78)	54 (40–69)	52 (38–68)	<0.001
	Males	69.2%	75.0%	0.769	0.901
	Deaths	53.9%	12.5%	7.7%	0.017
	Survival (range) d	537 (77–2275)	1392 (232–1988)	1278 (634–2445)	0.007
	follow-up (range) d	666 (284–2299)	1419 (542–2000)	1278 (634–2445)	0.029
Graft function	DGF	15.4%	12.5%	38.5%	0.268
	Grafts lost	30.8%	25.0%	7.7%	0.326
	Graft survived (range) d	537 (35–2275)	1370 (1–1988)	1278 (634–2445)	0.012
	Recent creatinine (range) mg/dL	1.4 (0.7–4.7)	1.8 (0.6–5.5)	1.6 (1.0–7.1)	0.589
Immunologic Complications	Any rejection episode	23.0%	12.5%	23.1%	0.811
	ACR	15.4%	12.5%	23.1%	0.274
	AHR	15.4%	12.5%	7.7%	0.829
	Both ACR and AHR	7.7%	12.5%	7.7%	0.916
	Any infection	92.3%	75.0%	69.2%	0.326
	Multiple infections	53.9%	50.0%	53.9%	0.982
Other Complications	Surgical complications	38.5%	12.5%	12.5%	0.124
	Cardiac complications	46.2%	12.5%	30.8%	0.274
	Squamous cell cancer	0.0%	12.5%	0.0%	0.188
	Other cancers	15.4%	0.0%	0.0%	0.180
Maintenance Immunosuppression	TAC	100.0%	100.0%	92.3%	0.435
	MMF	69.0%	50.0%	61.5%	0.678
	Pred	100.0%	100.0%	92.3%	0.435

TABLE 4

Liver Function Tests for the Six eD+/R− Recipients with Abnormalities Post-RT

Month post-RT	Total bilirubin median (range) mg/dL	*P* value	Alkaline phosphatase median (range) U/L	*P* value	Alanine transaminase median (range) U/L	*P* value	Aspartate transaminase median (range) U/L	*P* value
At RT	0.55 (0.3–1.2)		63 (38–94)		19 (13–119)		8.5 (6–31)	
1	0.45 (0.3–0.5)	0.284	72 (56–194)	0.257	45 (24–140)	0.040	42 (28–129)	0.451
2	0.50 (0.3–1.5)	0.943	126 (59–188)	0.029	32 (16–55)	0.020	40 (11–53)	0.857
3	0.60 (0.6–2.1)	0.320	100 (78–328)	0.112	176 (42–553)	0.020	225 (23–374)	0.100
4	2.90 (0.6–4.6)	0.017	177 (133–204)	<0.001	113 (45–693)	0.074	114 (58–599)	0.158
5	17.6 (3.7–22.7)	0.007	263 (160–524)	0.010	473 (136–1035)	<0.001	263 (128–298)	0.039
6–9 *	1.15 (0.7–8.9)	0.173	139 (72–170)	0.016	66 (33–202)	0.033	99 (47–218)	0.093
10–2 *	1.8 (0.9–25.9)	0.186	139 (106–302)	0.023	72 (35–144)	0.007	146 (48–226)	0.050

* Only 4 of 6 eD+/R− recipients with elevated LFTs were evaluated beyond 6 mo.

TABLE 5

eD+/R− Recipients' Complications Post-RT

Patient	Infectious complications	Surgical complications	Other complications
1	Retroperitoneal abscess	Lymphocele	Hyperglycemia
2	Wound infection, UTI, bacteremia	Hydronephrosis	MI, anemia, thrombocytopenia
3	UTI	None	None
4	none	Lymphocele	CHF
5	Shingles, PNA, UTI	Lymphocele	Prostate CA, CHF, pl eff, pHTN, DD, lymphedema, anemia
6	Cholestatic hepatitis, PNA, bacteremia, UTI, *C. difficile* colitis, osteomyelitis	None	MI
7	Wound infection	None	pHTN, edema, OSA, LE ulcer
8	UTI	None	Pancytopenia, fluid retention, PVD s/p amp, CAD s/p CABG
9	Wound infection, UTI, PNA	Retroperitoneal hematoma	Hypotension, DVT/PE, gastric ulcer, oro CA
10	UTI	None	Edema, anemia, CRF, RAS s/p angio, hematochezia, UE injury, AMS
11	UTI	None	Fatigue
12	*C. difficile* colitis, septic arthritis, endocarditis, bacteremia	None	Urinary retention, hypercalcemia, FTT,pancytopenia
13	UTI	None	Urinary retention, MI, seizures, hypercalcemia

UTI = urinary tract infection; MI = myocardial infarction; CHF = congestive heart failure; PNA = pneumonia; CA = cancer; pl eff = pleural effusion; pHTN = pulmonary hypertension; DD = diastolic dysfunction; *C. difficile* = *Clostridium difficile*; OSA = obstructive sleep apnea; LE = lower extremity; PVD = peripheral vascular disease; s/p = status post; amp = amputation; CAD = coronary artery disease; CABG = coronary artery bypass grafting; DVT/PE = deep venous thrombosis and pulmonary embolism; oro = oropharyngeal; CRF = chronic renal failure; RAS = renal artery stenosis; angio = angioplasty; UE = upper extremity; AMS = altered mental status; FTT = failure to thrive.

TABLE 6

Summary of OPTN Data 2003–2007

	n	%	Patient survival 1y	95% CI	*P* value	Graft survival 1y	95% CI	*P* value
adult D+/R−	127	0.4%	90%	83.29%–95.87%	0.0046	82%	75.03%–89.90%	0.0001
adult D−/R−	32773	99.6%	95%	94.55%–95.05%		90%	89.94%–90.6%	
eD+/R−	37	0.4%	83%	65.49%–100%		79%	61.40%–97.22%	
eD−/R−	10488	99.6%	93%	91.93%–93.26%		90%	88.86%–90.40%	