The incidence of cytomegalovirus infection after deceased-donor kidney transplantation from hepatitis-C antibody positive donors to hepatitis-C antibody negative recipients

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Abstract

Background: Deceased-donor kidney transplantation (KT) from hepatitis C (HCV)-infected donors into HCV-uninfected recipients (HCV D+/R−) could become standard care in the near future. However, HCV viral replication by viral transmission might lead to a higher incidence of cytomegalovirus (CMV) infection in these recipients.

Methods: A national-registry-based retrospective cohort study was conducted using the Scientific Registry of Transplant Recipients (SRTR) data set. We assessed the incidence of CMV infection in HCV antibody (Ab) negative recipients receiving kidneys from HCV Ab positive (HCVAb D+/R−) and negative (HCVAb D−/R−) donors. The risk of CMV infection was analyzed by Cox regression analysis in a propensity score (PS) matched-cohort of HCVAb D+/R− (n = 950) versus HCVAb D−/R− (n = 950). Sensitivity analysis was also conducted in the entire cohort (n = 181 082).

Results: The mean age at baseline was 54 years, 75% were male, and 55% of the patients were African American in PS-matched cohort. Compared to the HCVAb D+/R− patients, recipients with HCVAb D−/R− showed identical probability for the incidence of CMV infection (Hazard Ratio (HR) = 1.00, 95% Confidence Interval (CI): 0.82–1.22). In the sensitivity analysis, compared to the HCVAb D−/R− patients, the HCVAb D+/R− group had a significantly lower risk of CMV infection in the unadjusted analysis (HR = 0.75, 95%CI: 0.65–0.85), while this risk difference disappeared after the adjusted analysis (HR = 0.99, 95%CI: 0.87–1.14).

Conclusion: The incidence of CMV infection was similar in recipients who received HCVAb D+ and HCVAb D− KT. Further studies are needed to assess this association in KT from HCV nucleic acid positive donors.

Introduction

Not only strictly designed clinical trials [1–3], but also real-world experience outside of clinical trials [4] have strongly advocated for the utility and safety of deceased-donor kidney transplantation (KT) from hepatitis-C (HCV)-infected donors to HCV-uninfected recipients (HCV D+/R−), followed by the administration of direct-acting antiviral agents (DAA). In an era plagued by both organ shortage and a crisis of opioid-abuse-related deaths, this strategy may offer an opportunity of increasing the donor pool and decreasing the organ discard rate [5–8]. According to data from national registry data analyses, KT from HCV D+/R− fared similarly or better than KT from HCV D−/R− KT recipients during the initial six to twelve months, matched for each recipient’s and donor’s characteristics, including KDPI [7,9]. Furthermore, this new strategy of donation (HCV D+/R−) followed by DAA treatment has accomplished a 100% sustained virologic...
response (SVR) by week 12, irrespective of viral-load, genotypes, or the timing of DAA administration after KT [1–4, 8]. The aggressive utilization of HCV-donor kidneys would reduce the excess mortality and morbidity experienced by waitlisted patients with end-stage kidney disease (ESKD) [10] and save medical costs, owing to a shortened waiting time [11]. This new strategy of using HCV-infected donor kidneys for transplantation into uninfected recipients might indeed become the new standard in industrialized societies.

Despite excellent overall clinical outcomes reported from well-designed clinical trials [1–3], there were a few reports of unfavorable consequences of HCV infected kidney transplantation into uninfected recipients, such as a higher risk of BK polyoma and cytomegalovirus (CMV) viremia [4]. We previously documented that the incidence rate of CMV viremia after D+/-R− KT was approximately double compared to the expected incidence in non-HCV-related KT with appropriate CMV prophylaxis [4, 12, 13]. However, it is not known whether HCV infection directly stimulates CMV reactivation/infection or contributes to immunosuppression. Indeed, HCV viral replication might theoretically create a milieu for secondary viral infections by enhancing pro-inflammatory and profibrotic processes in BK virus infection [14] and by the modification of the natural killer (NK) cells’ subset in CMV infection [15, 16]. In real-world experience, the approval of DAA by a third-party payer may take a considerable amount of time, that is, our former study reported a median duration of 76 days for starting DAA after KT [4]. This relatively longer delay preceding DAA administration may enable an interim massive HCV replication and a higher incidence of CMV infection [5]. Furthermore, although CMV infection is now easily controlled by prophylaxis treatment and, once CMV infection has occurred, it will confirm worse patient and kidney allograft outcomes [17, 18].

Our study hypothesis was that transplanting patients across a hepatitis-C discordant status, those with HCV D+/-R− transplantation are more likely to experience a higher incidence of CMV virus infection, compared to those undergoing HCV D−/-R− KT. To test this hypothesis, we conducted a propensity score (PS) matched cohort study using the Scientific Registry of Transplant Recipients (SRTR) data set.

Materials and methods

Cohort definition and data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The datasets generated during and/or analyzed during the current study are available in the SRTR repository (www.srtr.org). This national-registry-based retrospective cohort study was conducted from a publicly available United States SRTR data set. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors [19]. Unfortunately, the outcomes of interest (CMV infection) have not been collected systematically after April 2015, while our original exposure of interest [nucleic acid test (NAT) results of donor HCV] was reported in the SRTR database only after April 1st, 2015. Therefore, we decided to use a cohort, which was transplanted before April 2015 together with the donors’ HCVAb-based definition for exposure.

The baseline cohorts contained 244742 deceased-kidney-transplant recipients from October 1st, 1987 to March 31st, 2015. Of those, we excluded non-eligible recipients according to the following criteria: HCVAb positive recipients (n = 12 576), donors with an unknown HCVAb status (n = 47 150) and those without outcome data (n = 3934). After extracting the participants based on the above exclusion criteria, 181 082 HCVAb-negative recipients (HCVAb R−) with outcome data were included in the analysis. For the analysis, we divided the recipients into two groups based on the donors’ HCVAb seropositivity; one group received kidneys from HCVAb-positive donors (HCVAb D+/-R−, n = 1093) and the other from HCVAb-negative donors (HCVAb D−/-R−, n = 179 989). For our main analysis, we created a propensity-score-matched cohort including 950 HCVAb D+/-R− and 950 HCVAb D−/-R− recipients (Figure 1).

The definition of the exposure and control groups

Exposure was defined based on donor HCVAb status. The exposure group was defined as recipients of kidneys from HCVAb-positive donors (HCVAb D+), while the control group’s donors were HCVAb negative (HCVAb D−). Unfortunately, records of the donors’ HCV nucleic acid test (NAT) results, which could prove the active infection of HCV and data about CMV infections on the national registry dataset, were not available in the same time period. Therefore, we used the serostatus of the HCV antibody (HCVAb) as a potential surrogate for active viral replication instead of the HCV nucleic acid test (NAT) assay. The exact numbers and
proportions of both exposure and control groups are shown in Figure 1.

**Outcome assessment**

The primary endpoint was the incidence of first CMV infection. The definition of first CMV infection was based on the captured first treatment for CMV after transplantation. The treatment was defined as using any of the following medications: Immune Globulin Intravenous (CytoGam®), valganciclovir, ganciclovir, and valacyclovir. However, the data set did not clearly distinguish the actual treatment from prophylaxis therapy for CMV infection. Therefore, we created an algorithmic classification for CMV infection based on risk and its captured medical treatment. Briefly, we divided the CMV risk classification into three categories based on CMV IgG before KT in both donors and recipients. The low-risk group was defined as the combination of CMV IgG D−/R−, or D+/R+. The high-risk group was defined as CMV IgG D+/R− (Supplementary Figure 1). According to these three categories and the usual prophylaxis strategy, those who were administrated valacyclovir within 90 days after KT in the low-risk group and valacyclovir or valganciclovir within 90 days after KT in the intermediate-risk group and 180 days after KT in the high-risk group were assigned as prophylaxis treatment during prophylactic period. The

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**Figure 1.** Flow chart of patient selection. Abbreviations. SRTR: Scientific Registry of Transplant Recipients; HCV: hepatitis C virus; HCVAb: hepatitis C virus antibody; HCVAb D+/R−: kidney transplantation from hepatitis-C-antibody-positive donor into negative recipient; HCVAb D−/R−: kidney transplantation from hepatitis-C-antibody-negative donor into negative recipient.
administration of any of these drugs after the above-mentioned prophylactic periods was counted as evidence for the ‘first CMV infection’, which is defined as an outcome event in this study (Supplementary Figure 1).

**Covariates**

The following information has been collected from the SRTR database about our recipients: age, sex, race, body mass index (BMI), induction therapy including antithymocyte globulin (ATG), any calcineurin inhibitors (CNI) and mycophenolate acids (MPA) at discharge, history of KT and organ transplantation, a history of delayed graft function (DGF) defined as a need for at least one dialysis session within 1 week after transplantation, results of the calculated panel reactive antibody (cPRA), and the numbers of human leukocyte antigen (HLA) mismatches.

The following information has been extracted from the SRTR database about deceased donors: age, sex, race, BMI, history of diabetes (DM), cause of death, donation after cardiac death, and serum creatine before donation. CMV risk classification, as mentioned above, was a critical confounder and was used as a matching covariate (Supplementary Figure 1).

**Statistical analysis**

Baseline characteristics were presented in the HCVAb D+/R− and HCVAb D−/R− groups as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and numbers and percentages (%) for categorical variables, as appropriate. Differences between groups were analyzed by student t-tests or the Mann–Whitney test for continuous variables and the chi-square test for categorical variables. Standard differences that were compared between the HCVAb D+/R− and HCVAb D−/R− groups were also described in both the entire cohort and the PS matched cohort.

For the survival analysis in both the main (PS matched) and sensitivity (entire cohort) analyses, the start of the observational period was the date of KT, and all recipients were followed-up until the date of CMV incidence or any of the following censoring events: death, allograft loss or end of follow-up (1 April 2015), whichever came first.

For the main analysis, the propensity score (PS) method was used to account for the confounding effects arising from differences in the participants’ baseline characteristics in those who were assigned as HCVAb D+/R− and HCVAb D−/R−. First, to detect the covariates likely to influence the probability of HCVAb D+/R−, a logistic regression analysis was conducted (presented in Supplemental Table 1). Subsequently, variables associated with HCVAb D+/R− were identified and used for calculating PSs. We used the ‘psmatch2’ command in STATA to generate the 1:1 PS matched cohort using the nearest neighbor matching without replacement (Figure 1 and Table 1). The following variables were used for the logistic regression model to create the PS: recipients’ age, sex, race, induction therapy, CNI, type of prior organ transplantation if any, DGF and HLA mismatches; donor’s age, sex, race, DM, donation after cardiac death (DCD), cause of death, and CMV risk classification. The distribution of PSs in both the HCVAb D+/R− and HCVAb D−/R− groups before and after matching are shown in Supplementary Figure 2.

The association between the donors’ HCVAb status and the incidence of CMV infection was assessed using the Kaplan–Meier method with the Log-rank test and using Cox proportional hazard models. Since the PS matched cohort was already well-matched, the Cox regression analysis was not additionally adjusted for covariates. We performed additional subgroup analyses to assess the association between HCVAb status and the incidence of CMV infection in the following a priori defined groups: age (less than or equal to 55 versus greater than 55 years), sex, race (non-African American versus African American), induction therapy (no induction versus any induction therapy), prior organ transplantation, cPRA (0–80% versus greater than 80%), and DCD. Potential interactions were formally tested by including relevant interaction terms.

For the sensitivity analysis, the entire cohort was used to compare the HCVAb D+/R− and HCVAb D−/R− groups (Figure 1). The association between the donors’ HCVAb status and the incidence of CMV infection was assessed using the Kaplan–Meier method, the Log-rank test, and the unadjusted and adjusted Cox proportional hazard models. We adjusted for the following confounders: recipients’ age, sex, race, induction therapy, CNI, prior organ transplantation, DGF and HLA mismatches; donor’s age, sex, race, DM, DCD, cause of death, and CMV risk classification. A sub-group analysis was also conducted by the same stratification that we applied at the PS-matched analysis. Potential interactions were formally tested by including relevant interaction terms.

P values were two-sided and the significance level was set at less than 0.05 for all analyses. All analyses were conducted using STATA Version 13 (STATA Corporation, College Station, TX). This study was approved by the Institutional Review Committee of The University of Tennessee Health Science Center (18-
Table 1. Baseline characteristics of the entire cohort and the propensity matching cohort compared between HCVAb D+/R− and HCVAb D−/R−.

| Baseline characteristics | Entire cohort, n = 181 082 | PS matching cohort n = 1900 | p-Value* | Standardized difference | Total missingNo. | p-Value† | Standardized difference |
|--------------------------|-----------------------------|-----------------------------|----------|-------------------------|-----------------|----------|-------------------------|
| Recipient information    |                             |                             |          |                         |                 |          |                         |
| Age, years, mean ± SD    | 53.8 ± 11.7                 | 48.7 ± 15.4                 | <0.001   | 0.381                   | 0               |          |                         |
| Sex, male, n (%)         | 823 (75.3)                  | 107 581 (59.8)              | <0.001   | −0.340                  | 0               | 27.0 ± 5.2 | 27.2 ± 5.4              | 0.377 |
| BMI, kg/m², mean ± SD    | 26.9 ± 5.2                  | 27.2 ± 5.7                  | 0.107    | 0.253                   | 4               |          |                         |
| Race, n (%)              |                             |                             |          |                         |                 |          |                         |
| Caucasian                | 468 (42.8)                  | 115 235 (64.0)              |          |                         |                 |          |                         |
| African American         | 587 (53.7)                  | 51 537 (28.6)               |          |                         |                 |          |                         |
| Asian                    | 28 (2.6)                    | 9979 (5.5)                  |          |                         |                 |          |                         |
| Native American          | 4 (0.4)                     | 1949 (1.1)                  |          |                         |                 |          |                         |
| Pacific Islander         | 3 (0.3)                     | 899 (0.5)                   |          |                         |                 |          |                         |
| Multiracial              | 3 (0.3)                     | 386 (0.2)                   |          |                         |                 |          |                         |
| Induction therapy, n (%) |                             |                             | <0.001   | −0.100                  | 11 376          |          |                         |
| Non-induction            | 354 (36.2)                  | 41 438 (24.6)               |          |                         |                 |          |                         |
| ATG                      | 256 (26.2)                  | 68 849 (40.8)               |          |                         |                 |          |                         |
| Alemtuzumab              | 51 (5.2)                    | 12 838 (7.6)                |          |                         |                 |          |                         |
| IL-2 receptor blocker    | 232 (23.7)                  | 36 346 (21.5)               |          |                         |                 |          |                         |
| OKT3                     | 85 (8.7)                    | 9257 (5.4)                  |          |                         |                 |          |                         |
| CNI use at discharge, n (%) | 1015 (95.9)              | 168 693 (95.1)              | 0.269    | 0.015                   | 2659            |          |                         |
| MPA use at discharge, n (%) | 770 (72.7)                | 144 636 (81.6)              | <0.001   |                         | 2659            |          |                         |
| Previous any organ transplantation, n (%) | 192 (17.6)          | 24 783 (13.8)               | <0.001   | 0.077                   | 55              |          |                         |
| Previous kidney transplantation, n (%) | 137 (12.5)           | 22 877 (12.7)               | <0.001   |                         | 0               |          |                         |
| HLA mismatch, n (%)      |                             |                             | <0.001   |                         | 779             |          |                         |
| 0                       | 15 (1.4)                    | 22 221 (12.4)               |          |                         |                 |          |                         |
| 1                       | 16 (1.5)                    | 3358 (1.9)                  |          |                         |                 |          |                         |
| 2                       | 37 (3.4)                    | 11 601 (6.5)                |          |                         |                 |          |                         |
| 3                       | 140 (12.9)                  | 28 262 (15.8)               |          |                         |                 |          |                         |
| 4                       | 284 (26.1)                  | 45 295 (25.3)               |          |                         |                 |          |                         |
| 5                       | 377 (34.7)                  | 46 455 (25.9)               |          |                         |                 |          |                         |
| 6                       | 218 (20.1)                  | 22 024 (12.3)               |          |                         |                 |          |                         |
| Total HLA mismatches, n, mean ± SD | 4.5 ± 1.3                  | 3.7 ± 1.8                   | <0.001   | 0.518                   | 779             |          |                         |
| cPRA, %, median (IQR)    | 0 (0.2)                     | 0 (0.5)                     | <0.001   |                         | 4840            |          |                         |
| Delayed graft function, n (%) | 285 (26.2)                | 42 371 (23.6)               | 0.044    | 0.079                   | 310             |          |                         |
| Donor information        |                             |                             |          |                         |                 |          |                         |
| Age, years, mean ± SD    | 39.7 ± 10.9                 | 36.8 ± 17.0                 | <0.001   | 0.205                   | 0               |          |                         |
| Sex, male, n (%)         | 735 (67.3)                  | 107 546 (59.8)              | <0.001   | −0.147                  | 0               | 39.8 ± 11.0 | 39.4 ± 16.9              | 0.531 |
| BMI, kg/m², mean ± SD    | 25.4 ± 5.3                  | 26.3 ± 6.4                  | <0.001   |                         | 2311            |          |                         |
| Donor Race, n (%)        |                             |                             | <0.001   | 0.041                   | 51              |          |                         |
| Caucasian                | 922 (84.4)                  | 151 463 (84.2)              |          |                         |                 | 807 (85.0) | 810 (85.3)              | 0.063 |
| African American         | 164 (15.0)                  | 23 005 (12.8)               |          |                         |                 | 133 (14.4) | 132 (13.9)              | 0.189 |
| Asian                    | 7 (0.6)                     | 3847 (2.1)                  |          |                         |                 | 6 (0.6)   | 8 (0.8)                 | 0.009 |
| Other                    | 0                           | 1623 (0.9)                  |          |                         |                 | 0         | 0                       | 0.000 |
| Donation after cardiac death, n (%) | 34 (3.1)                  | 15 558 (8.7)                | <0.001   | −0.237                  | 47              |          |                         |
| Cause of death, n (%)    |                             |                             | 0.007    | 0.016                   | 19              |          |                         |
| Anoxia                   | 177 (16.2)                  | 33 098 (18.4)               |          |                         |                 | 157 (16.5)| 150 (15.8)              | 0.087 |

(continued)
Table 1. Continued.  

| Baseline characteristics                          | HCVAb D+/R−, n = 1093 | HCVAb D−/R−, n = 179 989 | p-Value* | Standardized difference | Total missing No. | HCVAb D+/R−, n = 950 | HCVAb D−/R−, n = 950 | p-Value† | Standardized difference |
|---------------------------------------------------|------------------------|---------------------------|----------|-------------------------|-------------------|------------------------|------------------------|----------|-------------------------|
| Cerebrovascular/stroke                            | 398 (36.5)             | 66 622 (35.9)             |          |                         |                   |                       | 345 (36.3)             | 332 (35.0)                    |      |                         |
| Head trauma                                       | 498 (45.7)             | 76 774 (42.7)             |          |                         |                   |                       | 435 (45.8)             | 453 (47.7)                    |      |                         |
| Central nerve system tumor                        | 1 (0.1)                | 1331 (0.7)                |          |                         |                   |                       | 1 (0.1)                | 2 (0.2)                     |      |                         |
| Other                                             | 17 (1.6)               | 4417 (2.3)                |          |                         |                   |                       | 12 (1.3)               | 13 (1.4)                      |      |                         |
| Comorbidity-diabetes, n (%)                       | 37 (3.5)               | 9842 (5.5)                |          |                         | 0.004             | −0.114                 | 995                    | 31 (3.3)                      | 31 (3.3) | 1.000                   | 0.001 |
| Serum creatinine before donation, mg/dL, mean ± SD| 1.07 ± 1.16            | 1.13 ± 1.14               |          |                         | 0.050             | 0.114                  | 420                    | 1.03 ± 0.88                   | 1.21 ± 1.46 | 0.001                   | 0.000 |
| Serum creatinine > 1.5 mg/dL before donation, n (%)| 97 (9.0)               | 24 490 (13.6)             | <0.001   |                         |                   |                       | 78 (8.3)               | 142 (15.0)                   | <0.001 |                         |
| CMV risk classification                            |                        |                           |          |                         |                   |                       |                        |                       |                        | 0.817 | 0.011                   |
| Low-risk group, n (%)                             | 43 (3.9)               | 18 382 (10.2)             |          |                         |                   |                       | 42 (4.4)               | 38 (4.0)                     |      |                         |
| Intermediate-risk group, n (%)                    | 473 (43.3)             | 92 312 (51.3)             |          |                         |                   |                       | 439 (46.2)             | 445 (46.8)                    |      |                         |
| High-risk group, n (%)                            | 105 (9.6)              | 26 782 (14.9)             |          |                         |                   |                       | 95 (10.0)              | 105 (11.1)                    |      |                         |
| Unknown-risk group, n (%)                         | 472 (43.2)             | 42 513 (23.6)             |          |                         |                   |                       | 374 (39.4)             | 362 (38.1)                    |      |                         |

Abbreviations. PS: propensity score; HCVAb: hepatitis-C antibody; HCVAb D+/R−: kidney transplantation from hepatitis-C-antibody-positive donor into negative recipient; HCVAb D−/R−: kidney transplantation from hepatitis-C-antibody-negative donor into negative recipient; No.: number; SD: standard deviation; BMI: body mass index; ATG: anti-thymocyte globulin; IL-2: interleukin 2; OKT3: anti-CD3 antibody; CNI: calcineurin inhibitor; MPA: mycophenolate acid; HLA: human leukocyte antigen; cPRA: calculated panel reactive antibody; IQR: interquartile range; CMV: cytomegalovirus.

Definitions. Low risk: CMV IgG D+/R− or CMV IgG D+/R−; intermediate risk: CMV IgG D+/R−/C0 or CMV IgG D+/R−/C0; high risk: CMV IgG D+/R−/C0.

*Compared between HCVAb D+/C3 and HCVAb D+/R− in the entire cohort; †Compared between HCVAb D+/R− and HCVAb D−/R− in the PS matching cohort.

p-Values for continuous variables with mean ± SD are results of t-test and with median (IQR) are result of the Mann–Whitney test, and categorical variables are chi-square test.
Sensitivity analysis for the incidence of CMV infection in the entire cohort

The median follow-up time was 6.0 (IQR: 0.7–13.6) years and CMV infection occurred in 46,020 patients (incidence rate: 33.4 cases/1000 person-year, 95%CI: 33.1–33.7) in the entire cohort. The incidence rate was 20.3/1000 person-years (95%CI: 17.8–23.1) in the HCVAb D+/R− group and 33.5/1000 person-years (95%CI: 33.2–33.8) in the HCVAb D−/R− group (Figure 2(B), Log-rank test p < 0.001). The HCVAb D+/R− group had a significantly lower risk of CMV infection in the unadjusted analysis (HR = 0.75, 95%CI: 0.65–0.85) compared to the HCVAb D−/R− group, whereas the HCVAb D+/R− group was not exposed to any significant risk of CMV infection in the adjusted analysis (HR = 0.99, 95%CI: 0.87–1.14) compared to the HCVAb D−/R− group (Table 2).

Sub-group analysis or the incidence of CMV infection in the entire cohort

Figure 4 shows the results of the unadjusted and adjusted sub-group analyses. In the unadjusted analysis, only the group with a history of organ transplantation had significant interaction, however, both hazard ratios indicated a lower risk of CMV infection. In the adjusted analysis, only younger age, male sex, a history of any organ transplantation, and non-DCD donors were significantly associated with a lower risk of CMV infection. However, no interaction existed in any of these sub-groups.

Discussion

Contrary to our hypothesis, applying PS matching analysis and adjusted Cox regression analysis in the sensitivity analysis of the entire cohort in this national-registry-based cohort study showed a comparable incidence of first CMV infection between the HCVAb D+/R− and D−/R− groups. Moreover, subgroup analyses yielded similar outcomes. To the best of our knowledge, this is the first large, nationally representative study comparing the incidence of CMV infection between those with a potential for HCV transmission (HCVAb D+/R−) and those without. Altogether, these results provide cautious reassurance regarding the current strategy of accepting donations from HCV-infected deceased donors. However, additional qualifiers need to be considered when interpreting our results.

Previous data indicated potential pathophysiological connections between CMV and HCV virus infection in organ transplant recipients. It has long been known that CMV infection in liver transplant recipients due to HCV cirrhosis is strongly associated with HCV replication and a recurrence of HCV hepatitis and cirrhosis [20,21]. However, it is unknown whether HCV replication would have an effect on the risk of CMV disease in non-liver organ recipients through modification of the immune system. Some studies have not corroborated this...
association and exact mechanisms have not been well
known, but CMV may confer an immunomodulatory
effect via indirect effects and dysregulate specific cyto-
kines against HCV replication [22]. Indeed, HCV infec-
tion per se can also promote conditions that are likely
to reactivate both BK [14] and CMV infections via se-
veral mechanisms [15,16]. Chronic viral infections such as
HCV and HIV alter natural killer (NK) cell subsets and
impair the defensive ability against viral infections,
including CMV [15,16].

When thinking about the association between HCV
transmission and CMV reactivation/infection, we have
to take into consideration whether DAA treatment is
administered, as well as the duration between KT and
the initiation of DAA. Delays with starting DAA might
contribute to massive HCV replication and conse-
quently might be associated with a higher incidence of
CMV infection [4,5]. Our results are strictly applicable to
the pre-DAA era as DAA treatment became available for
kidney transplant recipients only after 2015 [23,24].
Further studies are needed to assess the association
between HCV NAT+ donor transplantation and CMV
viremia risk in kidney and other solid organ trans-
plant recipients.

Although this is a national-registry-based and
adequately powered study, we should acknowledge its
several limitations. First, the definition of exposure

Table 2. Association between HCVAb D+/R− and CMV infec-
tion using the univariate and adjusted Cox proportional models.

| PS matching cohort | CMV infection |
|--------------------|---------------|
| Univariate analysis |               |
| HCVAb D+/R− (vs. HCVAb D−/R−) | 1.00 0.82–1.22 0.994 |
| Entire cohort       |               |
| HCVAb D+/R− (vs. HCVAb D−/R−) | 0.75 0.65–0.85 <0.001 |
| Multivariate analysis |           |
| HCVAb D+/R− (vs. HCVAb D−/R−) | 0.99 0.87–1.14 0.935 |

Multivariate analysis in entire cohort was adjusted by recipient’s age, sex, race, induction therapy, use of calcineurin inhibitor, previous any type of transplantation, delayed graft function, HLA mismatch and donor’s age, sex, race, diabetes, donation after circulation death, cause of death, and CMV risk classification.

Abbreviations: HCVAb: Hepatitis C antibody; HCVAb D+/R−: Kidney transplantation from hepatitis-C-antibody-positive donor into negative recipient; HCVAb D−/R−: Kidney transplantation from hepatitis-C-antibody-negative donor into negative recipient; CMV: cytomegalovirus; HR: hazard ratio; 95%CI: 95% confidence interval; DSA: donor specific antibody.

Figure 3. Association between HCVAb D+/R− and CMV infection in selected sub-group analyzed by Cox regression analysis among PS matching cohort. Abbreviations. PS: propensity score; cPRA: calculated panel-reacted antibody; DCD: donation after cardiac death.
measurement is not precise due to the fact that we could not use the NAT results representing actual HCV infection. About one-third of the HCVAbþ cases [25] are known to not represent real infected patients secondary to false-positive results, self-cleared, or post-HCV treatment status. In this regard, actual results might be interpreted as underestimation in the direction of either harm or benefit. Second, we were only able to use CMV treatment as outcome measurement instead of actual CMV viremia, therefore we likely underestimated the real incidence rate since we could not capture the actual incidence of CMV viremia or disease. To elucidate a proper association between HCV D+/R and CMV infection, one would have to conduct a more specific cohort study using CMV viremia and disease as an outcome measure and HCV NAT results as an exposure. Third, this study was a retrospective cohort study. Ultimately, we could not clarify the causality between HCV transmission and the incidence of CMV infection. Fourth, we have recognized the immortal period until three to six months after KT due to the universal prophylaxis strategy shown in Figure 2.

In conclusion, the incidence of first CMV infection was similar in recipients who received HCVAb D+ and HCVAb D – kidney transplantations. To further confirm these findings on this evolving topic, further studies using more rigorous exposure variables (HCV NAT results) and outcome criteria (CMV viremia and treatment) are strongly encouraged.

**Authors’ contributions**

M.Y. and M.Z.M. participated in research design. M.Y., M.Z.M., and T.F. participated in the writing of the paper. M.Y. and M.Z.M., participated in data analysis. M.Y., O. C., M. T., V. B., A. B., A.A., C.P.K., J. D. E., and M.Z.M. participated in the performance of the research.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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**Figure 4.** Association between HCVAb D+/R and CMV infection in selected sub-group analyzed by unadjusted and adjusted Cox regression analysis among the entire cohort. Abbreviations. PS: propensity score; cPRA: calculated panel-reacted antibody; DCD: donation after cardiac death. Adjusted confounders were recipient’s age, sex, race, induction therapy, use of calcineurin inhibitor, previous organ of transplantation, delayed graft function, HLA mismatch and donor’s age, sex, race, diabetes, donation after circulation death, cause of death, and CMV risk classification.
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