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Association of Donor and Recipient Cytomegalovirus Serostatus on Graft and Patient Survival in Liver Transplant Recipients

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Abstract

Among solid organ transplant recipients, donor cytomegalovirus (CMV) seropositive (D+) and recipient seronegative (R-) status are associated with an increased risk of graft loss and mortality after kidney or lung transplantation. Whether a similar relationship exists among liver transplant recipients (LTR) is unknown. We assessed graft loss and mortality among adult LTRs from January 1, 2010, to March 14, 2020, in the Organ Procurement and Transplantation Network database. We used multivariable mixed Cox proportional hazards regression to analyze the association of donor and recipient CMV serostatus group with graft loss and mortality, with donor seronegative (D-) and recipient seronegative (R-) as the reference group. Among 54,078 LTRs, the proportion of D-R-, D- and recipient seropositive (R+), D+R-, and D+R+ was 13.4%, 22.5%, 22%, and 42%, respectively. By unadjusted Kaplan-Meier survival curve estimates, survival by the end of follow-up was 73.3%, 73.5%, 70.1%, and 69.7%, among the D-R-, D-R+, D+R-, and D+R+ groups, respectively. By multivariable Cox regression, the CMV D+R- serogroup, but not other serogroups, was independently associated with increased risks of graft loss (adjusted hazard ratio [aHR], 1.13; 95% confidence interval [CI], 1.05–1.22) and mortality (aHR, 1.13; 95% CI, 1.05–1.22). The magnitude of the association of the CMV D+R- serostatus group with mortality was similar when the Cox regression analysis was restricted to the first year after transplant and beyond the first year after transplant: aHR, 1.13 (95% CI, 1.01–1.27) and aHR, 1.13 (95% CI, 1.02–1.25), respectively. Even in an era of CMV preventive strategies, CMV D+R- serogroup status remains independently associated with increased graft loss and mortality in adult LTRs. Factors in addition to direct CMV-associated short-term mortality are likely, and studies to define the underlying mechanism(s) are warranted.

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Cytomegalovirus (CMV) disease has been associated with significant morbidity and mortality in solid organ transplant recipients.⁽¹⁻³⁾ CMV seronegative recipients (R-) of an organ transplant from CMV seropositive donors (D+) are at highest risk for developing CMV infection and disease. The underlying mechanism is the impaired ability of CMV R- recipients, who are immunologically naïve to CMV, to develop an effective immune response to primary CMV infection transmitted from the D+ in the context of immunosuppression. This is in contrast to CMV seropositive recipients (R+), who already have some degree of preexisting immunity from prior CMV infection before transplantation and are therefore at lower risk of developing CMV infection and disease compared with the D+R- subgroup.

Despite widespread implementation of CMV preventive strategies, CMV disease continues to occur, most commonly within the first year following transplant.^(2,3) CMV disease directly causes morbidity and mortality.^(1,4,5) In addition to these direct short-term effects of CMV disease, CMV has also been implicated in a broad range of indirect (ie, not directly related to overt CMV disease) biological effects that could contribute to worse clinical outcomes. These indirect effects include increased systemic inflammation that could increase the risk for cardiovascular and thrombotic complications,^(6,7) allograft inflammation that could lead to allograft injury,⁽⁸⁾ and systemic immunosuppression that could predispose to secondary infection.^(6,9,10) These biological effects of CMV can be mediated even during CMV latency or subclinical CMV reactivation (ie, independent of clinically recognized CMV disease) and occur more frequently in D+R- patients.^(6,10) Thus, it has been hypothesized that both the direct and indirect effects of CMV would disproportionately impact D+R- patients and lead to worse overall outcomes in this specific group of transplant recipients, as previously demonstrated among kidney and lung transplant recipients.^(11,12)

There are important differences among organ transplant populations, and whether a similar relationship between donor and recipient CMV serostatus and outcomes exists in liver transplant recipients (LTR) is unknown. Thus, the aim of this study was to analyze the association of donor and recipient CMV serostatus with graft and patient survival using the Organ Procurement and Transplantation Network (OPTN) database in adult LTRs.

Patients and Methods

STUDY POPULATION AND DATA SOURCE

We conducted a retrospective analysis of all US recipients undergoing liver transplantation (LT) from January 1, 2010, to March 14, 2020, who had complete graft and patient survival data in the OPTN database. This time period was selected to encompass the current era of transplant practices including immunosuppression and CMV preventive strategies. Recipients were excluded if they were younger than 18 years old at the time of transplant, were missing recipient and/or donor CMV serostatus, had a prior history of LT, received simultaneous organ transplants, or received a living donor transplant. Patients were categorized into the following 4 CMV serogroups based on the recipient and donor CMV

serostatus: donor seronegative (D-) and R-, D-R+, D+R-, and D+R+. The D-R- group was the reference group for all analyses.

The United Network for Organ Sharing (UNOS), as the contractor for OPTN, supplied these data. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the US government. The University of Washington Human Subjects Division deemed the OPTN database as de-identified and publicly available and thus not human subject data. Therefore, this study was exempt from human subject review. The OPTN released these data on April 1, 2020.

BASELINE RECIPIENT, DONOR, AND TRANSPLANT CHARACTERISTICS

Baseline donor, recipient, and transplant characteristics were defined as those collected at the time of transplant. In addition to these variables, we also used donor and recipient height and weight to calculate the body surface area. The donor's body surface area was divided by the recipient's body surface area to calculate the donor-to-recipient body surface area ratio used in the final analysis.

OUTCOME MEASURES

We evaluated the association between CMV donor and recipient serostatus group with graft loss and all-cause mortality. Graft loss is defined in the OPTN database as either death or retransplant before the last OPTN follow-up date. Date of death or retransplant date was used as the graft loss date. Any subsequent death or retransplant after this initial graft loss date is not included in the analyses.

STATISTICAL ANALYSIS

Continuous variables are given as mean \pm standard deviation (SD) or median and interquartile range (IQR), and categorical variables are presented as count and percentages. Kaplan-Meier survival curve analysis was used to determine the graft and patient survival of the donor and recipient CMV groups. The log-rank test was used to compare survival curves. We used univariable and multivariable mixed Cox proportional hazards models to determine the association between donor and recipient CMV serostatus group with graft loss or death. As the goal of the multivariable analysis was to assess whether CMV serostatus group was independently associated with graft loss and/or recipient survival, we included in our multivariable model potential confounders including recipient, donor, and transplant variables previously described to be associated with graft loss or mortality. These variables include those used to calculate the donor risk index and also donor-to-recipient body surface area ratio, which has been previously associated with long-term graft survival.⁽¹³⁻¹⁹⁾ In the mixed Cox model, we also used the de-identified center code and the year of LT as random effect variables to address any differences in management by donor and recipient CMV serostatus by center or transplant year.

The donor, recipient, and transplant factors used as covariates are described in Supporting Table 1. To minimize the risk of bias by inclusion of a large number of covariates, we assessed for collinearity between CMV donor and recipient serostatus group and other

covariates and also stratified analyses to assess for potential effect modifications. Follow-up time started at the time of LT and extended until time of death or last follow-up date as reported to UNOS, whichever date was earlier. In our primary analyses, follow-up occurred until death or last follow-up as reported to UNOS, whichever date was earlier. In the primary analyses we compared survival by CMV donor and recipient serostatus groups during the entire duration of follow-up.

We also performed 2 separate sensitivity analyses. In the first analysis, we analyzed associations between CMV serostatus group and graft loss or mortality and up to the first year after transplant. The entire study population was included in this sensitivity analysis. In the second sensitivity analysis, we performed a subgroup analysis: we analyzed these associations only for patients who had a minimum 1 year of follow-up time after transplant (ie, patients who died or were lost to follow-up in the first year were excluded from this sensitivity analysis). The baseline characteristics, stratified by follow-up time (< 1 compared with >1 year) are shown in Supporting Table 2. The rationale for these sensitivity analyses was to explore whether the association of CMV D+R- status differed between the first year after transplant, during which CMV disease is most likely to occur, and the subsequent posttransplant time period beyond the first year, when CMV disease is uncommon. Although recipient cause of death (COD) is included in the OPTN database, we excluded the analysis of this outcome for the following reasons: a high proportion of missing values, the lack of independent verification of this outcome, and known challenges in accurately establishing COD.

Results were considered statistically significant if the *P* value was less than 0.05. All analyses were done with R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). The mixed Cox proportional hazards model was performed using the *coxme* 2.2-16 package in R.

Results

BASELINE CHARACTERISTICS OF THE RECIPIENT AND DONOR POPULATION

Among 54,078 adult LTRs, 7251 (13.4%) were D-R-; 12,194 (22.5%) were D-R+; 11,903 (22%) were D+R-; and 22,730 (42%) were D+R+ (Table 1). There were important differences in recipient and donor characteristics according to CMV donor/recipient serostatus groups: in the D-R- and D+R- CMV groups, compared with the D-R+ and D+R+ groups, recipients were younger, more likely to be male and Caucasian, and less likely to have viral hepatitis as the etiology of their liver disease (*P* < 0.001; Table 1). Among the donors, in the CMV D-R- and D-R+ groups, compared with the D+R- and D+R+ groups, donors were younger and had higher rates of donation after circulatory death (DCD; 9% in D-R- and 8.9% in D-R+ versus 5.7% in D+R- and 5.6% in D+R+; *P* < 0.001; Table 2).

ASSOCIATION BETWEEN CMV DONOR AND RECIPIENT SEROSTATUS GROUPS AND GRAFT LOSS

During a mean follow-up of 3.3 ± 2.7 years after transplant, 9703 (17.9%) recipients had graft loss (Table 3). Overall unadjusted graft survival by the end of the study period was 71.6% for D–R–, 71.4% for D–R+, 68.2% for D+R–, and 67.8% for D+R+ (Fig. 1). The observed cumulative incidence rate for graft loss, per 100 person-years, was highest in D+R– (5.98 per 100 person-years [P-Ys]) and D+R+ (5.91 per 100 P-Ys) and lower in D–R+ (5.49 per 100 P-Ys) and D–R– (5.19 per 100 P-Ys). On univariable analysis, both D+R– serogroup status (hazard ratio [HR], 1.15; 95% confidence interval [CI], 1.07–1.24) and D+R+ serostatus (HR, 1.15; 95% CI, 1.08–1.23) compared with the reference group D–R– were significantly associated with graft loss. However, on multivariable analyses, only CMV D+R– (adjusted hazard ratio [aHR], 1.13; 95% CI, 1.05–1.22), but not D+R+ serostatus (aHR, 1.07; 95% CI, 0.99–1.15), remained significantly associated with graft loss.

On sensitivity analyses, the magnitude of the association of CMV D+R– serogroup with graft loss was similar when multivariable regression analysis was restricted to those with follow-up beyond the first year after transplant: aHR, 1.13 (95% CI, 1.02–1.25) for the analysis within 1 year after transplant. The magnitude of the association of CMV D+R– serogroup with graft loss was also similar for the analysis restricted within 1 year post-transplant, however this association was just below the threshold for statistical significance (aHR, 1.09; 95% CI, 0.99–1.21).

ASSOCIATION BETWEEN DONOR AND RECIPIENT CMV SEROSTATUS GROUP AND MORTALITY

During a mean follow-up of 3.31 ± 2.7 years after LT, 9039 (16.7%) of patients had died (Table 3). In unadjusted Kaplan-Meier survival curve estimates, survival by the end of the study period was 73.3% for D–R–, 73.5% for D–R+, 70.1% for D+R–, and 69.7% for D+R+ (Fig. 1). The crude mortality rate was highest in the D+R+ cohort (5.24 per 100 P-Ys) and D+R– (5.24 per 100 P-Ys) versus D–R+ (4.8 per 100 P-Ys) versus D–R– (4.57 per 100 P-Ys). On unadjusted Cox regression analysis, with CMV D–R– as the reference, the D+R– (HR, 1.15; 95% CI, 1.07–1.24 [versus D–R–]) and D+R+ serostatus groups (HR, 1.16; 95% CI, 1.08–1.24) were both associated with an increased risk of mortality. However, on multivariable regression analysis, only CMV D+R– status (aHR, 1.13; 95% CI, 1.05–1.22) remained significantly associated with mortality. D–R+ CMV serostatus was not associated with increased mortality risk on either univariable or multivariable analysis. We also explored, before constructing these regression models, potential interactions and collinearity between CMV serostatus groups and other covariates in our final multivariable regression model including recipient age, etiology of liver disease, and recipient comorbidities; no effect modification of other covariates on the association between CMV serostatus group and risk of graft loss or mortality was found. We did not find evidence for collinearity between CMV donor and recipient serostatus and any other variables.

On sensitivity analyses, the magnitude of the association of CMV D+R– serogroup with mortality was similar when the Cox regression analysis was restricted to the first year after

transplant and beyond the first year after transplant: aHR, 1.13 (95% CI, 1.01–1.27) and aHR, 1.13 (95% CI, 1.02–1.25), respectively.

Discussion

Using rigorous statistical approaches to adjust for potential confounders and data from a large national transplant database with well-validated outcomes, we demonstrated that CMV D+R– serogroup status was independently associated with an increased risk of graft loss and mortality among adult LTRs, even in an era of CMV preventive strategies. The magnitude of the association between CMV D+R– status and patient survival also did not differ between the first year (the time period when the majority of CMV disease occurs) and the subsequent time period after transplant, suggesting that factors beyond short-term CMV disease-associated mortality (eg, “indirect effects of CMV”) are likely to be important in mediating this association. These results confirm and extend the previous demonstration of an independent association of CMV D+R– serostatus with graft and patient survival in kidney and lung transplant recipients to LTRs and have implications for future CMV prevention strategies.

The strength and independence of the association of CMV D+R– serostatus with graft loss and mortality in this study, combined with similar findings in kidney and lung transplant recipient populations, and the presence of biologically plausible mechanisms (direct CMV-associated mortality and indirect effects of CMV), support a possible causal association. However, as for all observational studies, causality cannot be definitively concluded. Leeaphorn and colleagues⁽¹²⁾ created a “paired kidney cohort” using OPTN data and assessed outcomes among CMV serostatus discordant recipients from a single donor (ie, donor seropositive, 1 recipient seronegative/1 recipient seropositive). In their analysis of 9134 kidney transplant recipients, CMV D+R–, compared with D+R+ serostatus, had a 21% higher risk of all-cause mortality and 47% higher risk of infection-associated mortality.⁽¹²⁾ This was despite a more favorable comorbidity profile in CMV D+R– compared with D+R+ serostatus, including a lower rate of diabetes mellitus and a higher proportion of preemptive transplants. A similar association between CMV D+R– serostatus and mortality has also been described in adult LTRs: in the annual report from the International Thoracic Organ Transplant Registry, CMV D+R– was independently associated with a higher risk of 5-year mortality (aHR, 1.23; 95% CI, 1.15–1.31).⁽¹¹⁾ Collectively, these studies demonstrate a consistent body of evidence linking D+R– status with an increased risk for worse long-term graft and patient outcomes across several solid organ transplant populations.

The mechanism(s) underlying the observed association of CMV D+R– status is/are uncertain. In the current era of CMV preventive strategies, CMV disease occurs in ~10% to 30% of D+R– LTRs, and the majority of CMV disease occurs within the first transplant year.^(2,4) The short-term mortality rate for those who develop CMV disease is <10%.^(2,20,21) In addition, in this current study, the magnitude of the association between CMV D+R– serostatus and graft and patient survival was similar in the analysis restricted to the first year after transplant and for the analysis of those who had follow-up beyond 1 year after transplant. If the association had been driven primarily by direct CMV disease-associated short-term mortality, the magnitude of the mortality association for those with follow-up

beyond 1 year would have been anticipated to be lower than that for the analysis restricted to the first posttransplant year (the period when CMV disease was most likely). Both of these lines of evidence suggest that direct CMV-associated mortality is unlikely to be the only mechanism underlying the observed association of CMV D+R– serostatus with worse graft and patient survival. Instead, these results are compatible with the hypothesis that the association is mediated by a combination of direct CMV disease-associated short-term mortality and CMV-associated indirect biological effects, including increased risk of thrombotic events, more severe hepatitis C virus (HCV) recurrence, and graft rejection. (2,6,7,10,12,22,23) Unfortunately, the accuracy and level of detail in the OPTN database preclude such assessments. Future studies to define the mechanism(s) through which CMV D+R– serostatus increases the risk for graft loss and death are warranted. Given the known significantly increased risk for CMV-associated direct and indirect effects conferred by D+R– serostatus, these findings raise the testable hypothesis that improved prevention or control of CMV infection and disease would lead to improved graft and patient survival.

The strengths of the current study include the use of a large database with well-validated and clinically relevant endpoints, a well-defined prestudy hypothesis based on data from other solid organ transplant populations, and rigorous analytic approaches to control for potential confounding. Specifically, we used multivariable modeling to assess whether CMV D+R– serostatus group was independently associated with graft and mortality loss, even after adjusting for differences and potential confounding of these baseline characteristics. We also acknowledge potential limitations. The results of this study do not demonstrate causality but raise a specific and potentially testable hypothesis: better prevention of CMV infection/disease in the D+R– group leads to improved long-term graft and patient survival in LTRs. This is relevant with the advent of new strategies such as CMV vaccines and other immune-based prevention and treatment strategies that hold significant promise for improved control of CMV infection and disease.^(24,25) The OPTN registry data do not include details on CMV prevention methods or CMV disease events, so we specifically chose a study period, between 2010 and 2020, during which all major transplant guidelines recommended CMV prevention and treatment guidelines and were therefore in widespread clinical use. The OPTN data are also not granular with respect to cause of recipient death and had a high proportion of missing data. Thus, we were unable to perform a robust analysis of the association between CMV serostatus and specific cause(s) of death.

In summary, we demonstrated a robust and independent association of CMV D+R– serostatus with increased graft loss and mortality in LTRs that is unlikely to be explained solely by direct CMV disease-associated short-term mortality. We hypothesize that a combination of direct CMV disease-associated short-term mortality and longer term CMV-associated indirect biological effects may underlie the observed association, but future studies to precisely define the mechanism(s) are warranted. New strategies such as CMV vaccination or immune therapies that could improve control of CMV in D+R– patients have the potential to reduce the negative impact of D+R– serostatus on important clinical outcomes in LTRs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

aHR	adjusted hazard ratio
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CIT	cold ischemia time
CMV	cytomegalovirus
CVA	cerebrovascular accident
COD	cause of death
D-	donor seronegative
D+	donor seropositive
DCD	donation after circulatory death
EBV	Epstein-Barr virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
ICU	intensive care unit
IQR	interquartile range
LT	liver transplantation

LTR	liver transplant recipient
MELD	Model for End-Stage Liver Disease
MELD-Na	Model for End-Stage Liver Disease–sodium
NASH	nonalcoholic steatohepatitis
OPTN	Organ Procurement and Transplantation Network
P-Y	person-year
PVT	portal vein thrombosis
R–	recipient seronegative
R+	recipient seropositive
sAg	surface antigen
SD	standard deviation
TIPS	transjugular intrahepatic portosystemic shunt
UNOS	United Network for Organ Sharing

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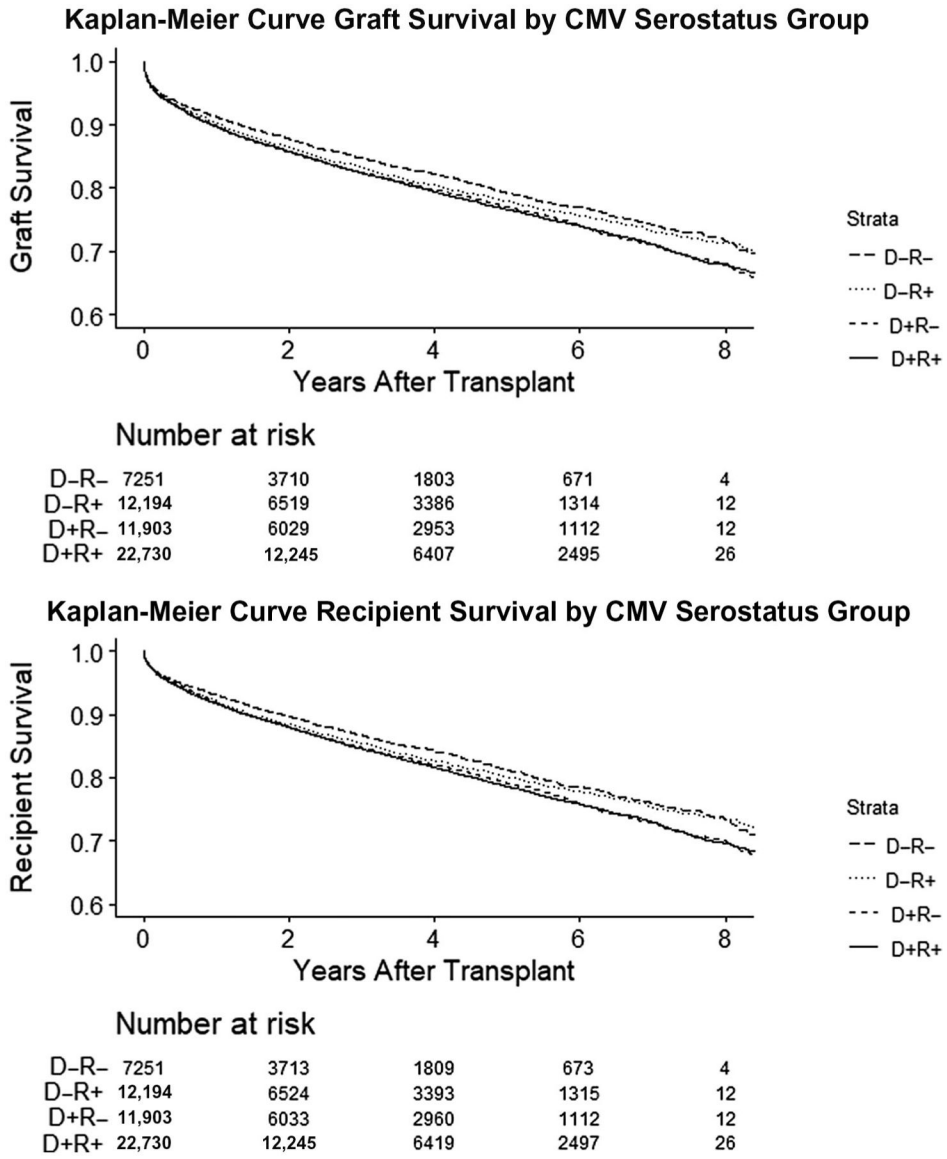


FIG. 1. Unadjusted Kaplan-Meier curve graft or recipient survival stratified by CMV donor and recipient serostatus group. Graft survival was highest in the D-R- (71.6%) group, followed by the D-R+ (71.4%), D+R- (68.2%), and D+R+ (67.8%, $P < 0.001$) groups. Patient survival was highest in the D-R+ (73.5%) group, followed by the D-R- (73.3%), D+R- (70.1%), and D+R+ (69.7%, $P < 0.001$) groups.

TABLE 1.

LTR Characteristics by CMV Donor and Recipient Serostatus

Recipient Baseline Characteristic	CMV Donor and Recipient Serostatus at Time of Transplant				P Value
	D-R- n = 7251	D-R+ n = 12,194	D+R- n = 11,903	D+R+ n = 22,730	
Age, years	57 (50–64)	58 (51–63)	57 (50–62)	58 (51–64)	<0.001
Male	76.1	63	73.9	61.6	<0.001
Race/ethnicity					<0.001
Caucasian	86.3	64.6	84.5	63.1	
Asian	1	6	1	6.2	
Black, non-Hispanic	4.8	10.6	5.3	10.5	
Hispanic	6.9	17.1	8.1	18.3	
Other	1	1.9	1.1	1.9	
Reason for LT					<0.001
Acute liver failure	2.7	3.7	3.3	3.9	
Autoimmune hepatitis	2.2	2.8	2	2.7	
Malignancy	26.1	29.4	26.8	29.3	
Cholestatic liver disease	9.1	7.2	8	6.5	
Cryptogenic	3.9	4.2	4	4.1	
Alcohol	21.6	16	21.7	16	
Metabolic	3.1	2.5	3.2	2.4	
NASH	13.2	11.1	12.9	11.8	
Viral	16.9	22.1	16.5	22.4	
Other	1.1	1	1.5	0.9	
Concurrent HCC	9.4	9.3	8.2	9.3	0.004
Recipient diabetes mellitus	25.9	27.3	26.5	27.8	0.004
Location at time of graft offer					<0.001
Home	70.6	66.1	69.8	66.9	
Hospital	18.8	19.4	18.8	18.3	
ICU	10.6	14.6	11.5	14.8	
Status 1	2.3	2.8	2.6	3	0.01

Recipient Baseline Characteristic	CMV Donor and Recipient Serostatus at Time of Transplant				P Value
	D-R- n = 7251	D-R+ n = 12,194	D-R- n = 11,903	D-R+ n = 22,730	
On life support	6	8.2	6.2	8.8	<0.001
Allocation MELD score	22.1 ± 10.7	22.7 ± 11.3	22.2 ± 10.6	22.6 ± 11.2	0.002
Albumin, g/dL	3.2 ± 0.7	3.2 ± 0.7	3.1 ± 0.7	3.1 ± 0.7	0.10
Encephalopathy					0.03
None	39	37	38	37	
Grade 1-2	50.3	50.9	50.3	51	
Grade 3-4	10.8	12	11.9	11.9	
Ascites					0.4
Absent	26.7	26.6	26.6	26.5	
Slight	43	43	42.7	43.7	
Moderate	30.4	30.4	30.8	29.8	
Dialysis in the week preceding LT	8.7	11.2	9.2	11.3	<0.001
PVT	14	15.3	14.7	14.7	0.13
History of abdominal surgery	49.4	52.3	49.2	52.3	<0.001
History of TIPS	10.3	10.5	11.7	10.8	0.004
HBV sAg positive	2.1	5.3	2.1	5.5	<0.001
HCV-antibody positive	29.6	36.4	28.8	36.3	<0.001
EBV donor and recipient status					<0.001
D-R-	0.9	0.6	0.4	0.3	
D-R+	5.6	5.7	2.3	2.3	
D+R-	10.8	6.7	10.8	6.7	
D+R+	65.8	66.6	65.9	65.2	
Unknown	16.9	20.4	20.6	25.5	

NOTE: Data are expressed as proportion, median (IQR), or mean ± SD.

TABLE 2.

Donor and Transplant Characteristics by CMV Donor and Recipient Serostatus Group

Donor Baseline Characteristic	CMV Donor and Recipient Serostatus at Time of Transplant				P Value
	D-R- n = 7251	D-R+ n = 12,194	D+R- n = 11,903	D+R+ n = 22,730	
Age, years	40 (27–53)	38 (25–52)	45 (30–56)	44 (29–56)	<0.001
Male	68.1	66.7	56.8	54.9	<0.001
Race/ethnicity					<0.001
Caucasian	79.9	79.1	58.6	55.4	
Asian	0.8	1.1	2.8	3.5	
Black, non-Hispanic	11.5	10.9	22.2	21.8	
Hispanic	6.5	7.4	14.3	17.1	
Other	1.4	1.6	2.2	2.2	
Whole donor graft	98.4	98.3	99.1	98.8	<0.001
DCD liver donation	9	8.9	5.7	5.6	<0.001
Donor laboratory results					
AST, units/L	43 (25–83)	43 (25–82)	43 (25–83)	43 (25–85)	0.6
ALT, units/L	38 (22–79)	38 (22–79)	36 (21–72)	35 (21–70)	<0.001
Total bilirubin, mg/dL	0.6 (0.4–1)	0.6 (0.4–1)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	<0.001
COD					<0.001
Anoxia	42.7	41.3	32.8	30	
CVA	29.4	29.2	35	35.8	
Head trauma	25.4	26.7	30	31.9	
Other	2.6	2.9	2.2	2.3	
Donor diabetes mellitus	10.9	9.7	14.5	14.1	<0.001
UNOS sharing area					<0.001
Local	70.3	68	69.6	68.7	
Regional	25.3	28.2	25.1	27	
National	4.3	3.8	5.3	4.3	
Donor hypertension	32.9	30.8	40.4	39.6	<0.001
Donor blood infection	5.9	11%	11%	11%	0.9

Donor Baseline Characteristic	CMV Donor and Recipient Serostatus at Time of Transplant				P Value
	D-R- n = 7251	D-R+ n = 12,194	D+R- n = 11,903	D+R+ n = 22,730	
Donor HCV-antibody positive	5.9	6.4	6.8	6.3	0.08
CIT, hours	6.1 ± 2.3	6.2 ± 2.5	6.1 ± 2.4	6.2 ± 2.5	0.047
ABO blood group match					<0.001
Compatible	5.1	5.6	5.3	5.8	
Identical	93.5	93.1	93.7	93.2	
Incomplete	1.4	1.3	1	1	

NOTE: Data are expressed as proportion, median (IQR), or mean ± SD.

Association of Donor and Recipient CMV Serostatus Group With Overall Graft Loss and Mortality

TABLE 3.

Donor/Recipient CMV Status	Number of Patients	P-Y	Number with Outcome, %	Incidence per 100 P-Ys	HR	aHR*
D-R-	7251	23,109	1200	5.19	1	1
D-R+	12,194	40,966	2251	5.49	1.07 (0.99-1.15)	1.00 (0.93-1.08)
D+R-	11,903	37,731	2257	5.98	1.15 (1.07-1.24)	1.13 (1.05-1.22)
D+R+	24,100	76,817	4540	5.91	1.15 (1.08-1.23)	1.07 (0.99-1.15)
Overall recipient mortality						
D-R-	7251	23,141	1058	4.57	1	1
D-R+	12,194	40,997	1970	4.80	1.06 (0.99-1.15)	1.00 (0.93-1.08)
D+R-	11,903	37,776	1981	5.24	1.15 (1.07-1.24)	1.13 (1.05-1.22)
D+R+	24,100	76,904	4,030	5.24	1.16 (1.08-1.24)	1.07 (0.99-1.15)

* Adjusted for recipient sociodemographic characteristics (age, sex, race/ethnicity), etiology of liver disease, HCC, recipient diabetes mellitus, recipient location at time of LT, recipient life support status, ascites, hepatic encephalopathy, status 1, allocation MELD/MELD-Na score, recipient albumin, recipient receipt of dialysis in the week preceding transplant, recipient HBV sAg status, recipient HCV antibody status, PVT, TIPS, prior abdominal surgery, donor sociodemographic characteristics (age, sex, race/ethnicity), donor-to-recipient body surface area ratio, donor AST, donor ALT, donor blood infection, CIT, geographic allocation status, donor HBV sAg status, donor HCV antibody status, donor COD, type of graft (whole versus partial), donor hypertension, donor diabetes mellitus, EBV donor and recipient serostatus, and ABO donor/recipient match.