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Clinical impact and risk factors for cytomegalovirus infection in deceased donor liver transplantation without prophylaxis: Single center experience

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Background: The study aims to elucidate the relationship between cytomegalovirus (CMV) infection and graft survival, as well as to identify risk factors for CMV infection in deceased donor liver transplantation (DDLT) recipients without prophylaxis.
Methods: A retrospective study was conducted on 465 DDLT recipients at Severance Hospital, South Korea, employing a nested case-control design to explore CMV infection risk factors.
Results: All study population showed CMV antibody seropositivity and did not received CMV prophylaxis. CMV infection was observed in 38.6% of DDLT recipients within the first year. Patients with CMV infection showed reduced graft survival rates within 5 years after matched time points compared to those without infection (57.9% vs. 67.5%, p=0.039), which confirmed in multivariable analysis (hazard ratio 1.44, p=0.047). Risk factor analysis revealed that Child-Pugh class C, donor liver macrovesicular steatosis ≥20%, and elevated pretransplant neutrophil levels were independently associated with an increased risk of CMV infection.
Conclusion: This study confirms that CMV infection post-DDLT is a significant predictor of reduced graft survival. Addressing risk factors of CMV infection through targeted interventions could potentially improve patient management and post-transplant outcomes after DDLT.

Keywords: Liver transplantation; Cytomegalovirus; Deceased donor

INTRODUCTION

Cytomegalovirus (CMV), a prevalent infection in solid organ transplant recipients, notably influences long-term survival and graft viability [1]. Its replication rate is swinging between 46% to 91% in cases lacking prophylactic measures, depending on the serostatus of the donor and recipient before transplantation [2]. Recognized as a pivotal factor for graft loss, CMV's manifestation as disease occurs in 18%–29% of liver transplant (LT) cases [3], marking it as a critical determinant of patient survival [4].

Adhering to international guidelines, the management strategy ranges from antiviral prophylaxis to preemptive therapy, especially for those in the intermediate to high-risk

categories, monitored closely for the initial 3 to 4 months post-transplant [5]. In the country where CMV prophylaxis is not available due to cost and insurance problem, clinical implication of CMV in LT patients could be different from where prophylaxis is routinely applied. Recently, we published the impact of CMV and its risk factors in living donor liver transplantation (LDLT) patients without prophylaxis [6]. This study expands our investigation to the deceased donor liver transplantation (DDLT) population with Korean single center data.

MATERIALS AND METHODS

Study Population

We retrospectively analyzed data of 465 patients who underwent LDLT between July 2005 and December 2022 in Severance Hospital, South Korea. Age <18 years (n=37), were excluded (Fig. 1). For 428 patients who qualified, patient characteristics that had been prospectively gathered in the institutional LT database were obtained. Extra data was gathered from the electronic medical record, including the CMV antibody level before to donation and the CMV polymerase chain reaction (PCR) outcomes. The study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (IRB no. 4-2023-0002). The requirement to obtain informed consent was waived.

Screening and Management for CMV Infection

Our methodical approach included a detailed collection of patient data, both pre-scheduled within our institutional LT database and supplementary details retrieved from electronic medical records, specifically focusing on CMV serology (CMV immunoglobulin [Ig] M and IgG) and the dynamics of viral load through PCR assessments. Given the absence of national insurance coverage for CMV prophylaxis in Korea, our management strategy for CMV pivoted towards a preemptive model. This involved regular CMV screening via PCR, adjusting the frequency from weekly in the first three months to quarterly up to the first year post-transplantation, besides additional tests triggered by febrile episodes among the patients. In defining CMV infection, our criteria were stringent, relying on quantitative PCR markers of over 1,000 copies of CMV or positive results from qualitative PCR tests. Treatment regimens were tailored according to renal function and were continued until the eradication of the virus was confirmed through subsequent PCR tests [5].

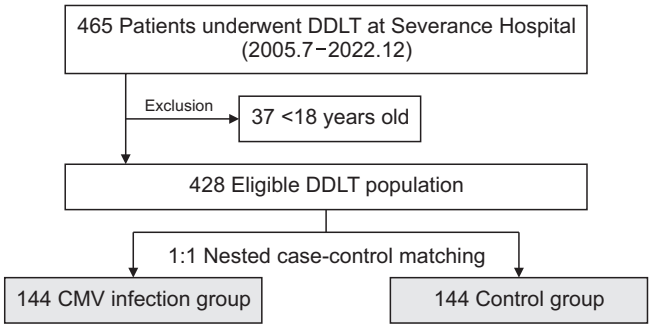

Fig. 1. Study flow for nested case-control study. DDLT, deceased donor liver transplantation; CMV, cytomegalovirus.

Statistical Methods

By nested case-control study design, patients diagnosed with CMV infection were matched to those without at the postoperative day (POD) of CMV infection and corresponding POD in the control patients, ensuring a 1:2 ratio for a comprehensive analysis. This structure allowed for a nuanced exploration of CMV's impact on post-transplant outcomes, employing robust statistical tools for data analysis. We used chi-square tests for categorical variables and either Student's t-test or Wilcoxon rank sum tests for continuous variables, depending on their distribution. Graft survival was defined as patient death or retransplantation and the survival impact of CMV infection post-LDLT was examined through Kaplan-Meier curves and Cox regression models. Advanced risk factor analysis utilized logistic regression. Variables showing a p-value of less than 0.1 in univariable analyses were considered for multivariable models. All analyses were performed using the R statistical package, version 4.2.0 for macOS (http://cran.r-project.org) with the threshold for significance set at $p<0.05$.

RESULTS

CMV Infection Rate in DDLT Patients

At one month, three, six, and twelve months, the incidences of CMV infection in our 465 DDLT population were 29.7%, 35.9%, 37.0%, and 38.9% (Supplementary Fig. 1). Of the 159 patients that experienced CMV, 144 (90.6%) did so within a year. Nineteen days (interquartile range [IQR] 7–28 days) were the median amount of time from DDLT to CMV infection (Supplementary Fig. 2). Every patient had positive CMV antibody results and did not received CMV prophylaxis but preemptive management.

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Baseline Characteristics

The baseline characteristics revealed no significant difference in age (median 53 years for both groups, p=0.420) and gender distribution (35.4% female in both groups, p=0.985) (Table 1). However, underlying liver disease etiologies showed significant disparity, particularly viral causes being less prevalent in the CMV group (43.1% for the CMV group vs. 63.9% for the control group, p=0.002). Our cohort showed that the CMV group had more severe liver disease, such as more Child-Pugh class C (69.4% vs. 45.8%, p<0.001), higher pretransplant model for end-stage liver disease (MELD) score (31 [IQR 20–40] vs. 22 [IQR 12–32], p<0.001). For the operation-related variables, macrovesicular steatosis ≥20% (18.8% vs. 9.9%, p=0.048) and intraoperative continuous renal replacement therapy (26.4% vs. 14.6%, p=0.019) were higher in the CMV group than the control group. Intraoperative transfusion of red blood cell was also higher in the CMV group than the control group (6 packs [IQR, 3–10 packs] vs. 8 packs [IQR, 5–12 packs], p=0.009).

Table 1. Baseline characteristics

Variable	CMV infection (n=144)	Control (n=144)	p-value
Age (yr)	53 (45–61)	53 (44–60)	0.420
Sex (female)	51 (35.4)	51 (35.4)	0.985
BMI (kg/m^2)	24.1 (22.2–27.2)	23.7 (21.8–25.9)	0.085
Hypertension	41 (28.5)	30 (20.8)	0.172
Diabetes mellitus	49 (34.0)	37 (25.7)	0.157
Cardiovascular disease	21 (14.6)	23 (16.0)	0.870
Underlying liver disease			0.002
Viral	62 (43.1)	92 (63.9)	
Alcoholic	46 (31.9)	30 (20.8)	
Others	36 (25.0)	22 (15.3)	
HCC	47 (32.6)	61 (42.4)	0.114
Child-Pugh score			<0.001
A	11 (7.6)	28 (19.4)	
B	33 (22.9)	50 (34.7)	
C	100 (69.4)	66 (45.8)	
Pretransplant MELD	31 (20–40)	22 (12–32)	<0.001
Pretransplant stay			0.064
Out-patient day	42 (29.2)	60 (41.7)	
Ward	70 (48.6)	62 (43.1)	
ICU	32 (22.2)	22 (15.3)	
Refractory ascites	42 (30.7)	44 (31.0)	0.969
Encephalopathy	64 (46.4)	51 (35.9)	0.097
Retransplantation	8 (5.6)	2 (1.4)	0.108
Donor age (yr)	50 (39–59)	48 (36–55)	0.065
Donor sex (female)	49 (34.0)	51 (35.4)	0.901
Donor BMI (kg/m^2)	23.4 (21.6–26.3)	22.8 (21.0–24.8)	0.093
Macrovesicular steatosis ≥20%	27 (18.8)	14 (9.9)	0.048
Operation time (min)	486 (420–591)	510 (433–574)	0.241
Pretransplant dialysis	53 (36.8)	25 (17.4)	<0.001
Intraoperative CRRT	38 (26.4)	21 (14.6)	0.019
Transfusion of RBC (pack)	8 (5–12)	6 (3–10)	0.009

Values are presented as median (interquartile range) or number (%).

BMI, body mass index; CMV, cytomegalovirus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; ICU, intensive care unit; CRRT, continuous renal replacement therapy; RBC, red blood cell.

Blood Testing Before to Transplantation and Immunosuppressions

The CMV group showed higher pretransplant white blood cell (8.0 10^3/μL [IQR, 4.7–11.8 10^3/μL] vs. 5.3 10^3/μL [IQR, 3.4–9.0 10^3/μL], p<0.001), neutrophil (6.0 10^3/μL [IQR, 3.3–9.7 10^3/μL] vs. 3.7 10^3/μL [IQR, 1.8–6.4 10^3/μL], p<0.001), and serum creatinine (1.1 mg/dL [IQR, 0.7–2.1 mg/dL] vs. 0.9 mg/dL [IQR, 0.6–1.3 mg/dL], p=0.021) than those of the control group. Also the CMV group showed lower hemoglobin than that of the control group (9.4 g/dL [IQR, 8.2–11.2 g/dL] vs. 10.5 g/dL [IQR, 8.9–12.4 g/dL], p=0.002) (Table 2). Nearly all patients in both groups (94.4% vs. 93.8%, p=0.985) utilized tacrolimus. All immunosuppressants, including tacrolimus, mycophenolate mofetil, mTOR inhibitors, and steroids, were used similarly by the two groups. Similarities were seen between the groups' mean and maximum tacrolimus trough levels (6.4 ng/dL [IQR, 4.3–8.3 ng/dL] vs. 6.7 ng/dL [IQR, 4.7–9.0 ng/dL], p=0.079 for the mean level and 10.6 ng/dL [IQR, 6.5–16.2 ng/dL] vs. 10.0 ng/dL [IQR, 7.2–15.6 ng/dL], p=0.978 for the maximum level).

Graft Survival and Risk Factors for CMV Infection

Following index POD, the CMV infection group's graft survival (death or re-LT) was substantially lower than the control group's (70.6%, 63.0%, and 57.9% at 1, 3, and 5 years in the CMV infection group vs. 80.3%, 73.3%, and 67.5% at 1, 3, and 5 years in the control group; p=0.039; Fig. 2). CMV infection was an independent risk factor for graft survival in the matched group in uni- and multivariable Cox regression models (hazard ratio [HR] 1.44, p=0.047) (Supplementary Table 1). In uni- and multivariable logistic regression (Table 3, Supplementary Table 2), independent risk factors for CMV infection were Child-Pugh class C (OR 3.28, p=0.003), donor liver macrovasicular steatosis ≥20%

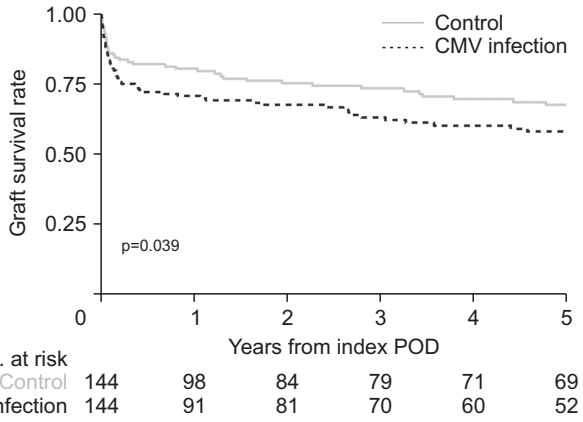

Fig. 2. Kaplan-Meier curves for death or retransplantation after index date. Index date was set at the date of cytomegaloviru (CMV) viremia identification in the CMV viremia group and the corresponding date in the control group. POD, postoperative day.

Table 2. Pretransplant blood tests and use of immunosuppressants

Variable	CMV infection (n=144)	Control (n=144)	p-value
White blood cell (10^3/μL)	8.0 (4.7–11.8)	5.3 (3.4–9.0)	<0.001
Neutrophil (10^3/μL)	6.0 (3.3–9.7)	3.7 (1.8–6.4)	<0.001
Lymphocyte (10^3/μL)	0.7 (0.5–1.1)	0.8 (0.5–1.2)	0.102
Hemoglobin (g/dL)	9.4 (8.2–11.2)	10.5 (8.9–12.4)	0.002
Platelet (10^3/μL)	69 (52–103)	66 (48–85)	0.090
Albumin (g/dL)	3.0 (2.7–3.3)	3.0 (2.8–3.5)	0.362
Glucose (mg/dL)	130.0 (104.5–169.5)	121.5 (97.5–163.5)	0.166
Creatinine (mg/dL)	1.1 (0.7–2.1)	0.9 (0.6–1.3)	0.021
Use of immunosuppressants[a]			
TAC	136 (94.4)	135 (93.8)	0.985
Mycophenolate mofetil	68 (47.2)	64 (44.4)	0.723
mTOR inhibitor	3 (2.1)	3 (2.1)	0.974
Steroid	123 (85.4)	120 (83.3)	0.746
Mean TAC trough level (ng/dL)[b]	6.4 (4.3–8.3)	6.7 (4.7–9.0)	0.079
Maximum TAC trough level (ng/dL)[b]	10.6 (6.5–16.2)	10.0 (7.2–15.6)	0.978

Values are presented as median (interquartile range) or number (%).
CMV, cytomegalovirus; mTOR, mammalian target of rapamycin; TAC, tacrolimus.
[a]Use of each immunosuppressants was defined as prescription at over 50% of post-transplant days before index postoperative day (POD). [b]Values were acquired from liver transplantation to index POD in each patients.

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Table 3. Risk factor analyses for cytomegalovirus infection in deceased donor liver transplantation patients

Variable	Univariable[a]		Multivariable[b]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	1.01 (0.99–1.03)	0.320	1.02 (1.00–1.04)	0.102
BMI (kg/m^2)	1.05 (0.99–1.12)	0.116	1.05 (0.98–1.12)	0.184
Child-Pugh score class				
A	Reference		Reference	
B	1.68 (0.75–3.95)	0.217	1.59 (0.70–3.78)	0.277
C	3.86 (1.84–8.59)	0.001	3.28 (1.53–7.47)	0.003
Macrovesicular steatosis				
<20%	Reference		Reference	
≥20%	2.14 (1.09–4.39)	0.031	2.17 (1.07–4.59)	0.037
Pretransplant neutrophil (per 10^3/μL)	1.07 (1.03–1.13)	0.004	1.06 (1.01–1.11)	0.021

BMI, body mass index; OR, odds ratio; CI, confidence interval.
[a]Full results are provided in Supplementary Table 2. [b]Model was established by stepwise selection.

(OR 2.17, p=0.037), and pretransplant neutrophil (OR 1.06, p=0.021).

DISCUSSION

Without prophylaxis, the incidence of CMV infection within a 12-month period was 38.6% in this single-centric DDLT cohort. We found that CMV infection was independently linked to worse graft survival in the DDLT group using nested case-control approach. Child-Pugh class C, donor liver macrovesicular steatosis ≥20%, and pretransplant neutrophil were risk factors for CMV infection. Risk factors should be included in the surveillance and treatment for CMV following DDLT since CMV infection has a significant impact on the outcome of DDLT.

The risk of infection is often higher with DDLT than with LDLT because it has a higher MELD and more severe comorbidity at the time of LT [7]. While CMV infection in LDLT has been reported to occur in approximately 20% of cases within a year in the preemptive context [6], the DDLT group in this study had a greater incidence of CMV infection than LDLT, with 38.9% of cases occurring within a year. Previous studies showed CMV infection was related with patient mortality in Korean LT patients with seropositivity of CMV antibody [4]. However, about 75% of study population was LDLT in that study, so clinical implication of CMV infection in DDLT patients needs more investigation in Korean LT population where prophylaxis is not available. Also, DDLT generally showed higher graft loss than LDLT in Korea because deceased donor liver could be allocated in very high MELD patients due to severe organ shortage [8]. This inevitably results in immortal time bias because CMV infection could occur in patient who survived longer than in those who died earlier. This study showed that CMV was identified as an independent risk factor for long-term graft outcomes after DDLT only population using nested case-control design.

In clinical practice, the diagnosis of CMV infection leverages a spectrum of methodologies, reflecting the complexity of the virus's presentation. PCR assays are paramount for quantifying viral load, offering high sensitivity and specificity [9]. However, the reliance on PCR and other molecular techniques, such as antigenemia assays and culture methods, introduces the risk of false positives, necessitating careful interpretation of results. This is particularly critical in the DDLT setting, where the immunosuppressed status of patients can alter viral kinetics and immune response. Additionally, the prevalence of coinfections with other opportunistic pathogens complicates the clinical picture, demanding a comprehensive diagnostic approach [10,11]. These coinfections can mask or mimic CMV symptoms, leading to diagnostic challenges. Thus, a nuanced understanding of diagnostic tools, alongside an awareness of the potential for false positives and coinfections, is essential for managing CMV in the post-DDLT population, ensuring accurate diagnosis and tailored treatment plans.

In LT recipients who are D+/R− and/or R+, the worldwide consensus guidelines state that universal prophylaxis and a proactive strategy involving once weekly CMV surveillance for three to four months are equivalent means of preventing CMV illness and graft failure [5]. Universal prophylaxis reduces rejection and opportunistic infections, but early

CMV infection is more likely in the proactive method [12-14].

The cost of the CMV medication is significant for prophylaxis, but the cost of surveillance is significant for preventive care in terms of cost-effectiveness, one of the key criteria. In South Korea, where national insurance covers the majority of LT treatments, prophylactic use of CMV drugs is not reimbursed by insurance; however, insurance does fund surveillance, therefore most patients are protected against CMV illness by taking preventative measures [4]. In a setting like South Korea, where LDLT is more prevalent than DDLT, it's important to think about the right insurance coverage and CMV prevention tactics.

As there are few R−/D+ patients and a high pretransplant CMV seropositivity in South Korea and other Asian nations, the majority of recipients are seropositive, meaning that there is a low risk of CMV infection from seropositive donors [15,16]. No patients in the nested case-control matched population in this investigation displayed CMV seronegativity. As a result, in South Korea, it's critical to research recipient or donor risk factors in addition to CMV Ab status, and customized CMV care will be crucial. Significant clinical insight into the risk factors of CMV infection may be gained from this investigation.

In this study, among the variables Child-Pugh class C, donor liver macrovasicular steatosis ≥20%, and pretransplant neutrophil were identified as independent risk factors of CMV infection after DDLT. The Child-Pugh score, which assesses liver disease severity, may influence the risk of CMV infection post-deceased DDLT [17]. Higher scores, indicating more severe liver dysfunction, could predispose patients to infections due to their compromised immune status, exacerbated by immunosuppressive therapies post-transplant. However, the relationship is multifaceted, with factors like immunosuppression level, donor and recipient CMV serostatus, and prophylactic antiviral use also playing crucial roles [18]. Understanding this complex interplay is vital for developing targeted CMV prevention strategies after DDLT in patients with progressed liver disease.

The presence of steatosis in donor livers can lead to prolonged graft recovery times and a higher likelihood of postoperative complications, which may indirectly impact the recipient's immune response and increase the risk of infections such as CMV [19]. Studies suggest that the inflammatory milieu associated with steatotic livers might exacerbate the recipient's vulnerability to infectious agents post-transplant [20]. Moreover, the management of recipients with steatotic liver grafts often requires adjustments in immunosuppressive therapy, potentially influencing CMV infection rates [21]. Despite these associations, direct evidence linking donor liver steatosis to CMV infection risk remains sparse, underscoring the need for further research to clarify this relationship and its implications for transplant outcomes.

There are various restrictions on this study. Initially, this was a retrospective analysis of a single center study. Secondly, there was heterogeneity in the CMV PCR test method used for CMV infection screening. Finally, there might be lead time bias in the nested case-control design given that the CMV PCR interval was 1 to 4 weeks.

In conclusion, among the DDLT population who did not receive prophylaxis but managed with preemptive setting for CMV, CMV infection was an independent risk factor for graft survival. The monitoring and treatment of CMV infection during LDLT should take into account risk factors for the infection, such as Child-Pugh class C, macrovasicular steatosis of the donor liver, and pretransplant neutrophil.

SUPPLEMENTARY MATERIAL

Supplementary data related to this article can be found online at https://doi.org/10.52604/alt.24.0001.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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AUTHORS' CONTRIBUTIONS

Conceptualization: DGK. Data curation: DGK, EKM, JGL, DJJ. Formal analysis: DGK, MSK. Investigation: DGK, JGL, DJJ, MSK. Methodology: DGK, EKM, MSK. Project administration: DGK, DJJ. Resources: DGK, JGL. Software: DGK. Supervision: DGK, MSK. Validation: DGK. Visualization: DGK. Writing – original draft: DGK. Writing – review & editing: DGK.

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