Epidemiology and Long-term Outcomes of Cytomegalovirus (CMV) in Pediatric Liver Transplant Recipients (PLTR) at Texas Children's Hospital (TCH)

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Abstract

Background: Despite widespread use of prevention strategies, CMV DNAemia remains common in PLTR. Contemporary data, however, is limited. We sought to determine the frequency of, risk factors for, and long-term outcomes of CMV DNAemia in a large, single center cohort of PLTR.

Methods: A retrospective cohort study of PLTR < 22 yrs of age transplanted from 2011-2018 was completed. Per protocol, CMV prophylaxis with ganciclovir/valganciclovir was universally implemented; high risk (HR)(D+/R-) and intermediate risk (IR)(R+) patients received 6 months while low risk (LR)(D-/R-) patients received 3 months. Primary outcomes included any CMV DNAemia, CMV DNAemia >1000 IU/mL and long-term outcomes including rejection, graft failure, hepatic steatosis (HS), and de novo autoimmune hepatitis (AIH). Associations with CMV DNAemia were measured using Fisher exact and multivariate regression. Survival analysis, time to CMV infection, and time to PLTR long term outcomes were assessed using Kaplan-Meier plots.

Results: Among 258 PLTR, 76 (29%) had quantifiable CMV DNAemia; 35 (14%) had CMV DNAemia >1000 IU/mL. 46 (18%) developed CMV DNAemia while on prophylaxis. Median time (range) to CMV DNAemia was 162 days (5-2213). HR (OR 4.13; 95% CI 1.74-9.476, p<0.01) status was associated with CMV DNAemia and time to CMV DNAemia. CMV DNAemia was not associated with age at transplantation or cold ischemic time.

Seven PLTR (3%) developed CMV syndrome (4 HR, 3 IR), the median peak (range) DNAemia was 2133 IU/mL (202-58000) for these patients. Two PLTR (1%) developed CMV tissue invasive disease, one with gastritis (HR) and one with hepatitis (HR). The median peak (range) DNAemia was 10379 IU/mL (9445-24172) for these two patients.

CMV DNAemia was not associated with rejection (53% vs. 44%, p=0.35) or HS (7% vs. 15%, p=0.16). CMV DNAemia appeared to be protective for graft failure (0% vs. 15%, p<0.01) and AIH (1% vs. 12%, p= 0.04). CMV DNAemia was associated with a longer time to rejection (p=0.03) and graft failure (p=0.02). Time to development of HS and AIH were not associated with CMV DNAemia (Figure 2). Finally, there was no difference in survival during the study follow-up period (1 – 9 yrs) for PLTR with vs. without CMV DNAemia (p=0.26).

Conclusions: This large cohort of PLTR demonstrates high rates of CMV DNAemia but low rates of CMV disease. HR status remains associated with CMV DNAemia. CMV DNAemia did not increase the risk of long-term adverse outcomes such as rejection, graft failure, HS, and AIH.

Background

- CMV DNAemia occurs in up to 23% of SOT recipients in the first year post transplant
- Risk factors for developing CMV DNAemia and disease include high risk CMV status (D+/R-), young age at time of transplant and prolonged ischemic time
- CMV DNAemia has negative direct effects on SOT recipients including CMV syndrome and CMV tissue invasive disease, as well as indirect effects including chronic allograft rejection, decline in graft function/graft loss, opportunistic infections, and complications such as hepatic steatosis (HS) and de novo autoimmune hepatitis (AIH)
- Limited data regarding CMV DNAemia in pediatric liver transplant recipients (PLTR) exists

- We hypothesize that 20-25% percent of PLTR at Texas Children's Hospital will develop CMV DNAemia
- We hypothesize that PLTR who receive immunosuppressive induction therapy, who have high risk CMV status (D+/R-) or are <1 year of age at time of transplant will have a higher incidence of CMV DNAemia
- We hypothesize that PLTR who develop CMV DNAemia will have a higher rate of adverse outcomes including all cause mortality, graft loss, rejection, HS, and AIH

Objectives/Methods

- Retrospective review of first time liver transplant recipients < 22 years of age at TCH from January 1, 2011 to December 31, 2018 to determine the epidemiology and variables which may impact rates of CMV infection and disease
- Primary Outcomes: Any CMV DNAemia, CMV DNAemia >1,000, and long-term outcomes including rejection, graft failure, HS, and AIH
- Post-transplant universal prophylaxis was given per protocol as described below:

Organ	Serostatus	Risk Status	Prophylaxis
Liver	D+/R- R+ D-/R-	High Intermediate Low	6 mo of ganciclovir/valganciclovir 6 mo of ganciclovir/valganciclovir 3 mo of ganciclovir/valganciclovir

- Statistics:
  - Demographic and transplantation characteristics were compared using chi-square or Fisher exact tests for categorical data.
  - Associations with CMV DNAemia were measured using Fisher exact and multivariate logistic regression.
  - Survival analysis, time to CMV infection, and time to PLTR long-term outcomes were assessed using Kaplan-Meier calculations.
  - All statistical analyses were completed with SAS v 9.4.

Results

Table 1: Patient Demographics and Clinical Characteristics

	No CMV DNAemia N= 183	Any CMV DNAemia N= 76	P-value
Sex (female), n (%)	95 (51.9%)	41 (53.9)	0.79
Race, n (%)			
African American	23 (12.6%)	11 (14.5%)	
Asian	6 (3.3%)	3 (3.9%)	0.96
Hispanic	83 (45.3%)	36 (47.4%)	
White	65 (35.5%)	24 (31.6%)	
Unknown/Other	6 (3.3%)	2 (2.6%)	
CMV risk status, n (%)			
High risk (D+/R-)	53 (29.0%)	33 (43.4%)	<0.01
Intermediate risk (R+)	77 (42.0%)	35 (46.1%)	
Low risk (D-/R-)	53 (29.0%)	8 (10.5%)	
EBV recipient serology, n (%)			
Positive	69 (37.7%)	29 (38.2%)	0.13
Negative	96 (52.5%)	33 (43.3%)	
Unkown	18 (9.8%)	14 (18.5%)	
Age at Transplant, n (%)			
<1 year	44 (24.1%)	15 (19.7%)	
1-5 years	71 (38.8%)	34 (44.7%)	0.78
6-10 years	32 (17.5%)	10 (13.3%)	
11-17 years	31 (16.9%)	15 (19.7%)	
18+ years	5 (2.7%)	2 (2.6%)	
Year transplanted, n(%)			
2011-2014	99 (54.1%)	38 (50%)	0.56
2015-2018	84 (45.9%)	38 (50%)	
Mean ischemic time in hours (SD)	6.42 (2.48)	6.34 (2.62)	0.8
Rejection prior to CMV, n(%)	59 (32.2%)	20 (26.3%)	0.38

Figure 1: CMV DNAemia and disease in pediatric liver transplant recipients at TCH, 2011-2018

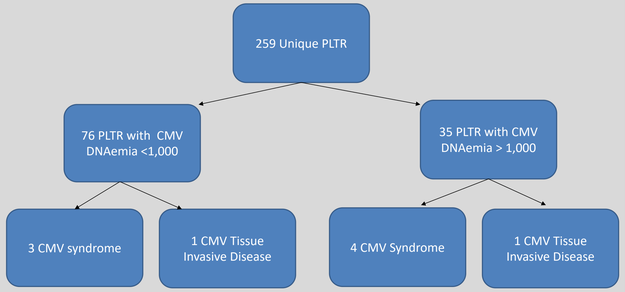
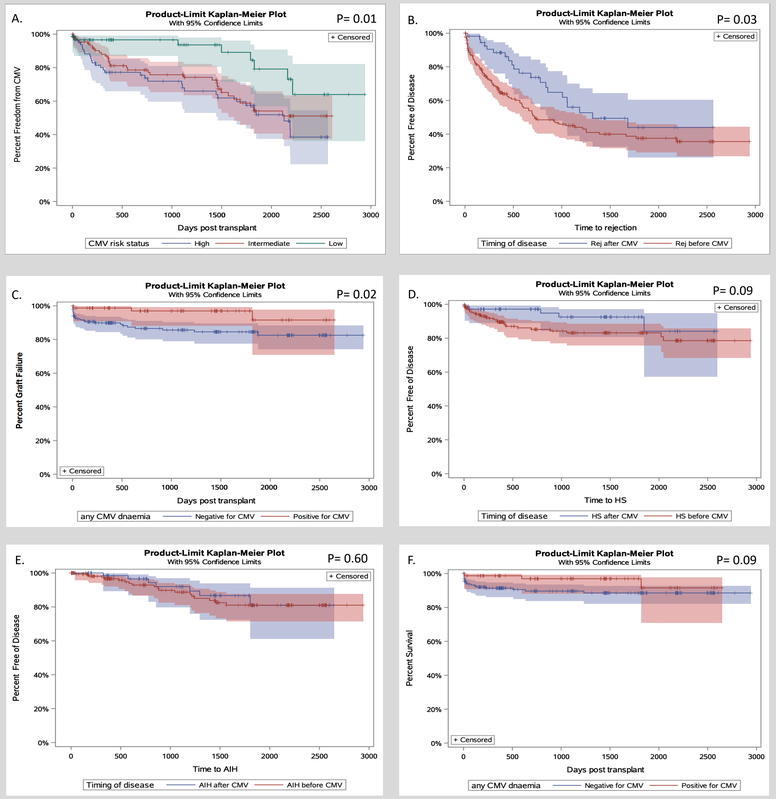


Figure 2: Time to CMV DNAemia in relation to time post transplant and other outcomes



A. Proportion of PLTR free from CMV DNAemia by risk status. **B.** Proportion of PTLR free from rejection with and without CMV DNAemia.
C. Proportion of PTLR free from graft failure with and without CMV DNAemia. **D.** Proportion of PTLR free from with and without CMV DNAemia.
E. Proportion of PTLR free from de novo AIH with and without CMV DNAemia. **F.** Survival in PTLR with and without CMV DNAemia

Table 2: Associations with CMV DNAemia

Risk Status	Odds Ratio	95% CI
High Risk	4.13	1.7 – 9.8
Intermediate Risk	3.05	1.31 – 7.10
Low Risk	1	(ref)

* Donor age, recipient age, race, EBV serostatus, and ischemic time were not associated with CMV DNAemia

Table 3: PTLR Long- Term Outcomes

	CMV prior to rejection N= 38	No CMV or CMV after rejection N= 221	P-value
Rejection N=117	20 (53%)	97 (44%)	0.35
	CMV prior to GF N= 73	**No CMV or CMV after GF N= 186**	**P-value**
Graft Failure N=28	0 (0%)	28 (15%)	<0.01
	CMV prior to HS N= 71	**No CMV or CMV after HS N= 188**	**P-value**
Hepatic Steatosis N= 33	5 (7%)	28 (15%)	0.16
	CMV prior to AIH N= 68	**No CMV or CMV after AIH N= 191**	**P-value**
De Novo AIH N= 26	1 (1%)	23 (12%)	0.04
	CMV prior to mortality N= 76	**No CMV N= 183**	**P-value**
Mortality N= 21	18 (10%)	3 (4%)	0.26

Conclusions

- High risk CMV status is associated with CMV DNAemia
- CMV DNAemia occurs post prophylaxis in the majority of patients
- CMV disease is associated with higher plasma levels than asymptomatic DNAemia
- CMV DNAemia was not associated with an increased rate of rejection, de novo autoimmune hepatitis, hepatic steatosis nor mortality in the liver recipient cohort
- CMV DNAemia and disease continues to occur despite prophylaxis regimens

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