Incidence and severity of cytomegalovirus infection in seropositive heart transplant recipients

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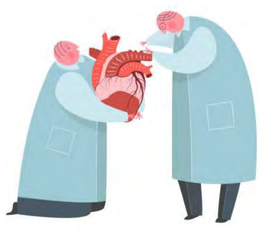
Background

- Cytomegalovirus (CMV) infection contributes to morbidity and mortality in heart transplant recipients (HTRs)
- Donor positive, recipient seronegative (D+/R-) patients are at highest risk and routinely receive CMV prophylaxis
- The burden of CMV reactivation in recipient seropositive (R+) HTRs is less clear, with preventative recommendations mostly extrapolated from other solid organ transplant groups

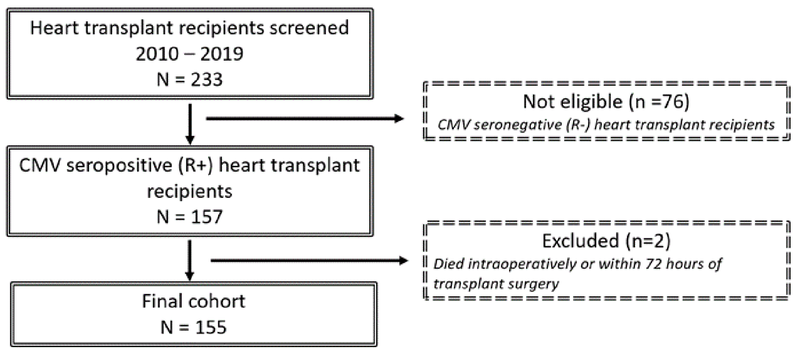
Aim: To define the incidence, risk factors for and severity of CMV infection in R+ HTR and understand its impact on post-transplant outcomes.



Methods

- **Study design:** Retrospective cohort study at Alfred Health, Melbourne, Australia.
- **Inclusion criteria:** CMV R+ heart transplant recipients, 2010-2019
- **Exclusion criterion:** Death <72hrs post-transplant
- **Immunosuppression:** tacrolimus, mycophenolate and prednisone, with basiliximab induction in patients at risk for renal dysfunction
- **CMV prevention:** Prophylaxis not routine in R+ unless high risk (e.g. thymoglobulin induction or acute rejection). Viral load testing performed when clinically indicated
- **Primary outcome:** CMV infection within 1 year of transplant
- **Analysis:** Univariate and multivariate hazard ratios (HR) calculated using Cox models

***Figure 1**: Number and flow of study participants.*



Results

- 155 CMV R+ patients were included (median age 53 years, 72% male, 56% D+/R+, 68% basiliximab & 8% thymoglobulin induction), *Figure 1*
- 35 (23%) received valganciclovir prophylaxis
- 27/155 (17%) developed CMV infection, median onset 67 days (IQR 45, 123). Median viral load was 1250 IU/mL (IQR 221-6539) & 22/27 (82%) had end-organ disease, 14 (52%) gastrointestinal
- CMV infection was associated with a longer length of stay (32 vs. 20 days, p=0.009) & higher rates of ICU readmission (26% vs. 9%, p=0.01)
- Valganciclovir prophylaxis was protective against CMV infection (4% vs 27%, p=0.033), *Figure 2*, even though patients receiving prophylaxis were more likely to have had thymoglobulin induction (31% vs 2%, p<0.001)
- Significantly higher mortality was observed in patients who developed CMV infection (HR 4.74, 95% CI 1.92-11.7, p=0.001)

***Figure 2**. Prophylaxis use and subsequent CMV infection*

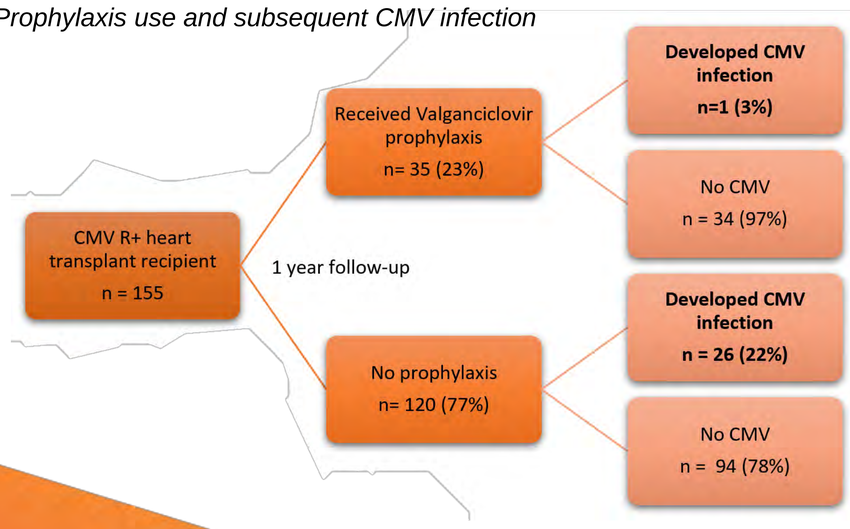


***Table 1:** Characteristics of patients with CMV infection compared to those without (n=155). P-values reflect univariate Cox analyses.*

Characteristic	No CMV infection (n=128)	CMV infection (n=27)	p-value
Age at transplant, median, IQR	53, 42-60	55, 43-61	0.521
Male sex, no. (%)	94 (73%)	17 (63%)	0.267
Year of transplant	2015, 2012-2018	2015, 2012-2017	0.889
Cardiac disease			
Non-ischemic cardiomyopathy	81 (63%)	14 (52%)	
Ischemic cardiomyopathy	33 (26%)	10 (37%)	0.218
Other	14(11%)	3 (11%)	0.778
Pre-transplant diabetes	19 (15%)	2 (7%)	0.400
Previous transplant	6 (5%)	3 (11%)	0.142
Recipient EBV status positive	126 (98%)	26 (96%)	0.394
Pre-transplant ventricular assist device	63 (49%)	13 (48%)	0.837
Ischemic time (minutes)	183, 155-238	211, 147-254	0.981
Donor CMV seropositive	69 (54%)	17 (63%)	0.326
Cardiac bypass time (minutes, n=152)	143, 118-192	138, 115-170	0.418
>1 organ transplanted	3 (2%)	1 (4%)	0.446
Transplant related return to surgery	32 (25%)	11 (41%)	0.061
Post-operative ECMO	**26 (20%)**	**9 (33%)**	**0.045**
Days intubated post-transplant	3, 1-6	4, 1-6	0.506
Days in intensive care	7, 5-11	8, 5-13	0.143
Readmission to ICU	**11 (9%)**	**7 (26%)**	**0.005**
Days hospitalized	**20, 16-28**	**32, 19-54**	**0.011**
Induction immunosuppression			
Basiliximab	88 (69%)	17 (63%)	0.606
Thymoglobulin	12 (9%)	1 (4%)	0.364
Valganciclovir prophylaxis	**34 (27%)**	**1 (4%)**	**0.033**
Steroid-treated rejection	85 (66%)	18 (67%)	0.876
Antilymphocyte agent for rejection	22 (17%)	4 (15%)	0.736
Death within 1 year of transplant	**10 (8%)**	**9 (33%)**	**<0.001**

***Figure 3:** Unadjusted Kaplan-Meier estimates of freedom from (a) CMV infection, stratified by use of valganciclovir prophylaxis and (b) mortality, stratified by CMV infection (n=155).*

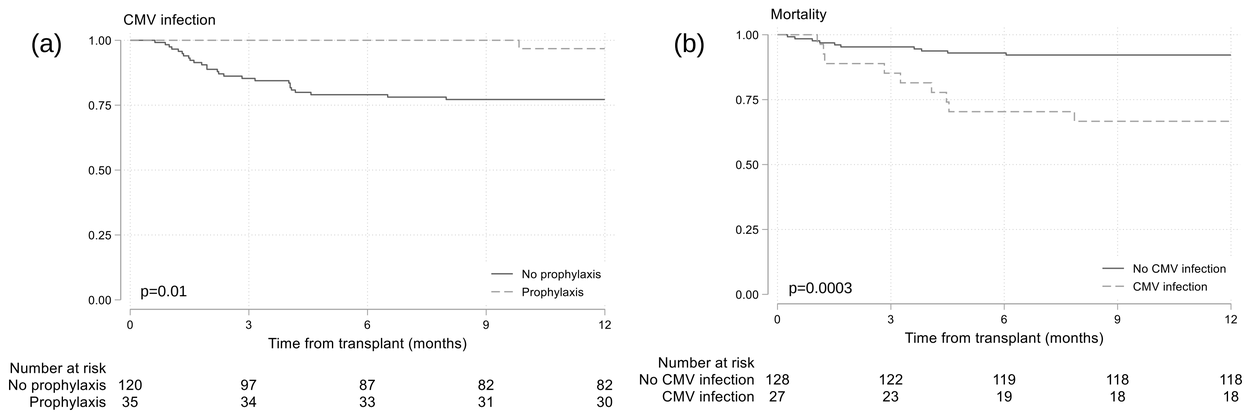


***Table 2:** Univariate and multivariate hazard ratios (HR) for CMV infection.*

Variable	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Readmission to ICU	3.46 (1.46-8.20)	0.005	1.88 (0.57-6.20)	0.302
Days hospitalized	1.01 (1.00-1.02)	0.011	1.02 (1.00-1.03)	0.024
Thymoglobulin induction	0.40 (0.05-2.92)	0.364	1.12 (0.08-15.8)	0.934
Valganciclovir prophylaxis	0.11 (0.02-0.84)	0.033	0.05 (0.003-0.76)	0.031

Conclusions

- Despite prior immunity to CMV, 17% of R+ HTRs developed clinically significant CMV infection
- This was associated with worse post-transplant outcomes and higher mortality
- Patients who received valganciclovir prophylaxis were less likely to develop CMV infection, even though they were higher risk
- These findings support the use of CMV preventative strategies, such as prophylaxis, in all CMV R+ HTR. Prophylaxis with valganciclovir has now been implemented at our center

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