Impact of CMV Infection on Longitudinal AlloMap & AlloSure Levels in Heart Transplant Recipients

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Disclosures

- Advisory board for CareDx
- Analysis provided by CareDx

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Introduction

- The post-operative management of a HT recipient relies on appropriate immunosuppression that balances the risk of rejection with the risk of infection
- Immunosuppressed transplant recipients are susceptible to CMV-associated complications either from primary infection or viral reactivation, which are both associated with significant morbidity (including ACR) and occasional mortality

Testing

- AlloMap: Gene-expression profiling score derived from quantitative measurements of intracellular mRNA levels in peripheral blood mononuclear cells

  - Negative predictive value for acute cellular rejection (ACR) in low-risk patients

- AlloSure: Donor-derived cell-free DNA test to screen low-risk patients for both ACR and antibody mediated rejection (AMR)

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CMV Infection

CMV viremia is defined as presence of CMV replication in the absence of symptoms

CMV disease is further subclassified :

- CMV syndrome is defined as CMV viremia accompanied by clinical signs and symptoms such as fever and/or malaise, leukopenia, thrombocytopenia
- Tissue-invasive CMV disease is characterized by additional tissue invasiveness (e.g. gastrointestinal disease, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, retinitis, etc.).

Objective

- Analysis of the Outcomes AlloMap Registry (OAR) and D-OAR database to study the relationship between CMV infection, longitudinal AlloMap and AlloSure levels

Methods

- 26 US clinical sites
- Outcomes data include rejection (ACR and AMR), allograft function, major infections (including CMV), hospitalizations, immunosuppression regimen, cardiac allograft vasculopathy, malignancy and death
- Multiorgan transplant recipients were excluded

- Included patients who had documented absence or presence of CMV infection at the time of AlloMap score results

- Regular surveillance schedule for testing was determined by each participating center's standard of care

- The registry also did not collect individual prophylaxis and treatment strategies for CMV infection at each participating site.

Cohorts

- Patients were included in the ‘CMV group’ if they were documented as having CMV infection (viremia, syndrome or disease) by the study site and had an AlloMap score reported at the time of the infection

- Patients in the ‘no CMV group’ did not have diagnosis of CMV infection reported at any time, but had at least one AlloMap score recorded

Results

- Data from 14,985 samples collected from 2,288 adult HT recipients were included in the analysis.

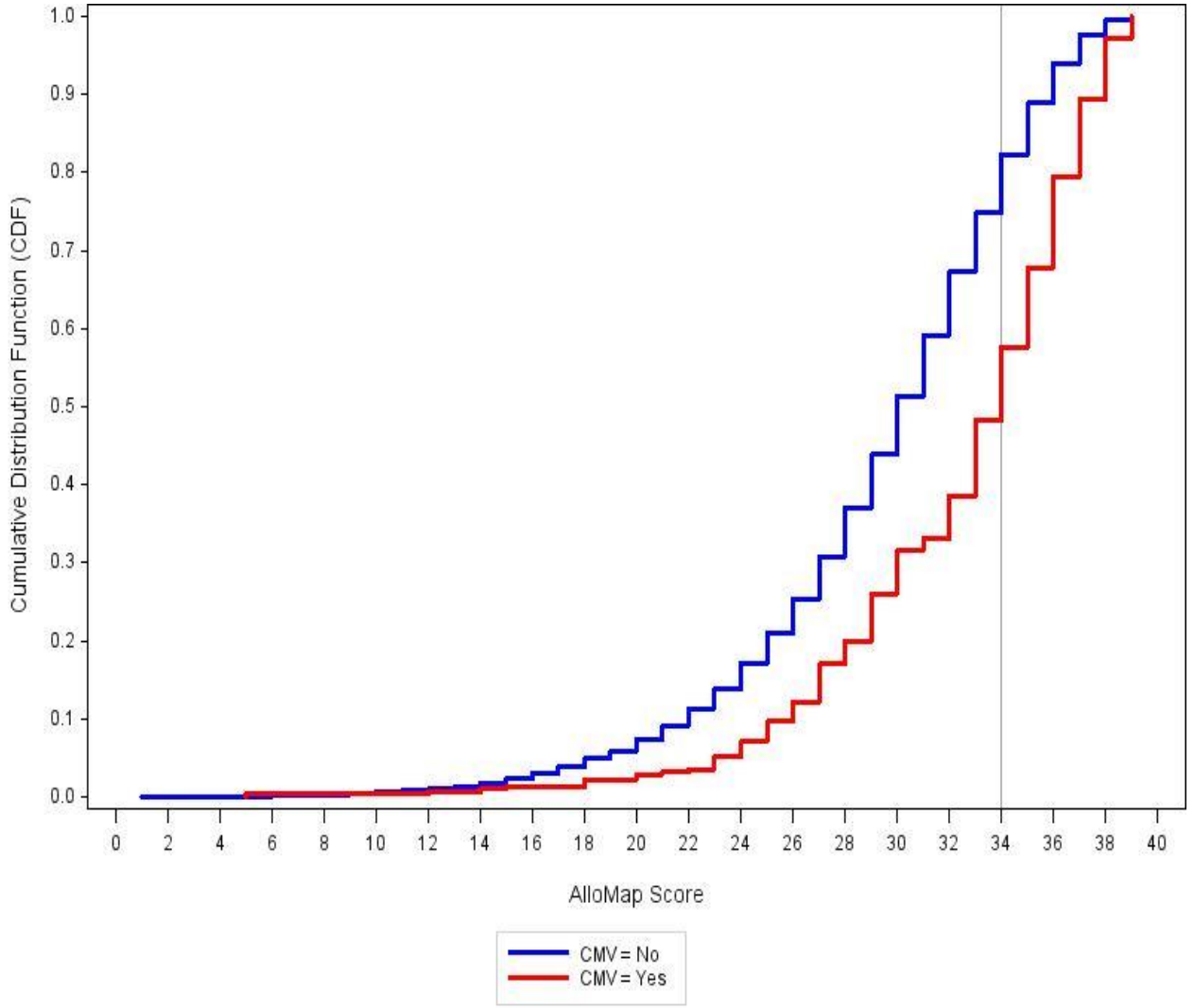
Gender (N=2288)	**Male**	**1714 (75%)**
	Female	574 (25%)
Race (N=2288)	Caucasian	1630 (71%)
	Black	411 (18%)
	Hispanic	137 (6%)
	Asian	65 (3%)
	Other	45 (2%)
Pre-transplant Diagnosis (N=2287)	Non-Ischemic Cardiomyopathy	1098 (48%)
	Ischemic Cardiomyopathy	746 (33%)
	Other	306 (13%)
	Congenital	79 (3%)
	Dual Organ	32 (1%)
	Re-transplant	26 (1%)
CMV Serology (donor/recipient) (N=2167)	Positive/Positive	783 (36%)
	Positive/Negative	542 (25%)
	Negative/Negative	413 (19%)
	Negative/Positive	429 (20%)
Pre-transplant Mechanical Circulatory Support (N=2216)	None	1034 (47%)
	Left Ventricular Assist Device	976 (44%)
	Temporary Circulatory Support	168 (8%)
	Total Artificial Heart	38 (2%)

Results

- Of the 2,288 patients enrolled in the OAR study, 218 (10%) patients had at least one CMV infection noted during their post-surveillance visits
- The median time from HT to diagnosis of CMV infection was 277 days (range 61-9303; IQR 167 - 373)
- AlloSure results were available for 776 samples, of which 18 were drawn at the time of CMV infection

Results

- Samples obtained at the time of CMV infection (n=311) had a median GEP score of 34 (range 29-36) which was significantly higher than the GEP score from samples obtained in the absence of CMV infection (n= 14,674; median GEP score 30, range 26-34) (p<0.0001)



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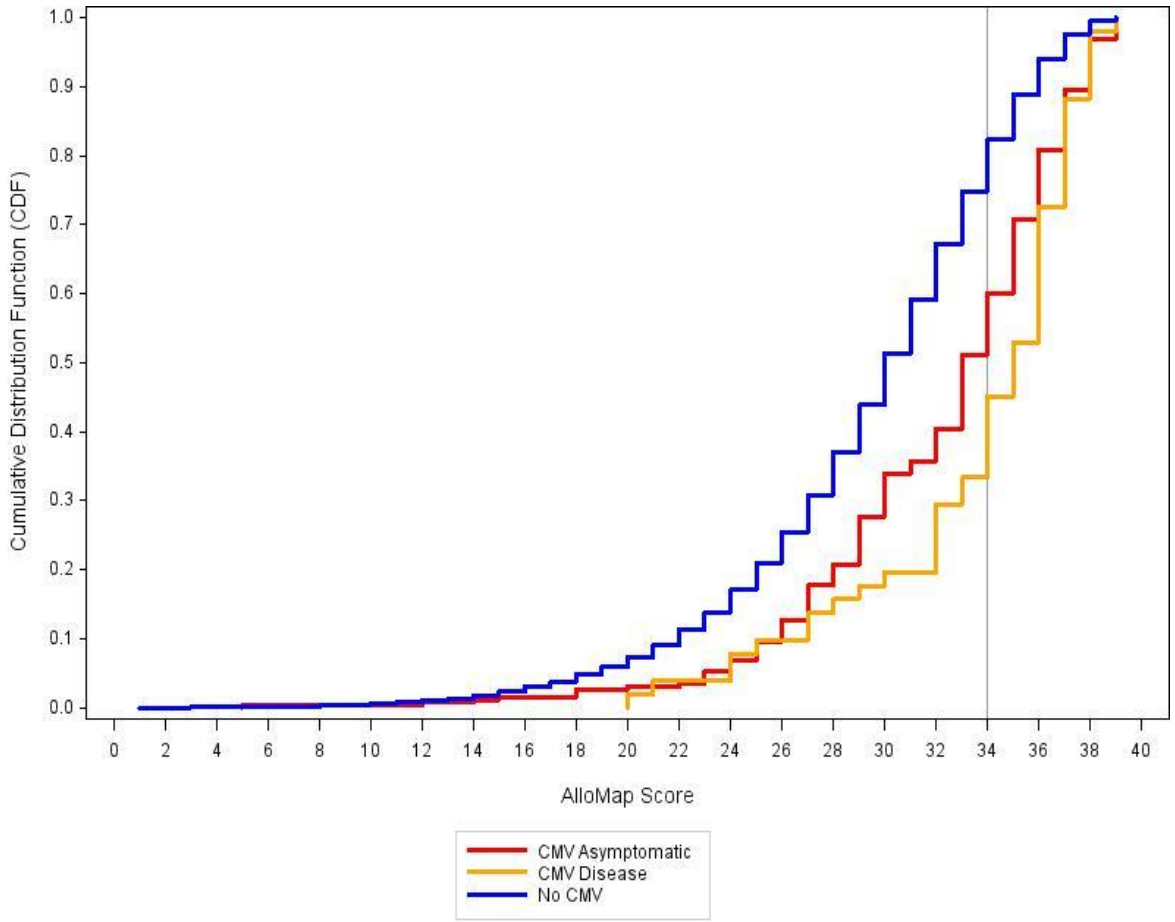
- 311 CMV +
- Median GEP score in asymptomatic viremia (n=260) was GEP score 33, and in those with CMV disease (n=51) was 35, which were both significantly higher than scores in no CMV ($p<0.0001$)



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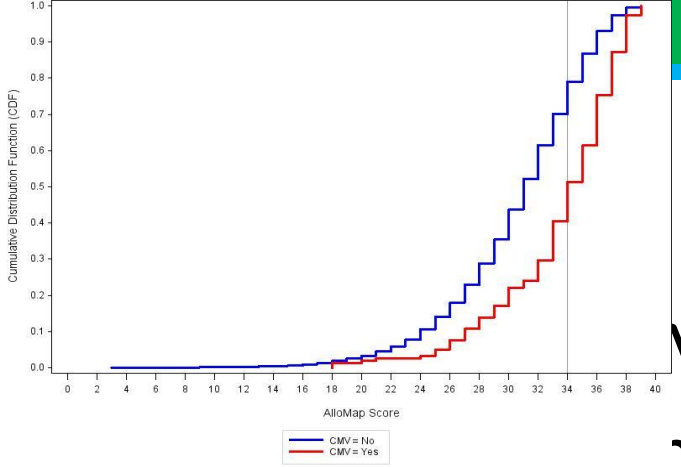
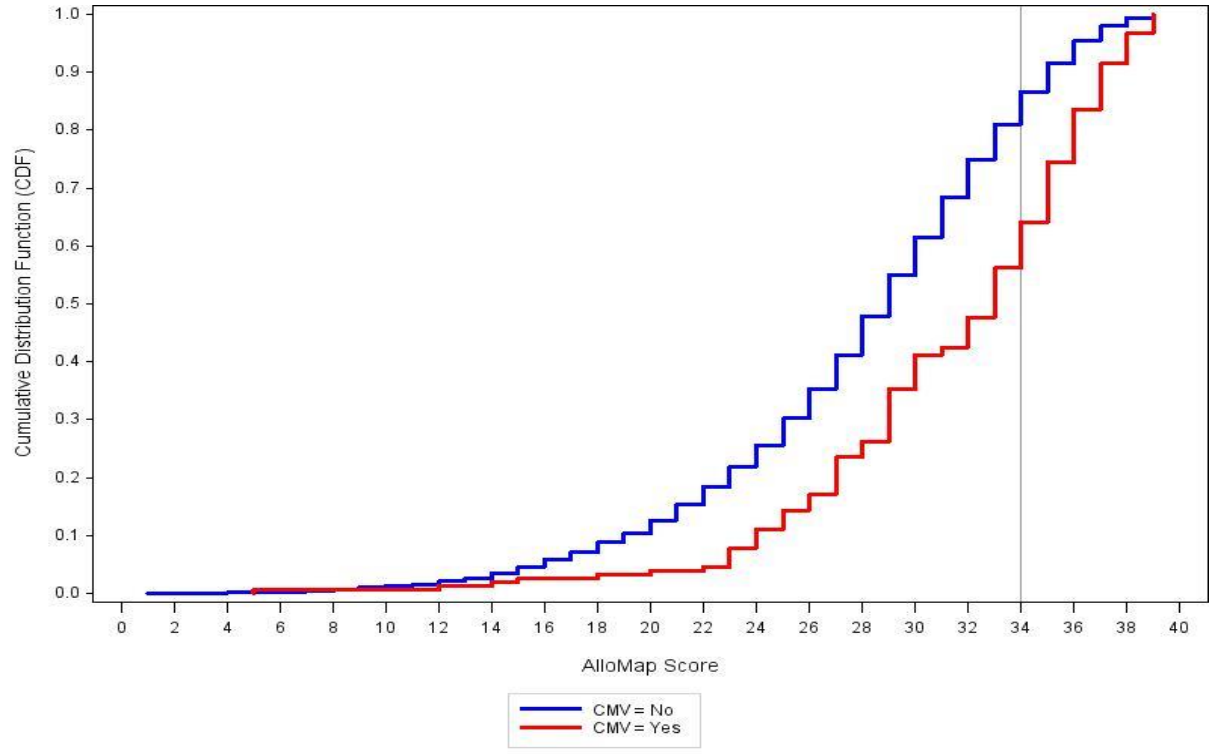
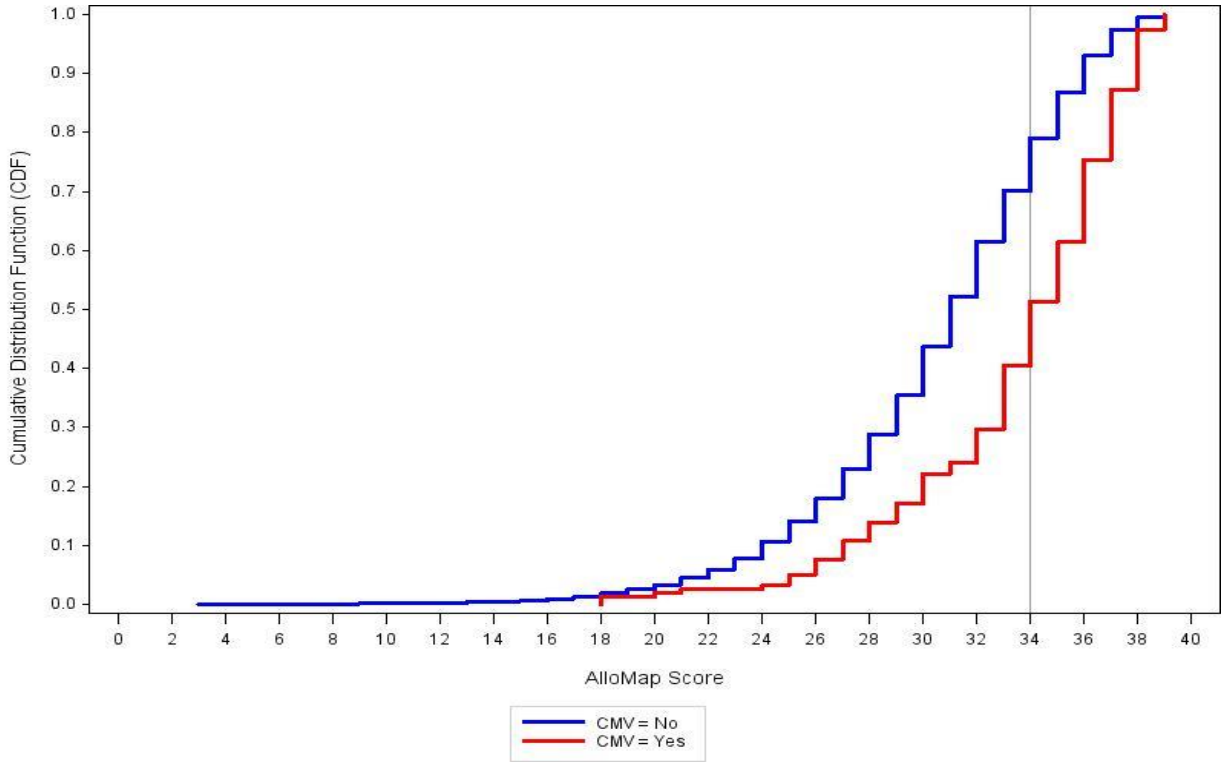
Time since HT

MV infection on GEP score distribution remains statistically significant after controlling for time post-transplant, p < 0.0001.

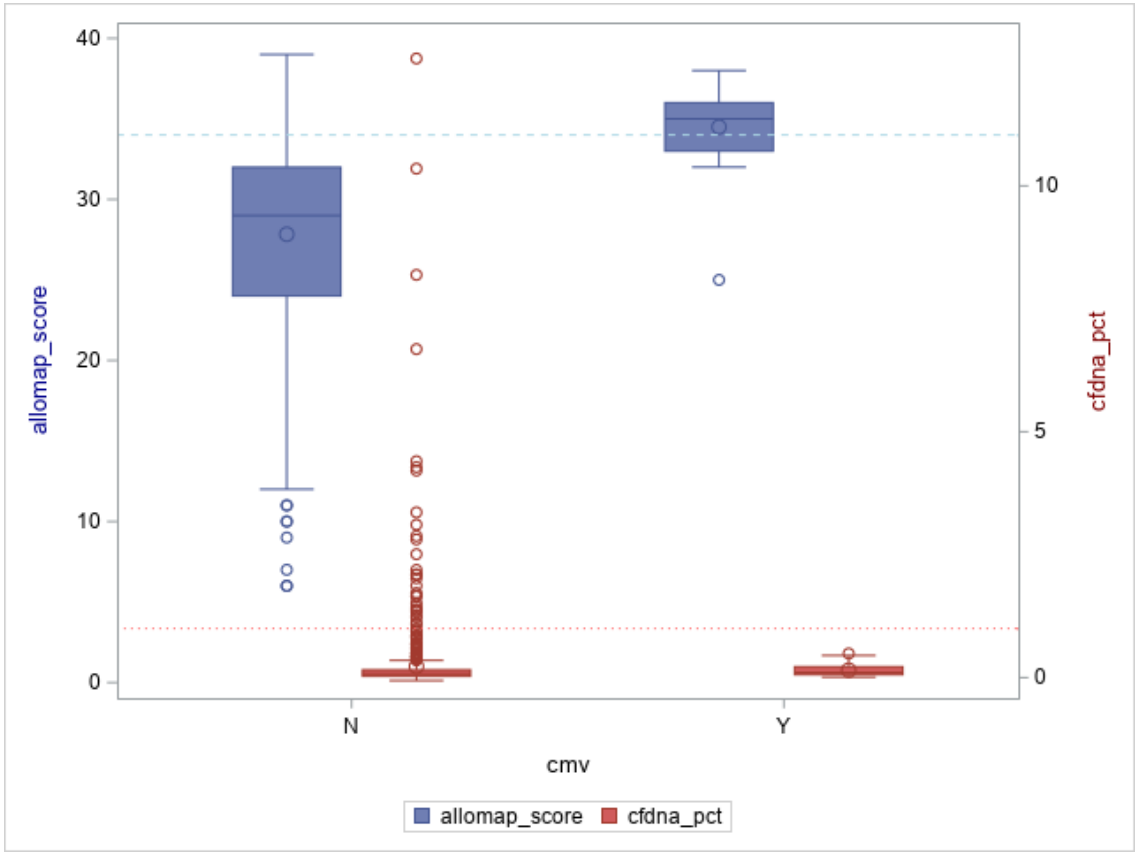






AlloMap and AlloSure

- AlloSure were not significantly different (median 0.23% in 18 samples with CMV infection versus 0.15% in 776 samples without CMV infection, p=0.66)
- AlloMap scores were significantly higher in the setting of CMV infection (median 35 vs 29, p<0.0001)



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Discussion

- Patients with active CMV infection have significantly higher AlloMap scores, as compared to those without CMV infection
- Amongst those with CMV infection, patients with CMV disease have higher AlloMap scores than those with asymptomatic viremia
- The presence of CMV infection had no impact on AlloSure

- CMV infection encodes membrane-bound proteins that induce cytokine release, resulting in inflammation and viral dissemination to the phagocytic cells
- Once viral infection (or activation of latent virus) is detected by the recipient, CMV-specific CD4+ and CD8+ T cells respond in a similar fashion as they would to cellular rejection
- Activation and migration of T-lymphocytes-- effects that cause upregulation of many of the genes that are measured in the AlloMap GEP test
- AlloSure is a dd-cfDNA is a marker of allograft damage, it would not be expected to change

Conclusion

- CMV should be considered in the differential diagnosis while interpreting a high AlloMap score

- AlloSure results do not appear to be impacted

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