Marginal Structural Models to Estimate the Effect of Cytomegalovirus Infection on Hospitalization among Children Undergoing Allogeneic Hematopoietic Cell Transplantation

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Background

- Children receiving an allogeneic hematopoietic cell transplant (HCT) are at risk for cytomegalovirus (CMV) infection in the post-transplant period.
- After transplant, some patients will not have CMV detected while others will have intermittent or persistent CMV detection. Hence, CMV status is time-varying.
- Prior analyses assessing the association between CMV infection and hospitalization have been limited by methods that did not consider the time-varying nature of the exposure (CMV reactivation) and the confounders.

Objective

- We aimed to assess the causal effect of CMV reactivation on hospitalization using a causal modeling approach, properly accounting for time-varying nature of CMV status.

Methods

Study Design & Population: A cohort of allogeneic HCT patients transplanted at Children's Hospital of Philadelphia January 2004–April 2017 was assembled and followed for 100 days after transplant.

Inclusion criteria: Eligible patients included those under CMV surveillance after transplant, defined as having ≥2 CMV whole blood polymerase chain reaction tests in the first month after HCT.

Variable Definitions:

CMV Status: Before transplantation, donors and patients were tested for their CMV infection status. After transplantation, patients were tested for CMV infection weekly from day 15 to 100 days using quantitative PCR tests.

CMV infection was detected by the PCR testing of viral proteins or nucleic acid in the whole blood specimen. Patients were classified as having CMV infection if they were detected as having >600 CMV copies/mL on 2 consecutive PCR analyses in blood measured within a 1-week interval. Patients who tested were considered to be positive until their next negative test.

Follow-up was divided into weeks. Each week, patients were classified as CMV positive for that whole week if the number of CMV positive positive days was greater than the number of CMV negative days.

Outcome: Our primary outcome of interest is the likelihood of hospitalization.

Baseline confounders: acute graft-versus-host-disease (GVHD) (yes/no) at baseline, reason for transplantation (immunodeficiency, bone marrow failure/dysplasia, hematologic malignancy, other malignancy, HLH, other), race (black, white, other), gender and age (in years).

Time-dependent confounders: GVHD status (yes/no) over time, history of CMV infection and history of hospitalization

Analysis: The association of CMV reactivation on the rate of hospitalization was estimated using traditional generalized estimating equations and repeated using a marginal structural model that accounted for time-varying exposure, confounders and non-random drop-out and obtained effects with causal interpretations.

Results

- **Table: The Characteristics of Study Sample and CMV infection rate per person-week**

		CMV rate per person-week*			
	N (%)	Overall	Week 2 to 6	Week 7 to 11	Week 12 to 15
Overall	340 (100%)	0.08	0.08	0.09	0.06
Age (years)					
< 4	74 (22%)	0.05	0.05	0.05	0.04
4-9	110 (32%)	0.10	0.12	0.11	0.07
10-14	68 (20%)	0.05	0.06	0.06	0.03
15+	88 (26%)	0.10	0.08	0.13	0.08
Race					
Black	54 (16%)	0.12	0.14	0.15	0.07
Other	80 (24%)	0.14	0.15	0.16	0.10
White	206 (61%)	0.05	0.04	0.05	0.04
Transplant Reason					
Primary immunodeficiency	49 (14%)	0.07	0.10	0.09	0.03
Bone Marrow Failure/Dysplasia	36 (11%)	0.09	0.10	0.10	0.07
Hematologic Malignancy	205 (60%)	0.08	0.05	0.10	0.08
Immune Dysregulation Syndrome	21 (6%)	0.09	0.12	0.08	0.05
Metabolic Disease	6 (2%)	0.06	0.13	0.03	0.00
Hemoglobinopathy	23 (7%)	0.11	0.23	0.05	0.01
Donor / Recipient Status					
D- / R-	119 (35%)	0.01	0.01	0.01	0.01
D+ / R-	59 (17%)	0.05	0.04	0.07	0.03
D- / R+	95 (28%)	0.11	0.11	0.12	0.09
D+ / R+	67 (20%)	0.19	0.20	0.22	0.13

** Calculated as the total number of CMV positive person-weeks over the total number of person weeks in the noted time period.*

- **Table: The Effect of CMV Infection on Hospitalization Using Generalized Estimating Equations and Marginal Structural Models**

Model	Incidence Rate Ratio	95% Confidence Interval	p-value
0. GEE (TC CMV + TC Confounders)	1.10	1.04 -- 1.17	0.0014
1. GEE (TD CMV + TD Confounders)	1.22	1.12 – 1.34	<0.001
2. MSM (TD CMV + TD Confounders)	1.03	0.91 – 1.16	0.61

0. Generalized estimating equations treating CMV as a time-constant variable (ever present vs. not) and adjusting for baseline time-constant confounders (gender, age, race, graph versus host disease, reason for transplant)

1. Generalized estimating equations treating CMV as a time-dependent variable and adjusting for baseline and time-dependent confounders (gender, age, race, graph versus host disease, reason for transplant, history of CMV infection, history of hospitalization)

2. Marginal Structural models treating CMV as a time-dependent variable and adjusting for baseline covariates and time-dependent confounders (gender, age, race, graph versus host disease, reason for transplant, history of CMV infection, history of hospitalization)

- A traditional model using generalized estimating equations and incorrectly treating CMV as a time-constant variable (ever present vs. not) was associated with a 10% increase in average weekly hospitalization (Incidence rate ratio: 1.10, 95%: 1.04 - 1.17).
- A traditional model using generalized estimating equations and treating CVM as time-dependent variable, but incorrectly adjusting for time-dependent confounders estimates an additional week of CMV infection was associated with a 22% increase in average weekly hospitalization (Incidence rate ratio: 1.22, 95%: 1.12 -1.34).
- A marginal structure model that correctly accounts for time-varying nature of CMV infection and time-dependent confounders estimates an additional week of CMV infection is associated with 3% increase in average weekly hospitalization (Incidence rate ratio: 1.03, 95%: 0.91-1.16).

Conclusions

- Our research showed different modeling approaches can lead to different conclusions on the association between CMV infection and hospitalization.
- The effect of CMV on hospitalization diminished when we use the marginal structure model, which correctly accounts for the time-varying nature of the CMV infection status, its time-varying confounders and non-random dropouts.

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