Positive predictive model of adenovirus (HAdV) infection among asymptomatic pediatric human stem cell transplant (HSCT) recipients undergoing weekly surveillance testing

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Background

- Adenovirus (HAdV) infections are associated with significant morbidity and mortality in pediatric human stem cell transplant (HSCT) recipients.
- Serial HAdV PCR testing can identify adenoviremia with a goal of early intervention.
- It is laborious and costly to serially test all HSCT recipients.
- An accurate prediction model could allow for more focused HAdV testing.

Objectives

- Derive a prediction rule using baseline data to identify patients that will develop adenoviremia post-transplant
- Determine incidence of adenoviremia in a pediatric cohort of HSCT patients undergoing surveillance testing

Methods

- Surveillance testing defined as two or more HAdV PCR blood/plasma tests within first month post-transplant
- Retrospective study of pediatric HSCT patients that underwent surveillance HAdV PCR testing between 2006 and 2012 at The Children's Hospital of Philadelphia
- Univariate analyses were conducted to summarize patient characteristics
- Stochastic gradient boosting (SGB) was used to discriminate between patients who did and did not develop adenoviremia within 6-months post-transplant based on characteristics available at the time of HSCT

Univariate Results:

Table 1: Baseline Patient Characteristics

Characteristic*	Total 123 (100)	HAdV + 26 (21)	HAdV – 97 (79)	p-value
Sex				
Female	63 (51)	11 (42)	52 (54)	0.306
Male	60 (49)	15 (58)	45 (46)	
Race				
White	83 (68)	16 (62)	67 (69)	0.467
Non-White[1]	25 (20)	4 (15)	21 (22)	0.481
Not reported	15 (12)	6 (23)	9 (9)	0.056
Median Age, Years	8 (2 to 14)	9 (6 to 12)	7 (1 to 14)	0.543
Median # CCC[2]	2 (1 to 3)	2 (1 to 4)	2 (1 to 3)	0.289

*summarized as n(%) or median (IQR)
[1] Non-white includes Asian (n=2), African-American/Black (n=21) and >1 race (n=2)
[2] Chronic comorbid conditions. Includes: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defect, malignancy

Table 2: Baseline Transplant Characteristics

Characteristic - n(%)	Total 123 (100)	HAdV + 26 (21)	HAdV – 97 (79)	p-value
Indication for HSCT				
Leukemia/lymphoma†	77 (63)	15 (58)	62 (64)	0.560
Primary immune deficiency#	15 (12)	3 (12)	12 (12)	0.908
Bone marrow dysfunction^	18 (15)	4 (15)	14 (14)	0.903
Genetic or metabolic condition*	9 (7)	4 (12)	5 (5)	0.075
Unknown	4 (3)	0	4 (5)	0.293
HSCT Match Status				
Matched Related	21 (17)	3 (11)	18 (19)	0.398
Matched Unrelated	101 (82)	23 (89)	78 (90)	0.342
Mismatched Related	1 (1)	0	1 (1)	0.603
HSCT Source				
Bone Marrow	36 (29)	6 (23)	30 (31)	0.435
Human Stem Cells	58 (47)	12 (46)	46 (47)	0.908
Cord Blood	29 (24)	8 (31)	21 (22)	0.331
T-Cell Depletion				
Yes	57 (46)	12 (46)	45 (46)	0.983
No	66 (54)	14 (54)	52 (54)	0.983
Total Body Irradiation				
Yes	65 (53)	12 (46)	53 (55)	0.499
No	58 (47)	14 (54)	44 (45)	0.442

†Also includes patients with myelodysplastic syndrome (MDS)
#Includes aplastic anemia, Beta thalassemia, Sickle-Cell, congenital neutropenia, NEMO, Kostman Syndrome,, IFN Gamma receptor 2 deficiency, Ommen's syndrome
^Includes SCID, immune dysregulation, polyendocrinopathy, enteropathy, IPEX-like syndrome, congenital thrombocytopenia
*Includes LiFraumeni syndrome, HLH, Langerhan's cell histocytosis, Hurler's syndrome, leukodystrophy

Predictive Model Results:

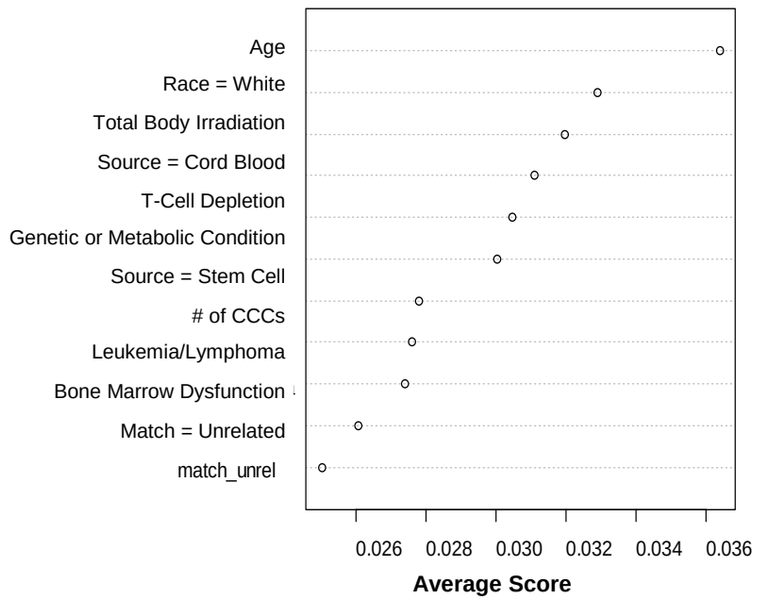
Baseline Predictors of Adenoviremia

- Age
- Race
- Sex
- Indication for HSCT
- HSCT Match status
- Stem cell source
- T-cell depletion
- Total body irradiation
- Chronic comorbid conditions (CCC)

Table 3: Average Confusion Matrix

Predicted Value	True Value 1	True Value 0
1	19.11	7.59
0	6.89	18.41

Figure: Average Variable Importance Over 100 Runs



Model Performance

- There was no single predictor that could discriminate between HAdV positive vs. negative patients
- Boosting was used to combine multiple predictors to improve the performance of the model
- Sensitivity: 73.5% and Specificity: 70.8%
- Positive post-test probability: 40% (CI: 27% - 55%)
- Negative post-test probability: 9% (CI: 4% - 21%)
- False positive rate: 29% (CI: 12% - 46%)
- False negative rate: 27% (CI: 10% - 44%)
- Average out of bag error: 26%

Conclusions

- PCR surveillance testing in pediatric HSCT recipients commonly identified adenoviremia
- A predictive model using baseline characteristics reasonably discriminated between patients with and without adenoviremia
- Study was limited by lack of a single key discriminating predictor as well as limited sample size
- Additional predictors need to be considered including conditioning regimen and time-varying changes post-transplant such as presence of co-infections and GVHD