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Machine learning classification of neurocognitive performance in children with perinatal HIV initiating de novo antiretroviral therapy

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Abstract

Objective: To develop a predictive model of neurocognitive trajectories in children with perinatal HIV (pHIV).

Design: Machine learning analysis of baseline and longitudinal predictors derived from clinical measures utilized in pediatric HIV.

Methods: 285 children (ages 2–14 years at baseline; $M_{age}=6.4$ years) with pHIV in Southeast Asia underwent neurocognitive assessment at study enrollment and twice annually thereafter for an average of 5.4 years. Neurocognitive slopes were modeled to establish two subgroups (above ($n=145$) and below average ($n=140$) trajectories). Gradient-boosted multivariate regressions (GBM) with five-fold cross validation were conducted to examine baseline (pre-ART) and longitudinal predictive features derived from demographic, HIV disease, immune, mental health, and physical health indices (i.e., complete blood count; CBC).

Results: The baseline GBM established a classifier of neurocognitive group designation with an average AUC of 79% built from HIV disease severity and immune markers. GBM analysis of longitudinal predictors with and without interactions improved the average AUC to 87% and 90%, respectively. Mental health problems and hematocrit levels also emerged as salient features in the

longitudinal models, with novel interactions observed between mental health problems and both CD4 count and hematocrit levels. Average AUCs derived from each GBM model were higher than results obtained using logistic regression.

Conclusions: Our findings support the feasibility of machine learning to identify children with pHIV at risk for suboptimal neurocognitive development. Results also point towards interactions between HIV disease and mental health problems as early antecedents to neurocognitive difficulties in later childhood among individuals with pHIV.

Keywords

perinatal HIV; cognition; machine learning; mental health; development

Introduction

A subset of children with perinatal human immunodeficiency virus (pHIV) experience long-term neurocognitive difficulties [1–3]. While initial findings from a prospective investigation of newborns with pHIV [4] described neurocognitive gains associated with the initiation of anti-retroviral treatment (ART) within the first 30 days of life, a recent follow-up study of the same cohort identified neurocognitive difficulties in a subset of children after approximately 5 years of treatment [5]. Similar findings of persistent neurocognitive symptoms have been reported in separate cohorts of older children with pHIV who initiated ART within the first weeks after birth [6,7], and children with pHIV who initiated de novo ART after surviving the first year or longer without ART [8–13].

Predicting individual neurocognitive outcomes for young children with pHIV is challenging, especially for individuals residing in resource-limited environments where the majority of the global population of pHIV reside. Prior investigations of youth with pHIV reveal independent risk factors of suboptimal neurodevelopment, including HIV disease indices (e.g., low CD4 T-cell count, high viral load [14–16]) and numerous psychosocial factors (e.g., poverty, parental mental health problems) [17–22]. However, previous investigations have utilized traditional analytic methods that are generally insensitive to nonlinearities and multiple interactions among predictor variables [23].

Machine learning provides a complementary approach to traditional statistical models by leveraging methods capable of defining structure in complex, multi-dimensional data [23–30]. Machine learning methods have been shown to improve diagnostic accuracy and prediction of disease and treatment outcomes when compared to traditional analytics [26–33]. Additionally, machine learning provides a unique opportunity to discover linear and nonlinear (e.g., polynomial) mechanisms and multiple high-level interactions among risk factors that can then facilitate the development of tailored clinical interventions [23, 27]. Only a handful of studies have applied machine learning to investigate neurobehavioral features of HIV, and none have focused on pediatric samples [28–30]. For example, Ogishi et al. [30] utilized machine learning to discover three viral proteins that distinguished HIV-infected adults with dementia from those without dementia with approximately 90% accuracy. The identification of novel HIV disease mechanisms associated with severe cognitive impairment is an important finding, but the results do not readily translate to the

larger population of individuals affected by HIV with less severe neurocognitive problems or to pediatric populations. To date, no studies have utilized machine learning to establish a data-driven predictive model of neurocognitive development in children with pHIV.

The current study was designed to address these gaps and contribute to the existing literature on pediatric HIV. Following precedence by Papini et al. [31], we built the predictive algorithms using risk factors (i.e., input features) from readily accessible clinical information. Second, we compared model performance between additive and interactive algorithms built from information obtained only at the first study visit (baseline, pre-ART) and information acquired over the course of structured follow-up visits (average of 5.4 years). These comparisons established an empirical benchmark to quantify the gain in accuracy using more complex models. Finally, we compared the machine learning algorithms to a standard analytic approach using the same number of predictive features in each method.

Methods

Study Design

Data from 285 children with pHIV were included in the current study. Participants included Thai (n=170) and Cambodian (n=115) children enrolled in the Pediatric Randomized to Early vs. Deferred Initiation in Cambodia and Thailand (PREDICT) clinical trial (clinicaltrials.gov identification: U19AI53741) [8]. The PREDICT study began enrollment in 2006, when HIV treatment guidelines in Thailand recommended ART in children with CD4<15%. Accordingly, the PREDICT study enrolled male and female children with pHIV who had survived the first year of life (PREDICT enrollment age=1–14 years) with a CD4 between 15–25% and no history of ART (including no exposure to ART in utero). Participants were then randomized to begin ART at CD4 <25% (immediate treatment arm) or CD4<15% (deferred treatment arm). The main outcomes of PREDICT included mortality and the frequency of AIDS-defining illnesses 3 years after enrollment, neither of which differed by treatment arm [8].

The exclusion criteria from PREDICT were applied for the current study. Specifically, individuals were excluded if they reported a history of brain infection, neurological disorder, congenital abnormalities, previous use of immune modulators within 4 weeks of enrollment, baseline absolute neutrophil count <750 cells/ μ L, hemoglobin <7.5 g/dL, baseline platelet counts <50,000/ μ L, or alanine aminotransferase >4 times the upper limit of normative values. The protocols were approved by the Institutional Review Boards in Thailand, Cambodia, and the US. Caregivers provided informed consent with assent obtained from children over 7 years of age.

First-line ART included zidovudine, lamivudine, and nevirapine. Prior to the last study visit for this analysis, 124 (43%) participants enrolled in the deferred arm experienced a decline in CD4 to <15%, at which point ART was initiated. The remaining 33 (11%) children in the deferred treatment arm maintained a CD4>15% throughout the observation period for this study. One participant was diagnosed with an opportunistic infection within weeks of

enrollment (prompting initiation of ART). Otherwise, no cases of AIDS-defining illnesses were observed during the study.

Outcome measure

Neurocognitive development was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration, Fourth Edition (Beery VMI) [34]. The Beery VMI is a test of graphomotor construction of 30 increasingly complex line drawings presented in sequential order. The test is suitable for individuals age 2 and older and provides a sensitive measure of neurocognitive development for individuals from diverse environmental, educational, and cultural backgrounds [34]. Performance is strongly correlated with chronological age [35] and is closely linked to performance on functional skills, academic achievement, learning difficulties, and neurodevelopmental delay [35–39]. The Beery VMI was administered to Thai and Cambodian children at baseline and again twice per year for an average of 5.4 years. Baseline scores were not available for 12 participants (6 in each treatment arm of PREDICT). For these cases, performance acquired at the next clinic visit (approximately 6 months after enrollment) was utilized as the first assessment for the slope analysis.

Neurocognitive trajectories on the Beery VMI were defined by the average percent change in raw score performance modeled across all follow-up visits. Individual trajectories (i.e., slopes) were designated as above average (positive slope; $n=145$) or below average (negative slope; $n=140$) in comparison to the within sample mean. This approach yielded a robust set of features (approximately 220,000 data elements) for analysis.

Predictors

Multi-dimensional predictor variables included: **1) demographics** (e.g., age, sex, family income); **2) HIV disease** (plasma viral load); **3) immune markers** (e.g., CD4% and count, CD8% and count, total lymphocyte count, white blood cell count), **4) blood markers of physical health** (e.g., red blood cell count (RBC), platelet count, hematocrit, hemoglobin, glucose); and **5) mental health indices** (subscale and overall indices from the Child Behavior Checklist-Caregiver version; CBCL) [40]. The CBCL was translated into Thai [9, 41] and Khmer [9] in prior studies. Primary caregivers completed the preschool (age 2–6 years) and school-age (age 6–18 years) versions at the baseline visit and every six months thereafter (following the same sequence as the Beery VMI). Raw scores on the composite scales (Internalizing, Externalizing, and Total Problem scores) and subscales (Anxiousness, Aggressive Behavior, Rule-Breaking Behaviors, Thought Problems, Affective, Somatic Complaints, and Social Competence) were included as predictors.

Machine learning approach

Gradient boosted multivariate regression (GBM), a form of ensemble machine learning, was utilized to build the algorithms. GBM leverages a “wisdom of crowds” approach to combine accuracy and error information from multiple individual algorithms to establish a robust overall model that optimizes accuracy while controlling for overfitting of the data [23]. Recent studies have utilized GBM to identify novel features of psychiatric conditions (e.g., Post-Traumatic Stress Disorder) [31], neurodegenerative disease (e.g., probable Alzheimer’s

disease) [42], and complex brain structure-function relationships (e.g., subcortical-cortical networks) [43].

Neurocognitive trajectories were assigned using probability scores based on the sigmoid function by a $(1/(1+e^{-x}))$, using a 0.5 decision boundary, and gradient descent to minimize prediction error. Accuracy defined from Receiver Operator Curves (AUC) served as the main metric of model performance. Sensitivity, specificity, F1 score (i.e., harmonic balance between sensitivity and specificity), and AUC interpretation followed standard convention (poor = 0.6–0.7, fair = 0.7–0.8, good = 0.8–0.9; excellent = 0.9) [44].

Feature selection

Feature selection was conducted using an in-house program based on SciKit [45] and PDPBox [46]. Consistent with prior studies [31], we examined several GBM models that differed by model complexity to determine relative gain in average AUC [31]. The first model focused on baseline features acquired before participants began ART. The second model included longitudinal features acquired during the follow-up study visits of the PREDICT trial. Measures of central tendency (e.g., average, max value) and dispersion were included in the longitudinal approach to facilitate discovery of novel mechanisms. A third GBM examined the relative gain in model performance by allowing for up to 2-way interactions among input features.

Model stability and validity

Several methods were employed to optimize stability and validity. First, as described above we utilized a form of ensemble machine learning that is robust to overfitting compared to other machine learning methods [23,31]. Second, we focused the final algorithms on the 6 risk features with the highest classification strengths (i.e., mutual information criterion scores). This approach provided additional control against overfitting the data and aided clinical interpretation of the final model. Finally, we conducted 5-fold cross validation with multiple repeats (total of 25 validation trials) using data that were not included in the development of the algorithms. To accomplish this task, we partitioned the data into four training sets as well as a fifth validation set. The algorithms were trained using each iteration of the folds, and then validated on the remaining data. As noted above, the accuracy from the ROC analyses, averaged across the validation trials, served as the final metric of model performance.

Additional analyses

Repeated measures univariate analyses of variance (RM-ANOVA) models examined change from the first to last assessment among key risk factors. These analyses compared change by neurocognitive group trajectory subclass (below vs above average) as well as the time by group interaction (subgroup x time). Classification accuracy (AUC) was also examined using logistic regression to serve as a benchmark comparison to the GBM models. Logistic regression is a traditional statistical method that utilizes the base principle of machine learning (i.e., iterative learning) to establish an algorithm to predict a binary outcome. Logistic regression is ideally suited for hypothesis confirmation (rather than discovery) because the algorithm is based on a limited number of pre-defined predictors [23]. To

facilitate comparison to GBM, the logistic regression was conducted using a two-step procedure; the first step ranked the relative importance of the same input features as utilized in the GBM models, and the second step determined classification accuracy using 6 features with highest coefficient rankings from the first step.

Results

Baseline GBM analysis

Results from the baseline GBM are depicted in Figure 1. The algorithm classified children with pHIV according to neurocognitive trajectory designation (above average/below average) with 71% accuracy (AUC of 79%, sensitivity of 76%, specificity of 66%, and F1 score of 72%). Top predictor variables of the baseline GBM included **HIV disease** (higher viral load) and **immune markers** (higher CD8% and CD8 count, and higher white blood cell and lymphocyte counts) (Fig. 2).

Longitudinal GBM without interactions

The addition of predictor data from the follow-up visits improved accuracy to 77%, with an average AUC of 87%, sensitivity of 78%, specificity of 76%, and F1 score of 77%. Key predictor variables of the longitudinal GBM included **HIV disease** (higher viral load), **immune indices** (lower average CD4 cell count), **blood markers of physical health** (hematocrit levels), and **mental health indices** (raw scores on the Affective Problems, Withdrawn, and Somatic Complaints scales).

Longitudinal GBM with 2-way interactions

The longitudinal analysis allowing for up to 2-way interactions yielded the best model performance, with an average accuracy of 80% (AUC of 90%, sensitivity of 83%, specificity of 78%, and F1 score of 81%). Predictors (Fig. 3) included interactions between **blood markers of physical health** (average hematocrit level) with **mental health** (Somatic Complaints scale), **immune status** (baseline CD4 count) with **mental health** (CBCL Total Score), and interactions between **mental health indices** representing severity and chronicity of problems reported on the CBCL (i.e., Thought Problems, Affective, Withdrawn, Internalizing, and Somatic Complaints scales) (Supp. Figs. 1–2).

Subgroup comparisons of predictor variables

At baseline, participants in the above average trajectory group had lower plasma viral load ($p < .001$), CD8 ($p < .001$), total lymphocyte ($p = .04$), and white blood cell counts ($p < .001$); CD4% did not differ at baseline ($p = .77$) (Table 2). Children in the below average trajectory group had lower hematocrit ($p < .001$) and hemoglobin ($p < .001$) at baseline. They also weighed less ($p < .001$) and they were shorter ($p < .001$) than individuals in the above average trajectory group. BMI did not differ by group ($p = .11$) at the baseline visit. On the CBCL, raw scores were higher on each subscale and composite scale among youth with pHIV in the below average trajectory group ($p < .05$).

When considered longitudinally, plasma viral load, CD8 count, and white blood cell count declined for both groups between the first and last study visit, with a trend for higher viral

load in the below average trajectory group at follow-up ($p = .07$). The two groups did not differ on CD8 cell count ($p = .13$) or white blood cell count ($p = .09$) at the final visit. Total lymphocytes ($p = .04$), and CD4%, ($p = .002$) were higher in the below average trajectory group at follow-up. Children in the low trajectory group continued to have lower body weight ($p < .001$), were shorter ($p < .001$) and had a lower BMI ($p < .001$) at the final follow-up visit. CBCL raw scores decreased for both groups ($p < .05$) overall, with no group differences at the final visit. The pattern of results was unchanged in adjusted analyses. The comparison to logistic regression revealed higher accuracy using the GBM algorithms ($p < .05$; Fisher's Exact test).

Conclusions

Study findings provide several novel contributions to the current understanding of long-term neurocognitive outcomes in children with pHIV. First, we demonstrate that HIV disease indices acquired using standard clinical measures distinguish children who are at risk for suboptimal neurocognitive development over a 5-year period. Second, we demonstrate significant gains in model accuracy using information acquired during structured follow-up visits compared to a single cross-sectional assessment before ART. The longitudinal GBM analyses identified novel features of suboptimal neurocognitive trajectories (i.e., emergence of mental health problems and elevations in a blood marker of anemia) that were not observed in the analysis of predictors from the baseline visit. Third, inclusion of 2-way interactions revealed relationships between mental health problems and laboratory measures of HIV disease, immune dysregulation, and laboratory indices of physical health. These findings have potential to guide the development of intervention strategies to maximize neurodevelopmental outcomes in youth exposed to HIV during critical stages of brain development.

Our predictive models were built using clinical measures that can be acquired in resource-limited settings. This is important because regions of the world that shoulder the highest prevalence of pHIV typically have the fewest resources (e.g., neuroimaging) to guide precision medicine initiatives. We further enhanced the clinical relevance of the present study by identifying risk factors using information from the baseline assessment (pre-ART). This mirrors the initial point of contact in a clinical environment, when clinicians are limited to a "snapshot" of information to predict long-term outcomes and help guide treatment decisions. Risk variables identified in the baseline GBM underscore the importance of early HIV disease (plasma viral load) and immune (CD8%, CD8 count, white blood cells, lymphocytes) indices, which collectively yielded an average AUC of nearly 80% using five-fold cross validation with multiple repeats.

Interestingly, baseline HIV viral load was significantly elevated in children in the below average trajectory group. Total lymphocyte count and CD8 T-cell count were also higher in these children. In adults with HIV, increased CD8 activity precipitates T-cell exhaustion, which corresponds to worse disease outcomes [47,48]. Whether children and adolescents with pHIV exhibit T-cell exhaustion in the context of suppressive ART is unknown. Ongoing efforts by our team include studies focused on the interplay between viremia in early childhood, initial immune response (particularly CD8 T-cell activation and exhaustion), and

chemokine co-receptor tropism (i.e., X4 and CCR5 chemokine co-receptors). These variables were not available for analysis in the present study, but there is strong precedence from recent work in adults with acute HIV that early viral-host dynamics set the stage for mental health complications in a subset of individuals [49]. Our previous study demonstrating neurocognitive difficulties in young children with pHIV in PREDICT who subsequently met criteria as long-term non-progressors [11] is consistent with the importance of early life immunological dynamics on cognitive and mental health outcomes.

Results from the longitudinal GBM models (with and without interactions) revealed hematocrit as an important predictor of neurocognitive trajectory subgroup. Hematocrit represents the percentage of oxygen-rich red blood cells in the total volume of blood. Low hematocrit is suggestive of anemia and is common in youth with pHIV residing in resource limited environments, including Southeast Asia [1,7,50–52]. Levels of hematocrit, hemoglobin, and red blood cell count were lower in children in the below average trajectory group. Hematocrit level was not a top predictor in the baseline (pre-ART) model, but this variable emerged as a strong risk factor in the longitudinal analyses. Participants enrolled in the PREDICT trial were prescribed zidovudine as first-line ART, and this drug is known to cause anemia [53–55]. However, abnormal hematocrit levels may also reflect disease duration and/or other environmental factors unrelated to HIV and ART per se. Hoare et al. [56] reported that blood markers of anemia were strong correlates of brain white matter abnormalities in children with pHIV who were not taking zidovudine, arguing against an iatrogenic effect from this drug. In the present study, children in the below average trajectory group weighed less and were shorter at baseline (before ART) than their counterparts in the above average subgroup which further implicates variables other than drug regimen.

Accuracy of the GBMs improved when information from follow-up visits was included as predictor variables. More importantly, the longitudinal GBMs (with and without interactions) discovered features that were not observed in the baseline analysis. Specifically, mental health problems became prominent predictors of neurocognitive development as children aged, involving interactions between caregiver ratings of anxiousness, withdrawn behavior, and thought problems with HIV disease (i.e., viral load), immune (e.g., CD4, CD8) and physical health (i.e., hematocrit level) indices. The Affective and Withdrawn subscales of the CBCL include symptoms of depression, and a robust literature from studies of adults with HIV demonstrate poor treatment compliance among individuals with symptoms of depression [57–60]. The association between developmental trajectories and Thought Disorder is more complicated because the items that comprise this scale on the CBCL are heterogeneous (e.g., sleep problems, hearing voices, mind wandering) and they are more likely to be misinterpreted and endorsed by caregivers of children living in lower socioeconomic settings [61]. Item level analyses are needed to more fully understand the symptom profiles that correspond to divergent neurocognitive trajectories.

Additionally, our results reinforce the need for psychosocial interventions to address the mental health needs in children with pHIV [62–65]. Prior work conducted in Thailand by members of our team demonstrate significant gains in mental health of youth and their caregivers following a brief, theoretically-informed psychosocial intervention [66]. Other

studies using cognitive training strategies demonstrate improved cognitive performance with evidence of task transfer [67,68]. Additional studies are needed using data-driven models to continue the development of precision health initiatives capable of delivering the most effective therapeutic strategy, or combination of strategies, tailored to individual needs/strengths. Complimentary application of data science and traditional statistics methods are essential to achieve this goal.

It is important to note that participants enrolled in the PREDICT trial represent a unique group of children with pHIV who survived at least the first year of life without ART. As such, the results may not generalize to all children with pHIV (e.g., individuals exposed to ART in utero) or to uninfected children who do not share HIV disease risk factors. Information related to environmental stressors (e.g., early life trauma, food insecurity, pollution) that have potential to impact neurodevelopment was not available for this study [6,69,70]. Future investigations utilizing independent cohorts are needed to determine whether these factors and others (e.g., hospital admissions, neuropsychiatric diagnosis) represent key explanatory variables.

In summary, our study demonstrates that common clinical measures can identify youth with pHIV who are at risk for long-term neurodevelopmental problems. Synergies between mental health indices, hematocrit levels from blood, and HIV disease dynamics merit additional investigation to delineate causal pathways. Further, our finding that viral suppression was more common, albeit modestly, in children with worse neurocognitive trajectories suggests that traditional HIV clinical metrics of disease severity (i.e., viral detection) are not reliable markers of developmental risk in youth with pHIV. Our results add to a growing body of evidence that early HIV disease mechanisms and mental health problems represent key risk variables among youth with pHIV. Adjunctive interventions are needed to support neurodevelopment in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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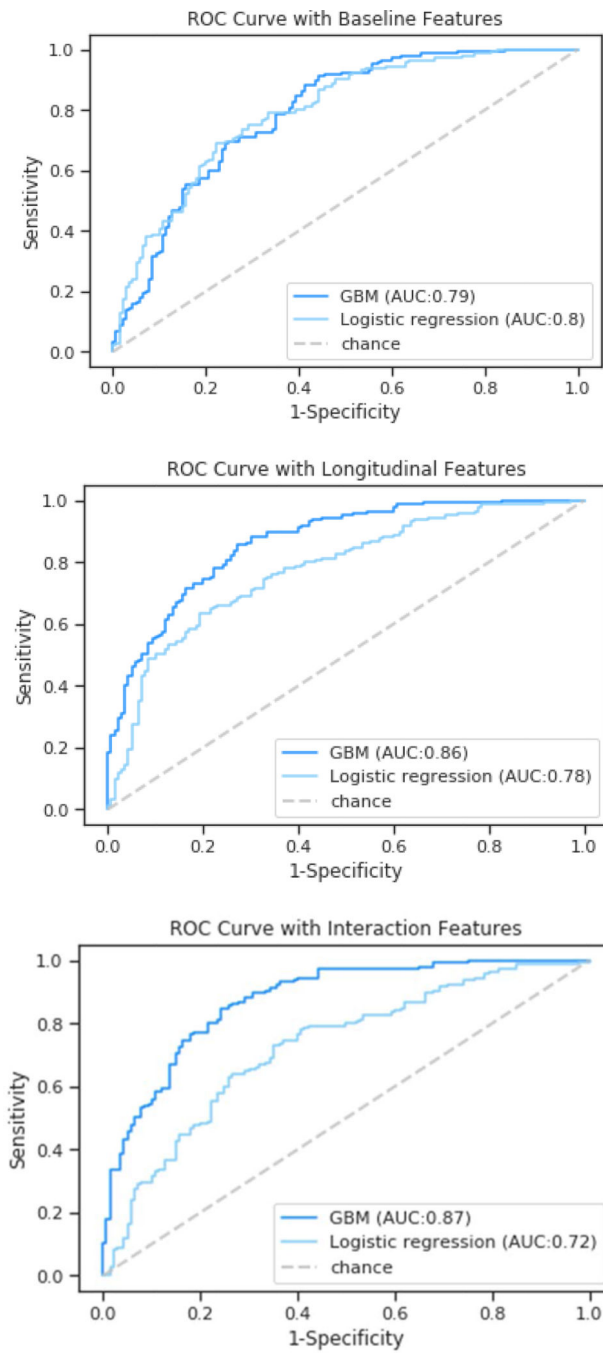
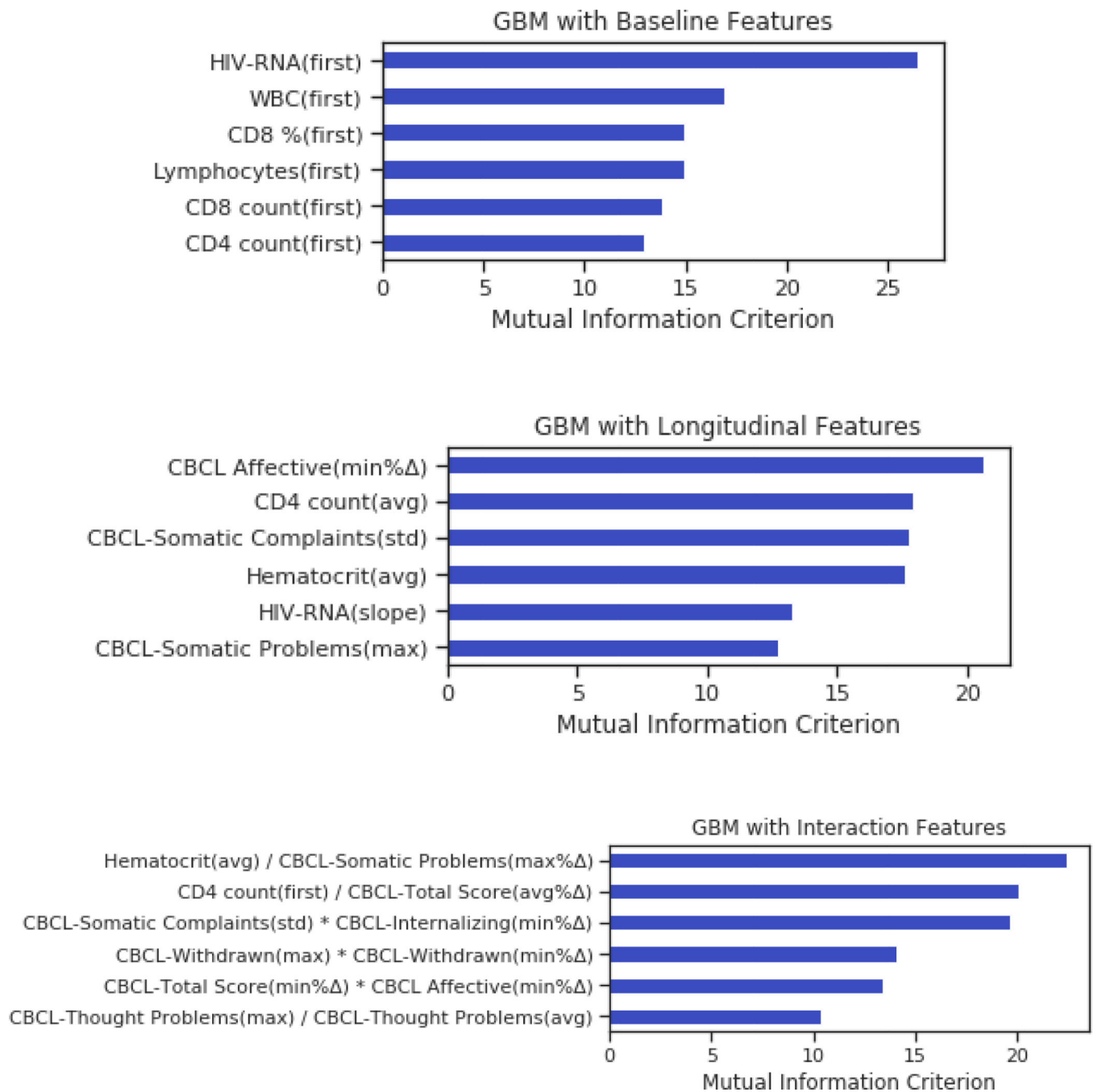


Fig. 1. Receiver Operator Curves comparing average AUC for the baseline, longitudinal and interactive GBM and logistic regression analyses.

**Fig. 2.**

Feature importance ranking for the baseline, longitudinal, and interactive GBM models.

Baseline model (top panel): HIV-RNA (copies/mL), white blood cell count (WBC) CD8 T cell %, Lymphocytes, CD8 T cell count, and CD4 T cell count. **Longitudinal model** (middle panel): CBCL Affective score minimum percent change (min % Δ); CD4 T cell count average value (avg), CBCL Somatic Complaints standard deviation (std), hematocrit (avg), HIV RNA slope, and CBCL Somatic Problems score maximum (max). **Interaction model** (bottom panel): hematocrit (avg) x CBCL Somatic Problems score (max % Δ), CD4

count at baseline (first) x CBCL Total Score (avg %), CBCL Somatic Complaints score (std) x CBCL Internalizing score (min %), CBCL Withdrawn score (max) x CBCL Withdrawn score (min %), CBCL Total Score (min %) x CBCL Affective score (min %), and CBCL Thought Problems score (max) x CBCL Thought Problems score (avg).

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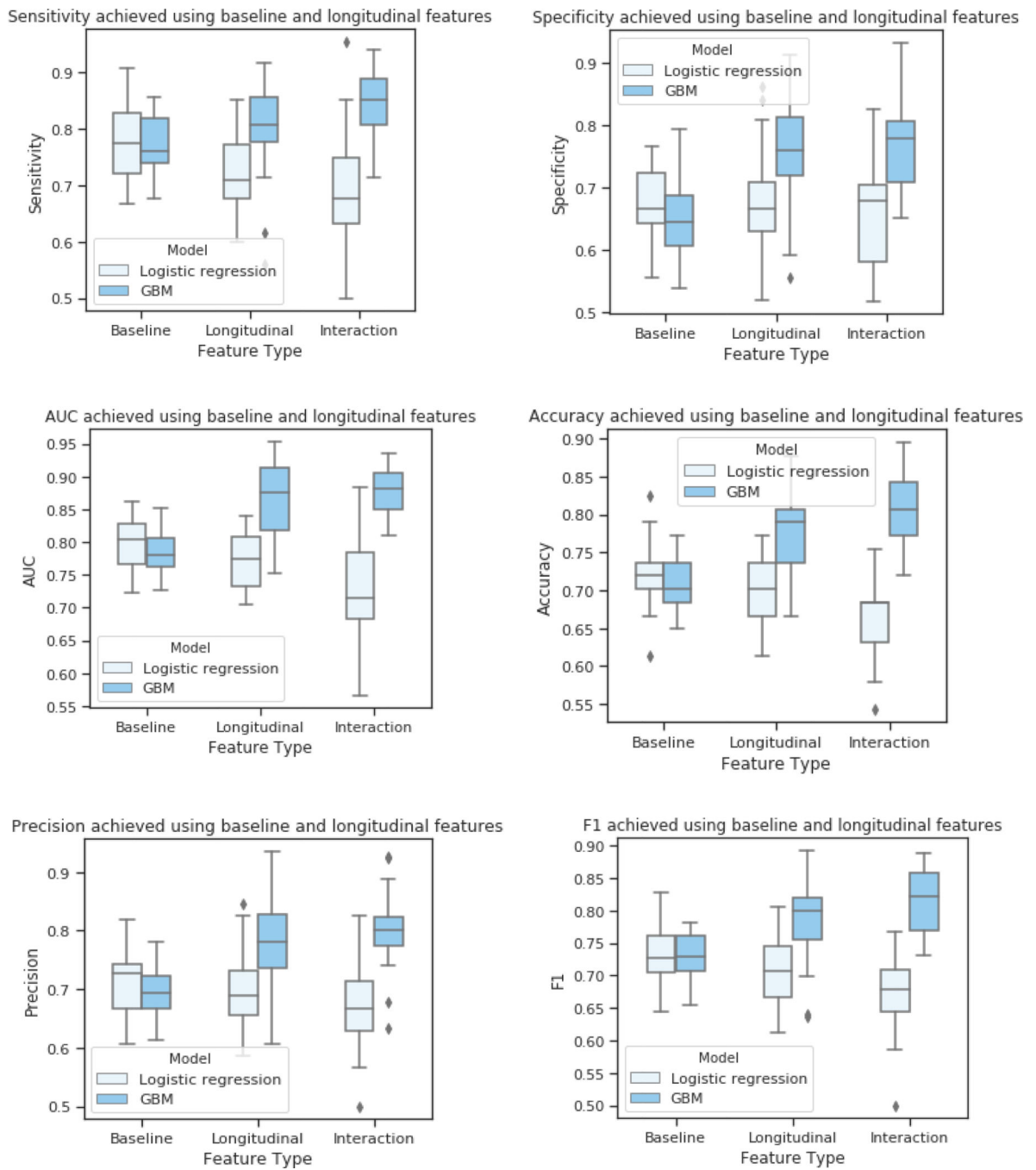


Fig. 3. Classification performance comparing baseline, longitudinal and interactive GBM to logistic regression.

Table 1.

Baseline demographics and clinical variables for all participants.

Demographic Variables	
Sex	42% male; 58% female
Age at enrollment (years)	6.21 (2.8)
Ethnicity: Percent Thai / Cambodian	60% / 40%
HIV Disease	
Plasma HIV viral load (copies/mL); median	63,300
Immune Markers: Mean (Standard Deviation)	
Plasma CD4 T cell count (cells/mm ³)	725.80 (390.35)
Plasma CD4 T cell percent	20.06 (24.0)
Plasma CD8 T cell count (cells/mm ³)	1,637.30 (964.59)
Plasma CD8 T cell percent	44.30(9.05)
Plasma CD4/CD8 ratio	0.48 (0.14)
Blood Indices of Physical Health: Mean (Standard Deviation)	
Hematocrit (%)	33.92 (3.02)
Neutrophils (10 ³ /ul)	8.59 (13.39)
Monocytes (10 ³ /ul)	1.54 (2.64)
Lymphocytes (10 ³ /ul)	7.78 (12.42)
White blood cell count	9.02 (3.65)
Red blood cell count (10 ⁶ /ul)	4.66 (0.49)
Hemoglobin (pg/cell)	11.15 (1.11)
Triglycerides (ml/dL)	118.20 (62.5)
Mental Health Indices (CBCL Scales): Mean (Standard Deviation)	
Anxious	2.98 (3.40)
Withdrawn	2.39 (2.05)
Somatic Complaints	2.85 (2.88)
Social Problem	2.02 (2.07)
Thought Problems	1.68 (2.10)
Attention Problems	3.74 (2.94)
Rule-Breaking Problems	2.46 (2.59)
Aggressive Behavior	6.41 (4.62)
Internalizing	8.11 (6.01)
Externalizing	8.86 (6.60)
Total Score	29.77 (18.87)

Table 2.
Predictive classifiers of each neurocognitive trajectory subgroup at first and last assessment and tested over time.

Child Behavior Checklist Values (CBCL) values represent raw scores. Caregivers completed age-appropriate versions of the CBCL (age 2 to 5 years or age 6 years and over). Green highlight identifies significant differences in unadjusted analyses.

Predictor Variable	First Assessment			Last Assessment			Repeated Measures Analyses		
	Above Average (n=145)	Below Average (n=140)	P	Above Average (n=145)	Below Average (n=140)	P	Time Main Effect: Δ , p-value	Group x Time Effect: Δ , p-value	Group x Time Effect: Δ , p-value
HIV Disease Markers									
Viral load (mL) / % detectable	33,100 / 100%	100,000 / 100%	<.001	34,100 / 26%	11,230 / 17%	.07	.76, p<.001		.96, p=.001
Immune Markers									
CD8 cell count (cells/mm ³)	1,311 (607.17)	1,974.90 (113.31)	<.001	1,071.54 (429.10)	1,152.92 (464.83)	.13	.73, p<.001		.90, p<.001
CD4 %	20.01 (2.93)	20.12 (2.94)	0.77	27.47 (8.33)	30.37 (7.10)	.002	.47, p<.001		.97, p=.005
Lymphocytes (10 ³ /ul)	6.26 (10.85)	9.35 (13.72)	.04	3.48 (5.98)	5.64 (10.65)	.04	.93, p<.001		.99, p=.49
White blood cell count	7.75 (2.52)	10.33 (4.14)	<.001	6.84 (2.15)	7.27 (2.10)	.09	.76, p<.001		.92, p<.001
Blood Indices of Physical Health									
Hematocrit	34.71 (2.61)	33.11 (3.21)	<.001	36.89 (3.38)	34.97 (3.37)	<.001	.76, p<.001		.99, p=.47
Hemoglobin	11.45 (1.00)	10.86 (1.14)	<.001	12.49 (1.29)	11.97 (1.25)	.001	.56, p<.001		.99, p=.64
Mental Health Indices (CBCL Scales)									
CBCL Affective	2.95 (2.32)	2.27 (2.08)	.01	2.14 (3.61)	1.82 (2.45)	.39	.96, p=.002		.99, p=.37
CBCL Internalizing	9.65 (6.26)	6.75 (5.36)	<.001	6.72 (7.83)	5.41 (6.17)	.12	.91, p<.001		.98, p=.06
CBCL Somatic Problems	2.52 (2.26)	1.50 (1.69)	<.001	1.42 (2.12)	1.05 (1.89)	.12	.90, p<.001		.98, p=.02
CBCL Withdrawn	2.79 (2.22)	1.99 (1.78)	.01	2.06 (2.28)	1.66 (1.85)	.11	.96, p=.001		.99, p=.19
CBCL Thought Problems	1.98 (2.16)	1.38(2.00)	.02	1.60 (3.27)	.99 (2.10)	.06	.98, p<.02		1.00, p=.99
CBCL Total Score	31.86 (19.25)	27.61 (18.29)	.06	23.86 (23.98)	20.31 (19.36)	.17	.88, p<.001		1.00, p=.77
Physical Development									
Weight (Kg)	23.97 (7.62)	19.06 (6.11)	<.001	39.72 (11.18)	28.39 (10.42)	<.001	.26, p<.001		.84, p<.001

Predictor Variable	First Assessment			Last Assessment			Repeated Measures Analyses		
	Above Average (n=145)	Below Average (n=140)	P	Above Average (n=145)	Below Average (n=140)	P	Time Main Effect: Λ , p-value	Group x Time Effect: Λ , p-value	Group x Time Effect: Λ , p-value
Height (cm)	123.45 (12.74)	111.55 (10.62)	<.001	146.78 (12.65)	130.64 (13.81)	<.001	.16, p<.001	.95, p<.001	
BMI (weight/ height ²)*10000	15.38 (2.02)	15.03 (1.63)	.11	18.10 (3.15)	16.13 (2.51)	<.001	.51, p<.001	.85, p<.001	