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Transfer learning of a methylation-based COVID-19 severity model for DNA viral infection by eczema herpeticum

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SIGNIFICANCE

- This is the first study to predict **severity of atopic dermatitis with eczema herpeticum** (**ADEH+**) using a **machine learning (ML) approach** predicated on **methylation risk scoring (MRS)**.
- Our study is significant because it reveals the occurrence of both common and differential methylation states in infectious diseases caused by different viral classes.
- In addition, our study provides evidence to delineate host-DNA modifications utilized by unique viruses to cause infections in humans.
- Overall, this work serves as a case study to evaluate the validity and utility of MRS in its implementation towards infectious disease healthcare.

BACKGROUND

- **Atopic dermatitis (AD)** is a complex chronic skin disease affecting up to 30% of children and often persists into adulthood.
- **Eczema herpeticum (EH)** is a rare but serious complication of AD (<3% of patients) for which the primary predisposing factor is **HSV-1 exposure**.
- ADEH+ patients typically **represent the severe end of the disease spectrum**, have more severe skin disease, reduced interferon responses, and are highly allergic with increased serum IgE levels and eosinophilia.
- DNA methylation is affected by **both genetics and environmental insults** and is a useful tool for characterizing disease predisposition and severity.
- **Methylation risk scores (MRS)** are an algorithmic aggregation of methylation states that can capture multi-factorial predispositions.
- Previously we demonstrated that risk of AD and EH are correlated with changes in **DNA methylation patterns** (Boorgula et al 2019).

STUDY POPULATION

Feature	Controls (N=87)	ADEH - (N = 291)	ADEH+ (N = 194)
Female	56 (55%)	146 (50%)	99 (51%)
Age median (IQR)	40 (25)	21 (26)	14 (28)
IgE	17 (45)	762 (3707)	1592 (4630)
Eosinophils	87 (108)	314 (484)	352 (481)

METHODS

- **Data collection**: Genome-wide DNA methylation was measured in whole blood cells from 194 ADEH+, 291 ADEH-, and 101 non-atopic, healthy control subjects using the Illumina EPIC 850K array.
- **Quality Control**: require patient to have <200K NA methylation measures, only keep methylation sites that are found in all patients
- **Multimodal modeling**: samples were randomly split into training (70%) and testing (30%). 1,000 methylation probes along with demographic, lab, and severity data were used as predictors in an elasticnet model. Cross-validation was performed with the training set for hyperparameter selection, and evaluation was performed on the test set.

RESULTS

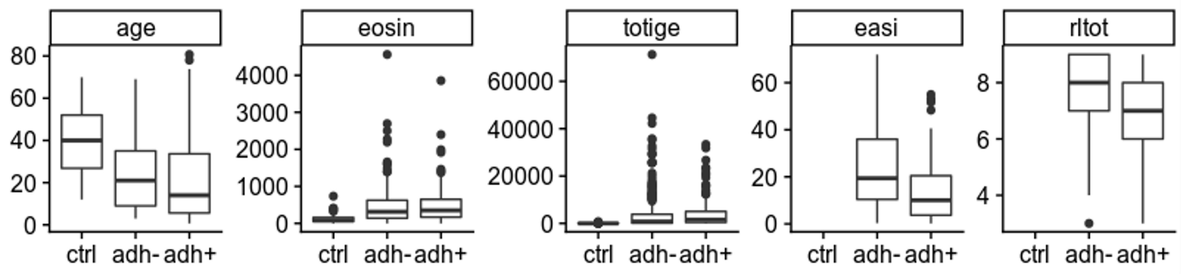
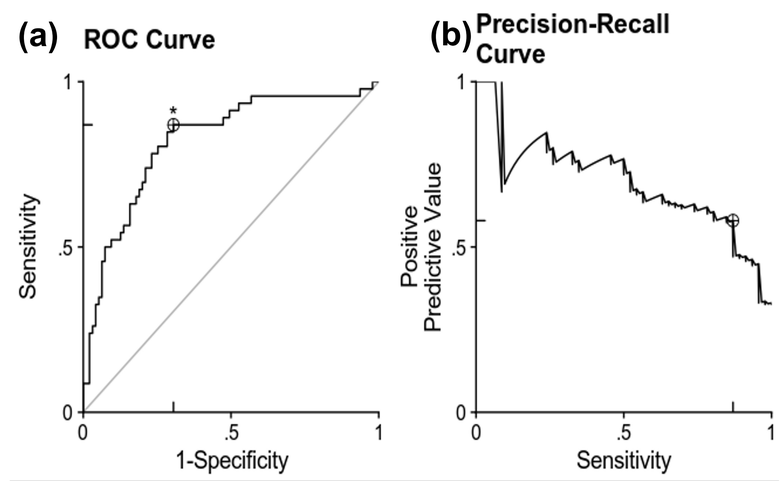


Figure 1. Age, immunology lab, and disease severity distributions
AD is associated with higher immunological marker concentrations than controls. ADEH+ infection is associated with slightly higher immunology concentrations than ADEH-.



Statistic	Performance
AUC	0.82
specificity	69%
sensitivity	87%
accuracy	75%

Figure 2. Classification Performance for ADEH+ infection. Here we show **(a)** receiver-operating characteristic (ROC) curve and **(b)** Precision Recall Curve for the herpes infection classification model tested on 145 test cases.

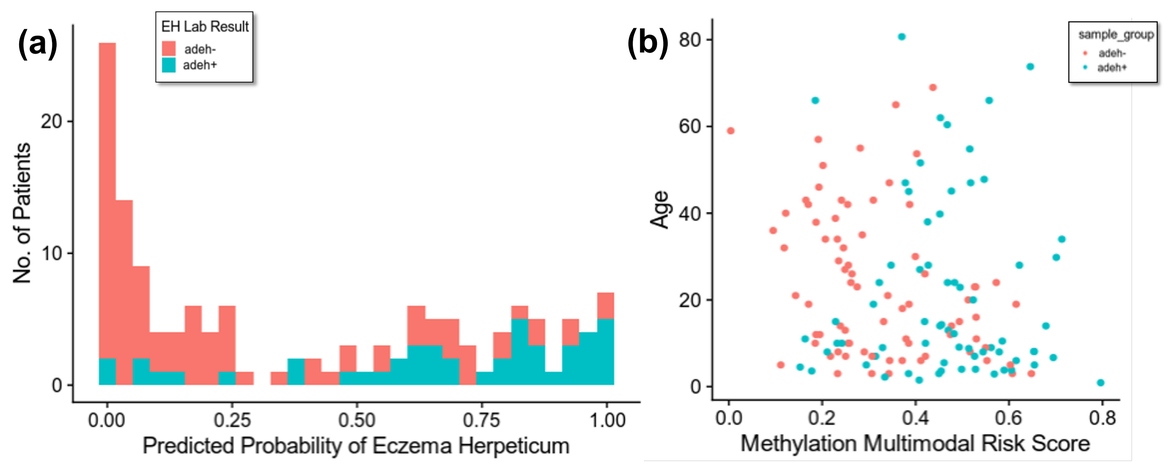


Figure 3. Distribution of model predictions and stratification by age
Here we show **(a)** univariate EH+ probabilities and **(b)** bivariate distributions of mMRS and age. Younger patients have more overlap in predicted risk; whereas older patients are better resolved.

FUTURE WORK

- Epigenome-wide association analyses (EWAS) and methylation quantitative trait loci (meQTL) analyses are underway to identify genes and pathways involved ADEH severity.
- Sensitivity analysis to assess the modulation of case-control relationships with gene expression adjusting for methylation are also being done.

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