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A methylation-based COVID-19 classification model to predict severe disease in vaccinated individuals

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INTRODUCTION

- Mitigating the worst outcomes of an infection with SARS-COV-2, and managing burdens on hospital systems, is reliant on our ability to identify persons at high risk of developing severe COVID-19.
- **Epigenomic pattern alterations in response to SARS-COV-2 infection** are evident in circulating white blood cells.
- Before vaccines were available, we designed a **machine learning (ML) platform that leveraged methylation risk scores (MRS)** derived from differentially methylated signatures in infected and uninfected individuals: SARS-COV2_infection AUC=93.6%, COVID19 disease severity AUC 79.1-84.4% (Konigsberg et al 2021 *Comm. Med.*).
- The goal of this work was to determine the prediction efficacy of a sparse regression based MRS model towards infection status and disease severity in vaccinated patients.

METHODS

- Our study cohort included vaccinated individuals who visited the Emergency Department after March 2021.
- We profiled peripheral blood samples from 347 additional patients (221 cases, 126 controls, 93 vaccinated with at least one dose) on the customized Infinium MethylationEPIC array.
- Disease severity was assessed by hospitalization status, as discharged, admitted, or ICU and death. This information along with vaccination status was extracted from patient electronic health records.
- We assessed the efficacy of our previously developed sparse regression based MRS model (N = 542), from which we excluded the EPIC + positions, in predicting disease severity in vaccinated individuals.
- We also trained a new model that included vaccinated individuals. This was achieved by comparing infection status and severity AUCs between the aforementioned cohort and an unvaccinated cohort from the original study.

Feature	COVID19 + (N = 221)	COVID19 - (N = 126)
Biological Sex is Female	109	63
Biological Sex is Male	112	62
Black or African American	54	30
White	102	66
Native American	3	1
Asian	4	2
Native Hawaiian or Pacific Islander	2	0
Mean Age	49 (IQR = 30)	50 (IQR = 23)

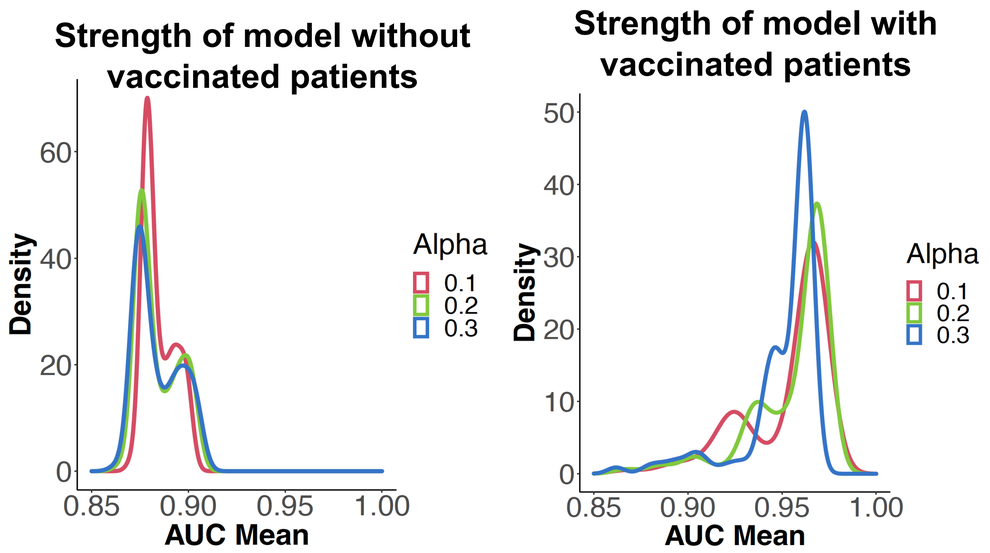
Table 1. Summary of study cohort

SIGNIFICANCE

Our approach used an ML approach predicated on MRS to predict COVID-19 severity and **demonstrated its utility in vaccinated and unvaccinated populations**. Our study provides insights into **how vaccination affects methylation status thereby offering protection from severe immune reactions due to deadly infections**. In summary, our model previously designed and implemented on biospecimens from patients with SARS-CoV-2 infection prior to vaccination provides a powerful tool for clinicians to evaluate a patient's propensity to develop severe COVID-19 disease **regardless of vaccination status** and to ensure early and appropriate interventions.

RESULTS

Figure 1. Predictive models strengthen when vaccinated patients are included. Here we show density plots of the out of sample model fit across each iteration by receiver-operating characteristic from two ML models of sparse regression trained by cross validation using the glmnet program. One model contained unvaccinated patients (train-N = 542, test-N = 135), while the other was created from a cohort of vaccinated patients (train-N = 172, test-N = 174).



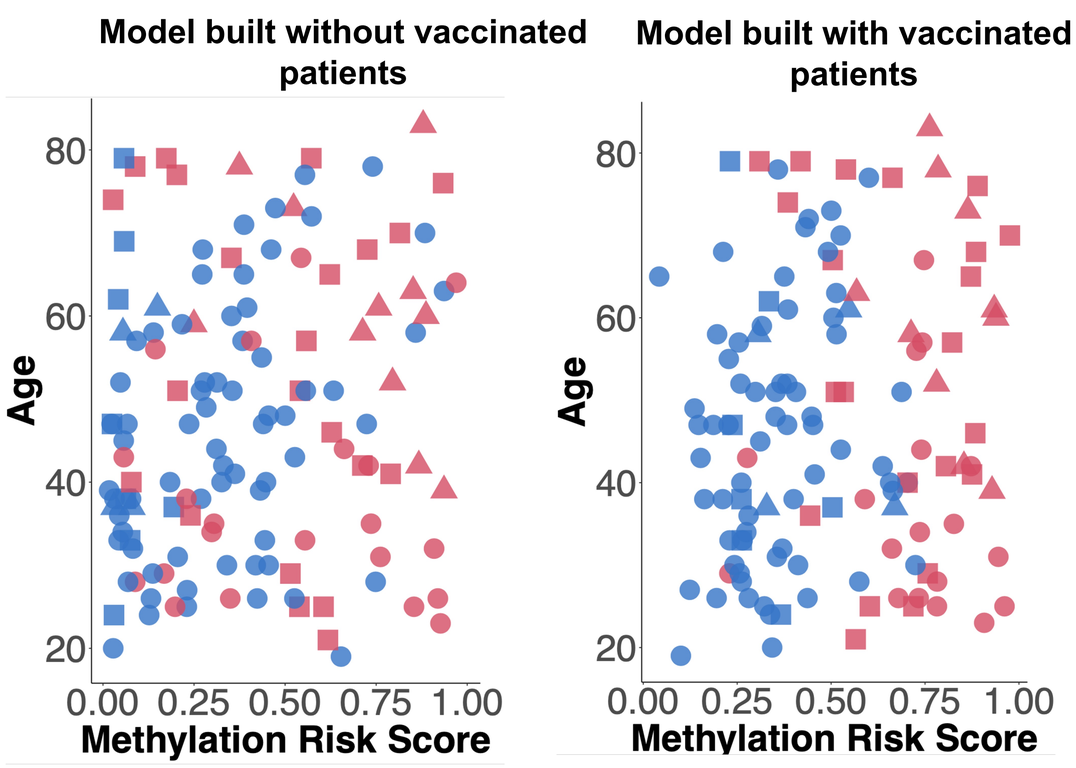


Figure 2. Models with vaccinated patients in the training set improve prediction of SARS-COV-2 infection status. Here we show the out-of-sample SARS-COV-2 status scores for 170 individuals (79 SARS-COV-2-, 91 SARS-COV-2+) plotted by age at time of sample collection. A designation of vaccinated was given if a patient received the original series and / or a booster.

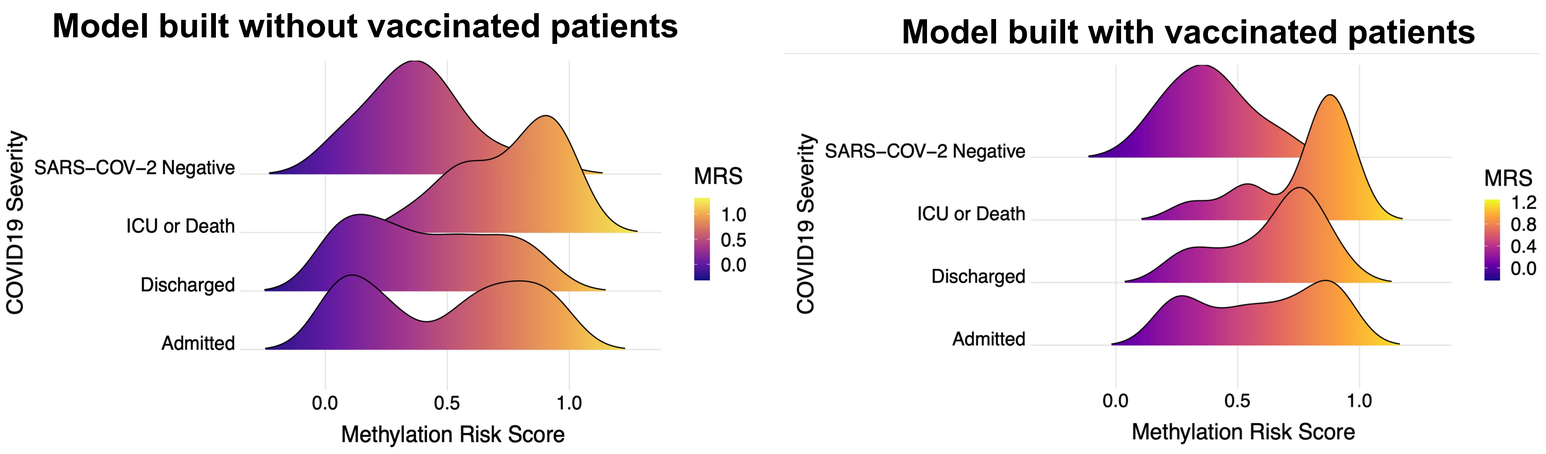


Figure 3. Models built with vaccinated patients improve prediction of COVID19 disease severity Here we show the distribution of methylation risk scores for COVID19 severity.

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