Using COVID-19 Patients' Cytokine Biomarkers and Clinical Data to Predict Acute Lung Injury and Deep Vein Thrombosis

Dylan Nun, MD[1]; Renhua Li, PhD[1,2]; Ruowei Zhong[3]; Scott F. Grey, PhD[1,2]; Eric A. Elster, MD[1,4]; Seth A. Schobel, PhD[1]

[1] Uniformed Services University (USU) Surgical Critical Care Initiative (SC2i), Bethesda, MD; [2] The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD;
[3] Graduate School of Arts and Sciences Computational Biology & Biomedical Informatics, Yale University, New Haven, CT; [4] Walter Reed National Military Medical Center, Bethesda, MD

INTRODUCTION

- COVID-19 is an infectious disease process that can present with a mild, moderate, and severe clinical disease burden
- COVID-19 can lead to various complications with significant morbidity and mortality. Specific complications include deep vein thrombosis (DVT) and acute lung injury (ALI)
- Previous studies in non-COVID patients identified 12 biomarkers that can predict DVT and ALI

Hypothesis: Cytokine profiles influence the development of DVT and ALI in COVID-19 patients

METHODS

- 88 inpatients who tested positive for SARS-CoV-2 at Duke University Medical Center from 2021-2023 with moderate-to-severe disease were selected
- 103 clinical variables were collected per patient, including age, sex, bioassay measurements, and presence of DVT and ALI. These data were split into an initial (I_data) component used for model training and a follow up (F_data) component used for model validation
- Hierarchical cluster analysis was performed based on Gower's distance metric and Ward's method using I_data and F_data
- Machine learning models were applied to the 12 biomarkers used in a previous study, age, and sex (collectively termed F14) to form multiple predictive models. Sensitivity and specificity were measured
  - The models used were: logistic regression (Logis), neural network (Nnet), random forest (RF), least absolute shrinkage and selection operator (LASSO), support vector machine (SVM), and extreme gradient boosting (XGB)
- Models were evaluated by estimating the area under the curve (AUC) for receiver operating characteristic (ROC) and calibrated via sigmoid calibration, with improvement measured by slope and intercept. Their net benefit was analyzed with decision curve analysis (DCA)

RESULTS

Table 1. Characteristics of COVID-19 patients with and without complications

Characteristic	With n = 76	Without n = 12	*P*
Age, median [IQR]	56.4 [47.0, 68.8]	47.0 [38.3, 65.0]	0.172*
Sex, n (%)			0.832†
Female	51 (67.1%)	9 (75.0%)	
Male	25 (32.9%)	3 (25.0%)	
Complications, n (%)			
Acute kidney injury	46 (60.5%)	0 (0%)	<0.001†
Bacteremia	18 (23.7%)	0 (0%)	0.006†
Deep vein thrombosis	25 (32.9%)	0 (0%)	0.019†
Pneumonia (HAP or VAP)	52 (68.4%)	0 (0%)	<0.001†
Acute lung injury	26 (34.2%)	0 (0%)	0.016†
Total hospital days, median [IQR]	28.5 [13.8, 46.0]	16.0 [13.8, 24.3]	0.156*
Total ICU days, median [IQR]	20.5 [11.0, 33.3]	8.5 [4.8, 12.3]	0.006*

**P-value calculated via Kruskall-Wallis test*
†P-value calculated via chi-squared test

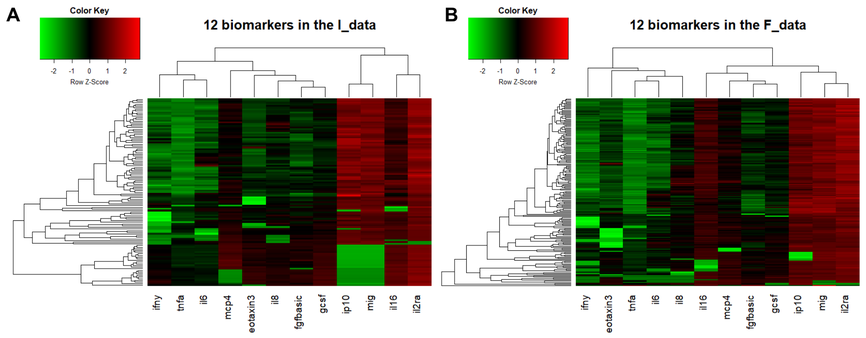

Figure 1. Heat maps of initial (**A**) and follow-up (**B**) biomarkers of 12 biomarkers in COVID-19 patients

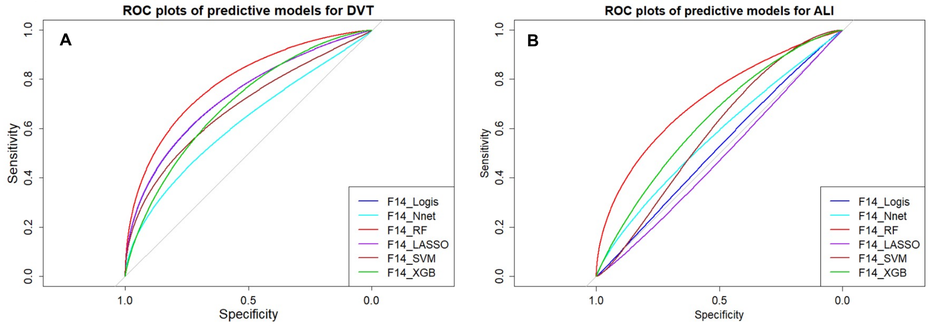

Figure 2. Initial, uncalibrated ROC plots for DVT **(A)** and ALI **(B)** predictions using 12 biomarkers, sex, and age

Models	AUC	Specificity	Sensitivity	Intercept	Slope
RF Pre-calibration	0.789	0.718	0.738	0.209	1.554
RF Post-calibration	0.789	0.718	0.738	0	1
LASSO Pre-calibration	0.744	0.618	0.803	-0.738	0.407
LASSO Post-calibration	0.743	0.618	0.803	0	1
RF Pre-calibration	0.701	0.811	0.551	-0.198	1.495
RF Post-calibration	0.701	0.811	0.551	0.001	1.001
XGB Pre-calibration	0.635	0.475	0.776	-0.700	0.173
XGB Post-calibration	0.636	0.467	0.776	0.000	1.000

Table 2. Pre- and post-calibration model statistics for the 2 best models for DVT (blue) and ALI (green)

Deep Vein Thrombosis
Acute Lung Injury

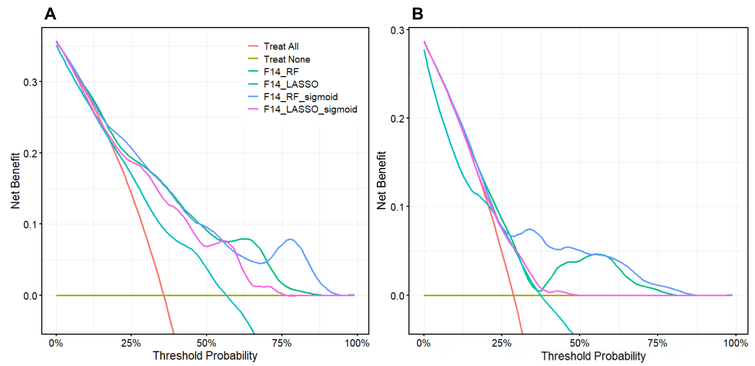

Figure 3. DCA and pre-/post-calibration statistics for DVT **(A)** and ALI **(B).** External data was not available for validation. The DCA shows a notable benefit from using predictive models. Calibrated models showed improved benefit relative to the uncalibrated models. Overall, the calibrations were shown to preserve AUC, sensitivity, and specificity **(Table 2)**. The intercept and slope were improved with calibration, showing that the calibration was successful and further improved the models. Overall, the RF model using 12 biomarkers, age, and sex with a sigmoid calibration demonstrated the greatest net benefit across both complications (DVT and ALI). Model statistics were acceptable for DVT. For ALI, AUC values were moderately acceptable, but sensitivity (0.55 for the RF model) and specificity (0.47 for the XGB model) values were unacceptably low.

CONCLUSION

- DVT and ALI represent moderate-to-severe COVID-19 complications that occurred in 28% and 30% of our patients, respectively
- Random forest models were the strongest predictive models for both DVT and ALI
- Net benefit was demonstrated on decision curve analysis. Net benefit improved with sigmoid calibration. If validated with external data, this work can be used to help clinicians select appropriate treatment or preventative measures
- Overall, models using F14 were able to successfully predict COVID-19 complications. More research is needed to understand specific mechanisms for the immune system's role in COVID-19 complications

References and Supplemental Figures

*SC2i is a consortium of Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Duke Health, Emory University School of Medicine, and Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.