

# Predictive biomarkers of ICU and mechanical ventilation duration in critically-ill COVID19 patients

**Sara Taleb**

Division of Genomics and Translational Biomedicine, College of Health and Life Sciences

**Hadi A Yassine**

Biomedical Research Center (BRC),

**Fatiha A Benslimane**

Biomedical Research Center (BRC),

**Maria Smatti**

Biomedical Research Center (BRC)

**Sven Schuchardt**

Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM)

**Omar Albagha**

College of Health and Life Sciences,

**Asmaa A Al-Thani**

Biomedical Research Center (BRC)

**Ali Ait Hssain**

Medical Intensive Care Unit, Hamad Medical Corporation

**Ilhame Diboun**

College of Health and Life Sciences

**Mohamed A Elrayess** (✉ [m.elrayess@qu.edu.qa](mailto:m.elrayess@qu.edu.qa))

Qatar University <https://orcid.org/0000-0003-3803-4604>

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## Research

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# Abstract

Background: Detection of early metabolic changes in critically-ill COVID-19 patients under invasive mechanical ventilation (IMV) at the intensive care unit (ICU) could predict recovery patterns and help in disease management.

Methods: Targeted metabolomics of serum samples from 39 COVID-19 patients under IMV in ICU was performed within 48 hours of intubation and a week later. A generalized linear model (GLM) was used to identify, at both time points, metabolites and clinical traits that predict the length of stay (LOS) at ICU (short  $\leq 14$  days /long  $>14$  days) as well as the duration under IMV. All models were initially trained on a set of randomly selected individuals and validated on the remaining individuals in the cohort. Further validation in recently published Metabolomics data of COVID-19 severity was performed.

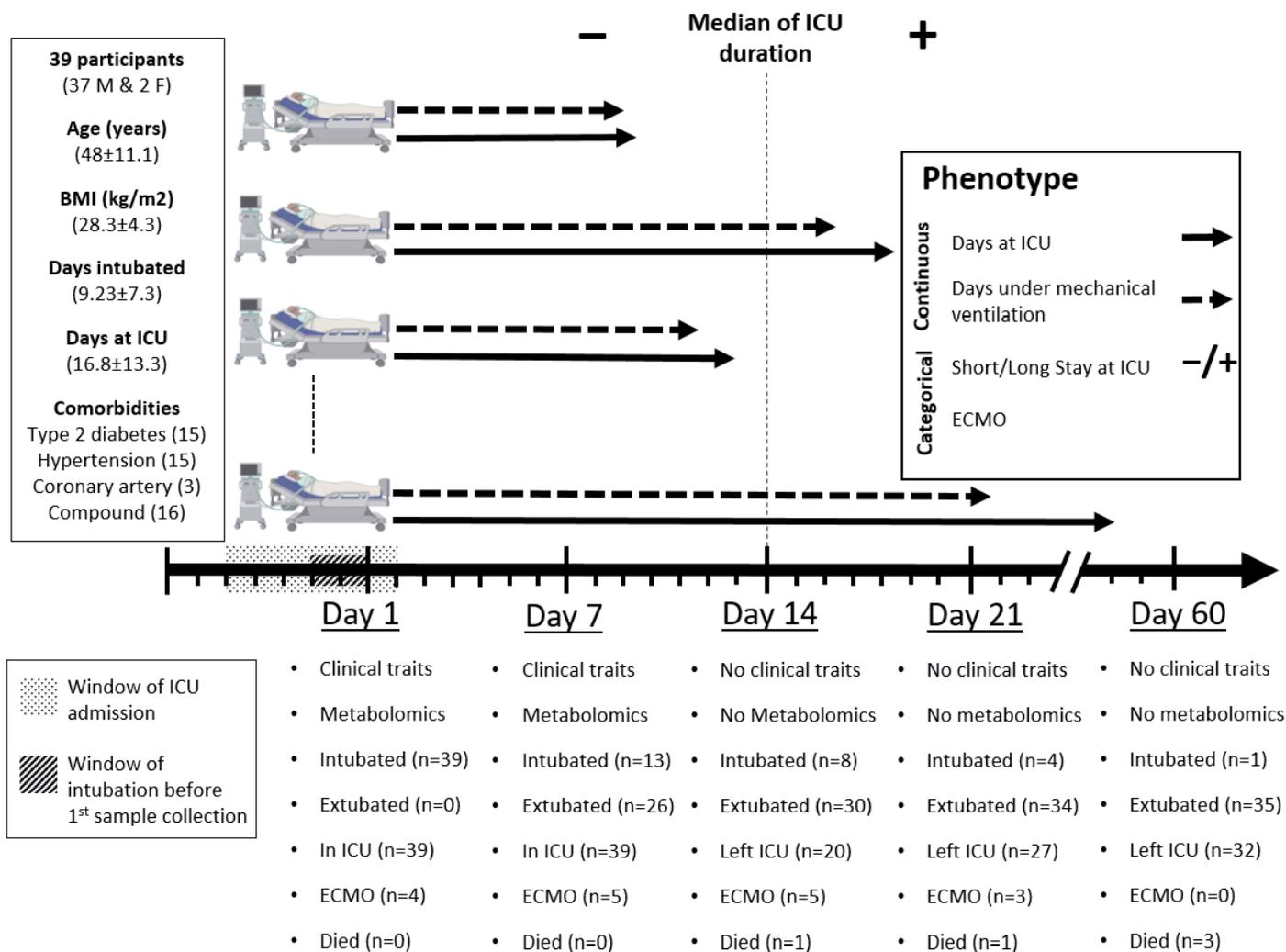
Results: A model based on hypoxanthine and betaine measured at first time point was best at predicting whether a patient is likely to experience a short or long stay at ICU (AUC=0.92). A further model based on kynurenine, 3-methylhistidine, Ornithine, p-Cresol sulfate and C24.0 sphingomyelin, measured one-week later, accurately predicted the duration of IMV (Pearson correlation=0.94). Both predictive models outperformed APACHE II scores and differentiated COVID-19 severity in published data.

Conclusion: This study has identified specific metabolites that can predict in advance LOS and IMV, which could help in the management of COVID-19 cases at ICU.

## Full Text

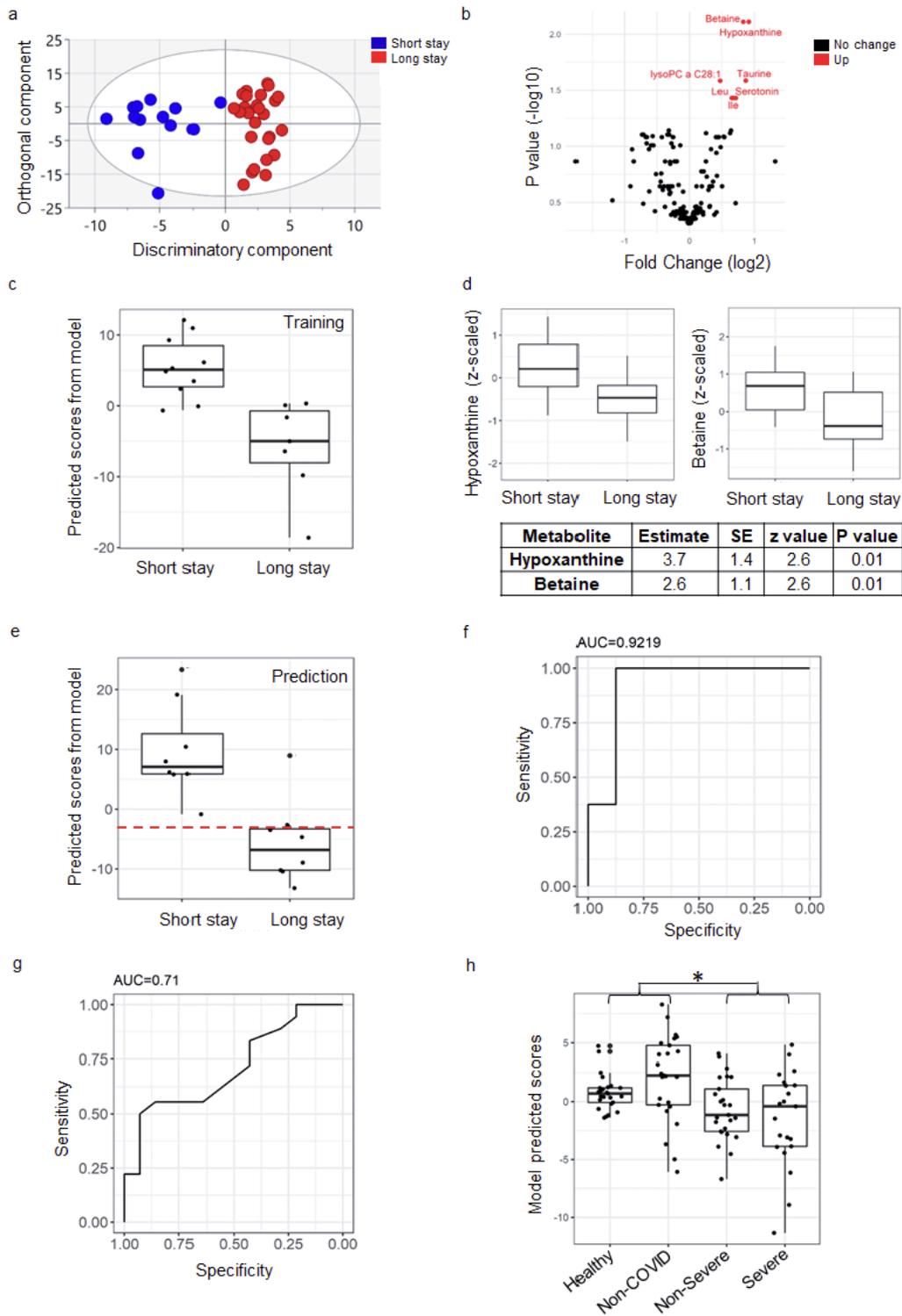
Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

## Figures



**Figure 1**

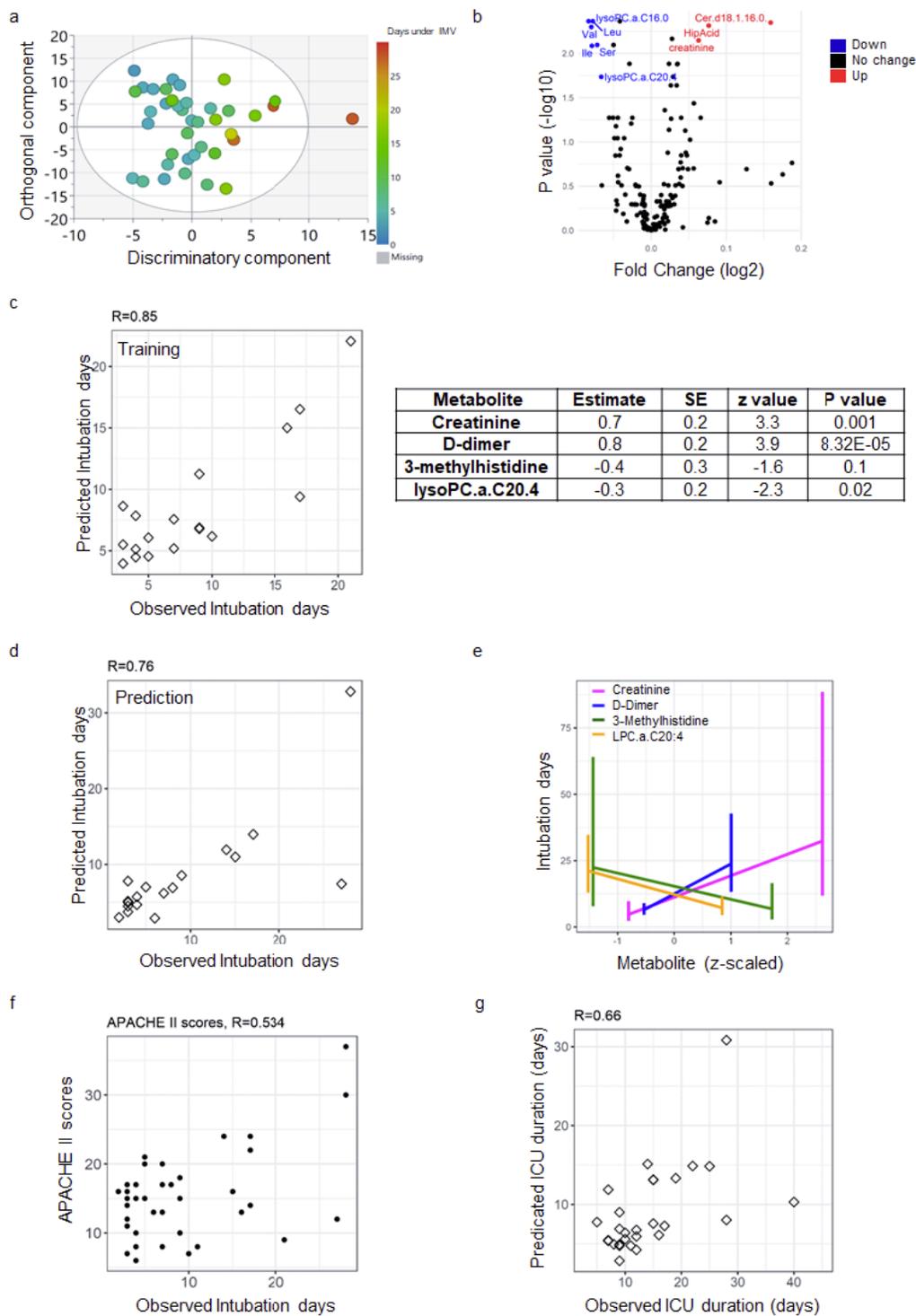
Study design. Day one represents the day of inclusion and first sample collection when all participants were already under mechanical ventilation. Patients' intubation started two days before to four days after ICU admission (window of intubation). Blood samples were collected from ICU patients one day before ICU admission to five days after ICU admission (window of ICU admission), then seven days later. Clinical and metabolic profiles were measured at day one and day seven and were correlated with four phenotypes: two continuous (days at ICU and days under mechanical ventilation) and two categorical (short ( $\leq 14$  days) or long ( $>14$  days) stay at ICU and progression to ECMO). Clinical outcomes were recorded at days one, seven, fourteen, twenty- one and sixty. Participants' data for age, BMI, days under mechanical ventilation and days at ICU are presented as mean  $\pm$  standard deviation (SD).



**Figure 2**

Predictive model of length of stay (LOS) categorized into short/long based on measurement from day one. OPLS-DA score plot from the whole cohort showing the class-discriminatory component (x-axis) versus the orthogonal confounding component (y-axis) for long versus short LOS groups, the discriminatory component explaining up to 86% of the variation in the Y phenotype variable (a). Volcano plot showing significantly associated metabolites (log fold change > 0.06, adjusted pvalue ≤ 0.05)

differentiating long from short LOS groups from the linear model based on the training set (b). A predictive model of LOS based on the training set showing perfect separation of patients with short versus long ICU-stay from the same set (n=17) (c). The model featured two explanatory metabolites: Hypoxanthine and Betaine with independent effects (d). Validation of the model using the prediction set (n=16) and assuming a hypothetical separation line (dashed line in red), the model only misclassified one ICU long stay patient (e). The AUC value from ROC curve analysis was 0.92 (f). Although the APACHE II score is significantly higher at day 1 in patients that remain at ICU for longer than 14 days (p=0.01, table1), in terms of discriminatory power it is inferior to our model (AUC=0.71, n=39) (g). Testing the model on published metabolomics data (28 healthy subjects, 25 non-COVID-19 patients, 25 non-severe COVID-19 patients, and 28 severe COVID-19 patients) revealed that the predicted scores from COVID19 patients are lower than controls, and similar to the lower predicted scores by ICU long stay patients when compared to short stay (\* p value <0.001) (h). Data points were slightly scattered across the x-axis for ease of visualization in all boxplots.



**Figure 3**

Predictive model of duration of invasive mechanical ventilation (IMV) based on 280 measurements from day 1. OPLS score plot showing the class-discriminatory component (x-axis) versus orthogonal component (y-axis) for duration of IMV, the discriminatory component explaining up to 86% of the variation in the Y phenotype variable (a). Volcano plot showing top associated metabolites (log fold change > 0.06, adjusted p value ≤ 0.05) with duration of IMV from the linear model based on the training

set (b). The predictive model was trained on metabolites and clinical traits measured from the training set (n=17) on day one (c), then validated on the prediction set (n=16) (d). The model comprised of three metabolites and one clinical trait (e) that together showed a better predictive power compared to APACHE II score (f). Using the model to predict the highly correlated number of days at ICU produced a correlation level of 0.66 with their observed counterparts (g).

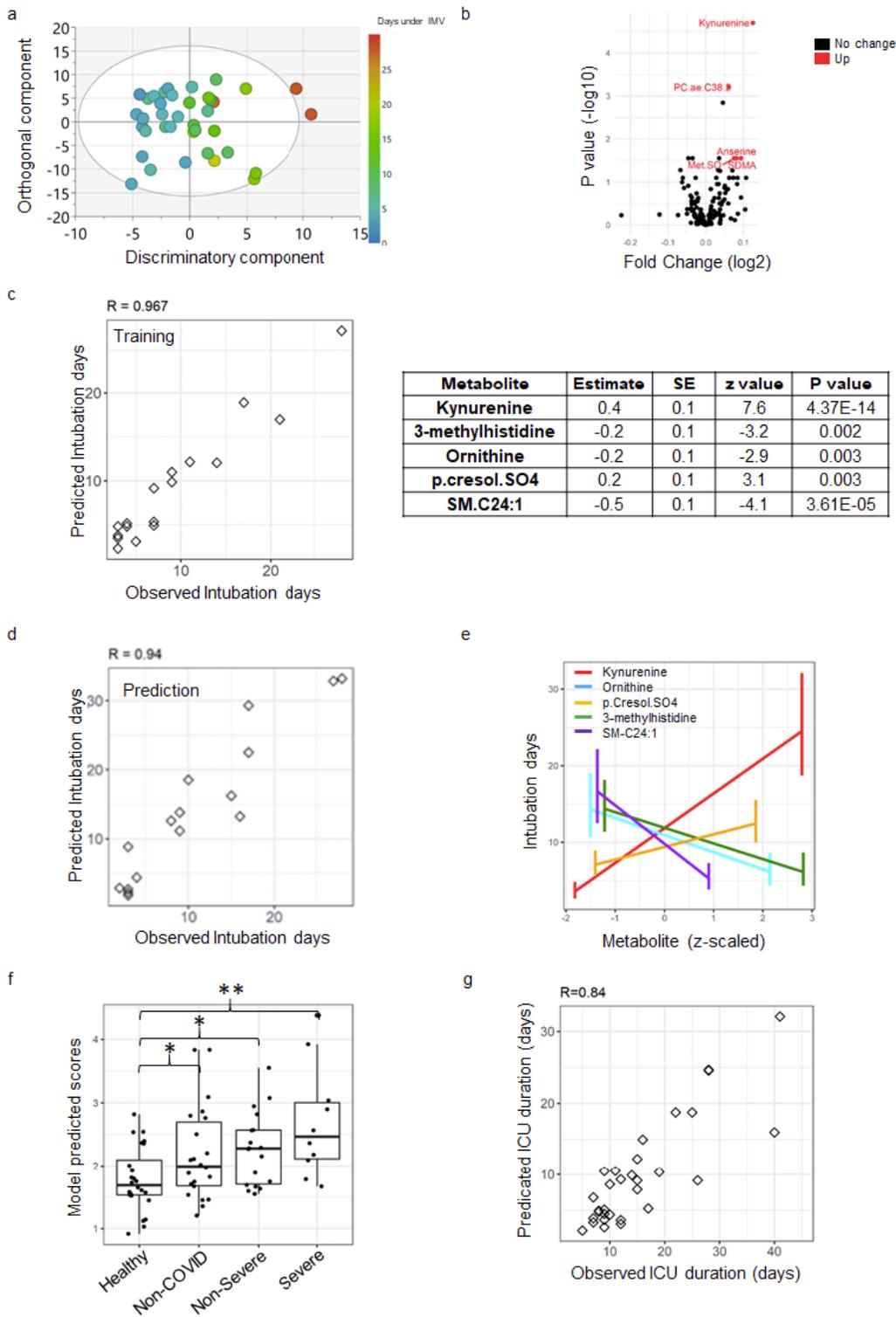


Figure 4

Predictive model of duration of invasive mechanical ventilation (IMV) based on measurements from day 7. OPLS score plot showing the class-discriminatory component (x-axis) versus orthogonal component (y-axis) for duration of IMV, the discriminatory component explaining up to 94% of the variation in the Y phenotype variable (a). Volcano plot showing top associated metabolites (log fold change > 0.06, adjusted p value  $\leq 0.05$ ) with duration of IMV from the linear model based on the training set (b). Analysis of the training set (n=17) revealed that the best predictive model only featured metabolites and none of the clinical traits (c), the model was validated on the prediction set (n=16) (d). The model comprised of five predictive metabolites that either increased or decreased at day 7 with longer intubation days (e). When tested on published metabolomics data from non-ICU patients, it could reveal the extent of severity (\* p value <0.05, \*\* p value <0.001) (e). Data points were slightly scattered across the x-axis for ease of visualization in the boxplot in (f). Using the model to predict the highly correlated number of days at ICU produced a correlation level of 0.84 with their observed counterparts (g), superior to that based on day 1.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FigS1.png](#)
- [FigS2.png](#)