Flying the Plane While Improving It – Learning from COVID Patient Data in Close to Real Time

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Disclosures

- We will mention the use of specific therapeutics for COVID-19 such as remdesivir and tocilizumab
- We have no disclosures related to these therapies
- BTG is a consultant for Janssen Research and Development, LLC

Disclosures

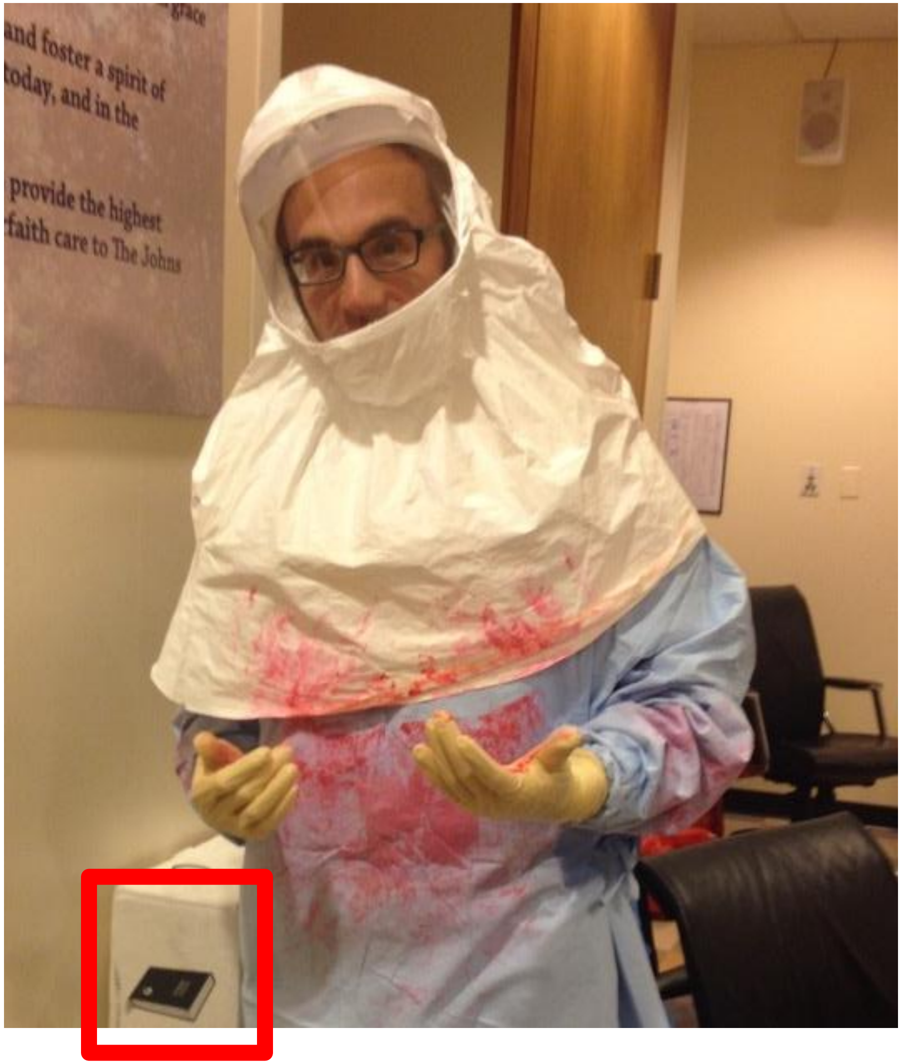
JOHNS HOPKINS MEDICINE

Objectives

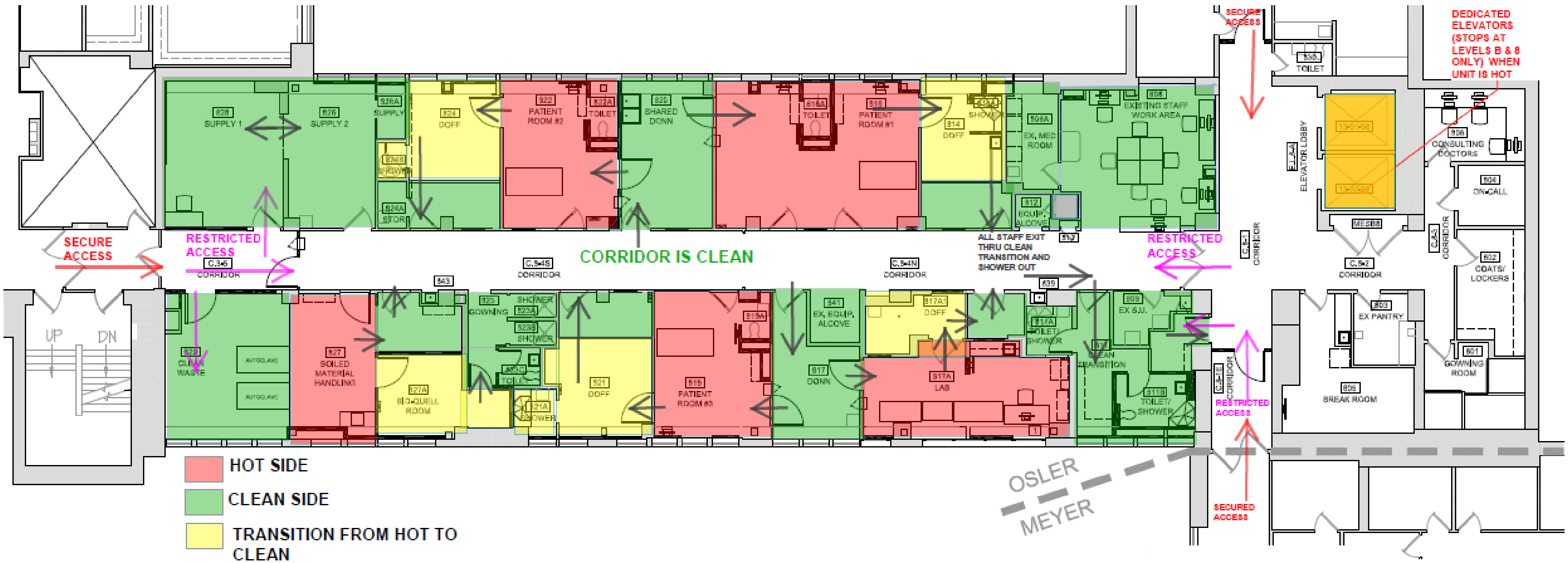
By the conclusion of this talk, you will be able to:

- Describe the purpose of the JH-CROWN registry
- Cite one challenge that was encountered during the development of JH-CROWN and the method(s) used to address the challenge
- Summarize one research insight that was enabled by the use of JH-CROWN
- Feel good to know clinical and data scientist are collaborating to improve Covid-19 outcomes

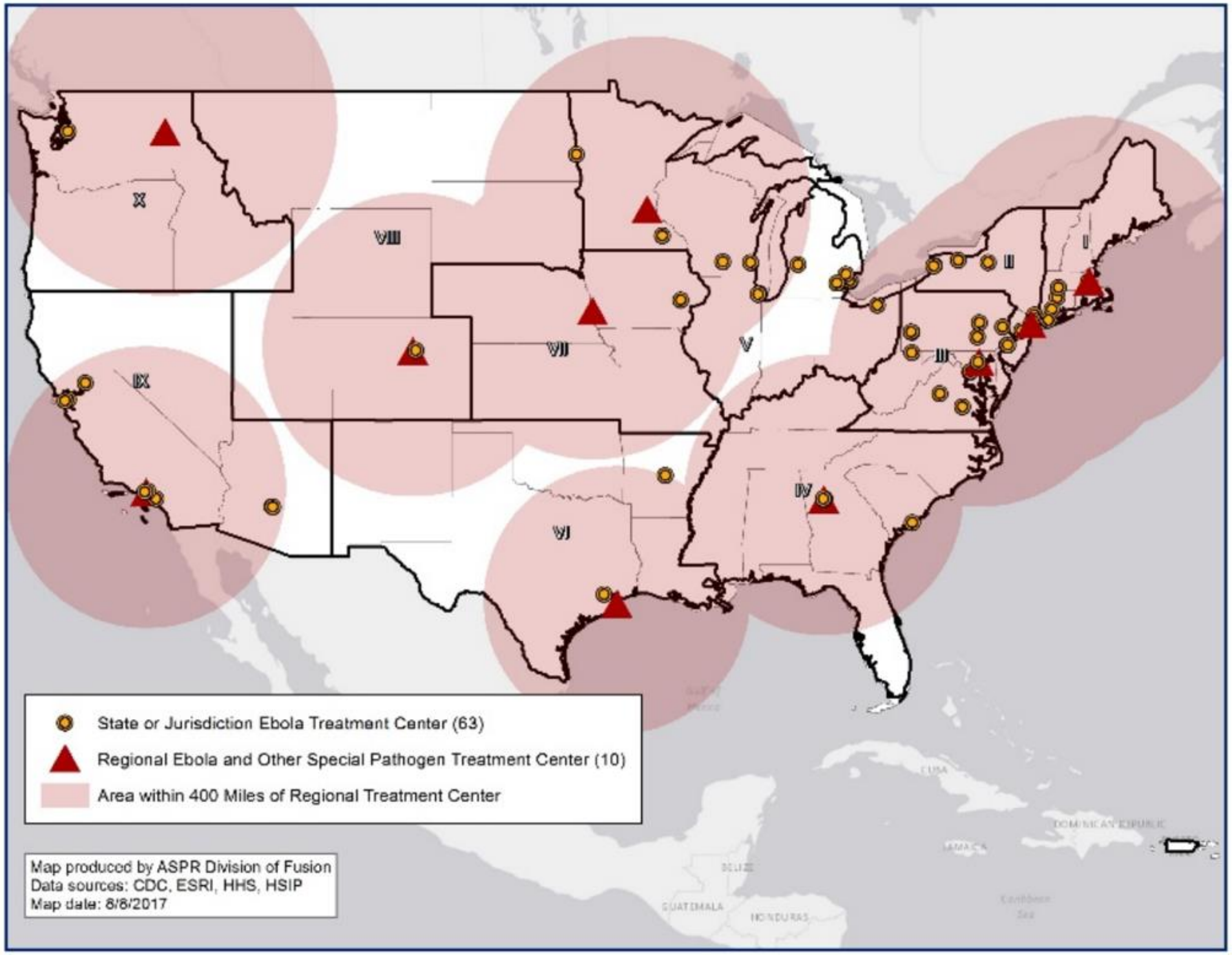
September 2014



The JH Biocontainment Unit



Regional Ebola and Special Pathogen Treatment Centers (RESPTCs)



The Hopkins BCU Vision

Patient Care
Federal recognition as a national center for highly infectious diseases

The Johns Hopkins Biocontainment Unit

Research and Innovation
Technology, The Built Environment, Work Flow, Patient-Centered Care, Clinical Research

Education and Training
JHU Staff
Local Community
Other Institutions

BCU Activation for COVID-19

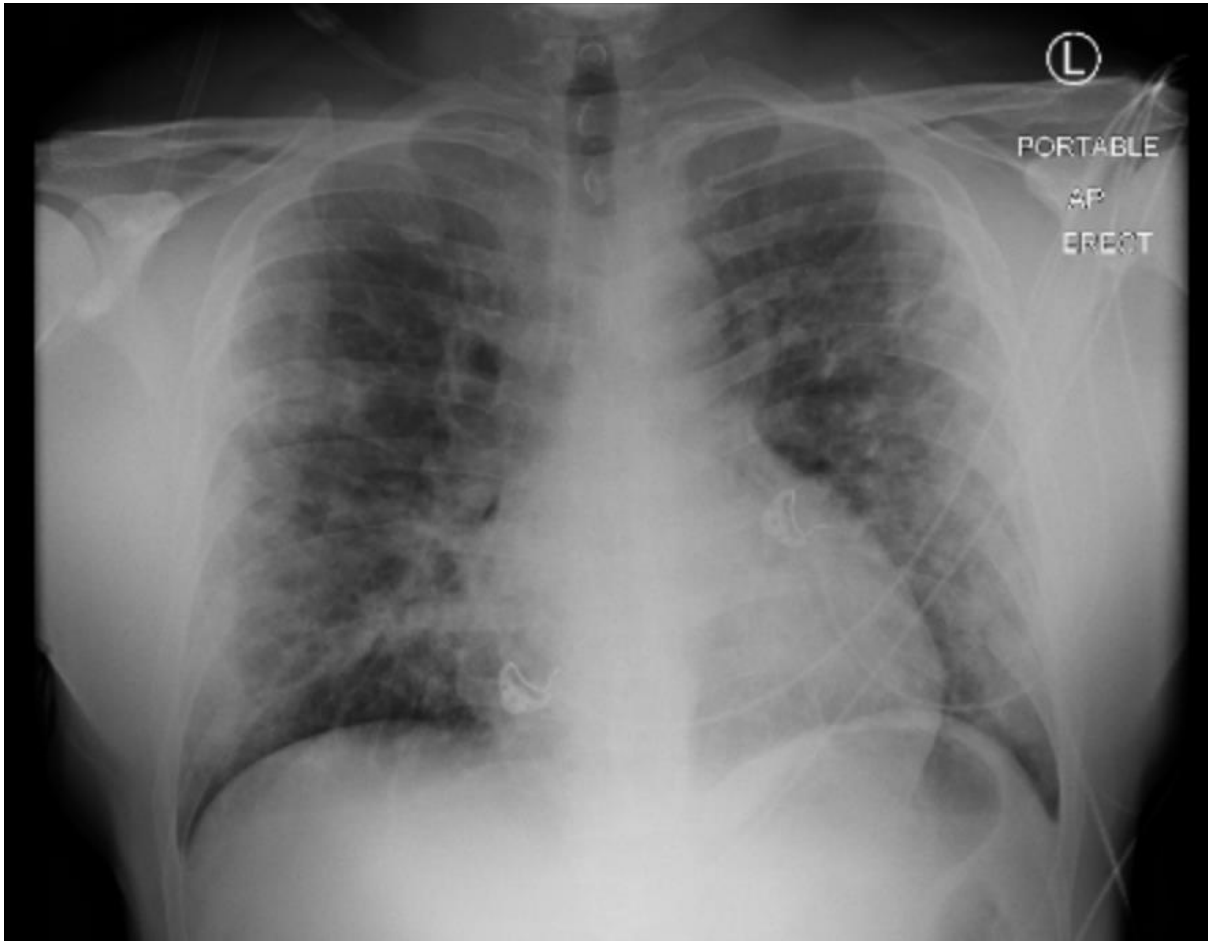
	Dates	Patients
Activation #1	February 29th-March 4th	2 PUIs
Activation #2	March 6th-March 8th	1 PUI
Activation #3	March 13th-March 20th	11 COVID-19+


GIVE THE VTE MED DOSE!
Decrease likelihood

ICU Patient 1

- 40 y/o male with 4-day history of fever and cough
- Recent travel to Florida 1 week before
- No significant PMH

T 38.9 RR 44 P 115 BP 119/59 92% NRB



How do we treat him?

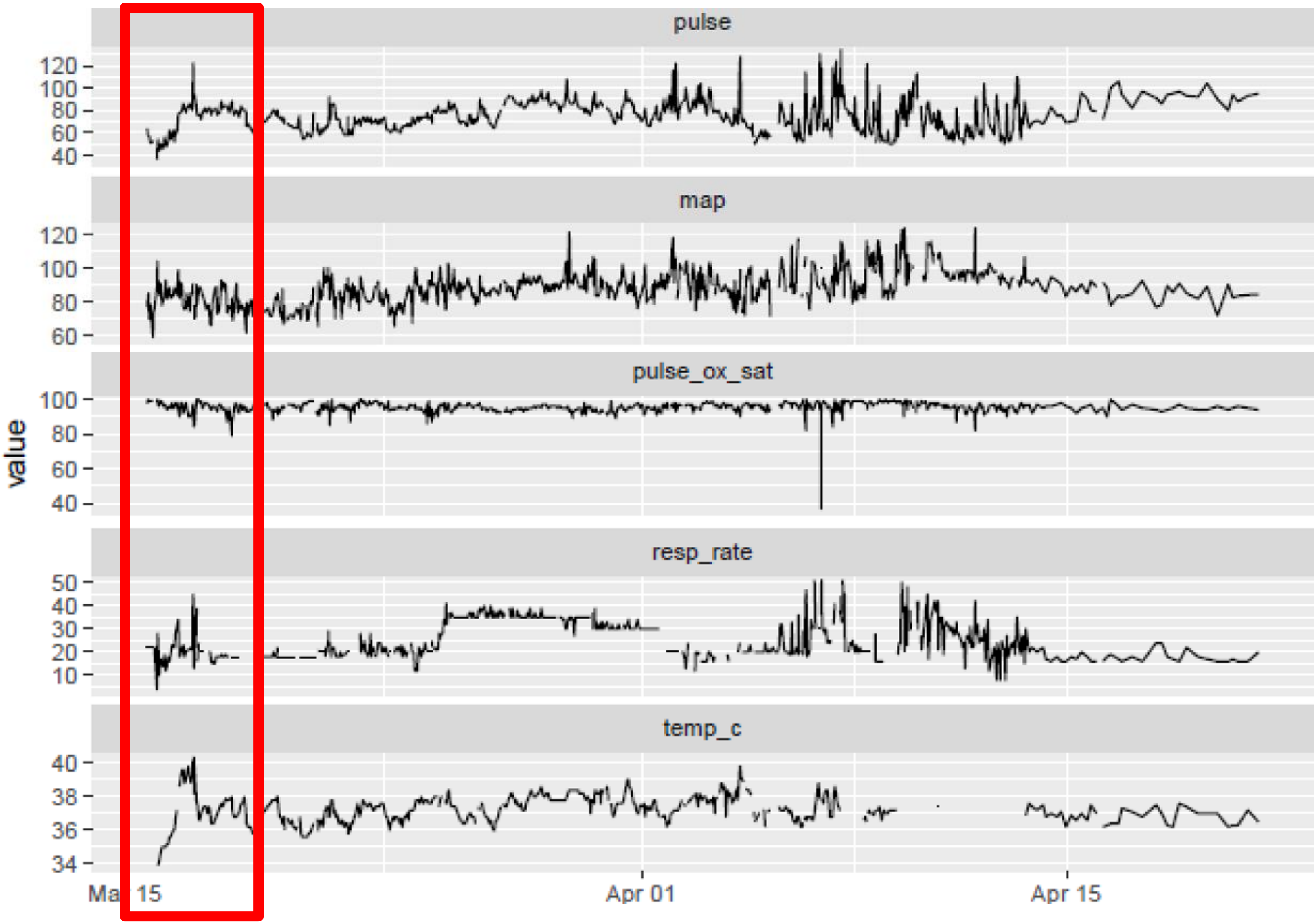
- Intubation and mechanical ventilation
- Proning
- Hydroxychloroquine
- Remdesivir
- Steroids
- Lopinavir/Ritonavir
- Tocilizumab
- Anticoagulation

Clinical Course

- Intubated for 26 days
- Proned multiple times
- Mildly reduced EF
- Left brachial vein DVT
- Ventilator associated pneumonia
- Prolonged delirium
- 50-pound weight loss

Lab Highlights

- D-dimer>30 mg/L FEU
- Fibrinogen 914 mg/dl
- Absolute lymphocyte count 690 K/cu mm
- CRP 21.5 mg/dl
- IL-6 905 pg/ml

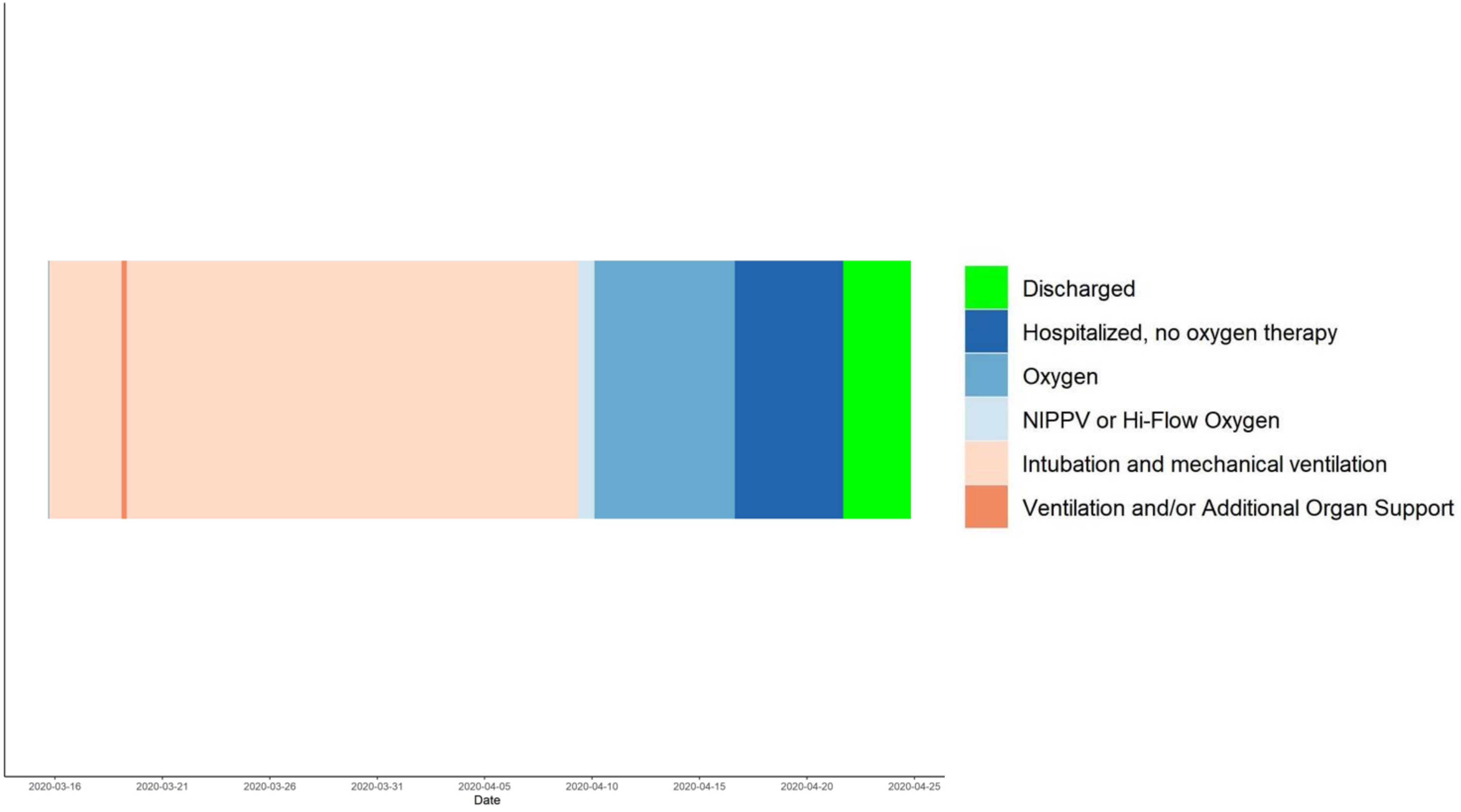


pulse
map
pulse_ox_sat
resp_rate
temp_c
value
120
100
80
60
40
50
30
20
10
38
36
34
Mar 15
Apr 01
Apr 15

WHO 'States' of COVID-19

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Trajectory for Patient AA




JOHNS HOPKINS
in
HEALTH
"PRECISION MEDICINE IS NOT ABOUT MAKING DISCOVERIES THAT ARE INTERESTING, PRECISION MEDICINE IS ABOUT CHANGING THE WORLD AND BRINGING EFFICIENT HEALTH CARE OF GREAT VALUE TO SOCIETY AND THE POPULATION." ANTONY ROSEN

Precision Medicine Analytics Platform (PMAP)

https://pm.jh.edu/

THE JH-CROWN REGISTRY

- Patients across Johns Hopkins with a positive test for SARS-CoV-2 or a diagnosis of COVID-19
- Any patient who is tested for SARS-CoV-2 at JHM
- EPIC data (labs, meds, vital signs, notes, etc.), Radiology Data, Physiologic Monitoring
- Built by a village (faculty, students)
- Basis for novel statistical analytics
- 6000 COVID inpatients, 20,000 COVID outpatients, 150,000 negative controls

https://ictr.johnshopkins.edu/coronavirus/jh-crown/

Clinical and statistical objectives

Support clinicians to provide valid, science-based (partial) answers to three questions patients ask:

1. What is my current disease state and how does it compare to other patients?
2. What is my likely disease trajectory?
3. Among the available treatments, which is best for me now?
   - What is the population-average effect of this treatment on people “like me?
   - How heterogeneous is the treatment efficacy and safety?

Statistical Challenges

1. Wrangling gigabytes of transactional EHR data into a longitudinal data set for thousands of patients; limitations of measurements
2. Brand new disease without a clinical evidence base
3. Observational, not experimental data

   …=> Treatments(i,t-1) => Outcomes(I,t) => Treatments(I,t) =>…

3. Outcomes comprise many biomarkers, major events and treatment choices
4. Competing risks of three major events: discharge, intubation, death
5. Significant fraction of deaths complicate off-the-shelf LDA
6. Predictors are numerous and dynamic; many are irrelevant; need to find the important ones
7. Potentially useful results are unhelpful until translated into terms clinicians can understand to improve their decisions

Project 1 Question: *What is my risk of having severe disease given my condition on time 0 – start of hospitalization?*

- Severe disease definition: high flow nasal cannula, non-invasive ventilation, intubation, death before discharge
- Competing risks survival analysis
- Predict risk of severe outcome from baseline variables
- Clinical judgement + Lasso for variable selection
- Covid Inpatient Risk Calculator (CIRC) *(Garibaldi, et al, 2020)*

Annals of Internal Medicine

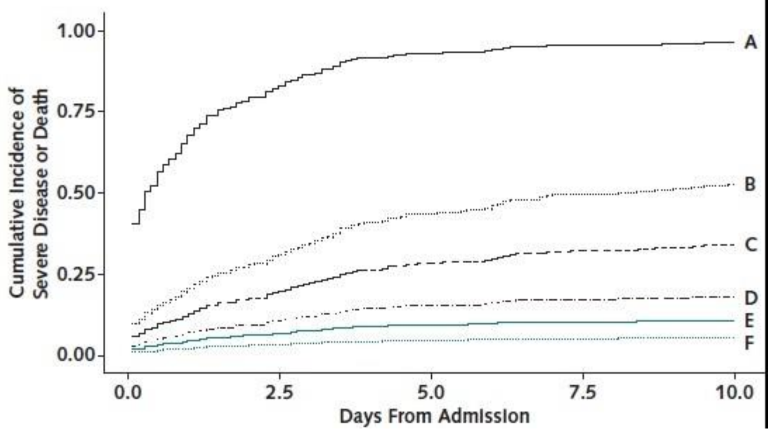
ORIGINAL RESEARCH

Patient Trajectories Among Persons Hospitalized for COVID-19

A Cohort Study

Brian T. Garibaldi, MD, MEHP*; Jacob Fiksel, PhD*; John Muschelli, PhD; Matthew L. Robinson, MD; Masoud Rouhizadeh, PhD; Jamie Perin, PhD; Grant Schumock, BS; Paul Nagy, PhD; Josh H. Gray, BS; Harsha Malapati, BS; Mariam Ghobadi-Krueger, BS; Timothy M. Niessen, MD, MPH; Bo Soo Kim, MD; Peter M. Hill, MD; M. Shafeeq Ahmed, MD, MBA; Eric D. Dobkin, MD; Renee Blanding, MD; Jennifer Abele, MD, MBA; Bonnie Woods, MS; Kenneth Harkness, MS; David R. Thiemann, MD; Mary G. Bowring, MPH; Aalok B. Shah, MEng; Mei-Cheng Wang, PhD; Karen Bandeen-Roche, PhD; Antony Rosen, MBChB, MS; Scott L. Zeger, PhD†; and Amita Gupta, MD, MHS†

Patient	Description	Cumulative Incidence of Severe Disease or Death		
		2 Days	4 Days	7 Days
A	81-year-old Black woman with diabetes and hypertension; BMI, 35 kg/m²; respiratory rate, 32 breaths/min; febrile; high CRP level; D-dimer level > 1 mg/L	80%	92%	96%
B	69-year-old Black man with diabetes, coronary disease, and hypertension; BMI, 38 kg/m²; respiratory rate, 23 breaths/min	28%	41%	50%
C	47-year-old Black man with diabetes and hypertension; BMI, 34 kg/m²; respiratory rate, 18 breaths/min; febrile; detectable troponin level	18%	27%	32%
D	79-year-old White man with a CCI of 0; BMI, 24 kg/m²; respiratory rate, 19 breaths/min; afebrile; detectable troponin level	10%	15%	18%
E	60-year-old White woman with a CCI of 0; BMI, 28 kg/m²; respiratory rate, 18 breaths/min; afebrile	6%	9%	11%
F	39-year-old Latinx man with a CCI of 0; BMI, 23 kg/m²; respiratory rate, 18 breaths/min; afebrile	3%	5%	5%



COVID Inpatient Risk Calculator (CIRC)

The COVID Inpatient Risk Calculator: CIRC

Preset values are the mean values of the study participants. For laboratory values, please input the first available lab value in the first 48 hours after admission for each of the requested parameters. For respiratory rate and pulse, enter the median value over the first 24hrs. Use preset values when patient values are unavailable.

Age:

62

Sex:

- (●) Male
- ( ) Female

Admitted from nursing home?:

- (●) Yes
- ( ) No

BMI:

30.4

White race?:

- (●) Yes
- ( ) No

Charlson score: (For help see Calculator)

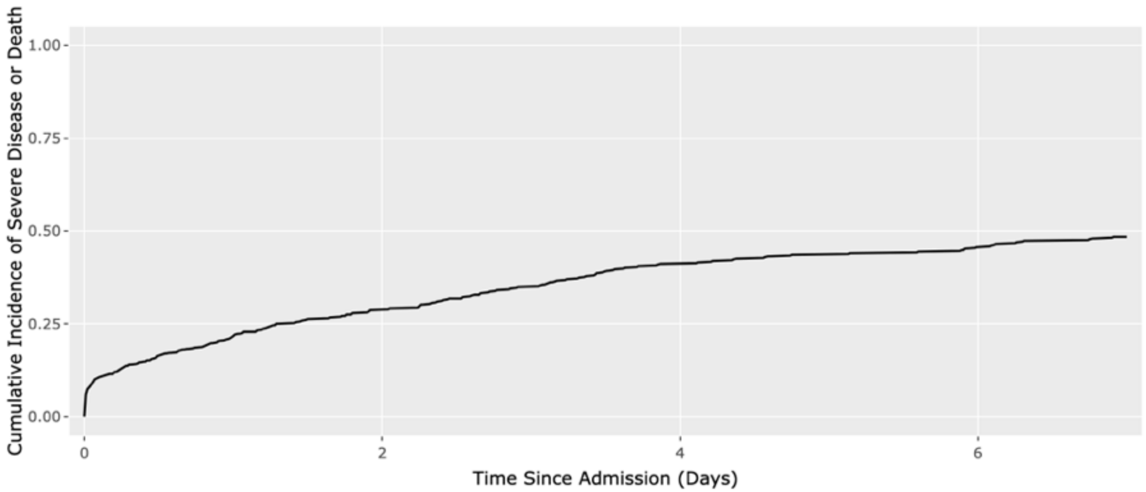
0

Has respiratory symptoms?:

- (●) Yes
- ( ) No

The COVID Inpatient Risk Calculator (CIRC) uses factors on admission to the hospital to predict the likelihood that a patient admitted with COVID-19 will progress to severe disease* or death within 7 days of arrival. This model was derived from the first 832 patients admitted to the Johns Hopkins Health System between March 1, 2020 and April 24, 2020, with follow-up through June 24, 2020 (REFERENCE ONCE AVAILABLE).

*severe disease - requiring any of the following: high flow nasal cannula, non-invasive positive pressure ventilation, invasive mechanical ventilation, ECMO, vasopressor support



Probability of Severe Disease or Death by 2 Days: 0.29
Probability of Severe Disease or Death by 4 Days: 0.41
Probability of Severe Disease or Death by 7 Days: 0.48

This application was made and developed by Grant Schumock and John Muschelli, with modeling from Jacob Fiksel and Jamie Perin.

Garibaldi, et al. Ann Int Med, 2020.

Project 2 Question: *What is my risk of having severe disease given my current condition on time t?*

- Predict risk of severe outcome from baseline and all intervening measures prior to t with 6-hourly updates
- Random Forest for Survival, Longitudinal and Multivariate (RF-SLAM) outcomes (Wongvibulsin, et al, 2019)
- Approximating tree to explain predictions to clinicians and patients (Wongvibulsin, et al, 2020)
- Severe Covid 19 Adaptive Risk Predictor (SCARP) (Wongvibulsin, et al, 2021)
- SCARP-lite implemented in JH Epic HER (Robinson, et al in 2021)

Results

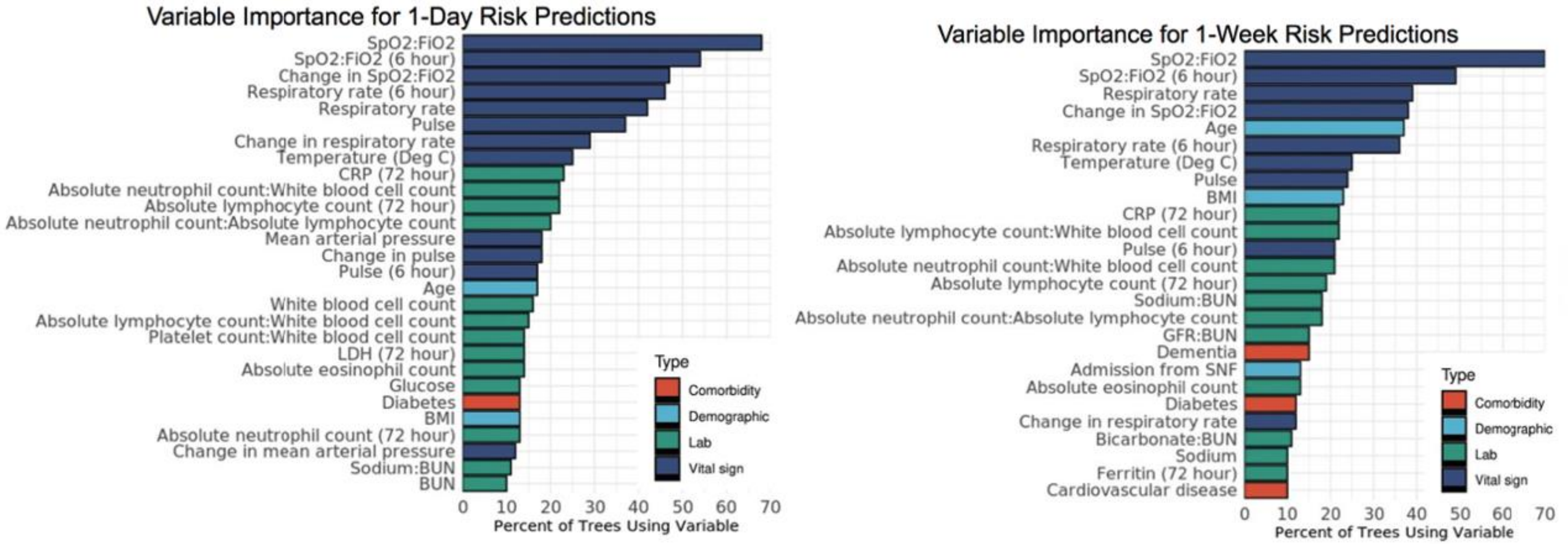
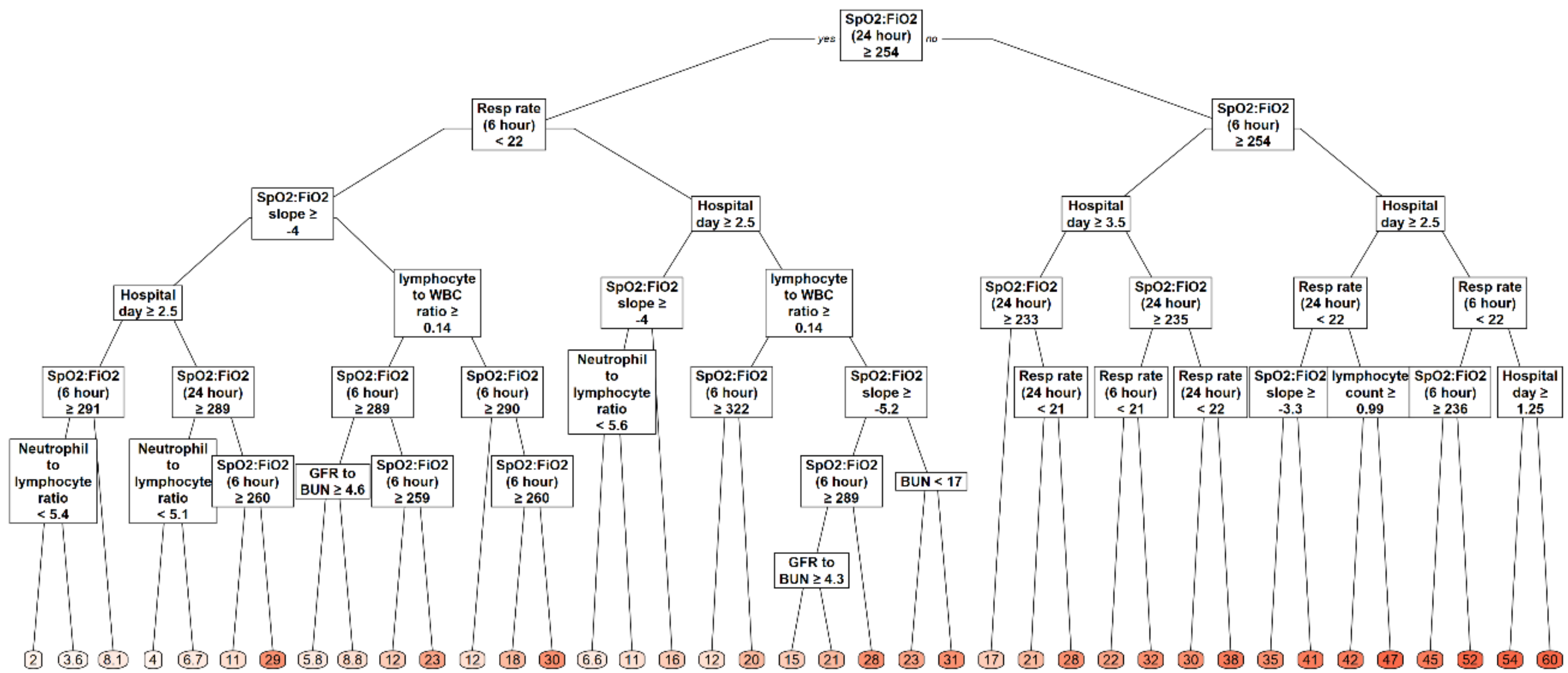


Figure 2: 1-Day risk prediction variable importance plot and 1-week risk prediction variable importance plot: The percentage of trees incorporating each of the variables is used as a simple and interpretable measure of variable importance. The variables used by 10% or greater of the trees are shown in the plots. Note: values for labs and vital signs correspond to values in the past 24 hours unless otherwise specified (e.g., 6 hour indicates that the value corresponds to the past 6 hours).

Summary of RF-SLAM predictions



Summary tree of RF-SLAM predictions of 1-week risk of severe disease or death. The predicted probabilities are expressed in the terminal nodes and shaded according to lowest risk (0%) to highest risk (100%) prediction

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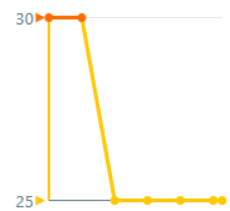
7-Day Severe COVID-19 Probability (%)	My Stick Note	1-Day Severe COVID-19 Probability (%)
35		13
16		2
12		4
8		2
5		1
5		1
4		0
3		1
2		0

JHM CUSTOM COVID-19 7-DAY PREDICTION

Score calculated: 1/27/2021 12:22

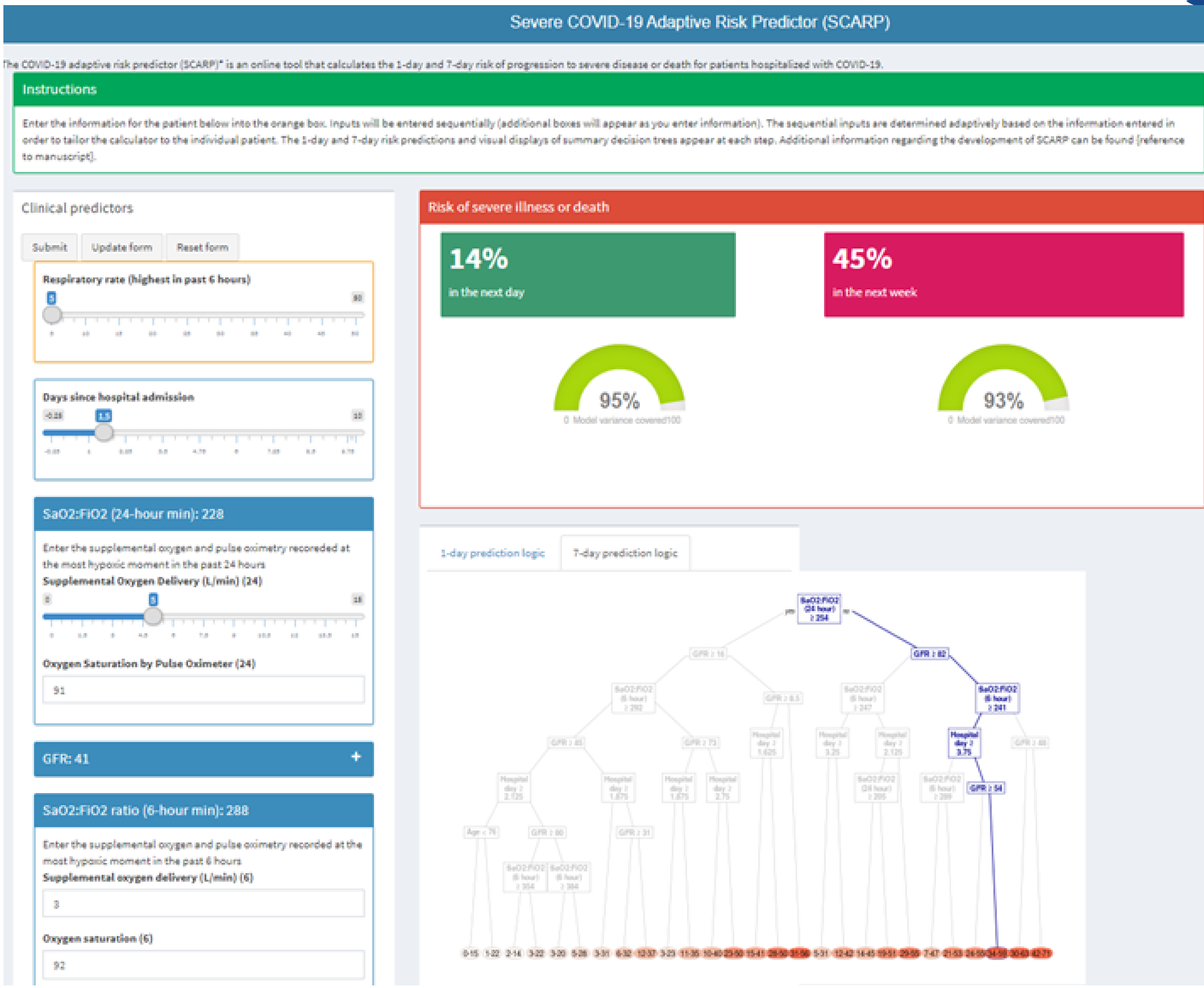
25



Factors Contributing to Score

- Last BMI is 29.83
- Age (Years) is 83
- Patient Sex Numeric is 1
- IP LOS Q6 is 7.52
- MAP Min 24H is 94
- Pulse Max 24H is 101
- Resp Max 24H is 20
- Temp Max 24H is 98.4
- SpO2:FiO2 Min 24H is 247.22
- MAP Min 6H is 111
- Pulse Max 6H is 92
- Resp Max 6H is 20
- Temp Max 6H is 97.5
- SpO2:FiO2 Min 6H is 357.14
- ANIONGAP Max 24H is 20
- BUN Max 24H is 119
- CL, CLWB Max 24H is 109
- CO2 Min 24H is 18
- GLU, GLUWB Max 24H is 152
- K, KWB Max 24H is 4.9
- NA, NAWB Max 24H is 148
- GFRAA, GFRNA Max 24H is 17
- LYMPHOABS Min 72H is 0.6
- NEUTROABS Max 72H is 9.15
- HCT Min 24H is 23.8
- HGB Min 24H is 7.2
- PLT Min 24H is 509
- WBC Max 24H is 12.58
- MCV Max 24H is 110.2
- RDW Max 24H is 14.8

3 more factors not shown

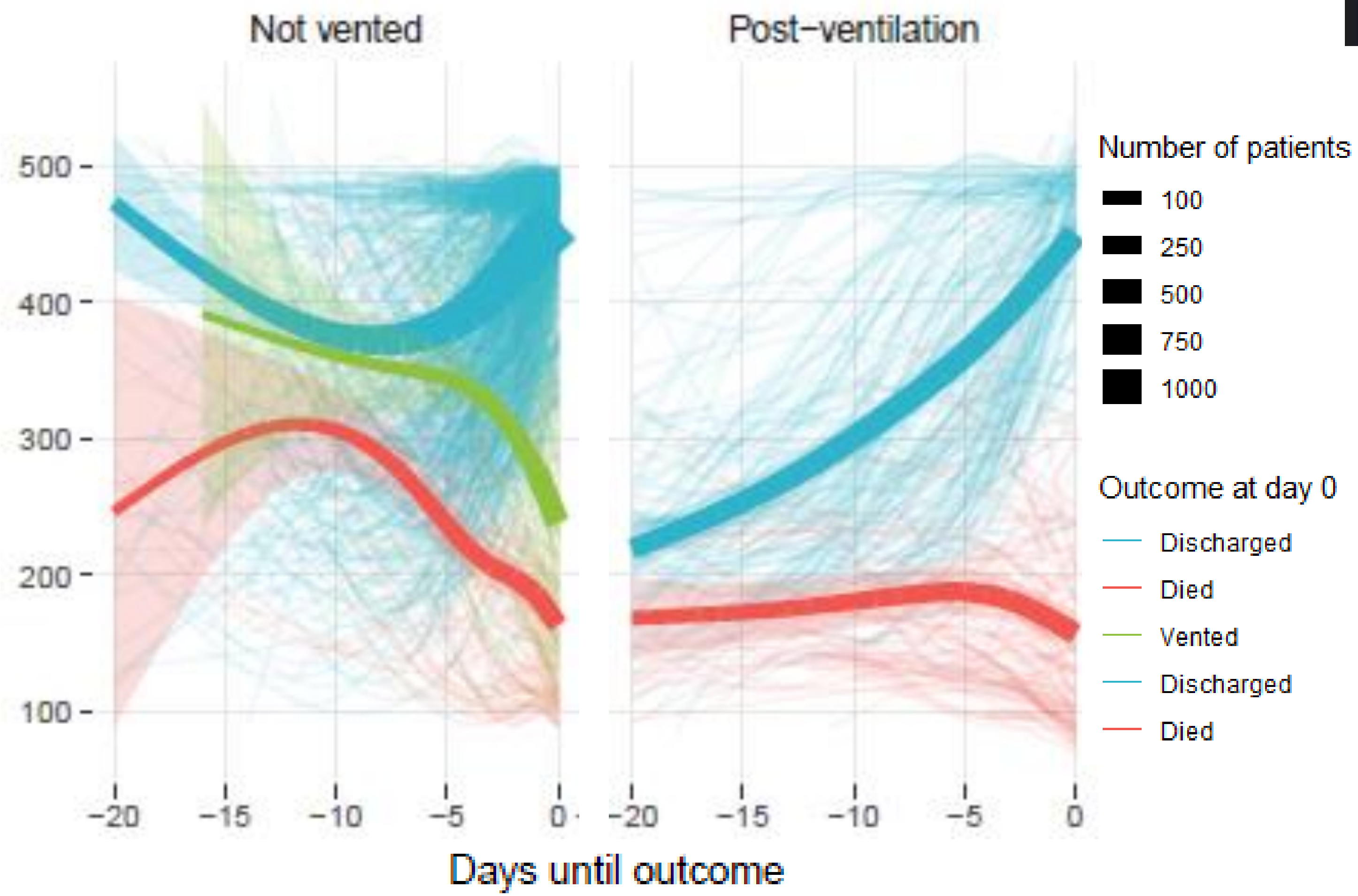

Severe COVID-19 Adaptive Risk Predictor (SCARP)
The COVID-19 adaptive risk predictor (SCARP)* is an online tool that calculates the 1-day and 7-day risk of progression to severe disease or death for patients hospitalized with COVID-19.
Instructions
Enter the information for the patient below into the orange box. Inputs will be entered sequentially (additional boxes will appear as you enter information). The sequential inputs are determined adaptively based on the information entered in order to tailor the calculator to the individual patient. The 1-day and 7-day risk predictions and visual displays of summary decision trees appear at each step. Additional information regarding the development of SCARP can be found [reference to manuscript].
Clinical predictors
Submit
Update form
Reset form
Respiratory rate (highest in past 6 hours)
Days since hospital admission
SaO2:FiO2 (24-hour min): 228
Enter the supplemental oxygen and pulse oximetry recorded at the most hypoxic moment in the past 24 hours
Supplemental Oxygen Delivery (L/min) (24)
Oxygen Saturation by Pulse Oximeter (24)
91
GFR: 41
SaO2:FiO2 ratio (6-hour min): 288
Enter the supplemental oxygen and pulse oximetry recorded at the most hypoxic moment in the past 6 hours
Supplemental oxygen delivery (L/min) (6)
3
Oxygen saturation (6)
92
Risk of severe illness or death
14%
in the next day
45%
in the next week
95%
93%
1-day prediction logic
7-day prediction logic

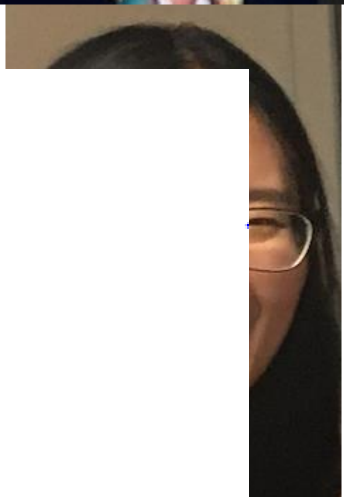
Project 3 Question: Given my current state, what are my future risks of discharge, intubation or death; what are my expected biomarker trajectories?

- Competing discrete hazards of (3) events on each future day (Project 1 approach)
- Retrospective longitudinal data analysis of multiple biomarkers *given event outcome* (define t=0 at event time) (Bowring, MG, Wang, Z et al, 2021)
- Bayes rule to calculate the probability of a future event given baseline and biomarker data until current time.

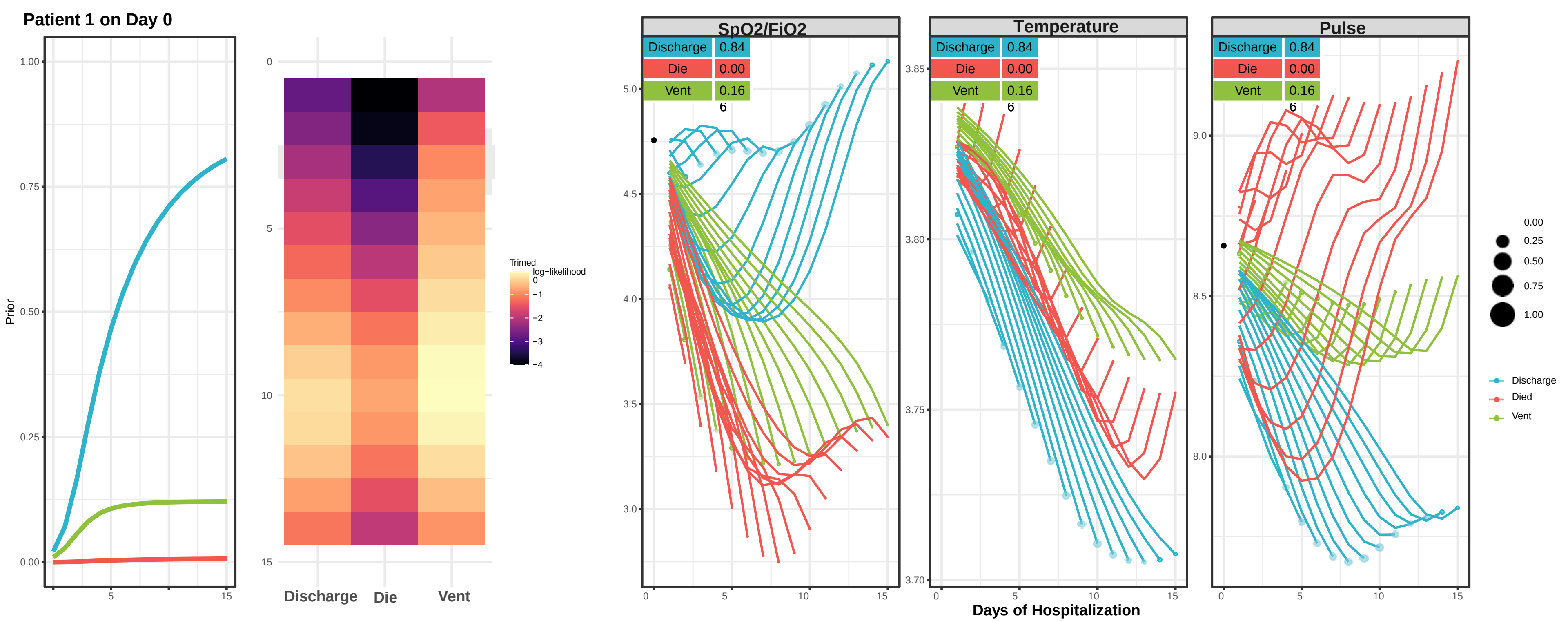
Longitudinal Data Analysis

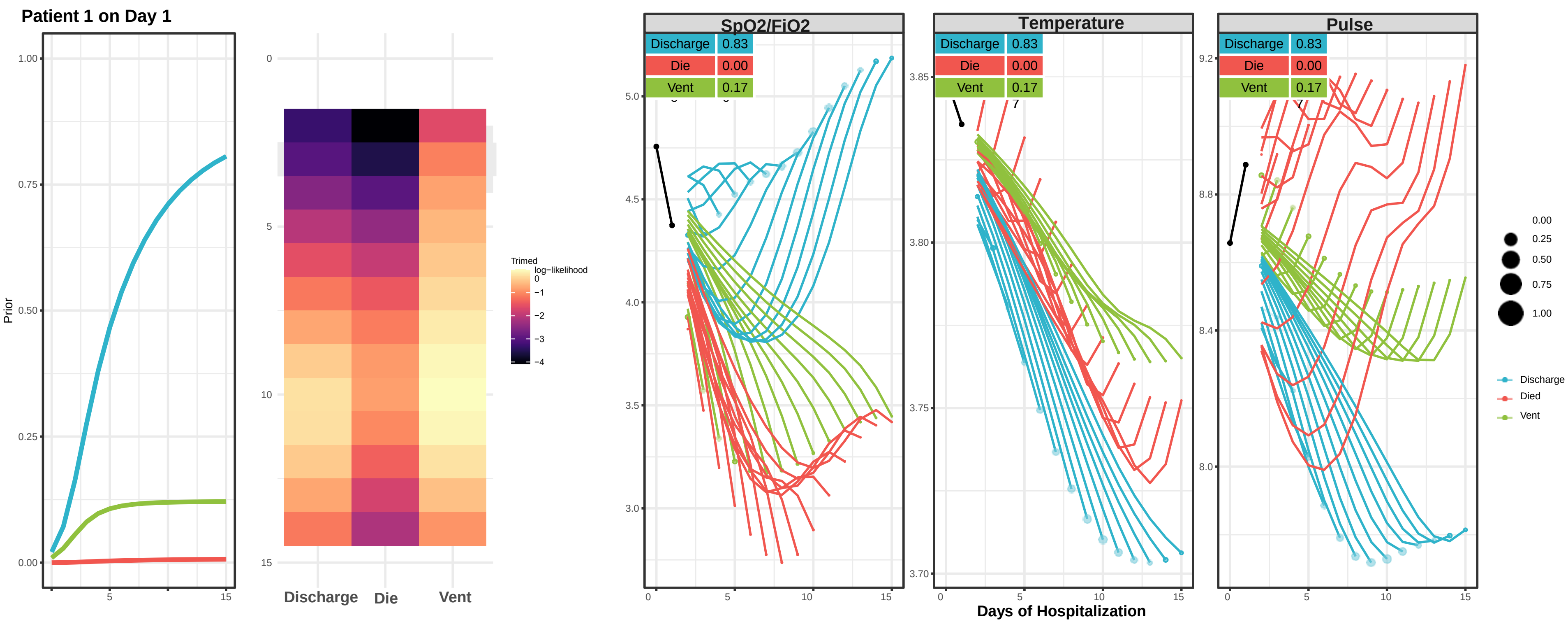
SpO2/FiO2

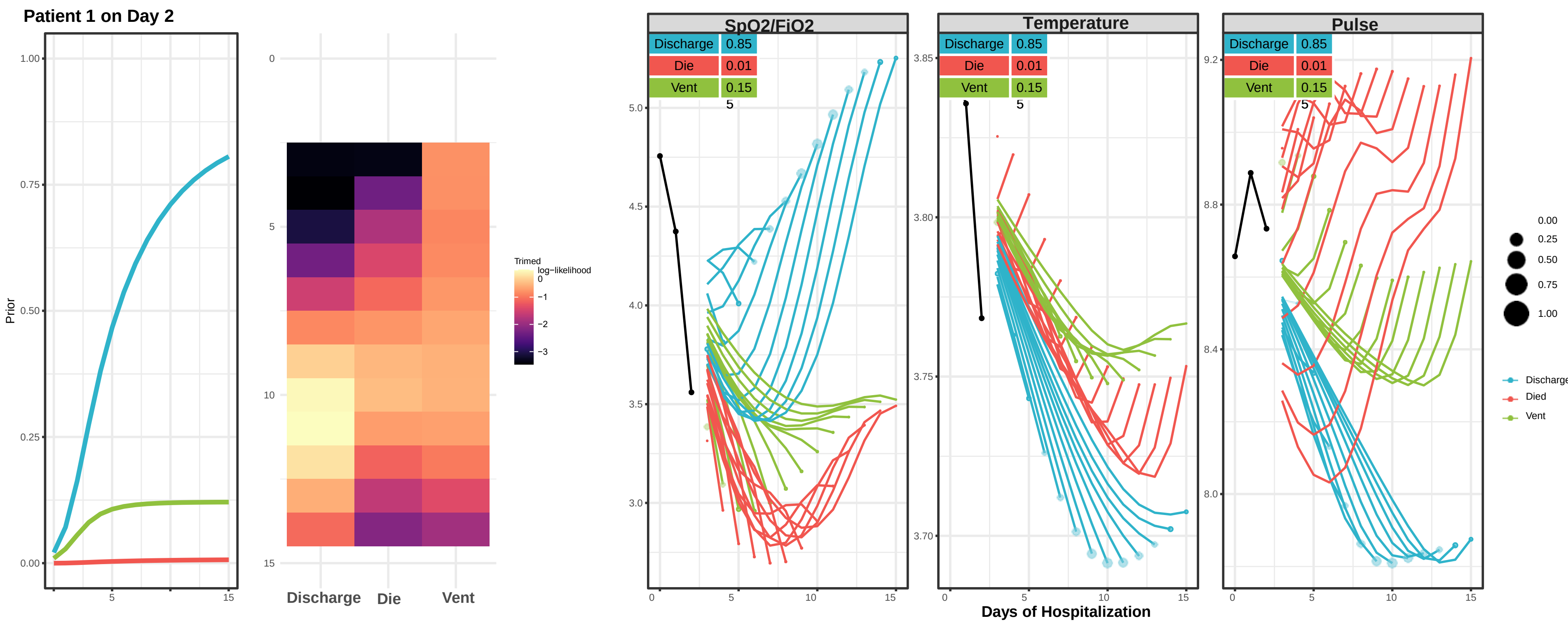




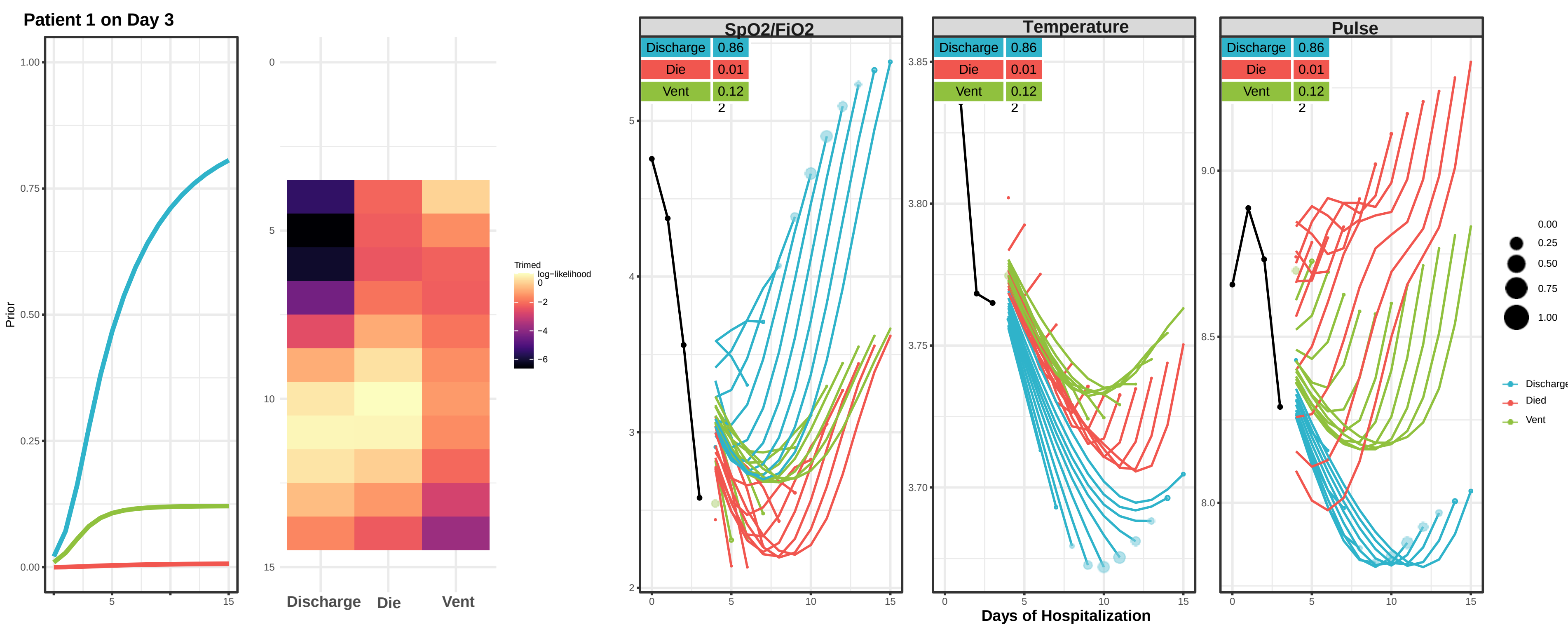
Bowring MB, in press


Patient 1 on Day 0
Prior
Discharge
Die
Vent
Trimed log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 0.84
Die 0.00
Vent 0.16
Days of Hospitalization
Discharge
Died
Vent

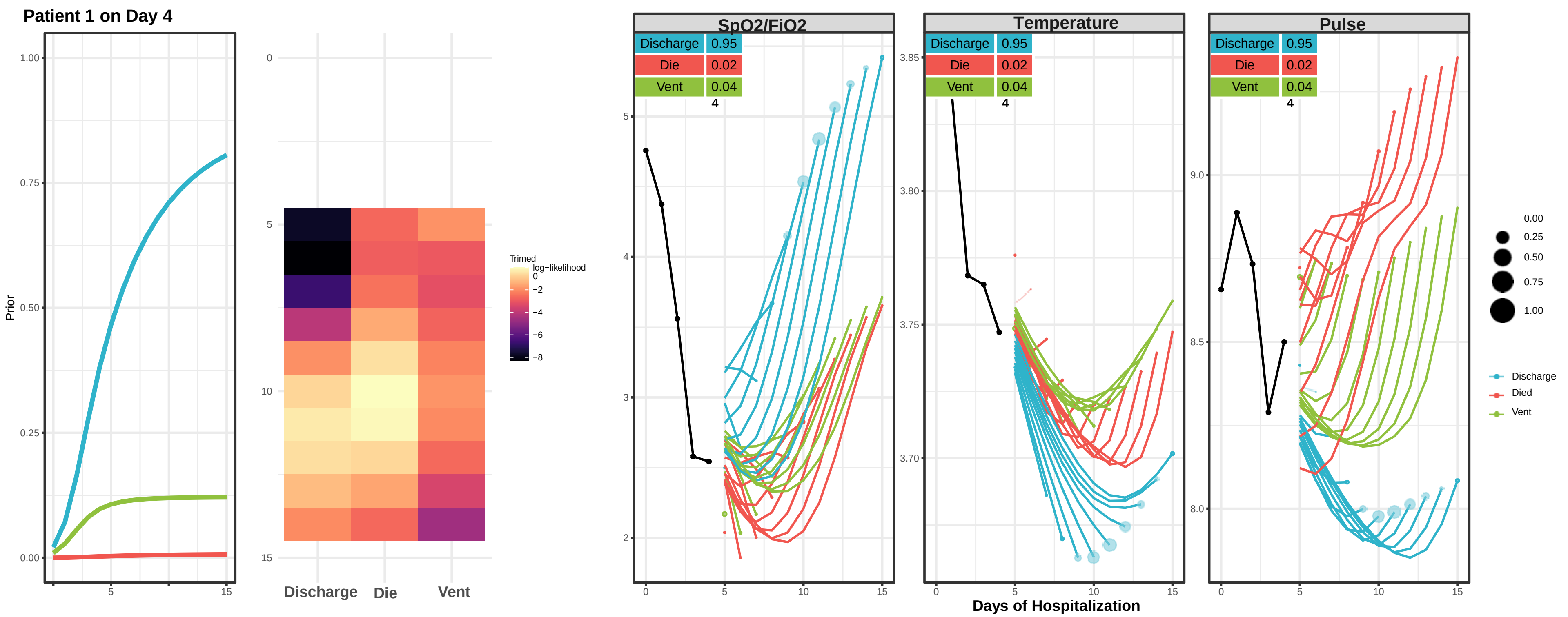

Patient 1 on Day 1
Prior
1.00
0.75
0.50
0.25
0.00
5
15
0
5
10
15
Discharge
Die
Vent
Trimed
log−likelihood
0
−1
−2
−3
−4
SpO2/FiO2
Temperature
Pulse
Discharge 0.83
Die 0.00
Vent 0.17
Days of Hospitalization
0.00
0.25
0.50
0.75
1.00
Discharge
Died
Vent



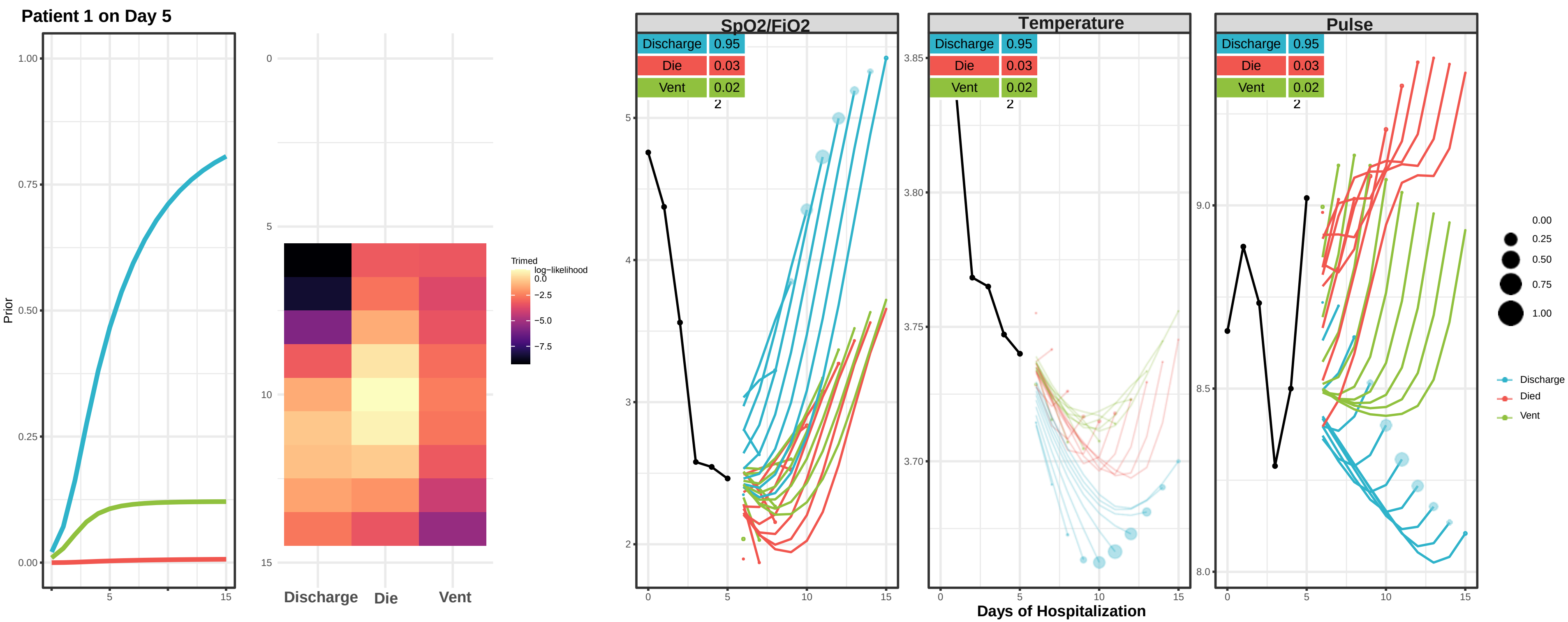
Patient 1 on Day 2
Prior
Discharge
Die
Vent
Trimed log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 0.85
Die 0.01
Vent 0.15
Days of Hospitalization
Discharge
Died
Vent

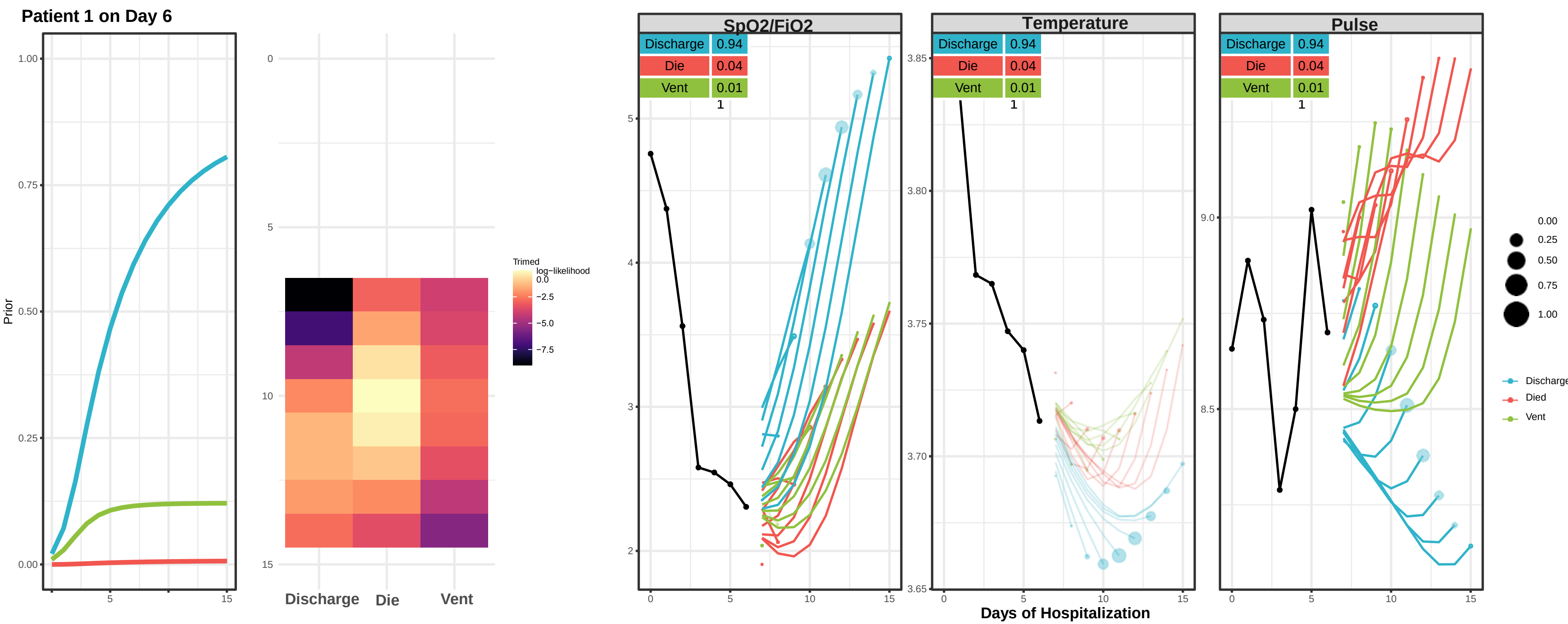


Patient 1 on Day 3
Prior
Discharge
Die
Vent
Trimed log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 0.86
Die 0.01
Vent 0.12
Days of Hospitalization
Discharge
Died
Vent

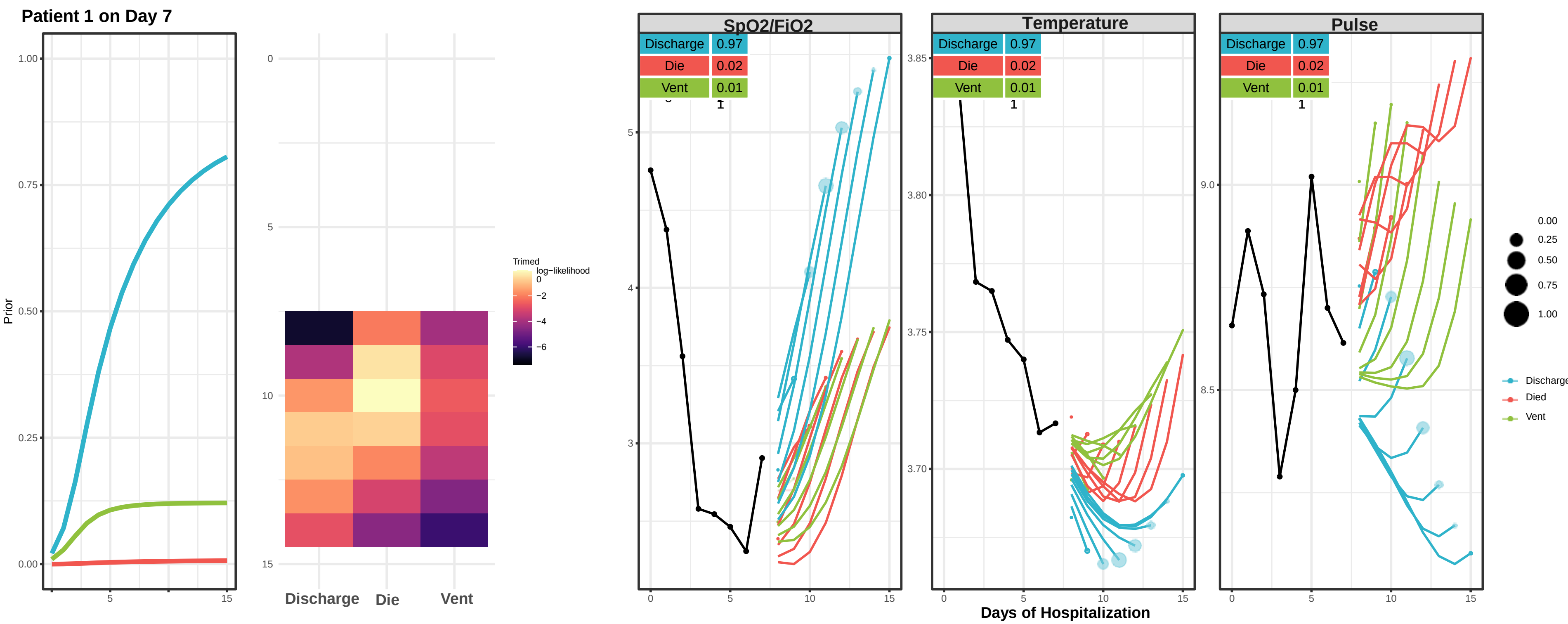


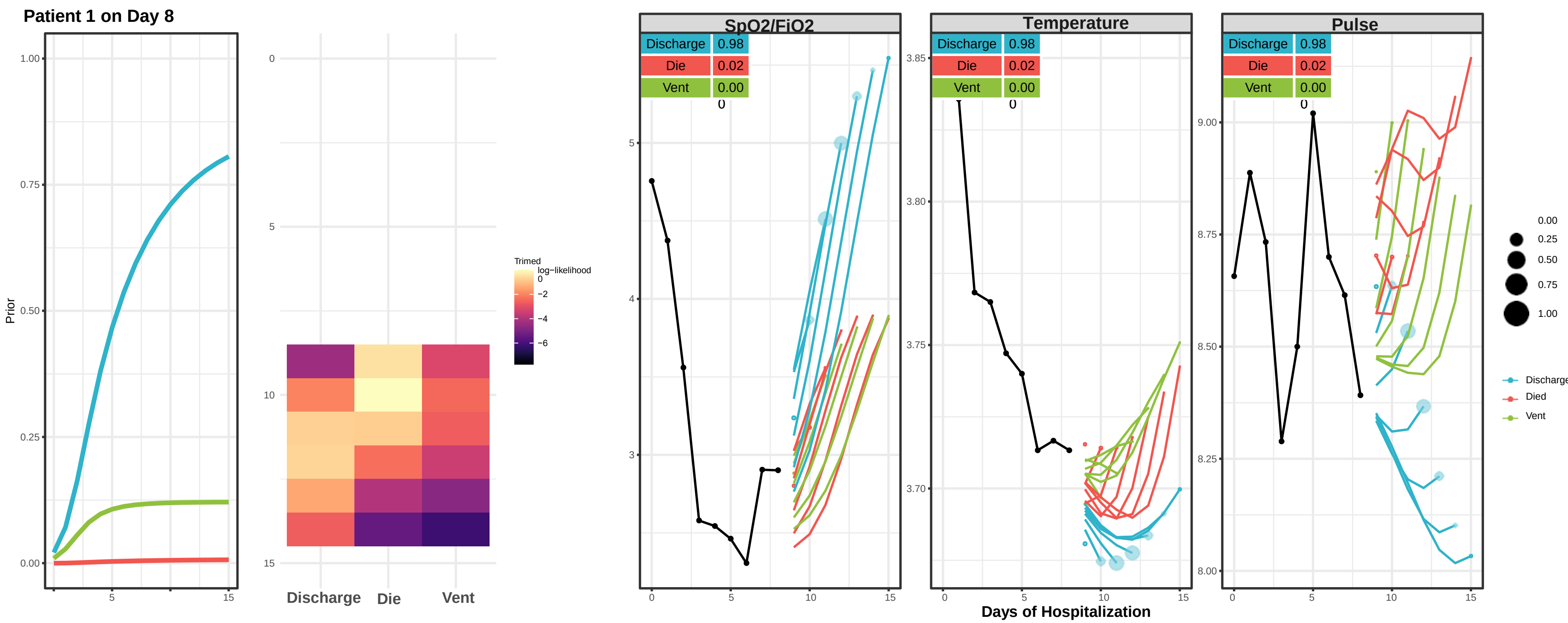
Patient 1 on Day 4
Prior
Discharge
Die
Vent
Trimed
log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 0.95
Die 0.02
Vent 0.04
Days of Hospitalization
Discharge
Died
Vent


Patient 1 on Day 5
Prior
Trimed log−likelihood
Discharge
Die
Vent
SpO2/FiO2
Temperature
Pulse
Discharge 0.95
Die 0.03
Vent 0.02
Days of Hospitalization
Discharge
Died
Vent

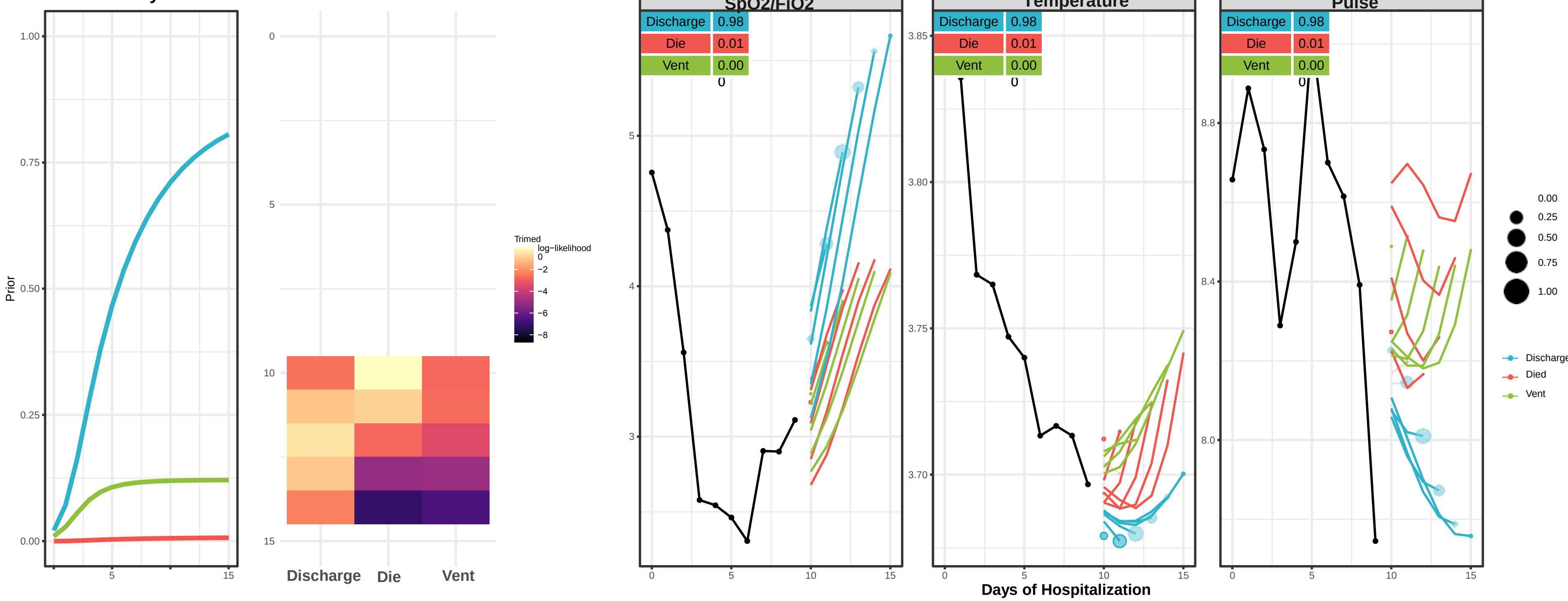


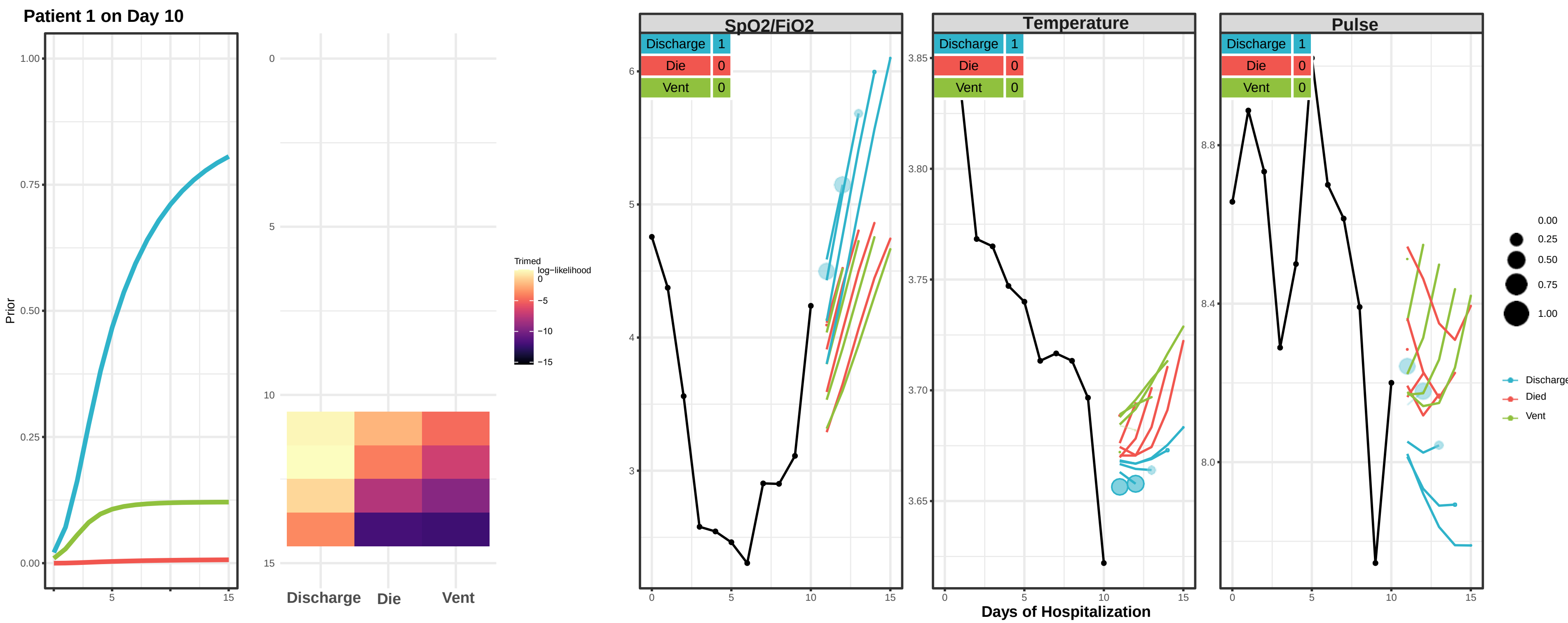
Patient 1 on Day 6
Prior
1.00
0.75
0.50
0.25
0.00
5
15
0
5
10
15
Discharge
Die
Vent
Trimed
log−likelihood
0.0
−2.5
−5.0
−7.5
SpO2/FiO2
Discharge 0.94
Die 0.04
Vent 0.01
1
Temperature
Discharge 0.94
Die 0.04
Vent 0.01
1
Pulse
Discharge 0.94
Die 0.04
Vent 0.01
1
Days of Hospitalization
0.00
0.25
0.50
0.75
1.00
Discharge
Died
Vent

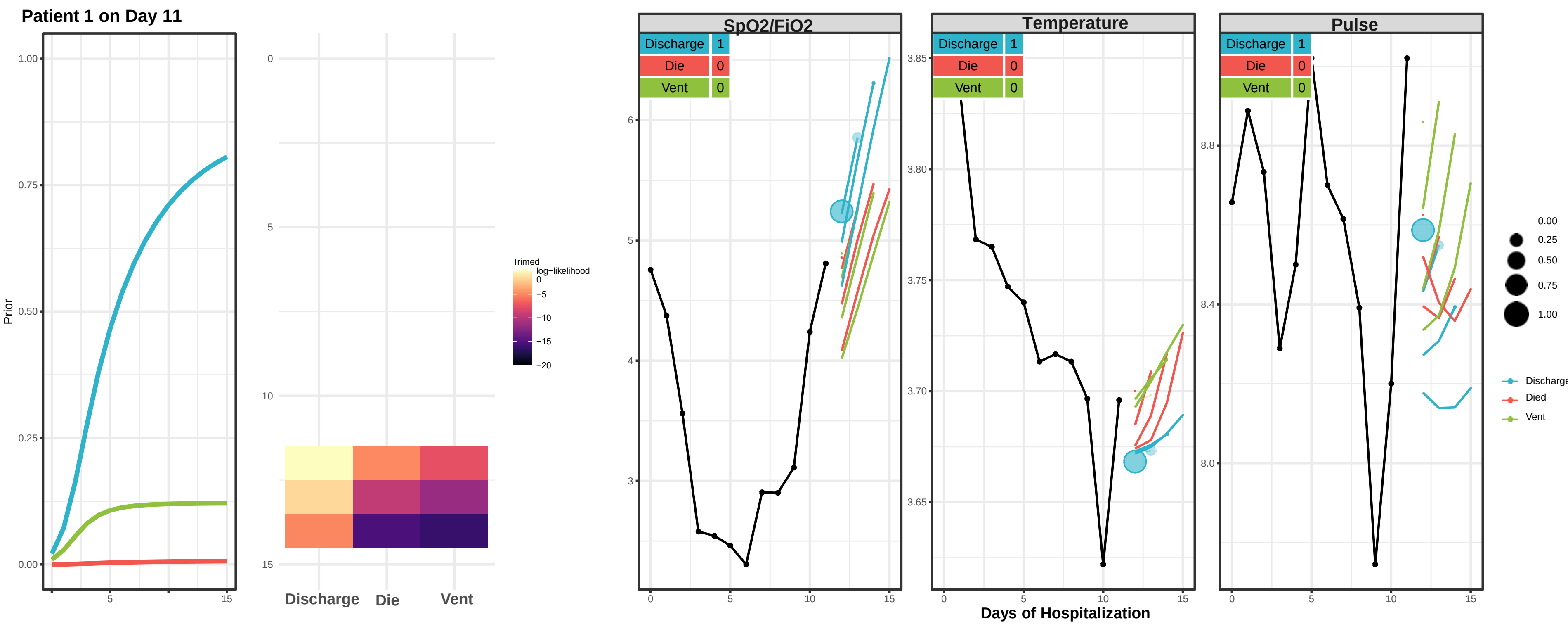

Patient 1 on Day 7
Prior
Trimed
log−likelihood
Discharge
Die
Vent
SpO2/FiO2
Temperature
Pulse
Discharge 0.97
Die 0.02
Vent 0.01
Days of Hospitalization
Discharge
Died
Vent
0.00
0.25
0.50
0.75
1.00

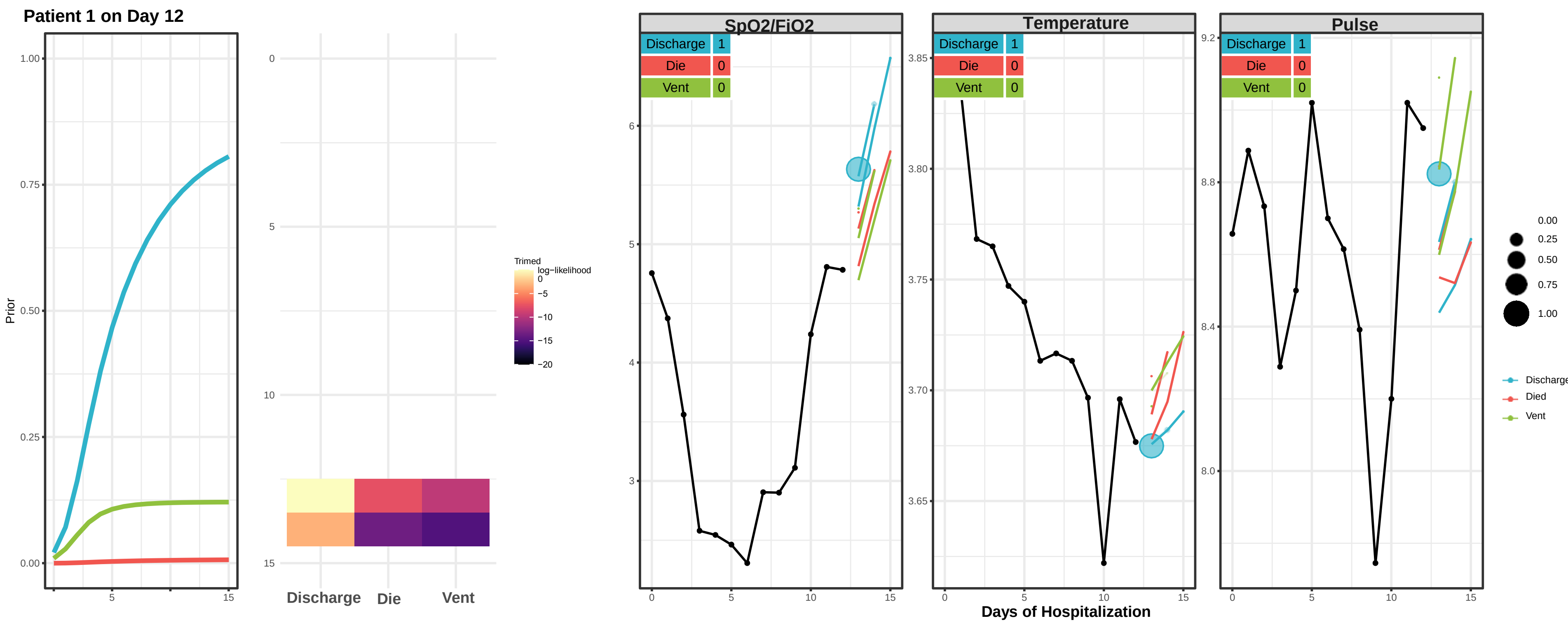

Patient 1 on Day 8
Prior
Discharge
Die
Vent
Trimed log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 0.98
Die 0.02
Vent 0.00
Days of Hospitalization
Discharge
Died
Vent

Patient 1 on Day 9

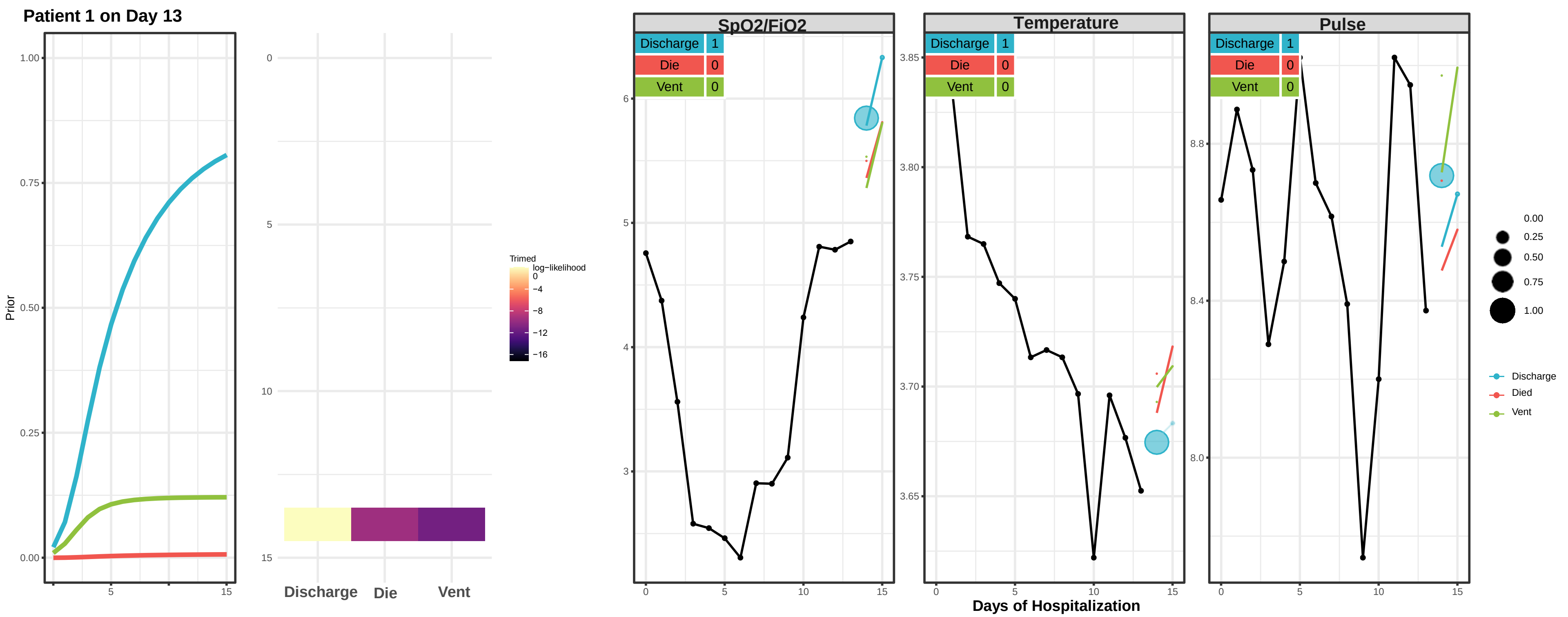



Patient 1 on Day 10
Prior
Discharge
Die
Vent
Trimed log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 1
Die 0
Vent 0
Days of Hospitalization
0.00
0.25
0.50
0.75
1.00
Discharge
Died
Vent


Patient 1 on Day 11
Prior
1.00
0.75
0.50
0.25
0.00
5
15
0
5
10
15
Discharge
Die
Vent
Trimed
log−likelihood
0
−5
−10
−15
−20
SpO2/FiO2
Temperature
Pulse
Discharge 1
Die 0
Vent 0
Days of Hospitalization
0.00
0.25
0.50
0.75
1.00
Discharge
Died
Vent



Patient 1 on Day 12
Prior
Discharge
Die
Vent
Trimed
log−likelihood
SpO2/FiO2
Temperature
Pulse
Discharge 1
Die 0
Vent 0
Days of Hospitalization
Discharge
Died
Vent
0.00
0.25
0.50
0.75
1.00



Patient 1 on Day 13
Prior
Discharge
Die
Vent
Trimed
log−likelihood
SpO2/FiO2
Temperature
Pulse
Days of Hospitalization
Discharge 1
Die 0
Vent 0
Discharge
Died
Vent

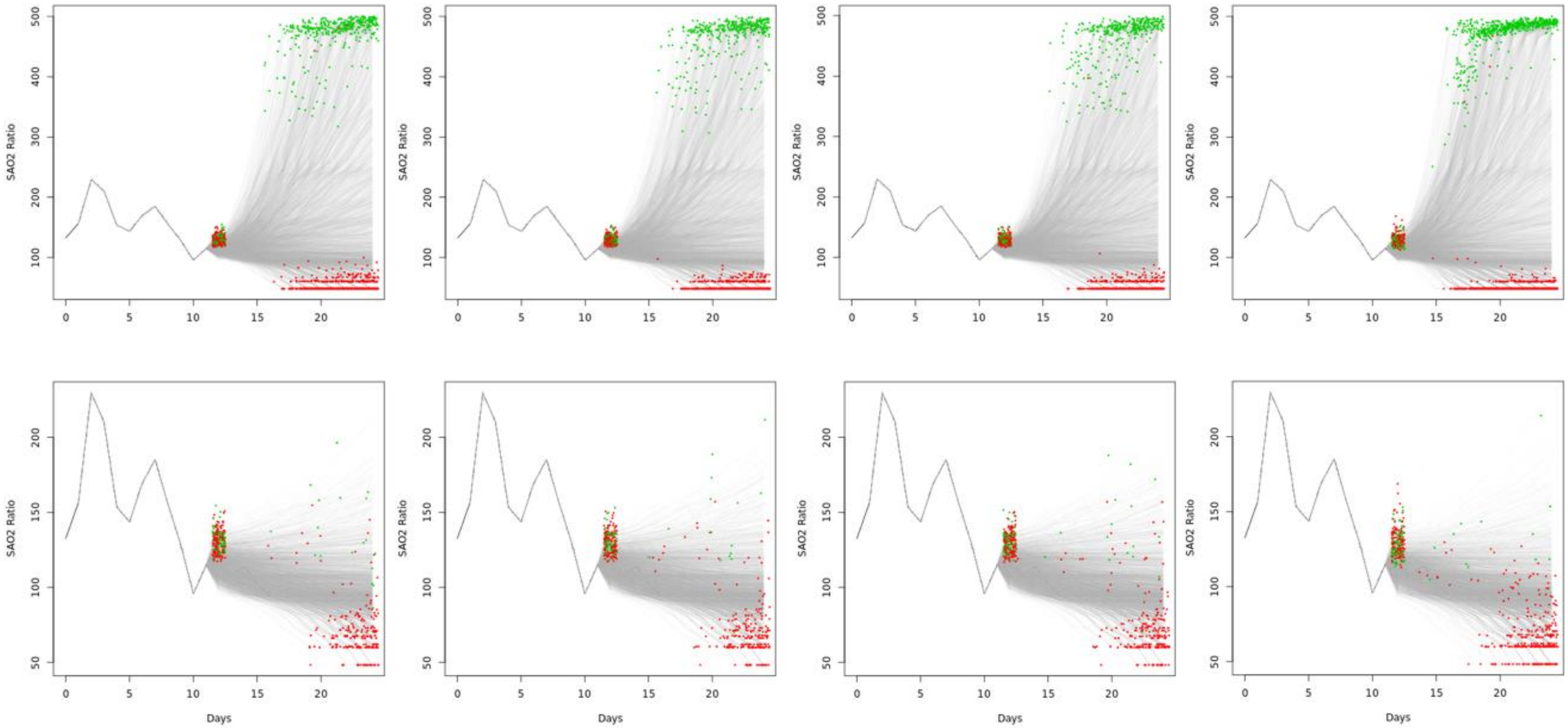
Project 4 Question: Which treatment is best for for me now given my outcomes to date; should I be intubated today?

- Hard statistical problem - first try
- Bayesian multivariate mixed model of three outcomes given exogenous covariates:
  A. biomarkers given treatments and random effects
  B. events given biomarkers and treatments and random effects;
  C. treatment choice given biomarkers and events and random effects
- Prior distributions reflect clinical trials results for models A and B and knowledge about likely degrees of patient-to-patient heterogeneity
- Built in sensitivity analysis by varying random effects

Simulated Trajectories and Events between Day 12 and Day 24 ($var(b^A) = 0.01, N_{post} = 4000$)

Vented

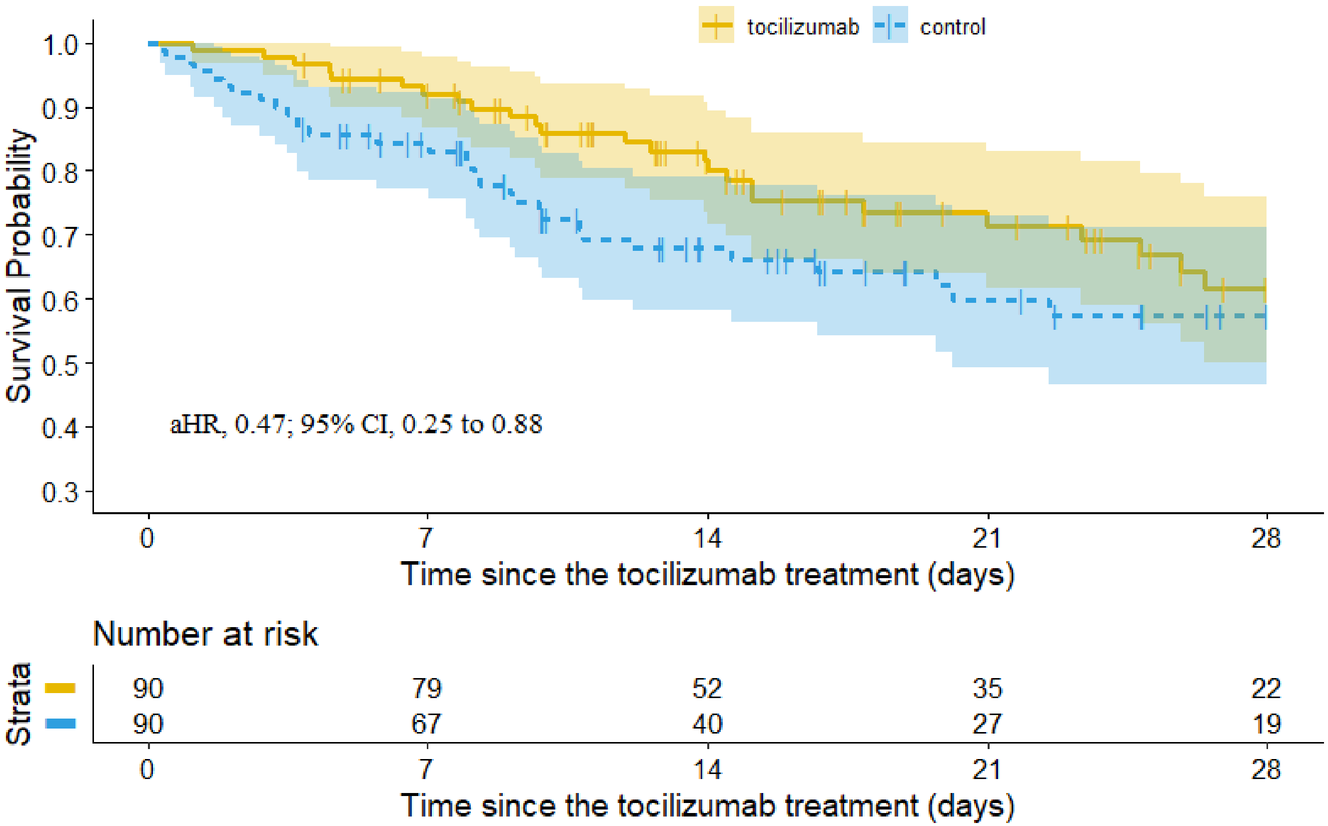
Not Vented



b^A: $25th\ percentile(-0.067)$ | $50th\ percentile\ (0)$ | $75th\ percentile\ (0.067)$ | None

Project 4 Sub-Question: What is the population average treatment effect?

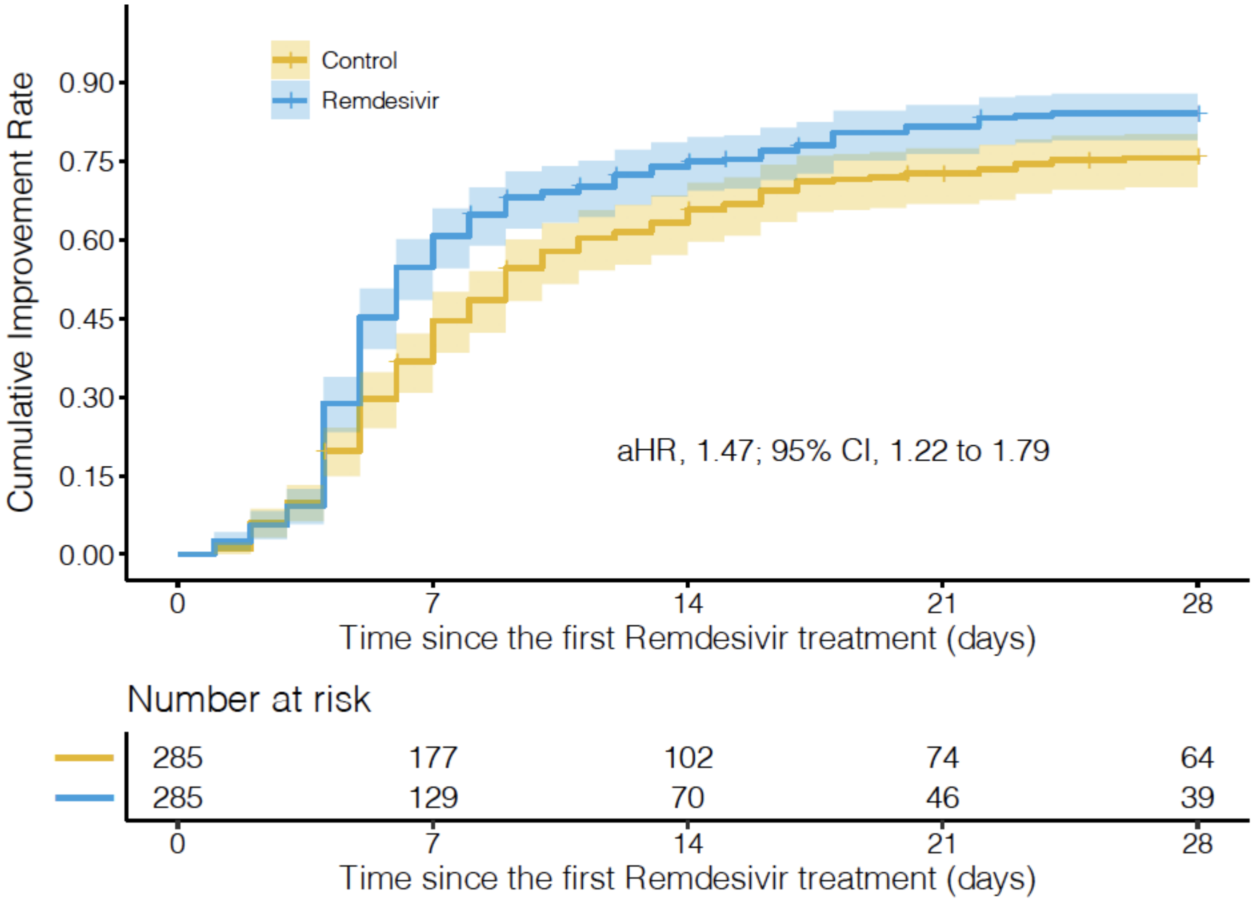
Tocilizumab reduces mortality



Elisa Ignatius

Ignatius E, et al. OFID, 2020

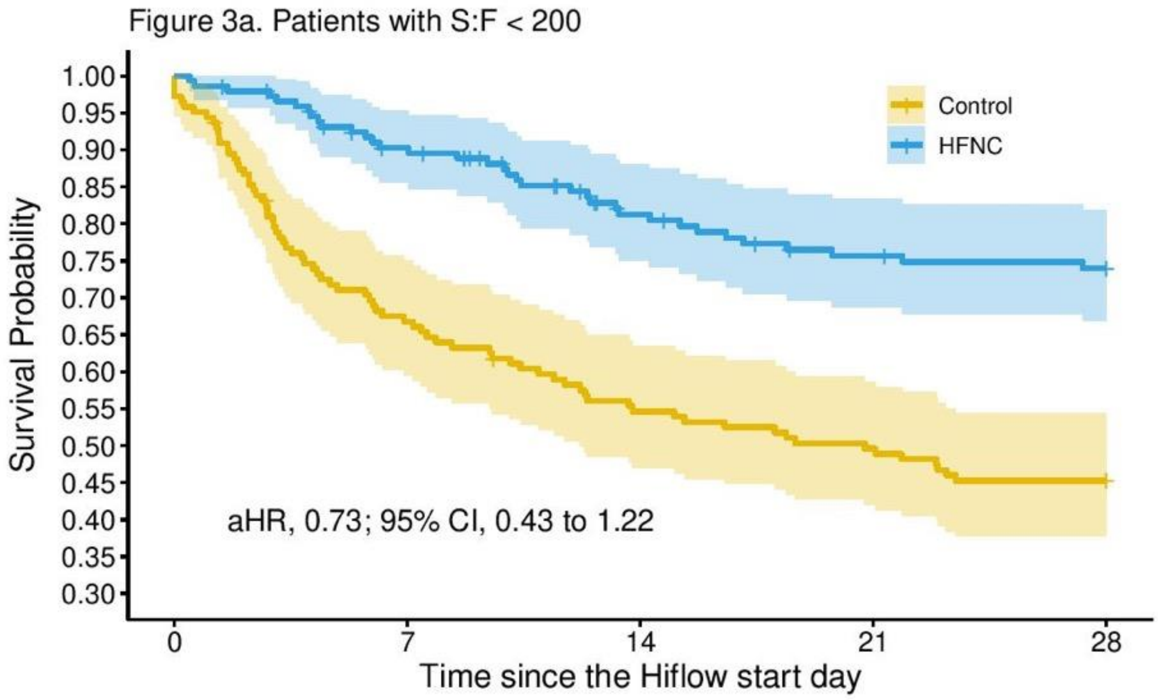
Redemsivir speeds clinical improvement



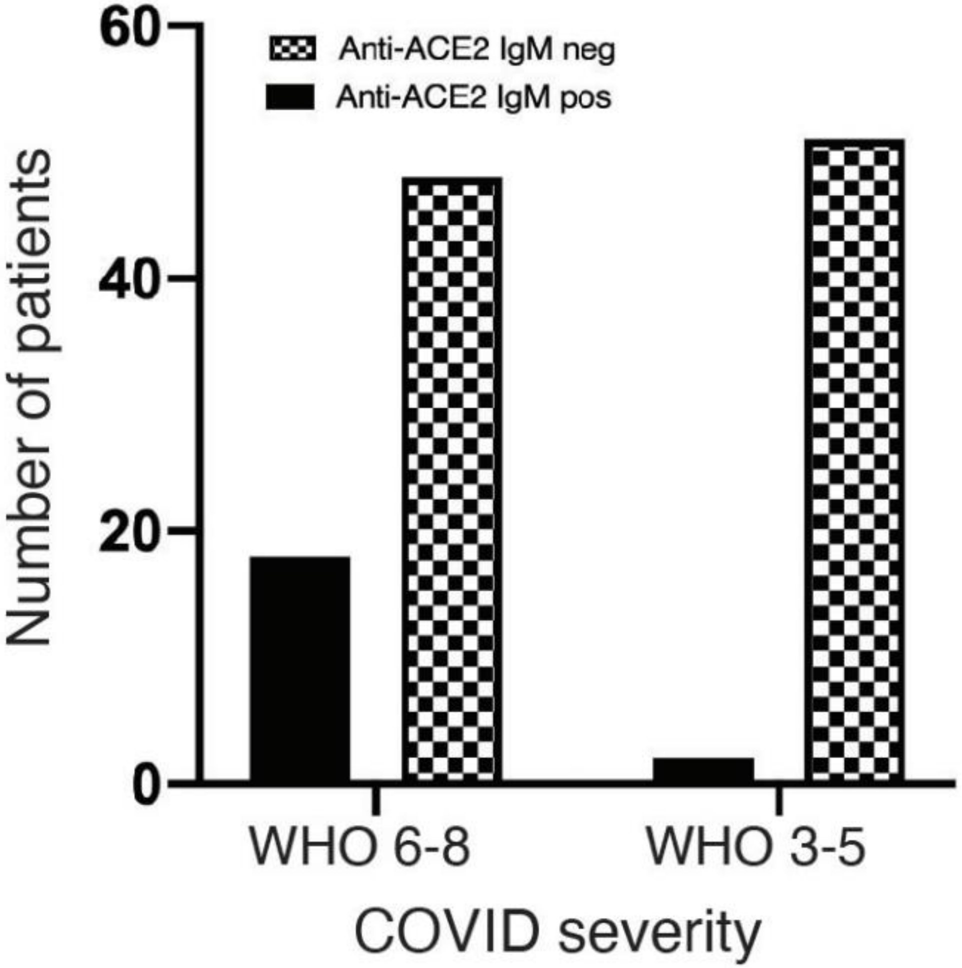
Kunbo Wang

Yanxun Xu

High flow nasal cannula improves outcomes in sicker patients



IgM Autoantibodies to ACE-2



Livia Casciola-Rosen

Antony Rosen

Remaining Questions…

- Combination therapy
- Impact of vaccines
- Post-acute sequelae of COVID-19

The JH-CROWN Team

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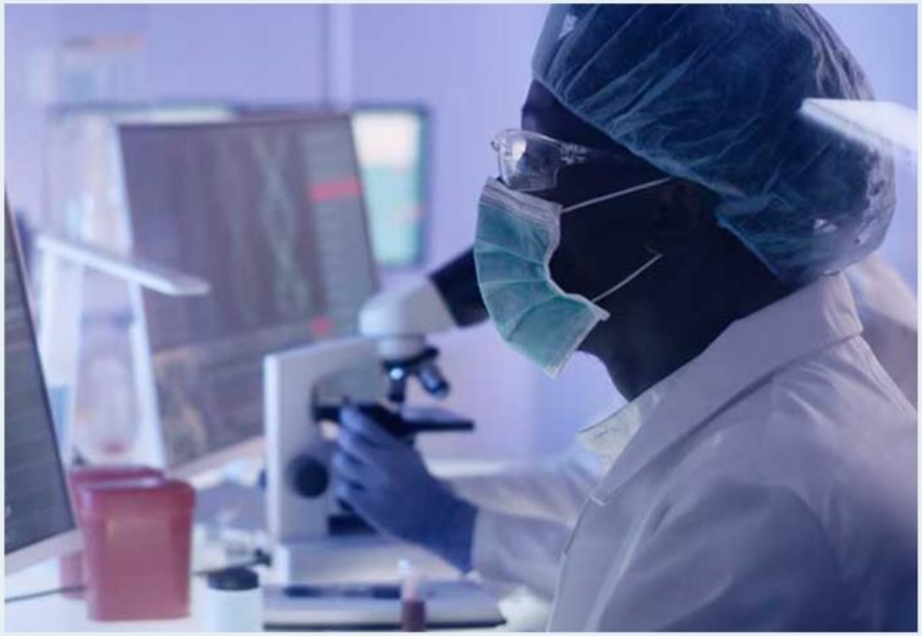
Johns Hopkins Precision Medicine Center of Excellence for COVID-19

The team at the Johns Hopkins Precision Medicine Center of Excellence for COVID-19 is working to improve the care of patients infected with SARS-CoV-2 by studying COVID-19 pathobiology, likelihood of disease progression and impact of specific therapeutic interventions.

Learn more about the center ›



https://www.hopkinsmedicine.org/inhealth/precision-medicine-centers/covid-19/index.html

Extra slides

Wongvibulsin *et al. BMC Medical Research Methodology* (2020) 20:1
https://doi.org/10.1186/s12874-019-0863-0

BMC Medical Research Methodology

TECHNICAL ADVANCE **Open Access**

Clinical risk prediction with random forests for survival, longitudinal, and multivariate (RF-SLAM) data analysis

Shannon Wongvibulsin[1*], Katherine C. Wu[2] and Scott L. Zeger[3]

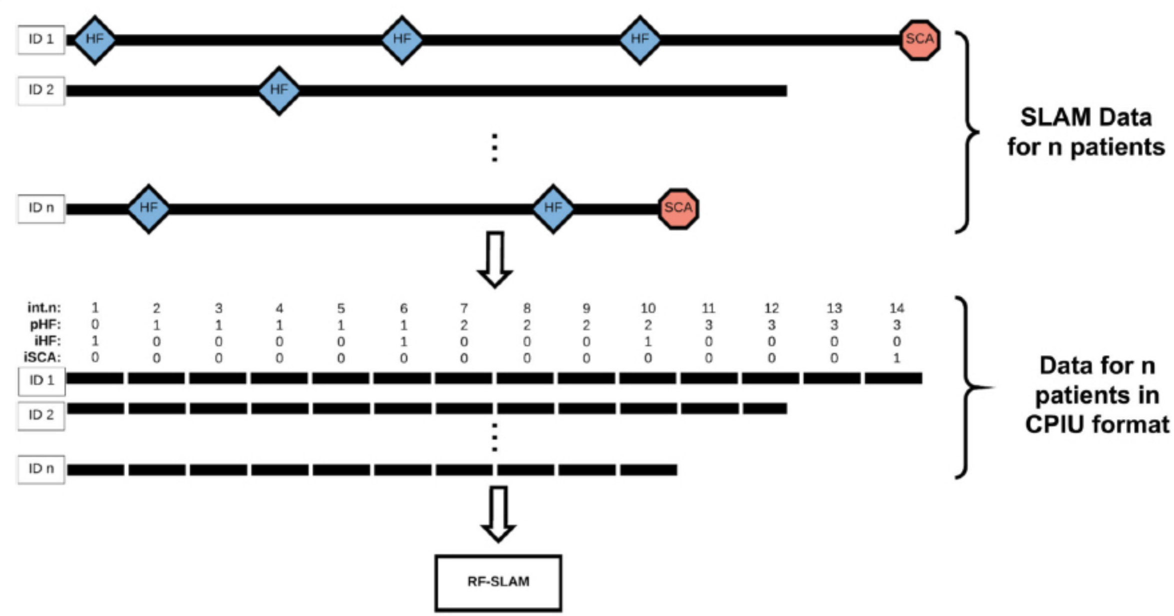


Fig. 1 Random Forests for Survival, Longitudinal, and Multivariate (RF-SLAM) Data Analysis Overview. The Random Forests for Survival, Longitudinal, and Multivariate (RF-SLAM) data analysis approach begins with a pre-processing step to create counting process information units (CPIUs) within which we can model the possibly multivariate outcomes of interest (e.g. SCA, HF) and accommodate time-dependent covariates. For the LV Structural Predictors Registry, the time-varying covariates of interest relate to heart failure hospitalizations (HFs), indicated by the blue diamonds. In this case, CPIUs are created from the Survival, Longitudinal, and Multivariate (SLAM) data by creating a new CPIU every half year, corresponding to the frequency of follow up. The variable *int.n* represents the interval number indicating time since study enrollment in half-years. The time-varying covariates are *int.n* and *pHF* (total number of previous heart failure hospitalizations since study enrollment). Then, these CPIUs (containing the time-varying covariates along with the baseline predictors) are used as inputs in the RF-SLAM algorithm to generate the predicted probability of an SCA. The SCA event indicator is denoted with *iSCA* (0 if no event within CPIU, 1 if the event occurs within CPIU) and the heart failure hospitalization event indicator is *iHF* (0 if no event within CPIU, 1 if the event occurs within CPIU)