Outcome Stratified Analysis of Biomarker Trajectories for Patients With SARS-CoV-2 Infection

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Funding: This work was supported by the National Institutes of Health (Grants T32 GM007309 to M.G.B). The JH-CROWN registry was funded by Hopkins inHealth. Dr. Garibaldi received funding from the COVID-19 Administrative Supplement for the HHS Region 3 Treatment Center from the Office of the Assistant Secretary for Preparedness and Response.

Acknowledgment: The authors thank the Johns Hopkins Health System and its surrounding communities for working together to provide outstanding patient care and to keep each other safe during these extraordinary times. The authors thank members of the COVID Statistical Template Analysis Team: Dr. Brian Garibaldi, Dr. William Gray Roncal, Kenneth Harkness, Hannah Cowley, Dr. Panagis Galiatsatos, Nanette Bell, Zitong Wang, Mary Grace Bowring, Joshua Betz, Dr. Jacob Fiksel, Dr. Scott L Zeger, Dr. Aki Nishimura, Martina Fu, Dr. Eileen Scully, Dr. Annie Antar, Dr. Amita Gupta, Dr. Sherita Golden, Josh Gray, Dr. Yizhen Xu, Dr. Karen Bandeen Roche, Grant Schumock, Dr. John Muschelli, Mariam Ghobadi-Krueger, Bonnie Woods, Dr. Matthew Robinson, Dr. Paul Nagy, Dr. Timothy Niessen, Masoud Rouhizadeh, Aalok Shah, Dr. Ji Soo Kim, Dr. Jamie Perin, and Dr. Robert Bollinger

Conflict of interest: None declared.

Data availability: Data set and study protocol not available. Statistical code available from Dr. Zeger (email, sz@jhu.edu).

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Abstract

Longitudinal trajectories of vital signs and biomarkers during admission remain poorly characterized for COVID-19 patients despite their potential to provide critical insights about disease progression. We studied 1884 patients with SARS-CoV2 infection from 3/4/2020-6/25/2020 within one Maryland hospital system and used a retrospective longitudinal framework with linear mixed-effects models to investigate relevant biomarker trajectories leading up to three critical outcomes: mechanical ventilation, discharge, and death. Trajectories of four vital signs (respiratory rate, SpO_2/FiO_2, pulse, and temperature) and four lab values (C-reactive protein (CRP), absolute lymphocyte count (ALC), estimated glomerular filtration rate (eGFR), and D-dimer) clearly distinguished the trajectories of COVID-19 patients. Prior to any ventilation, log-CRP, log-ALC, respiratory rate, and SpO_2/FiO_2 trajectories diverge approximately 8-10 days before discharge or death. Following ventilation, log-CRP, log-ALC, respiratory rate, SpO_2/FiO_2, and eGFR trajectories again diverge 10-20 days prior to death or discharge. Trajectories improved until discharge and remained unchanged or worsened until death. Our approach characterizes the distribution of biomarker trajectories leading up to competing outcomes of discharge versus death. Moving forward, this model can contribute to quantifying the joint probability of future biomarkers and outcomes provided clinical data up to a given moment.

Key words: case-control design; longitudinal data; linear mixed effects models; COVID-19

Abbreviations: ALC, absolute lymphocyte count; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IQR interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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The pandemic caused by SARS-CoV-2 continues to progress with 134 million global cases and over 2.9 million deaths as of April, 9th, 2021.[1] Several studies have identified risk factors for progression to severe disease or death from COVID-19 (the syndrome caused by SARS-CoV-2).[2-4,5-7] However, these studies have focused largely on baseline demographic (e.g. age, race) or clinical variables (e.g. obesity, inflammatory markers) without considering longitudinal trends in biomarkers and vital signs. Biomarker and vital signs trajectories leading up to initiation of mechanical ventilation, discharge, and death contain valuable information that can guide clinical decisions and elucidate the pathobiology of COVID-19. Since different therapeutics may have efficacy at different time points in disease progression, understanding patient trajectories before and after events such as mechanical ventilation can motivate specific hypotheses about which patients are more likely to benefit from specific interventions. Finally, an understanding of longitudinal trajectories of clinical features of COVID-19 will inform the development of robust and accurate prediction tools to guide resource allocation and inform conversations with patients and families.

In this paper, we propose a linear mixed-effects model to retrospectively study individual biomarker trajectories preceding the key clinical events of initiation of mechanical ventilation, discharge, and death.[8] We use a longitudinal case-control design and outcome-specific strata to describe population and individual biomarker trajectories preceding clinical events to better understand how biomarkers change over time relative to clinical milestones.

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METHODS

Data source

The data source for this study was JH-CROWN: The COVID-19 Precision Medicine Analytics Platform Registry, which utilizes the Hopkins Precision Medicine Analytics Platform. [4] JH-CROWN includes data from five hospitals (Johns Hopkins Hospital, Baltimore, MD; Bayview Hospital, Baltimore, MD; Howard County General Hospital, Columbia, MD; Suburban Hospital, Bethesda, MD; Sibley Hospital, Washington DC) that comprise the Johns Hopkins Medicine System. The institutional review boards of these hospitals approved this study as minimal risk and waived requirement for informed consent. All patients consecutively admitted with confirmed SARS-CoV-2 infection by microbiological testing from 3/4/2020-6/25/2020 were included. Time of admission was defined as the time the admission order was written. Readmissions are excluded as data represent the initial episode of care for each patient. Data in JH-CROWN include demographics, medical history, comorbid conditions, symptoms, vital signs, respiratory events, medications, and laboratory results.

Study population

We studied 1884 patients who died during admission or were discharged prior to data extraction on 6/25/2020 with at least one biomarker value reported during admission. Some patients were included in prior descriptions of the cohort.[4] Ninety-nine patients in the hospital at the time of data extraction were excluded. The number of unique patients with reported values varied (Table 1), with vitals reported more regularly and lab values measured less frequently. We multiplied the number of individual patients by length of stay to determine the total patients-days that we would expect measurements. For example, 1856 patients had a median of 6 (Interquartile range ([IQR] 3-11) days with respiratory rate data (28 patients had no respiratory rate data), and of the total patient-days we would have expected data, 4.5% had no reported value.

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Clinical events

We followed patients from hospital admission until the first of mechanical ventilation, discharge, or death. We then followed patients who underwent ventilation until the first of discharge or death. Based upon outcome events, we identified four patient strata: those who were (1) admitted and discharged without ventilation, (2) admitted and died without ventilation, (3) admitted, ventilated during admission, and discharged, and (4) admitted, ventilated during admission, and died. Patients with multiple ventilation episodes were followed from initial date of ventilation until their final outcome. We compared demographics and clinical characteristics across the four strata using Kruskal Wallis tests for continuous variables, χ^2 tests for categorical variables, and Fisher's exact tests with Monte Carlo simulation for categorical variables with expected values below 5. Clinical outcomes (ventilation, discharge, or death) were treated as independent strata indicators in longitudinal models. In effect, we performed a longitudinal case-control study by identifying patients based on their outcome and retrospectively characterizing trajectories preceding their outcome.

Biomarkers

We selected eight biomarkers (4 vital signs and 4 laboratory measures) to represent components of inflammation, end-organ disease, and coagulation: respiratory rate, temperature, pulse, SpO_2/FiO_2, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), D-dimer, and absolute lymphocyte count (ALC). These factors are associated with severe illness and/or death from COVID-19.[9] Respiratory rate, temperature, CRP and ALC were found to be predictive of severe disease or death from COVID-19, and SpO2/FiO2 was associated with mortality using

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data from the Johns Hopkins Health System.[4] Elevated pulse is a marker of sepsis and may be associated with worse mortality in sepsis as well as in COVID-19.[10] Patients with pre-existing kidney disease are at higher risk of death from COVID-19.[11] Acute kidney injury is also a risk factor for poor outcomes.[12] D-dimer is associated with severe COVID-19 and has been linked to mortality from COVID-19.[13] Laboratory values reported with ">" or "<" (4.0% of values) were changed to reflect the limit of quantification. For example, if D-dimer was reported as <0.19, 0.19 was used. We calculated daily means for each biomarker.

Trajectories preceding clinical events

We aimed to characterize population-average and patient-specific biomarker trajectories leading up to major clinical outcomes. For each patient, we treated the day of their outcome as day 0 and studied repeated biomarker measures over previous time from their admission until day 0. Previous time from admission to day 0 will be designated as u. If a patient was admitted for COVID-19 20 days before their outcome, we considered admission to be day –20. This approach aligned patient trajectories proximal to event time rather than admission time and allowed us to characterize trajectories immediately preceding major clinical outcomes.

We fit two linear mixed-effects models for each biomarker. The first model describes trajectories from admission up to a patient's first major event of interest: ventilation, discharge, or death. The second model describes trajectories from the initiation of ventilation up to their second event of interest: discharge or death. Patients admitted prior to ventilation contribute data to both models. The fixed effects were indicators for the patient's outcome stratum and interactions between the stratum and smooth time trends represented by natural cubic splines with three degrees of

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freedom. The random effects included random intercepts and smooth time trends represented by natural cubic splines with three degrees of freedom. Random effects allowed each patient's trajectory to deviate from the mean level and shape of their subgroup's overall curve. We performed likelihood ratio tests to test the null hypotheses that the smoothed time trend is the same across the outcome strata for each model. To study the total effect of each covariate on the level or shape of each biomarker's trajectory, we fit a series of models in which the interaction between the smooth time trend and outcome stratum also interacted with one of the patient characteristics: age, sex, race, body mass index, Charlson comorbidity score, or smoking status. We displayed the estimated intercept (value at day 0) and 3-day linear trend preceding day 0 (from day –3 to 0) for each subgroup in Web Figures 1 and 2. Programs were written in the R statistical language.[14]

Statistical Model

Let Y_{ij} be the jth biomarker value for patient i measured at day t_{ij} from the day of admission for which $t_{ij} = 0$. Denote baseline predictor variables as X_i and major clinical events as E_i. Consider two possible events after admission denoted by $E_i^{(1)}$ and $E_i^{(2)}$where $E_i^{(1)} = 0, 1, 2$ indicates whether the patient was discharged, died, or mechanically ventilated. When $E_i^{(1)} = 2$, then $E_i^{(2)} \in \{0, 1\}$ indicating whether the person who required ventilation was eventually discharged or died. The 5 clinical outcome strata coincide with 4 patient groups: $E_i^{(1)} = 0$: those who were admitted, never received mechanical ventilation, and were discharged, $E_i^{(1)} = 1$: those who were admitted, never received mechanical ventilation, and died, $E_i^{(2)} = 0 | E_i^{(1)} = 2$: those who were admitted, received mechanical ventilation, and were discharged, and

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$E_i^{(2)} = 1 \mid E_i^{(1)} = 2$: those who were admitted, received mechanical ventilation, and died. We define $\tau_i^{(1)}$ to be the date of event $E_i^{(1)}$for patient i and $\tau_i^{(2)}$the date of event $E_i^{(2)}$ conditioned on event $E_i^{(1)}$. We define the times prior to each of the events by $u_{ij}^{(1)} = t_{ij} - \tau_i^{(1)}$, $u_{ij}^{(2)} = t_{ij} - \tau_i^{(2)}$. The linear mixed effects models take the form:

$$Y_{ij}^{(k)} | E_i^{(k)}, u_{ij}^{(k)}, \mathbf{b_i^{(k)}} = \beta_0^{(k)} + E_i^{(k)} f^{(k)}\left(u_{ij}^{(k)};\ \boldsymbol{\beta}^{(\mathbf{k})}, \nu^{(k)}\right) + b_{0i}^{(k)} + \delta^{(k)}\left(u_{ij}^{(k)};\ \mathbf{b_i^{(k)}}, \xi^{(k)}\right) + \epsilon_{ij}^{(k)}$$

where $k = 1$ pre-ventilation or k = 2 post-ventilation. $\nu^{(k)}$ is the degree of freedom that determines smoothness of the fixed effects curves (population-averaged) while $\xi^{(k)}$ determines smoothness of the random effects curves (patient-specific). The residuals $\epsilon_{ij}^{(k)}$ are assumed to follow a multivariate Gaussian (normal) distribution with mean 0 and covariance matrix $R^{(k)}$ or $Gaussian(0, R^{(k)})$. Similarly, we assume the random effects $\mathbf{b_i^{(k)}} = \left(b_{0i}^{(k)}, b_{1i}^{(k)}, \dots, b_{\xi i}^{(k)}\right) \sim Gaussian\left(0, \mathbf{G^{(k)}}\right)$. In this application to simplify the computation, we do not model the joint distribution of $\mathbf{b_i^{(k)}}$ for $k = 1, 2$ but treat trajectories pre- and post-ventilation as if they are independent. Questions involving both models can be addressed by fitting the two linear mixed effects in a single equation with random effects $\boldsymbol{b_i} = \left(\mathbf{b_i^{(1)}}, \mathbf{b_i^{(2)}}\right) \sim Gaussian(0, \mathbf{G})$.

Model checking

We created boxplots of standardized residuals against deciles of predicted values for each $\hat{Y}_{ij}$ to identify systematic deviations from residual mean of 0 or changing spread among residuals that would indicate an incorrect model for the variance of the observations. We produced quantile-quantile plots against the standard Gaussian distribution for the standardized residuals to assess

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the Gaussian assumption regarding random effects and residual errors. If we discovered a systematic deviation, we used bootstrapping to obtain robust variance estimators for the estimated population intercepts and linear slopes.

RESULTS

Study population

From among the 1884 patients, 1445 patients were admitted and discharged without ventilation, 118 were admitted and died without ventilation, 202 were admitted, ventilated during admission, and discharged, and 119 were admitted, ventilated during admission, and died. Compared to the other patient strata, patients discharged without ventilation were more likely to be younger (median [IQR] age 56 [41-71]), Latinx or Other race/ethnicity, have lower Charlson comorbidity scores, and less likely to have been a current/former smoker (Table 2). Patients who died without ventilation were more likely to be older (median [IQR] age 82.5 [73-91]), White, and have a do not resuscitate/do not intubate order. Patients who were ventilated and discharged were more likely to be younger (median age 60.5 [51-71]), Black, non-smokers, and to have lower Charlson comorbidity scores. Patients who were ventilated and died were more likely to be older (median age 70 [63-75]), Black, to have Charlson score of 1-2, and to have signed a do not resuscitate/do not intubate order. Among patients who were never ventilated, median times to discharge and death were 4 days (IQR 2-7) and 5 days (IQR 1-9), respectively. Among those ventilated, median times from admission to discharge or death were 20 days (IQR 12-32) and 11 days (IQR 6-20).

Trajectories preceding clinical events

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Mean biomarker trajectories preceding patient outcomes are displayed with 95% confidence intervals in Figure 1. The final fitted values on the day of each outcome (day 0) are presented with 95% CI in Table 3, and the slope of values over the three days leading up to each outcome are presented in Table 4. All likelihood ratio tests of the null hypothesis that the smoothed time trend is the same across the outcome strata were statistically significant ($p<0.001$). Patients discharged without ventilation had lower (better) log-CRP (Figure 1A), log-D-dimer (Figure 1C), pulse (Figure 1I), respiratory rate (Figure 1K), and temperature (Figure 1O) and higher (better) eGFR (Figure 1E), log-absolute lymphocyte count (log-ALC) (Figure 1G), and SpO_2/FiO_2 (Figure 1M) at discharge as compared to those who died without ventilation or were ventilated. Without ventilation, there was a divergence in log-CRP, log-ALC, respiratory rate, and SpO_2/FiO_2 trajectories approximately 8-10 days prior to death or discharge (Figures 1A, 1G, 1K, and 1M). We observed a steady increase in D-dimer that began 20 days prior to death without ventilation and minimal change in D-dimer among those discharged without ventilation (Figure 1C). Similarly, we observed a steady increase in eGFR that began 20 days prior to discharge without ventilation and minimal change in eGFR among those who died without ventilation apart from the last few days leading up to death (Figure 1E). In the days leading up to ventilation, patient trajectories more closely followed trajectories of patients who died without ventilation.

Among patients who required ventilation, log-CRP (Figure 1B), eGFR (Figure 1F), log-ALC (Figure 1H), respiratory rate (Figure 1L), and SpO_2/FiO_2 (Figure 1N) trajectories diverged between ventilated patients who were discharged versus died, such that values improved for those who were discharged or remained unchanged/worsened for those who died. This

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divergence was observed 10 or more days prior to discharge or death. Log-D-dimer and temperature diverged between ventilated patients who were discharged versus died approximately 8 days prior to discharge or death (Figures 1D and 1P). Almost immediately following ventilation, eGFR and SpO_2/FiO_2 increased among patients who were discharged compared to minimal changes among those who died (Figures 1F and 1N). Patients who required ventilation and were discharged reached SpO_2/FiO_2, respiratory rate, log-ALC, pulse, and temperatures comparable to patients who were discharged without ventilation. In contrast, patients discharged after ventilation were discharged at lower eGFRs than patients discharged without ventilation (75.9 [95% CI 70.1-81.7] vs 92 [90.2-93.8]) (Table 3). Log(D-dimer) remained elevated among patients discharged after ventilation when compared to those who were discharged without ventilation (0.6 [0.3-0.9] vs -0.2 [-0.3-0.1]) (Table 3).

Trajectories by subgroup

Among those discharged without ventilation, at the time of discharge there was minimal variation by sex, age, race, body mass index, Charlson score or smoking status in log-CRP, pulse, respiratory rate, SpO_2/FiO_2 or temperature. Black and White patients over 75 years old and patients with Charlson score >3 were discharged at lower eGFR. Among patients who required ventilation, older Black and White patients were ventilated at lower eGFR, patients with Latinx and Other race/ethnicity were ventilated at higher respiratory rate. Among patients who were ventilated and discharged, those with Charlson comorbidity score >3 were discharged at lower eGFR, D-dimer, log-ALC, and pulse than those with Charlson score of 0 or 1-2 (Web Figure 1). Fitted linear trends over the three days prior to each outcome across demographic and

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clinical subgroups are plotted in Web Figure 2. Overall, there were minimal variations in slope across subgroups.

Individual trajectory

The models offer patient-specific estimated curves (Figure 2). Here, we plotted observed and fitted biomarker trajectories for one random patient pre- and post-ventilation. The patient's observed and fitted values overlay the population-average model-based estimates to illustrate individual variation from trajectories conditioned on outcome.

Model checking

For all but one of the biomarkers, the distributions of residuals were approximately Gaussian with constant variance. The respiratory rate models produced residuals such that spread increased with the mean value (Web Figure 3) indicating an incorrect model for the variance of estimate coefficients. We introduced robust variance estimators for the respiratory rate models and used bootstraps with 500 iterations to determine whether this improved model validity. Quantile-quantile plots of bootstrapped estimates indicated that inferences with respect to respiratory rate using robust variance were valid (Web Figure 4).

DISCUSSION

In this study of 1884 patients with COVID-19 from one hospital system, we used a generalization of the case-control design by stratifying longitudinal data analysis into outcome-specific strata. We describe population and individual biomarker trajectories conditioned on each stratum. Trajectories of four vital signs (respiratory rate, SpO_2/FiO_2, pulse, and temperature) and

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four lab values (CRP, ALC, eGFR, and D-dimer) clearly distinguished patients admitted for COVID-19 based on their outcomes of 1) discharge without ventilation, 2) death without ventilation, 3) ventilation, 4) discharge after ventilation, and 5) death after ventilation. Prior to any ventilation, we observed a divergence in log-CRP, log-ALC, respiratory rate, and SpO_2/FiO_2 that began approximately 8-10 days prior to the event, such that values improved steadily up until discharge or remained unchanged or worsened up until ventilation or death. Following ventilation, we again observed a divergence in log-CRP, log-ALC, respiratory rate, SpO_2/FiO_2, and eGFR that began 10 or more days prior to death or discharge, such that values improved until discharge and remained unchanged or worsened until death.

Our findings that SpO_2/FiO_2 decreased in the days prior to death and increased in the days prior to discharge in patients with COVID-19 are consistent with how this measure correlates with the severity of lung injury and likelihood of death in patients who are mechanically ventilated or who have acute respiratory distress syndrome (ARDS) from other causes.[15,16] Multiple studies have identified respiratory failure and ARDS as primary complications in patients with COVID-19[7,17] and previous work by our group identified an association between SpO_2/FiO_2 and mortality in COVID-19.[4] Respiratory rate is also an important predictor of severe disease or death in patients with COVID-19.[4,18,19] This is not surprising given its prominence in well-known prediction calculators for in-hospital mortality.[20-22] Our trajectories of respiratory rate and SpO_2/FiO_2 extend these findings to illustrate patients' progression to respiratory failure prior to ventilation, and subsequent failure to regain respiratory function among patients who died following ventilation. We are also able to observe how patients who died following ventilation were unable to regain respiratory function while ventilated while those who survived to

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discharge following ventilation had clear and immediate improvement in respiratory function (as defined by a higher SpO_2/FiO_2 and lower respiratory rate). Given the ease with which these vitals can be measured continuously, understanding these trajectories is the first step towards applying a patient's individual data points to robust population-level trajectories and gaining a better understanding of that patient's disease course.

Our findings that patients who died with or without ventilation had persistently higher CRP and D-dimer and lower ALC are consistent with existing work on the importance of these inflammatory markers in severe SARS-CoV-2 infection.[4,5,23-25] For example, Manson et al. plotted CRP and ALC over time from a cohort of 269 patients with a positive swab for SARS-CoV2 and observed slightly elevated CRP among patients who required ventilation and among those who died.[26] We are able to provide further insight into the behavior of these inflammatory markers leading up to and following ventilation. Specifically, in our study population, CRP consistently declined over the 15 days prior to discharge following ventilation, yet remained elevated without decreasing among those who went on to die following ventilation. ALC consistently increased among patients who survived to discharge following ventilation, but increased only slightly and after some delay among those who died following ventilation. Understanding the behavior of these biomarkers independent of each other is clinically helpful as models of inflammatory states emerge.[20]

In our study, patients discharged following ventilation regained SpO_2/FiO_2, ALC, respiratory rate, and temperatures comparable to those of patients discharged without ventilation. In contrast, these patients were discharged at lower eGFRs and higher D-dimer than those

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discharged without ventilation. The eGFR trajectories we observed support existing evidence that COVID-19 leads to acute kidney injury in up to 25% of patients who develop critical illness.[27] This damage is likely compounded by the potential injurious impact of ventilation on kidney function.[28,29] The D-dimer trajectories we observed are consistent with prior studies linking elevated D-dimer to an increased risk of severe disease and death.[30] We were able to further show that patients who survived to discharge but required ventilation maintained elevated D-dimer when compared to patients who were discharged without ventilation.

The limitations of this study merit discussion. Our approach to modeling biomarker trajectories relevant to SARS-CoV-2 does not incorporate joint modeling of biomarkers which might provide a unified picture of health and disease trajectory for a given patient. We are bound by the restrictions of case-control design and unable to predict a given patient's trajectory, as each model requires that we know the patient's outcome. Thus, these models cannot be used for prediction, but rather provide the foundation for jointly modeling biomarker trajectories and the probability of each event. For patients on a ventilator, we modeled SpO_2/FiO_2 rather than PaO_2/FiO_2 which would allow minor changes to be better observed. SpO_2/FiO_2 data were reported more frequently for our study population and allowed us to compare pre- and post-ventilation trajectories. We chose to retrospectively characterize trajectories based on ventilation, discharge, or death, yet there is significant variation in health status and quality of life for patients within each of these outcomes, and in particular among discharged patients. We observed significant improvements in health up until discharge, yet there are unknown long-term consequences for patients discharged following COVID-19 that should be considered in the context of this work.[31] When interpreting patient trajectories, we must also recognize the

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circularity between medical and pharmacological interventions (mechanical ventilation and otherwise) and the biomarkers we observed throughout a patient's hospital stay. Biomarkers are both drivers of and responses to physician intervention and complicate our understanding of temporality in a longitudinal analysis. Finally, we did not capture the dynamic nature of ventilation (e.g. adjustments in ventilator mode, FiO_2, positive end expiratory pressure, tidal volume, respiratory rate, neuromuscular blockade, sedation, prone positioning, etc.), but treated patients for whom mechanical ventilation was ever initiated as on ventilation until their outcome and characterized their trajectories as a distinct patient population.

We provide robust population-level and patient-specific biomarker and vital sign trajectories for a cohort of patients admitted for COVID-19. This work is unique in our attempt to understand these trajectories conditioned on and preceding distinct outcomes. Our findings align with existing research, provide insight into the dynamic behavior of biomarkers and vital signs prior to clinical events, and lay the foundation for a joint modeling approach to predicting trajectories using population-level and patient-specific data.

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Table 1. Frequency of Patients With at Least One Reported Measure, Number of Reported Measures per Patient, and Unmeasured Data per Vital Sign and Laboratory Value From the JH-CROWN Registry Study of Patients With COVID-19, Baltimore MD 3/4/2020-6/25/2020.

Biomarker	Unique patients	Daily Measures	Days with Reported Measures (Median [IQR])	Days with Reported Measures (Range)	Percent of days with no reported measure[a]
Overall	1884[b]	16747	6 (3-11)	1-81	
Respiratory rate	1856	16117	6 (3-11)	1-79	4.5%
Temperature	1845	16130	6 (3-11)	1-79	4.4%
Pulse	1856	16183	6 (3-11)	1-79	4.1%
SpO_2/FiO_2	1847	16132	6 (3-11)	1-79	4.4%
D-dimer	1471	5668	2(1-5)	1-38	66.4%
CRP	1461	5631	3 (1-5)	1-40	66.6%
eGFR	1715	13023	5 (2-9)	1-77	22.8%
ALC	1316	7551	3 (1-6)	1-59	55.3%

Abbreviations, COVID-19 Coronavirus disease 2019, IQR interquartile range, CRP C-reactive protein, eGFR estimate glomerular filtration rate, ALC absolute lymphocyte count

[a]The denominator or days with an expected measure was based on number of individual patients and length of stay of each patient.

[b]Number of patients with at least one biomarker measure

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Table 2. Comparing Characteristics of Patients With COVID-19 Across Outcome Strata From Within the JH-CROWN Registry, Baltimore MD 3/4/2020-6/25/2020.

Patient characteristics	Admitted -> Discharged N=1445		Admitted -> Died N=118		Admitted -> Ventilated-> Discharged N=202		Admitted -> Ventilated -> Died N=119		Total N=1884	
	No.	%	No.	%	No.	%	No.	%	No.	%
Days to initial ventilation, Med [IQR][a, b]					1.00 [0, 2.00]		1.00 [0, 3.00]			
Days to discharge/death, Med [IQR] [a,b]	4.00 [2.00, 7.00]		5.00 [1.00, 9.00]		20.0 [12.0, 31.8]		11.0 [6.00, 20.0]		5.00 [2.00, 10.0]	
Age, Med [IQR] [a, b]	56.0 [41.0, 71.0]		82.5 [73.0, 91.0]		60.5 [51.0, 70.8]		70.0 [63.0, 80.5]		60.0 [44.0, 73.0]	
Age, % [a]										
<60	817	56.5	3	2.5	99	49.0	22	18.5	941	49.9
60-74	356	24.6	30	25.4	72	35.6	52	43.7	510	27.1
>74	272	18.8	85	72.0	31	15.3	45	37.8	433	23.0
Race, % [a]										
White	376	26.0	59	50.0	52	25.7	43	36.1	530	28.1
Black	499	34.5	39	33.1	80	39.6	47	39.5	665	35.3
Latinx/Other	569	39.4	20	16.9	70	34.7	29	24.4	688	36.5
Missing	1	0.1	0	0	0	0	0	0	1	0.1
Sex, %[c]										
Female	702	48.6	49	41.5	85	42.1	65352	43.7	888	47.1
Male	743	51.4	69	58.5	117	57.9	67	56.3	996	52.9
Body mass index, %[a]										
<18.5	35	2.4	12	10.2	4	2.0	2	1.7	53	2.8
18.5 to <25	304	21.0	44	37.3	32	15.8	29	24.4	409	21.7
25 to <30	379	26.2	23	19.5	48	23.8	30	25.2	480	25.5
30 to <40	405	28.0	14	11.9	58	28.7	27	22.7	504	26.8
≥40	116	8.0	2	1.7	22	10.9	13	10.9	153	8.1

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Missing	206	14.3	23	19.5	38	18.8	18	15.1	285	15.1
Diabetes [a,d]	374	25.9	28	23.7	72	35.6	46	38.7	520	27.6
Smoking history, % [a]										
Current Smoker	78	5.4	7	5.9	19	9.4	6	5.0	110	5.8
Former Smoker	284	19.7	35	29.7	57	28.2	33	27.7	409	21.7
Never Smoker	957	66.2	48	40.7	109	54.0	50	42.0	1164	61.8
Missing	126	8.7	28	23.7	17	8.4	30	25.2	201	10.7
Charlson, Med [IQR] [a]	1.00 [0, 2.00]		2.00 [1.00, 3.00]		1.00 [0, 3.00]		1.00 [1.00, 3.00]		1.00 [0, 2.00]	
Charlson, % [a]										
0	658	45.5	14	11.9	74	36.6	27	22.7	773	41.0
1-2	580	40.1	56	47.5	76	37.6	59	49.6	771	40.9
3-4	170	11.8	38	32.2	35	17.3	20	16.8	263	14.0
>5	30	2.1	10	8.5	17	8.4	13	10.9	70	3.7
Missing	7	0.5	0	0	0	0	0	0	7	0.4
Ever DNR/DNI, % [a]	175	12.1	112	94.9	35	17.3	105	88.2	427	22.7

Abbreviations, COVID-19 Coronavirus disease 2019, IQR interquartile range, DNR/DNI do not resuscitate/do not intubate

[a]Comparison across four strata statistically significant such that $p<0.001$.

[b]Values expressed as median [IQR].

[c]Comparison across four strata groups not statistically significant.

[d]Diabetes history missing for 7 patients (0.4%).

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Table 3. Fitted Values on the Day of Clinical Event (Discharge, Death, or Ventilation) From Outcome-Stratified Longitudinal Models Among Patients Within the JH-CROWN Registry, Baltimore MD 3/4/2020-6/25/2020.

Biomarker	Trajectory from Admission to Discharge		Trajectory from Admission to Death		Trajectory from Admission to Ventilation		Trajectory from Ventilation to Discharge		Trajectory from Ventilation to Death	
	Fitted value	95% CI	Fitted value	95% CI	Fitted value	95% CI	Fitted value	95% CI	Fitted value	95% CI
Log(CRP)	0.8[a]	0.7, 0.9	2.3	1.9, 2.7	2.5	2.3, 2.7	0.3	0, 0.6	2.5	2.1, 2.8
Log(D-dimer)	-0.2	-0.3, -0.1	1.3	1, 1.7	0.5	0.4, 0.7	0.6	0.3, 0.9	1.8	1.5, 2.1
eGFR	92	90.2, 93.8	51.7	44.8, 58.5	67.8	63.4, 72.3	75.9	70.1, 81.7	48.9	41.4, 56.4
Log(ALC)	0.4	0.4, 0.4	-0.3	-0.5, -0.1	-0.2	-0.3, -0.1	0.5	0.4, 0.6	0	-0.1, 0.2
Pulse	81.6	80.7, 82.4	103.9	101.1, 106.7	91.3	89.2, 93.4	86.1	83.9, 88.3	100.7	97.9, 103.6
Respiratory rate	18.6	18.4, 18.8	25.9	25.1, 26.6	26.1	25.6, 26.6	19.2	18.4, 20.1	27.3	26.2, 28.4
SpO_2/FiO_2	460.5	456.6, 464.3	163.5	149.7, 177.3	238.6	228.8, 248.3	450.6	438.4, 462.8	157.1	141.4, 172.9
Temperature	36.7	36.7, 36.7	37.3	37.237.4	37.3	37.2, 37.3	36.5	36.4, 36.6	37	36.8, 37.1

Abbreviations, ALC absolute lymphocyte count, CI Confidence intervals, COVID-19 Coronavirus disease 2019, CRP C-reactive protein, eGFR estimated, eGFR estimated glomerular filtration rate

[a]Fitted values calculated from 16 outcome-stratified longitudinal models (for each biomarker pre- and post-ventilation). In each column, the fitted value represents the population-average value on the day of the final event in each trajectory (i.e. day 0 in each model). For example, patients in our study population who were admitted and discharged without requiring mechanical ventilation were discharged with an average log-C-reactive protein of 0.8 (95% confidence interval 0.7, 0.9).

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Table 4. Linear Trend in Values Over the Three Days Preceding the Clinical Event From Outcome-Stratified Longitudinal Models Among Patients Within the JH-CROWN Registry, Baltimore MD 3/4/2020-6/25/2020.

Biomarker	Trajectory from Admission to Discharge		Trajectory from Admission to Death		Trajectory from Admission to Ventilation		Trajectory from Ventilation to Discharge		Trajectory from Ventilation to Death	
	Trend	95% CI	Trend	95% CI	Trend	95% CI	Trend	95% CI	Trend	95% CI
Log(CRP)	-0.2[a]	-0.2, -0.1	0	-0.1, 0.2	0.1	0, 0.2	-0.2	-0.2, -0.1	0	-0.1, 0.1
Log(D-dimer)	-0.1	-0.1, 0	0.1	0, 0.2	0.1	0.1, 0.2	-0.1	-0.1, 0	0.1	0, 0.2
eGFR	0.5	0.2, 0.9	-2.6	-4, -1.1	1.2	0.4, 2.1	0.3	-0.5, 1.1	-1.2	-2.3, -0.1
Log(ALC)	0	0, 0.1	0	-0.1, 0	0	-0.1, 0	0	0, 0	0	0, 0
Pulse	-0.5	-0.7, -0.2	3	2.1, 3.8	1	0.3, 1.8	-0.1	-0.7, 0.5	2.1	1.3, 2.9
Respiratory rate	-0.3	-0.4, -0.3	0.6	0.3, 0.9	1.1	0.8, 1.3	-0.5	-0.8, -0.3	0.2	-0.2, 0.5
SpO_2/FiO_2	17.4	15.9, 18.9	-14.2	-19.8, -8.6	-29	-34, -24	19.2	15.7, 22.7	-8.3	-13.1, -3.6
Temperature	-0.1	-0.1, 0	0.1	0.1, 0.1	0	0, 0	0	-0.1, 0	0	0, 0

Abbreviations, ALC absolute lymphocyte count, CI Confidence interval, COVID-19 Coronavirus disease 2019, CRP C-reactive protein, eGFR estimated glomerular filtration rate

[a]Trend represents the slope of fitted values over the three days immediately preceding the event (i.e. day -3 to day 0 in in each model). For example, for patients in our study population who were admitted and discharged without requiring mechanical ventilation, log-C-reactive protein decreased 0.2 units per day over the three days prior to discharge.

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Figure legends

Figure 1. Mean Population-Average and Patient-Specific Biomarker Trajectories Preceding Clinical Events for Eight Select Measures Using Outcome-Stratified Longitudinal Models Among Patients Within The JH-CROWN Registry, Baltimore MD 3/2020-6/2020. For panels A-H y-axes are fitted values for each biomarker and x-axes are days leading up to the clinical outcome. Thick lines represent population-average trajectories, and thin lines represent the patient-specific trajectories. The left-sided panel for each biomarker (A, C, E, G, I, K, M, and O) represents data among those "Not Vented." Trajectories in these panels are shown from admission to death in red, from admission to discharge in blue, and from admission to mechanical ventilation if later ventilated in green. The right-sided panel for each biomarker (B, D, F, H, J, L, N, and P) represents data among those "Post-Ventilation." Trajectories in these panels are shown from ventilation to death in red and from ventilation to discharge in blue. Individual trajectories of patients with less data more closely approximate the population-average curve with the same outcome. Line thickness is representative of the number of patients with available data at that time point: widest width the curves represent data from >1000 patients, and at the narrowest fewer than 50 patients. 95% confidence intervals are shown in corresponding colors with transparency. Abbreviations, CRP C-reactive protein, eGFR estimated glomerular filtration rate, ALC absolute lymphocyte count

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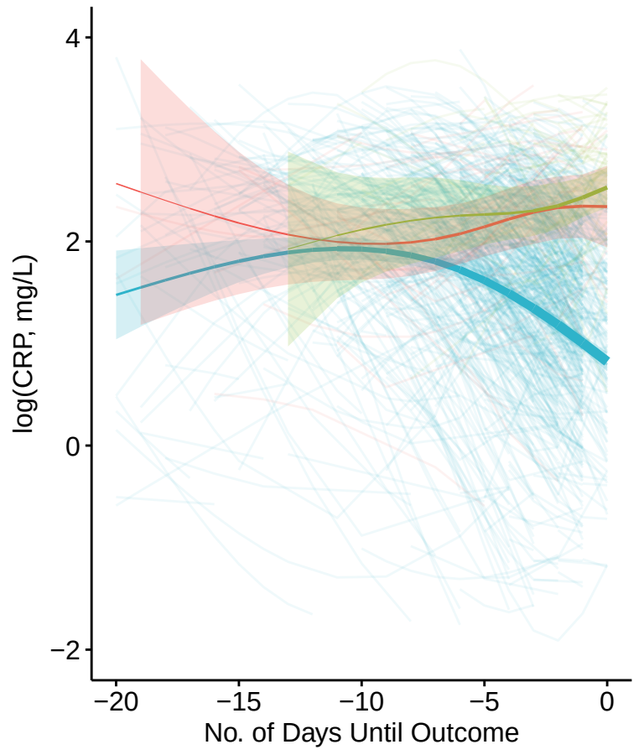

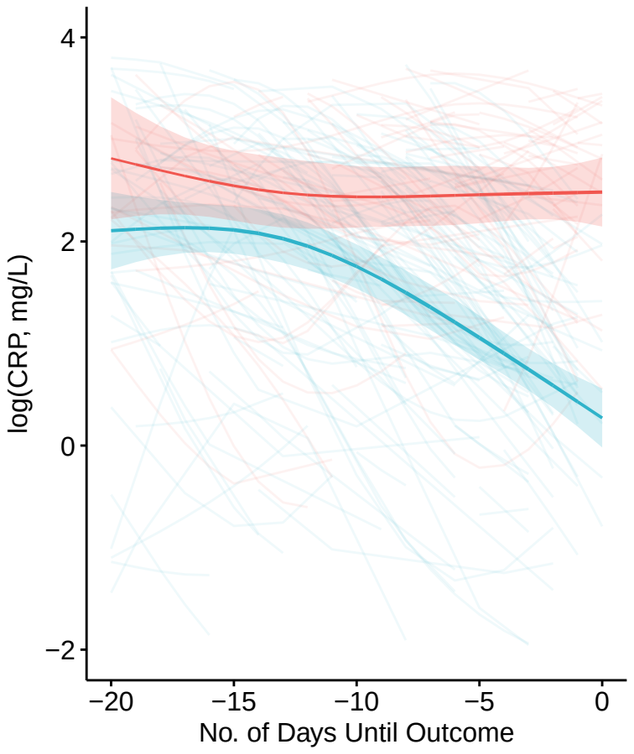

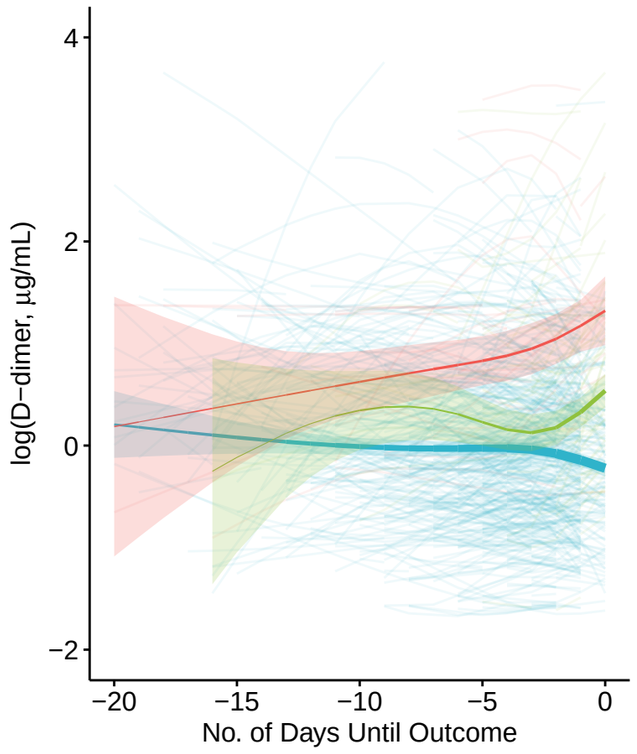

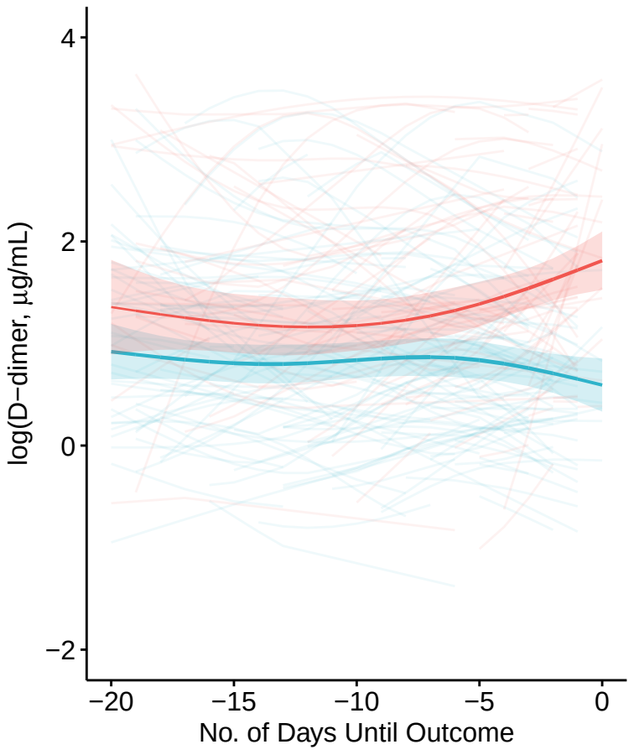

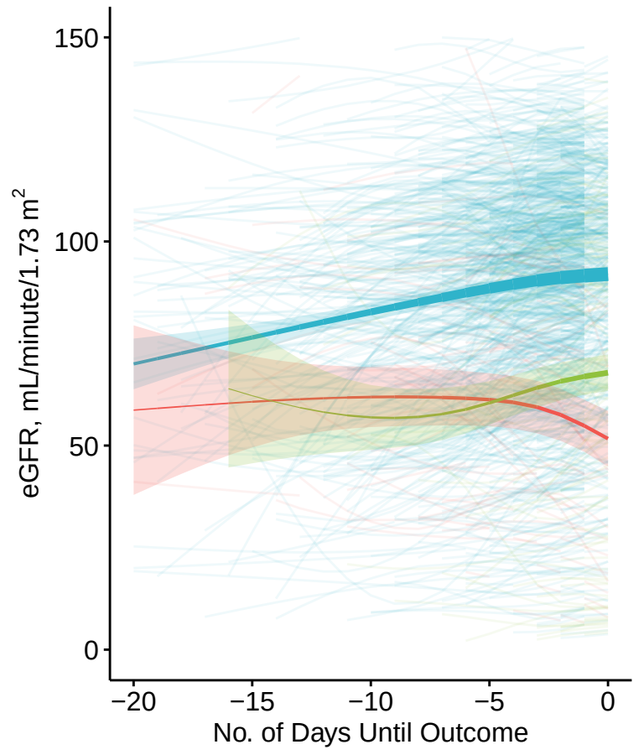

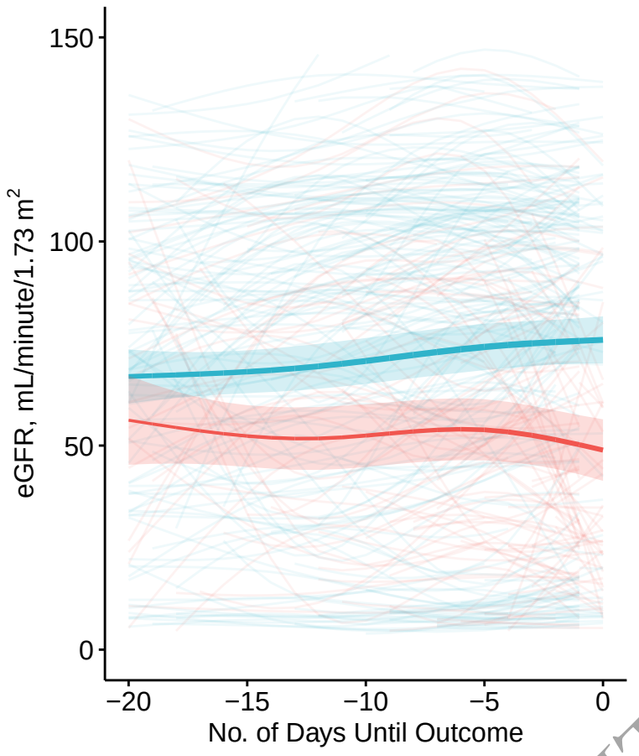

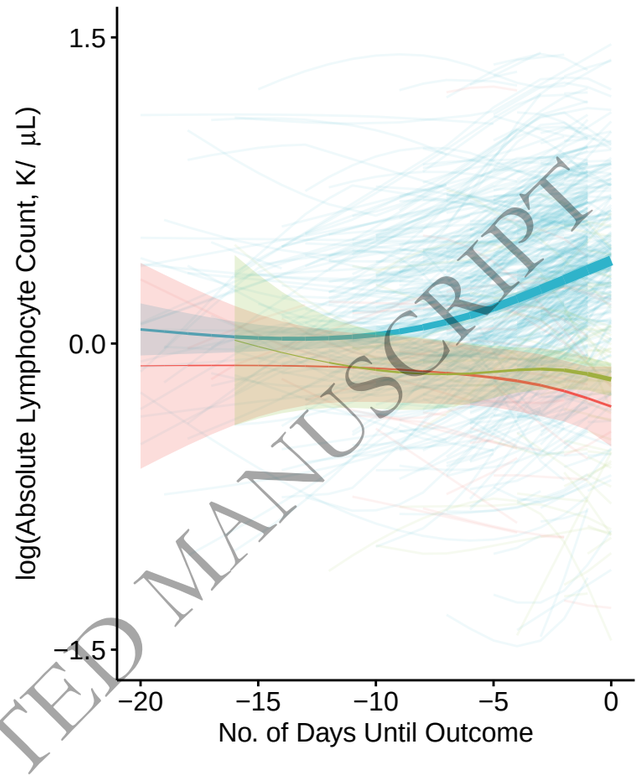

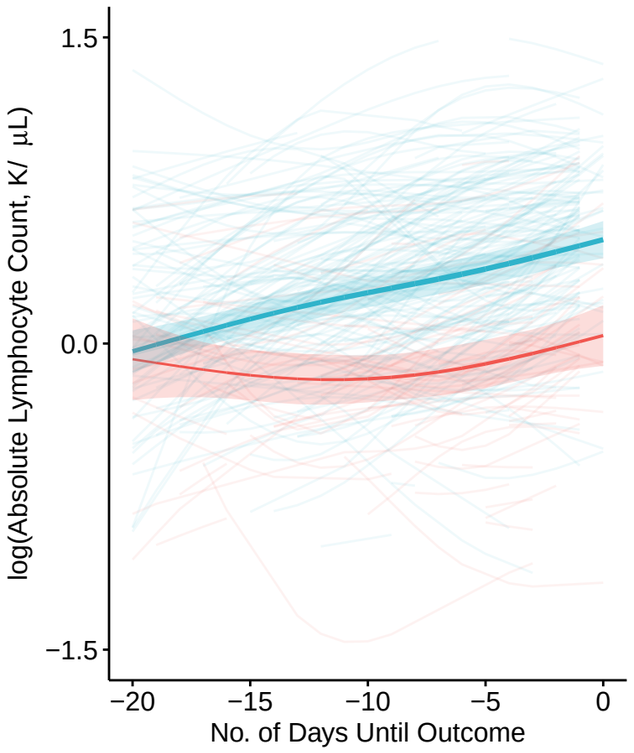

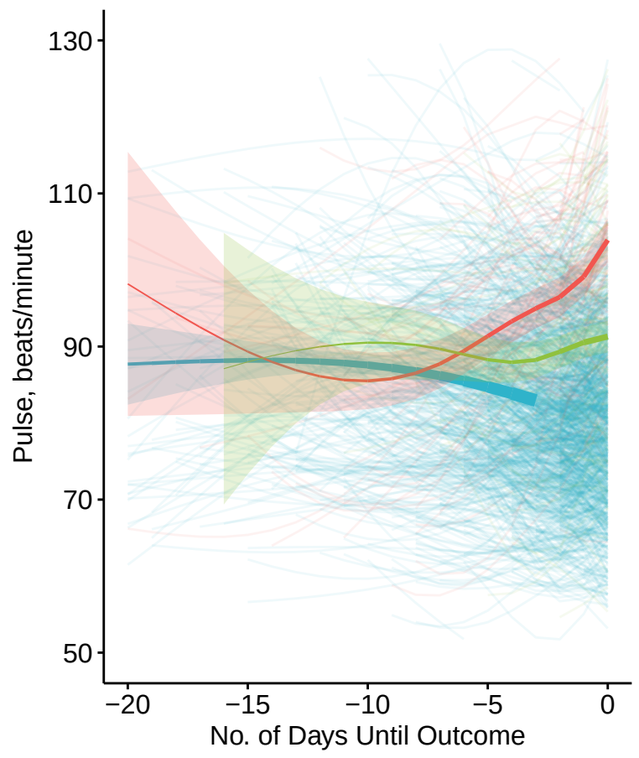

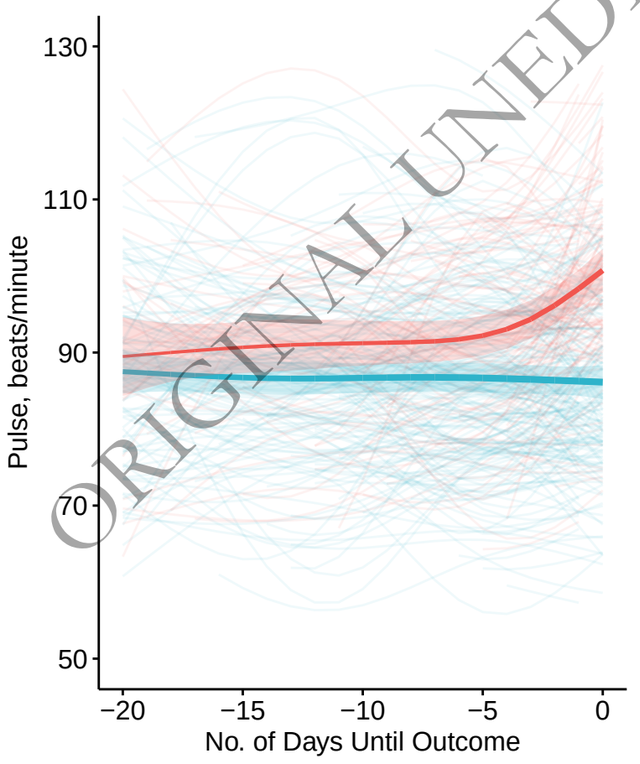

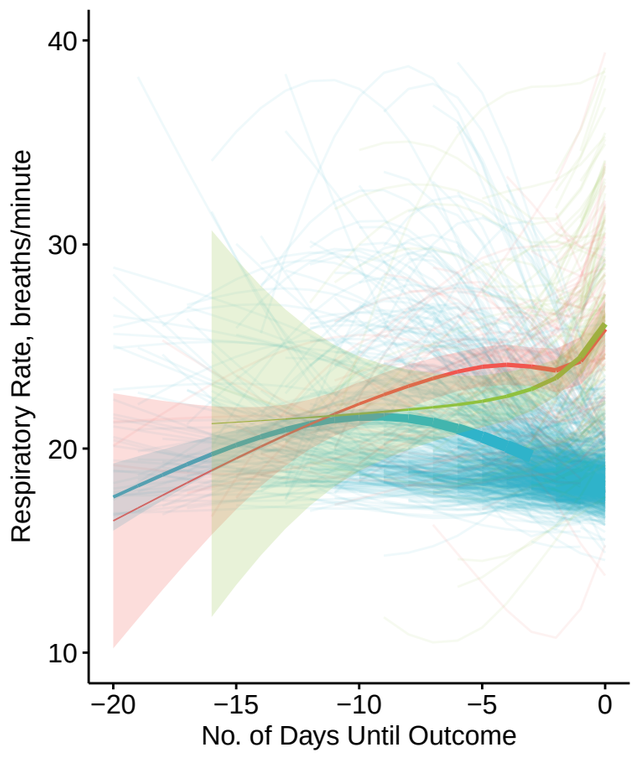

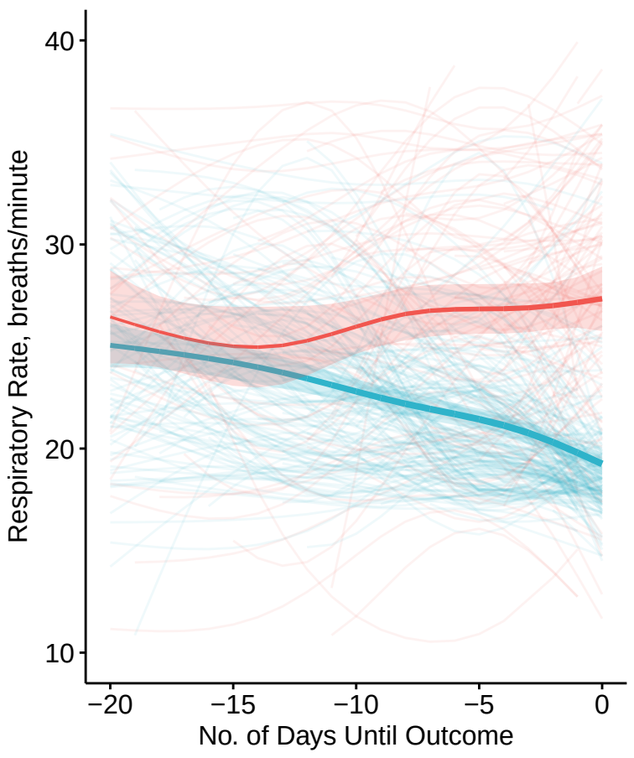

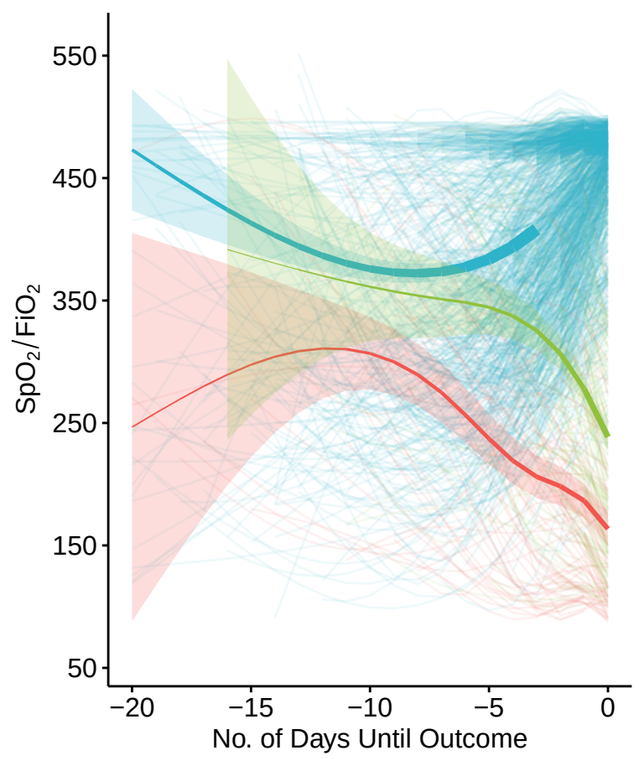

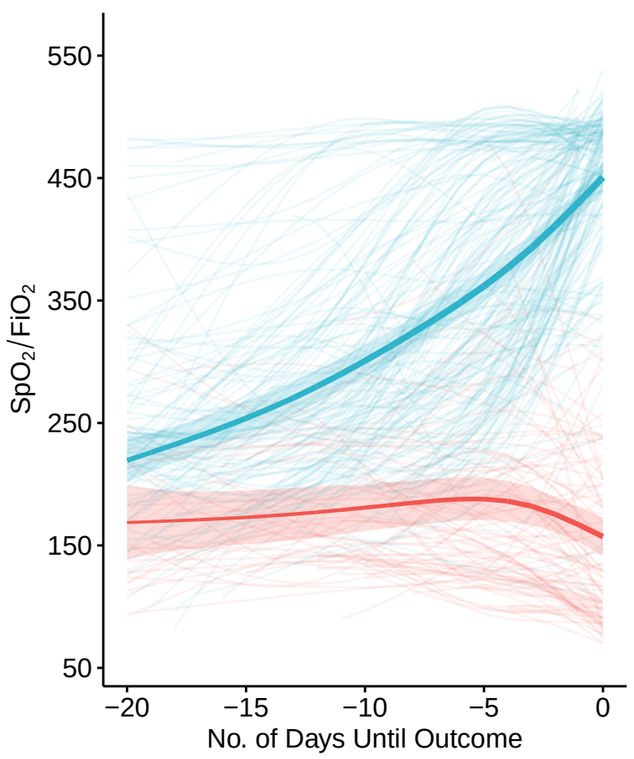

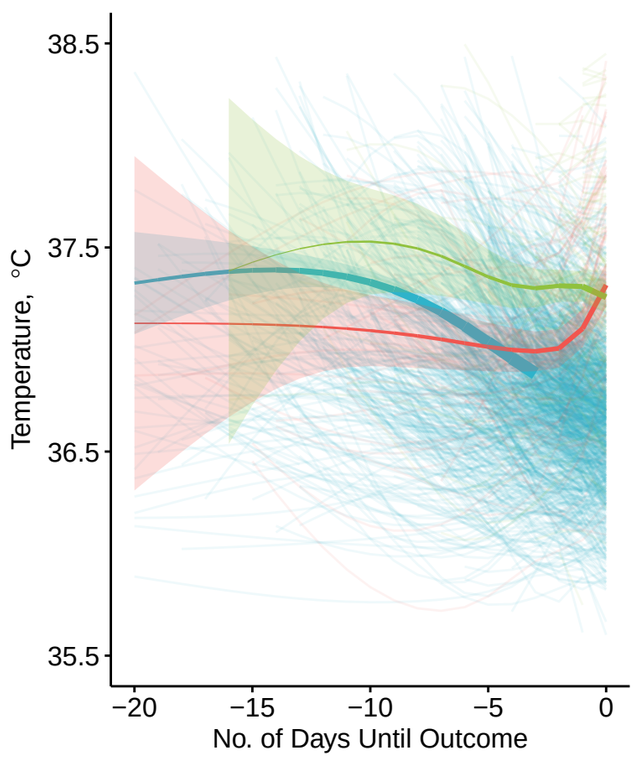

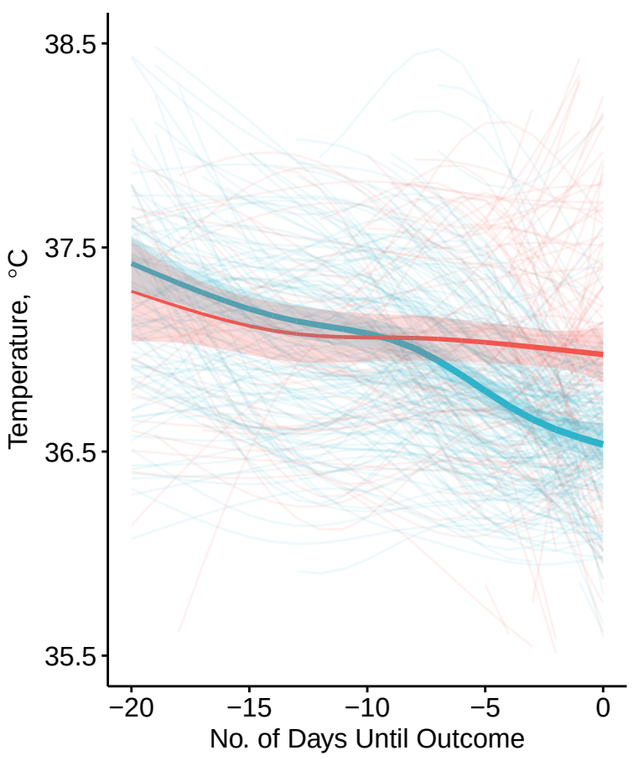

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Figure 2. Patient-Specific Trajectories for One Randomly Selected Patient Based on Outcome-Stratified Longitudinal Models Among Patients Within The JH-CROWN Registry, Baltimore MD 3/2020-6/2020. The randomly selected patient was discharged on day 0 and mechanically ventilated 15 days prior to discharge (day -15, dashed line). For panels A-P, solid gray lines with closed circles represent fitted values of this patient's trajectory and dashed gray lines with open circles represent observed values of this patient's trajectory. The patient was followed from admission until mechanical ventilation on day -15, and from ventilation until discharge on day 0. Dashed vertical line on day -15 delineates the pre- and post-ventilation data. Solid red, blue, and green lines represent population-average curves leading up to death, discharge, and ventilation in the overall population pre- and post-ventilation. The patient had no reported C-reactive protein (CRP) or D-dimer data over the 4 days prior to discharge. Abbreviations, CRP C-reactive protein, eGFR estimated glomerular filtration rate, ALC absolute lymphocyte count

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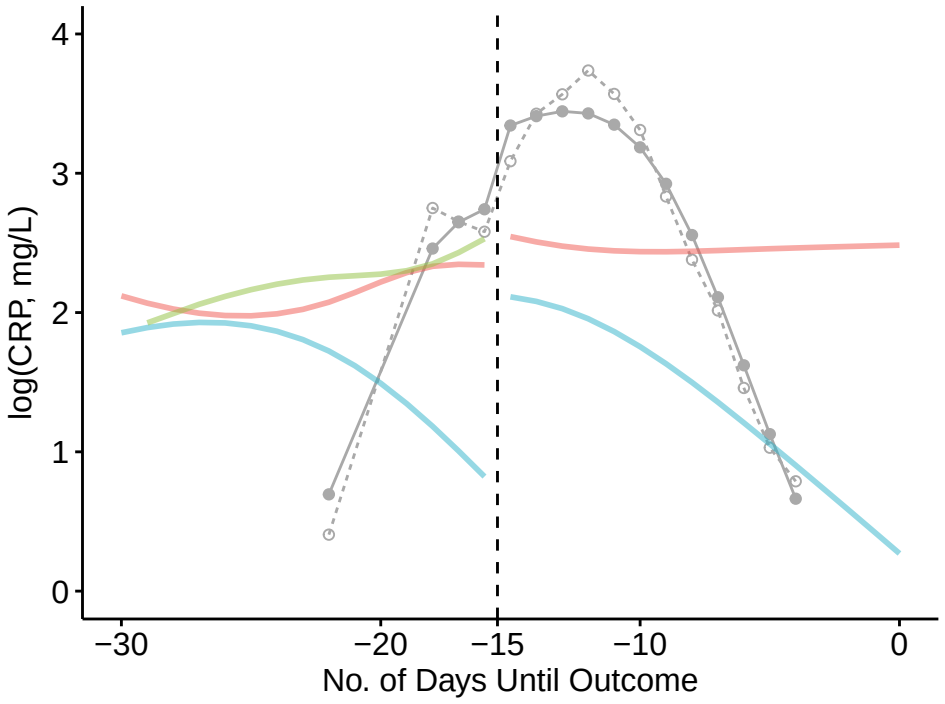

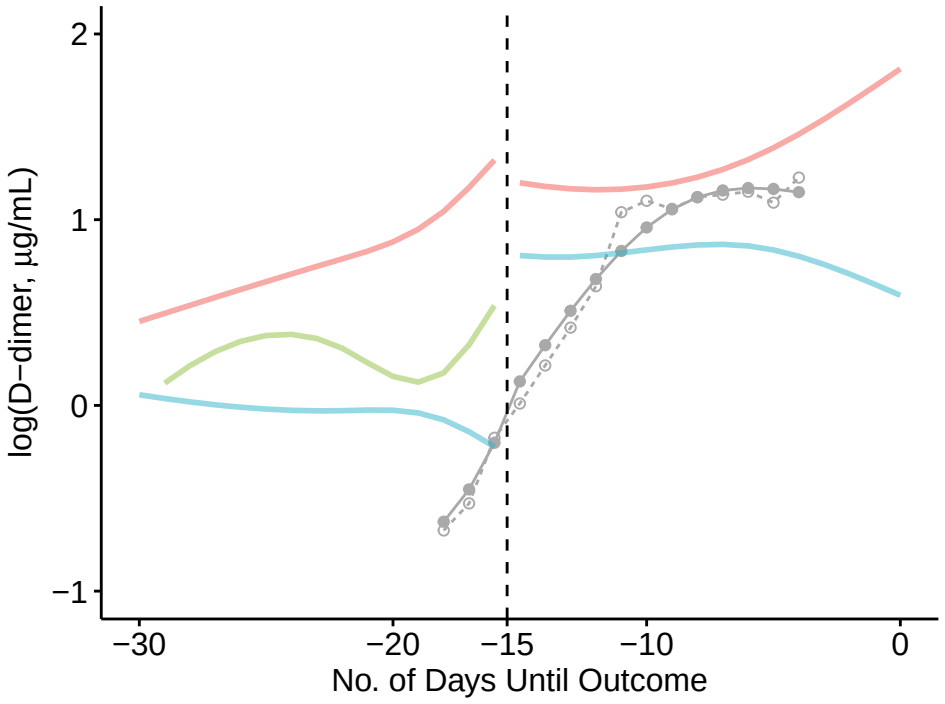

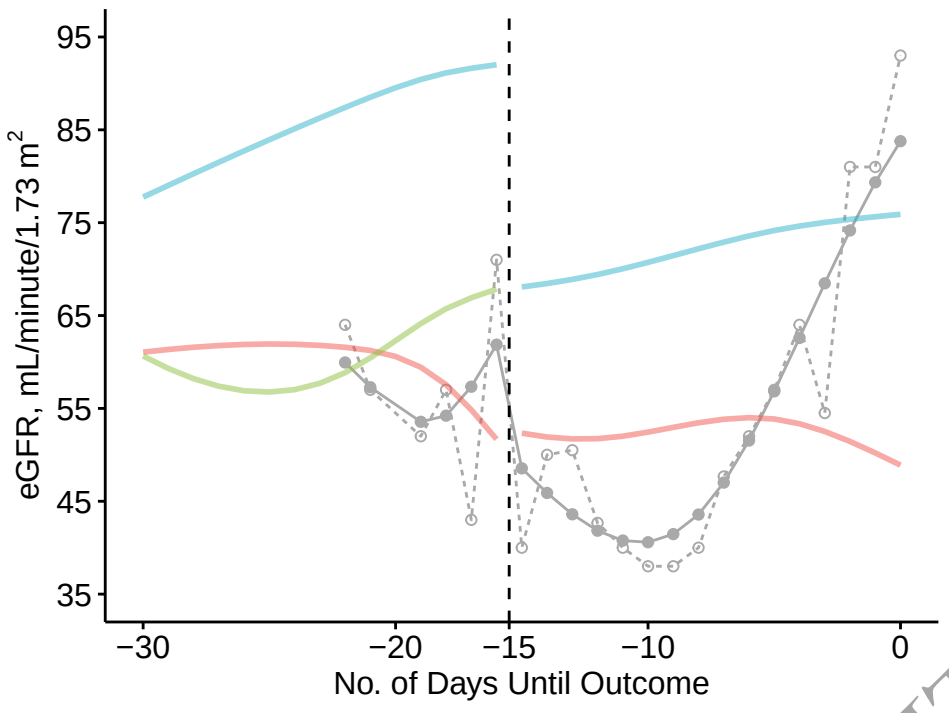

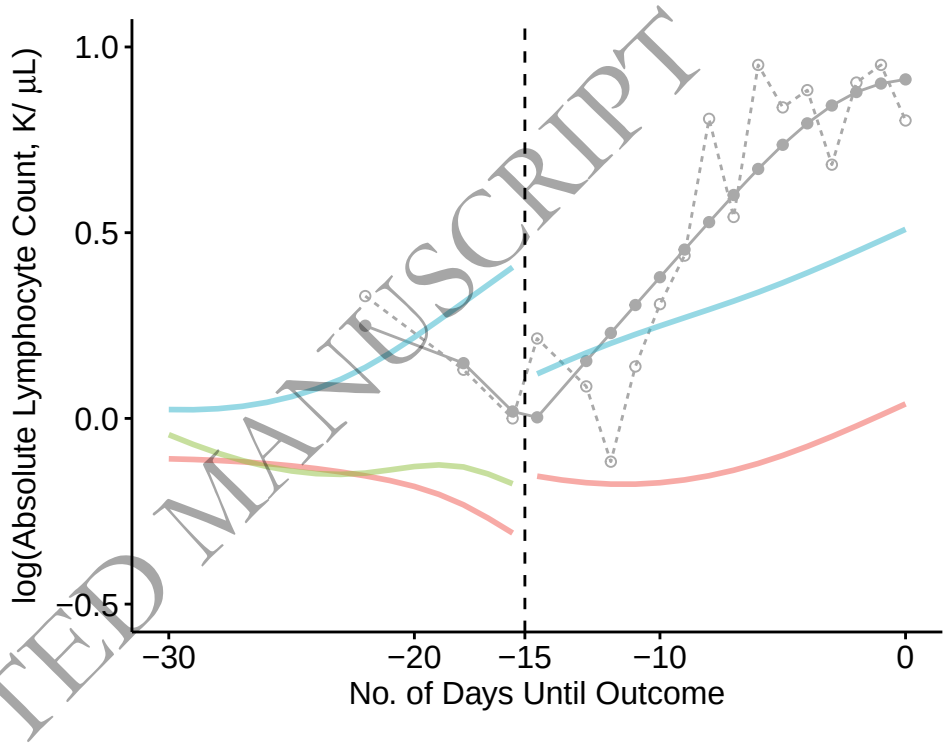

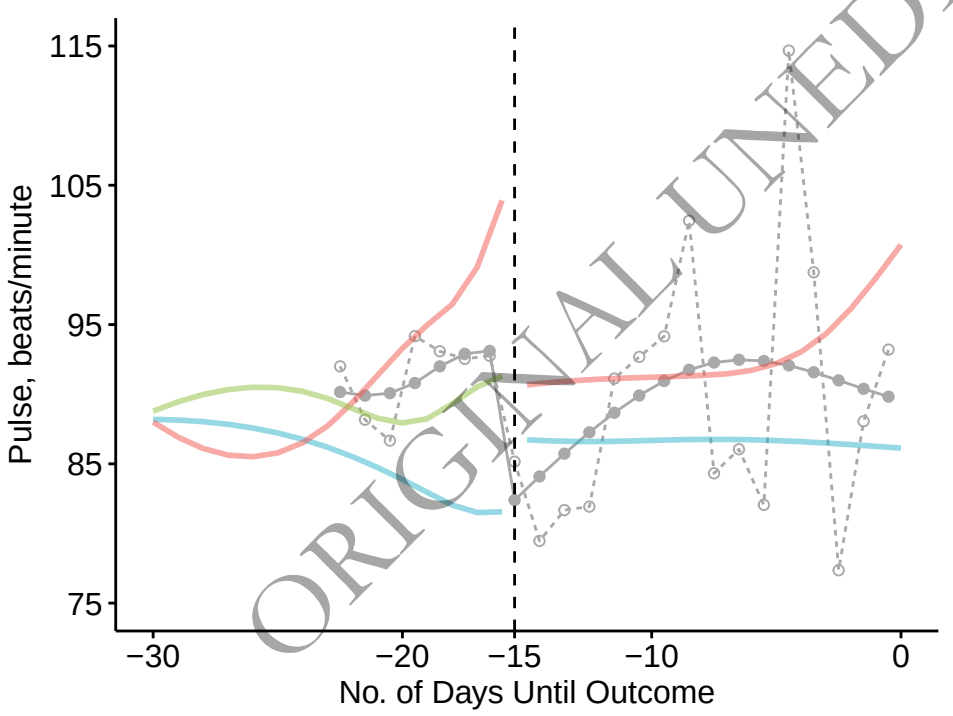

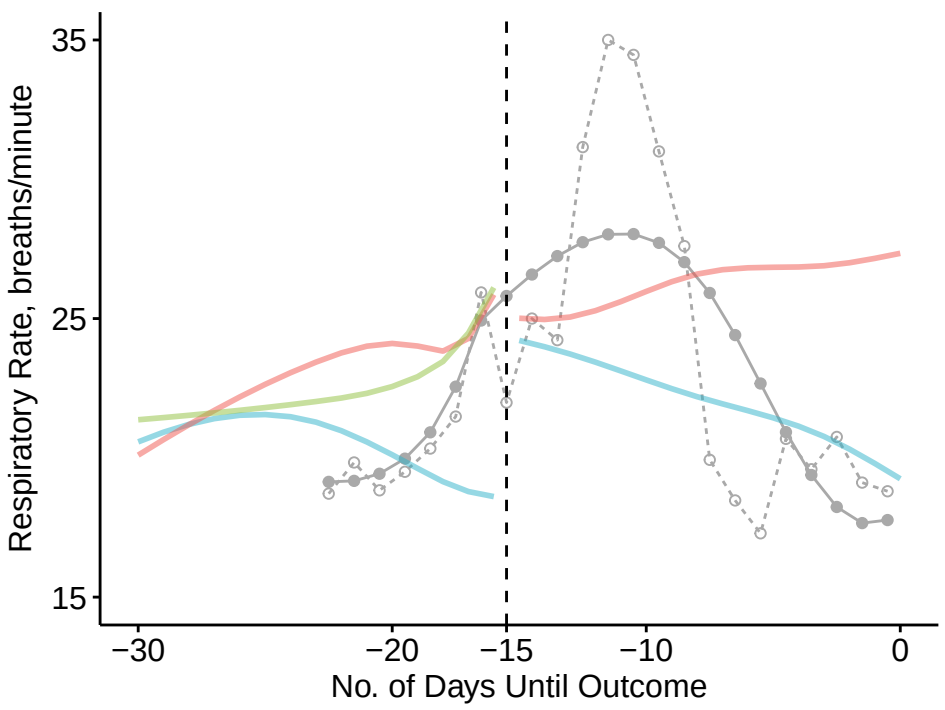

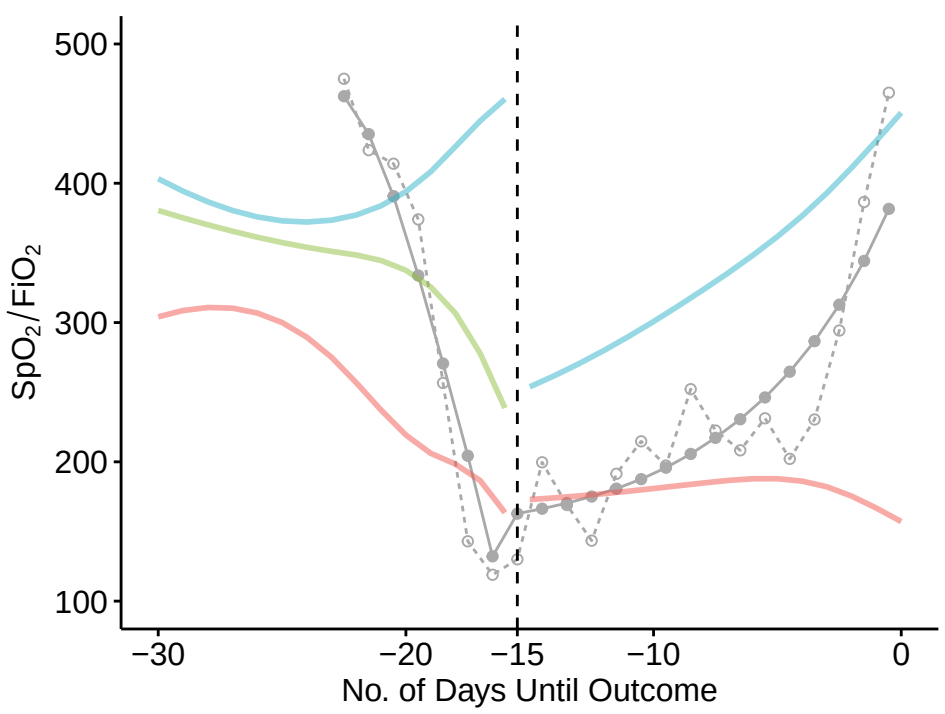

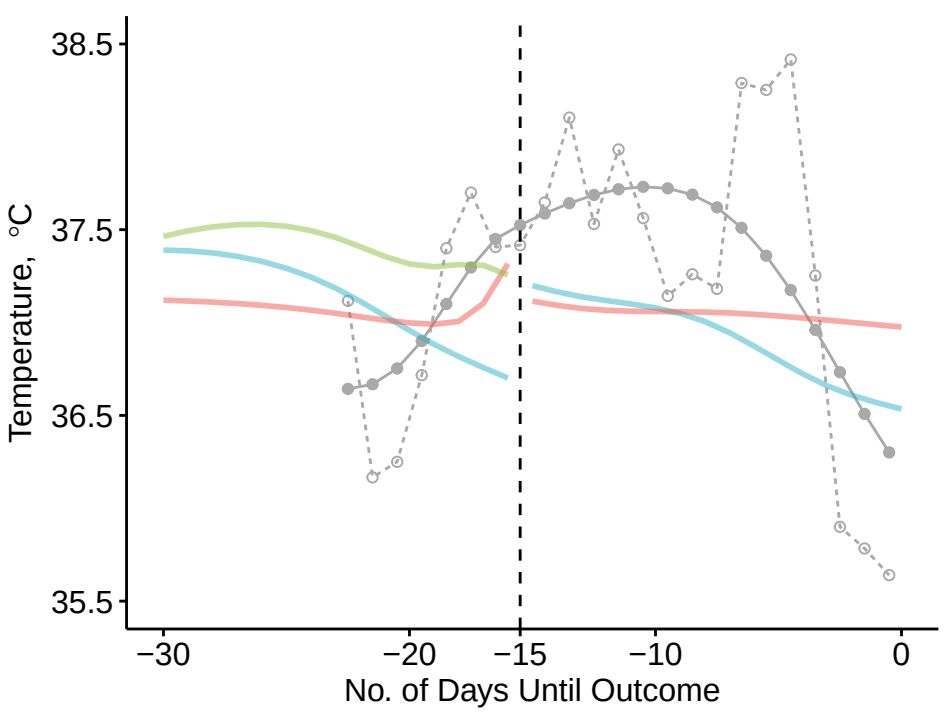

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