Estimating Discontinuous Time-Varying Risk Factors and Treatment Benefits for COVID-19 with Interpretable ML

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Abstract

Treatment protocols, disease understanding, and viral characteristics changed over the course of the COVID-19 pandemic; as a result, the risks associated with patient comorbidities and biomarkers also changed. We add to the conversation regarding inflammation, hemostasis and vascular function in COVID-19 by performing a time-varying observational analysis of over 4000 patients hospitalized for COVID-19 in a New York City hospital system from March 2020 to August 2021. To perform this analysis, we apply tree-based generalized additive models with temporal interactions which recover discontinuous risk changes caused by discrete protocols changes. We find that the biomarkers of thrombosis increasingly predicted mortality from March 2020 to August 2021, while the association between biomarkers of inflammation and thrombosis weakened. Beyond COVID-19, this presents a straightforward methodology to estimate unknown and discontinuous time-varying effects.

Keywords: COVID-19, Time-Varying, Additive Models

1. Introduction

Treatment protocols, disease understanding, and viral characteristics have changed over the course of the COVID-19 pandemic; as a result, the risks associated with patient comorbidities and biomarkers have also changed. Analyses of hospitalized patients have identified that inflammatory biomarkers correspond to case severity (Liu et al., 2020; García, 2020; Lengerich et al., 2022b); in addition, observations of clotting have suggested that hemostasis and vascular function are critically dysregulated processes in patients hospitalized with COVID-19 (Tang et al., 2020; Cui et al., 2020; Kalafatis, 2021; Alam, 2021; Al-Samkari et al., 2020; Mei et al., 2021). We add to this conversation by performing a time-varying observational analysis of over 4000 patients hospitalized for COVID-19 in the New York University Langone Health hospital system from March 2020 to August 2021 to elucidate the changing impacts of thrombosis, inflammation, and other risk factors on in-hospital mortality. We find that the association between mortality risk and thrombosis biomarkers increased over time, suggesting an opportunity for improved care.

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by identifying and targeting therapies for patients with elevated thrombophilic propensity. This strengthening association between thrombosis and mortality contrasts against a weakening association between biomarkers of inflammation and mortality.

2. Materials and Methods

Dataset Our dataset consists of patients hospitalized in the NYU Langone Health system who had lab-confirmed cases of Covid-19. The highest density of patients were admitted in April 2020 (days 30-50 of the pandemic); this period also saw many high-risk patients (Figure S1).

For each patient, we observe demographics, comorbidities, outpatient medications, initial in-patient vitals, and initial in-patient lab tests (listed in S1). To streamline analysis, we binarize each of the 11 continuous-valued lab tests into a discrete biomarker rule which approximately separates high-risk and low-risk regions (Table 1). This binarization was accomplished by fitting the model to the training dataset using continuous-valued lab tests to produce continuous-valued risk plots (Figure S3); to reduce the dimensionality of these covariates we select a data-driven threshold which separates the high-risk and low-risk regions. Finally, for analysis, we group the 11 biomarkers into 3 groups: thrombosis risk (high D-Dimer, high hematocrit), inflammatory risk (high C-Reactive protein, high Neutrophil/Lymphocyte ratio, low serum albumin), and other biomarkers.

Methods We use a generalized additive model (GAM) with interactions to predict in-hospital mortality from risk factors on hospital admission. The model (Figure S2) estimates an effect of each risk factor and an interaction with time for each lab test. We use the tree-based GAMs (Nori et al., 2019) which are invariant to all monotonic feature transforms and recover discontinuities in clinical practice (Lengerich et al., 2022a).

3. Results

The risk model is high accuracy, achieving an ROC of $0.939 \pm 0.001$, outperforming a logistic regression model which achieves an ROC of $0.859 \pm 0.001$.

Predictive Power of Thrombosis Biomarkers Increased The model estimates the time-varying contribution to mortality risk from each biomarker, and the mean mortality risk contributed by each biomarker group (thrombosis, inflammation, or other) after correcting for confounding from all other risk factors. The association between thrombosis biomarkers and in-hospital mortality strengthened over time (Figure 1A), rising from an OR of 0.92 (95% CI 0.85-1.00) in March 2020 to an OR of 1.55 (1.38-1.69) in August 2021. The biomarkers indicating thrombosis risk are: Hematocrit $> 45\%$, D-Dimer $> 1000$ (the effects of these individual biomarkers are displayed in Figure 2, Table 1).

Predictive Power of Biomarkers of Inflammation Decreased The rise in thrombosis risk contrasts against a decrease in risk associated with inflammation-related biomarkers, which dropped from an OR of 1.42 (1.37-1.49) in March 2020 to 1.16 (1.03-1.28) in August 2021 (Figure 1A). While other biomarkers had stable impacts on mortality risk (e.g. the risk associated with elevated temperature remained consistently strong), the risk associated with elevated ferritin increased from an OR of 1.29 (1.07-1.49) to 2.22 (1.82-2.69). In particular, the predictive power of Neutrophil / Lymphocyte Ratio (NLR), a measure of inflammation and Covid-19 severity (Lagunas-Rangel, 2020; Jimeno et al., 2021), decreased (Figure 2).
Time-Varying Risks with COVID-19

Figure 1: (A) The associations between biomarkers and mortality have changed over time. Biomarkers of inflammation risk (elevated C-reactive protein, low albumin, high Neutrophil/Lymphocyte ratio) were initially powerful predictors of in-hospital mortality, but have become less predictive over time. In contrast, biomarkers of thrombosis risk (elevated D-Dimer, elevated hematocrit) are more predictive of mortality in August 2021 than during March 2020. This suggests that the successful treatment of patients hospitalized with indicators of thrombosis risk lagged behind the treatment of other groups. (B) The in-hospital mortality rate decreased over time for all patients, but at a reduced rate for patients satisfying at least one biomarker rule for thrombosis risk. (C) Treatment protocols changed over time, with a trend toward glucocorticoid and anticoagulant (overwhelmingly prophylactic heparin) prescriptions for the majority of patients. We mark the dates of several important publications and the rise of the Delta strain in NYC along the horizontal axis.
Table 1: Biomarkers and rules analyzed by the GAM presented in Figure 1. In addition, we supplement the statistically more powerful GAM results with odds ratios of in-hospital mortality under (1) a univariable analysis without any correction for confounding factors, (2) a multivariable logistic regression model trained on patients admitted in the first 100 days of the pandemic, (3) a multivariable logistic regression model trained on patients admitted from days 100 to 300 of the pandemic, and (4) a multivariable logistic regression model trained on patients admitted after day 300 of the pandemic. The strongest risk factor is elevated temperature, and the only risk factors estimated to consistently increase in predictive power under the logistic regression model are elevated ferritin and elevated hematocrit.

| Group | Biomarker | High-Risk Rule | Mortality Odds Ratio (95% CI) |
|-------|-----------|----------------|-----------------------------|
| Univariable Logistic Regression | Day < 100 (n=2827) | 1.88 (1.43, 2.49) | 109 > 0.3 ml/ml |
| | 100 ≤ Day < 300 (n=612) | 2.00 (1.60, 2.50) | 109 > 0.3 ml/ml |
| | Day ≥ 300 (n=821) | 2.18 (1.63, 2.95) | 109 > 0.3 ml/ml |

Table: Biomarkers and rules analyzed by the GAM presented in Figure 1. In addition, we supplement the statistically more powerful GAM results with odds ratios of in-hospital mortality under (1) a univariable analysis without any correction for confounding factors, (2) a multivariable logistic regression model trained on patients admitted in the first 100 days of the pandemic, (3) a multivariable logistic regression model trained on patients admitted from days 100 to 300 of the pandemic, and (4) a multivariable logistic regression model trained on patients admitted after day 300 of the pandemic. The strongest risk factor is elevated temperature, and the only risk factors estimated to consistently increase in predictive power under the logistic regression model are elevated ferritin and elevated hematocrit.
Corroboration  These trends are qualitatively corroborated by raw mortality rates (Figure 1B), LR (Table 1), and correspond to trends in prescription rates (Figure 1C): clinical trials suggested the utility of glucocorticoids (Group, 2020) and remdesivir (Beigel et al., 2020), and the prescription rates of these treatments increased following publication of these studies. However, despite recognition of the importance of thrombosis and clotting in COVID-19 (Tang et al., 2020; Cui et al., 2020; Kalafatis, 2021; Alam, 2021; Al-Samkari et al., 2020; Mei et al., 2021), anticoagulant prescription rates varied as the effectiveness of thromboprophylaxis with heparin was questioned (REMAP-CAP et al., 2021; Helms et al., 2020).

4. Discussion

These results suggest that success in care for patients at risk for thrombosis lagged behind the success in care for patients with inflammation. As with all observational analyses, this study has limitations and cannot identify a singular cause of the trends. Several hypotheses would be consistent with these data, including: (1) the SARS-CoV-2 Delta strain shifted the importance of intrinsic risk factors, (2) successful efforts for early detection and treatment of thrombosis risk (Ierardi et al., 2021) widened the difference in mortality risk between a serologically defined prothrombotic state and active thromboses, (3) potential interactions between anti-inflammation treatments and...
haemostasis, vascular function, and thrombophilic propensity (Orsi et al., 2021; Johannesson et al., 2013), (4) a lack of effective thromboprophylaxis treatments in COVID-19: there is little evidence for thromboprophylaxis from heparin in COVID-19 patients (REMAP-CAP et al., 2021; Helms et al., 2020) which may be due to heparin’s reliance on endogenous Antithrombin (AT) (Bussey et al., 2004) which can be reduced in COVID-19 patients (Gross et al., 2020) — anticoagulants such as Argatroban (Arachchillage et al., 2020) or Bivalirudin (Smith et al., 2020) which do not rely on AT may exert more powerful thromboprophylaxis than heparin in COVID-19 patients, or (5) an alternate process linked to thrombosis risk factors but also potentially implicating other aspects of endothelial and vascular dysfunction.

5. Conclusions

GAMs with interactions are effective at identifying both homogeneous (static) and time-varying risk factors. When applied to rapidly-changing medical situations such as a pandemic outbreak, the appropriate risk model must accommodate both discontinuous risk factors influenced by treatment thresholds and discontinuous shifts in risk factors arising from changes in viral characteristics and treatment protocols. Tree-based GAMs recover high-resolution pictures of risk factors and treatment benefits, and interactions with time recover discontinuous effects. This approach reveals that for COVID-19 patients in NYC, the association between mortality and pro-inflammatory biomarkers decreased from March 2020 to August 2021 while the association between mortality and pro-thrombotic biomarkers strengthened.

Acknowledgments

Yin Aphinyanaphongs was partially supported by NIH 3UL1TR001445-05 and National Science Foundation award #1928614.

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Appendix S1. Dataset Construction

Pre-Processing Our dataset consists of 11080 total hospitalized patients who have lab-confirmed cases of Covid-19. To filter out patients who were hospitalized for reasons other than Covid-19, we excluded patients who have indicators of (1) pregnancy: outpatient prenatal vitamins, in-patient oxytocics, folic acid preparations; or (2) scheduled surgery: urinary tract radiopaque diagnostics, laxatives, general anesthetics, antiemetic/antivertigo agents, or antiparasitics. We also require that the patients have recorded temperature, age, BMI, and Admission Day. Finally, we remove patients who died within six hours of admission. The patient population changed over time. The majority of patients were admitted from days 30-50. As Figure S1 shows, this period also contained the majority of patients with extremely high risk.

Figure S1: Predicted probability of mortality and admission day for each patient. In this figure, each point represents an individual patient, with the vertical location indicating the probability of mortality predicted by the mortality risk model. There is a high density of patients in the first 60 days of the pandemic, and the most high-risk patients were also observed at that time.

To correct for patient risk confounding, we observe pre-admission features including demographics, comorbidities, outpatient medications, initial in-patient vitals, and initial in-patient lab tests. We exclude any measurement taken within 24 hours of the patient mortality. The 45 total features are listed below.

- Demographics/Vitals:
  - Age
  - Sex
  - BMI
  - Day
  - Temperature

- Comorbidities:
  - Myocardial Infarction
  - Congestive Heart Failure
– Peripheral Vascular Disease
– Cerebrovascular Disease
– Dementia
– Chronic Obstructive Pulmonary Disease
– Peptic Ulcer Disease
– Mild Liver Disease
– Diabetes without chronic complications
– Diabetes with chronic complications
– Hemiplegia or paraplegia
– Renal disease
– Cancer (any malignancy)
– Metastatic solid tumor
– Charlson score
– Hypertension
– Atrial fibrillation
– Valve Replacement
– Rheumatoid Arthritis

• Outpatient Medications taken before hospitalization (limited to medication classes taken by at least 100 patients):
  – Antihyperglycemic, Biguanide Type
  – Laxatives And Cathartics
  – Platelet Aggregation Inhibitors
  – Vitamin D Preparations
  – Calcium Channel Blocking Agents
  – Proton-Pump Inhibitors
  – Antihyperlipidemic-Hmgcoa Reductase Inhib (Statins)
  – Beta-Adrenergic Agents, Inhaled, Short Acting
  – Blood Sugar Diagnostics
  – Anticonvulsants
  – Analgesic/Antipyretics,Non-Salicylate
  – Beta-Adrenergic Blocking Agents

• Lab Values:
  – Potassium (0.5% Missing)
  – Ferritin (8.3% Missing)
  – Calcium (0.5% Missing)
  – Neutrophil % (0.0% Missing)
  – Lymphocyte % (0.0% Missing)
Appendix S2. Extended Description of Methods

Figure S2: Model Architecture. We use a generalized additive model to estimate homogeneous (static) risk factors, and an interaction with day (day of pandemic) to estimate time-varying risk factors.

Figure S3: Effects of continuous lab values before binarization to biomarker rules. In both panes, blue areas represent reduced risk of mortality while red areas represent increased risk of mortality. (A) Low calcium is consistently associated with increased risk of mortality. (B) Low hematocrit levels were originally associated with increased risk of mortality, but after 50 days, the association changed sharply and high hematocrit became associated with increased risk of mortality.

The GAM provides odds ratios (ORs) for the mortality risk associated with each biomarker on each day. We supplement these daily ORs with ORs from 3 logistic regression (LR) models each trained on approximately one third of the patients (LR1 was trained on patients hospitalized from day 1 to day 100, LR2 was trained on patients hospitalized from day 100 to 300, while LR3 was trained on patients hospitalized from day 300 to 527) and observe qualitatively similar patterns in the GAM and the LR models, although the GAM provides more statistical power and better temporal resolution.
Appendix S3. Extended Results

Figure S4: Effects of In-Hospital Medications, ordered by mean effect size. In each pane, we plot the additive effect on mortality log-odds (lower is more protective). The only medications which appear consistently helpful are Ketorolac and Ibuprofen, although the effectiveness of these medications appear to decrease.

S3.1. Decreasing Effectiveness of Anti-Inflammatory Medications

Just as the predictive power of inflammation reduced over time, so too did the apparent effectiveness of anti-inflammatory medications (Figure S4) reduce over time. In particular, glucocorticoids shifted from having no association with any significant homogeneous effect to an association with a deleterious homogeneous. This could correspond to glucocorticoids having a beneficial effect for only a subset of the patient population (Lengerich et al., 2021b), but being used as standard care. In addition non-steroidal antiflammatory drugs (NSAIDs) Ketorolac and Ibuprofen shifted from an association with decreased mortality to no significant association (confidence intervals that overlap zero effect). This corresponds to previously-observed benefits of NSAIDs (Lengerich et al., 2021a) being reduced by anti-inflammatory steroids becoming a standard of care.

S3.2. Comorbidities and Pre-Hospitalization Medications

The baseline mortality risks of comorbidities and pre-admission out-patient medications are shown in Figure S5. In general, these effects of comorbidities and out-patient medications concord with mechanisms of mortality involving inflammation and/or thromboses. The most protective effect is peptic ulcer disease, the effect of which is offset in some patients by a deleterious effect of proton-pump inhibitors. The second-most protective effect is platelet aggregation inhibitors (low-dose aspirin), which can prevent thromboses. The third-most
protective effect is valve replacement, for which patients are continually on out-patient anti-coagulation medications. The most deleterious effects are dementia, congestive heart failure, beta-adrenergic agents, and myocardial infarction.

Figure S5: Effects of Comorbidities and Pre-hospitalization medications.
Appendix S4. Homogeneous Effects

Figure S6: Homogeneous (static) effects of lab values and comorbidities. (A-P) Effects of lab values, with shaded regions representing 95% confidence intervals. Each pane displays the uncorrected effect estimated by univariable marginalization (gray) and by the multivariable GAM (red). Each yellow tick mark along the horizontal axis denotes 10 patients. (Q) Estimated mortality odds ratio associated with comorbidities and outpatient (pre-hospitalization) medications, with 95% confidence intervals.