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Title: Personalized Prediction of Hospital Mortality in COVID-19 positive patients

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Key words: Personalized prediction, COVID-19, mortality
Abstract:

Objective: To develop predictive models for in-hospital mortality and length of stay (LOS) for COVID-19 positive patients.

Patients and Methods: We performed a multicenter retrospective cohort study of hospitalized COVID-19 positive patients. A total of 764 patients admitted to 14 different hospitals within the Cleveland Clinic from 03/09/2020 to 05/20/2020 who had reverse transcriptase-polymerase chain reaction proven coronavirus infection were included. We used LightGBM, a machine learning algorithm, to predict in-hospital mortality at different time points (after 7 days, 14 days, and 30 days of hospitalization) and in-hospital LOS.

Results: Among 764 patients, 116 (15%) either died (n = 87) or were transitioned to hospice care (n = 29) during their hospitalization. The median LOS was 5 days (range 1 - 44 days) for patients admitted to the regular nursing floor and 10 days (range 1-38 days) for patients admitted to the intensive care unit (ICU). Patients who died during hospitalization were older, initially admitted to the ICU, more likely to be white and to have worse organ dysfunction compared to patients who survived their hospitalization. Using the 10 most important variables only, the final model’s area under the Receiver Operating Characteristics curve was 0.86 for 7-day, 0.88 for 14-day, and 0.85 for 30-day mortality in the validation cohort.

Conclusions: We developed a decision tool that can provide explainable and patient-specific prediction of in-hospital mortality and LOS for COVID-19 positive patients. The model can aid healthcare systems in bed allocation and distribution of vital resources.

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Abbreviations:

COVID-19: Coronavirus disease 2019

ICU: Intensive care unit

LOS: Length of stay

ROC AUC: Area under the Receiver Operating Characteristics curve
BACKGROUND

Despite several international and local efforts, the coronavirus pandemic caused by the acute respiratory virus (SARS-CoV-2) has infected more than 122 million individuals worldwide, and more than 2.7 million people have died to date. The pandemic is far from over with rising new cases in several parts of the United States and the world. Consequently, healthcare systems continue to face several challenges regarding bed availabilities/allocations and resource utilization.

While some infected patients can be asymptomatic, others can suffer from severe respiratory distress syndrome, multiorgan failure, and death. Thus, identifying patients with higher risk of early mortality during their hospitalization could aid hospitals and healthcare providers in predicting the disease trajectory, distributing vital resources efficiently, and consequently, improving patients’ outcomes.

Here, we developed a clinical-decision tool that uses clinical and demographic variables within twenty-four hours of hospitalization to provide personalized predictions of patient mortality and length of stay (LOS) that are specific for a given patient.

METHODS

Study population:

All patients admitted to our healthcare system from 03/09/2020 to 05/20/2020 who had reverse transcriptase-polymerase chain reaction proven COVID19 infection were included in our database (n = 962). We excluded patients: 1) that had not been discharged or died by 05/21/2020.
(n = 103); 2) for whom discharge disposition was unknown (due to missing information or transfer to another hospital; n = 89); and 3) who were younger than 18 years (n = 6). The study was approved by the Cleveland Clinic Institutional Review Board and conducted in accordance with the declaration of Helsinki.

Dataset and Outcomes Definition

For each patient, demographic, clinical, and laboratory variables (109 variables, Supplementary Table 1) were included and structured from the electronic healthcare record. All variables were collected within the first 24 hours of hospitalization. Twenty two percent of our data was missing, mostly because some laboratory tests were not ordered on the day of admission or the test was not ordered at all for the patient. Missing data was handled by the built-in algorithm from the machine learning model used in our analysis.

The main outcomes evaluated were mortality at 7, 14, and 30 days of hospitalization and length of hospital stay, which was defined as the time between hospitalization and death or discharge from the hospital. We also built a model for prediction of ICU transfer (or death before ICU transfer) among patients admitted to the regular nursing floor.

Statistical Analysis

To assure that all variables are treated equally regardless of their significance in univariate analysis and to account for the variables that can be significant only in the context of other variables, we used a machine learning model, LightGBM,\(^2\) in our analysis. LightGBM is a model based on the gradient boosting framework. In gradient boosting, models with weak predictive capability, such as decision trees, are used together to achieve high predictive
performance. During training of a gradient boosting model, decision trees are created using the available variables to separate instances belonging to different classes (e.g., survivors versus non-survivors). These decision trees are created in a sequential fashion to minimize the prediction errors made by the previous trees. Once facing a new case, the model will use the framework of decision trees created during training to classify the new example.

The dataset was divided randomly into training (80%) and test (20%) sets and the models were initially trained with all our variables. The most influential ten variables as determined by the values originated by the SHapley Additive exPlanations (SHAP) algorithm$^3$ (algorithm that is widely used to determine the most important variables that impacted a model’s decision) were extracted. These were ranked from the most to the least important variable, and used to fit reduced, clinically usable, versions of our models.

Hyperparameter optimization using a Bayesian optimization algorithm was obtained to assure the most robust models were used and 10-fold cross-validation was also used to assure the reproducibility of the final models. Model performance in the validation set is reported using the area under the receiver operating characteristics curve (ROC AUC).

RESULTS

Patient Population

A total of 764 patients were included in the analysis; 116 (15%) either died (n = 87) or were transitioned to hospice care (n = 29). The median age was 64 years (range: 19-98 years) and 147 patients (19%) were admitted directly to the intensive care unit (ICU). The median LOS was 5 days (range 1 - 44 days) for patients admitted to the regular nursing floor and 10 days (range 1-
38 days) for patients admitted to the ICU. Table 1 summarizes the clinical characteristics of our cohort. As expected, patients who died during their hospitalization were older, more likely to be initially admitted to the ICU, and had worse organ dysfunction and inflammatory biomarkers compared to patients who survived their hospitalization, Table 1. Interestingly, males did not have worse outcomes compared to females and African American patients had lower mortality rate compared to whites in our cohort, Table 1.

Mortality models

A total of 109 clinical variables (Supplementary Table 1) were included in the algorithm to predict mortality after 7, 14, and 30 days of hospitalization. A feature extraction algorithm was used to identify the top 10 variables that impacted the mortality at each time point. While variables such as age, lactate dehydrogenase, ferritin and C-reactive protein were shown as important at each time point but at a different level of importance, others like procalcitonin and being on a mechanical ventilator in the first 24 hours only impacted mortality at 30 days, Figure 1.

Using the top 10 variables only, the final model ROC AUC when applied to the validation cohort was 0.86 for 7-day mortality, 0.88 for 14-day mortality, and 0.85 for 30-day mortality. The model can provide personalized and explainable prediction for an individual patient, Figure 2.

Length of Stay Model

Using similar methodology, the top ten variables that impacted the hospital length of stay > 7 days and > 14 days are shown in Figure 1. Using these variables, the final model ROC AUC was 0.80 for > 7 days and 0.82 days for > 14 days LOS.

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Other Outcomes

We also used the same methodology to build a model to predict ICU transfer (or death prior to ICU transfer) among patients admitted initially to the regular nursing floor. The final model ROC AUC with only the top 10 variables was 0.80. The top 10 clinical variables that impacted risk of ICU transfer as well as 30-day mortality in patients older than 70 years old can also be found in Figure 1.

DISCUSSION

In this study, we developed personalized prediction models that use clinical variables within 24-hours of admission to predict mortality and LOS that are specific for COVID-19 patients. The proposed models showed robust AUC in predicting mortality and LOS at different time points during hospitalization. Our models’ predictions could alert physicians regarding adverse outcomes for hospitalized patients with COVID such as hospital mortality and transfer to ICU. It can also help hospitals manage a COVID surge by identifying the expected length of stay in the hospital and ICU. We also explored the clinical variables that impacted these outcomes during hospitalization and showed that while some variables like age, lactate dehydrogenase, and ferritin have a significant impact on mortality at each time point, others like procalcitonin can only affect mortality after 14 and 30 days. More importantly, our models can provide an explainable prediction that is specific for a given patient. This explainability will allow physicians to understand the significant clinical variables that impacted their patients’ outcomes.

Several studies have evaluated the impact of clinical variables on mortality during hospitalization for COVID-19 patients.\textsuperscript{4-7} Although all showed that age and comorbidities could impact the
outcome, the impact of other clinical variables varies. These differences in the outcomes could be related to the difference in the methodology of conducting the multivariate analyses. Our machine learning model included all the clinical variables initially to assure that all variables are treated equally regardless of their significance in univariate analyses. We then focused on the analysis of the top 10 variables that impacted the overall outcomes. Although machine learning models are often viewed as a "black-box," our model can provide an explainable output that is specific for a given patient.

Our study has important limitations. First, as a retrospective study importing data from the EMR, a high proportion of missing data is expected. While missing data will worsen the performance of a prediction algorithm, empirically we were able to verify that the model still had robust performance on our test set (i.e., validation cohort). Second, given that each surge may have its own specific characteristics and that all patients came from hospitals within the same healthcare system, our ability to generalize our findings may be limited to some extent.

In conclusion, we built personalized prediction models to predict outcomes for hospitalized COVID19 patients. The models can aid physicians and healthcare systems in understating the disease trajectory and expected outcomes for a given patient.

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Table 1: Patients’ Characteristics

| Patients’ Characteristics | All Patients (n = 764) | Death or Hospice (n = 116) | Survived (n = 648) | P-value |
|---------------------------|------------------------|---------------------------|-------------------|---------|
| **Demographics**          |                        |                           |                   |         |
| Race, n (%)               |                        |                           |                   |         |
| White                     | 433 (56.7)             | 82 (70.7)                 | 351 (54.2)        | .001    |
| African American          | 277 (36.3)             | 30 (25.9)                 | 247 (38.1)        | .02     |
| Asian                     | 10 (1.3)               | 1 (0.9)                   | 9 (1.4)           | 1       |
| Multiracial               | 28 (3.7)               | 1 (0.9)                   | 27 (4.2)          | .11     |
| Ethnicity, n (%)          |                        |                           |                   |         |
| Non-Hispanic              | 705 (94.8)             | 109 (96.5)                | 596 (94.5)        | .51     |
| Hispanic                  | 39 (5.2)               | 4 (3.5)                   | 35 (5.5)          |         |
| Age, median [Q1,Q3]       | 64.4 [53.8,76.7]       | 80.7 [72.6,84.5]          | 62.0 [52.3,73.0]  | <.001   |
| Gender, n (%)             |                        |                           |                   |         |
| Female                    | 366 (47.9)             | 57 (49.1)                 | 309 (47.7)        | .85     |
### Male

|                      | 398 (52.1)       | 59 (50.9)       | 339 (52.3)       |
|----------------------|------------------|-----------------|------------------|
| **BMI (kg/m²), median [Q1,Q3]** | 30.1 [25.9,35.4] | 30.3 [26.5,35.6] | 28.6 [22.9,32.7] |
| **Previous Medical History, n (%)** |                   |                 |                  |
| Chronic Obstructive Pulmonary Disease | 95 (13.5)        | 17 (16.2)       | 78 (13.0)        |
| Asthma               | 156 (22.1)       | 16 (15.1)       | 140 (23.3)       |
| Diabetes             | 284 (39.9)       | 50 (46.3)       | 234 (38.7)       |
| Hypertension         | 528 (72.3)       | 96 (83.5)       | 432 (70.2)       |
| Coronary Artery Disease | 152 (21.6)     | 44 (40.4)       | 108 (18.1)       |
| Heart Failure        | 139 (19.6)       | 44 (40.0)       | 95 (15.9)        |
| Any Cancer           | 142 (19.4)       | 35 (31.5)       | 107 (17.3)       |
| **Laboratory parameters, median [Q1,Q3]** |                   |                 |                  |
| **Metabolic indices** |                 |                 |                  |
| Sodium (mEq/L)       | 137.0 [134.0,139.0] | 138.0 [134.0,141.0] | 137.0 [134.0,139.0] |
| Potassium (mEq/L)    | 4.0 [3.7,4.4]    | 4.2 [3.8,4.5]   | 4.0 [3.7,4.3]    |
| Creatinine (mg/dL)   | 1.0 [0.8,1.4]    | 1.6 [1.1,2.3]   | 1.0 [0.8,1.3]    |
| Lactate (mg/dL)      | 1.4 [1.0,1.8]    | 1.5 [1.2,2.1]   | 1.3 [1.0,1.8]    |
| **Hepatic indices**  |                 |                 |                  |
| Alanine Aminotransferase (units/L) | 24.0 [15.0,40.0] | 27.0 [15.0,41.0] | 23.0 [15.0,39.0] |
| Aspartate Aminotransferase (units/L) | 34.0 [24.0,52.0] | 43.0 [32.0,79.0] | 32.0 [23.0,49.0] |
| Total Bilirubin (mg/dL) | 0.4 [0.3,0.6]   | 0.5 [0.3,0.7]   | 0.4 [0.3,0.6]    |
| Alkaline Phosphatase (units/L) | 72.0 [57.5,94.5] | 82.0 [63.5,104.0] | 71.0 [57.0,93.2] |
| Albumin (g/dL)       | 3.7 [3.4,4.0]    | 3.4 [3.0,3.8]   | 3.7 [3.4,4.0]    |
| **Hematologic indices** |                   |                 |                  |
| Hemoglobin (g/dL)    | 13.1 [11.6,14.5] | 11.9 [9.9,13.8] | 13.3 [11.9,14.6] |
| White Blood Cell Count (k/ul) | 6.4 [4.8,8.5]   | 7.7 [5.4,10.9]  | 6.3 [4.8,8.2]    |
| Platelet Count (k/ul) | 207.0 [160.0,267.0] | 198.5 [144.2,245.2] | 209.0 [163.0,268.0] |
| International Normalized Ratio | 1.0 [1.0,1.1]   | 1.1 [1.0,1.2]   | 1.0 [1.0,1.1]    |
| Partial Thromboplastin Time (s) | 29.6 [27.1,33.4] | 30.8 [27.0,33.7] | 29.4 [27.1,33.2] |
| D-dimer (ng/mL)      | 840.0 [490.0,1615.0] | 1470.0 [825.0,3380.0] | 780.0 [470.0,1390.0] |
| **Inflammatory indices** |                   |                 |                  |
| Lactate Dehydrogenase (units/L) | 299.0 [229.8,401.0] | 400.0 [308.0,531.0] | 288.0 [223.5,366.5] |
| C Reactive Protein (mg/dl) | 6.5 [3.0,12.2] | 11.9 [5.7,17.5] | 5.9 [2.5,11.3] |
| Procalcitonin (ng/mL) | 0.1 [0.1,0.4] | 0.3 [0.2,1.4] | 0.1 [0.1,0.3] |
| Ferritin (ng/mL)     | 511.4 [255.3,1009.2] | 852.9 [351.9,1747.5] | 485.5 [235.1,1893.2] |
| **Troponin T (ng/mL)** | 0.0 [0.0,0.1] | 0.1 [0.0,0.2] | 0.0 [0.0,0.1] |

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| Treatment-Related Variables, n (%) | ICU on Admission | Need for Noninvasive Mechanical Ventilation | Mechanical Ventilation on Day 1 | Mechanical Ventilation During Stay | Use of Hydroxychloroquine | Use of Tocilizumab | New use of Steroids |
|----------------------------------|-----------------|------------------------------------------|-------------------------------|----------------------------------|--------------------------|------------------|-------------------|
|                                  | 147 (19.2)      | 96 (12.6)                                | 74 (9.7)                      | 133 (17.4)                      | 293 (52.6)               | 50 (9.0)         | 94 (12.3)         |
|                                  | 48 (41.4)       | 34 (29.3)                                | 34 (29.3)                     | 59 (74.7)                       | 39 (48.1)                | 8 (9.9)          | 32 (27.6)         |
|                                  | 99 (15.3)       | 62 (9.6)                                 | 40 (6.2)                      | 74 (27.4)                       | 254 (53.4)               | 42 (8.8)         | 62 (9.6)          |
|                                  | <.001           | <.001                                    | <.001                         | <.001                           | .45                      | .92              | <.001             |
| Creatine Kinase (units/L)        | 135.0 [69.5,297.0] | 242.0 [105.0,753.0]                    | 115.0 [65.8,228.2]            |                                  |                          |                  |                   |

**Figure Legends:**

Figure 1 Title: Ten most important variables for each model

Figure 1 Legend: Bar plots showing the ten most important variables for each model based on their SHAP values (values generated using the SHAP algorithm indicating how much a variable contributed to the model’s decisions).

Abbreviations: ANC, Absolute Neutrophil Count; AST, Aspartate Aminotransferase; BMI, Body Mass Index; BUN, Blood Urea Nitrogen; CK, Creatinine Kinase; COVID, Coronavirus Disease;
CRP, C-Reactive Protein; CXR, Chest Radiograph; INR, International Normalized Ratio; LDH, Lactate Dehydrogenase; NC, Nasal Cannula; PTT, Partial Thromboplastin Time.

Figure 2 Title: Personalized prediction of mortality and LOS

Figure 2 Legend: Decision plots showing how the probability of the outcome (7-day mortality on the left and LOS > 7 days on the right) shifts as each variable is considered for three different patients on each side. The starting point in the bottom of each graph is the pre-test probability (i.e., overall percentage of patients who died within 7 days or whose LOS was > 7 days). For instance, in the top panel left, the probability of dying goes from around 40% to 90% as the patient’s age (of 85 years) is considered by the algorithm. On the left, the three patients depicted had similar ages but different outcomes (top one died, while the other two survived), all of which were correctly predicted by the model. On the right, from top to bottom, LOS was 5, 8 and 24 days.

Abbreviations: BMI, Body Mass Index; CRP, C-Reactive Protein; Nan, missing value; LDH, Lactate Dehydrogenase; PTT, Partial Thromboplastin Time
### Supplementary Table 1

**Title:** Variables considered in model development (n = 109)

| Variables Considered                      |
|-------------------------------------------|
| Age                                       |
| Race                                      |
| Ethnicity                                 |
| Gender                                    |
| Height                                    |
| Body Mass Index                           |
| Time since symptom onset to testing (days)|
| Time since symptom onset to admission (days)|
| Time since testing to admission (days)    |
| Testing location (ED*, drive-through or inpatient) |
| Cough                                     |
| Fever                                     |
| Fatigue                                   |
| Sputum production                         |
| Flu-like symptoms                         |
| Diarrhea                                  |
| Loss of appetite                          |
| Vomiting                                  |
| Smoking                                   |
| Pack years                                |
| COPD*/emphysema                           |
| Asthma                                    |
| Diabetes                                  |
| Hypertension                              |
| Coronary artery disease                   |

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| Heart failure                                      |
| Cancer                                             |
| Cancer status (active versus in remission)         |
| Immunosuppressive treatment                        |
| History of transplant                              |
| Multiple sclerosis                                 |
| Connective tissue disease                          |
| Inflammatory bowel disease                         |
| Epilepsy                                           |
| Pregnant at time of testing                        |
| Other immunosuppressive disease                    |
| Any heart disease                                  |
| Any lung disease                                   |
| C-reactive protein                                 |
| Lactate dehydrogenase                              |
| Creatine kinase                                    |
| Procalcitonin                                      |
| Lactate                                            |
| D-dimer                                            |
| White blood cells                                  |
| Platelets                                          |
| Albumin                                            |
| Hemoglobin A1C                                     |
| Absolute eosinophil count                          |
| Absolute lymphocyte count                          |
| Absolute neutrophil count                          |
| Alkaline Phosphatase                               |
| Alanine aminotransferase                           |
| Aspartate aminotransfer                            |
| Bicarbonate                                        |
| Blood urea nitrogen                                |
| Chloride                                           |
| Creatinine                                         |
| Hematocrit                                         |
| Hemoglobin                                         |
| Potassium                                          |
| International normalized ratio                     |
| Partial thromboplastin time                        |
| Sodium                                             |
| Total Bilirubin                                    |
| Troponin T                                         |
| Creatine kinase-MB                                 |
| Interleukin-6                                      |
| Serum ferritin                                     |
| NSAID use                                          |
| Corticosteroid use                                 |

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| Carvedilol | Angiotensin-converting enzyme inhibitor |
|-----------|----------------------------------------|
|           | Angiotensin receptor blocker            |
| Diagnosis of pneumonia | Assisted breathing required |
| Oxygen use | High-flow oxygen |
| Noninvasive ventilation | Mechanical ventilation |
| Ventilation duration | Highest PEEP<sup>d</sup> |
| Highest FiO2<sup>e</sup> | Highest PO2/FiO2 ratio |
| Infiltrates present on chest x-ray | Infiltrates present on chest CT<sup>g</sup> |
| Admitted to ICU on D1 | ECMO<sup>h</sup> |
| Need for tracheostomy | Proning |
| Norepinephrine | Highest norepinephrine dose |
| Epinephrine | Vasopressin |
| Dopamine | Highest dopamine dose |
| Phenylephrine | Highest phenylephrine dose |
| Dobutamine | Highest dobutamine dose |
| Neuromuscular blocking agents | Inhaled epoprostenol |
| Inhaled NO | Dialysis/hemofiltration |

<sup>a</sup>: Emergency Department

<sup>b</sup>: Chronic obstructive pulmonary disease

<sup>c</sup>: Nonsteroidal anti-inflammatory drug use

<sup>d</sup>: Positive end-expiratory pressure

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e: Fraction of inspired oxygen

f: Arterial oxygen partial pressure

g: Computed Tomography

h: Extracorporeal membrane oxygenation
