Cardiovascular Diabetology

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Proteomic analysis of cardiometabolic biomarkers and predictive modeling of severe outcomes in patients hospitalized with COVID-19

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Abstract

Background: The high heterogeneity in the symptoms and severity of COVID-19 makes it challenging to identify high-risk patients early in the disease. Cardiometabolic comorbidities have shown strong associations with COVID-19 severity in epidemiologic studies. Cardiometabolic protein biomarkers, therefore, may provide predictive insight regarding which patients are most susceptible to severe illness from COVID-19.

Methods: In plasma samples collected from 343 patients hospitalized with COVID-19 during the first wave of the pandemic, we measured 92 circulating protein biomarkers previously implicated in cardiometabolic disease. We performed proteomic analysis and developed predictive models for severe outcomes. We then used these models to predict the outcomes of out-of-sample patients hospitalized with COVID-19 later in the surge (N = 194).

Results: We identified a set of seven protein biomarkers predictive of admission to the intensive care unit and/or death (ICU/death) within 28 days of presentation to care. Two of the biomarkers, ADAMTS13 and VEGFD, were associated with a lower risk of ICU/death. The remaining biomarkers, ACE2, IL-1RA, IL6, KIM1, and CTSL1, were associated with higher risk. When used to predict the outcomes of the future, out-of-sample patients, the predictive models built with these protein biomarkers outperformed all models built from standard clinical data, including known COVID-19 risk factors.

Conclusions: These findings suggest that proteomic profiling can inform the early clinical impression of a patient's likelihood of developing severe COVID-19 outcomes and, ultimately, accelerate the recognition and treatment of high-risk patients.

Keywords: COVID-19, Predictive modeling, Cardiometabolic biomarkers, Proteomics

Background

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of deaths and persists as a global health threat [1]. COVID-19 causes a spectrum of symptoms, from mild upper respiratory tract infection to severe acute respiratory distress syndrome (ARDS) and

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death [2–4]. Most patients who develop severe COVID-19 deteriorate after one week of symptom onset [5]. As existing viral modifying therapies, such as monoclonal antibodies, are most effective when given before patients develop critical symptoms [6], early recognition is crucial to the triage and treatment of severe cases.

Previous studies of patients hospitalized with COVID-19 have consistently found significant associations between comorbidities and poor COVID-19 outcomes [7–29]. A cross-sectional study of over half a million hospitalized adults with COVID-19 found that 95% had at least one underlying medical condition and observed a strong dose–response association between the total number of underlying conditions (e.g., hypertension, obesity, lipid disorder, diabetes, and coronary artery disease) and risk of severe COVID-19 illness. Compared to patients with no documented underlying medical conditions, having one medical condition (7% of patients) was associated with 1.5 times higher risk of death, and having more than 10 conditions (17% of patients) was associated with a fourfold increase in the risk of death [7]. While little progress has been made in the development of tests that reliably predict which patients will suffer poor outcomes from COVID-19 (e.g., need for intensive care, assisted ventilation, septic shock, multiorgan system dysfunction, or death) [10], the presence of certain comorbid conditions, including higher body mass index (BMI) [7, 11–16], coronary artery disease [17–19], chronic kidney disease [20–25], and type 2 diabetes [7, 8, 21, 26–29], can help identify the patients most susceptible to severe forms of COVID-19.

Circulating protein biomarkers reflect underlying physiologic or disease states and can serve as measurable indicators of disease severity for prognostication in clinical practice. Interrogating the relationship between COVID-19 outcomes and protein biomarkers previously implicated in cardiometabolic disease may yield actionable insights regarding how common cardiometabolic comorbidities contribute to COVID-19 pathogenesis and, ultimately, improve our ability to predict which patients are most likely to suffer poor outcomes.

Methods

Study design

During the first wave of the pandemic (March 10 to June 1, 2020), we collected discarded blood samples from patients who presented to care (i.e., first contact with the healthcare system) with COVID-19 symptoms and were subsequently hospitalized with PCR-confirmed SARS-CoV-2 infection at Massachusetts General Hospital (MGH), a large academic hospital in Boston, Massachusetts. In these samples, we measured 92 protein biomarkers in the Olink Target 96 Cardiovascular II panel [30]. We performed proteomic analysis and developed predictive models for the combined outcome of death or admission to the intensive care unit (ICU/death) within 28 days of presentation to care in patients hospitalized early in the surge, between March 10 and April 21, 2020 ("in-sample" group; n = 343). We then used these models to predict the outcomes in a separate sample of patients hospitalized with COVID-19 later in the surge, between April 22 and June 1, 2020 ("out-of-sample" group; n = 194).

Data collection

Details of the hospitalization, past medical history, and demographic characteristics were collected for each patient by manual chart reviews. Hospital laboratory tests performed within three days of presentation to care were retrieved electronically through the Enterprise Data Warehouse, a repository derived from electronic health records. We excluded hospital laboratory tests with a missing rate greater than 30% and imputed those remaining with the median of the non-missing values (mean missing rate = 13%). For each patient, we generated the CURB-65 score, a risk score for pneumonia severity [31]. The CURB-65 score ranges from 0 to 5 based on the presence of the following factors: (1) confusion (defined as Glasgow Coma Scale < 15), (2) blood urea nitrogen > 19 mg/dL, (3) respiratory rate ≥ 30, (4) systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and (5) age ≥ 65. Study procedures were approved by the Mass General Brigham (formerly Partners) Human Research Committee, the governing institutional review board at MGH.

Plasma collection and proteomic assays

Blood samples were collected in EDTA tubes and processed within three days of collection in a biosafety level 2 + laboratory. Whole blood was centrifuged at 2800 rpm for 10 min. Plasma samples were extracted and stored at −80 °C. Prior to plating, samples were treated for two hours with 1% TritonX-100 at room temperature for virus inactivation. The Olink reagents were based on Proximity Extension Assay technology. Measurements were translated into normalized protein expression (NPX) units. Sample plates passed quality control if the standard deviations of internal controls were < 0.20 NPX and individual samples were < 0.30 NPX from the median value of the internal controls [30]. A total of 537 samples (95%) passed quality control. All 92 protein biomarkers were detected with intra-assay coefficient of variance (CV) < 15% (mean 4%) and inter-assay CV < 30% (mean 10%).

Statistical analysis

We performed all statistical analyses in Python version 3.9.2 and R version 4.0.5. To account for non-normality in the raw data, we applied rank-based inverse normal transformation for feature selection, modeling, and *P* value calculation. To preserve interpretability, the odds ratios (ORs) shown in the volcano plot and correlation matrix were calculated after standardizing the data to have a mean of 0 and standard deviation of 1. To account for multiple testing, the threshold $P < 0.05/116$ hospital laboratory tests and protein biomarkers $= 4 \times 10^{-4}$ was used to determine significance.

To uncover mechanistic links, we performed a core enrichment analysis using QIAGEN Ingenuity Pathway Analysis (IPA; Ingenuity Systems, Redwood City, CA) by matching a proteomic dataset, consisting of *P* values and ORs for each protein biomarker, with curated content of the Ingenuity Knowledge Base. We generated reports for molecular networks and canonical pathways, highlighting upstream regulators and pathways relevant to the observed changes, along with their predicted impact on downstream biological or disease processes.

Predictive modeling

To identify the subset of variables with the greatest predictive value for the logistic regression model, we ranked all variables by the frequency with which they were selected by LASSO (least absolute shrinkage and selection operator) regression when repeated across separate, random subsets of the in-sample data and different shrinkage parameters [32]. To identify the best model, we used an all-possible-regressions approach with these top-ranked variables. We used fivefold stratified cross-validation within the in-sample data to test the models formed by every possible combination of top-ranked variables. We then plotted the average area under the receiver operating characteristic curve (AUC), with the models sorted by the number of variables they included. The model that formed the elbow at which the plot of increasing AUC versus model size began to plateau was considered the best model, achieving the greatest performance without over-fitting the in-sample data. We performed this analysis with and without the 92 protein biomarkers and compared the AUCs of the best models built with and without the biomarkers using a two-sided DeLong test [33]. We repeated the modeling process using random forest models and using the Boruta algorithm to initially rank the variables by significance [34]. Data from the out-of-sample patients was not used at any point in the feature selection and modeling process.

Results

Characteristics of the patients

Figure 1 shows the baseline characteristics of patients in the in-sample group and out-of-sample group. Table 1 shows the patient characteristics stratified by the ICU/death outcome in each group. Compared to the in-sample group, the out-of-sample group had a similar proportion of patients who died, but a smaller proportion of patients who were admitted to the ICU (Fig. 1). The out-of-sample group had a larger proportion of self-reported non-Hispanic White and non-Hispanic Black/African-American patients, a smaller proportion of self-reported Hispanic patients, a lower average BMI, higher levels of D-dimer, lower levels of lactate dehydrogenase, and lower levels of creatine kinase relative to the in-sample group. Patients who died or were admitted to the ICU had a higher average BMI, higher average CURB-65 score, and higher levels of D-dimer, LDH, C-reactive protein (CRP), and ferritin compared to those alive and not admitted to the ICU after 28 days of presentation to care (Table 1).

Cardiometabolic protein biomarkers

To evaluate the relative importance of each of the 92 protein biomarkers and the 24 hospital laboratory tests with respect to ICU/death, we built a logistic regression model, adjusted for age, gender, BMI, and self-reported race/ethnicity, for each biomarker and hospital laboratory test in the in-sample group (Additional file 1: Table S1). The protein biomarkers comprised 31 of the 36 significant associations ($P < 4 \times 10^{-4}$) with ICU/death (Fig. 2). The five hospital laboratory tests with significant associations included LDH, CRP, procalcitonin, aspartate aminotransferase, and alanine transaminase, with

Fig. 1 o16wAdc47m(o)6d7niffic4

Three of the identified biomarkers, KIM1, ACE2, and CTSL, are involved in host-virus interactions. KIM1, an indicator of renal insults, plays a role in viral entry and regulation of the host immune response to viral infections [51]. ACE2, the cellular receptor for SARS-CoV-2 [40, 42], undergoes shedding, leading to circulating ACE2, a biomarker of cardiovascular disease, diabetes, and death in patients with and without COVID-19 [52, 53]. The association of ACE2 with severity is supported by a recently reported rare genetic variant that is associated with a 37% reduction in ACE2 expression and a 40% reduction in risk of severe COVID-19 [54]. Finally, CTSL is one of the lysosomal proteases that can cleave the SARS-CoV-2 spike protein, a step necessary for cellular entry [41, 55].

Previous studies have reported hospital laboratory tests and clinical characteristics associated with severe COVID-19 [5, 35, 36, 44, 45, 56–62]. These studies used both prospective and retrospective analyses of clinical variables, imaging findings, and laboratory values predictive of severity. Laboratory values such as IL6 [35, 44], IL-1RA, IL10 [36], D-dimer [5, 45, 61], and troponin [5, 60, 62] were associated with disease severity. Clinical characteristics, such as BMI, age [5, 63], history of renal failure, cardiovascular and cerebrovascular disease [60, 63], were also associated with worse outcomes. Our study shows the best predictive model included many of these previously reported risk factors when the protein biomarkers were not included (Table S4). However, when the protein biomarkers were included in the model-building process, these risk factors were replaced with the set of seven biomarkers, resulting in models that significantly outperformed all models developed from the clinical features and laboratory tests alone, suggesting that the biomarkers provide unique predictive value not captured by patient data and hospital lab values. The protein biomarkers replaced known clinical risk factors for severe illness that had been selected in the model built without biomarkers (i.e., BMI, D-dimer, CRP, ALC, and troponin). Notably, BMI was replaced by IL-1RA, a biomarker that was strongly correlated with BMI (Fig. 3). IL-1RA, known to be highly expressed in white adipose tissue [64] and upregulated during inflammation, could serve as a better proxy than BMI for obesity-driven COVID-19 risk. D-dimer was another previously reported COVID-19 risk factor [5, 45, 61] that was selected in the model without protein biomarkers but replaced in the model with biomarkers. D-dimer was positively correlated with IL6, IL-1RA, KIM1, ACE2, and CTSL1 (Fig. 3: Box B) and negatively correlated with ADAMTS13 and VEGFD (Fig. 3: Box D). The replacement of D-dimer in the final model with these seven protein biomarkers suggests that the predictive value provided by D-dimer was captured by this combination of biomarkers. Nevertheless, the utility of these protein biomarkers for the purpose of risk stratification in real-world clinical settings will need to be prospectively assessed in the context of their practical considerations (e.g., cost, speed of results reporting, and access to testing) for them to be appropriately incorporated in the clinical evaluation of patients hospitalized with COVID-19.

We recognize that standards of care and resource availability evolved quickly during the first wave of the pandemic. As data on the efficacy and side effects of COVID-19 therapies accrued, the use of remdesivir and dexamethasone increased, while the use of hydroxychloroquine decreased. MGH hospital guidelines did not recommend routine systemic anticoagulation for patients with COVID-19 during the pandemic and did not recommend the use of steroids, such as dexamethasone, until the publication of the RECOVERY study [65], after the recruitment period of this study. Prone positioning, applied heterogeneously early in the pandemic, eventually became standard of care. It is possible that these exogenous factors contributed to differences in outcomes between the in-sample and out-of-sample cohorts. We expect that, as the SARS-CoV-2 virus mutates, the virulence pathways and host responses may change, as noted by both the delta and omicron variants [66]. The patients hospitalized with COVID-19 today are generally younger and consist of both unvaccinated and vaccinated patients with breakthrough infections or repeat infections. Emerging COVID-19 therapies and medication exposures for preexisting medical conditions could influence the proteomic profile of patients and its association with COVID-19 severity.

By evaluating the models in a sample separate from that used to develop the models, we showed that the predictive value of the biomarkers was robust to changes in clinical protocols and the patient characteristics during the highly dynamic study period. Compared to studies that develop and test predictive models within the same patient population, our approach provided a more rigorous assessment of the generalizability of our models and the conclusions derived from our analysis. As one of the largest proteomic analyses performed in COVID-19 patients, we were able to conduct age-stratified, gender-stratified, and race/ethnicity-stratified analyses, demonstrating the strong performance of the model with the protein biomarkers across various demographic strata (Additional file 1: Fig. S5, S6, and S7).

Similar to previous COVID-19 analyses [67–69], this study was limited by the precision with which COVID-19 severity could be captured and COVID-19 related outcomes could be tracked. We used ICU admission and death as proxies for severe illness from COVID-19;

however, patients may have died or been admitted to the ICU for reasons independent of their COVID-19 status. Further, patients who died after the 28-day follow-up period or outside the hospital or at other hospitals would not have been captured in our study. This underestimate of the true case-count for the death outcome may have biased results towards the null (Additional file 1: Fig. S9). Another limitation was that the hospital laboratory tests and protein biomarkers were not measured at the same time for all patients and the time between symptom onset and blood sample collection was not uniform across all patients. Despite this, we observed similar results when excluding patients with sample collection dates that were on or after the date of ICU admission or greater than three days or 14 days following presentation to care (Additional file 1: Fig. S2, Fig. S3, and Table S5). Finally, by only collecting discarded blood samples at a single time point, we were unable to perform longitudinal analyses; however, biomarkers that can be interpreted with single timepoint measurements may be more useful in clinical settings where only one lab draw is available. Our retrospective proteomic analysis shows that protein biomarkers improve prediction of severe outcomes over clinical biomarkers and risk factors that are routinely measured or obtained from hospitalized patients with COVID-19.

Conclusion

In this study, we identified a set of protein biomarkers that yield both mechanistic insight regarding how cardiometabolic disease contributes to COVID-19 pathology, as well as predictive value regarding which patients have the highest risk for severe outcomes. If considered early in the clinical evaluation of patients with COVID-19, these insights can help clinicians estimate a patient's cardiometabolic-driven risk, which, in turn, can inform downstream decisions regarding how to stratify patients across pathways of clinical care (e.g., in-hospital observation or early admission to ICU) and whether to institute treatments that reduce the risk of poor outcomes, such as monoclonal antibodies or novel antiviral therapies.

Abbreviations

AA: African American; ACE2: Angiotensin converting enzyme 2; ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALC: Absolute lymphocyte count; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; AUC: Area under the curve; BMI: Body mass index; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 19; CRP: C-reactive protein; CTSL1: Cathepsin L1; CV: Coefficient of variance; EGFR: Estimated glomerular filtration rate; ERS: Eerythrocyte sedimentation rate; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; ICU: Intensive care unit; IL-1RA: Interleukin 1 receptor antagonist; IL6: Interleukin 6; IPA: Ingenuity Pathway Analysis; KIM1: Kidney injury molecule 1; LASSO: Least absolute shrinkage and selection operator; LDH: Lactate dehydrogenase; MGH: Massachusetts General Hospital; NPX: Normalized protein expression; OR: Odds ratio; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: Standard deviation; TTP: Thrombotic thrombocytopenic purpura; VEGFD: Vascular endothelial growth factor D; WBC: White blood cells.

Supplementary Information

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Additional file 1. Additional figures and tables.

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Author contributions

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available but may be made available upon reasonable request.

Declarations

Ethics approval and consent to participate

Study procedures were approved by the Mass General Brigham (formerly Partners) Human Research Committee, the governing institutional review board at Massachusetts General Hospital.

Consent for publication

All authors consent to this publication.

Competing interests

SJC reports employment of a family member by a Johnson & Johnson company. The rest of the authors have no potential conflict of interest to declare.

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