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RESEARCH LETTER

Signature biomarker states and mortality among hospitalized SARS-CoV-2-infected patients

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Individual biomarkers, especially those of kidney injury, have been associated with poor outcomes and mortality among patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1–3]. Male sex is also a definitive risk factor for death [1] which may be due, in part, to sex differences in biological pathways including kidney injury [2]. Externally-validated risk strata based on a large number of biomarkers have not been described and could have implications for clinical management of SARS-CoV-2-infected patients. Our primary aim was to identify and replicate signature time-varying biomarker states, integrating kidney and other pathophysiologies, that associate with 28-day-mortality among hospitalized SARS-CoV-2-infected patients.

Primary analyses were based on a cohort of 987 confirmed SARS-CoV-2-infected adults hospitalized at Massachusetts General Hospital (MGH) March 11 to May 31, 2020 [4]. The outcome was 28-day-mortality. Patients were assigned to clusters at each observation time based on twenty biomarker values. These captured renal (blood urea nitrogen, creatinine, estimated glomerular filtration rate), cardio-thrombotic (creatine phosphokinase, d-dimer), inflammatory (c-reactive protein, white blood cell count, absolute lymphocyte count), hematological (hemoglobin, hematocrit, platelets, ferritin), hepatic (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin) and metabolic (glucose, anion gap, lactate dehydrogenase) dysfunction.

Biomarkers were measured repeatedly from date of hospitalization for up to 28 days. The analytic approach is illustrated in Supplement Fig. 1. Briefly, each biomarker was log-transformed and standardized to have mean zero and variance 1 and unsupervised learning was applied using each person and available time point. This step resulted in a sequence of clusters for each person. In the second step, cluster membership was defined as belonging to a cluster at any observation time. Fisher's exact tests evaluated differences in the proportions of men and women in each cluster. A separate multivariable model for each cluster, adjusted for BMI, race/ethnicity, sex, and age, was fit to evaluate the association between the corresponding cluster and death, overall and stratified by sex. Although individuals could belong to multiple clusters, by fitting separate models for each cluster, each individual contributed only a single data point to each model. Secondary analysis additionally adjusted for history of liver, kidney and cardiometabolic disease. Interactions between clusters and sex on mortality were explored. Replication was based on 2626 SARS-CoV-2-positive patients hospitalized at Columbia University Irving Medical Center/New York Presbyterian Hospital (CUIMC/NYP) [5]. In CUIMC/NYP data, observations were assigned to the closest MGH cluster and the same tests were applied.

In the MGH cohort, the median number of days with complete biomarker data was 2 (IQR = [1, 5]). The median follow-up time (from hospitalization to discharge, death or 28 days) was 11 days (IQR = [6,28]). Among the 119 individuals who died within 28 days, the median time to death was 12 days (IQR = [7,17]). Patients were 41.6% women, 10.9% Black/non-Hispanic and 37.0% Hispanic with median age 60.2 (IQR 48.4, 73.5) and BMI 29.4 (IQR 25.8, 33.9). Overall, 119 of 987 (12.1%) patients died, 84 of 576 (14.6%) men and 35 of 411 (8.5%) women. Additional information overall and by mortality are provided in Supplement Table 1.

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Renal biomarker trajectories over time, by mortality, are provided in Supplement Fig. 2.

Biomarker distributions by cluster, reflecting underlying biological pathophysiologies, are provided in Supplement Fig. 3. Clusters 1 and 2 had relatively normal biomarker levels apart from some synthetic liver dysfunction in Cluster 1 and low ferritin in Cluster 2; Cluster 4 exhibited myocardial injury as well as increased anion gap and lactate dehydrogenase; Cluster 5 had markers of severe kidney damage and lower hematocrit and hemoglobin; and Custer 6 also exhibited severe kidney damage and lower hematocrit and hemoglobin as well as liver dysfunction and abnormalities of inflammatory and metabolic biomarkers.

Table 1 provides cluster and sex level counts for 987 individuals in MGH with complete biomarker data. Patients in Clusters 4, 5 and 6 had significantly higher odds of death, while Clusters 1 and 2 had lower odds. Clusters capturing kidney injury (5 and 6) resulted in the highest estimated probabilities of death (17.9% and 39.1% for White/non-Hispanic males, median age and BMI, respectively) versus Clusters 1 and 2 (0.0% and 6.4%, respectively). Women were more likely than men to belong to Cluster 2 and less likely to belong to Clusters 4 and 6. In exploratory analysis, odds were different by sex in Clusters 2 and 6 (interaction p-value = 0.39 and 0.027, respectively). This result should be interpreted in light of the low number of deaths in women in Cluster 6. Results were consistent in fully adjusted model including baseline kidney disease.

The CUIMC cohort (43% female, 12% Black/non-Hispanic, 50% Hispanic, median age 66, median BMI 28.0, deaths 24%) had highly similar findings. Supplement Table 2 and Supplement Fig. 4 detail the cluster assignment approach. There were higher odds of death in Clusters 4 (OR 1.63, $p < 0.001$), 5 (OR 2.32, $p < 0.001$) and 6 (OR 5.46, $p < 0.001$) and lower odds in Clusters 1 (OR 0.51, $p < 0.001$) and 2 (OR 0.27, $p < 0.001$). Women were more likely to belong to Cluster 2 (78% versus 64%, $p < 0.001$) and less likely to belong to Clusters 4 (47% versus 64%, $p < 0.001$) and 6 (19% versus 27%, $p < 0.001$).

Our work defines combinations of biomarker disturbances that capture integrated inflammatory, metabolic, hematologic and end-organ states and mark patients at higher or lower risk of death. We identified three signature biomarker states, two marked by prominent kidney injury (Clusters 5 and 6), that were strongly associated with mortality among hospitalized SARS-CoV-2-infected patients, and two states with a lower probability of death. Furthermore, men were more likely to belong to the more harmful states while women were more likely to belong to one of the better prognosis states. These findings were robustly supported in analysis of an independent cohort. Translation to a clinically viable tool requires implementation of learning health system approaches involving real-time integration of machine

Table 1 Cluster membership counts and multivariable adjusted odds ratios for death overall and by sex within the MGH cohort

Cluster[a]	*Overall (n = 987)*			*Men (n = 576)*			*Women (n = 411)*			P value[c]
	Count (%)	Deaths (%)	OR[b] (95% CI)	Count (%)	Deaths (%)	OR[b] (95% CI)	Count (%)	Deaths (%)	OR[b] (95% CI)	
1	259 (26.2%)	3 (1.2%)	0.09[d] (0.02,0.39)	155 (26.9%)	1 (0.6%)	0 (0, Inf)	104 (25.3%)	2 (1.9%)	0.48 (0.1,2.25)	0.608
2	465 (47.1%)	31 (6.7%)	0.24[d] (0.15,0.41)	217 (37.7%)	24 (11.1%)	0.38[d] (0.21,0.69)	248 (60.3%)	7 (2.8%)	0.09[d] (0.03,0.25)	< 0.001
3	177 (17.9%)	24 (13.6%)	1.35 (0.77,2.37)	109 (18.9%)	19 (17.4%)	1.41 (0.73,2.7)	68 (16.5%)	5 (7.4%)	1.62 (0.5,5.23)	0.355
4	409 (41.4%)	61 (14.9%)	1.66[e] (1.05,2.61)	290 (50.3%)	48 (16.6%)	1.68 (0.97,2.89)	119 (29.0%)	13 (10.9%)	1.39 (0.59,3.24)	< 0.001
5	118 (12.0%)	33 (28.0%)	2.28[e] (1.32,3.91)	78 (13.5%)	20 (25.6%)	1.95[e] (1.01,3.76)	40 (9.7%)	13 (32.5%)	3.35[e] (1.27,8.88)	0.074
6	94 (9.5%)	29 (30.9%)	5.23[e] (2.81,9.72)	75 (13.0%)	27 (36.0%)	7.72[e] (3.82,15.63)	19 (4.6%)	2 (10.5%)	0.37 (0.04,3.69)	< 0.001

[a]Cluster membership is defined as ever belonging to the corresponding cluster during hospitalization

[b]Models are adjusted for age, sex, body mass index and race/ethnicity

[c]P values correspond to Fisher's exact test for difference in proportions of men and women within each cluster

[d]OR significantly less than 1; lower odds of death for patients who belong to this cluster during hospitalization compared to patients who never belong to this cluster

[e]OR significantly greater than 1; higher odds of death for patients who belong to this cluster during hospitalization compared to patients who never belonged to this cluster

learning techniques with electronic health record data as these algorithms involve complex decision rules. However, findings point to distinctive biological and sex-related pathways that include kidney injury and myocardial damage with potential for monitoring risk and optimizing care in hospitalized SARS-CoV-2-infected patients.

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Declarations

Conflict of interest Dr. Foulkes receives sponsored research support from Bristol Myers Squibb / Pfizer and Fitbit and has received expert witness testimonial fees from Round Table Group. The remaining authors have nothing to disclose.

Ethical approval The Partners HealthCare Institutional Review Board (IRB) (#2020P000829) approved collection of curated data based on comprehensive manual chart reviews and data extractions from electronic health records (EHR) on patients who receive care through the Mass General Brigham (MGB, formerly Partners) system. The CUIMC IRB approved this study (#AAAS9835) and waived the requirement for obtaining informed consent.

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