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Title Page

Risk Assessment for Acute Kidney Injury and Death among New COVID-19 Positive Adult Patients without Chronic Kidney Disease

Short Title: AKI and Death among COVID-19 Patients without CKD

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Abstract

Objective: To develop simple but clinically informative risk stratification tools using a few top demographic factors and biomarkers at COVID-19 diagnosis to predict acute kidney injury (AKI) and death.

Design: Retrospective cohort analysis, follow-up from February 1 through May 28, 2020.

Setting: 3 teaching hospitals, 2 urban and 1 community-based in the Boston area.

Participants: Eligible patients were at least 18 years old, tested COVID-19 positive from February 1 through May 28, 2020, and had at least two serum creatinine measurements within 30 days of a new COVID-19 diagnosis. Exclusion criteria were having CKD or having a previous AKI within 3 months of a new COVID-19 diagnosis.

Main Outcomes and Measures: Time from new COVID-19 diagnosis until AKI event, time until death event.

Results: Among 3,716 patients, there were 1,855 (49.9%) males and the average age was 58.6 years (SD 19.2 years). Age, sex, white blood cell, hemoglobin, platelet, C-reactive protein, and D-dimer levels were most strongly associated with AKI and/or death. We created risk scores using these variables predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis. Area under the curve (AUC) for predicting AKI within 3 days was 0.785 (95% CI, 0.758 to 0.813) and AUC for death within 30 days was 0.861 (95% CI, 0.843 to 0.878). Hemoglobin was the most predictive component for AKI, and age the most predictive for death. Predictive accuracies using all study variables were similar to using the simplified scores.

Conclusion: Simple risk scores using age, sex, a complete blood cell count, C-reactive protein, and D-dimer were highly predictive of AKI and death and can help simplify and better inform clinical decision making.

Key words: COVID-19; kidney injury; risk prediction

Strengths and limitations of this study

- Various associations between patient variables and COVID-19 acute kidney injury AKI and death have been reported, but it is unclear which variables are most predictive and important to focus on.
- We developed risk scores for predicting AKI and death among new COVID-19 positive patients.
- Readily obtainable demographic, vital sign, and laboratory values were considered evaluated.
- Findings are limited to patients without chronic kidney disease.

Introduction

Although respiratory failure and diffuse inflammatory lung tissue damage are key features of coronavirus disease 2019 (COVID-19), involvement of other organs such as the kidneys has been well documented. Pathologic autopsy examinations of COVID-19 kidneys have shown clusters of coronavirus-like particles in the tubular epithelium and podocytes, upregulation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor angiotensin-converting enzyme 2 and positive immunostaining with SARS-CoV-2 nucleoprotein antibodies.[1,2] Hemodynamic instability, systemic hypoxia, abnormal coagulation, and inflammation from severe COVID-19 can also directly contribute to acute kidney injury (AKI) and induce acute tubular necrosis.[3]

Various epidemiologic studies from China, Europe, and the United States have investigated AKI outcomes among COVID-19 patients. Early studies in China have reported AKI incidences ranging from 0.5-15% among hospitalized and outpatient COVID-19 patients.[4,5] One United Kingdom study found hospitalized COVID-19 patients with AKI had a 3-fold higher odds of death than those without AKI.[6] Large US population studies of hospitalized COVID-19 patients, primarily in the New York City metropolitan area, have reported AKI incidences ranging from 27-57%, with in-hospital mortality rates ranging from 35-71% among AKI COVID-19 patients.[7–10] Some of these studies have also explored variable associations with COVID-19 AKI, but none of these studies have investigated which subset of these variables are most predictive of AKI or built risk predictions models using demographic variables and biomarkers.

Risk prediction tools have been investigated for COVID-19 deaths. A small number of a priori determined biomarkers were investigated for their associations with

the risk of COVID-19 death.[11] However, a more data driven approach would compare the predictive accuracies of these biomarkers to other biomarkers and variables such as demographic factors and vital signs and build a more powerful risk prediction model using a comprehensive set of biomarkers, demographic variables, and vital signs. Different risk factors should also be weighted differently, and understanding the relative importance of different variables in predicting poor outcomes will allow for more accurate holistic patient evaluations.

In this study we developed and evaluated new risk assessment tools that can be easily implemented at the bedside or during chart reviews to predict AKI and death after a positive COVID-19 test. Our contributions include (1) identifying the top biomarkers and demographic variables that predict AKI events among COVID-19 patients, (2) investigating a greater number of potential biomarkers and risk factors in predicting death, (3) developing clinical risk assessment tools for both AKI and death using a small number of predictors, and (4) validating that these tools are nearly as predictive as using all available study variables. By understanding which subset of risk factors are most important to focus on, medical providers can more efficiently work up and risk stratify their newly diagnosed COVID-19 patients.

Methods

Study Population

The Mass General Brigham (MGB) Health system serves a large diverse patient population around Boston and Eastern Massachusetts. Electronic health records from

three major hospitals in this system (Massachusetts General Hospital in Boston, Brigham and Women's Hospital in Boston, and Newton-Wellesley Hospital in Newton) were used. The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661.

We included all patients that 1) were at least 18 years old, 2) tested COVID-19 positive at one of the three hospitals above between February 1, 2020 through May 28, 2020, and 3) had at least 2 serum creatinine tests within 30 days of their SARS-Cov-2 PCR test. We excluded patients that 1) met the criteria of acute kidney injury within 3 months before their SARS-CoV-2 test and 2) had chronic kidney disease (CKD) identified as a preexisting condition from International Classification of Disease (ICD-9 and ICD-10) codes (see below).

Data Collection

Information in electronic health records (EHR) of patients who met the inclusion criteria were extracted from the enterprise data warehouse and included demographic, comorbidities, clinical, laboratory, and outcome data (death). Demographic and laboratory data information closest to the time of first SARS-Cov-2 PCR test were kept (except for serum creatinine, multiple values were kept). Serum creatinine laboratory test results and timestamps within 3 months before and 30 days after the SARS-Cov-2 polymerase chain reaction test were extracted. We categorized ethnic groups other than White, Black, Hispanic, and Asian into a single subgroup. All documented comorbidity related medical history in MGB healthcare system enterprise data warehouse before the

first time of SARS-Cov-2 test were extracted. Preexisting conditions, including hypertension, diabetes, cardiovascular disease, and heart failure, were classified using their ICD-9 or ICD-10 codes.

Definitions of Outcomes

Per the Kidney Disease Improving Global Outcomes (KDIGO) criteria, AKI was defined as a change in serum creatinine (SCr) of 0.3 mg/dl over a 48-hour period, a 50% increase in baseline creatinine in 7 days, or urine value <0.5 ml/kg/hour for 6 hours.[12] Due to difficulties obtaining accurate urine volumes from electronic health record data, we only use serum creatinine to define AKI events. If patients had more than 2 SCr tests in their EHR, we used all available SCr tests to define the earliest time. Death times were directly extracted from the data warehouse.

Statistical Analyses

Continuous variables were transformed into categorical variables to improve interpretability of results and account for nonlinear associations. Counts and percentages were presented, and two proportion z-tests were used to compare the proportion of deaths among AKI and non-AKI patients. For AKI survival analyses, observations without AKI were censored after 30 days, at the time of death, or at 5/28/2020, whichever came first. For death survival analyses, observations without death were censored at 5/28/2020. Multiple multivariable Cox proportional hazards models included age, sex, race, diabetes, cardiovascular disease, hypertension, heart

failure, body mass index (BMI), temperature, heart rate, systolic blood pressure, white blood cell count (WBC), hemoglobin, platelets, C-reactive protein (CRP), ferritin, D-and dimer. Given the missing data with respiratory rate interleukin-6 (IL-6) values, we performed exploratory multiple imputation Cox regression analyses. Additional details are in the sensitivity analysis section.

We next built a simplified Cox model for clinical use by using a stepwise variable selection procedure for Cox models alternating between "forward" and "backwards" steps to identify the first 5 variables to be included.[13] Simplified Cox models were fit using only the selected 5 variables and Harrell's C-Statistics were obtained (survival outcome). Model coefficient (linear prediction) accuracy was evaluated. We evaluated area under receive operating characteristic (ROC) curves (AUC) for predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcome). Net reclassification improvement (NRI) of adding all remaining covariates was also calculated.

Risk scores were obtained by rounding simplified model coefficients for easier clinical risk assessment use. For suggested risk score cutoffs, Kaplan-Meier event curves were plotted, log rank tests were performed, and sensitivities, specificities, positive and negative likelihood ratios were calculated. Approximate pre-test to post-test probability changes from likelihood ratios were calculated using the linear approximation proposed by McGee.[14] Cutoffs for low risk were chosen so that the negative likelihood ratio would be ≈0.20 with a pre- to post-test probability decrease of ≈30%, while cutoffs for high risk were chosen so that the positive likelihood ratio would be ≈5.0 with a pre- to post-test probability increase of ≈30% and that at least 15% of patients (560) would be

identified as high risk.[14]We ran 1,000 internal cross validation iterations in which 70% of data were randomly assigned to training, the other 30% to testing. For each iteration, simplified Cox models were fit to the training data, coefficients were rounded to obtain risk scores, and AUC's were calculated using the predicted testing data risk scores.

We performed two sensitivity analyses. First, the multivariable cause-specific and subdistribution hazard to documented AKI events within 30 days accounting for the competing risk of death was modeled.[15] Second, we performed a multiple imputation analysis by creating 10 imputation datasets with imputed values for missing respiratory rate and IL-6 and then calculating pooled multivariable Cox hazard ratios.[16] All analyses were performed with R version 4.0.4 and all code for analyses are available online (to be posted during revisions).

Results

Demographic and Clinical Characteristics

There were 3,716 eligible adult COVID-19 positive patients without CKD, of which 1,855 (49.9%) were male. The average age was 58.6 years (SD 19.2 years). There were 696 patients that developed AKI (18.7%) and 249 (35.8%) were within three days of a new COVID-19 diagnosis. There were 347 deaths (9.3%) and 322 (92.8%) were within thirty days of a new COVID-19 diagnosis. Among the AKI group there were 192 deaths (27.6%), and among the non-AKI group there were 155 deaths (5.1%, p<0.001). Patient demographics, preexisting conditions, vital signs, and laboratory values stratified by patients with AKI and patients that died are displayed in **Table 1**.

Patients with AKI and patients that died were more likely to be older, male, have multiple comorbidities, and have on admission higher temperatures, lower systolic blood pressures, higher respiratory rates, elevated white blood cell counts, lower hemoglobin and platelets, and elevated CRP, ferritin, D-dimer, and IL-6 levels.

Fully Adjusted Multivariable Regression

Multivariable Cox regression was performed to identify risk factors associated with time to AKI and death. **Table 2** displays pooled multivariable adjusted hazard ratios. Adjusting for all other variables, older age, increased medical conditions, increased temperature, decreased systolic blood pressure, increased white blood cells, decreased platelets, and increased CRP and D-Dimer were associated with increased hazards for both AKI and death. Elevated BMI, decreased hemoglobin, and increased ferritin were associated with increased hazards for AKI but not death. Black and Asian race were associated with decreased hazards and increased heart rate was associated with increased hazards for death but not AKI.

Top Risk Factor/Biomarker Selection

The top five variables selected for being most associated with AKI events were hemoglobin, D-dimer, CRP, WBC, and male sex. The top five variables most associated with death were age, CRP, platelets, WBC, and D-Dimer. **Table S1** shows model coefficients and Harrell's C-statistic (survival concordance) from the simplified model using just these selected variables. **Table S2** shows similar results for the fully adjusted

model. The simplified AKI Cox model had a survival C-statistic of 0.785 (95% CI, 0.769 to 0.800), while the fully adjusted AKI Cox model had a C-statistic of 0.813 (95% CI, 0.798 to 0.827). The simplified death Cox model had a survival C-statistic of 0.857 (95% CI, 0.841 to 0.874), while the fully adjusted death Cox model had a C-statistic of 0.878 (95% CI, 0.863 to 0.892).

Cox model coefficients were used to predict AKI events within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcomes). **Table S1** and **Table S2** also displays AUC's for the simplified and fully adjusted coefficients respectively. For AKI in 3 days, using the simplified coefficients had an AUC of 0.787 (95% CI, 0.759 to 0.814), using the fully adjusted coefficients had an AUC of 0.820 (95% CI, 0.794 to 0.845), and the NRI was 0.041 (95% CI, 0.003 to 0.082). For death in 30 days, using the simplified coefficients had an AUC of 0.872 (95% CI, 0.854 to 0.890), the fully adjusted coefficients had an AUC of 0.893 (95% CI, 0.878 to 0.909), and the NRI was 0.010 (95% CI, -0.007 to 0.029).

Risk Score

Model coefficients were rounded to obtain risk score component values for easier clinical use. **Table 3** shows the risk score and internal validation results. For AKI in 3 days, the risk score had an AUC 0.785 (95% CI, 0.758, 0.813) and a cross validation AUC of 0.776 (95% CI, 0.732, 0.816). For death in 30 days, the risk score had an AUC of 0.861 (95% CI, 0.843 to 0.878) and a cross validation AUC of 0.860 (95% CI, 0.831, 0.886). **Figure 1A** plots ROC curves for using fully adjusted coefficients (from **Table S2**)

versus using risk scores (from **Table 3**) in predicting AKI in 3 days and death in 30 days.

Suggested risk stratification cutoffs were obtained. **Table S3** presents sensitivity, specificity, and positive and negative likelihood ratios for all possible risk score cutoffs. **Table 4** shows suggested risk stratification cutoffs and stratified observed and estimated event rates. Higher risk scores had higher observed and estimated AKI and death rates. **Figure 1B** plots Kaplan Meier event curves of AKI and death events by simplified risk score categories. Event rates different by risk category for AKI ($p<0.001$) and death ($p<0.001$).

Sensitivity Analysis

We performed a competing risk regression analysis for AKI and death within 30 days. **Table S4** displays the multivariable cause-specific and subdistribution hazard ratios for AKI events. Cause-specific and subdistribution hazard ratio estimates and confidence intervals were nearly identical. We also performed a multiple imputation analysis by imputing missing values for respiratory rate and IL-6 to evaluate their associations. **Table S5** shows that results were similar to non-imputation results, and increased respiratory rate and IL-6 were associated with increased hazards of AKI and death.

Discussion

In this retrospective study of over 3,700 adult patients without chronic kidney disease diagnosed with COVID-19 through May 2020 in the Boston area, we identified risk factors and biomarkers associated with AKI and death, and we developed and internally validated risk scores for predicting AKI and death. We found about one in five patients developed AKI and one in ten patients died. Increased age, male sex, increased white blood cells, C-reactive protein and D-Dimer and decreased hemoglobin and platelet levels were associated with AKI within 3 days and/or death within 30 days of a new COVID-19 diagnosis. A risk score using just these variables had similar internal accuracy as using all study variables. These results can assist in risk stratification of COVID-19 patients without CKD.

Many studies have found markedly increased COVID-19 fatality rates among older people. Studies from China, Spain, and Italy, and a meta-analysis of studies from 34 different geographical locations have all found increased case or infection fatality rates among people >60 and >65 years old compared to younger populations.[17–20] We similarly observed older age had some of the strongest associations with death. Earlier studies have found various physiologic changes among elderly patients that may contribute to this age-related risk, such as decreased small airway clearance, decreased number of cilia and ciliated cells, and decreased upper airway size.[21–23]

Other studies have also reported worse COVID-19 outcomes among men. A study of over 3,300 patients in Montefiore Medical Center found male sex was associated with AKI in both COVID-19 positive and negative patients.[8] This study also provided a more complete discussion of other animal studies and meta-analyses to date that that have found associations between male sex and AKI in general. Studies of

COVID-19 outcomes from March 2020 in Italy and the US also reported increased hospitalization and intensive care unit admission rates among male patients.[24,25] We similarly observed that AKI patients (60.3%) and patients that died (58.2%) were more likely to be male (overall 49.9%). However, after adjusting for other demographics, medical conditions, vital signs, and laboratory values, we found male sex was associated with AKI but not death.

Among laboratory values, C-reactive protein, hemoglobin, white blood cells, D-Dimer, and platelets were significantly associated with AKI and death and were included in risk scores. Although there has been debate about a standard definition for COVID-19 cytokine storm syndrome, patients with C-reactive protein may have excessive immune activation, with C-reactive protein being produced by hepatocytes in response to IL-6 or ferritin.[26] Decreased hemoglobin may be reflective of kidney disease with decreased erythropoietin production or directly lead to decreased oxygenation of the kidneys. A study from Korea also found a higher risk of AKI in critically ill patients with a hemoglobin <10.5 g/dL.[27] Elevated white blood cell counts may suggest sepsis and be associated with life-threatening organ dysfunction.[28] Elevated D-Dimer levels may be indicative of a pro-thrombotic state, and a retrospective study from China found that D-Dimer >2000 ng/mL was associated with increased mortality.[29] However D-dimer levels have also been reported to be elevated at baseline in CKD patients,[30] so it is possible elevated D-Dimer may only be prognostic in non-CKD patients. Low platelets may also indicate a systemic coagulopathic process that places patients at an increased risk for death.[28]

The biomarker IL-6 was found to be a significant risk factor in regression analyses. However, a substantial proportion of patients in our study were missing IL-6 values (78.3%), so IL-6 was not considered for risk score development. Previous studies have found IL-6 cutoffs of 80 and 86 IU/mL to have prognostic value for predicting respiratory failure and death respectively.[31,32]

We proposed risk scores for identifying AKI within 3 days and death within 30 days of a new COVID-19 diagnosis along with suggested cutoffs. Although risk scores still need to be externally validated, being able to identify a few key biomarkers that are widely accessible can help focus chart reviews of new COVID-19 positive patients. Varying score weights further highlight biomarkers to focus on, such as hemoglobin and male sex for AKI, age and platelets for death, and WBC, CRP, and D-Dimer for both. Larger scores directly correlate with worse outcomes and can help shape physician gestalt.

We explored death being a competing risk for AKI events as patients with death will not have any more creatinine measurements. Although an AKI does not exclude the possibility of death, competing risk analyses can still be performed investigating which event type occurs first.[15] The cause-specific hazards ratios (Cox hazard ratios) describe the rate of AKI events among those still alive and with no previous AKI events, while the subdistribution hazard ratios describes the overall rate of AKI events occurring before death. In our study both cause-specific and subdistribution hazard ratios were similar. Competing risk analyses were not performed for death events as having an AKI does not exclude death.

Limitations to our study include the following. All results are associational and no causal effects should be interpreted. Vital and signs and laboratory values were those closest to COVID-19 diagnosis, and time-varying covariates were not incorporated into analyses. As the study was retrospective, selection bias cannot be excluded, and only events within the MGB system were recorded. Our identified risk factors and risk scores are most applicable during a patient's initial COVID-19 positive test. Patients in the Boston area may not be reflective of those in other healthcare systems, and the study population included only COVID-19 positive patients without CKD. Future work may further stratify AKI events by stage, investigate outpatient, hospitalized, and critically ill patients separately, focus on CKD patients, and validate results on a separate cohort.

We investigated AKI and death outcomes among adult COVID-19 patients without CKD in the Boston area. We identified risk factors and developed and evaluated risk assessment tools for identifying COVID-19 patients developing AKI and death. Hemoglobin, D-Dimer, CRP, WBC, and male sex were the strongest predictive biomarkers for AKI. Age, CRP, platelets, WBC, and D-Dimer were most predictive for death. Our study significantly contributes to epidemiological knowledge of COVID-19 outcomes and introduces simple tools to assist with rapid risk assessment.

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Authors' contributions: DL and HR drafted the manuscript. HR, PX, DW obtained the data. DL performed the analyses. DL, HR, DJV, PS, QL, and XL contributed to the

design of the study. All authors were involved with interpretation of the data and critical revision and final approval of the article.

Availability of data and materials: Patient data is not available, but requests for surrogate data may be made to the corresponding authors. However, code for all analyses will be available at https://github.com/lin-lab.

Patient and public involvement: Patients were not involved in planning of this project.

Research ethics approval human subjects: The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661. Only deidentified patient electronic health record data were used.

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Figure Legends

Fig. 1 Receiver Operating Characteristics and Kaplan Meier Event Curves Using Selected Variables.

(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.

(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

Table 1. Characteristics of Patients with Acute Kidney Injury, Patients that Died, and All Patients.

Variable, n (%)	**AKI** (n=696)	**Died** (n=347)	**Total** (n=3,716)
Age (years)			
<45	86 (12.4)	7 (2.0)	980 (26.4)
45-65	245 (35.2)	55 (15.9)	1,310 (35.3)
>65	365 (52.4)	285 (82.1)	1,426 (38.4)
Sex (Male)	420 (60.3)	202 (58.2)	1,855 (49.9)
Race			
White	407 (58.5)	242 (69.7)	2,091 (56.3)
Black	110 (15.8)	50 (14.4)	568 (15.3)
Hispanic	22 (3.2)	9 (2.6)	135 (3.6)
Asian	27 (3.9)	8 (2.3)	140 (3.8)
Other	130 (18.7)	38 (11.0)	782 (21.0)
Diabetes	197 (28.3)	87 (25.1)	727 (19.6)
Cardiovascular Disease	67 (9.6)	49 (14.1)	231 (6.2)
Hypertension	135 (19.4)	65 (18.7)	484 (13.0)
Heart Failure	39 (5.6)	38 (11.0)	134 (3.6)
Medical Conditions (number)			
0	397 (57.0)	189 (54.5)	2,565 (69.0)
1	190 (27.3)	95 (27.4)	811 (21.8)
2	83 (11.9)	47 (13.5)	264 (7.1)
3+	26 (3.7)	16 (4.6)	76 (2.0)
Body Mass Index (kg/m^2)			
<25	165 (23.7)	115 (33.1)	833 (22.4)
25-30	229 (32.9)	110 (31.7)	1,334 (35.9)
>30	302 (43.4)	122 (35.2)	1,549 (41.7)
Temperature (F)			
97-100.4	423 (60.8)	201 (57.9)	2,745 (73.9)
<97	35 (5.0)	22 (6.3)	190 (5.1)
>100.4	238 (34.2)	124 (35.7)	781 (21.0)
Heart Rate (beats/min)			
60-110	576 (82.8)	274 (79.0)	3,194 (86.0)
<60	61 (8.8)	30 (8.6)	275 (7.4)
>110	59 (8.5)	43 (12.4)	247 (6.6)
Systolic Blood Pressure (mmHg)			
90-180	635 (91.2)	305 (87.9)	3,549 (95.5)
<90	48 (6.9)	35 (10.1)	117 (3.1)
>180	13 (1.9)	7 (2.0)	50 (1.3)
Respiratory Rate (per minute)			

<20	245 (35.2)	92 (26.5)	1,692 (45.5)
>20	364 (52.3)	202 (58.2)	1,237 (33.3)
NA (Missing)	87 (12.5)	53 (15.3)	787 (21.2)
White Blood Cell (thousand cells/mm^3)			
3.5-11	428 (61.5)	189 (54.5)	2,942 (79.2)
<3.5	39 (5.6)	26 (7.5)	267 (7.2)
>11	229 (32.9)	132 (38.0)	507 (13.6)
Hemoglobin (g/dL)			
12+	201 (28.9)	138 (39.8)	2,250 (60.5)
10-12	204 (29.3)	88 (25.4)	883 (23.8)
<10	291 (41.8)	121 (34.9)	583 (15.7)
Platelets (per μL)			
>100	643 (92.4)	310 (89.3)	3,600 (96.9)
<100	53 (7.6)	37 (10.7)	116 (3.1)
C-Reactive Protein (mg/L)			
<50	197 (28.3)	62 (17.9)	1,706 (45.9)
50-100	149 (21.4)	63 (18.2)	1,011 (27.2)
>100	350 (50.3)	222 (64.0)	999 (26.9)
Ferritin (μg/L)			
<250	105 (15.1)	52 (15.0)	950 (25.6)
250-1000	327 (47.0)	155 (44.7)	1,894 (51.0)
>1000	264 (37.9)	140 (40.3)	872 (23.5)
D-Dimer (ng/mL)			
<1000	136 (19.5)	60 (17.3)	1,726 (46.4)
1000-2000	217 (31.2)	101 (29.1)	1,076 (29.0)
>2000	343 (49.3)	186 (53.6)	914 (24.6)
Interleukin-6 (IU/mL)			
<40	121 (17.4)	26 (7.5)	438 (11.8)
40-80	68 (9.8)	33 (9.5)	137 (3.7)
>80	136 (19.5)	58 (16.7)	196 (5.3)
NA (Missing)	371 (53.3)	230 (66.3)	2,945 (79.3)

AKI = acute kidney injury

Table 2. Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**5.33 (2.42, 11.8)**
>65	**2.16 (1.66, 2.80)**	**23.4 (10.9, 50.1)**
Sex (Male)	**1.51 (1.28, 1.77)**	1.16 (0.92, 1.45)
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	**0.66 (0.48, 0.92)**
Hispanic	0.89 (0.58, 1.38)	0.62 (0.32, 1.23)
Asian	0.96 (0.65, 1.43)	**0.46 (0.22, 0.93)**
Other	1.11 (0.90, 1.37)	0.72 (0.50, 1.02)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.07 (0.83, 1.38)**
2	**1.67 (1.30, 2.13)**	**1.40 (1.01, 1.95)**
3+	**1.82 (1.21, 2.75)**	**1.61 (0.95, 2.73)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	0.78 (0.59, 1.02)
>30	**1.42 (1.17, 1.74)**	0.94 (0.72, 1.22)
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.18 (0.75, 1.85)
>100.4	**1.59 (1.34, 1.88)**	**1.54 (1.22, 1.96)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	0.97 (0.66, 1.43)
>110	1.11 (0.85, 1.47)	**1.78 (1.28, 2.48)**
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**2.10 (1.45, 3.04)**
>180	0.96 (0.55, 1.67)	0.90 (0.42, 1.92)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	1.10 (0.72, 1.68)
>11	**1.77 (1.49, 2.12)**	**2.32 (1.82, 2.95)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	0.88 (0.67, 1.16)
<10	**3.72 (3.03, 4.57)**	1.03 (0.78, 1.35)

Platelets (per µL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**2.60 (1.79, 3.77)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	**1.46 (1.02, 2.10)**
>100	**1.57 (1.29, 1.91)**	**3.61 (2.65, 4.93)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	0.91 (0.65, 1.26)
>1000	**1.69 (1.31, 2.17)**	1.14 (0.80, 1.62)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	1.21 (0.87, 1.69)
>2000	**2.11 (1.68, 2.65)**	**1.82 (1.31, 2.52)**

1

Table 3. Risk Score and Internal Validation Results.

AKI in 3 days (max 6)		Death in 30 days (max 7)	
Risk Score			
Variable	**Value**	**Variable**	**Value**
Hemoglobin <10 g/dL	2	Age > 65 years	3
Hemoglobin 10-12 g/dL	1	Age 45-65 years	2
D-Dimer > 1,000 ng/mL	1	CRP > 100 mg/L	1
CRP > 100 mg/L	1	Platelets < 100 per µL	1
WBC > 11,000 cells/mm^3	1	WBC > 11,000 cells/mm^3	1
Male Sex	1	D-Dimer > 2,000 ng/mL	1
Internal Validation			
Validation Type	**AUC (95% intervals)**	**Validation Type**	**AUC (95% intervals)**
Whole Data	0.785 (0.758, 0.813)	Whole Data	0.861 (0.843, 0.878)
Cross Validation	0.776 (0.732, 0.816)	Cross Validation	0.860 (0.831, 0.886)

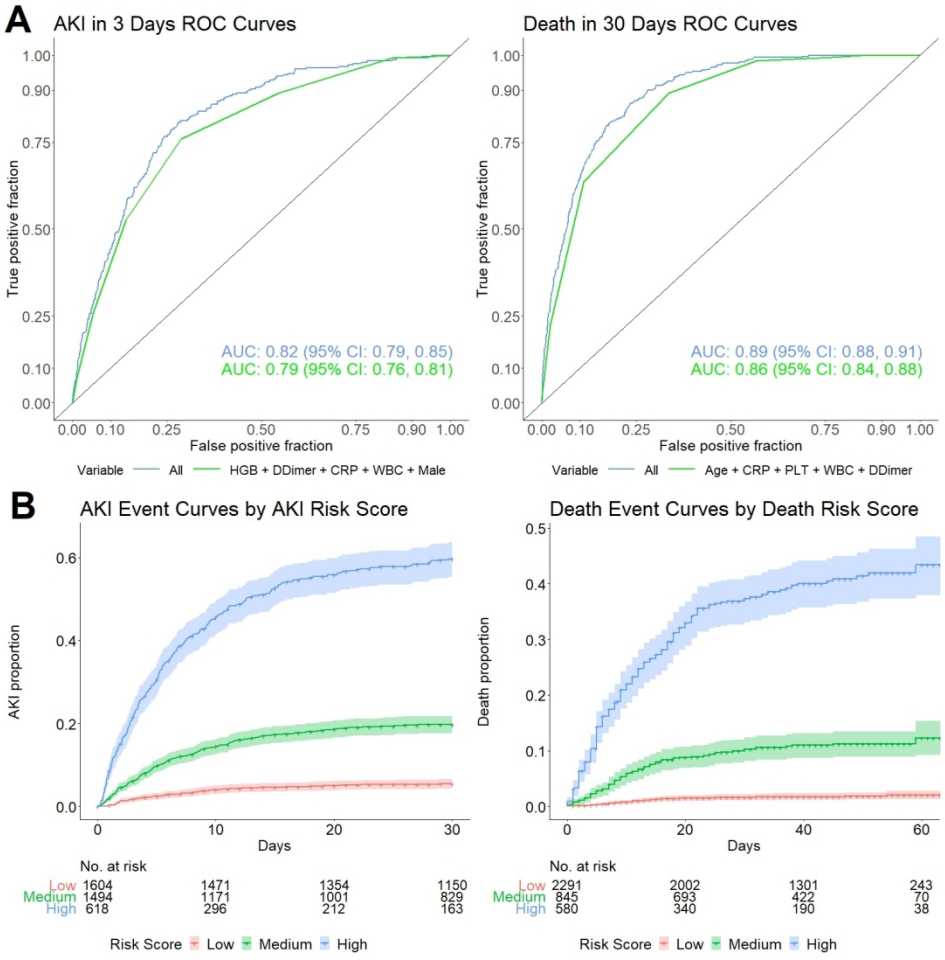
CRP = C-reactive protein, WBC = white blood cells.
Whole data validation presents area under the curve (AUC) estimates and 95% confidence intervals.
Internal cross validation presents mean AUC and 95% central interval (2.5th and 97.5th percentiles).

Table 4. Suggested Risk Stratification Cutoffs and Observed and Estimated Event Rates.

AKI Risk Score				
Risk Level	**Total Score**	**Observed Total AKI (%)**	**Estimated 3 Day AKI (%)**	**Estimated 30 Day AKI (%)**
Low Risk	0-1	5.2	1.7	5.4
Moderate Risk	2-3	18.4	6.2	19.7
High Risk	4-6	54.7	21.6	59.7
Death Risk Score				
Risk Level	**Total Score**	**Observed Total Death (%)**	**Estimated 30 Day Death (%)**	**Estimated 60 Day Death (%)**
Low Risk	0-3	1.7	1.6	2.0
Moderate Risk	4	10.4	10.2	12.3
High Risk	5-7	37.9	37.3	43.4

Observed percentages are from the observed data

Estimated percentages are from Kaplan-Meier event curves



(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.
(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

450x448mm (96 x 96 DPI)

Supplemental Methods – Additional Details

Statistical Analyses

Descriptive statistics and receiver operating characteristics (ROC) were calculated using R base functions. Cox proportional hazards models were fit using the "survival" package. Inspection of AKI and death Kaplan-Meier event curves stratified by each variable revealed no obvious violations of the proportional hazards assumption.

The variable selection procedure was implemented using the "My.stepwise" package. In addition to the variables included in fully adjusted Cox proportional hazards models, age >45 years, medical conditions >1, medical conditions >2, BMI > 25 kg/m^2, hemoglobin <12 g/dL, CRP > 500 mg/L, ferritin >250 µg/L, and D-Dimer > 1,000 ng/mL were also included. The package "glmnet" was used to reformat data so that the variable selection procedure could be applied. The selection procedure alternates between "forward" steps of adding variables and "backwards" steps of removing variables. The significance level for entry and for staying was conservatively set at 0.15 as suggested by function details. The top 5 variables (top 6 dummy variables) were included in risk scores. Simplified risk score values were obtained by rounding model coefficients to the nearest integer.

ROC curves were created using "plotROC" and AUC values and confidence intervals were obtained from "pROC". Event curves were created using "survminer" and "mstate". Harrell's C-statistics were obtained from Cox proportional hazards model output, and net reclassification of improvement was obtained from "nricens".

Competing risk analyses used the “cmprsk” package, and multiple imputation analyses used the “mice” package. The packages “ggplot2”, “dplyr”, “plyr”, “ggfortify”, and “cowplot” were used to process results and create figures. Code for replicating all analyses will be available online.

Table S1. Coefficients from simplified Cox regression models to calculated and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Simplified Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Hemoglobin <10 g/dL	1.50	Age > 65 years	3.19
Hemoglobin 10-12 g/dL	0.85	Age 45-65 years	1.65
D-Dimer > 1,000 ng/mL	0.76	CRP > 100 mg/L	1.21
CRP > 100 mg/L	0.64	Platelets < 100 per µL	1.20
WBC > 11,000 cells/mm^3	0.59	WBC > 11,000 cells/mm^3	0.87
Male Sex	0.54	D-Dimer > 2,000 ng/mL	0.58
Internal Validation			
Statistic	**Estimate (95% CI)**	**Statistic**	**Estimate (95% CI)**
Harrell's Survival C-Statistic (Concordance)	0.785 (0.769, 0.800)	Harrell's Survival C-Statistic (Concordance)	0.857 (0.841, 0.874)
AKI in 3 Days AUC	0.787 (0.759, 0.814)	Death in 30 Days AUC	0.872 (0.854, 0.890)

AKI = acute kidney injury, CRP = C-reactive protein, WBC = white blood cells, AUC = area under the curve, CI = confidence interval

Table S2. Coefficients from fully adjusted Cox regression models and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Fully Adjusted Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Age 45-65 years	0.54	Age 45-65 years	1.67
Age > 65 years	0.77	Age > 65 years	3.15
Male Sex	0.41	Male Sex	0.14
Race Black	-0.12	Race Black	-0.41
Race Hispanic	-0.12	Race Hispanic	-0.47
Race Asian	-0.04	Race Asian	-0.79
Race Other	0.11	Race Other	-0.33
Medical Conditions 1	0.25	Medical Conditions 1	0.07
Medical Conditions 2	0.51	Medical Conditions 2	0.34
Medical Conditions 3+	0.60	Medical Conditions 3+	0.48
BMI 25-30 kg/m^2	0.08	BMI 25-30 kg/m^2	-0.25
BMI >30 kg/m^2	0.35	BMI >30 kg/m^2	-0.06
Temp < 97 F	0.06	Temp < 97 F	0.16
Temp > 100.4 F	0.46	Temp > 100.4 F	0.43
Heart rate < 60 beats/min	0.22	Heart rate < 60 beats/min	-0.03
Heart rate < 110 beats/min	0.11	Heart rate < 110 beats/min	0.58
SBP < 90 mmHg	0.64	SBP < 90 mmHg	0.74
SBP > 180 mmHg	-0.04	SBP > 180 mmHg	-0.11
WBC < 3,500 cells/mm^3	-0.25	WBC < 3,500 cells/mm^3	0.09
WBC > 11,000 cells/mm^3	0.57	WBC > 11,000 cells/mm^3	0.84
Hemoglobin <10 g/dL	0.77	Hemoglobin <10 g/dL	-0.13
Hemoglobin 10-12 g/dL	1.31	Hemoglobin 10-12 g/dL	0.03
Platelets < 100 per µL	0.56	Platelets < 100 per µL	0.96
CRP 50-100 mg/L	-0.04	CRP 50-100 mg/L	0.38
CRP > 100 mg/L	0.45	CRP > 100 mg/L	1.28
Ferritin 250-1000 µg/L	0.26	Ferritin 250-1000 µg/L	-0.10
Ferritin >1000 µg/L	0.52	Ferritin >1000 µg/L	0.13
D-Dimer 1,000-2,000 ng/mL	0.51	D-Dimer 1,000-2,000 ng/mL	0.19
D-Dimer > 2,000 ng/mL	0.75	D-Dimer > 2,000 ng/mL	0.60
Internal Validation			

Statistic	Estimate (95% CI)	Statistic	Estimate (95% CI)
Harrell's Survival C-Statistic (Concordance)	0.813 (0.798, 0.827)	Harrell's Survival C-Statistic (Concordance)	0.878 (0.863, 0.892)
AKI in 3 Days AUC	0.820 (0.794, 0.845)	Death in 30 Days AUC	0.893 (0.878, 0.909)

Table S3. Sensitivity, specificity, and likelihood ratios (LR) for positive and negative results of risk scores predicting acute kidney injury (AKI) within 3 days and death within 30 days of a positive COVID-19 test.

Cutoff	Sensitivity	Specificity	Positive LR	Negative LR
Simplified AKI Risk Score (max 6)				
Rule in				
0	1.000	0.000	1.000	NA
1	0.992	0.154	1.170	0.050
2	0.892	0.455	1.640	0.240
3	0.759	0.713	2.640	0.340
4	0.526	0.860	3.750	0.550
5	0.257	0.946	4.770	0.790
6	0.068	0.989	6.400	0.940
7	0.000	1.000	NA	1.000
Simplified Death Risk Score (max 7)				
0	1.000	0.000	1.000	NA
1	1.000	0.156	1.190	0.000
2	0.994	0.233	1.300	0.030
3	0.984	0.433	1.740	0.040
4	0.891	0.665	2.660	0.160
5	0.637	0.890	5.760	0.410
6	0.224	0.978	10.400	0.790
7	0.019	1.000	Inf	0.980
8	0.000	1.000	NA	1.000

Cutoff denotes treating a score greater than or equal a cutoff value as a positive.
Positive likelihood ratio (LR) is sensitivity / (1-specificity)
Negative likelihood ratio (LR) is (1-sensitivity) / specificity
Sensitivity 1 specificity 0 indicates all individuals identified as positive
Sensitivity 0 specificity 1 indicates all individuals identified as negative
Approximate probability changes can be obtained by ≈0.18 * ln(LR) (McGee 2002)

Table S4. Multivariable AKI cause-specific hazard (AKI event, death censor) and AKI subdistribution hazard (AKI and death competing risks) model results.

Variable	Cause-Specific	Subdistribution
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**1.67 (1.31, 2.14)**
>65	**2.16 (1.66, 2.80)**	**1.92 (1.48, 2.50)**
Sex (Male)	**1.51 (1.28, 1.77)**	**1.53 (1.29, 1.81)**
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	0.91 (0.73, 1.14)
Hispanic	0.89 (0.58, 1.38)	0.96 (0.65, 1.41)
Asian	0.96 (0.65, 1.43)	0.97 (0.67, 1.41)
Other	1.11 (0.90, 1.37)	1.13 (0.91, 1.40)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.27 (1.06, 1.53)**
2	**1.67 (1.30, 2.13)**	**1.66 (1.29, 2.12)**
3+	**1.82 (1.21, 2.75)**	**1.81 (1.18, 2.77)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	1.11 (0.90, 1.38)
>30	**1.42 (1.17, 1.74)**	**1.47 (1.19, 1.81)**
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.03 (0.71, 1.48)
>100.4	**1.59 (1.34, 1.88)**	**1.62 (1.37, 1.91)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	1.30 (0.98, 1.72)
>110	1.11 (0.85, 1.47)	1.04 (0.78, 1.38)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**1.73 (1.28, 2.35)**
>180	0.96 (0.55, 1.67)	1.00 (0.55, 1.84)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	0.79 (0.56, 1.12)
>11	**1.77 (1.49, 2.12)**	**1.68 (1.39, 2.04)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	**2.27 (1.83, 2.81)**

<10	**3.72 (3.03, 4.57)**	**3.94 (3.17, 4.90)**
Platelets (per μL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**1.63 (1.19, 2.24)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	0.94 (0.76, 1.18)
>100	**1.57 (1.29, 1.91)**	**1.48 (1.20, 1.82)**
Ferritin (μg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	**1.33 (1.05, 1.69)**
>1000	**1.69 (1.31, 2.17)**	**1.70 (1.31, 2.21)**
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	**1.70 (1.36, 2.13)**
>2000	**2.11 (1.68, 2.65)**	**2.07 (1.63, 2.63)**

Table S5. Multiple Imputation Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.58 (1.22, 2.04)**	**4.60 (2.07, 10.3)**
>65	**1.86 (1.43, 2.43)**	**18.3 (8.47, 39.6)**
Sex (Male)	**1.42 (1.20, 1.68)**	1.05 (0.83, 1.33)
Race		
White	Reference	Reference
Black	0.87 (0.69, 1.08)	**0.65 (0.47, 0.89)**
Hispanic	0.97 (0.63, 1.50)	0.66 (0.33, 1.32)
Asian	0.92 (0.61, 1.38)	**0.39 (0.19, 0.80)**
Other	1.05 (0.85, 1.30)	**0.67 (0.47, 0.96)**
Medical Conditions (number)		
0	Reference	Reference
1	**1.32 (1.10, 1.58)**	1.07 (0.82, 1.39)
2	**1.62 (1.25, 2.09)**	1.33 (0.94, 1.89)
3+	**1.88 (1.24, 2.87)**	1.62 (0.94, 2.79)
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.10 (0.90, 1.36)	0.81 (0.61, 1.07)
>30	**1.33 (1.09, 1.63)**	0.86 (0.65, 1.13)
Temperature (F)		
97-100.4	Reference	Reference
<97	0.95 (0.66, 1.36)	1.11 (0.69, 1.77)
>100.4	**1.40 (1.18, 1.66)**	**1.40 (1.09, 1.81)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.13 (0.86, 1.48)	0.86 (0.58, 1.30)
>110	0.98 (0.74, 1.31)	1.41 (0.95, 2.08)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.74 (1.28, 2.37)**	**1.76 (1.19, 2.60)**
>180	1.22 (0.68, 2.19)	1.16 (0.52, 2.55)
Respiratory Rate (per minute)		
<20	Reference	Reference
>20	**1.72 (1.45, 2.03)**	**1.98 (1.53, 2.55)**
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.81 (0.58, 1.15)	1.25 (0.81, 1.95)
>11	**1.61 (1.34, 1.93)**	**1.95 (1.52, 2.51)**
Hemoglobin (g/dL)		

>12	Reference	Reference
10-12	**2.02 (1.64, 2.49)**	0.81 (0.60, 1.09)
<10	**3.31 (2.68, 4.08)**	0.86 (0.65, 1.14)
Platelets (per μL)		
>100	Reference	Reference
<100	**1.85 (1.37, 2.49)**	**2.51 (1.72, 3.68)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.99 (0.79, 1.24)	**1.60 (1.10, 2.33)**
>100	**1.47 (1.20, 1.80)**	**3.18 (2.32, 4.37)**
Ferritin (μg/L)		
<250	Reference	Reference
250-1000	1.18 (0.93, 1.50)	0.77 (0.54, 1.12)
>1000	**1.48 (1.14, 1.91)**	0.89 (0.60, 1.32)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.59 (1.27, 2.00)**	1.16 (0.82, 1.63)
>2000	**2.03 (1.60, 2.57)**	**1.73 (1.23, 2.44)**
Interleukin-6 (IU/mL)		
<40	Reference	Reference
40-80	**1.39 (1.03, 1.86)**	**2.75 (1.80, 4.21)**
>80	**1.91 (1.50, 2.43)**	**3.07 (2.01, 4.69)**

Pooled hazard ratios calculated using 10 different imputation datasets with imputed values for missing respiratory rate and IL-6.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk Assessment for Acute Kidney Injury and Death among New COVID-19 Positive Adult Patients without Chronic Kidney Disease

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Title Page

Risk Assessment for Acute Kidney Injury and Death among New COVID-19 Positive Adult Patients without Chronic Kidney Disease: Retrospective Cohort Study among 3 US Hospitals

Short Title: AKI and Death among COVID-19 Patients without CKD

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Abstract

Objective: To develop simple but clinically informative risk stratification tools using a few top demographic factors and biomarkers at COVID-19 diagnosis to predict acute kidney injury (AKI) and death.

Design: Retrospective cohort analysis, follow-up from February 1 through May 28, 2020.

Setting: 3 teaching hospitals, 2 urban and 1 community-based in the Boston area.

Participants: Eligible patients were at least 18 years old, tested COVID-19 positive from February 1 through May 28, 2020, and had at least two serum creatinine measurements within 30 days of a new COVID-19 diagnosis. Exclusion criteria were having CKD or having a previous AKI within 3 months of a new COVID-19 diagnosis.

Main Outcomes and Measures: Time from new COVID-19 diagnosis until AKI event, time until death event.

Results: Among 3,716 patients, there were 1,855 (49.9%) males and the average age was 58.6 years (SD 19.2 years). Age, sex, white blood cell, hemoglobin, platelet, C-reactive protein, and D-dimer levels were most strongly associated with AKI and/or death. We created risk scores using these variables predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis. Area under the curve (AUC) for predicting AKI within 3 days was 0.785 (95% CI, 0.758 to 0.813) and AUC for death within 30 days was 0.861 (95% CI, 0.843 to 0.878). Hemoglobin was the most predictive component for AKI, and age the most predictive for death. Predictive accuracies using all study variables were similar to using the simplified scores.

Conclusion: Simple risk scores using age, sex, a complete blood cell count, C-reactive protein, and D-dimer were highly predictive of AKI and death and can help simplify and better inform clinical decision making.

Key words: COVID-19; kidney injury; risk prediction

Strengths and limitations of this study

- Various associations between patient variables and COVID-19 acute kidney injury AKI and death have been reported, but it is unclear which variables are most predictive and important to focus on.
- We developed risk scores for predicting AKI and death among new COVID-19 positive patients.
- Readily obtainable demographic, vital sign, and laboratory values were considered evaluated.
- Findings are limited to patients without chronic kidney disease.

Introduction

Although respiratory failure and diffuse inflammatory lung tissue damage are key features of coronavirus disease 2019 (COVID-19), involvement of other organs such as the kidneys has been well documented. Pathologic autopsy examinations of COVID-19 kidneys have shown clusters of coronavirus-like particles in the tubular epithelium and podocytes, upregulation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor angiotensin-converting enzyme 2 and positive immunostaining with SARS-CoV-2 nucleoprotein antibodies.[1,2] Hemodynamic instability, systemic hypoxia, abnormal coagulation, and inflammation from severe COVID-19 can also directly contribute to acute kidney injury (AKI) and induce acute tubular necrosis.[3]

Various epidemiologic studies from China, Europe, and the United States have investigated AKI outcomes among COVID-19 patients. Early studies in China have reported AKI incidences ranging from 0.5-15% among hospitalized and outpatient COVID-19 patients.[4,5] One United Kingdom study found hospitalized COVID-19 patients with AKI had a 3-fold higher odds of death than those without AKI.[6] Large US population studies of hospitalized COVID-19 patients, primarily in the New York City metropolitan area, have reported AKI incidences ranging from 27-57%, with in-hospital mortality rates ranging from 35-71% among AKI COVID-19 patients.[7–10] Some of these studies have also explored variable associations with COVID-19 AKI, but none of these studies have investigated which subset of these variables are most predictive of AKI or built risk predictions models using demographic variables and biomarkers.

Risk prediction tools have been investigated for COVID-19 deaths. A small number of a priori determined biomarkers were investigated for their associations with

the risk of COVID-19 death.[11] However, a more data driven approach would compare the predictive accuracies of these biomarkers to other biomarkers and variables such as demographic factors and vital signs and build a more powerful risk prediction model using a comprehensive set of biomarkers, demographic variables, and vital signs. Different risk factors should also be weighted differently, and understanding the relative importance of different variables in predicting poor outcomes will allow for more accurate holistic patient evaluations.

In this study we developed and evaluated new risk assessment tools that can be easily implemented at the bedside or during chart reviews to predict AKI and death after a positive COVID-19 test. Our contributions include (1) identifying the top biomarkers and demographic variables that predict AKI events among COVID-19 patients, (2) investigating a greater number of potential biomarkers and risk factors in predicting death, (3) developing clinical risk assessment tools for both AKI and death using a small number of predictors, and (4) validating that these tools are nearly as predictive as using all available study variables. By understanding which subset of risk factors are most important to focus on, medical providers can more efficiently work up and risk stratify their newly diagnosed COVID-19 patients.

Methods

Study Population

The Mass General Brigham (MGB) Health system serves a large diverse patient population around Boston and Eastern Massachusetts. Electronic health records from

three major hospitals in this system (Massachusetts General Hospital in Boston, Brigham and Women's Hospital in Boston, and Newton-Wellesley Hospital in Newton) were used. The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661. Patients and the public were not involved in the planning of this project.

We included all patients that 1) were at least 18 years old, 2) tested COVID-19 positive at one of the three hospitals above between February 1, 2020 through May 28, 2020, and 3) had at least 2 serum creatinine tests within 30 days of their SARS-Cov-2 PCR test. We excluded patients that 1) met the criteria of acute kidney injury within 3 months before their SARS-CoV-2 test and 2) had chronic kidney disease (CKD) identified as a preexisting condition from International Classification of Disease (ICD-9 and ICD-10) codes (see below).

Data Collection

Information in electronic health records (EHR) of patients who met the inclusion criteria were extracted from the enterprise data warehouse and included demographic, comorbidities, clinical, laboratory, and outcome data (death). Demographic and laboratory data information closest to the time of first SARS-Cov-2 PCR test were kept (except for serum creatinine, multiple values were kept). Serum creatinine laboratory test results and timestamps within 3 months before and 30 days after the SARS-Cov-2 polymerase chain reaction test were extracted. We categorized ethnic groups other than White, Black, Hispanic, and Asian into a single subgroup. All documented comorbidity

related medical history in MGB healthcare system enterprise data warehouse before the first time of SARS-Cov-2 test were extracted. Preexisting conditions, including hypertension, diabetes, cardiovascular disease, and heart failure, were classified using their ICD-9 or ICD-10 codes.

Definitions of Outcomes

Per the Kidney Disease Improving Global Outcomes (KDIGO) criteria, AKI was defined as a change in serum creatinine (SCr) of 0.3 mg/dl over a 48-hour period, a 50% increase in baseline creatinine in 7 days, or urine value <0.5 ml/kg/hour for 6 hours.[12] Due to difficulties obtaining accurate urine volumes from electronic health record data, we only use serum creatinine to define AKI events. If patients had more than 2 SCr tests in their EHR, we used all available SCr tests to define the earliest time. Death times were directly extracted from the data warehouse.

Statistical Analyses

Continuous variables were transformed into categorical variables to improve interpretability of results and account for nonlinear associations. Counts and percentages were presented, and two proportion z-tests were used to compare the proportion of deaths among AKI and non-AKI patients. For AKI survival analyses, observations without AKI were censored after 30 days, at the time of death, or at 5/28/2020, whichever came first. For death survival analyses, observations without death were censored at 5/28/2020. Multiple multivariable Cox proportional hazards

models included age, sex, race, diabetes, cardiovascular disease, hypertension, heart failure, body mass index (BMI), temperature, heart rate, systolic blood pressure, white blood cell count (WBC), hemoglobin, platelets, C-reactive protein (CRP), ferritin, D-and dimer. Respiratory rate and interleukin-6 (IL-6) variables were not included in primary analyses given missing data. However, we performed exploratory analyses imputing the missing respiratory rate and IL-6 values (additional details are in the sensitivity analysis section).

We next built a simplified Cox model for clinical use by using a stepwise variable selection procedure for Cox models alternating between "forward" and "backwards" steps to identify the first 5 variables to be included.[13] Simplified Cox models were fit using only the selected 5 variables and Harrell's C-Statistics were obtained (survival outcome). Model coefficient (linear prediction) accuracy was evaluated. We evaluated area under receive operating characteristic (ROC) curves (AUC) for predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcome). Net reclassification improvement (NRI) of adding all remaining covariates was also calculated.

Risk scores were obtained by rounding simplified model coefficients for easier clinical risk assessment use. For suggested risk score cutoffs, Kaplan-Meier event curves were plotted, log rank tests were performed, and sensitivities, specificities, positive and negative likelihood ratios were calculated. Approximate pre-test to post-test probability changes from likelihood ratios were calculated using the linear approximation proposed by McGee.[14] Cutoffs for low risk were chosen so that the negative likelihood ratio would be ≈0.20 with a pre- to post-test probability decrease of ≈30%, while cutoffs

for high risk were chosen so that the positive likelihood ratio would be ≈5.0 with a pre- to post-test probability increase of ≈30% and that at least 15% of patients (560) would be identified as high risk.[14] We ran 1,000 internal cross validation iterations in which 70% of data were randomly assigned to training, the other 30% to testing. For each iteration, simplified Cox models were fit to the training data, coefficients were rounded to obtain risk scores, and AUC's were calculated using the predicted testing data risk scores.

We performed three sensitivity analyses. First, the multivariable cause-specific and subdistribution hazard to documented AKI events within 30 days accounting for the competing risk of death was modeled.[15] Second, we performed a multiple imputation analysis by creating 10 imputation datasets with imputed values for missing respiratory rate and IL-6 and then calculating pooled multivariable Cox hazard ratios.[16] Third, we investigated the AKI risk score accuracy in identifying stage 2 or 3 AKI as defined in the KDIGO criteria, and we investigated the death score accuracy among patients with stage 2 or 3 AKI.[12] All analyses were performed with R version 4.0.4 and all code for analyses are available online (to be posted during revisions).

Results

Demographic and Clinical Characteristics

There were 3,716 eligible adult COVID-19 positive patients without CKD, of which 1,855 (49.9%) were male. The average age was 58.6 years (SD 19.2 years). There were 696 patients that developed AKI (18.7%) and 249 (35.8%) were within three days of a new COVID-19 diagnosis. There were 347 deaths (9.3%) and 322 (92.8%)

were within thirty days of a new COVID-19 diagnosis. Among the AKI group there were 192 deaths (27.6%), and among the non-AKI group there were 155 deaths (5.1%, p<0.001). Patient demographics, preexisting conditions, vital signs, and laboratory values stratified by patients with AKI and patients that died are displayed in **Table 1**. Patients with AKI and patients that died were more likely to be older, male, have multiple comorbidities, and have on admission higher temperatures, lower systolic blood pressures, higher respiratory rates, elevated white blood cell counts, lower hemoglobin and platelets, and elevated CRP, ferritin, D-dimer, and IL-6 levels.

Fully Adjusted Multivariable Regression

Multivariable Cox regression was performed to identify risk factors associated with time to AKI and death. **Table 2** displays pooled multivariable adjusted hazard ratios. Adjusting for all other variables, older age, increased medical conditions, increased temperature, decreased systolic blood pressure, increased white blood cells, decreased platelets, and increased CRP and D-Dimer were associated with increased hazards for both AKI and death. Elevated BMI, decreased hemoglobin, and increased ferritin were associated with increased hazards for AKI but not death. Black and Asian race were associated with decreased hazards and increased heart rate was associated with increased hazards for death but not AKI.

Top Risk Factor/Biomarker Selection

The top five variables selected for being most associated with AKI events were hemoglobin, D-dimer, CRP, WBC, and male sex. The top five variables most associated with death were age, CRP, platelets, WBC, and D-Dimer. **Table S1** shows model coefficients and Harrell's C-statistic (survival concordance) from the simplified model using just these selected variables. **Table S2** shows similar results for the fully adjusted model. The simplified AKI Cox model had a survival C-statistic of 0.785 (95% CI, 0.769 to 0.800), while the fully adjusted AKI Cox model had a C-statistic of 0.813 (95% CI, 0.798 to 0.827). The simplified death Cox model had a survival C-statistic of 0.857 (95% CI, 0.841 to 0.874), while the fully adjusted death Cox model had a C-statistic of 0.878 (95% CI, 0.863 to 0.892).

Cox model coefficients were used to predict AKI events within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcomes). **Table S1** and **Table S2** also displays AUC's for the simplified and fully adjusted coefficients respectively. For AKI in 3 days, using the simplified coefficients had an AUC of 0.787 (95% CI, 0.759 to 0.814), using the fully adjusted coefficients had an AUC of 0.820 (95% CI, 0.794 to 0.845), and the NRI was 0.041 (95% CI, 0.003 to 0.082). For death in 30 days, using the simplified coefficients had an AUC of 0.872 (95% CI, 0.854 to 0.890), the fully adjusted coefficients had an AUC of 0.893 (95% CI, 0.878 to 0.909), and the NRI was 0.010 (95% CI, -0.007 to 0.029).

Risk Score

Model coefficients were rounded to obtain risk score component values for easier clinical use. **Table 3** shows the risk score and internal validation results. For AKI in 3 days, the risk score had an AUC 0.785 (95% CI, 0.758, 0.813) and a cross validation AUC of 0.776 (95% CI, 0.732, 0.816). For death in 30 days, the risk score had an AUC of 0.861 (95% CI, 0.843 to 0.878) and a cross validation AUC of 0.860 (95% CI, 0.831, 0.886). **Figure 1A** plots ROC curves for using fully adjusted coefficients (from **Table S2**) versus using risk scores (from **Table 3**) in predicting AKI in 3 days and death in 30 days.

Suggested risk stratification cutoffs were obtained. **Table S3** presents sensitivity, specificity, and positive and negative likelihood ratios for all possible risk score cutoffs. **Table 4** shows suggested risk stratification cutoffs and stratified observed and estimated event rates. Higher risk scores had higher observed and estimated AKI and death rates. **Figure 1B** plots Kaplan Meier event curves of AKI and death events by simplified risk score categories. Event rates different by risk category for AKI ($p<0.001$) and death ($p<0.001$).

Sensitivity Analysis

We performed a competing risk regression analysis for AKI and death within 30 days. **Table S4** displays the multivariable cause-specific and subdistribution hazard ratios for AKI events. Cause-specific and subdistribution hazard ratio estimates and confidence intervals were nearly identical. We also performed a multiple imputation analysis by imputing missing values for respiratory rate and IL-6 to evaluate their

associations. **Table S5** shows that results were similar to non-imputation results, and increased respiratory rate and IL-6 were associated with increased hazards of AKI and death.

Of the 696 patients with an AKI event, 580 had a stage 1 AKI (83.3%), 29 had stage 2 (4.2%), and 87 had stage 3 (12.5%). Of the 117 patients with stage 2 or 3 AKI, there were 39 deaths (33.6%). In predicting stage 2 or 3 AKI as a single composite outcome among all 3,716 patients, the AKI risk score in **Table 3** had an AUC of 0.850 (95% CI, 0.819 to 0.881). In predicting death among the 117 patients with stage 2 or 3 AKI, the death risk score in **Table 3** had an AUC of 0.758 (95% CI, 0.671 to 0.846).

Discussion

In this retrospective study of over 3,700 adult patients without chronic kidney disease diagnosed with COVID-19 through May 2020 in the Boston area, we identified risk factors and biomarkers associated with AKI and death, and we developed and internally validated risk scores for predicting AKI and death. We found about one in five patients developed AKI and one in ten patients died. Increased age, male sex, increased white blood cells, C-reactive protein and D-Dimer and decreased hemoglobin and platelet levels were associated with AKI within 3 days and/or death within 30 days of a new COVID-19 diagnosis. A risk score using just these variables had similar internal accuracy as using all study variables. These results can assist in risk stratification of COVID-19 patients without CKD.

Many studies have found markedly increased COVID-19 fatality rates among older people. Studies from China, Spain, and Italy, and a meta-analysis of studies from 34 different geographical locations have all found increased case or infection fatality rates among people >60 and >65 years old compared to younger populations.[17–20] We similarly observed older age had some of the strongest associations with death. Earlier studies have found various physiologic changes among elderly patients that may contribute to this age-related risk, such as decreased small airway clearance, decreased number of cilia and ciliated cells, and decreased upper airway size.[21–23]

Other studies have also reported worse COVID-19 outcomes among men. A study of over 3,300 patients in Montefiore Medical Center found male sex was associated with AKI in both COVID-19 positive and negative patients.[8] This study also provided a more complete discussion of other animal studies and meta-analyses to date that that have found associations between male sex and AKI in general. Studies of COVID-19 outcomes from March 2020 in Italy and the US also reported increased hospitalization and intensive care unit admission rates among male patients.[24,25] We similarly observed that AKI patients (60.3%) and patients that died (58.2%) were more likely to be male (overall 49.9%). However, after adjusting for other demographics, medical conditions, vital signs, and laboratory values, we found male sex was associated with AKI but not death.

Among laboratory values, C-reactive protein, hemoglobin, white blood cells, D-Dimer, and platelets were significantly associated with AKI and death and were included in risk scores. Although there has been debate about a standard definition for COVID-19 cytokine storm syndrome, patients with C-reactive protein may have excessive

immune activation, with C-reactive protein being produced by hepatocytes in response to IL-6 or ferritin.[26] Decreased hemoglobin may be reflective of kidney disease with decreased erythropoietin production or directly lead to decreased oxygenation of the kidneys. A study from Korea also found a higher risk of AKI in critically ill patients with a hemoglobin <10.5 g/dL.[27] Elevated white blood cell counts may suggest sepsis and be associated with life-threatening organ dysfunction.[28] Elevated D-Dimer levels may be indicative of a pro-thrombotic state, and a retrospective study from China found that D-Dimer >2000 ng/mL was associated with increased mortality.[29] However D-dimer levels have also been reported to be elevated at baseline in CKD patients,[30] so it is possible elevated D-Dimer may only be prognostic in non-CKD patients. Low platelets may also indicate a systemic coagulopathic process that places patients at an increased risk for death.[28]

The biomarker IL-6 was found to be a significant risk factor in regression analyses. However, a substantial proportion of patients in our study were missing IL-6 values (78.3%), so IL-6 was not considered for risk score development. IL-6 measurements were obtained at physician discretion and were likely reserved for severe cases. This may have also contributed to the missingness profile of IL-6. Previous studies have found IL-6 cutoffs of 80 and 86 IU/mL to have prognostic value for predicting respiratory failure and death respectively.[31,32]

We proposed risk scores for identifying AKI within 3 days and death within 30 days of a new COVID-19 diagnosis along with suggested cutoffs. Although risk scores still need to be externally validated, being able to identify a few key biomarkers that are widely accessible can help focus chart reviews of new COVID-19 positive patients.

Varying score weights further highlight biomarkers to focus on, such as hemoglobin and male sex for AKI, age and platelets for death, and WBC, CRP, and D-Dimer for both. Larger scores directly correlate with worse outcomes and can help shape physician gestalt.

We explored death being a competing risk for AKI events as patients with death will not have any more creatinine measurements. Although an AKI does not exclude the possibility of death, competing risk analyses can still be performed investigating which event type occurs first.[15] The cause-specific hazards ratios (Cox hazard ratios) describe the rate of AKI events among those still alive and with no previous AKI events, while the subdistribution hazard ratios describes the overall rate of AKI events occurring before death. In our study both cause-specific and subdistribution hazard ratios were similar. Competing risk analyses were not performed for death events as having an AKI does not exclude death.

We also explored a subgroup of patients which developed stage 2 or 3 AKI. Our AKI risk score also performed well in identifying patients who developed stage 2 or 3 AKI, suggesting higher risk scores also correlate with developing a higher stage AKI. Among patients who developed stage 2 or 3 AKI, the death risk score AUC had a larger confidence interval likely because of the smaller sample size and smaller number of death events.

Limitations to our study include the following. All results are associational and no causal effects should be interpreted. Vital and signs and laboratory values were those closest to COVID-19 diagnosis, and time-varying covariates were not incorporated into analyses. As the study was retrospective, selection bias cannot be excluded, and only

events within the MGB system were recorded. Our identified risk factors and risk scores are most applicable during a patient's initial COVID-19 positive test. Results may not be generalizable to more specific subgroups such as those requiring intensive care admission. Patients in the Boston area may not be reflective of those in other healthcare systems, and the study population included only COVID-19 positive patients without CKD. The study population included patients in the first wave of COVID-19, and results should be cautiously applied to subsequent waves of COVID-19 due to differences in COVID-19 variants and treatment protocols. Future work may further stratify AKI events by stage and time of acquisition (relative to hospital admission), investigate outpatient, hospitalized, and critically ill patients separately, focus on CKD patients, validate results on a separate cohort, and explore hospital specific effects.

We investigated AKI and death outcomes among adult COVID-19 patients without CKD in the Boston area. We identified risk factors and developed and evaluated risk assessment tools for identifying COVID-19 patients developing AKI and death. Hemoglobin, D-Dimer, CRP, WBC, and male sex were the strongest predictive biomarkers for AKI. Age, CRP, platelets, WBC, and D-Dimer were most predictive for death. Our study significantly contributes to epidemiological knowledge of COVID-19 outcomes and introduces simple tools to assist with rapid risk assessment.

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Authors' contributions: DL and HR drafted the manuscript. HR, PX, DW obtained the data. DL performed the analyses. DL, HR, DJV, PS, QL, and XL contributed to the design of the study. All authors were involved with interpretation of the data and critical revision and final approval of the article.

Availability of data and materials: Patient data is not available, but requests for surrogate data may be made to the corresponding authors. However, code for all analyses will be available at https://github.com/lin-lab.

Patient and public involvement: Patients and the public were not involved in the planning of this project.

Research ethics approval human subjects: The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661. Only deidentified patient electronic health record data were used.

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Figure Legends

Fig. 1 Receiver Operating Characteristics and Kaplan Meier Event Curves Using Selected Variables.

(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.

(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

Table 1. Characteristics of Patients with Acute Kidney Injury, Patients that Died, and All Patients.

Variable, n (%)	**AKI** (n=696)	**Died** (n=347)	**Total** (n=3,716)
Age (years)			
<45	86 (12.4)	7 (2.0)	980 (26.4)
45-65	245 (35.2)	55 (15.9)	1,310 (35.3)
>65	365 (52.4)	285 (82.1)	1,426 (38.4)
Sex (Male)	420 (60.3)	202 (58.2)	1,855 (49.9)
Race			
White	407 (58.5)	242 (69.7)	2,091 (56.3)
Black	110 (15.8)	50 (14.4)	568 (15.3)
Hispanic	22 (3.2)	9 (2.6)	135 (3.6)
Asian	27 (3.9)	8 (2.3)	140 (3.8)
Other	130 (18.7)	38 (11.0)	782 (21.0)
Diabetes	197 (28.3)	87 (25.1)	727 (19.6)
Cardiovascular Disease	67 (9.6)	49 (14.1)	231 (6.2)
Hypertension	135 (19.4)	65 (18.7)	484 (13.0)
Heart Failure	39 (5.6)	38 (11.0)	134 (3.6)
Medical Conditions (number)			
0	397 (57.0)	189 (54.5)	2,565 (69.0)
1	190 (27.3)	95 (27.4)	811 (21.8)
2	83 (11.9)	47 (13.5)	264 (7.1)
3+	26 (3.7)	16 (4.6)	76 (2.0)
Body Mass Index (kg/m^2)			
<25	165 (23.7)	115 (33.1)	833 (22.4)
25-30	229 (32.9)	110 (31.7)	1,334 (35.9)
>30	302 (43.4)	122 (35.2)	1,549 (41.7)
Temperature (F)			
97-100.4	423 (60.8)	201 (57.9)	2,745 (73.9)
<97	35 (5.0)	22 (6.3)	190 (5.1)
>100.4	238 (34.2)	124 (35.7)	781 (21.0)
Heart Rate (beats/min)			
60-110	576 (82.8)	274 (79.0)	3,194 (86.0)
<60	61 (8.8)	30 (8.6)	275 (7.4)
>110	59 (8.5)	43 (12.4)	247 (6.6)
Systolic Blood Pressure (mmHg)			
90-180	635 (91.2)	305 (87.9)	3,549 (95.5)
<90	48 (6.9)	35 (10.1)	117 (3.1)
>180	13 (1.9)	7 (2.0)	50 (1.3)
Respiratory Rate (per minute)			

<20	245 (35.2)	92 (26.5)	1,692 (45.5)
>20	364 (52.3)	202 (58.2)	1,237 (33.3)
NA (Missing)	87 (12.5)	53 (15.3)	787 (21.2)
White Blood Cell (thousand cells/mm^3)			
3.5-11	428 (61.5)	189 (54.5)	2,942 (79.2)
<3.5	39 (5.6)	26 (7.5)	267 (7.2)
>11	229 (32.9)	132 (38.0)	507 (13.6)
Hemoglobin (g/dL)			
12+	201 (28.9)	138 (39.8)	2,250 (60.5)
10-12	204 (29.3)	88 (25.4)	883 (23.8)
<10	291 (41.8)	121 (34.9)	583 (15.7)
Platelets (per μL)			
>100	643 (92.4)	310 (89.3)	3,600 (96.9)
<100	53 (7.6)	37 (10.7)	116 (3.1)
C-Reactive Protein (mg/L)			
<50	197 (28.3)	62 (17.9)	1,706 (45.9)
50-100	149 (21.4)	63 (18.2)	1,011 (27.2)
>100	350 (50.3)	222 (64.0)	999 (26.9)
Ferritin (μg/L)			
<250	105 (15.1)	52 (15.0)	950 (25.6)
250-1000	327 (47.0)	155 (44.7)	1,894 (51.0)
>1000	264 (37.9)	140 (40.3)	872 (23.5)
D-Dimer (ng/mL)			
<1000	136 (19.5)	60 (17.3)	1,726 (46.4)
1000-2000	217 (31.2)	101 (29.1)	1,076 (29.0)
>2000	343 (49.3)	186 (53.6)	914 (24.6)
Interleukin-6 (IU/mL)			
<40	121 (17.4)	26 (7.5)	438 (11.8)
40-80	68 (9.8)	33 (9.5)	137 (3.7)
>80	136 (19.5)	58 (16.7)	196 (5.3)
NA (Missing)	371 (53.3)	230 (66.3)	2,945 (79.3)

AKI = acute kidney injury

Table 2. Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**5.33 (2.42, 11.8)**
>65	**2.16 (1.66, 2.80)**	**23.4 (10.9, 50.1)**
Sex (Male)	**1.51 (1.28, 1.77)**	1.16 (0.92, 1.45)
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	**0.66 (0.48, 0.92)**
Hispanic	0.89 (0.58, 1.38)	0.62 (0.32, 1.23)
Asian	0.96 (0.65, 1.43)	**0.46 (0.22, 0.93)**
Other	1.11 (0.90, 1.37)	0.72 (0.50, 1.02)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.07 (0.83, 1.38)**
2	**1.67 (1.30, 2.13)**	**1.40 (1.01, 1.95)**
3+	**1.82 (1.21, 2.75)**	**1.61 (0.95, 2.73)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	0.78 (0.59, 1.02)
>30	**1.42 (1.17, 1.74)**	0.94 (0.72, 1.22)
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.18 (0.75, 1.85)
>100.4	**1.59 (1.34, 1.88)**	**1.54 (1.22, 1.96)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	0.97 (0.66, 1.43)
>110	1.11 (0.85, 1.47)	**1.78 (1.28, 2.48)**
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**2.10 (1.45, 3.04)**
>180	0.96 (0.55, 1.67)	0.90 (0.42, 1.92)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	1.10 (0.72, 1.68)
>11	**1.77 (1.49, 2.12)**	**2.32 (1.82, 2.95)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	0.88 (0.67, 1.16)
<10	**3.72 (3.03, 4.57)**	1.03 (0.78, 1.35)

Platelets (per µL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**2.60 (1.79, 3.77)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	**1.46 (1.02, 2.10)**
>100	**1.57 (1.29, 1.91)**	**3.61 (2.65, 4.93)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	0.91 (0.65, 1.26)
>1000	**1.69 (1.31, 2.17)**	1.14 (0.80, 1.62)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	1.21 (0.87, 1.69)
>2000	**2.11 (1.68, 2.65)**	**1.82 (1.31, 2.52)**

1

Table 3. Risk Score and Internal Validation Results.

AKI in 3 days (max 6)		Death in 30 days (max 7)	
Risk Score			
Variable	**Value**	**Variable**	**Value**
Hemoglobin <10 g/dL	2	Age > 65 years	3
Hemoglobin 10-12 g/dL	1	Age 45-65 years	2
D-Dimer > 1,000 ng/mL	1	CRP > 100 mg/L	1
CRP > 100 mg/L	1	Platelets < 100 per µL	1
WBC > 11,000 cells/mm^3	1	WBC > 11,000 cells/mm^3	1
Male Sex	1	D-Dimer > 2,000 ng/mL	1
Internal Validation			
Validation Type	**AUC (95% intervals)**	**Validation Type**	**AUC (95% intervals)**
Whole Data	0.785 (0.758, 0.813)	Whole Data	0.861 (0.843, 0.878)
Cross Validation	0.776 (0.732, 0.816)	Cross Validation	0.860 (0.831, 0.886)

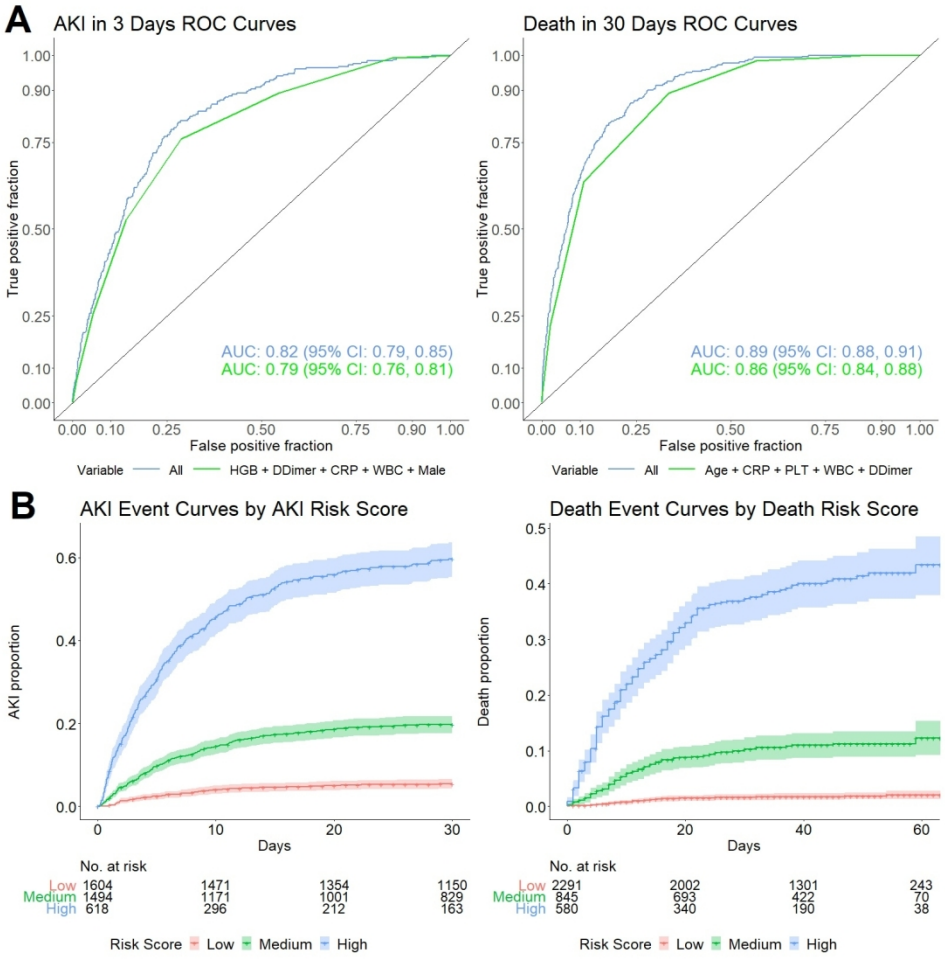
CRP = C-reactive protein, WBC = white blood cells.
Whole data validation presents area under the curve (AUC) estimates and 95% confidence intervals.
Internal cross validation presents mean AUC and 95% central interval (2.5th and 97.5th percentiles).

Table 4. Suggested Risk Stratification Cutoffs and Observed and Estimated Event Rates.

AKI Risk Score				
Risk Level	**Total Score**	**Observed Total AKI (%)**	**Estimated 3 Day AKI (%)**	**Estimated 30 Day AKI (%)**
Low Risk	0-1	5.2	1.7	5.4
Moderate Risk	2-3	18.4	6.2	19.7
High Risk	4-6	54.7	21.6	59.7
Death Risk Score				
Risk Level	**Total Score**	**Observed Total Death (%)**	**Estimated 30 Day Death (%)**	**Estimated 60 Day Death (%)**
Low Risk	0-3	1.7	1.6	2.0
Moderate Risk	4	10.4	10.2	12.3
High Risk	5-7	37.9	37.3	43.4

Observed percentages are from the observed data

Estimated percentages are from Kaplan-Meier event curves



(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.
(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

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Supplemental Methods – Additional Details

Statistical Analyses

Descriptive statistics and receiver operating characteristics (ROC) were calculated using R base functions. Cox proportional hazards models were fit using the "survival" package. Inspection of AKI and death Kaplan-Meier event curves stratified by each variable revealed no obvious violations of the proportional hazards assumption.

The variable selection procedure was implemented using the "My.stepwise" package. In addition to the variables included in fully adjusted Cox proportional hazards models, age >45 years, medical conditions >1, medical conditions >2, BMI > 25 kg/m^2, hemoglobin <12 g/dL, CRP > 500 mg/L, ferritin >250 µg/L, and D-Dimer > 1,000 ng/mL were also included. The package "glmnet" was used to reformat data so that the variable selection procedure could be applied. The selection procedure alternates between "forward" steps of adding variables and "backwards" steps of removing variables. The significance level for entry and for staying was conservatively set at 0.15 as suggested by function details. The top 5 variables (top 6 dummy variables) were included in risk scores. Simplified risk score values were obtained by rounding model coefficients to the nearest integer.

ROC curves were created using "plotROC" and AUC values and confidence intervals were obtained from "pROC". Event curves were created using "survminer" and "mstate". Harrell's C-statistics were obtained from Cox proportional hazards model output, and net reclassification of improvement was obtained from "nricens".

Competing risk analyses used the “cmprsk” package, and multiple imputation analyses used the “mice” package. The packages “ggplot2”, “dplyr”, “plyr”, “ggfortify”, and “cowplot” were used to process results and create figures. Code for replicating all analyses will be available online.

Table S1. Coefficients from simplified Cox regression models to calculated and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Simplified Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Hemoglobin <10 g/dL	1.50	Age > 65 years	3.19
Hemoglobin 10-12 g/dL	0.85	Age 45-65 years	1.65
D-Dimer > 1,000 ng/mL	0.76	CRP > 100 mg/L	1.21
CRP > 100 mg/L	0.64	Platelets < 100 per µL	1.20
WBC > 11,000 cells/mm^3	0.59	WBC > 11,000 cells/mm^3	0.87
Male Sex	0.54	D-Dimer > 2,000 ng/mL	0.58
Internal Validation			
Statistic	**Estimate (95% CI)**	**Statistic**	**Estimate (95% CI)**
Harrell's Survival C-Statistic (Concordance)	0.785 (0.769, 0.800)	Harrell's Survival C-Statistic (Concordance)	0.857 (0.841, 0.874)
AKI in 3 Days AUC	0.787 (0.759, 0.814)	Death in 30 Days AUC	0.872 (0.854, 0.890)

AKI = acute kidney injury, CRP = C-reactive protein, WBC = white blood cells, AUC = area under the curve, CI = confidence interval

Table S2. Coefficients from fully adjusted Cox regression models and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Fully Adjusted Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Age 45-65 years	0.54	Age 45-65 years	1.67
Age > 65 years	0.77	Age > 65 years	3.15
Male Sex	0.41	Male Sex	0.14
Race Black	-0.12	Race Black	-0.41
Race Hispanic	-0.12	Race Hispanic	-0.47
Race Asian	-0.04	Race Asian	-0.79
Race Other	0.11	Race Other	-0.33
Medical Conditions 1	0.25	Medical Conditions 1	0.07
Medical Conditions 2	0.51	Medical Conditions 2	0.34
Medical Conditions 3+	0.60	Medical Conditions 3+	0.48
BMI 25-30 kg/m^2	0.08	BMI 25-30 kg/m^2	-0.25
BMI >30 kg/m^2	0.35	BMI >30 kg/m^2	-0.06
Temp < 97 F	0.06	Temp < 97 F	0.16
Temp > 100.4 F	0.46	Temp > 100.4 F	0.43
Heart rate < 60 beats/min	0.22	Heart rate < 60 beats/min	-0.03
Heart rate < 110 beats/min	0.11	Heart rate < 110 beats/min	0.58
SBP < 90 mmHg	0.64	SBP < 90 mmHg	0.74
SBP > 180 mmHg	-0.04	SBP > 180 mmHg	-0.11
WBC < 3,500 cells/mm^3	-0.25	WBC < 3,500 cells/mm^3	0.09
WBC > 11,000 cells/mm^3	0.57	WBC > 11,000 cells/mm^3	0.84
Hemoglobin <10 g/dL	0.77	Hemoglobin <10 g/dL	-0.13
Hemoglobin 10-12 g/dL	1.31	Hemoglobin 10-12 g/dL	0.03
Platelets < 100 per µL	0.56	Platelets < 100 per µL	0.96
CRP 50-100 mg/L	-0.04	CRP 50-100 mg/L	0.38
CRP > 100 mg/L	0.45	CRP > 100 mg/L	1.28
Ferritin 250-1000 µg/L	0.26	Ferritin 250-1000 µg/L	-0.10
Ferritin >1000 µg/L	0.52	Ferritin >1000 µg/L	0.13
D-Dimer 1,000-2,000 ng/mL	0.51	D-Dimer 1,000-2,000 ng/mL	0.19
D-Dimer > 2,000 ng/mL	0.75	D-Dimer > 2,000 ng/mL	0.60
Internal Validation			

Statistic	Estimate (95% CI)	Statistic	Estimate (95% CI)
Harrell's Survival C-Statistic (Concordance)	0.813 (0.798, 0.827)	Harrell's Survival C-Statistic (Concordance)	0.878 (0.863, 0.892)
AKI in 3 Days AUC	0.820 (0.794, 0.845)	Death in 30 Days AUC	0.893 (0.878, 0.909)

Table S3. Sensitivity, specificity, and likelihood ratios (LR) for positive and negative results of risk scores predicting acute kidney injury (AKI) within 3 days and death within 30 days of a positive COVID-19 test.

Cutoff	Sensitivity	Specificity	Positive LR	Negative LR
Simplified AKI Risk Score (max 6)				
Rule in				
0	1.000	0.000	1.000	NA
1	0.992	0.154	1.170	0.050
2	0.892	0.455	1.640	0.240
3	0.759	0.713	2.640	0.340
4	0.526	0.860	3.750	0.550
5	0.257	0.946	4.770	0.790
6	0.068	0.989	6.400	0.940
7	0.000	1.000	NA	1.000
Simplified Death Risk Score (max 7)				
0	1.000	0.000	1.000	NA
1	1.000	0.156	1.190	0.000
2	0.994	0.233	1.300	0.030
3	0.984	0.433	1.740	0.040
4	0.891	0.665	2.660	0.160
5	0.637	0.890	5.760	0.410
6	0.224	0.978	10.400	0.790
7	0.019	1.000	Inf	0.980
8	0.000	1.000	NA	1.000

Cutoff denotes treating a score greater than or equal a cutoff value as a positive.
Positive likelihood ratio (LR) is sensitivity / (1-specificity)
Negative likelihood ratio (LR) is (1-sensitivity) / specificity
Sensitivity 1 specificity 0 indicates all individuals identified as positive
Sensitivity 0 specificity 1 indicates all individuals identified as negative
Approximate probability changes can be obtained by ≈0.18 * ln(LR) (McGee 2002)

Table S4. Multivariable AKI cause-specific hazard (AKI event, death censor) and AKI subdistribution hazard (AKI and death competing risks) model results.

Variable	Cause-Specific	Subdistribution
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**1.67 (1.31, 2.14)**
>65	**2.16 (1.66, 2.80)**	**1.92 (1.48, 2.50)**
Sex (Male)	**1.51 (1.28, 1.77)**	**1.53 (1.29, 1.81)**
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	0.91 (0.73, 1.14)
Hispanic	0.89 (0.58, 1.38)	0.96 (0.65, 1.41)
Asian	0.96 (0.65, 1.43)	0.97 (0.67, 1.41)
Other	1.11 (0.90, 1.37)	1.13 (0.91, 1.40)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.27 (1.06, 1.53)**
2	**1.67 (1.30, 2.13)**	**1.66 (1.29, 2.12)**
3+	**1.82 (1.21, 2.75)**	**1.81 (1.18, 2.77)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	1.11 (0.90, 1.38)
>30	**1.42 (1.17, 1.74)**	**1.47 (1.19, 1.81)**
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.03 (0.71, 1.48)
>100.4	**1.59 (1.34, 1.88)**	**1.62 (1.37, 1.91)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	1.30 (0.98, 1.72)
>110	1.11 (0.85, 1.47)	1.04 (0.78, 1.38)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**1.73 (1.28, 2.35)**
>180	0.96 (0.55, 1.67)	1.00 (0.55, 1.84)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	0.79 (0.56, 1.12)
>11	**1.77 (1.49, 2.12)**	**1.68 (1.39, 2.04)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	**2.27 (1.83, 2.81)**

<10	**3.72 (3.03, 4.57)**	**3.94 (3.17, 4.90)**
Platelets (per µL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**1.63 (1.19, 2.24)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	0.94 (0.76, 1.18)
>100	**1.57 (1.29, 1.91)**	**1.48 (1.20, 1.82)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	**1.33 (1.05, 1.69)**
>1000	**1.69 (1.31, 2.17)**	**1.70 (1.31, 2.21)**
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	**1.70 (1.36, 2.13)**
>2000	**2.11 (1.68, 2.65)**	**2.07 (1.63, 2.63)**

Table S5. Multiple Imputation Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.58 (1.22, 2.04)**	**4.60 (2.07, 10.3)**
>65	**1.86 (1.43, 2.43)**	**18.3 (8.47, 39.6)**
Sex (Male)	**1.42 (1.20, 1.68)**	1.05 (0.83, 1.33)
Race		
White	Reference	Reference
Black	0.87 (0.69, 1.08)	**0.65 (0.47, 0.89)**
Hispanic	0.97 (0.63, 1.50)	0.66 (0.33, 1.32)
Asian	0.92 (0.61, 1.38)	**0.39 (0.19, 0.80)**
Other	1.05 (0.85, 1.30)	**0.67 (0.47, 0.96)**
Medical Conditions (number)		
0	Reference	Reference
1	**1.32 (1.10, 1.58)**	1.07 (0.82, 1.39)
2	**1.62 (1.25, 2.09)**	1.33 (0.94, 1.89)
3+	**1.88 (1.24, 2.87)**	1.62 (0.94, 2.79)
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.10 (0.90, 1.36)	0.81 (0.61, 1.07)
>30	**1.33 (1.09, 1.63)**	0.86 (0.65, 1.13)
Temperature (F)		
97-100.4	Reference	Reference
<97	0.95 (0.66, 1.36)	1.11 (0.69, 1.77)
>100.4	**1.40 (1.18, 1.66)**	**1.40 (1.09, 1.81)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.13 (0.86, 1.48)	0.86 (0.58, 1.30)
>110	0.98 (0.74, 1.31)	1.41 (0.95, 2.08)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.74 (1.28, 2.37)**	**1.76 (1.19, 2.60)**
>180	1.22 (0.68, 2.19)	1.16 (0.52, 2.55)
Respiratory Rate (per minute)		
<20	Reference	Reference
>20	**1.72 (1.45, 2.03)**	**1.98 (1.53, 2.55)**
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.81 (0.58, 1.15)	1.25 (0.81, 1.95)
>11	**1.61 (1.34, 1.93)**	**1.95 (1.52, 2.51)**
Hemoglobin (g/dL)		

>12	Reference	Reference
10-12	**2.02 (1.64, 2.49)**	0.81 (0.60, 1.09)
<10	**3.31 (2.68, 4.08)**	0.86 (0.65, 1.14)
Platelets (per µL)		
>100	Reference	Reference
<100	**1.85 (1.37, 2.49)**	**2.51 (1.72, 3.68)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.99 (0.79, 1.24)	**1.60 (1.10, 2.33)**
>100	**1.47 (1.20, 1.80)**	**3.18 (2.32, 4.37)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	1.18 (0.93, 1.50)	0.77 (0.54, 1.12)
>1000	**1.48 (1.14, 1.91)**	0.89 (0.60, 1.32)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.59 (1.27, 2.00)**	1.16 (0.82, 1.63)
>2000	**2.03 (1.60, 2.57)**	**1.73 (1.23, 2.44)**
Interleukin-6 (IU/mL)		
<40	Reference	Reference
40-80	**1.39 (1.03, 1.86)**	**2.75 (1.80, 4.21)**
>80	**1.91 (1.50, 2.43)**	**3.07 (2.01, 4.69)**

Pooled hazard ratios calculated using 10 different imputation datasets with imputed values for missing respiratory rate and IL-6.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Title Page

Risk Assessment for Acute Kidney Injury and Death among New COVID-19 Positive Adult Patients without Chronic Kidney Disease: Retrospective Cohort Study among 3 US Hospitals

Short Title: AKI and Death among COVID-19 Patients without CKD

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Abstract

Objective: To develop simple but clinically informative risk stratification tools using a few top demographic factors and biomarkers at COVID-19 diagnosis to predict acute kidney injury (AKI) and death.

Design: Retrospective cohort analysis, follow-up from February 1 through May 28, 2020.

Setting: 3 teaching hospitals, 2 urban and 1 community-based in the Boston area.

Participants: Eligible patients were at least 18 years old, tested COVID-19 positive from February 1 through May 28, 2020, and had at least two serum creatinine measurements within 30 days of a new COVID-19 diagnosis. Exclusion criteria were having CKD or having a previous AKI within 3 months of a new COVID-19 diagnosis.

Main Outcomes and Measures: Time from new COVID-19 diagnosis until AKI event, time until death event.

Results: Among 3,716 patients, there were 1,855 (49.9%) males and the average age was 58.6 years (SD 19.2 years). Age, sex, white blood cell, hemoglobin, platelet, C-reactive protein, and D-dimer levels were most strongly associated with AKI and/or death. We created risk scores using these variables predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis. Area under the curve (AUC) for predicting AKI within 3 days was 0.785 (95% CI, 0.758 to 0.813) and AUC for death within 30 days was 0.861 (95% CI, 0.843 to 0.878). Hemoglobin was the most predictive component for AKI, and age the most predictive for death. Predictive accuracies using all study variables were similar to using the simplified scores.

Conclusion: Simple risk scores using age, sex, a complete blood cell count, C-reactive protein, and D-dimer were highly predictive of AKI and death and can help simplify and better inform clinical decision making.

Key words: COVID-19; kidney injury; risk prediction

Strengths and limitations of this study

- Various associations between patient variables and COVID-19 acute kidney injury AKI and death have been reported, but it is unclear which variables are most predictive and important to focus on.
- We developed risk scores for predicting AKI and death among new COVID-19 positive patients.
- Readily obtainable demographic, vital sign, and laboratory values were considered evaluated.
- Findings are limited to patients without chronic kidney disease.

Introduction

Although respiratory failure and diffuse inflammatory lung tissue damage are key features of coronavirus disease 2019 (COVID-19), involvement of other organs such as the kidneys has been well documented. Pathologic autopsy examinations of COVID-19 kidneys have shown clusters of coronavirus-like particles in the tubular epithelium and podocytes, upregulation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor angiotensin-converting enzyme 2 and positive immunostaining with SARS-CoV-2 nucleoprotein antibodies.[1,2] Hemodynamic instability, systemic hypoxia, abnormal coagulation, and inflammation from severe COVID-19 can also directly contribute to acute kidney injury (AKI) and induce acute tubular necrosis.[3]

Various epidemiologic studies from China, Europe, and the United States have investigated AKI outcomes among COVID-19 patients. Early studies in China have reported AKI incidences ranging from 0.5-15% among hospitalized and outpatient COVID-19 patients.[4,5] One United Kingdom study found hospitalized COVID-19 patients with AKI had a 3-fold higher odds of death than those without AKI.[6] Large US population studies of hospitalized COVID-19 patients, primarily in the New York City metropolitan area, have reported AKI incidences ranging from 27-57%, with in-hospital mortality rates ranging from 35-71% among AKI COVID-19 patients.[7–10] Some of these studies have also explored variable associations with COVID-19 AKI, but none of these studies have investigated which subset of these variables are most predictive of AKI or built risk predictions models using demographic variables and biomarkers.

Risk prediction tools have been investigated for COVID-19 deaths. A small number of a priori determined biomarkers were investigated for their associations with

the risk of COVID-19 death.[11] However, a more data driven approach would compare the predictive accuracies of these biomarkers to other biomarkers and variables such as demographic factors and vital signs and build a more powerful risk prediction model using a comprehensive set of biomarkers, demographic variables, and vital signs. Different risk factors should also be weighted differently, and understanding the relative importance of different variables in predicting poor outcomes will allow for more accurate holistic patient evaluations.

In this study we developed and evaluated new risk assessment tools that can be easily implemented at the bedside or during chart reviews to predict AKI and death after a positive COVID-19 test. Our contributions include (1) identifying the top biomarkers and demographic variables that predict AKI events among COVID-19 patients, (2) investigating a greater number of potential biomarkers and risk factors in predicting death, (3) developing clinical risk assessment tools for both AKI and death using a small number of predictors, and (4) validating that these tools are nearly as predictive as using all available study variables. By understanding which subset of risk factors are most important to focus on, medical providers can more efficiently work up and risk stratify their newly diagnosed COVID-19 patients.

Methods

Study Population

The Mass General Brigham (MGB) Health system serves a large diverse patient population around Boston and Eastern Massachusetts. Electronic health records from

three major hospitals in this system (Massachusetts General Hospital in Boston, Brigham and Women's Hospital in Boston, and Newton-Wellesley Hospital in Newton) were used. The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661.

We included all patients that 1) were at least 18 years old, 2) tested COVID-19 positive at one of the three hospitals above between February 1, 2020 through May 28, 2020, and 3) had at least 2 serum creatinine tests within 30 days of their SARS-Cov-2 PCR test. We excluded patients that 1) met the criteria of acute kidney injury within 3 months before their SARS-CoV-2 test and 2) had chronic kidney disease (CKD) identified as a preexisting condition from International Classification of Disease (ICD-9 and ICD-10) codes (see below).

Patient and Public Involvement

Patients and the public were not involved in the planning of this project.

Data Collection

Information in electronic health records (EHR) of patients who met the inclusion criteria were extracted from the enterprise data warehouse and included demographic, comorbidities, clinical, laboratory, and outcome data (death). Demographic and laboratory data information closest to the time of first SARS-Cov-2 PCR test were kept (except for serum creatinine, multiple values were kept). Serum creatinine laboratory

test results and timestamps within 3 months before and 30 days after the SARS-Cov-2 polymerase chain reaction test were extracted. We categorized ethnic groups other than White, Black, Hispanic, and Asian into a single subgroup. All documented comorbidity related medical history in MGB healthcare system enterprise data warehouse before the first time of SARS-Cov-2 test were extracted. Preexisting conditions, including hypertension, diabetes, cardiovascular disease, and heart failure, were classified using their ICD-9 or ICD-10 codes.

Definitions of Outcomes

Per the Kidney Disease Improving Global Outcomes (KDIGO) criteria, AKI was defined as a change in serum creatinine (SCr) of 0.3 mg/dl over a 48-hour period, a 50% increase in baseline creatinine in 7 days, or urine value <0.5 ml/kg/hour for 6 hours.[12] Due to difficulties obtaining accurate urine volumes from electronic health record data, we only use serum creatinine to define AKI events. If patients had more than 2 SCr tests in their EHR, we used all available SCr tests to define the earliest time. Death times were directly extracted from the data warehouse.

Statistical Analyses

Continuous variables were transformed into categorical variables to improve interpretability of results and account for nonlinear associations. Counts and percentages were presented, and two proportion z-tests were used to compare the proportion of deaths among AKI and non-AKI patients. For AKI survival analyses,

observations without AKI were censored after 30 days, at the time of death, or at 5/28/2020, whichever came first. For death survival analyses, observations without death were censored at 5/28/2020. Multiple multivariable Cox proportional hazards models included age, sex, race, diabetes, cardiovascular disease, hypertension, heart failure, body mass index (BMI), temperature, heart rate, systolic blood pressure, white blood cell count (WBC), hemoglobin, platelets, C-reactive protein (CRP), ferritin, D-and dimer. Respiratory rate and interleukin-6 (IL-6) variables were not included in primary analyses given missing data. However, we performed exploratory analyses imputing the missing respiratory rate and IL-6 values (additional details are in the sensitivity analysis section).

We next built a simplified Cox model for clinical use by using a stepwise variable selection procedure for Cox models alternating between “forward” and “backwards” steps to identify the first 5 variables to be included.[13] Simplified Cox models were fit using only the selected 5 variables and Harrell’s C-Statistics were obtained (survival outcome). Model coefficient (linear prediction) accuracy was evaluated. We evaluated area under receive operating characteristic (ROC) curves (AUC) for predicting AKI within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcome). Net reclassification improvement (NRI) of adding all remaining covariates was also calculated.

Risk scores were obtained by rounding simplified model coefficients for easier clinical risk assessment use. For suggested risk score cutoffs, Kaplan-Meier event curves were plotted, log rank tests were performed, and sensitivities, specificities, positive and negative likelihood ratios were calculated. Approximate pre-test to post-test

probability changes from likelihood ratios were calculated using the linear approximation proposed by McGee.[14] Cutoffs for low risk were chosen so that the negative likelihood ratio would be ≈0.20 with a pre- to post-test probability decrease of ≈30%, while cutoffs for high risk were chosen so that the positive likelihood ratio would be ≈5.0 with a pre- to post-test probability increase of ≈30% and that at least 15% of patients (560) would be identified as high risk.[14] We ran 1,000 internal cross validation iterations in which 70% of data were randomly assigned to training, the other 30% to testing. For each iteration, simplified Cox models were fit to the training data, coefficients were rounded to obtain risk scores, and AUC's were calculated using the predicted testing data risk scores.

We performed four sensitivity analyses. First, the multivariable cause-specific and subdistribution hazard to documented AKI events within 30 days accounting for the competing risk of death was modeled.[15] Second, we performed a multiple imputation analysis by creating 10 imputation datasets with imputed values for missing respiratory rate and IL-6 and then calculating pooled multivariable Cox hazard ratios.[16] Third, we investigated the AKI risk score accuracy in identifying stage 2 or 3 AKI as defined in the KDIGO criteria, and we investigated the death score accuracy among patients with stage 2 or 3 AKI.[12] Fourth, we investigated including mechanical ventilation (noninvasive and invasive) and lymphopenia defined as lymphocytes <800 cells/mm^3 as covariates for modeling AKI and death events. All analyses were performed with R version 4.0.4 and all code for analyses are available online (to be posted during revisions).

Results

Demographic and Clinical Characteristics

There were 3,716 eligible adult COVID-19 positive patients without CKD, of which 1,855 (49.9%) were male. The average age was 58.6 years (SD 19.2 years). There were 696 patients that developed AKI (18.7%) and 249 (35.8%) were within three days of a new COVID-19 diagnosis. There were 347 deaths (9.3%) and 322 (92.8%) were within thirty days of a new COVID-19 diagnosis. Among the AKI group there were 192 deaths (27.6%), and among the non-AKI group there were 155 deaths (5.1%, p<0.001). Patient demographics, preexisting conditions, vital signs, and laboratory values stratified by patients with AKI and patients that died are displayed in **Table 1**. Patients with AKI and patients that died were more likely to be older, male, have multiple comorbidities, and have on admission higher temperatures, lower systolic blood pressures, higher respiratory rates, elevated white blood cell counts, lower hemoglobin and platelets, and elevated CRP, ferritin, D-dimer, and IL-6 levels.

Fully Adjusted Multivariable Regression

Multivariable Cox regression was performed to identify risk factors associated with time to AKI and death. **Table 2** displays pooled multivariable adjusted hazard ratios. Adjusting for all other variables, older age, increased medical conditions, increased temperature, decreased systolic blood pressure, increased white blood cells, decreased platelets, and increased CRP and D-Dimer were associated with increased hazards for both AKI and death. Elevated BMI, decreased hemoglobin, and increased ferritin were associated with increased hazards for AKI but not death. Black and Asian

race were associated with decreased hazards and increased heart rate was associated with increased hazards for death but not AKI.

Top Risk Factor/Biomarker Selection

The top five variables selected for being most associated with AKI events were hemoglobin, D-dimer, CRP, WBC, and male sex. The top five variables most associated with death were age, CRP, platelets, WBC, and D-Dimer. **Table S1** shows model coefficients and Harrell's C-statistic (survival concordance) from the simplified model using just these selected variables. **Table S2** shows similar results for the fully adjusted model. The simplified AKI Cox model had a survival C-statistic of 0.785 (95% CI, 0.769 to 0.800), while the fully adjusted AKI Cox model had a C-statistic of 0.813 (95% CI, 0.798 to 0.827). The simplified death Cox model had a survival C-statistic of 0.857 (95% CI, 0.841 to 0.874), while the fully adjusted death Cox model had a C-statistic of 0.878 (95% CI, 0.863 to 0.892).

Cox model coefficients were used to predict AKI events within 3 days and death within 30 days of a new COVID-19 diagnosis (binary outcomes). **Table S1** and **Table S2** also displays AUC's for the simplified and fully adjusted coefficients respectively. For AKI in 3 days, using the simplified coefficients had an AUC of 0.787 (95% CI, 0.759 to 0.814), using the fully adjusted coefficients had an AUC of 0.820 (95% CI, 0.794 to 0.845), and the NRI was 0.041 (95% CI, 0.003 to 0.082). For death in 30 days, using the simplified coefficients had an AUC of 0.872 (95% CI, 0.854 to 0.890), the fully

adjusted coefficients had an AUC of 0.893 (95% CI, 0.878 to 0.909), and the NRI was 0.010 (95% CI, -0.007 to 0.029).

Risk Score

Model coefficients were rounded to obtain risk score component values for easier clinical use. **Table 3** shows the risk score and internal validation results. For AKI in 3 days, the risk score had an AUC 0.785 (95% CI, 0.758, 0.813) and a cross validation AUC of 0.776 (95% CI, 0.732, 0.816). For death in 30 days, the risk score had an AUC of 0.861 (95% CI, 0.843 to 0.878) and a cross validation AUC of 0.860 (95% CI, 0.831, 0.886). **Figure 1A** plots ROC curves for using fully adjusted coefficients (from **Table S2**) versus using risk scores (from **Table 3**) in predicting AKI in 3 days and death in 30 days.

Suggested risk stratification cutoffs were obtained. **Table S3** presents sensitivity, specificity, and positive and negative likelihood ratios for all possible risk score cutoffs. **Table 4** shows suggested risk stratification cutoffs and stratified observed and estimated event rates. Higher risk scores had higher observed and estimated AKI and death rates. **Figure 1B** plots Kaplan Meier event curves of AKI and death events by simplified risk score categories. Event rates different by risk category for AKI ($p<0.001$) and death ($p<0.001$).

Sensitivity Analysis

We performed a competing risk regression analysis for AKI and death within 30 days. **Table S4** displays the multivariable cause-specific and subdistribution hazard ratios for AKI events. Cause-specific and subdistribution hazard ratio estimates and confidence intervals were nearly identical. We also performed a multiple imputation analysis by imputing missing values for respiratory rate and IL-6 to evaluate their associations. **Table S5** shows that results were similar to non-imputation results, and increased respiratory rate and IL-6 were associated with increased hazards of AKI and death.

Of the 696 patients with an AKI event, 580 had a stage 1 AKI (83.3%), 29 had stage 2 (4.2%), and 87 had stage 3 (12.5%). Of the 117 patients with stage 2 or 3 AKI, there were 39 deaths (33.6%). In predicting stage 2 or 3 AKI as a single composite outcome among all 3,716 patients, the AKI risk score in **Table 3** had an AUC of 0.850 (95% CI, 0.819 to 0.881). In predicting death among the 117 patients with stage 2 or 3 AKI, the death risk score in **Table 3** had an AUC of 0.758 (95% CI, 0.671 to 0.846).

Of the 696 patients with an AKI event, 207 (29.7%) had lymphopenia with lymphocytes <800 cells/mm^3 and 328 (47.1%) had received mechanical ventilation. Of the 347 patients with a death event, 150 (43.2%) had lymphopenia and 124 (35.7%) had received mechanical ventilation. Of all 3,716 patients, 690 (18.6%) had lymphopenia and 449 (12.1%) had received mechanical ventilation. For AKI in 3 days, the fully adjusted coefficients in the primary analyses had an AUC of 0.820 (95% CI, 0.794 to 0.845) while additionally adding lymphopenia and mechanical ventilation only increased the AUC to 0.838 (95% CI, 0.814, 0.861). For death in 30 days, the fully adjusted coefficients had an AUC of 0.893 (95% CI, 0.878 to 0.909), while additionally

adding lymphopenia and mechanical ventilation only increased the AUC to 0.906 (95% CI, 0.893 to 0.920).

Discussion

In this retrospective study of over 3,700 adult patients without chronic kidney disease diagnosed with COVID-19 through May 2020 in the Boston area, we identified risk factors and biomarkers associated with AKI and death, and we developed and internally validated risk scores for predicting AKI and death. We found about one in five patients developed AKI and one in ten patients died. Increased age, male sex, increased white blood cells, C-reactive protein and D-Dimer and decreased hemoglobin and platelet levels were associated with AKI within 3 days and/or death within 30 days of a new COVID-19 diagnosis. A risk score using just these variables had similar internal accuracy as using all study variables. These results can assist in risk stratification of COVID-19 patients without CKD.

Many studies have found markedly increased COVID-19 fatality rates among older people. Studies from China, Spain, and Italy, and a meta-analysis of studies from 34 different geographical locations have all found increased case or infection fatality rates among people >60 and >65 years old compared to younger populations.[17–20] We similarly observed older age had some of the strongest associations with death. Earlier studies have found various physiologic changes among elderly patients that may contribute to this age-related risk, such as decreased small airway clearance, decreased number of cilia and ciliated cells, and decreased upper airway size.[21–23]

Other studies have also reported worse COVID-19 outcomes among men. A study of over 3,300 patients in Montefiore Medical Center found male sex was associated with AKI in both COVID-19 positive and negative patients.[8] This study also provided a more complete discussion of other animal studies and meta-analyses to date that that have found associations between male sex and AKI in general. Studies of COVID-19 outcomes from March 2020 in Italy and the US also reported increased hospitalization and intensive care unit admission rates among male patients.[24,25] We similarly observed that AKI patients (60.3%) and patients that died (58.2%) were more likely to be male (overall 49.9%). However, after adjusting for other demographics, medical conditions, vital signs, and laboratory values, we found male sex was associated with AKI but not death.

Among laboratory values, C-reactive protein, hemoglobin, white blood cells, D-Dimer, and platelets were significantly associated with AKI and death and were included in risk scores. Although there has been debate about a standard definition for COVID-19 cytokine storm syndrome, patients with C-reactive protein may have excessive immune activation, with C-reactive protein being produced by hepatocytes in response to IL-6 or ferritin.[26] Decreased hemoglobin may be reflective of kidney disease with decreased erythropoietin production or directly lead to decreased oxygenation of the kidneys. A study from Korea also found a higher risk of AKI in critically ill patients with a hemoglobin <10.5 g/dL.[27] Elevated white blood cell counts may suggest sepsis and be associated with life-threatening organ dysfunction.[28] Elevated D-Dimer levels may be indicative of a pro-thrombotic state, and a retrospective study from China found that D-Dimer >2000 ng/mL was associated with increased mortality.[29] However D-dimer levels

have also been reported to be elevated at baseline in CKD patients,[30] so it is possible elevated D-Dimer may only be prognostic in non-CKD patients. Low platelets may also indicate a systemic coagulopathic process that places patients at an increased risk for death.[28]

The biomarker IL-6 was found to be a significant risk factor in regression analyses. However, a substantial proportion of patients in our study were missing IL-6 values (78.3%), so IL-6 was not considered for risk score development. IL-6 measurements were obtained at physician discretion and were likely reserved for severe cases. This may have also contributed to the missingness profile of IL-6. Previous studies have found IL-6 cutoffs of 80 and 86 IU/mL to have prognostic value for predicting respiratory failure and death respectively.[31,32]

We proposed risk scores for identifying AKI within 3 days and death within 30 days of a new COVID-19 diagnosis along with suggested cutoffs. Although risk scores still need to be externally validated, being able to identify a few key biomarkers that are widely accessible can help focus chart reviews of new COVID-19 positive patients. Varying score weights further highlight biomarkers to focus on, such as hemoglobin and male sex for AKI, age and platelets for death, and WBC, CRP, and D-Dimer for both. Larger scores directly correlate with worse outcomes and can help shape physician gestalt.

We explored death being a competing risk for AKI events as patients with death will not have any more creatinine measurements. Although an AKI does not exclude the possibility of death, competing risk analyses can still be performed investigating which event type occurs first.[15] The cause-specific hazards ratios (Cox hazard ratios) describe

the rate of AKI events among those still alive and with no previous AKI events, while the subdistribution hazard ratios describes the overall rate of AKI events occurring before death. In our study both cause-specific and subdistribution hazard ratios were similar. Competing risk analyses were not performed for death events as having an AKI does not exclude death.

We looked at a subgroup of patients which developed stage 2 or 3 AKI. Our AKI risk score also performed well in identifying patients who developed stage 2 or 3 AKI, suggesting higher risk scores also correlate with developing a higher stage AKI. Among patients who developed stage 2 or 3 AKI, the death risk score AUC had a larger confidence interval likely because of the smaller sample size and smaller number of death events.

We explored including lymphopenia and mechanical ventilation as variables in analyses. Lymphopenia has been found to be associated with greater COVID-19 disease severity and poorer outcomes,[33] and hypoxemia requiring mechanical ventilation may affect kidney perfusion and also lead to poorer outcomes. We found that additionally including lymphopenia and mechanical ventilation to our study variables only led to small improvements in AUC in predicting AKI and death events. Nonetheless, we expect that patients who score high on our risk scores but also have lymphopenia and/or require mechanical ventilation will be at even greater risk of AKI and death events. Future work can further investigate including these variables into risk scores.

Limitations to our study include the following. All results are associational and no causal effects should be interpreted. Vital and signs and laboratory values were those

closest to COVID-19 diagnosis, and time-varying covariates were not incorporated into analyses. As the study was retrospective, selection bias cannot be excluded, and only events within the MGB system were recorded. Our identified risk factors and risk scores are most applicable during a patient's initial COVID-19 positive test. Results may not be generalizable to more specific subgroups such as those requiring intensive care admission. Patients in the Boston area may not be reflective of those in other healthcare systems, and the study population included only COVID-19 positive patients without CKD. The study population included patients in the first wave of COVID-19, and results should be cautiously applied to subsequent waves of COVID-19 due to differences in COVID-19 variants and treatment protocols. Future work may further stratify AKI events by stage and time of acquisition (relative to hospital admission), investigate outpatient, hospitalized, and critically ill patients separately, focus on CKD patients, validate results on a separate cohort, explore hospital specific effects, and include medication use such as renin-angiotensin-aldosterone system inhibitors.

We investigated AKI and death outcomes among adult COVID-19 patients without CKD in the Boston area. We identified risk factors and developed and evaluated risk assessment tools for identifying COVID-19 patients developing AKI and death. Hemoglobin, D-Dimer, CRP, WBC, and male sex were the strongest predictive biomarkers for AKI. Age, CRP, platelets, WBC, and D-Dimer were most predictive for death. Our study significantly contributes to epidemiological knowledge of COVID-19 outcomes and introduces simple tools to assist with rapid risk assessment.

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Availability of data and materials: Patient data is not available, but requests for surrogate data may be made to the corresponding authors. However, code for all analyses will be available at https://github.com/lin-lab.

Patient and public involvement: Patients and the public were not involved in the planning of this project.

Research ethics approval human subjects: The Mass General Brigham Institutional Review Board approved this study, and the approval number was 2020P001661. Only deidentified patient electronic health record data were used.

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Figure Legends

Fig. 1 Receiver Operating Characteristics and Kaplan Meier Event Curves Using Selected Variables.

(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.

(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

Table 1. Characteristics of Patients with Acute Kidney Injury, Patients that Died, and All Patients.

Variable, n (%)	**AKI** (n=696)	**Died** (n=347)	**Total** (n=3,716)
Age (years)			
<45	86 (12.4)	7 (2.0)	980 (26.4)
45-65	245 (35.2)	55 (15.9)	1,310 (35.3)
>65	365 (52.4)	285 (82.1)	1,426 (38.4)
Sex (Male)	420 (60.3)	202 (58.2)	1,855 (49.9)
Race			
White	407 (58.5)	242 (69.7)	2,091 (56.3)
Black	110 (15.8)	50 (14.4)	568 (15.3)
Hispanic	22 (3.2)	9 (2.6)	135 (3.6)
Asian	27 (3.9)	8 (2.3)	140 (3.8)
Other	130 (18.7)	38 (11.0)	782 (21.0)
Diabetes	197 (28.3)	87 (25.1)	727 (19.6)
Cardiovascular Disease	67 (9.6)	49 (14.1)	231 (6.2)
Hypertension	135 (19.4)	65 (18.7)	484 (13.0)
Heart Failure	39 (5.6)	38 (11.0)	134 (3.6)
Medical Conditions (number)			
0	397 (57.0)	189 (54.5)	2,565 (69.0)
1	190 (27.3)	95 (27.4)	811 (21.8)
2	83 (11.9)	47 (13.5)	264 (7.1)
3+	26 (3.7)	16 (4.6)	76 (2.0)
Body Mass Index (kg/m^2)			
<25	165 (23.7)	115 (33.1)	833 (22.4)
25-30	229 (32.9)	110 (31.7)	1,334 (35.9)
>30	302 (43.4)	122 (35.2)	1,549 (41.7)
Temperature (F)			
97-100.4	423 (60.8)	201 (57.9)	2,745 (73.9)
<97	35 (5.0)	22 (6.3)	190 (5.1)
>100.4	238 (34.2)	124 (35.7)	781 (21.0)
Heart Rate (beats/min)			
60-110	576 (82.8)	274 (79.0)	3,194 (86.0)
<60	61 (8.8)	30 (8.6)	275 (7.4)
>110	59 (8.5)	43 (12.4)	247 (6.6)
Systolic Blood Pressure (mmHg)			
90-180	635 (91.2)	305 (87.9)	3,549 (95.5)
<90	48 (6.9)	35 (10.1)	117 (3.1)
>180	13 (1.9)	7 (2.0)	50 (1.3)
Respiratory Rate (per minute)			

<20	245 (35.2)	92 (26.5)	1,692 (45.5)
>20	364 (52.3)	202 (58.2)	1,237 (33.3)
NA (Missing)	87 (12.5)	53 (15.3)	787 (21.2)
White Blood Cell (thousand cells/mm^3)			
3.5-11	428 (61.5)	189 (54.5)	2,942 (79.2)
<3.5	39 (5.6)	26 (7.5)	267 (7.2)
>11	229 (32.9)	132 (38.0)	507 (13.6)
Hemoglobin (g/dL)			
12+	201 (28.9)	138 (39.8)	2,250 (60.5)
10-12	204 (29.3)	88 (25.4)	883 (23.8)
<10	291 (41.8)	121 (34.9)	583 (15.7)
Platelets (per μL)			
>100	643 (92.4)	310 (89.3)	3,600 (96.9)
<100	53 (7.6)	37 (10.7)	116 (3.1)
C-Reactive Protein (mg/L)			
<50	197 (28.3)	62 (17.9)	1,706 (45.9)
50-100	149 (21.4)	63 (18.2)	1,011 (27.2)
>100	350 (50.3)	222 (64.0)	999 (26.9)
Ferritin (μg/L)			
<250	105 (15.1)	52 (15.0)	950 (25.6)
250-1000	327 (47.0)	155 (44.7)	1,894 (51.0)
>1000	264 (37.9)	140 (40.3)	872 (23.5)
D-Dimer (ng/mL)			
<1000	136 (19.5)	60 (17.3)	1,726 (46.4)
1000-2000	217 (31.2)	101 (29.1)	1,076 (29.0)
>2000	343 (49.3)	186 (53.6)	914 (24.6)
Interleukin-6 (IU/mL)			
<40	121 (17.4)	26 (7.5)	438 (11.8)
40-80	68 (9.8)	33 (9.5)	137 (3.7)
>80	136 (19.5)	58 (16.7)	196 (5.3)
NA (Missing)	371 (53.3)	230 (66.3)	2,945 (79.3)

AKI = acute kidney injury

Table 2. Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**5.33 (2.42, 11.8)**
>65	**2.16 (1.66, 2.80)**	**23.4 (10.9, 50.1)**
Sex (Male)	**1.51 (1.28, 1.77)**	1.16 (0.92, 1.45)
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	**0.66 (0.48, 0.92)**
Hispanic	0.89 (0.58, 1.38)	0.62 (0.32, 1.23)
Asian	0.96 (0.65, 1.43)	**0.46 (0.22, 0.93)**
Other	1.11 (0.90, 1.37)	0.72 (0.50, 1.02)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.07 (0.83, 1.38)**
2	**1.67 (1.30, 2.13)**	**1.40 (1.01, 1.95)**
3+	**1.82 (1.21, 2.75)**	**1.61 (0.95, 2.73)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	0.78 (0.59, 1.02)
>30	**1.42 (1.17, 1.74)**	0.94 (0.72, 1.22)
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.18 (0.75, 1.85)
>100.4	**1.59 (1.34, 1.88)**	**1.54 (1.22, 1.96)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	0.97 (0.66, 1.43)
>110	1.11 (0.85, 1.47)	**1.78 (1.28, 2.48)**
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**2.10 (1.45, 3.04)**
>180	0.96 (0.55, 1.67)	0.90 (0.42, 1.92)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	1.10 (0.72, 1.68)
>11	**1.77 (1.49, 2.12)**	**2.32 (1.82, 2.95)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	0.88 (0.67, 1.16)
<10	**3.72 (3.03, 4.57)**	1.03 (0.78, 1.35)

Platelets (per µL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**2.60 (1.79, 3.77)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	**1.46 (1.02, 2.10)**
>100	**1.57 (1.29, 1.91)**	**3.61 (2.65, 4.93)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	0.91 (0.65, 1.26)
>1000	**1.69 (1.31, 2.17)**	1.14 (0.80, 1.62)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	1.21 (0.87, 1.69)
>2000	**2.11 (1.68, 2.65)**	**1.82 (1.31, 2.52)**

1

Table 3. Risk Score and Internal Validation Results.

AKI in 3 days (max 6)		Death in 30 days (max 7)	
Risk Score			
Variable	**Value**	**Variable**	**Value**
Hemoglobin <10 g/dL	2	Age > 65 years	3
Hemoglobin 10-12 g/dL	1	Age 45-65 years	2
D-Dimer > 1,000 ng/mL	1	CRP > 100 mg/L	1
CRP > 100 mg/L	1	Platelets < 100 per µL	1
WBC > 11,000 cells/mm^3	1	WBC > 11,000 cells/mm^3	1
Male Sex	1	D-Dimer > 2,000 ng/mL	1
Internal Validation			
Validation Type	**AUC (95% intervals)**	**Validation Type**	**AUC (95% intervals)**
Whole Data	0.785 (0.758, 0.813)	Whole Data	0.861 (0.843, 0.878)
Cross Validation	0.776 (0.732, 0.816)	Cross Validation	0.860 (0.831, 0.886)

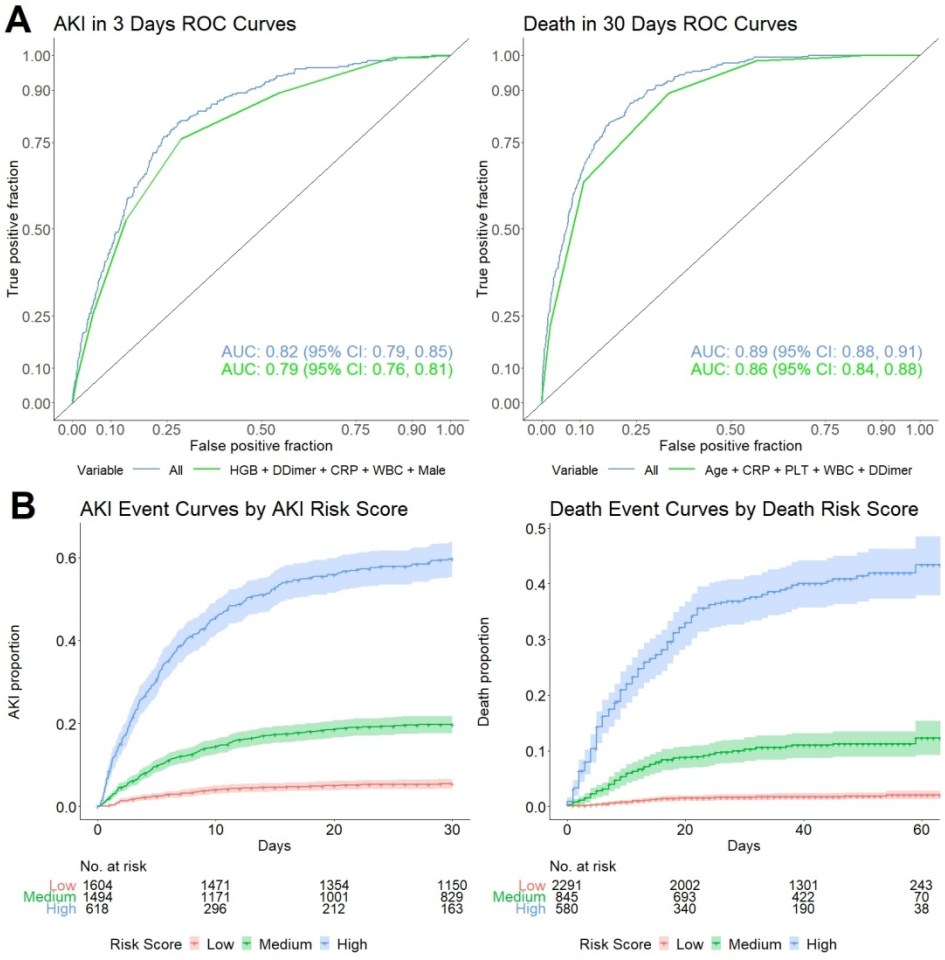
CRP = C-reactive protein, WBC = white blood cells.
Whole data validation presents area under the curve (AUC) estimates and 95% confidence intervals.
Internal cross validation presents mean AUC and 95% central interval (2.5th and 97.5th percentiles).

Table 4. Suggested Risk Stratification Cutoffs and Observed and Estimated Event Rates.

AKI Risk Score				
Risk Level	**Total Score**	**Observed Total AKI (%)**	**Estimated 3 Day AKI (%)**	**Estimated 30 Day AKI (%)**
Low Risk	0-1	5.2	1.7	5.4
Moderate Risk	2-3	18.4	6.2	19.7
High Risk	4-6	54.7	21.6	59.7
Death Risk Score				
Risk Level	**Total Score**	**Observed Total Death (%)**	**Estimated 30 Day Death (%)**	**Estimated 60 Day Death (%)**
Low Risk	0-3	1.7	1.6	2.0
Moderate Risk	4	10.4	10.2	12.3
High Risk	5-7	37.9	37.3	43.4

Observed percentages are from the observed data

Estimated percentages are from Kaplan-Meier event curves



(A) Receiver operating characteristic (ROC) curves for acute kidney injury (AKI) within 3 days and death within 30 days using fully adjusted model coefficients and developed risk score. Each line represents a different model's predictions with the given variables. HGB = Hemoglobin, CRP = C-reactive protein, WBC = white blood cell, PLT = Platelets.
(B) Kaplan-Meier event curves for AKI events and death events stratified by AKI and death scores. Time begins at positive COVID-19 test.

450x448mm (96 x 96 DPI)

Supplemental Methods – Additional Details

Statistical Analyses

Descriptive statistics and receiver operating characteristics (ROC) were calculated using R base functions. Cox proportional hazards models were fit using the "survival" package. Inspection of AKI and death Kaplan-Meier event curves stratified by each variable revealed no obvious violations of the proportional hazards assumption.

The variable selection procedure was implemented using the "My.stepwise" package. In addition to the variables included in fully adjusted Cox proportional hazards models, age >45 years, medical conditions >1, medical conditions >2, BMI > 25 kg/m^2, hemoglobin <12 g/dL, CRP > 500 mg/L, ferritin >250 µg/L, and D-Dimer > 1,000 ng/mL were also included. The package "glmnet" was used to reformat data so that the variable selection procedure could be applied. The selection procedure alternates between "forward" steps of adding variables and "backwards" steps of removing variables. The significance level for entry and for staying was conservatively set at 0.15 as suggested by function details. The top 5 variables (top 6 dummy variables) were included in risk scores. Simplified risk score values were obtained by rounding model coefficients to the nearest integer.

ROC curves were created using "plotROC" and AUC values and confidence intervals were obtained from "pROC". Event curves were created using "survminer" and "mstate". Harrell's C-statistics were obtained from Cox proportional hazards model output, and net reclassification of improvement was obtained from "nricens".

Competing risk analyses used the “cmprsk” package, and multiple imputation analyses used the “mice” package. The packages “ggplot2”, “dplyr”, “plyr”, “ggfortify”, and “cowplot” were used to process results and create figures. Code for replicating all analyses will be available online.

Table S1. Coefficients from simplified Cox regression models to calculated and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Simplified Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Hemoglobin <10 g/dL	1.50	Age > 65 years	3.19
Hemoglobin 10-12 g/dL	0.85	Age 45-65 years	1.65
D-Dimer > 1,000 ng/mL	0.76	CRP > 100 mg/L	1.21
CRP > 100 mg/L	0.64	Platelets < 100 per µL	1.20
WBC > 11,000 cells/mm^3	0.59	WBC > 11,000 cells/mm^3	0.87
Male Sex	0.54	D-Dimer > 2,000 ng/mL	0.58
Internal Validation			
Statistic	**Estimate (95% CI)**	**Statistic**	**Estimate (95% CI)**
Harrell's Survival C-Statistic (Concordance)	0.785 (0.769, 0.800)	Harrell's Survival C-Statistic (Concordance)	0.857 (0.841, 0.874)
AKI in 3 Days AUC	0.787 (0.759, 0.814)	Death in 30 Days AUC	0.872 (0.854, 0.890)

AKI = acute kidney injury, CRP = C-reactive protein, WBC = white blood cells, AUC = area under the curve, CI = confidence interval

Table S2. Coefficients from fully adjusted Cox regression models and internal validation statistics using these coefficient linear predictions.

AKI		Death	
Fully Adjusted Model Coefficients			
Variable	**Coefficient Value**	**Variable**	**Coefficient Value**
Age 45-65 years	0.54	Age 45-65 years	1.67
Age > 65 years	0.77	Age > 65 years	3.15
Male Sex	0.41	Male Sex	0.14
Race Black	-0.12	Race Black	-0.41
Race Hispanic	-0.12	Race Hispanic	-0.47
Race Asian	-0.04	Race Asian	-0.79
Race Other	0.11	Race Other	-0.33
Medical Conditions 1	0.25	Medical Conditions 1	0.07
Medical Conditions 2	0.51	Medical Conditions 2	0.34
Medical Conditions 3+	0.60	Medical Conditions 3+	0.48
BMI 25-30 kg/m^2	0.08	BMI 25-30 kg/m^2	-0.25
BMI >30 kg/m^2	0.35	BMI >30 kg/m^2	-0.06
Temp < 97 F	0.06	Temp < 97 F	0.16
Temp > 100.4 F	0.46	Temp > 100.4 F	0.43
Heart rate < 60 beats/min	0.22	Heart rate < 60 beats/min	-0.03
Heart rate < 110 beats/min	0.11	Heart rate < 110 beats/min	0.58
SBP < 90 mmHg	0.64	SBP < 90 mmHg	0.74
SBP > 180 mmHg	-0.04	SBP > 180 mmHg	-0.11
WBC < 3,500 cells/mm^3	-0.25	WBC < 3,500 cells/mm^3	0.09
WBC > 11,000 cells/mm^3	0.57	WBC > 11,000 cells/mm^3	0.84
Hemoglobin <10 g/dL	0.77	Hemoglobin <10 g/dL	-0.13
Hemoglobin 10-12 g/dL	1.31	Hemoglobin 10-12 g/dL	0.03
Platelets < 100 per µL	0.56	Platelets < 100 per µL	0.96
CRP 50-100 mg/L	-0.04	CRP 50-100 mg/L	0.38
CRP > 100 mg/L	0.45	CRP > 100 mg/L	1.28
Ferritin 250-1000 µg/L	0.26	Ferritin 250-1000 µg/L	-0.10
Ferritin >1000 µg/L	0.52	Ferritin >1000 µg/L	0.13
D-Dimer 1,000-2,000 ng/mL	0.51	D-Dimer 1,000-2,000 ng/mL	0.19
D-Dimer > 2,000 ng/mL	0.75	D-Dimer > 2,000 ng/mL	0.60
Internal Validation			

Statistic	Estimate (95% CI)	Statistic	Estimate (95% CI)
Harrell's Survival C-Statistic (Concordance)	0.813 (0.798, 0.827)	Harrell's Survival C-Statistic (Concordance)	0.878 (0.863, 0.892)
AKI in 3 Days AUC	0.820 (0.794, 0.845)	Death in 30 Days AUC	0.893 (0.878, 0.909)

Table S3. Sensitivity, specificity, and likelihood ratios (LR) for positive and negative results of risk scores predicting acute kidney injury (AKI) within 3 days and death within 30 days of a positive COVID-19 test.

Cutoff	Sensitivity	Specificity	Positive LR	Negative LR
Simplified AKI Risk Score (max 6)				
Rule in				
0	1.000	0.000	1.000	NA
1	0.992	0.154	1.170	0.050
2	0.892	0.455	1.640	0.240
3	0.759	0.713	2.640	0.340
4	0.526	0.860	3.750	0.550
5	0.257	0.946	4.770	0.790
6	0.068	0.989	6.400	0.940
7	0.000	1.000	NA	1.000
Simplified Death Risk Score (max 7)				
0	1.000	0.000	1.000	NA
1	1.000	0.156	1.190	0.000
2	0.994	0.233	1.300	0.030
3	0.984	0.433	1.740	0.040
4	0.891	0.665	2.660	0.160
5	0.637	0.890	5.760	0.410
6	0.224	0.978	10.400	0.790
7	0.019	1.000	Inf	0.980
8	0.000	1.000	NA	1.000

Cutoff denotes treating a score greater than or equal a cutoff value as a positive.
Positive likelihood ratio (LR) is sensitivity / (1-specificity)
Negative likelihood ratio (LR) is (1-sensitivity) / specificity
Sensitivity 1 specificity 0 indicates all individuals identified as positive
Sensitivity 0 specificity 1 indicates all individuals identified as negative
Approximate probability changes can be obtained by ≈0.18 * ln(LR) (McGee 2002)

Table S4. Multivariable AKI cause-specific hazard (AKI event, death censor) and AKI subdistribution hazard (AKI and death competing risks) model results.

Variable	Cause-Specific	Subdistribution
Age (years)		
<45	Reference	Reference
45-65	**1.71 (1.33, 2.21)**	**1.67 (1.31, 2.14)**
>65	**2.16 (1.66, 2.80)**	**1.92 (1.48, 2.50)**
Sex (Male)	**1.51 (1.28, 1.77)**	**1.53 (1.29, 1.81)**
Race		
White	Reference	Reference
Black	0.89 (0.72, 1.11)	0.91 (0.73, 1.14)
Hispanic	0.89 (0.58, 1.38)	0.96 (0.65, 1.41)
Asian	0.96 (0.65, 1.43)	0.97 (0.67, 1.41)
Other	1.11 (0.90, 1.37)	1.13 (0.91, 1.40)
Medical Conditions (number)		
0	Reference	Reference
1	**1.28 (1.07, 1.53)**	**1.27 (1.06, 1.53)**
2	**1.67 (1.30, 2.13)**	**1.66 (1.29, 2.12)**
3+	**1.82 (1.21, 2.75)**	**1.81 (1.18, 2.77)**
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.09 (0.89, 1.33)	1.11 (0.90, 1.38)
>30	**1.42 (1.17, 1.74)**	**1.47 (1.19, 1.81)**
Temperature (F)		
97-100.4	Reference	Reference
<97	1.07 (0.75, 1.51)	1.03 (0.71, 1.48)
>100.4	**1.59 (1.34, 1.88)**	**1.62 (1.37, 1.91)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.24 (0.95, 1.63)	1.30 (0.98, 1.72)
>110	1.11 (0.85, 1.47)	1.04 (0.78, 1.38)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.90 (1.41, 2.57)**	**1.73 (1.28, 2.35)**
>180	0.96 (0.55, 1.67)	1.00 (0.55, 1.84)
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.78 (0.55, 1.09)	0.79 (0.56, 1.12)
>11	**1.77 (1.49, 2.12)**	**1.68 (1.39, 2.04)**
Hemoglobin (g/dL)		
>12	Reference	Reference
10-12	**2.15 (1.75, 2.64)**	**2.27 (1.83, 2.81)**

<10	**3.72 (3.03, 4.57)**	**3.94 (3.17, 4.90)**
Platelets (per µL)		
>100	Reference	Reference
<100	**1.74 (1.30, 2.34)**	**1.63 (1.19, 2.24)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.96 (0.77, 1.20)	0.94 (0.76, 1.18)
>100	**1.57 (1.29, 1.91)**	**1.48 (1.20, 1.82)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	**1.29 (1.03, 1.63)**	**1.33 (1.05, 1.69)**
>1000	**1.69 (1.31, 2.17)**	**1.70 (1.31, 2.21)**
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.67 (1.33, 2.09)**	**1.70 (1.36, 2.13)**
>2000	**2.11 (1.68, 2.65)**	**2.07 (1.63, 2.63)**

Table S5. Multiple Imputation Multivariable Cox Regression Results.

Variable	AKI	Death
Age (years)		
<45	Reference	Reference
45-65	**1.58 (1.22, 2.04)**	**4.60 (2.07, 10.3)**
>65	**1.86 (1.43, 2.43)**	**18.3 (8.47, 39.6)**
Sex (Male)	**1.42 (1.20, 1.68)**	1.05 (0.83, 1.33)
Race		
White	Reference	Reference
Black	0.87 (0.69, 1.08)	**0.65 (0.47, 0.89)**
Hispanic	0.97 (0.63, 1.50)	0.66 (0.33, 1.32)
Asian	0.92 (0.61, 1.38)	**0.39 (0.19, 0.80)**
Other	1.05 (0.85, 1.30)	**0.67 (0.47, 0.96)**
Medical Conditions (number)		
0	Reference	Reference
1	**1.32 (1.10, 1.58)**	1.07 (0.82, 1.39)
2	**1.62 (1.25, 2.09)**	1.33 (0.94, 1.89)
3+	**1.88 (1.24, 2.87)**	1.62 (0.94, 2.79)
Body Mass Index (kg/m^2)		
<25	Reference	Reference
25-30	1.10 (0.90, 1.36)	0.81 (0.61, 1.07)
>30	**1.33 (1.09, 1.63)**	0.86 (0.65, 1.13)
Temperature (F)		
97-100.4	Reference	Reference
<97	0.95 (0.66, 1.36)	1.11 (0.69, 1.77)
>100.4	**1.40 (1.18, 1.66)**	**1.40 (1.09, 1.81)**
Heart Rate (beats/min)		
60-110	Reference	Reference
<60	1.13 (0.86, 1.48)	0.86 (0.58, 1.30)
>110	0.98 (0.74, 1.31)	1.41 (0.95, 2.08)
Systolic Blood Pressure (mmHg)		
90-180	Reference	Reference
<90	**1.74 (1.28, 2.37)**	**1.76 (1.19, 2.60)**
>180	1.22 (0.68, 2.19)	1.16 (0.52, 2.55)
Respiratory Rate (per minute)		
<20	Reference	Reference
>20	**1.72 (1.45, 2.03)**	**1.98 (1.53, 2.55)**
White Blood Cell (thousand cells/mm^3)		
3.5-11	Reference	Reference
<3.5	0.81 (0.58, 1.15)	1.25 (0.81, 1.95)
>11	**1.61 (1.34, 1.93)**	**1.95 (1.52, 2.51)**
Hemoglobin (g/dL)		

>12	Reference	Reference
10-12	**2.02 (1.64, 2.49)**	0.81 (0.60, 1.09)
<10	**3.31 (2.68, 4.08)**	0.86 (0.65, 1.14)
Platelets (per µL)		
>100	Reference	Reference
<100	**1.85 (1.37, 2.49)**	**2.51 (1.72, 3.68)**
C-Reactive Protein (mg/L)		
<50	Reference	Reference
50-100	0.99 (0.79, 1.24)	**1.60 (1.10, 2.33)**
>100	**1.47 (1.20, 1.80)**	**3.18 (2.32, 4.37)**
Ferritin (µg/L)		
<250	Reference	Reference
250-1000	1.18 (0.93, 1.50)	0.77 (0.54, 1.12)
>1000	**1.48 (1.14, 1.91)**	0.89 (0.60, 1.32)
D-Dimer (ng/mL)		
<1000	Reference	Reference
1000-2000	**1.59 (1.27, 2.00)**	1.16 (0.82, 1.63)
>2000	**2.03 (1.60, 2.57)**	**1.73 (1.23, 2.44)**
Interleukin-6 (IU/mL)		
<40	Reference	Reference
40-80	**1.39 (1.03, 1.86)**	**2.75 (1.80, 4.21)**
>80	**1.91 (1.50, 2.43)**	**3.07 (2.01, 4.69)**

Pooled hazard ratios calculated using 10 different imputation datasets with imputed values for missing respiratory rate and IL-6.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	7-8
		(*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.