Observational Study

Medicine

OPEN

Laboratory test trends within 72 hours of hospital admission associated with death among COVID-19 patients

Sarah Zambrano, MD[a], Megan Davis, MD[a], David R. Leeds, MD, MBA[a], Kelvin Noronha, MD[a], Angela McLaughlin, MD, MPHTM[b] , Rebecca H. Burns, MD[c], Elizabeth Mulvey, JD, MA[d], Benjamin P. Linas, MD, MPH[b,e], Sabrina A. Assoumou, MD, MPH[b,e,*]

Abstract

Early identification of patients at risk for severe coronavirus disease 2019 (COVID-19) is crucial for appropriate triage and determination of need for closer monitoring. Few studies have examined laboratory trends in COVID-19 infection and sought to quantify the degree to which laboratory values affect mortality. We conducted a retrospective cohort (n = 407) study of hospitalized patients with COVID-19 early in the course of the pandemic, from March 16th to April 8th, 2020 and compared baseline to repeat laboratory testing 72 hours into admission. The primary outcome was death. We found that rises of 25 mg/L C-reactive protein, 50 units/L lactate dehydrogenase, and 100 ng/mL ferritin were associated with 23%, 28%, and 1% increased odds of death, respectively. In contrast, changes in fibrinogen, D-dimer, white blood cell count, and creatinine in the first few days of hospital admission were not associated with mortality. These quantitative findings may assist clinicians in determining the risk of potential clinical decline in patients with COVID-19 and influence early management.

Abbreviations: BMC = Boston Medical Center, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, FiO_2 = fraction of inspired oxygen, ICU = intensive care unit, LDH = lactate dehydrogenase, ORs = odds ratios, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SpO_2 = peripheral capillary oxygen saturation.

Keywords: COVID-19, hospitalization, laboratory tests, mortality, prognosis

1. Introduction

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have improved outcomes in some high-income countries, coronavirus disease 2019 (COVID-19) continues to be responsible for many fatalities around the world.[1] Since the start of the pandemic, treatment strategies and new therapies have emerged, with the goal of preventing severe disease, allowing for earlier hospital discharge and increased outpatient management. Timely identification of hospitalized patients at risk for COVID-19-related death allows clinicians to better anticipate the clinical trajectory of hospitalized patients and identify individuals who may benefit from closer monitoring or early administration of COVID 19-related therapies such as tocilizumab or baricitinib.

Few studies have sought to understand the significance of laboratory trends over the course of COVID-19 infection. To our knowledge, no studies have explored both the laboratory value trends over time and quantified the degree to which specific laboratory values collected early in admission are associated with inpatient mortality. The current study sought to determine whether early changes in certain laboratory tests were associated with mortality among patients hospitalized with COVID-19 in a diverse urban hospitalized patient population. The study was conducted at the beginning of the pandemic, prior to the adoption of many current treatment strategies and provides insight into the natural trend of laboratory values in COVID-19 disease.

This work was supported by the National Institute of Drug Abuse [K23DA044085 to SAA] and a Boston University School of Medicine Department of Medicine Evans Career Investment and Evans Junior Faculty Merit Awards to SAA. AM is supported by BU-CHART (T32 AI052074).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This manuscript has not been previously presented or published and is not being considered at this time for publication in any other journal.

Supplemental Digital Content is available for this article.

[a] Boston University School of Medicine, Boston, MA, USA, [b] Department of Medicine, Section of Infectious Diseases, Boston Medical Center, Boston, MA, USA, [c] Department of Medicine, Boston Medical Center, Boston, MA, USA, [d] Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA, [e] Department of Medicine, Section of Infectious Diseases, Boston University School of Medicine, Boston, MA, USA.

** Correspondence: Sabrina A. Assoumou, Boston University School of Medicine, Boston Medical Center, Section of Infectious Diseases, 801 Massachusetts Ave., Crosstown Center, 2nd Floor, Boston, MA 02118, USA (e-mail: Sabrina.Assoumou@bmc.org).*

How to cite this article: Zambrano S, Davis M, Leeds DR, Noronha K, McLaughlin A, Burns RH, Mulvey E, Linas BP, Assoumou SA. Laboratory test trends within 72 hours of hospital admission associated with death among COVID-19 patients. Medicine 2022;101:50(e31154).

Received: 8 April 2022 / Received in final form: 7 September 2022 / Accepted: 14 September 2022

http://dx.doi.org/10.1097/MD.0000000000031154

2. Methods

2.1. Study design, site, population and inclusion criteria

We conducted a retrospective cohort study at Boston Medical Center (BMC), the largest safety net hospital in New England. Patients were included in the study if they were over the age of 18 and admitted to the hospital for COVID-19 between March 16th, 2020, and April 8th, 2020. The current timeframe was selected to include individuals admitted to BMC before the hospital protocol was revised on April 8th. On March 16th, the first patient with COVID-19 was admitted to BMC. On April 8th BMC's COVID-19 treatment protocol was revised. All patients had laboratory-confirmed SARS-CoV-2 using reverse transcription polymerase chain reaction performed at BMC. We excluded patients without SARS-CoV-2 test results in our system, those who were admitted for reasons unrelated to COVID-19, patients who incidentally tested positive for SARS-CoV-2, or individuals who developed COVID-19 during their hospital stay. All patients were followed to either discharge from the hospital or in-hospital death.

Patients were treated with standard supportive therapy during this time period. this time period. Additionally, the use of immunomodulatory therapy, under close monitory, was part of BMC's protocol early in the pandemic when there was little information on effective treatment for COVID-19.[2] During the study period, conditions for the administration of immunomodulators included elevated fraction of inspired oxygen (FiO_2) requirements of >45% and elevated inflammatory markers: CRP > 100 mg/L, ferritin > 700 ng/mL, or LDH > 450 U/L. Tocilizumab is now part of national guidelines for treatment of severe progressive COVID-19.[3] All statistical analyses were performed in R (R Core Team, 2020, Vienna, Austria).

2.2. Data collection

We extracted demographic information, patient medical histories and in-hospital clinical data from the electronic health records.

Patients' oxygenation statuses were estimated on arrival to better characterize clinical severity of respiratory illness. As blood gases were not routinely collected on arrival, we used the ratio of peripheral capillary oxygen saturation (SpO_2) to FiO_2. Previous literature has demonstrated that this ratio approximates the partial pressure of oxygen to FiO_2 ratio, which is commonly utilized to estimate severity of acute respiratory distress syndrome.[4] When patients were not mechanically ventilated or receiving noninvasive positive pressure ventilation, FiO_2 was calculated using the EPIC II Study "Estimating FiO_2" table.[5]

2.3. Primary outcome

The primary outcome was death during the hospital admission.

2.4. Statistical analyses

We used descriptive statistics to characterize the cohort and logistic regression to evaluate factors associated with death in a series of models. Each multivariate model included the change in one of seven laboratory tests over the first 72 hours after admission. In cases for which no laboratory data were available at 72 hours, we used data collected at 48 hours. If no laboratory data was available at 72 or 48 hours, we used data collected at 96 hours from admission. We selected laboratory tests that were part of the hospital's protocol for patients admitted with COVID-19 because of their possible effect on pathogenesis: C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, fibrinogen, white blood cell count, and creatinine. For each laboratory test, we identified units of change anticipated to be clinically significant based on expert consensus between two infectious diseases physicians and calculated the odds ratios (ORs) of death during the hospital admission. Statistical significance was prospectively determined to be a *P*-value of <.05. We performed chi-squared tests for categorical variables and *t*-tests for continuous variables.

In addition to controlling for the change in a particular laboratory test, we performed multivariate modeling to control for covariates including age, sex, race/ethnicity, SpO_2/FiO_2 ratio on admission, and the administration of at least one of three immunomodulators (anakinra, sarilumab, or tocilizumab).

2.5. Ethics and patient consent statement

The Boston University Medical Center Institutional Review Board approved this study. The IRB waived the requirement for written consent as the study did not include factors necessitating patient consent. This is a retrospective study of existing medical records and patient information was de-identified prior to analysis.

3. Results

3.1. Patient characteristics

Patient demographic characteristics, comorbidities, and outcomes are summarized in Table 1. Four hundred and seven patients met inclusion criteria (Fig. 1). At time of abstraction, all patients had either been discharged from the hospital (n = 370, 90.9%) or were deceased (n = 37, 9.1%). Notably, patients who died from COVID-19 infection were more likely male, older and have comorbid conditions including malignancy and pulmonary diseases such as chronic obstructive pulmonary disease, interstitial lung disease, pulmonary hypertension and asthma. Nonsurvivors were more likely than survivors to have had longer median length of stay, increased number of intensive care unit admissions, intubations and treatment with immunomodulators.

3.2. Laboratory results

Separate multivariable models controlling for age, sex, race/ethnicity, administration of immunomodulators during admission, and baseline SpO_2/FiO_2 demonstrated that three of the assessed laboratory tests measured at approximately 72 hours of hospital admission were associated with death during that admission. We determined that a rise of 25 mg/L in CRP around 72 hours of admission was associated with a 23% increase in the odds of mortality (OR, 1.23; 95% CI, 1.11-1.37; Table S1, Supplemental Digital Content, http://links.lww.com/MD/H633). Similarly, a 50 unit/L rise in LDH around 72 hours of admission resulted in a 28% increased odds of mortality (OR, 1.28; 95% CI, 1.14-1.46; Table S2, Supplemental Digital Content, http://links.lww.com/MD/H634). Furthermore, a 100 ng/mL increase in ferritin around 72 hours of admission was associated with a 1% increase in the odds of death (OR, 1.01; 95% CI, 1.00-1.03; Table S3, Supplemental Digital Content, http://links.lww.com/MD/H635). Changes in 0.1mg/dL of creatinine, 1000 cells/μL white blood cells, 100 ng/mL of D-dimer, and 100 mg/dL fibrinogen at 72 hours of hospital admission were not associated with increased odds of mortality (Tables S4-S7, Supplemental Digital Content, http://links.lww.com/MD/H636). Of note, over half of the patients had each laboratory test checked at 72 hours, although up to approximately one-third had at least one missing laboratory value (Table S8, Supplemental Digital Content, http://links.lww.com/MD/H637).

4. Discussion

In a retrospective cohort at an urban safety net hospital, we found that a 25 mg/L rise in CRP, a 50 units/L rise in LDH, and 100 ng/mL rise in ferritin were associated with a 23%, 28%

Table 1

Patient demographics and comorbidities by survival status (n = 407).

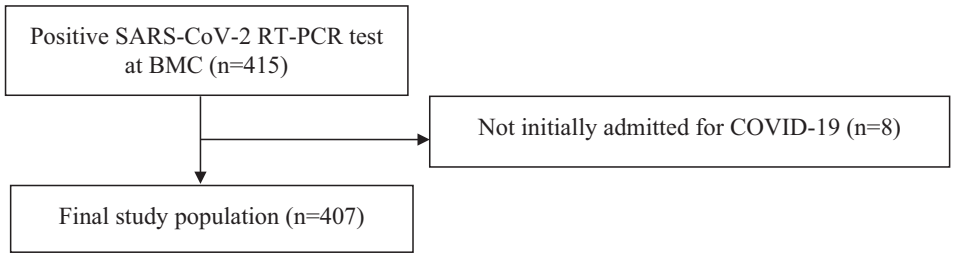
	Total = 407	n (%)	
	Survived n = 370 (90.9%)	Died n = 37 (9.1%)	*P*-value
Baseline characteristics			
Median age (IQR), years	56 (43-67)	68 (61 - 79)	**<.001***
Male sex - no. (%)	202 (54.6)	27 (73.0)	**.048***
Race/ethnicity - no. (%)			**.023***
Black	164 (44.3)	17 (45.9)	
Hispanic/Latinx	146 (39.5)	9 (24.3)	
White	26 (7.0)	8 (21.6)	
Asian	5 (1.4)	1 (2.7)	
Unknown	29 (7.8)	2 (5.4)	
Mean BMI - (SD)	32.6 (17.4)	30.6 (7.4)	.491
Diabetes - no. (%)	150 (40.5)	19 (51.4)	.272
CKD stage III-V - no. (%)	60 (16.2)	11 (29.7)	.066
Dialysis - no. (%)	23 (6.2)	3 (8.1)	.923
Malignancy - no. (%)	27 (7.3)	7 (18.9)	**.034***
Pulmonary diseasea - no.(%)	70 (18.9)	10 (27.0)	**.033***
Median admission SpO_2/FiO_2 (IQR)	457 (438- 467)	419 (278 - 457)	**<.001***
Outcomes of hospitalization			
Immunomodulator administered during admission - no. (%)	121 (32.7)	19 (51.4)	**.036***
Median length of stay (IQR), days	7 (4.0–10.8)	12 (7.0 - 18.0)	.001*
ICU admission - no. (%)	79 (21.4)	30 (81.1)	**<.001***
Intubated - no. (%)	48 (13.0)	27 (73.0)	**<.001***

BMI = body mass index; CKD = chronic kidney disease; ICU = intensive care unit; SpO_2/FiO_2 = oxygen saturation/fraction of inspired oxygen.

a Chronic obstructive pulmonary disease, interstitial lung disease, pulmonary hypertension, or asthma.

b Tocilizumab, sarilumab, or anakinra administered as COVID-19-directed therapy.

c Chi-squared tests were performed for categorical variables and *t*-tests were performed for continuous variables.



SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
RT-PCR: Reverse transcription polymerase chain reaction
BMC: Boston Medical Center
COVID-19: Coronavirus disease 2019

Figure 1. Study flow. BMC = Boston Medical Center, COVID-19 = coronavirus disease 2019, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

and 1% increase in odds of death, respectively, in hospitalized patients within 72 hours of admission. We did not find associations between mortality and increases in fibrinogen, D-dimer, creatinine, or white blood cell count within 72 hours of admission. Of note, additional longitudinal data would be needed to determine if there are further increases in mortality associated with rising CRP, LDH, and ferritin beyond 72 hours. As this study uses information from early in the pandemic, prior to the advent of many of the current treatment modalities, it provides insight into the natural history of laboratory trends in COVID-19 infection from the ancestral SARS CoV-2 virus before the development of variants of concern. Monitoring early trends in these key laboratory values may assist in the identification of hospitalized patients at high risk of mortality prior to the development of adverse outcomes, helping clinicians to triage and make timely management decisions.

Prior studies have focused on identifying certain comorbidities as clinical risk factors for severe COVID-19 disease and mortality.[6] Consistent with these studies, non-survivors in our cohort (9%) were more likely to be older, male, and with multiple comorbidities, although notably in our cohort there was no statistically significant difference in rates of diabetes or renal disease. Prior studies have also shown that baseline laboratory findings such as lymphopenia,[7–10] thrombocytopenia,[6,9,10] and elevations in CRP,[8] white blood cell count,[9,10] ferritin,[9] LDH,[11] and D-dimer[6,11,12] are associated with mortality from COVID-19. In addition, data from early in the pandemic showed different trends in laboratory values over time between COVID-19 survivors and non-survivors.[6,13] Specifically, it was noted that non-survivors had increasing values of D-dimer, IL-6, ferritin, cardiac troponin I, and LDH, and decreasing values of lymphocyte count and platelets over time.[6,14]

There are several limitations to this study. We are presenting associations between laboratory parameters and patient outcomes from a retrospective cohort at a single site urban hospital, which may limit the generalizability of our findings. Given that this study was performed early in the pandemic, we are not able to comment on the influence of newer treatments that are now included in the management of patients with COVID-19. Our center was an early adopter of immunomodulator therapies to treat COVID-19 infections. However, while administration of immunomodulators was standardized across the hospital, we do not have access to the exact timing of immunomodulator dosing and its impact on laboratory trends. In addition, as laboratory results were analyzed retrospectively, some laboratory data used within the models were collected beyond 72 hours of admission due to missing data. White blood cell count was not broken down into its components, including neutrophil and lymphocyte count to provide a general estimate for the influence of white blood cell count.[15] Marked lymphopenia has been associated with severe COVID-19 infection and future studies should investigate the influence of individual components of white blood cell count. Furthermore, missing laboratory data did not allow for the inclusion of some patients in all models. We cannot determine if individuals with missing data had different COVID-19 disease severity from those with complete data, although it is possible that patients with missing data were considered to be clinically improving by clinicians and so did not warrant repeated laboratory testing.

5. Conclusions

We found that increases in CRP, LDH, and ferritin within 72 hours of admission are associated with mortality in hospitalized COVID-19 infected patients, while changes in D-dimer, fibrinogen, creatinine, and white blood cell count are not. These findings can help to assist clinicians with determining which patients may need closer monitoring and additional intervention early in the hospital course. Future studies should confirm our findings using larger data sets and predictive modeling and additionally investigate the impact of newer therapies and variants on these laboratory trends.

Acknowledgements

The authors acknowledge the contributions of Kelly Drozdowicz, Alina Razak, and Wafaa Abbasi in the design of the data management tool. The authors also thank Annie Heyman, Preetha Velu, Erin Smith, Faizah Shareef, Janhavee Deshpande, Judy Wang, Nirupa Gadi, Aneesha Pydi, Nivedita Mandal, Tyler Ryan, Lauren Dzera, and Alina Razak for participating in chart review and data abstraction. We also would like to thank Dr Heather Hsu and Melissa Hofman from the BMC/BUMC clinical data warehouse Team. This work was supported by the National Institute of Drug Abuse [K23DA044085 to S.A.A] and a Boston University School of Medicine Department of Medicine Evans Career Investment and Evans Junior Faculty Merit Awards to SAA. The content is solely the responsibility of the authors and does not necessarily represent the official views of National Institutes of Health.

Author contributions

M.D., S.Z., D.L., and K.N. performed data abstraction, were involved in the analysis and interpretation of the data and drafted the initial manuscript. A.M. and R.B. were involved in the analysis and interpretation of the data and critically revised the manuscript. E.M. performed the analysis, interpretation of the data and critical review of the manuscript. S.A.A. designed the study, was involved in the analysis and interpretation of the data, and critically revised the manuscript. BPL was involved in the analysis and interpretation of the data, and critically revised the manuscript.

Conceptualization: Sabrina A. Assoumou.
Investigation: Sabrina A. Assoumou.
Data curation: David R. Leeds, Kelvin Noronha, Megan Davis, Sarah Zambrano.
Formal analysis: David R. Leeds, Elizabeth Mulvey, Kelvin Noronha, Megan Davis, Sarah Zambrano.
Methodology: Elizabeth Mulvey, Sabrina A. Assoumou.
Supervision: Sabrina A. Assoumou.
Validation: Elizabeth Mulvey.
Writing – original draft: David R. Leeds, Kelvin Noronha, Megan Davis, Sarah Zambrano.
Writing – review & editing: Angela McLaughlin, Benjamin P. Linas, Rebecca H. Burns, Sabrina A. Assoumou.

References

[1] World Health Organization. WHO Coronavirus disease 2019 (COVID-19) dashboard. Available at: https://covid19.who.int [Access date March 25, 2022].
[2] Sinha P, Mostaghim A, Bielick CG, et al. Early administration of interleukin-6 inhibitors for patients with severe COVID-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. Int J Infect Dis. 2020;99:28–33.
[3] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases society of America guidelines on the treatment and management of patients with COVID-19. 2021. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ [Access date June 8, 2022].
[4] Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the sequential organ failure assessment score. Crit Care Med. 2009;37:1317–21.
[5] Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323–9.
[6] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
[7] Castro VM, McCoy TH, Perlis RH. Laboratory findings associated with severe illness and mortality among hospitalized individuals with Coronavirus disease 2019 in Eastern Massachusetts. JAMA Netw Open. 2020;3:e2023934e2023934.
[8] Garibaldi BT, Fiksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19: a cohort study. Ann Intern Med. 2021;174:33–41.
[9] Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58:1021–8.
[10] Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110–8.
[11] Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020;7:e671–8.
[12] Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
[13] Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;384:20–30.
[14] Chen R, Sang L, Jiang M, et al. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020;146:89–100.
[15] Ghizlane EA, Manal M, Abderrahim EK, et al. Lymphopenia in Covid-19: a single center retrospective study of 589 cases. Ann Med Surg (Lond). 2021;69:102816.