Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Inflammatory markers are poorly predictive of clinical outcomes among hospitalized patients with COVID-19

Brendan Barrett a,b,⁎, Styve Pamphile a,b, Fan Yang a,b, Farnia Naeem c, Jinsung Kim d, Jayabhargav Annam d, Rachel Borczuk d, Shira Yellin d, Carly Bass d, Sabrina Fowler d, Maykl Mosheye d, Yael Jessica Mayer d, Benjamin W. Friedman a

a Department of Emergency Medicine, Albert Einstein College of Medicine, Montefiore Health System, Bronx, NY, USA
b Department of Emergency Medicine, Jacobi Medical Center, Bronx, NY, USA
c Department of Emergency Medicine, Mount Sinai Hospital, New York, NY, USA
d Albert Einstein College of Medicine, Bronx, NY, USA

Article history:
Received 6 August 2020
Received in revised form 12 November 2020
Accepted 17 November 2020

Keywords:
COVID-19
Inflammatory markers
Prognosis

Abstract

Background: Inflammatory markers are often elevated in patients with COVID-19. The objective of this study is to assess the prognostic capability of these tests in predicting clinical outcomes.

Methods: This was a retrospective cohort study including all patients at least 16 years old with COVID-19 who were admitted from one of five Emergency Departments between March 6th and April 4th, 2020. We included 1123 laboratory-confirmed cases of COVID-19. We analyzed white blood cell count (WBC), absolute lymphocyte count (ALC), lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, ferritin, and erythrocyte sedimentation rate (ESR). We looked at clinical outcomes including death, the need for endotracheal intubation (ETT), the need for renal replacement therapy (RRT), and ICU admission. We report Spearman’s ρ² and statistical significance for each correlation with outcomes. We also report positive predictive value, negative predictive value, sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios.

Results: The mean age of our patient population was 62 (SD 16). Thirty-seven percent of patients self-reported Spanish/Hispanic/Latino ethnicity, 47% reported their race as Black or African-American, and 10% reported their race as non-Hispanic white. Inter-rater reliability was 96%. There was no laboratory value that had both sensitivity and specificity of at least 0.90, or that had a positive predictive value and negative predictive value of at least 0.90, or that had likelihood ratios that could reliably predict a severe course of disease.

Conclusion: Inflammatory markers drawn within 48 h of arrival, though often correlated with clinical outcomes, are not individually highly predictive of which patients in a predominantly older and minority population will die or require intubation, RRT, or ICU admission.

© 2020 Elsevier Inc. All rights reserved.

1. Introduction

Inflammatory markers are often elevated in patients with COVID-19, notably C-reactive protein (CRP), D-dimer, procalcitonin (PCT), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and ferritin. Multiple prior studies have found correlations between various biomarkers and clinical outcomes in patients with COVID-19 [1–7]. However, the clinical utility of these various biomarkers for risk-stratification and determining prognosis among patients with COVID-19 is evolving and still ill-defined. The objective of this study is to determine the prognostic capability of laboratory tests in predicting clinical outcomes among a diverse population of ED patients with COVID-19.

2. Methods

This was a retrospective review of the electronic health records (EHR) of five hospitals in one of the most socio-economically depressed urban counties in the US. These five hospitals included a quaternary referral center, two community hospitals, a pediatric hospital, and a free-standing Emergency Department. The majority of the patient population of these hospitals is Hispanic and/or African-American. The Institutional Review Board reviewed and approved this protocol, and waived informed consent.

We screened all patients tested for COVID-19 before March 29th, 2020 who were admitted to the hospital within 1 week of that test. Patients were included in the study if they were admitted to the hospital before April 5th, 2020. We included patients aged 16 years and above who tested positive on reverse transcriptase polymerase chain reaction...
(PCR) assays performed on nasopharyngeal specimens. We completed EHR review on Sept 24th, 2020.

2.1. Outcome variables

We used both automatic and manual data abstraction. We abstracted data automatically using Clinical Looking Glass (CLG), a proprietary search and abstraction program (see Supplement for more detail). For data not amenable to automatic search, the authors manually abstracted data. We standardized manual data abstraction by conducting training sessions for all data abstractors and providing periodic feedback on randomly selected cases.

Clinical outcomes included death, the need for endotracheal intubation (ETT), the need for renal replacement therapy (RRT), and admission to the intensive care unit (ICU). Death was automatically determined from the discharge code in the EHR; the other variables were manually abstracted from the EHR. RRT included hemo- and peritoneal dialysis as well as continuous veno-venous hemofiltration. A separate reviewer abstracted data from an overlapping 10% of charts, which were randomly selected.

2.2. Predictor variables

We obtained the following laboratory values: white blood cell count (WBC), absolute lymphocyte count (ALC), lactate dehydrogenase (LDH), C-reactive protein, procalcitonin, D-dimer, ferritin, and erythrocyte sedimentation rate (ESR). The first lab value drawn within 48 h of arrival to the ED was recorded. If the laboratory test was not drawn within 48 h of ED arrival, we considered the data to be missing. As with the outcome variables, a separate reviewer obtained laboratory values from a randomly selected 10% of charts.

We also recorded the following information: age, sex, and race and ethnicity, all determined by patient self-report and automatically abstracted by Clinical Looking Glass. We reported sociodemographic variables as mean with standard deviation (SD) or n/N (%), as appropriate.

2.3. Analysis

To determine the association between laboratory values and outcomes, we assessed correlation using Spearman’s $\rho$, and reported $\rho^2$ along with significant $p$ values. A $p$ value <0.05 was considered statistically significant. We also reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio for laboratory values and clinical outcomes. For these latter analyses, laboratory values were dichotomized at the upper limit of normal, based on standard laboratory cutoffs used at all hospital sites during data collection (Table 2).

3. Results

Between March 6, 2020 and April 4, 2020, 1698 patients were admitted to one of the participating hospitals and had a COVID-19 test performed. Of these, 1123 were included with laboratory-confirmed COVID-19 (Fig. 1). The weighted and non-weighted averages of inter-rater reliability were both 96%.

The mean age of our patient population was 62 (SD 16) with 532 (47%) identifying themselves as female. Of the 1123 patients, 373 (37%) identified themselves as Hispanic, 478 (47%) as African-American, and 101 (10%) as non-Hispanic white (Table 1).

Of the entire cohort, as of the end of data collection on Sept 24th, 2020, 305/1123 (27%) died, 269/1123 (24%) were intubated, 161/1123 (14%) required RRT, and 199/1123 (17%) were admitted to the ICU. A total of 438 patients (39%) experienced at least one of these outcomes. Table 2 lists the laboratory value thresholds, the N for each laboratory value, the range, the mean, the standard deviation, and the percent of each laboratory test that was outside the reference threshold. Only the WBC count and procalcitonin had a majority of results fall within the reference threshold. A majority of the patients in the study had abnormalities in ALC, LDH, CRP, D-dimer, ferritin, and ESR on presentation. Graphs of the distribution of each laboratory test can be found in the Supplement.

We listed correlations between laboratory tests and clinical outcomes in Table 3. The correlations were not strong, despite the majority of correlations achieving statistical significance. However, ESR and ferritin were not significantly correlated with any clinical outcomes, which may be related to these laboratory values only being available in 10% and 18%, respectively, of the study population.

We computed sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for correlations with $\rho^2 > 0.10$ in Table 4. All test characteristics for correlations with $\rho^2 < 0.10$ are available in the Supplement.

---

Table 1
Sociodemographic features and medical history of the cohort.

| Patient characteristics | All patients (1123) |
|-------------------------|---------------------|
| Mean age (±SD)          | 62 ± 16             |
| Mean BMI (±SD)          | 30.5 ± 7.4          |
| Female                  | 515 (46%)           |
| Nursing Home Resident   | 211 (19%)           |
| Ethnicity/Race          |                     |
| Hispanic                | 373 (33%)           |
| Black                   | 478 (47%)           |
| Asian                   | 25 (2%)             |
| Non-Hispanic White      | 101 (10%)           |
| Comorbidities           |                     |
| Diabetes                | 507 (45%)           |
| Hypertension            | 795 (71%)           |
| Hyperlipidemia          | 571 (51%)           |
| Asthma                  | 191 (17%)           |
| COPD                    | 126 (11%)           |
| CKD                     | 293 (26%)           |
| ESRD                    | 88 (8%)             |
| Coronary Artery Disease | 182 (16%)           |
| Chronic Heart Failure   | 153 (14%)           |
| History of Malignancy   | 156 (14%)           |
| Cirrhosis               | 20 (2%)             |
| Former smoker           | 355 (31%)           |
| Current smoker          | 56 (5%)             |
physician. Another potential source of bias is that our patients did not receive all of the same laboratory tests. It is therefore impossible to exclude the possibility that patients who initially appeared sicker received more tests.

The outcome variables (aside from death) may also be somewhat subjective; ICU placement during the peak of the pandemic was sometimes determined in part by bed availability. The need for intubation, especially among COVID-19 patients, is not a decision that every pair of clinicians would agree on every time. It may be that the decisions made by the clinicians were impacted by the very variables under study.

By including all patients who had a positive COVID test within 1 week of admission, we cannot exclude the possibility that some of these patients may have contracted COVID while in the hospital. Additionally, our data on laboratory values captures only a single moment in time; it is possible that following trends in laboratory values may correlate better with outcomes. Finally, we treat each laboratory value as independent, which does not account for the possibility that the relationship of one inflammatory marker to another could be informative.

In Table 4, we report only one negative predictive value >0.90, between PCT and the need for RRT. The highest likelihood ratio was 3.44 (2.54–4.67) for an elevated PCT predicting the need for intubation. There were no laboratory tests that had both sensitivity and specificity >0.90, or both PPV and NPV >0.90.

### 3.1. Limitations

As a retrospective review of an EHR, this study suffers from biases inherent to all retrospective studies, including incomplete, potentially inaccurate, or contradictory medical records. We attempted to minimize selection bias by including all patients admitted with a positive COVID test, although early limitations on COVID testing meant that there may be subjective; ICU placement during the peak of the pandemic was sometimes determined in part by bed availability. The need for intubation, especially among COVID-19 patients, is not a decision that every pair of clinicians would agree on every time. It may be that the decisions made by the clinicians were impacted by the very variables under study.

By including all patients who had a positive COVID test within 1 week of admission, we cannot exclude the possibility that some of these patients may have contracted COVID while in the hospital. Additionally, our data on laboratory values captures only a single moment in time; it is possible that following trends in laboratory values may correlate better with outcomes. Finally, we treat each laboratory value as independent, which does not account for the possibility that the relationship of one inflammatory marker to another could be informative.

### 4. Discussion

In this cohort of 1123 patients with COVID-19 infection, we calculated correlations between test characteristics of laboratory values and clinical outcomes. We were not surprised that many laboratory values correlated with clinical outcomes, but we were surprised that the correlations were not strong, and that we did not identify a more robust prognostic link between inflammatory markers and adverse outcomes, since SARS-CoV-2 infection is at times marked by a pro-inflammatory state that has been described as a cytokine storm [8]. As above, there was no one test that provided both sensitivity and specificity >0.90, or both PPV and NPV >0.90.

Other studies have investigated associations between laboratory values and various outcomes related to COVID [5–7,9–11]. As in our study, CRP has been previously associated with severe COVID-19 [12], and D-dimer with mortality [13]. Elevated CRP, PCT, D-dimer and ferritin were found in a meta-analysis of 5350 patients by Huang et al. [14] to be associated with a composite marker of poor outcomes. In a parallel to our data, however, the sensitivities and specificities for laboratory values in predicting clinical outcomes in Huang et al.’s meta-analysis never reached 90%.

In a meta-analysis by Soraya and Ulhaq [15], lymphocyte count (at a cutoff of 0.83 × 10^9 cells/L) was 72% sensitive and 96% specific for severe vs non-severe COVID (with severity defined as causing death, needling ICU admission, or mechanical ventilation), and D-dimer at a cutoff of 0.44 μg/mL was 91% sensitive and 95% specific for severe vs non-severe COVID. In our cohort, ALC’s highest value for either sensitivity or specificity was only 0.61. D-dimer in our study showed similar sensitivity as in Soraya and Ulhaq’s meta-analysis, but its specificity for outcomes only ranged from 0.14 to 0.15. Notably, their meta-analysis...
reported a high heterogeneity and studied a dissimilar population. Our population consisted largely of African-Americans and Hispanics living in a socioeconomically depressed urban area, with very high endemic rates of chronic conditions such as hypertension and diabetes. Our population was thus dissimilar even to other populations within our broad geographic region [16,17]. There is an urgent need to focus more attention on this vulnerable population.

There was a discordance between the mortality rate (27%) and the rate of ICU admission (17%), which is likely due to the fact that during the study period, many patients with very poor prognoses were admitted to the floor rather than the ICU in order to preserve critical care resources for those patients who might derive more benefit from an ICU stay.

An important caveat with PPVs and NPVs is that they are responsive to disease prevalence. In our population, 100% of patients had PCR-confirmed COVID-19. The sensitivities, specificities, and LRs should in theory not change based on disease prevalence.

Several laboratory values that did not have the strongest correlations with outcomes (CRP, D-dimer, ESR) were mostly abnormal in our population (84%, 87%, and 93%, respectively). Of the few patients who had normal levels of these laboratory values, even fewer had poor outcomes. Thus, in the Supplement, there are examples of high sensitivities, high negative predictive values, and low negative likelihood ratios for these laboratory tests, although they are paired with low specificities, low positive predictive values, and low positive likelihood ratios. It is therefore conceivable that normal levels of these biomarkers help exclude severe disease if a larger sample were studied. However, because the correlation of these laboratory values to outcomes was poor, and the sample size for these values was small, we cannot draw this conclusion from these data.

Despite many papers attempting to find a role for these inflammatory markers in COVID-19, and despite tantalizing correlations and isolated instances of impressive test characteristics, such findings have been difficult to replicate in different populations. It is possible that inflammatory markers may still be useful in future clinical decision rules, but we have not seen compelling evidence for this yet.

While the trend in these inflammatory markers or their relationship with the patient’s length of symptoms may provide prognostic utility that this paper does not address, the initial laboratory values that we studied did not appear to be individually both sensitive and specific for outcomes. Clinicians should continue to rely on the patient’s clinical status to guide management and disposition, and should not place undue emphasis on initial inflammatory markers that have only dubious prognostic value.

5. Conclusion

Laboratory values drawn within 48 h of Emergency Department presentation, though often correlated with clinical outcomes, are not individually highly predictive of which patients in a predominantly older and minority population will die or require endotracheal intubation, renal replacement therapy, or ICU admission.

Funding sources/disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Presentations

Presented at ACEP 2020 Research Forum, Abstract Presentation Session: Diagnostics, Oct 26, 2020.

CRediT authorship contribution statement

Brendan Barrett: Conceptualization, Supervision, Investigation, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. 

Soye Pambule: Conceptualization, Supervision, Investigation, Data curation, Writing - original draft.

Fan Yang: Formal analysis, Visualization, Investigation, Data curation, Writing - original draft, Writing - review & editing.

Farkia Naeem: Software, Resources.

Jinsung Kim: Investigation, Data curation.

Jayabhargav Annam: Investigation, Data curation.

Rachel Borczuk: Investigation, Data curation.

Shira Yellin: Investigation, Data curation.

Carly Bass: Investigation, Data curation.

Sabrina Fowler: Investigation, Data curation.

Maykl Mosheyev: Investigation, Data curation, Writing - original draft.

Yael Jessica Mayer: Investigation, Data curation.

Benjamin W. Friedman: Supervision, Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of competing interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2020.11.038.

References

[1] Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – a systematic review. Life Sci. 2020;254 117788.

[2] Chen W, Zheng K, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob. 2020;19(1):18.

[3] Potempa LA, Rajab IM, Hart PC, Bordon J, Fernandez-Botran R. Insights into the use of C-reactive protein as a diagnostic index of disease severity in COVID-19 infections. Am J Trop Med Hyg. 2020;103(2):361–3.

[4] Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81(2):e16–25.

[5] Punti G, Maccaferroni M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;1–11.

[6] Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis. 2020;96:467–74.

[7] Henry BM, Aggarwal G, Wong J, Benoit S, Vilkos J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med. 2020;38(9):1722–6.

[8] Coperchini F, Chiavoto L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:52–32.

[9] Zhang J, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. China Allergy. 2020;75(7):1730–41.

[10] Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1469–72.

[11] Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5).

[12] Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020;92(7):856–62.

[13] Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1324–9.

[14] Huang I, Pranata R, Liem MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 2020;14:1715346620937175.

[15] Soraya GV, Ullahk ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: an updated meta-analysis. Med Clin (Barc). 2020;155(4):143–51.

[16] Singer AJ, Morley EJ, Meyers K, Fernandes R, Rowe AL, Vicedo P, et al. Cohort of four thousand four hundred four persons under investigation for COVID-19 in a New York hospital and predictors of ICU care and ventilation. Ann Emerg Med. 2020;76(4):394–404.

[17] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372–4.