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Common hematological values predict unfavorable outcomes in hospitalized COVID-19 patients

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Keywords:
COVID-19
SARS-CoV-2
Complete blood cell (CBC) count
Mortality predictors
Critical illness

ABSTRACT

COVID-19 can range from asymptomatic to life-threatening. Early identification of patients who will develop severe disease is crucial. A number of scores and indexes have been developed to predict severity. However, most rely on measurements not readily available. We evaluated hematological and biochemical markers taken on admission and determined how predictive they were of development of critical illness or death. We observed that higher values of readily available tests, including neutrophil:lymphocyte ratio; derived neutrophil index; and troponin I were associated with a higher risk of death or critical care admission (P < 0.001). We show that common hematological tests can be helpful in determining early in the course of illness which patients are likely to develop severe forms, as well as allocating resources to those patients early, while avoiding overuse of limited resources in patients with reduced risk of progression to severe disease.

1. Introduction

In December of 2019 in Wuhan, China, a respiratory illness caused by a new coronavirus (SARS-CoV-2) was described, giving place to a new syndrome known as COVID-19 (COronaVIrus Disease 2019) [1], spreading rapidly and reaching pandemic dimensions by March 2020 [2]. As of 1 January 2021, at least 81.9 million cases of (and 1.9 million deaths attributed to) COVID-19 had been reported globally [2]. In Mexico, 1.4 million confirmed cases and 126,851 deaths attributed to COVID-19 have occurred [3]. Most cases of COVID-19 are mild and self-limited, but progression to respiratory failure and death occur in up to a third of hospitalized patients [4,5].

COVID-19 has strained healthcare availability, particularly in the developing world and underserved areas, pushing resources to the brink of saturation. A number of tests and stratifying scores have been proposed; however, most rely on laboratory tests that are not readily available in non-academic settings. Moreover, there is no consensus on which can predict unfavorable outcomes early after hospital admission [6]. In that context, inexpensive and readily available tools to predict progression are crucial for clinical decision-making and allocation of limited resources. We aimed to evaluate the usefulness of blood biomarkers taken at the time of hospital admission as early predictors of

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https://doi.org/10.1016/j.clim.2021.108682
Received 12 January 2021; Received in revised form 26 January 2021; Accepted 28 January 2021
Available online 4 February 2021
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2.1. Study design

An ambispective cohort study evaluating the strength of prediction by laboratory variables of unfavorable outcomes among hospital-admitted COVID-19 patients.
information shown hereby.

2.3. Ethics and data management

The study was approved by the Institutional Review Board (NER-3632-21-21-1). All data was de-identified, such that data analyses used only individual identifier codes for each patient. All authors had access to the complete dataset.

2.4. Study definitions and outcomes

We included every admitted patient between 21 March and 30 April 2020 that had a positive SARS-CoV-2 RT-PCR test. Thereafter, outcomes were updated up to 15 May. The primary outcome was a composite of the following: 1) mechanical ventilation; 2) admission to a critical care area; or, 3) death (whichever occurred first). Clinical and demographic variables registered on admission included: age; sex; dates of symptom onset and hospital arrival; vital signs (heart rate, temperature, respiratory rate, blood pressure, and oxygen saturation); presence of dyspnea, chest pain, and cough; body mass index (BMI); past medical history of diabetes and hypertension; percentage of lung parenchyma affected by chest pain, and cough; body mass index (BMI); past medical history of diabetes and hypertension; percentage of lung parenchyma affected by CT scan as reported by the Department of Radiology [7,8]. For analysis, inflammatory hematological indexes were calculated with values obtained from CBCs, including: absolute neutrophil count (cells/mm³); absolute lymphocyte count (cells/mm³); neutrophil:lymphocyte ratio (NLR: absolute neutrophil count/absolute lymphocyte count); derived-neutrophil index (absolute neutrophil count/total white blood cell count – absolute neutrophil count); and platelet:lymphocyte ratio (absolute platelet count/absolute lymphocyte count). We also included D-dimer, ferritin, LDH, CRP, CK, and troponin I. All were treated as continuous variables.

2.5. Statistical analyses

We calculated crude incidence of the primary outcome, as well as of its composite parts. Standardized differences were calculated for clinical and laboratory variables between patients that had a primary outcome and those who did not.

We used a multivariate Cox proportional hazards’ model with each of the laboratory variables to estimate the hazard ratio of the primary outcome. All Cox models were adjusted for age, sex, BMI, presence of diabetes, presence of hypertension, and oxygen saturation at hospital arrival, as we hypothesized these were the variables that could have a causal effect or be surrogates of causal variables on the measured laboratory values. Pneumonia severity scores were not included in the risk models as most include variables that we are already controlled for. Laboratory variables were not adjusted for each other. Cubic splines with three nodes were used to transform laboratory continuous variables and include them in each model. We did not input missing data and thus each model had a slightly different number of patients included. A P value ≤ 0.05 was considered significant.

Data analysis was performed with R software version 4.0.0. The script used for the analysis is available at https://github.com/isaac-nunez/ncov19.

3. Results

Two hundred and eighty-two patients were hospitalized with a diagnosis of COVID-19 during the study period. Clinical, demographic and laboratory characteristics are described in Table 1. All patients had symptoms on arrival to the Emergency Room. Patients who developed the primary outcome were significantly older and had a higher BMI, but had no differences in prevalence of diabetes or hypertension. Dyspnea, cough, and chest pain were also more common among patients who developed an outcome. Respiratory rate and other vital signs were also modestly higher in the outcome group. Oxygen saturation was lower

| Variable | Univariate cox model (HR, 95% CI) | Multivariate cox model (HR, 95% CI) |
|----------|----------------------------------|------------------------------------|
| Neutrophil:lymphocyte ratio |  | |
| 2.5 | 0.59 (0.36–0.98) | 0.66 (0.38–1.14) |
| 5 | 1 (ref) | 1 (ref) |
| 10 | 1.79 (1.26–2.54) | 1.6 (1.07–2.38) |
| 15 | 1.96 (1.34–2.88) | 1.75 (1.13–2.73) |
| 20 | 1.96 (1.33–2.9) | 1.78 (1.15–2.76) |
| Derived neutrophil index |  | |
| 1 | 0.3 (0.14–0.64) | 0.43 (0.19–0.96) |
| 3 | 0.46 (0.38–0.56) | 0.54 (0.44–0.65) |
| 5 | 0.66 (0.51–0.85) | 0.66 (0.5–0.86) |
| 10 | 1 (ref) | 1 (ref) |
| 15 | 1.39 (0.82–2.35) | 1.48 (0.85–2.58) |
| Platelet:lymphocyte ratio |  | |
| 40 | 0.9 (0.44–1.86) | 1.08 (0.49–2.37) |
| 120 | 0.96 (0.73–1.26) | 1.03 (0.77–1.39) |
| 180 | 1 (ref) | 1 (ref) |
| 240 | 1.02 (0.83–1.27) | 0.98 (0.77–1.26) |
| 300 | 1.04 (0.78–1.38) | 0.98 (0.72–1.35) |
| Lymphocyte:monocyte ratio |  | |
| 0.5 | 1.63 (0.92–2.88) | 1.99 (1.08–3.7) |
| 1 | 1.26 (0.94–1.69) | 1.39 (1.01–1.91) |
| 1.5 | 1 (ref) | 1 (ref) |
| 2 | 0.89 (0.71–1.1) | 0.85 (0.69–1.06) |
| 2.5 | 0.91 (0.72–1.11) | 0.92 (0.74–1.13) |
| Total neutrophils (x10⁹/mm³) |  | |
| 2000 | 1.15 (0.48–2.72) | 1.71 (0.68–4.28) |
| 5000 | 1 (ref) | 1 (ref) |
| 10,000 | 1.15 (0.85–1.55) | 0.89 (0.64–1.24) |
| 15,000 | 1.79 (1.19–2.7) | 1.54 (0.97–2.44) |
| 20,000 | 2.81 (1.33–5.95) | 2.68 (1.18–6.06) |
| Total lymphocytes (x10⁹/mm³) |  | |
| 300 | 2.53 (1.48–4.3) | 2.96 (1.6–5.46) |
| 500 | 1.87 (1.31–2.66) | 2.07 (1.38–3.11) |
| 1000 | 1 (ref) | 1 (ref) |
| 1500 | 0.93 (0.78–1.1) | 0.97 (0.81–1.17) |
| 2000 | 1.22 (0.67–2.21) | 1.46 (0.82–2.6) |
| Creatine kinase (IU/L) |  | |
| 20 | 0.73 (0.5–1.07) | 0.81 (0.52–1.25) |
| 60 | 0.86 (0.7–1.07) | 0.9 (0.7–1.16) |
| 100 | 1 (ref) | 1 (ref) |
| 200 | 1.27 (0.97–1.68) | 1.17 (0.86–1.61) |
| 500 | 1.27 (0.86–1.87) | 1.1 (0.7–1.73) |
| Lactate dehydrogenase (U/L) |  | |
| 300 | 253 | 265 |
| 500 | 187 | 190 |
| 1000 | 1 | 1 |
| 1500 | 0.93 | 0.97 |
| 2000 | 1.22 | 1.46 |
| Ferritin (ng/mL) |  | |
| 100 | 0.94 (0.61–1.47) | 1.19 (0.69–2.06) |
| 200 | 0.96 (0.72–1.22) | 1.13 (0.77–1.67) |
| 400 | 0.99 (0.9–1.08) | 1.04 (0.94–1.16) |
| 500 | 1 (ref) | 1 (ref) |
| 1000 | 1.03 (0.78–1.37) | 0.91 (0.64–1.29) |
| C-reactive protein (mg/L) |  | |
| 0.5 | 0.74 (0.37–1.47) | 0.74 (0.37–1.47) |
| 1 | 0.75 (0.39–1.43) | 0.75 (0.4–1.42) |
| 10 | 1 (0.83–1.2) | 1 (0.83–1.2) |
| 20 | 1.26 (0.93–1.71) | 1.26 (0.93–1.71) |
| 30 | 1.51 (0.89–2.54) | 1.51 (0.89–2.55) |
| D-dimer (µg/mL) |  | |
| 200 | 1.06 (0.69–1.63) | 1.33 (0.78–2.25) |
| 500 | 1 (ref) | 1 (ref) |
| 2500 | 0.95 (0.66–1.39) | 0.62 (0.39–1.98) |

(continued on next page)
Among blood count values, total platelets, total leucocytes, total neutrophils, neutrophil-to-lymphocyte ratio, derived neutrophil index, and platelet-to-lymphocyte ratio were higher in the outcome group, while hemoglobin, total lymphocytes, total monocytes, and lymphocyte to monocyte ratio were lower in the outcome group. Inflammatory markers also were higher among those that developed an outcome. Of note, pneumonia score indexes were higher among patients who reached a primary outcome (Table 1).

All patients completed follow up by 15 May, with 80 (28.3%) developing a primary outcome, of which 66 were admitted to the ICU and 14 died without having been admitted to an ICU. Median time to primary outcome was five days (IQR 3–7). Two hundred (71%) patients were discharged from our center during the study period after a median of 9 days of hospitalization (IQR 7–12).

Univariate and multivariate Cox proportional hazard models are shown in Table 2. The adjusted models are also presented graphically in Fig. 1. Lower NLR, derived neutrophil index, LDH, and CRP, as well as higher total lymphocyte counts showed a protective hazard ratio of achieving the primary outcome.

4. Discussion

Several inflammatory markers have been evaluated as predictors of mortality among hospitalized patients with severe [9–12], as well as non-severe COVID-19 [13–15]. Circulating levels of cytokines and inflammatory biomarkers have been shown to successfully predict severity [16], but unfortunately these are not readily available outside of tertiary-care medical centers.

Here, we observed that NLR, the derived neutrophil ratio, lymphocyte-monocyte ratio, total neutrophil count, as well as total lymphocyte count successfully predict outcomes at the moment of hospital admission for COVID-19.

**Table 2 (continued)**

| Variable            | Univariate cox model (HR, 95% CI) | Multivariate cox model (HR, 95% CI) |
|---------------------|----------------------------------|------------------------------------|
| 5000                | 1.04 (0.73–1.49)                 | 0.67 (0.42–1.05)                   |
| 10,000              | 1.3 (0.9–1.89)                   | 0.82 (0.5–1.33)                    |
| Troponin I (ng/mL)  | n = 226                          | n = 220                            |
| 2                   | 0.56 (0.31–1.01)                 | 0.59 (0.29–1.21)                   |
| 5                   | 1 (ref)                          | 1 (ref)                            |
| 10                  | 1.95 (1.45–2.62)                 | 1.85 (1.28–2.66)                   |
| 15                  | 2.47 (1.58–3.85)                 | 2.28 (1.32–3.96)                   |
| 20                  | 2.56 (1.63–4.02)                 | 2.36 (1.35–4.12)                   |

*n = x, y* indicates the number of patients included in the univariate and multivariate model, respectively. These numbers differ in some cases because of missing values of the variables included in the multivariate model.

Fig. 1. Risk of ICU admission or death for hematological indexes and inflammatory markers (multivariate Cox models). *Adjusted for age, sex, BMI, hypertension, diabetes, and oxygen saturation at the moment of patient admission to the hospital. Abbreviation: NLR: neutrophil:lymphocyte ratio.
The NRL, lymphocyte-monocyte ratio, and platelet-lymphocyte ratio are thought to reflect physiologic stress. Stress leads to increased circulating cortisol, in turn triggering an increase in circulating neutrophils and a reduction in lymphocytes. Higher values of NRL, lymphocyte-monocyte ratio, and platelet-lymphocyte ratio are commonly seen in critically ill patients. If they are not specific to a particular disease, those indexes are not useful for diagnosing, but can guide in weighting the severity of a known an inflammatory illness [17–19].

NLR has been previously shown to predict in-hospital critical illness and mortality among COVID-19 patients [20–22]; NRL has also been incorporated into prediction scores of critical illness or mortality [12,23]. Lymphopenia has been described as a predictor of mortality in some models [24–26]; accordingly, we observed that lymphopenia is a good predictor of the primary outcome even in the absence of other laboratory biomarkers. To our knowledge, the utility of the derived neutrophil index, as well as the lymphocyte-monocyte ratio -two easily computed indexes obtainable from a simple and widely available CBC-have not been previously shown to predict unfavorable outcomes.

We observed that troponin I predicts worse outcome, probably reflecting myocardial injury. Myocardial injury has been linked to worse outcomes in other studies [26,27]. Nonetheless, troponin I measurement should be judicious and limited to patients that have clinical characteristics compatible with myocarditis. Interestingly, D-dimer showed a U-shaped curve with lower risk of outcome in the range of 1000–2000 μg/mL compared with lower and higher values. CRP and LDH were not associated with the development of primary outcomes, with the exception of the extremely high (but rarely observed) values.

We found a discrepancy between PaO2 and SaO2 with PaO2 being paradoxically higher in the primary outcome group, while SaO2 was higher in the group that did not develop an outcome. That may be explained by the moment in which those values were measured. Patients were frequently given supplementary O2 prior to the arterial blood gas analysis. A PaO2/FiO2 ratio analysis would be useful to confirm this, but unfortunately we lack accurate information on FiO2 values on admission. In our context, ambient air SaO2 is a more accurate value and thus is the one we included in the risk model.

Our study has limitations. First, it is partly retrospective. Also, we aimed to evaluate the usefulness of markers individually, and we did not incorporate them into a score with other laboratory values. Additionally, we lack information on treatment prior to hospital admission, which could have modified certain laboratory values. We are underpowered to determine if individual markers convey the same information. This would require an additional analysis, such as principal component analysis, which is beyond the scope of the present work.

This study also has strengths. Our sample is representative of Hispanic patients; also, ours is a public hospital; all patients had access to the best medical care regardless of their financial or insurance status. We had a very low rate of missing individual data; between-hospital transfers were exceedingly rare during the study period, such that if patients were discharged it is highly unlikely that they were sent to another hospital for critical care or further treatment. Also, discharges in general occurred after 72 h of in-hospital clinical stability, and while clinical worsening after discharge could be possible, it is unlikely. This kind of comparison allows for easier comparisons between patients that present different values of a certain variable.

In conclusion, here, we show that simple hematologic markers measured on admission to the Emergency Room can accurately predict progression to critical illness and mortality in hospitalized patients with COVID-19.

Acknowledgements

We would like to thank Dr. Reyniero Fagundo-Sierra for facilitating access to laboratory information. This work was supported by grants from CONACyT (Consejo Nacional de Ciencia y Tecnología) to SIIVF (289788 and 311783).
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