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Are there Biomarkers to Assess COVID-19 Severity?

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LETTER TO THE EDITOR

We read with interest the article by Ramos Rojas *et al*. about an observational, cross-sectional study of 308 patients with COVID-19 collected for two months at a single center in Peru [Ramos Rojas, M. C. *et al*., 2022]. The severity of COVID-19 has been found to correlate with high monocyte count, low lymphocyte count, high ferritin, and high C-reactive protein [Ramos Rojas, M. C. *et al*., 2022]. The study is stimulating but raises concerns that should be discussed.

A first limitation of the study is that it had a cross-sectional design [Ramos Rojas, M. C. *et al*., 2022]. Because biomarkers can change during disease progression, conclusions can vary significantly between time points at which biomarkers were determined. It would be interesting to know how the results and thus the value of the biomarkers changed each week during the hospital stay.

A second limitation of the study is that the influence of comorbidities on the biomarkers was not taken into account in the statistical analysis. Chronic disease can strongly influence the concentrations of biomarkers. The results may depend greatly on how many of the enrolled patients had a history of renal failure, chronic alcoholism, arterial hypertension, diabetes, heart failure, chronic immunological disorder, malignancy, and others.

A third limitation is that previous medications and treatments for COVID-19 during hospitalisation were not included in the assessment. Since many of the drugs used to treat COVID-19 can have severe side effects, that can also strongly affect the evaluated levels of biomarkers, it is crucial to include these drugs in the analysis. Severe side effects have been reported from chloroquine, tocilizumab, remdesivir, and glucocorticoids. Anticoagulants and low molecular weight heparins may strongly influence coagulation parameters. Anti-seizures drugs can increase liver or kidney function parameters.

A fourth limitation is that extra-pulmonary manifestations of COVID-19 were not considered in the analysis. Since the biomarker levels are highly dependent on the number of organs additionally affected by SARS-CoV-2, we should know how many of the patients manifested in organs other than the lungs. Of particular interest is how many of the included patients had neuro-COVID [Baig, A. M, 2022]. Increase of creatine-kinase may occur in patients with seizures. Patients with venous sinus thrombosis may have elevated D-dimer, and inflammatory parameters may increase in patients with encephalitis or meningitis. COVID-19 patients with myocarditis may have elevated levels of CK-MB, troponin, or pro-brain natriuretic peptide (proBNP).

A fifth limitation is that the choice of biomarkers was limited. Among the serological biomarkers, blood sedimentation rate, HbA1c, CK-MB, pro-BNP, immunoglobulins, and interleukins could be added to the examined panel. Biomarkers, such as blood pressure, ECG, X-ray of lungs, lung-CT, cerebral MRI, and EEG, were not considered to assess the severity of the infection.

A sixth limitation was that the study was carried out in a single center, which is why the results cannot be generalised.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could add value to the study. Serological biomarkers for assessing the severity of COVID-19 additionally depend on factors other than the infection. Serological biomarkers can only be of value in estimating the

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severity of COVID-19 if all influencing factors are taken into account.

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