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Letter to the Editor

Standard blood biomarkers are not reliable to distinguish vaccinated from unvaccinated COVID-19 patients

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We read with interest the article by Lagadinou *et al*. on a retrospective study on the difference in laboratory parameters between SARS-CoV-2 vaccinated (n=21, group-A) and unvaccinated patients (n=55, group-B) who have suffered a SARS-CoV-2 infection [1]. Evaluated parameters included total white blood cell count (WBC), absolute lymphocyte count (ALC), absolute monocyte count, D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, high-sensitive troponin, and the arterial oxygen partial pressure/fractional inspired oxygen (PO_2/FiO2) ratio [1]. LDH was lower in group-A compared to group-B and PO_2 was higher in group-A compared to group-B [1]. It was concluded that patients in group-B (unvaccinated) did not have higher levels of blood biomarkers such as ferritin, CRP or D-dimer, which have been shown to be associated with disease severity [1]. The study is excellent, but has limitations that are cause for concern and should be discussed.

The main limitation of the study is that blood parameters were chosen that depend not only on the presence or absence of infection but on several other influencing factors. For example, smoking can strongly affect WBC [2]. It is therefore important to know how many were smokers and how many were non-smokers. Leucocytosis may also be due to tissue necrosis, infarction, burns, arthritis, stress, overexertion, seizures, anxiety, anesthesia, trauma, splenectomy, hemolytic anemia, leukemia, myelodysplastic syndrome (MDS), or drugs (steroids, lithium, β-agonists). We should be told if all these differentials have been thoroughly ruled out. Since COVID-19 patients are often on steroids, we should know how many were on glucocorticoids treatment at the time of blood test.

Another limitation of the study is that group-A patients included both those who received a single anti-SARS-CoV-2 vaccination and those who received an anti-SARS-CoV-2 booster. Since the number of vaccinations can strongly influence the immunological fitness of a subject [3], the values of the blood biomarkers can depend heavily on the vaccination status.

Besides, the type of vaccine (mRNA or vector-based vaccine) and variations in the duration between the initial/booster dose to the blood test can influence certain blood parameters. For example, a second dose of mRNA vaccines (rather than the first or third doses) had the highest incidence of myocarditis (and probably high-sensitive troponin) when compared to the adenovirus-vectored vaccines [4].

Another limitation is that the current medications the patients were taking prior to hospitalisation and the medications patients were receiving during hospitalisation were not included in the analysis. Since several drugs can strongly influence the evaluated blood parameters, for example CRP [5], it is crucial to consider the current medication in the analysis. For example, both steroids and serotonin-reuptake inhibitors have an anti-inflammatory effect and thus reduced inflammatory markers [6].

A further limitation of the study is that the group sizes were small (group A (n=21)) making the conclusions unreliable.

Because blood biomarkers a highly dependent on the severity of COVID-19 infection, we should be informed of how many had sepsis, myocarditis, how many required non-invasive ventilation, mechanical ventilation, hemodialysis, and how many extracorporeal membrane oxygenation (ECMO).

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these limitations would strengthen the conclusions and could improve the study. Chemokines and cytokines as well as other immunological parameters are more important than the blood parameters examined in the index study. They reflect the severity of the SARS-CoV-2 infection and the immunological status of vaccinated subjects more adequately than the selected parameters. As long as group sizes are small and the cohorts of interest inhomogeneous in several aspects, a reliable comparison between vaccinated and non-vaccinated patients with regard to plasma biomarkers is not feasible.

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Guidelines: This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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