Editorial Note on Mendelian Randomization and COVID-19

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Abstract

Numerous observational studies have demonstrated a relationship between the various white blood cell counts, most frequently neutrophils, lymphocytes, and eosinophils, and the severity of COVID-19. Since the research' goal was to forecast the prognosis, a causal connection was not required. However, causality becomes crucial if we start considering these biomarkers as possible therapeutic targets. Randomized trials are not always practical, and observational studies cannot demonstrate a causal link. Mendelian randomization studies, which are thought to be more reliable than observational studies in this situation, could strengthen the claims of causation. The issue of causality is not resolved in this case because two Mendelian randomization studies that looked for a link between the variety of white cell populations and COVID-19 severity produced inconsistent findings.

Keywords: COVID19 • Mendelian randomization • Population • Basopenia

Introduction

Prior to the discovery of Omicron variants, COVID-19 was a disease with a significant mortality rate in people with severe forms. (respiratory failure). Numerous studies (the majority of which were retrospective) looked for prognostic variables in the laboratory or in the clinical setting (age and comorbidities). Studies revealed a strong correlation between white blood cell count and COVID-19 illness severity. The neutrophil-to-lymphocyte ratio emerged as an even better prognostic biomarker because the majority of studies that could link the white blood cells with a poor prognosis discovered that the patients with an elevated white blood cell count (mostly neutrophils) or a low count of lymphocytes were at a higher risk for a severe disease/death [1].

Eosinopenia was previously recognized as a sign of infection [2], and the majority of investigations [3] linked it to a severe COVID-19 disease. Regardless of severity, the majority of COVID-19 hospital patients were found to have some degree of eosinopenia at admission. In patients with a good prognosis, the eosinophil count started to recover during the first week, whereas in patients who passed away, eosinopenia persisted to the very end [4,5]. If the eosinophil count was zero, some studies even noted absolute or extreme eosinopenia. The cytokine storm emerged in patients with pulmonary involvement and severe disease, and it was accompanied by persistent lymphopenia and eosinopenia. A reduction in the number of basophils was only weakly correlated with disease severity in a few investigations on small samples.

At the start of the pandemic, diagnostic studies were also carried out in addition to these prognostic studies to more quickly differentiate patients infected with SARS-CoV-2 from those infected with other respiratory pathogens. Hematological parameters were evaluated as part of the diagnostic procedures, and the predictors for COVID-19 disease—lymphopenia, eosinopenia, and, in very rare cases, basopenia—were typically the same as for severe COVID-19.

The authors of the clinical studies were not particularly interested in a causal relationship because, in diagnostic or prognostic studies, we are interested in predicting, regardless of the presence or absence of confounding, even though at least some white blood cells were presumably involved in the pathogenesis of (severe) COVID-19 and other changes were only a result of inflammation. This changed, though, after Sun et al. made the decision to examine causal relationships and carried out a Mendelian randomization research.

In general, the more closely a relationship resembles the Bradford Hill criteria, the more causal it is. The study design is one of these factors that is most crucial. The least biased method for proving causation is the randomised experiment. Unfortunately, this experimental method is not always practical, particularly when considering the traits and role of white blood cells as a cause. Because of this, every study mentioned above was observational, and the majority of them were retroactive. Mendelian randomization studies are thought to be more valid than observational studies because they are situated just below randomised clinical studies and above cohort studies in the order of studies. Despite being called "randomized," they are not clinical or experimental studies because the researchers did not actually randomise the participants. These studies' central tenet is that all traits are at least partly influenced by genetic factors, and that our parents' genes are randomly transmitted to us when we are conceived. (There is random segregation of alleles). Additionally, the genes governing any potential confounder separately pass on the genes influencing one trait.

As in randomized clinical trials, the interference from other variables is therefore distributed equally among the groups. Additionally, because the genes are fixed at conception, the temporality criterion of causality will always be observed in these investigations.

However, there are three major presumptions that must be true for Mendelian randomization studies to be valid. The first is that there is a significant correlation between the genetic variant and the relevant risk factor (relevance presumption). (For example, the low number of basophils from the study by Sun). The majority of the time, this data comes from comprehensive Genome-Wide Association Studies (GWAS), which look for connections between genetic variations and a variety of traits and publish their findings in open databases.

The second presumption is that the associations between the genetic variation and outcome are independent of any unknown or unmeasured confounding factors and that the genetic variant is not related to any confounding variables. Otherwise, confounding would still exist, defeating the purpose of selection. In our illustration, we must be certain that the genetic variations linked to the low basophil count that causes severe COVID-19 are not also linked to other risk factors for severe COVID-19.

It is impossible to verify the absence of an association between an unknown confounder and the studied genetic variants, as is the case in observational studies, where it is only possible to account for the known/measured confounders, as this assumption is never guaranteed because we never know all the risk factors.

The third supposition states that there is no pleiotropy and that the genetic variants only affect the outcome in relation to the relevant risk factor (in our case, the genetic variants linked to severe COVID-19 are not caused by severe basopenia).

Although sophisticated methodology and statistics are available for this purpose, the other two assumptions cannot be verified with certainty, while the first premise can be tested in the GWAS. 50 studies using Mendelian randomization in the hunt for causal relationships between

various risk or prognostic factors for COVID-19 were discovered by a systematic review that searched for studies up until December 2021. Hematological traits were associated with a lower risk of COVID-19 severity and hospitalization, according to two studies that examined hematologic parameters as biomarkers for COVID-19 incidence and severity.

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