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Letter to the editor

Methodological Considerations for Assessing the Impact of Gastrointestinal Symptoms in Patients with COVID-19

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To the Editor:

I would like to extend my greetings to both the journal and the authors of the recent article titled "Morbidity and Mortality in COVID-19 Patients With and Without Gastrointestinal Symptoms." This observational cohort study of hospitalized patients at the Fundación Santa Fe de Bogotá evaluates whether gastrointestinal symptoms influence adverse outcomes in COVID-19, including mortality, ICU admission, mechanical ventilation, and bacterial coinfection. The authors conclude that gastrointestinal symptoms do not represent a progression risk but recommend including liver function markers in initial assessments due to their potential prognostic value.

However, analyzing gastrointestinal symptoms as a homogeneous group may limit the accuracy of conclusions regarding their impact on COVID-19 progression. Studies suggest that specific symptoms—such as diarrhea and abdominal pain—could have differential effects on disease course due to distinct pathophysiological mechanisms. Some research links both abdominal pain and diarrhea to an increased risk of severe COVID-19, while other studies associate diarrhea with better clinical outcomes[1-3]. These variations suggest that the relationship between gastrointestinal symptoms and COVID-19 severity may be complex and mediated by additional factors. Evaluating each symptom individually could identify specific associations with disease progression and improve risk stratification in patients—a key consideration for multisystemic infections like COVID-19.

Another relevant aspect is controlling for confounders in the relationship between liver markers and COVID-19 severity. The article suggests that elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and direct bilirubin levels are associated with higher rates of mechanical ventilation and ICU admission. However, liver dysfunction in COVID-19 patients may result not only from SARS-CoV-2 infection but also from potentially hepatotoxic medications such as lopinavir/ritonavir, remdesivir, or corticosteroids[4,5]. This warrants careful attention, as without proper adjustment for these confounders, it would be difficult to determine whether observed liver dysfunction is directly attributable to COVID-19 or to treatment side effects.

While the sample size of 414 patients is substantial, the subgroup with gastrointestinal symptoms (105 patients) may be insufficient to assess less frequent outcomes such as bacterial coinfection or mortality. This could limit the statistical power of the analyses and yield inconclusive results. Ensuring adequate sample sizes for each specific outcome

would produce more robust findings and prevent potentially relevant associations from being dismissed as insignificant.

Regarding mortality, the study concludes that it is not associated with gastrointestinal symptoms or liver markers. However, existing literature suggests a possible link between liver injury and adverse COVID-19 outcomes[4], particularly in patients with severe disease. Further exploration of discrepancies between this study's findings and others could help identify additional variables influencing mortality and clarify the role of liver function in COVID-19 prognosis.

Finally, while the study appropriately recommends using ALT, AST, and direct bilirubin levels in initial COVID-19 assessments, more specific guidance on how these markers could stratify clinical risk would benefit practice. A cutoff-based approach would facilitate interpretation and improve decision-making regarding ICU management, ventilation needs, and intensive monitoring.

I appreciate the opportunity to share these observations, which I hope may contribute to strengthening future research on COVID-19 and its multisystemic manifestations.

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Letter to the editor

Response to "Methodological Considerations for Assessing the Impact of Gastrointestinal Symptoms in Patients with COVID-19"

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Dear Editor,

Regarding Dr. Azañero-Haro's comments on our article "Morbidity and Mortality in COVID-19 Patients With and Without Gastrointestinal Symptoms," we, the authors, believe his analysis provides valuable considerations that enrich the scientific discussion on this topic.

Concerning the study period, it is important to clarify that our data were collected between March 2020 and September 2021—a time when understanding of COVID-19 and its multisystemic impact was still emerging. Although our article was published in 2024, the analysis was based on the information and management guidelines available during that earlier period. As we all know, the pandemic represented a dynamic clinical scenario in which evidence and therapeutic strategies evolved progressively as new studies and recommendations emerged[1,2].

We understand the author's concerns about liver function and its potential relationship with COVID-19 severity. At the time, altered liver markers were considered potentially relevant for prognosis[3,4]. However, the scientific community has since refined this interpretation, and it is now recognized that elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels may reflect a patient's clinical status without necessarily predicting outcomes.

Furthermore, COVID-19 management has changed substantially since the pandemic's onset[2]. During our cohort's data collection period, various therapeutic strategies were employed—some of which, such as certain antivirals or immunomodulators, are no longer part of standard treatment. This may have influenced the interpretation of results related to liver function. Current management has been simplified and focuses primarily on corticosteroids in selected cases, reinforcing the need to interpret our findings within their original temporal context[5].

Regarding sample size and statistical power, as is common in scientific research, our initial calculations were based on certain epidemiological and statistical assumptions whose validity could only be confirmed after data collection. Therefore, for outcomes with lower-than-expected frequency (such as mortality and bacterial coinfection), the analytical capacity—particularly statistical power—may have been affected. The knowledge-building process inherently involves refining such assumptions, and our study provides a valuable starting point for future research.

We appreciate this opportunity for academic exchange and reiterate the importance of continued investigation into COVID-19's multisystemic effects. Evidence in this field

continues to evolve, and future studies may address these questions with updated information and optimized methodological designs.

We thank Dr. Azañero-Haro for his comments and the editorial committee for allowing us to participate in this valuable discussion.

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