

PEER-REVIEW REPORT

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Title: Retrospective Analysis of Anti-Inflammatory Therapies During the First Wave of COVID-19 at a Community Hospital.

Reviewer's code: 05824934

Position: Peer Reviewer

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Scientific quality	[<input checked="" type="radio"/>] Grade A: Excellent [<input type="radio"/>] Grade B: Very good [<input type="radio"/>] Grade C: Good [<input type="radio"/>] Grade D: Fair [<input type="radio"/>] Grade E: Do not publish
Language quality	[<input checked="" type="radio"/>] Grade A: Priority publishing [<input type="radio"/>] Grade B: Minor language polishing [<input type="radio"/>] Grade C: A great deal of language polishing [<input type="radio"/>] Grade D: Rejection
Conclusion	[<input type="radio"/>] Accept (High priority) [<input type="radio"/>] Accept (General priority) [<input checked="" type="radio"/>] Minor revision [<input type="radio"/>] Major revision [<input type="radio"/>] Rejection
Re-review	[<input checked="" type="radio"/>] Yes [<input type="radio"/>] No
Peer-reviewer statements	Peer-Review: [<input type="radio"/>] Anonymous [<input checked="" type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No

SPECIFIC COMMENTS TO AUTHORS

Comments to “Retrospective Analysis of Anti-Inflammatory Therapies During the First Wave of COVID-19 at a Community Hospital” The hallmark of severe cases of COVID-19 is the hyper-inflammatory response of the immune system. This observational study investigated the use of anti-inflammatory medications glucocorticoid (GC) and tocilizumab in treating severe cases of COVID-19. The results show that patients’ survival was associated with GC intervention. The study presented in this manuscript is very interesting, and would be a considerable contribution to the global fighting against COVID-19 disease if it can be published. This review would be more compelling if the following minor revision points on the possible cause of hyper inflammation in the severe cases of COVID-19 could be included: 1) When we talk about microorganism infection, we need to take the human host immunity response into account. The human immune system emerged to manage the microorganisms inside and around human body for nutrition and against possible damage made by those microorganisms [1]. Because of the immune reactions like phagocytosis and xenophagy, most of infectious diseases caused by viruses (like this SARS-COV-2 virus) or bacteria are self-limiting [2-4]. This is why most of the COVID-19 cases are asymptomatic or mild [3, 4]. 2) Overnutrition has a dreadful effect on a person’s health and disease outcome. The damages made by the SARS-COV-2 virus to the human host cells before they are cleared by host immunity are determined by the virulence of SARS-COV-2 virus [4]. Yet, the virulence from SARS-CoV-2 virus alone doesn’t account for the virulence of the COVID-19 disease. Most part of the virulence of an infectious disease is actually the result of the inflammation response of our immune system [2, 4]. And nutrition disorder might be the main cause of hyper inflammation in severe cases of COVID-19. 3)

Inflammation is the immune response to tissue damage [5]. It is initially protective

for the removal of the injurious stimuli and damaged tissues as well as the initiation of tissue healing [5]. Yet, nutrition excess will disturb the tissue healing process. This is because, the nutrition from the degradation of the viruses and the damaged tissue together with the excessive nutrition already existed inside the body will be mostly turned into lipid intermediates and be deposited in healthy non-adipose tissues, causing lipotoxicity [9] and further tissue damage. Thus, over-nutrition will lead to a vicious cycle of excessive lean mass (like protein) broken down and lipid intermediates piling up, fuel excessive inflammation and lead to cytokine storm. There are two typos on page 10, line 339 and page 11, line 376: “NFK-beta” should be “TNF-alpha”. The following related references may be included in this review to provide a more complete picture on microbiome, infection, immunity and inflammation: Reference: 1. Levin BR, Antia R (2001) Why we don't get sick: The within-host population dynamics of bacterial infections. *Science*, 292:1112-1115. DOI: 10.1126/science.1058879 2. Levin BR, Baquero F, Ankomah P, McCall IC (2017) Phagocytes, Antibiotics, and Self-Limiting Bacterial Infections. *Trends in Microbiology*, 25(11):878-892. DOI: 10.1016/j.tim.2017.07.005 3.

Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Bruggen MC, O'Mahony L, Gao YD, Nadeau K, Akdis CA (2020) Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*, 75(7):1564-1581. DOI: 10.1111/all.14364 4. Troisi J, Venutolo G, Pujolassos Tanyà M, Delli Carri M, Landolfi A, Fasano A. (2021) COVID-19 and the gastrointestinal tract: Source of infection or merely a target of the inflammatory process following SARS-CoV-2 infection? *World J Gastroenterol*, 27(14): 1406-1418. DOI: 10.3748/wjg.v27.i14.1406 5. Costantini S, Sharma A and Colonna G (2011). *The Value of the Cytokine Profile, Inflammatory Diseases - A Modern Perspective*, Dr. Amit Nagal (Ed.), ISBN: 978-953-307-444-3, InTech, Available from:

<http://www.intechopen.com/books/inflammatory-diseases-a-modern-perspective/the>

-value-of-the-cytokinome-profile