Different death rates between COVID-19 waves among unvaccinated patients: moving beyond lessons learned

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Commentary

The COVID-19 pandemic has been one of the biggest global health crises faced in generations. Due to the unprecedented scale of ethical, organizational, and clinical challenges, medical communities around the world have been forced to work tirelessly to respond to the pandemic and important lessons have been learned in the process.

Leidi and colleagues in this issue of Internal and Emergency Medicine [1] confirm that COVID-19 waves are different in term of patients’ morbidity and mortality. In their paper, inpatient mortality was significantly higher (more than double) during the first wave than in the subsequent waves (24.2% vs. 11%). Yet, the strength of their work lies in the fact that this confirmation is presented in unvaccinated COVID patients admitted to hospital. Such a “clean” population may serve as a better model to explain why patients in the first wave had much poorer outcomes than those in subsequent waves.

First, severity of COVID at admission is different between waves, with patients of the first wave showing worse clinical and laboratory parameters. During the first phase of the pandemic, late presentations of cases to hospitals were frequent, because patients with mild symptoms of COVID-19 were encouraged to self-quarantine at home and advised to come to hospital only when illness was severe enough to justify access to healthcare [2]. Moreover, hospitals became seen as a place where active cases of COVID were concentrating in large numbers, where the risk of SARS-CoV-2 transmission was high, and many feared to come into hospitals if not necessary and were often in a compromised state [3, 4]. Critical shortage of acute hospital beds at the first wave was corrected only at subsequent waves by reconversion of hospital wards in COVID units with additional hospital beds [5]. Shortage of hospital beds is clearly represented in the paper by Leidi and colleagues by the noticeably longer period (8 vs. 6 days) between the onset of symptoms and hospital admission during the first wave compared to the second wave.

Second, better clinical outcomes in unvaccinated patients could have been the result of development of herd immunity in the population. Due to the widespread circulation of the virus among the population in the first 3 months of the pandemic, many could have acquired natural immunity against the virus [6–8], which mitigated the severity of clinical manifestation of COVID-19 in the subsequent waves. The need for mass vaccination programs when a high proportion of the population has already acquired natural immunity against the virus (i.e., herd immunity) requires careful evaluation.

Third, new variants of the SARS-CoV-2 virus do not fully escape already established acquired immunity and appears to cause less severe disease than the original Wuhan strain [9, 10].

Fourth, introduction of more effective treatment schemes for COVID-19 has certainly played a major role in improving patients’ survival between waves, in particular early use of systemic steroids and high-dose low-molecular-weight heparin (LMWH) [11, 12]. Thanks to autopsy studies, we gained a better understand of COVID pathophysiology and the key role of the massive inflammatory response (the so-called “cytokine storm”) triggered by SARS-CoV-2 [13]. The excessive inflammatory response was also responsible...
of a generalized prothrombotic state potentially leading to massive pulmonary embolism with poorly responsive ventilation/perfusion (V/Q) mismatch [14]. Accordingly, for patients with severe COVID-19, systemic corticosteroids, and high-dose LMWH are strongly recommended [15, 16]. In the study of Leidi et al., the use of systemic steroid increased threefold from 31.1% during the first phase to 92.0% at subsequent t waves. High-dose LMWH use increased fourfold from 11.9 to 43.9%.

Fifth, mortality rate during first wave was also elevated because of ineffective treatment with antibiotics, hydroxychloroquine, and antivirals [17], and those who made it through palliative management of respiratory failure (i.e., mechanical ventilation, high flow oxygen, etc.) did probably so because of natural selection (better immune system allowing them to survive) advanced age is a well-known predictor for risk of COVID death, and immunosenescence is likely to play a role. This is confirmed by the findings of the logistic regression analysis by Leidi et al. showing advanced age as a risk factor for poor survival only in patients of the first wave.

Advanced age and symptoms’ duration before hospitalization were the most important predictors associated with mortality during first wave in Leidi et al. Surprisingly, smoking rates of people hospitalized for COVID-19 in between waves were similar and very low at around 14%. This finding agrees with the other studies that have identified a significant lower prevalence of smoking among hospitalized COVID-19 patients than that expected based on population smoking prevalence [18, 19]. For the evidence about the effects of smoking on COVID-19, the accuracy of reporting has been questioned [20]. The potential bias in estimation of smoking prevalence by self-reporting was recently addressed in a recent population-based study [21]. The study used direct laboratory measures of smoking exposure (i.e., serum cotinine), to investigate the true association between SARS-CoV-2 infection susceptibility and active smoking [21]; the study reported a lower proportion of positive SARS-CoV-2 serology in current smokers compared with non-smokers/ex-smokers.

COVID losses have been available for some time now and have advanced our understanding of the ethical, organizational, and clinical challenges associated with the disease. Nonetheless, it is important to move beyond lessons learned and explore new uncharted territory preparing for future health crisis that may arise again.

References

1. Leidi F, Boari GEM, Scarano O, Mangili B, Gorla G, Corbani A et al (2022) Comparison of the characteristics, morbidity and mortality of COVID-19 between first and second/third wave in a hospital setting in Lombardy: a retrospective cohort study. Intern Emerg Med. https://doi.org/10.1007/s11739-022-03034-5
2. Società Italiana di Medicina Generale e delle cure Primarie (2020). Available online at: https://www.simg.it/covid-19-la-gestione-del-paziente-con-sintomi-compatibili/
3. Czeisler ME, Marynak K, Clarke KEN, Salah Z, Shakyar I, Thierry JM, Ali N, McMillan H, Wiley JF, Weaver MD, Czeisler CA, Rajaratnam SMW, Howard ME (2020) Delay or avoidance of medical care because of COVID-19-related concerns—United States, June 2020. MMWR Morb Mortal Wkly Rep 69(36):1250–1257. https://doi.org/10.15585/mmwr.mm6936a4
4. Einav S, Tankel J (2022) The unseen pandemic: treatment delays and loss to follow-up due to fear of COVID. J Anesth Analg Crit Care 2:5. https://doi.org/10.1186/s44158-021-00032-5
5. Grasselli G, Pesenti A, Cecconi M (2020) Critical care utilization for the covid-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA 323(16):1545–1546. https://doi.org/10.1001/jama.2020.4031
6. Randolph HE, Barreiro LB (2020) Herd immunity: understanding covid-19. Immunity 52(5):737–741. https://doi.org/10.1016/j.immuni.2020.04.012
7. Gomes MGM, Ferreira MU, Corder RM, King JG, Souto-Maior C, Penha-Gonçalves C, Gonçalves G, Chikina M, Pedgen W, Aguas R (2022) Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold. J Theor Biol 540:111063. https://doi.org/10.1016/j.jtbi.2022.111063
8. Krsak M, Harry BL, Palmer BE, Franco-Paredes C (2021) Postinfectious immunity after covid-19 and vaccination against SARS-CoV-2, Viral Immunol 34(8):504–509. https://doi.org/10.1089/vim.2021.0054
9. https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus-a-new-strain-of-coronavirus-what-you-should-know
10. https://asm.org/Articles/2021/July/How-Dangerous-is-the-Delta-Variant-B-1-617-2
11. Hong S, Wang H, Zhang Z, Qiao L (2022) The roles of methylprednisolone treatment in patients with COVID-19: a systematic review and meta-analysis. Steroids 183:109022. https://doi.org/10.1016/j.steroids.2022.109022
12. Pilia E, Belletti A, Fresilli S, Finco G, Landoni G (2022) Efficacy and safety of heparin full-dose anticoagulation in hospitalized non-critically ill COVID-19 patients: a meta-analysis of multicenter randomized controlled trials. J Thromb Thrombolysis. https://doi.org/10.1007/s11239-022-02681-x
13. Fajgenbaum DC, June CH (2020) Cytokine storm. N Engl J Med 383(23):2255–2273. https://doi.org/10.1056/NEJMra2026131
14. Jose RJ, Manuel A (2020) COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 6:e46–e47. https://doi.org/10.1016/S2213-2600(20)30216-2
15. British Medical Journal best practice (2020) Coronavirus disease 2019 (COVID-19). Last updated: Dec 21, 2020. https://bestpractice.bmj.com/topics/en-gb/3000201/management-recommendations
16. https://www.england.nhs.uk/coronavirus/documents/covid-19-therapy-corticosteroids-including-dexamethasone-and-hydrocortisone/
17. Roche N, Crichton ML, Goeminne PC et al (2022) Update june 2022: management of hospitalised adults with coronavirus disease 2019 (COVID-19): a european respiratory society living guideline. Eur Respir J 60:2200803. https://doi.org/10.1183/13993003.00803-2022
18. Farsalinos K, Barbouni A, Poulas K, Polosa R, Caponnetto P, Niaura R (2020) Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis. Ther Adv Chronic Dis 11:2040622320935765. https://doi.org/10.1177/2040622320935765
19. Miyara M, Tubach F, Pourcher V, Morélot-Panzini C, Pernet J, Haroche J, Lebbah S, Morawiec E, Gorochov G, Caumes E, Hausfater P, Combes A, Similowski T, Amoura Z (2022) Lower rate of daily smokers with symptomatic COVID-19: a monocentric self-report of smoking habit study. Front Med 5(8):668995. https://doi.org/10.3389/fmed.2021.668995

20. Polosa R, Caci G (2020) COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine. Intern Emerg Med 15(5):853–856. https://doi.org/10.1007/s11739-020-02361-9 (Epub 2020 May 19)

21. Tomaselli V, Ferrara P, Cantone GG, Romeo AC, Rust S, Saitta D, Caraci F, Romano C, Thangaraju M, Zuccarello P, Rose J, Ferrante M, Belsey J, Cibella F, Caci G, Ferri R, Polosa R (2022) The effect of laboratory-verified smoking on SARS-CoV-2 infection: results from the troina sero-epidemiological survey. Intern Emerg Med 17(6):1617–1630. https://doi.org/10.1007/s11739-022-02975-1 (Epub 2022 Apr 14)

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