EDITORIAL

Is It a Wave or a Tsunami? That is the Question

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Keywords: COVID-19 mortality, COVID-19, ICU admission.
Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-24060

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How to cite this article: Todi S. Is It a Wave or a Tsunami? That is the Question. Indian J Crit Care Med 2021;25(12):1331–1332.

Source of support: Nil

Conflict of interest: None

Coronavirus disease-2019 (COVID-19) has been striking mankind around the world repeatedly over the last 2 years with only recent respite due to global vaccination drive and other preventive measures.[1] A lurking fear still prevails regarding a new wave of this deadly infection of being round the corner. Four fundamental questions need to be addressed while discussing repeated waves of COVID-19 pandemic: firstly, what leads to this phenomenon of peaks and troughs of repeated waves of infection; secondly, why are these episodes different from each other; thirdly, what insights may be gained by studying the epidemiology and patient demographic during the waves; and lastly, predicting future waves and what measures may be taken to avoid it. This issue of the journal addresses the first three discussion points in two articles: one, a single-center study from a 27-bed intensive care unit (ICU), and the other, a multicenter study in nine ICUs in Western India, both comparing the epidemiology and the patient demographics during the first and second waves in India.[2,3] Data were analyzed from 104 patients during the first wave and 116 from the second wave in the single-center study, whereas the multicenter study analyzed 1,921 patients during the first wave and 1,577 during the second wave. The timing of the waves is somewhat arbitrary and based on reports of increasing positivity of reverse transcription–polymerase chain reaction tests. The first wave was reported as between March and November 2020 and second between March and May 2021 in the multicenter study in this issue. Neither of the studies mentioned the ICU occupancy rate during the two waves making it difficult to compare the incidence difference of new ICU admissions. Many theories abound regarding the phenomenon for these waves with the incidence decreasing due to effective preventive measures, like compliance with COVID-19 appropriate behavior and strict lockdowns while overcrowding without protective measures and relaxing lockdowns increasing it. Nationwide vaccination drive and increase in herd immunity either by natural infection or by vaccination will also lead to decrease in new cases, whereas infection in unvaccinated and partially vaccinated population and breakthrough infection lead to increased incidence of new infection. Over time, many new variants of COVID-19 virus have been reported worldwide with differential predominance in various geographical locations. This will also lead to new cases among vaccinated individuals (breakthrough infection) and may also result in changes in clinical profile of these new cases, which has been illustrated in the two articles in this issue of the journal.

In order to gain insights from epidemiological differences of ICU patients infected with COVID-19, analysis of age, gender, comorbidities, and clinical symptomatology of patients admitted during the two waves of the pandemic needs to be done. In the single-center study, significantly more younger patients with less comorbidities were admitted in the ICU during the second wave, whereas no age difference and higher incidence of associated comorbidities were noted in the multicenter study. Less compliance with preventive measures, predominantly unvaccinated younger population, and increased transmissibility of the newer variants may have led to reports of the younger age group being affected more during the second wave. Lowering the age threshold for vaccination may lead to protection of this vulnerable population. On the contrary, as elderly patients with more comorbidity have a more severe course, an ICU-based study may not find this difference in age or comorbidity incidence of patients. Moreover, ICU admission criteria and hospital demographics and protocols may also influence age of patients admitted in ICU. Both the studies observed that increasing number of females were admitted in ICU during the second wave. There is no plausible biological explanation for this, but this observation emphasizes the need for more vaccination drive in this group. On the contrary, mortality among male patients in ICU was high in both the studies during both waves. This finding is also supported by other international studies.[4] The reason for higher mortality among men could be due to higher incidence of comorbidities in this group or due to difference in immune system responses between the genders. The duration of symptoms prior to hospitalization was similar in both the studies and so was the clinical presentation with a lesser incidence of anosmia noted during the second wave in one study. Though the predominant infecting virus strain was different during the two waves, it may be difficult to differentiate them on the basis of clinical symptomatology. Duration of symptoms previous to hospitalization was similar during both waves in the single-center study but was found to be shorter in the multicenter study. Severity of illness as observed by sequential organ failure assessment score was similar during both the waves in single-center study, but this parameter was not mentioned in the multicenter study. These discrepancies in the two studies may be due to a shorter time period of observation and lesser sample size in single-center study as opposed to the multicenter study.

As the pandemic was evolving, multiple collaborative, international research initiatives were undertaken, and fast-track publication of these trials led to an unprecedented rapid

implementation of these trial results by clinicians worldwide. This led to major differences in resource utilization, ICU protocols, and therapies during the two waves. This is also reflected from the findings from the two studies in this issue. In the larger multicenter study, use of high-flow nasal oxygen (HFNO) was more common during the second wave, a practice change which has been observed globally. During the first wave, there was an apprehension among clinicians in using HFNO due to the fear of transmission of infection to healthcare workers which in later studies was not validated, if proper preventive measures were taken. Moreover, due to scarcity of ventilators, many patients were kept on HFNO for a prolonged period during the second wave. The incidence of invasive mechanical ventilation was also found to be high during the second wave in this study. This probably reflects the fact that due to scarcity of beds, more sick patients with comorbidities got admitted in ICUs during the second wave. Both the studies showed significantly higher use of corticosteroids during the second wave. As RECOVERY trial showing mortality benefit of dexamethasone was published during the first wave, the implementation of its results by physicians was reflected during the second wave.[5] The average duration of use of steroids was noted to be significantly shorter during the second wave, 9 days as compared to 12 days during the first wave in the multicenter study. The reason for this practice change is not entirely clear, but may reflect the apprehension of side effects, like secondary fungal infection, for example, invasive aspergillosis and mucormycosis, which were increasingly reported during the second wave from India. In the single-center study, methylprednisolone was the predominant steroid used during the second wave as compared to dexamethasone during the first wave, which is probably a center-specific practice and may not be generalizable. Neither of the two studies mentioned about the difference of dose of steroids used during the two waves as the practice pattern may have changed regarding this during the two waves. In the single-center study, tocilizumab was used more frequently during the first wave, a practice which was not reported by the multicenter study. Increasing use of steroids and apprehension of secondary infection may have led to decreased use of other immunesuppressants during the second wave.

In the multicenter study, the ICU and hospital mortality were significantly higher in the second wave compared to the first wave (26.1 vs 13.4%, $p < 0.001$, and 29.9 vs 18.2%, $p < 0.001$, respectively). This may be due to increasing demand for ICU beds, and only sicker patients got admitted during the second wave. By comparison, the mortality rate was higher during both waves in the single-center study, which also showed a nonsignificant trend toward higher mortality during the second wave (53.2 vs 56.3%). This observation reflects heterogeneity of ICU outcome among centers which averages out in a multicenter study. This also implies that in a multicenter study it should have a center-specific sensitivity analysis to differentiate disproportionate mortality outcome from a few centers. ICU stay was observed to be nonsignificantly longer during the first wave in the single-center study (7.2 vs 6.8 days), which was not analyzed in the multicenter study.

These two studies though differing in sample size bring out a common theme of increase in ICU mortality during the second wave. In order to avoid further tsunami of COVID-19 deaths, a multipronged approach of mass vaccination of the entire population and general preventive measures need to be adopted while relaxing the restriction policies.

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