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IM - COMMENTARY

# Value of hospital datasets of COVID-19 patients across different pandemic periods: challenges and opportunities

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The global health burden of the SARS-CoV-2 pandemic is well known [1]. In this context, there has been rapid changes in the epidemiology landscape steered by the appearance of new variants of the SARS-CoV-2 virus, some causing a more aggressive form of the disease, others setting off only mild form of the disease [2].

What is the severity of COVID-19 according to the variant of SARS-CoV-2? There are some limitations to the datasets obtained from hospitalized patients, but they are a rich source of important information. It is evident, however, that there is a marked difference in number of people infected, severity of the disease, and specific patients' characteristics among different epidemic waves'. This uniqueness of different epidemic waves hampers comparability and, consequently, the possibility of disentangling the role of variant-associated virulence from other determinants of disease severity unless a number of confounders are considered [3].

Hospital access can also change over time, depending on bed availability and admission policies. Indeed, protocols for hospitalization may change due to better knowledge of this new disease, and to new treatment opportunities, leading to different rates of hospitalization and case-mix on admission. Additional difficulties arise when attempting to calculate the risk of hospitalization across waves because test capabilities and completeness of diagnoses can introduce differences in the denominator.

Wang and colleagues in this issue of Internal and Emergency Medicine [4] report a detailed analysis of data from a large hospital in Melbourne, Australia. Based on the comparison of hospitalized COVID-19 patients across different periods (e.g., B.1.338, Delta (B.1.617.2), and Omicron (B.1.1.159)), the authors conclude that infection with the Omicron variant is less severe than with earlier SARS-CoV-2 variants, characterized by a milder clinical presentation, significantly lower inflammatory marker levels, and a lower risk of hospitalization.

Large population-based studies have confirmed that the risk of hospitalization is lower for Omicron than for Delta variant [5], and that the Omicron variant is associated with less severe disease in terms of risk of pneumonia, admission to intensive care units, and death, compared to Delta or other SARS-CoV-2 variants [6–8].

However, studies on previous variants yielded conflicting results [2], as B.1.1.7 (Beta) and B.1.617.2 (Delta) variants show overall increased severity compared to the Wuhan virus [9]. Large cohort studies accounting for a number of confounder confirmed this finding [10–12]. Thus, the Omicron variant and strains appear in line with the previous trend toward increased transmissibility but, contrary to other variants, which were previously dominant, are seemingly associated with decreased disease severity.

The level of immunity in the population plays a crucial role in determining disease severity; protection depends on previous infection with SARS-CoV-2, vaccination status, number of booster doses, combination of vaccine-derived and natural immunity, time elapsed since last episode of infection or vaccine dose, degree of escape of new variants from established immunity [13]. As a result of finding a

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different inflammatory pattern in vaccinated hospitalized Omicron patients, if confirmed, better prognostic models could be developed.

Interestingly, the paper by Wang et al. reports lower levels of laboratory markers of inflammation (CRP, D-dimer, LDH, ferritin) and better health outcomes (reduced need for assisted ventilation, COVID-19 specific death) among vaccinated persons hospitalized in 2022 [4]. It is important to note that available studies confirm that the Omicron variant and prior vaccination can reduce disease severity independently [5, 14]. According to a small Italian study, vaccinated patients showed lower levels of inflammatory markers despite the worst clinical conditions [15].

When giving proper relevance to these findings, important confounders need to be considered, which may tend to shift the picture of COVID-19 hospitalized patients toward a less severe condition *independently* of the actual decrease in disease severity. In fact, patients hospitalized in later waves were more likely to be vaccinated, and therefore protected to some extent from severe COVID-19. At the same time, it is also conceivable that hospitals got better organized to cope with the surge of COVID-19 patients. Together, this may have resulted in a larger fraction of patients with a less severe form of disease being hospitalized in a later phase of the pandemic, as opposed to the early phase when hospitals concentrated on worst cases, even at the expenses of other acute conditions [16]. In turn, this could lead to data accumulation from patients with less severe conditions, and in turn, with lower levels of inflammation.

Apart from discussing why patients in initial waves presented with much poorer outcomes than those in subsequent waves, Wang et al. used their data to develop a specific risk score for oxygen treatment requirements [4]. Since the first epidemic spread of SARS-CoV-2 a plethora of risk-prediction models have been proposed [17–19]. Many of these have been validated, but only a few if any have gained use in clinical practice due to challenges associated with patients' selection and random error [17, 20]. Moreover, risk-prediction models typically show worst performance in subsequent application than in the initial context of development [19, 20]. This is not unexpected. Reproducibility and generalizability of the method is likely to be questionable due to the space–time distribution of the analysis; their score, calculated on the basis of data from the first wave of COVID-19 of 2020, is unlikely to be applicable to subsequent waves due to the fast changing nature of this pandemic.

In conclusion, large and high quality hospital dataset may provide an opportunity to run detailed analyses and establish the prognostic value of 1) virulence of SARS-Cov-2 variants; 2) vaccination on disease severity, and 3) clinical and laboratory markers. However, important limitations decrease the strength of evidence obtained from these data. Ideally, the many existing hurdles should be overcome by analyzing data from all hospitalized patients within a circumscribed population, using well-defined study protocols, ensuring that variables can be compared across hospitals, and conducting formal case–control and cohort studies involving hospitalized and non-hospitalized patients. To develop useful predictive models, which can be used in clinical practice, multicenter studies must be conducted without selection bias and random errors, as well as updated to reflect current best practices.

**Data availability** There are no data presented.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** This article does not contain any studies with human participants or animal performed by any of the authors.

**Informed consent** For this type of study formal comnsent is not required.

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