who might have become infected during the first 48–72 hours of hospital stay and had shorter incubation periods (associated with severe disease progression[4]) would have been automatically excluded from further chart review. Consideration of using fewer days of hospitalization as a screening criterion for hospital-acquired COVID-19 is particularly relevant today given the emergence of SARS-CoV-2 strains (eg, α, β, δ, and o) with shorter incubation periods compared to that of the original strain. More specifically, the most recent predominant SARS-CoV-2 strain, o (omicron), appears to have a mean incubation period of only ~3 days.[5,6]

It would have also been helpful for the authors to have provided additional pertinent demographic features (eg, immunocompromised status and other comorbidities associated with severe COVID-19) of patients who might have acquired COVID-19 during their hospitalization because the incubation period of COVID-19 may reflect not only pathogen-specific characteristics of SARS-CoV-2 but also host factors such as immunity.[4] This information would have been helpful in further characterizing the at-risk population for hospital-acquired COVID-19.

The authors also concluded that "hospital-acquired SARS-CoV-2 *infection* was uncommon" even though SARS-COV-2 disease (ie, COVID-19), not infection, was the primary focus of the study as reflected by the title of the article and study case definitions.[1] Specifically, all SARS-CoV-2–positive patients with "onset during days 6–14" of hospitalization but without COVID-19 symptoms were automatically excluded from further consideration of acquisition in the hospital, whereas those diagnosed during the same period but with COVID-19 symptoms were considered hospital-acquired cases.[1] Furthermore, no patient without COVID-19 symptoms was classified as a "possible" hospital-acquired case unless testing was performed after 14 days of hospitalization. With an estimated 40%–45% of persons who test positive for SARS-CoV-2 considered asymptomatic at the time of testing,[7] a significant fraction of nosocomially transmitted SARS-CoV-2 infection or PCR-positive cases in this study might have gone undetected in the absence of reported symptoms that would have triggered testing by providers. Even among symptomatic patients, as stated by the authors, providers often preferentially ordered SARS-CoV-2 testing in those with more severe symptoms (eg, dyspnea or hypoxia) rather than those with milder symptoms.[1] For these reasons, we believe that no firm conclusion can be made on the frequency of hospital-acquired SARS-CoV-2 infection or even mild COVID-19 cases based on the study methodology and the data presented.

Last, we fully agree that quantification of the risk of transmission of SARS-CoV-2 to hospitalized patients based solely on a set of predefined temporal criteria relative to the hospital day of onset of symptoms poses a challenge given the dynamic nature of SARS-CoV-2, as well as other factors, including the everchanging host and healthcare provider immunity.[1] However, just as the authors raise legitimate concerns over misclassification of community-acquired cases as hospital-acquired, the converse should also be equally acknowledged. To this end, given the current state of COVID-19 and in the absence of simpler methods for distinguish community from hospital-acquired disease, we believe that a manual chart review of all newly diagnosed COVID-19 cases in hospitalized patients should be considered to quantify the burden of hospital-acquired COVID-19 more accurately.

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Author response: Quantifying healthcare-acquired coronavirus disease 2019 (COVID-19) in hospitalized patients: A closer look

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To the Editor—We thank Drs Manian and Karlapalem for their interest in our work and for raising several important points that promote discussion regarding monitoring hospital patients for acquisition of coronavirus disease 2019 (COVID-19).

Our work is part of a growing body of literature aiming to understand the risk of COVID-19 acquisition among hospital patients.[1–3] Reliably attributing COVID-19 acquisition to the hospital setting is beset with challenges similar to other hospital-acquired infection events. Misclassification of putative hospital-acquired infections is inevitable due to uncertainty engendered during determinations, and awareness of this uncertainty creates unease among infection control, clinical, research, and public health communities. Although surveillance methods require evaluators to assign a value of "infection=yes" or "infection=no" to their reviews, in reality, there are probabilistic underpinnings to these determinations.[4] For each potential infection event, evaluators' estimations are influenced by many factors including presence of symptoms, temporal associations of specimen acquisition to symptoms and healthcare exposures, patient comorbidities, clinician documentation, and their own probability threshold for binary classification.

For any surveillance definition, the selection of a temporal cutoff point for categorizing an event as hospital-acquired should be examined. Although we selected a cutoff point later in the hospital stay relative to other infection-related patient-safety events, other investigators have specified even later cutoff points for COVID-19.[2] Also, our study was conducted during the early phases of the pandemic and reflected the median incubation period (>4 days) for the ancestral strain of severe acute respiratory coronavirus virus 2 (SARS-CoV-2).[5] During pandemics such as COVID-19, a stringent temporal criterion for manual case reviews likely is necessary to avoid further burdening stressed infection control departments. Individual hospitals can choose a more permissive cutoff point (evaluating events early during a hospitalization) for manual review of potential hospital-acquired cases, or perhaps clusters of cases. Such decisions need to consider infection control resources as well as the dynamic epidemiology of COVID-19—strains emerge that differ in transmissibility, incubation period, virulence, and symptom profile.

Permissive cutoff points increase sensitivity but at a cost of a reduced likelihood that an event actually represents hospital acquisition. Given challenges associated with attributing events to the community or hospital (eg, gaps in information due to incomplete serial testing to evaluate community acquisition, unavailability of whole-genome sequencing of SARS-CoV-2 strains for patients and community populations, or incomplete capture of exposure history), we opted for a temporal criterion that avoided inflating the risk of misclassifying events as hospital acquired. Importantly, to avoid calculating an artificially low incidence caused by denominator inflation, our patient-days denominator rejected convention and only counted at-risk patient days. We excluded all patient days through hospital day 5 and patient days for those who were SARS-CoV-2 positive. Our estimated incidence was, in our estimation, sufficiently low in both hospitals to claim it as an uncommon event (3.3 and 1.3 per 10,000 patient days), especially in the context of a potentially high-risk environment with a high volume of SARS-CoV-2 inpatients.

The points raised by Drs Manian and Karlapalem are relevant for other hospital-acquired conditions. Incubation periods are dynamic and clinical expression heterogeneous—influenced by inoculum, organism characteristics (species and strain), and endogenous or exogenous host characteristics (eg, vaccination status or pharmacologic immunosuppression). The possibility of colonization or asymptomatic infection poses challenges when making transmission determinations for other pathogens, notably influenza infection, for which we do not routinely test for asymptomatic transmission events.[6] Fortunately, in our evaluation, a small minority (13%) of SARS-CoV-2 detection events that occurred after day 5 were asymptomatic.

We suspect that future, more comprehensive investigations (serial swab collection paired with exposure history and whole-genome sequencing) will better inform a temporal cutoff point for hospital-onset COVID-19 infection or possibly SARS-CoV-2 acquisition. A more permissive cutoff point for manual review of potential cases may be justifiable, especially since the volume of potential case reviews has dramatically decreased. Alternatively, the recognition that deterministic classifications of events as hospital-acquired can reduce reliability will allow for assignment of probability scores.[7] Probability estimates derived from intense data collection, expert review, and genomics could mitigate problems arising from the uncertainty in making determinations and variable application of surveillance definitions. Such probability estimates would account for a lower likelihood of hospital-acquisition among asymptomatic patients and early-onset episodes. Within the limitations of our study, our data and other publications suggest that hospital-acquired COVID-19 was uncommon during the early phases of the pandemic when hospitals enacted infection prevention control efforts to care for an unprecedented number of severely ill COVID-19 patients.

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