a single pharmacist leader is responsible for improving antibiotic use [6].

We agree with Bland and Jones that given their consistent presence and existing role within ASPs, pharmacists could greatly expand the accessibility of inpatient penicillin allergy assessments [7]. In our study, just 6 sites (13%, 5 academic medical centers and 1 community hospital), indicated that pharmacists were performing PST. While scope of practice limitations may be limiting pharmacists from performing PST in some US states, pharmacists have led programs addressing penicillin allergies with a variety of activities beyond performing skin testing: allergy history reconciliation, screening for PST, patient/provider education about penicillin allergy, protocol development for test doses/drug challenges, penicillin allergy delabeling, and penicillin allergy relabeling monitoring [3].

While there are still barriers to widespread pharmacist penicillin allergy assessments, such as lack of "full provider" status in many states and lack of standardized drug allergy education and credentialing [8, 9], we agree that pharmacists are ideal champions for inpatient β-lactam allergy programs and critical allies for allergists and infectious diseases doctors engaged in delabeling efforts [10].

Note

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References

1. Blumenthal KG, Kuper K, Schulz LT, et al. Association between penicillin allergy documentation and antibiotic use [manuscript published online ahead of print 29 June 2020]. JAMA Intern Med **2020**. doi:10.1001/jamainternmed.2020.2227.
2. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. Allergy **2017**; 72:1288–96.
3. Wolfson AR, Huebner EM, Blumenthal KG. Acute care beta-lactam allergy pathways: approaches and outcomes. Ann Allergy Asthma Immunol **2019**; 123:16–34.
4. Barlam TF, Cosgrove SE, Abbo LM, et al. Executive summary: implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:1197–202.
5. Mancini CM, Fu X, Zhang Y, et al. Penicillin allergy evaluation access: a national survey. Clin Infect Dis **2020**; 71: 2972–5.
6. Centers for Diseases Control and Prevention. Hospital antibiotic stewardship. National Healthcare Safety Network. Available at: https://arpsp.cdc.gov/profile/stewardship. Accessed 11 June 2020.
7. Bland CM, Jones BM. Pharmacists filling the gap within penicillin allergy assessment and skin testing [manuscript published online ahead of print 14 July 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa978.
8. Gebhart F. On the road to provider status. **2019**. Available at: https://www.drugtopics.com/latest/road-provider-status. Accessed 11 June 2020.
9. Kufel WD, Justo JA, Bookstaver PB, Avery LM. Penicillin allergy assessment and skin testing in the outpatient setting. Pharmacy (Basel) **2019**; 7:136.
10. Blumenthal KG, Shenoy ES, Wolfson AR, et al. Addressing inpatient beta-lactam allergies: a multihospital implementation. J Allergy Clin Immunol Pract **2017**; 5:616–25.e7.

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Nasopharyngeal SARS-CoV-2 Load at Hospital Admission as a Predictor of Mortality

TO THE EDITOR—We read with interest the article by Bhargava et al [1] that was recently published in the Journal, which significantly contributes to the definition of clinical risk factors for severe coronavirus disease 2019 (COVID-19) manifestations. However, despite the comprehensive analysis of multiple clinical and laboratory parameters, the virus is still a poorly represented piece of this puzzle. During the severe acute respiratory syndrome coronavirus (SARS-CoV-1) epidemic, higher viral loads were strongly correlated with disease severity and death [2]. Similarly, the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrated a strikingly fast, and intense, replication kinetics, whose contribution to the clinical evolution of COVID-19 is starting to be investigated [3–6]. The nasopharyngeal SARS-CoV-2 load expressed by cycle thresholds (Cts) of real-time polymerase chain reaction (RT-PCR), the standard-of-care for COVID-19 molecular diagnosis [7, 8], is a widely available parameter to be correlated with the severity of COVID-19. To prove this hypothesis, we investigated the correlation between the initial nasopharyngeal SARS-CoV-2 loads and 30-day in-hospital mortality in 206 consecutive adult patients with a laboratory-confirmed SARS-CoV-2 infection, admitted to Niguarda Hospital (Milan, Italy) since 5 March, and who have either died or been discharged by 23 April 2020 (study protocol: 92-15032020). Dynamic ranges of categorized Ct values of viral RdRp, E, and N genes were assessed by quantitative droplet-digital PCR.

The median (interquartile range) time from symptom onset to hospital admission was 6 (4–9) days. By then, 188 of 206 (91.3%) patients presented an interstitial pneumonia with ground-glass opacities. Survivors (n = 153) and nonsurvivors (n = 53) significantly

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differed in several anamnestic, clinical, virological, and laboratory characteristics (Supplementary Appendix). These included both the mean and the absolute Ct values of RdRp, N, and E genes that were significantly lower in nonsurvivors compared with survivors (P = .001), reflecting higher viral loads in the nasal/throat compartment of the former patients. Of note, 20.7% of nonsurvivors had initial Cts less than 20 (viral loads $\geq 10^7$ copies/mL) versus only 5.3% of survivors (P < .001).

Kaplan-Meier curves showed a progressive increase in 30-day mortality, by increase in nasopharyngeal SARS-CoV-2 load (Figure 1). Thirty days after disease onset, the survival rate dropped to 35.3% in patients with Cts less than 20 (viral loads $\geq 10^7$ copies/mL) versus 81.0% in patients with Cts greater than 35 (viral loads $<10^3$ copies/mL) (P = .001). Notably, the 36.4% of patients with initial Cts of less than 20 died within 7 days versus 14.3% and 0.0% of patients with initial Cts of 20–24.9 and higher (Cts >25) (P = .006).

In Cox proportional hazards models (Supplementary Appendix), out of 19 variables analyzed, Cts less than 20 remained one of the strongest predictors of in-hospital death, both in univariate (hazard ratio [HR], 8.38; 95% confidence interval [CI]: 2.66–26.37; P = .00015) and in multivariate analysis (HR, 3.94; 95% CI: 1.75–8.87; P = .001) (along with presence of comorbidities, creatinine, D-dimers, and C-reactive protein).

Overall, we identified the high initial nasopharyngeal viral load as an independent risk factor for in-hospital mortality, and for a significantly faster worsening of clinical conditions towards death. These results strengthen the recently reported correlation between viral load and severe disease [5, 6] and provide initial evidence of a role for viral load in influencing the definitive outcome. As RT-PCR on nasopharyngeal swabs is used worldwide, clinically validated Ct cutoffs (ie, <20) represent a ready-to-use prognostic marker to help stratify patients for risk of in-hospital death, and to consequently implement appropriate measures to contain fatalities.

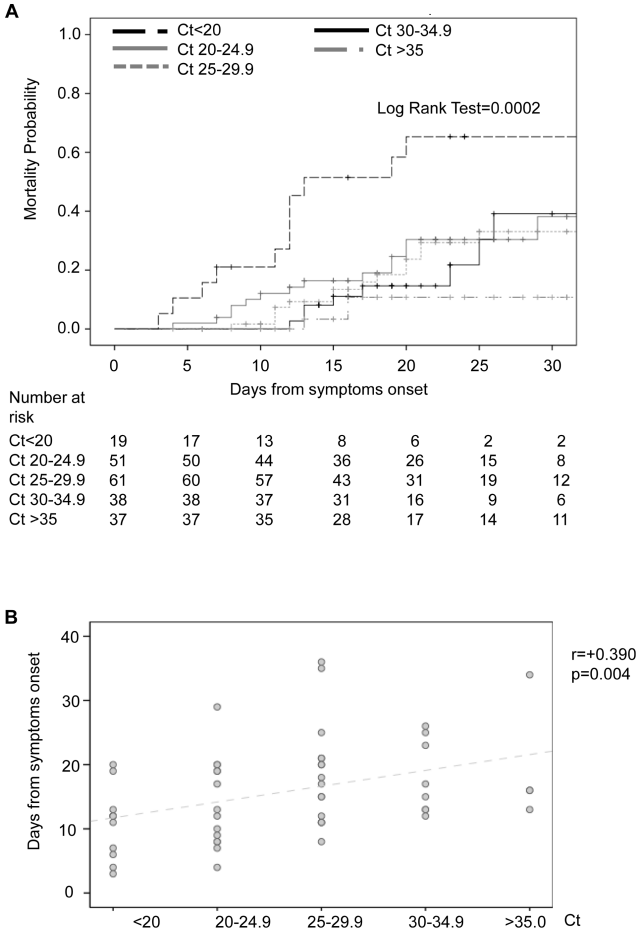

Figure 1. Contribution of nasopharyngeal SARS-CoV-2 shedding to in-hospital mortality. *A*, Kaplan-Meier estimates of mortality probability within the first 30 days from disease onset, according to nasopharyngeal Ct values at admission. *B*, Nasopharyngeal Ct values at admission against time of mortality from disease onset (days) in nonsurvivors. The Pearson correlation coefficient between Ct values and time of mortality is displayed in the top-right corner of the panel (r = +0.390). Abbreviations: Ct, cycle threshold; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

The SCoVA (***Sequenicing COronavirus and Variability Analysis***) ***Study Group:*** Claudia Alteri, Maria Antonello, Chiara Baiguera, Alessandra Bielli, Maurizio Bottiroli, Paolo Brioschi, Daniela Campisi, Stefania Carta, Giorgia Casalicchio, Valeria Cento, Arturo Chieregato, Luna Colagrossi, Valentino Costabile, Jacopo Colombo, Federica Di Ruscio, Oscar Massimiliano Epis, Diana Fanti, Roberto Fumagalli, Thomas Langer, Elisa Matarazzo, Marco Merli, Alice Nava, Silvia Nerini Molteni, Carlo Federico Perno, Massimo Puoti, Silvia Renica, Livia Tartaglione, Nicola Ughi, Chiara Vismara.

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References

1. Bhargava A, Fukushima EA, Levine M, et al. Predictors for severe COVID-19 infection. Clin Infect Dis **2020**; 71:1962–8.
2. Peiris JS, Chu CM, Cheng VC, et al; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet **2003**; 361:1767–72.
3. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis **2020**; 20:565–74.
4. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ **2020**; 369:m1443.
5. Yu X, Sun S, Shi Y, Wang H, Zhao R, Sheng J. SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression. Crit Care **2020**; 24:170.
6. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis **2020**; 20:656–7.
7. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America guidelines on the diagnosis of COVID-19. Clin Infect Dis. **2020** Jun 16:ciaa760. doi:10.1093/cid/ciaa760.
8. World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. Available at: https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117. Accessed 19 June 2020.

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Reply to Alteri et al

To the Editor—We thank Alteri et al for recognizing our work regarding predictors for severe coronavirus disease 2019 (COVID-19) infection [1]. We read with interest their work regarding initial nasopharyngeal viral load as measured by cycle thresholds of reverse transcriptase–polymerase chain reaction (RT-PCR) and correlation with 30-day in-hospital mortality. The endpoint of their study for severe COVID-19 infection was 30-day in-hospital mortality. In contrast, our study defined the need for mechanical ventilation as an endpoint for severe COVID-19 infection. Our study reported acute or pre-existing renal disease, supplemental oxygen at the time of hospitalization, and admission C-reactive protein (CRP) as independent predictors for the development of severe COVID-19 infections and did not examine predictors of mortality.

Although Alteri et al have shown that viral load is a predictor of inpatient mortality they have not demonstrated that this was a predictor of disease progression short of death. Furthermore, there needs to be some caution in predicting that high viral loads alone can serve as predictors of mortality based on this work as there were only 19 patients with the highest viral loads at presentation and only 2 observations made on day 30. The small numbers may be an accurate predictor of mortality; however, one would like to see more robust data to further support the conclusion of the value of high viral loads in predicting mortality.

Note

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1. Bhargava A, Fukushima EA, Levine M, et al. Predictors for severe COVID-19 infection. Clin Infect Dis. Published online May 30, 2020. doi: 10.1093/cid/ciaa674.

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