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Authors

Bershteyn, Anna
Dahl, Angela M
Dong, Tracy Q
et al.

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BRIEF REPORT

Self-Assessed Severity as a Determinant of Coronavirus Disease 2019 Symptom Specificity: A Longitudinal Cohort Study

Anna Bershteyn,[1,a] Angela M. Dahl,[2,a] Tracy Q. Dong,[3] Meagan E. Deming,[4] Connie L. Celum,[5] Helen Y. Chu,[6] Angelica C. Kottkamp,[7] Alexander L. Greninger,[3,8] Risa M. Hoffman,[9] Keith R. Jerome,[3,8] Christine M. Johnston,[10] Patricia J. Kissinger,[11] Raphael J. Landovitz,[12] Miriam K. Laufer,[4] Alfred Luk,[13] Kathleen M. Neuzil,[4] Michael K. Paasche-Orlow,[14] Robert A. Pitts,[15] Mark D. Schwartz,[1] Helen C. Stankiewicz Karita,[16] Lorna E. Thorpe,[1] Anna Wald,[3,8,17] Crystal Y. Zheng,[13] Mark H. Wener,[8] Ruanne V. Barnabas,[18,19] and Elizabeth R. Brown[2,20]

[1]Department of Population Health, New York University Grossman School of Medicine, New York, New York, USA; [2]Department of Biostatistics, University of Washington, Seattle, Washington, USA; [3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; [4]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland, USA; [5]International Clinical Research Center and Department of Global Health, University of Washington, Seattle, Washington, USA; [6]Department of Medicine and Department of Epidemiology, University of Washington, Seattle, Washington, USA; [7]Department of Medicine, New York University Grossman School of Medicine, New York, New York, USA; [8]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA; [9]Department of Medicine and Division of Infectious Diseases, University of California, Los Angeles, California, USA; [10]Department of Medicine and Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA; [11]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, USA; [12]Center for Clinical AIDS Research & Education, University of California, Los Angeles, California, USA; [13]John W. Deming Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA; [14]Department of Medicine and Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA; [15]Department of Medicine and Division of Infectious Diseases, NYC Health & Hospitals/Bellevue, New York, New York, USA; [16]Department of Medicine, University of Washington, Seattle, Washington, USA; [17]Department of Medicine, Department of Epidemiology, Seattle, Washington, USA; [18]Department of Global Health and Department of Medicine, University of Washington, Seattle, Washington, USA; [19]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA; and [20]Vaccine and Infectious Disease Division and Public Health Sciences Division, Fred Hutchinson Cancer Research Center, USA

Coronavirus disease 2019 symptom definitions rarely include symptom severity. We collected daily nasal swab samples and symptom diaries from contacts of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) case patients. Requiring ≥1 moderate or severe symptom reduced sensitivity to predict SARS-CoV-2 shedding from 60.0% (95% confidence interval [CI], 52.9%–66.7%) to 31.5% (95% CI, 25.7%– 38.0%) but increased specificity from 77.5% (95% CI, 75.3%–79.5%) to 93.8% (95% CI, 92.7%–94.8%).

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[a]A. B. and A. M. D. contributed equally to this work.

Correspondence: A. Bershteyn, Department of Population Health, New York University Grossman School of Medicine, 227 E 30th St, New York, NY 10016 (Anna.Bershteyn@nyulangone.org).

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Coronavirus disease 2019 (COVID-19) symptom assessments are widely used to screen attendees of congregate venues such as schools [1], workplaces [2], and entertainment facilities [3]. However, COVID-19 symptoms are nonspecific and overlap with other conditions [4]. Common COVID-19 symptom definitions, such as those of the US Centers for Disease Control (CDC) [5] and the World Health Organization (WHO) [6], do not include metrics of severity, giving equal weight to mild, moderate, and severe symptoms. We examined symptom severity among adults undergoing daily severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing.

METHODS

Between March and August 2020, a total of 780 asymptomatic outpatients in the US enrolled in a hydroxychloroquine postexposure prophylaxis trial after close contact with a confirmed COVID-19 case [7]. For 16.2% of participants (n = 126), exposure to SARS-CoV-2 occurred through caring for a patient with SARS-CoV-2 in a clinical setting without appropriate personal protective equipment. For the remaining 83.8% (n = 654), exposure occurred through shared residence or prolonged close contact in a confined space.

Participants completed symptom surveys and provided nasal swab samples daily for 14 days. Swab samples were tested for SARS-CoV-2 RNA, as described elsewhere [8]. Symptoms were self-assessed as "mild" (symptoms did not interfere with daily activities), "moderate" (symptoms interfered with daily activities), or "severe" (symptoms prevented daily activities, required an emergency room visit, or required hospitalization).

We studied the association between symptom severity and SARS-CoV-2 detection. In our primary analysis, viral detection was defined as cycle threshold (Ct) ≤40, symptom severity was defined as the most severe symptom reported, and COVID-19 symptoms were defined according to CDC criteria [5], which included cough, shortness of breath, loss of taste, or loss of smell; or ≥2 of the following: fever, chills, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion, and runny nose. We further performed alternative analyses in which viral detection was defined as Ct ≤30, symptom severity was defined as a minimum threshold below which symptoms were excluded from contributing toward criteria, and COVID-19 symptoms were defined according to WHO criteria [6], which included fever and dry cough; or loss of taste or smell; or ≥3 of the following: fever, dry cough, fatigue, headache, muscle aches,

sore throat, coryza (nasal congestion, runny nose, or sneezing), shortness of breath, nausea or vomiting, or diarrhea. Two-sided 95% confidence intervals (CIs) were produced using generalized estimating equations with clustering by participant [9].

The study was approved by the Western Institutional Review Board, with reliance agreements with the collaborating institutions. The study was registered with ClinicalTrials.gov (NCT04328961). All study participants provided written informed consent.

RESULTS

The median age of participants (interquartile range [IQR]) was 39 (26–51) years, and 59.6% (n = 465) were assigned female sex at birth. SARS-CoV-2 RNA was detected in 23.2% of participants (n = 181) during follow-up, with 10.6% testing positive on the first day of follow-up (prevalent infection) and 12.6% testing negative on the first day and positive on a subsequent day (incident infection). Age and sex were similar for participants with prevalent, incident, or no SARS-CoV-2 detected (median ages, 37, 37, and 39 years, respectively; proportion female, 55.4%, 57.1%, and 60.0%, respectively).

On a given day, the mean number of COVID-19 symptoms reported by any participant was 1.15, of which 83.3% were mild, 14.9% were moderate, and 1.8% were severe. For participants shedding SARS-CoV-2 on a given day, the mean number of symptoms reported was 3.11, of which 75.7% were mild, 20.5% were moderate, and 3.8% were severe. For participants not shedding SARS-CoV-2 on a given day, the mean number of symptoms reported was 0.95, of which 85.8% were mild, 13.1% were moderate, and 1.1% were severe.

Mild symptoms that met CDC criteria were reported on 28.5% of days when participants shed SARS-CoV-2 and 16.3% of days when they did not (Figure 1A and B). At least 1 moderate or severe symptom, combined with symptoms of any severity meeting CDC criteria, was reported on 31.5% of days when participants shed SARS-CoV-2 and 6.2% of days when they did not. Moderate or severe symptoms were mostly reported in the first week of shedding (Figure 1C) and rarely reported before shedding onset or among participants who never shed SARS-CoV-2 (Figure 1D).

Symptom severity changed frequently over the course of follow-up (Figure 1C, *lines between bars*). CDC symptom criteria were met at least once by 80.7% of participants who ever shed SARS-CoV-2 and 58.3% of participants who never shed SARS-CoV-2. CDC criteria plus ≥1 moderate or severe symptom occurred in 52.5% of participants who ever shed SARS-CoV-2 and 26.6% of participants who never shed SARS-CoV-2.

Adding ≥1 moderate or severe symptom to CDC criteria would decrease the sensitivity (ie, true-positive rate) of symptoms for concurrent SARS-CoV-2 shedding from 60.0% (95% CI, 52.9%–66.7%) to 31.5% (95% CI, 25.7%–38.0%), but would increase the specificity (ie, true-negative rate) from 77.5% (95% CI, 75.3%–79.5%) to 93.8% (95% CI, 92.7%–94.8%). Similar trade-offs were observed for shedding the following day or on any future day of follow-up (Supplementary Table 1). Adding ≥1 moderate or severe symptom increased the positive predictive value of CDC symptoms from 21.4% (95% CI, 17.8%–25.7%) to 34.3% (95% CI, 27.8%–41.4%), while the negative predictive value remained similar, decreasing from 95.0% (95% CI, 93.7%–96.0%) to 93.1% (95% CI, 91.7%–94.2%).

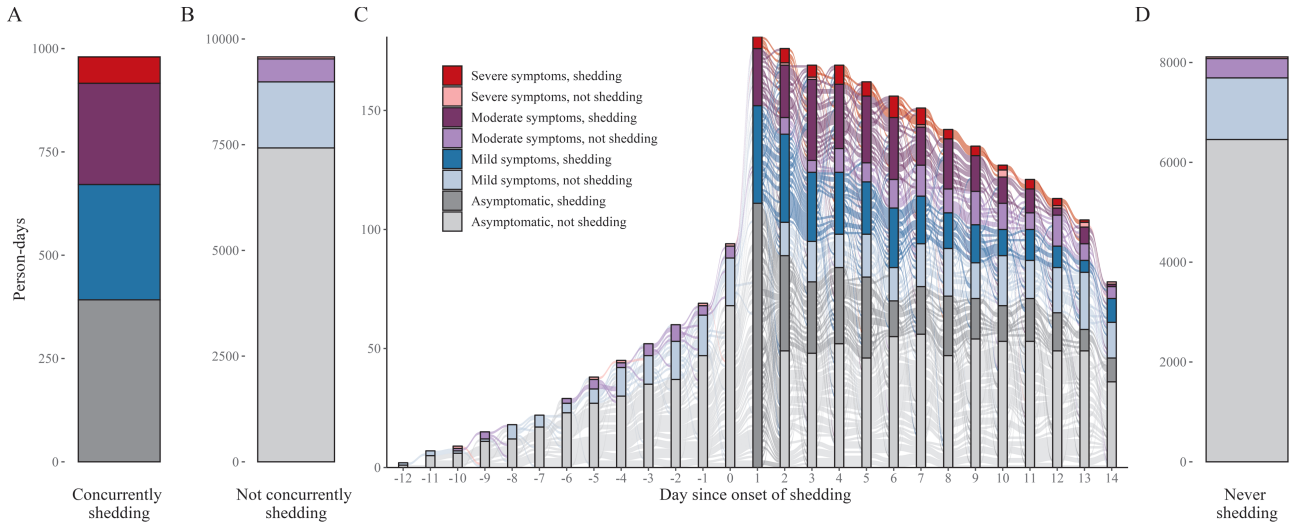

Figure 1. Number of person-days during which participants did not meet Centers for Disease Control and Prevention (CDC) symptom criteria (*gray*) or met CDC symptom criteria with only mild symptoms (*blue*), ≥1 moderate symptom (*purple*), or ≥1 severe symptom (*red*). Person-days are shown according to whether a participant is concurrently shedding (*A*), not concurrently shedding (*B*), or never shedding during follow-up (*D*) and by day since shedding onset (*C*). Lines between bars in (*C*) depict changes in symptom status of individual participants on sequential days.

In the alternative analyses, moderate or severe symptoms were more common with Ct values ≤30. With Ct ≤30, the true-positive rate was higher (41.5% [95% CI, 32.5%–51.1%]), the but true-negative rate was lower (92.7% [95% CI, 91.5%–93.8%]). When only moderate or severe symptoms were considered or when WHO criteria were used, the true-positive rate was lower and the true-negative rate was higher (Supplementary Table 1). Individual symptoms most predictive of SARS-CoV-2 infection were loss of smell, fever, and loss of taste (Supplementary Table 2). When restricting analysis to moderate or severe symptoms, individual symptoms most predictive of SARS-CoV-2 infection were loss of smell, chills, and loss of taste.

Participants who reported moderate or severe symptoms at least once during follow-up tended to be younger (median age [IQR], 36.5 [25–48] years) than those who remained asymptomatic or reported only mild symptoms (median age, 40 [27–51] years); however, those who reported moderate or severe symptoms and also tested positive at least once during follow-up tended to be older (median age [IQR], 39 [25–50] years) than those who remained asymptomatic or had only mild symptoms despite testing positive at least once during follow-up (median age, 36.5 [23–53] years). Similar proportions were female among those who reported moderate or severe symptoms (61%) and those who remained asymptomatic or reported only mild symptoms (59%).

DISCUSSION

In this cohort of US adults recently exposed to a confirmed SARS-CoV-2 case, COVID-19 symptom criteria were highly nonspecific. A majority of participants never shedding SARS-CoV-2 over a 2-week period met CDC symptom criteria on ≥1 day. On a given day, >1 in 5 participants not shedding SARS-CoV-2 met symptom criteria, predominantly owing to mild symptoms.

Augmenting COVID-19 symptom definitions to include ≥1 moderate or severe symptom increased the specificity of symptom criteria but decreased the sensitivity. Such a trade-off may be appropriate when specificity is desirable, such as when individuals not meeting symptom criteria will undergo further screening for SARS-CoV-2. For example, many work, education, travel, and entertainment venues require symptomatic individuals to remain at home, but also require SARS-CoV-2 testing for attendees.

Our study has several limitations. Study participants were US adults recently exposed to a confirmed COVID-19 case, and findings may not be generalizable to other populations. Symptom self-assessment occurred in the context of a clinical trial rather than screening for event attendance, which may have resulted in different reporting patterns, including a possible Hawthorne effect [10]. Symptom and shedding profiles do not account for SARS-CoV-2 variants that emerged since mid-2020. Finally, study participants were unvaccinated; symptoms likely differ for vaccinated individuals.

In conclusion, adding symptom severity can improve the specificity of COVID-19 symptom definitions. However, positive predictive values were low even when including symptom severity, highlighting the limitations of COVID-19 symptom self-assessment.

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

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