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Inflammatory but not respiratory symptoms are associated with ongoing upper airway viral shedding in outpatients with uncomplicated COVID-19

Karen B. Jacobson[a,1,**], Natasha Purington[b,1], Julie Parsonnet[a], Jason Andrews[a], Vidhya Balasubramanian[b], Hector Bonilla[a], Karlie Edwards[a], Manisha Desai[b], Upinder Singh[a,c], Haley Hedlin[b], Prasanna Jagannathan[a,c,*]

[a] Department of Medicine, Stanford University, Stanford, CA, USA
[b] Quantitative Sciences Unit, Stanford University, Stanford, CA, USA
[c] Department of Microbiology and Immunology, Stanford University, Stanford, CA, USA

ABSTRACT

Although the vast majority of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections are uncomplicated, our understanding of predictors of symptom resolution and viral shedding cessation remains limited. We characterized symptom trajectories and oropharyngeal viral shedding among 120 outpatients with uncomplicated Coronavirus Disease of 2019 (COVID-19) enrolled in a clinical trial of Peginterferon Lambda, which demonstrated no clinical or virologic benefit compared with placebo. In the combined trial cohort, objective fever was uncommon, inflammatory symptoms (myalgias, fatigue) peaked at 4 to 5 days post-symptom onset, and cough peaked at 9 days. The median time to symptom resolution from earliest symptom onset was 17 days (95% confidence interval 14−18). SARS-CoV-2 IgG seropositivity at enrollment was associated with hastened resolution of viral shedding (hazard ratio 1.80, 95% confidence interval 1.05−3.1, $P = 0.03$), but not with symptom resolution. Inflammatory symptoms were associated with a significantly greater odds of oropharyngeal SARS-CoV-2 RNA detection; respiratory symptoms were not. These findings have important implications for COVID-19 screening approaches and trial design.

1. Introduction

As of October 2021, 241 million individuals have been confirmed infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and over 4.9 million have died (COVID-19, 2021). Despite high mortality in the elderly and among those with medical comorbidities, the vast majority of individuals have uncomplicated disease, with only mild to moderate symptoms, and do not require hospitalization. However, these individuals contribute to ongoing transmission, and some develop prolonged symptoms and sustained disability (Petersen et al., 2021). A better understanding of the natural history of uncomplicated Coronavirus Disease of 2019 (COVID-19) would help guide the development of

therapeutics needed to shorten the duration of viral shedding, relieve symptoms, and prevent hospitalizations.

Most published reports of COVID-19 symptomatology are derived from hospitalized patients, in whom fever and shortness of breath are common (Ferguson et al., 2020; To et al., 2020; Wang et al., 2020). In contrast, outpatients with more mild disease report less fever, but hyposmia is more common (Kim et al., 2020; Skipper et al., 2020). Data on symptom trajectories and clusters are limited, as studies in outpatients have largely been limited to cross-sectional surveys. Furthermore, the relationship of these syndromes to viral shedding and SARS-CoV-2 antibody responses has not been described in detail.

In this study, we leveraged a cohort of participants with uncomplicated COVID-19 enrolled in a randomized, placebo-controlled trial of Peginterferon Lambda to perform a detailed examination of the symptomatology and natural history of uncomplicated SARS-CoV-2 infection. We aimed to (1) characterize symptom trajectories and clusters; (2) assess predictors of symptom resolution and cessation of oropharyngeal viral shedding; and (3) evaluate associations between symptoms and viral shedding.

2. Methods

2.1. Study setting and participants

SARS-CoV-2-infected outpatients were enrolled in a double-blind, placebo-controlled, phase 2 trial of Peginterferon Lambda-1a (Lambda, NCT04331899). Inclusion/exclusion criteria and the study protocol for the trial have been published (Jagannathan et al., 2021). Briefly, adults aged 18 to 75 years with any FDA emergency use authorized reverse transcription-polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 within 72 hours prior to enrollment were eligible for study participation. Exclusion criteria included hospitalization, respiratory rate >20 breaths per minute, room air oxygen saturation <94%, pregnancy or breastfeeding, decompensated liver disease, recent use of investigational and/or immunomodulatory agents for treatment of COVID-19, and prespecified lab abnormalities (Supplementary Methods). All participants gave written informed consent and all study procedures were approved by the Institutional Review Board of Stanford University (IRB-55619).

2.2. Study procedures

On the day of enrollment, participants completed a standardized history, including the duration of symptoms prior to enrollment, physical exam and bloodwork. Participants were randomized 1:1 to receive a single subcutaneous injection of Lambda or saline placebo and followed for 28 days. Participants completed a daily symptom questionnaire and recorded daily in-home measurements of temperature and oxygen saturation using study-provided devices (REDCap Cloud). In-person visits were conducted on Days 1, 3, 5, 7, 10, 14, 21, and 28 post-enrollment with assessment of symptoms and vitals, and collection of oropharyngeal swabs (FLOQ Swabs; Copan Diagnostics). Peripheral blood was collected for assessment of complete blood count, metabolic panel, and SARS-CoV-2 IgG antibodies against the SARS-CoV-2 spike receptor binding domain (RBD, Supplementary Methods).

2.3. Statistical analysis

Analyses were conducted in R version 4.0.2 (R Development Core Team, 2020) or Stata SE (version 14). Cohort demographics, baseline characteristics and distribution of symptom prevalence were summarized descriptively. Symptom duration prior to enrollment determined symptom start day. Symptoms reported pre-enrollment were assumed to have been continuously experienced from the first reported day until enrollment. Symptoms occurring more than 21 days prior to enrollment were deemed non-COVID related and excluded. Outcomes measured included symptom prevalence and duration, time to resolution of symptoms and cessation of viral shedding.

2.3.1. Symptom prevalence and duration

Differences in symptom prevalence and the proportion of participants reporting symptoms over time by treatment arm were tested using the Kruskal-Wallis rank sum test and Fisher's exact test, respectively. Given the duration of symptoms and duration of viral shedding were similar overall between treatment arms, (Jagannathan et al., 2021) we included participants from both the Lambda and placebo arms in this analysis. Repeated measures of at-home temperature and oxygen saturation were modeled using linear regression models with robust standard errors and generalized estimating equations to account for repeated measures within participants.

2.3.2. Symptom clusters

Spearman's correlation coefficient and exploratory factor analysis were used to assess pairwise correlations between symptom severity and whether symptoms clustered at various days from symptom onset, respectively. Exploratory factor analysis was carried out on symptoms reported at symptom onset and on days 4, 7, 10, 14, and 21 after symptom onset. Only symptoms with more than 5% overall study prevalence were chosen for examination (Supplementary Methods). Changes in factors derived and symptoms contributing to each factor were compared descriptively across time points of interest. The joint trajectory of symptoms was assessed to determine whether participant clusters persist over time (Supplementary Methods). Fisher's exact test and the Kruskal-Wallis rank sum test were used to test for differences in baseline characteristics and demographics by cluster assignment.

2.3.3. Time to event analyses

Time to first symptom resolution among those reporting symptoms was defined in 2 ways: (1) as time from reported symptom onset, and (2) as time from enrollment, until the first day when no symptoms were reported, given that vital signs and laboratory tests were not measured prior to enrollment. Participants who did not experience resolution were censored on the day of their last reported symptom. Cox proportional hazards models were fit as a function of covariates of interest. Both models included age at randomization, sex, body mass index (BMI), race/ethnicity, and treatment arm. The time from enrollment model additionally included pre-enrollment symptom duration, oxygen saturation, heart rate, alanine transaminase, white blood count, lymphocyte count, oropharyngeal PCR result, and seropositivity at enrollment. The proportional hazards assumption was assessed by evaluating scaled Schoenfeld residuals (Gill RaS, 1987).

Time to cessation of viral shedding was defined as time from first recorded positive test (pre-enrollment) until first of 2 consecutive negative oropharyngeal tests. Participants who did not experience shedding cessation were censored at the time of their last positive test or Day 1 if no positive test was observed. Cox proportional hazards model were fit as a function of all demographic and vital/lab measurements at enrollment described above, excluding pre-enrollment symptom duration.

For all models, crude and adjusted hazard ratios, 95% confidence intervals, and Kaplan-Meier estimates were reported.

2.3.4. Associations between viral detection and symptomology

Mixed effect logistic regression models were fit to PCR result (positive vs negative) as a function of symptom reported (yes vs no), days from randomization, continuous age at randomization, sex, treatment arm, and a random effect for participant to account for repeated measures over time within a participant. This model was fit to each of the 16 symptoms as defined in Fig. 1. Days from enrollment was used in order to align the longitudinal PCR and symptom data. Only days when both the symptom questionnaire and PCR results were available were included. Odds ratios, 95% CIs, and P values for symptom were reported from each model.

2.3.5. Additional analyses

Fisher's exact test and the Kruskal-Wallis rank sum test were used to test for differences in baseline characteristics and demographics.

P values <0.05 were considered statistically significant. As these were secondary analyses, we did not adjust for multiplicity, but instead consider our findings to be hypothesis generating.

3. Results

3.1. Study participants

We enrolled 120 participants between April 25 and July 17, 2020 (Fig. S1). The median age was 36 years, 50 participants (41.7%) were female, and 75 (62.5%) were LatinX ethnicity (Table S1). At enrollment, 3 (2.5%) of participants had a temperature >100.4°F, and 49
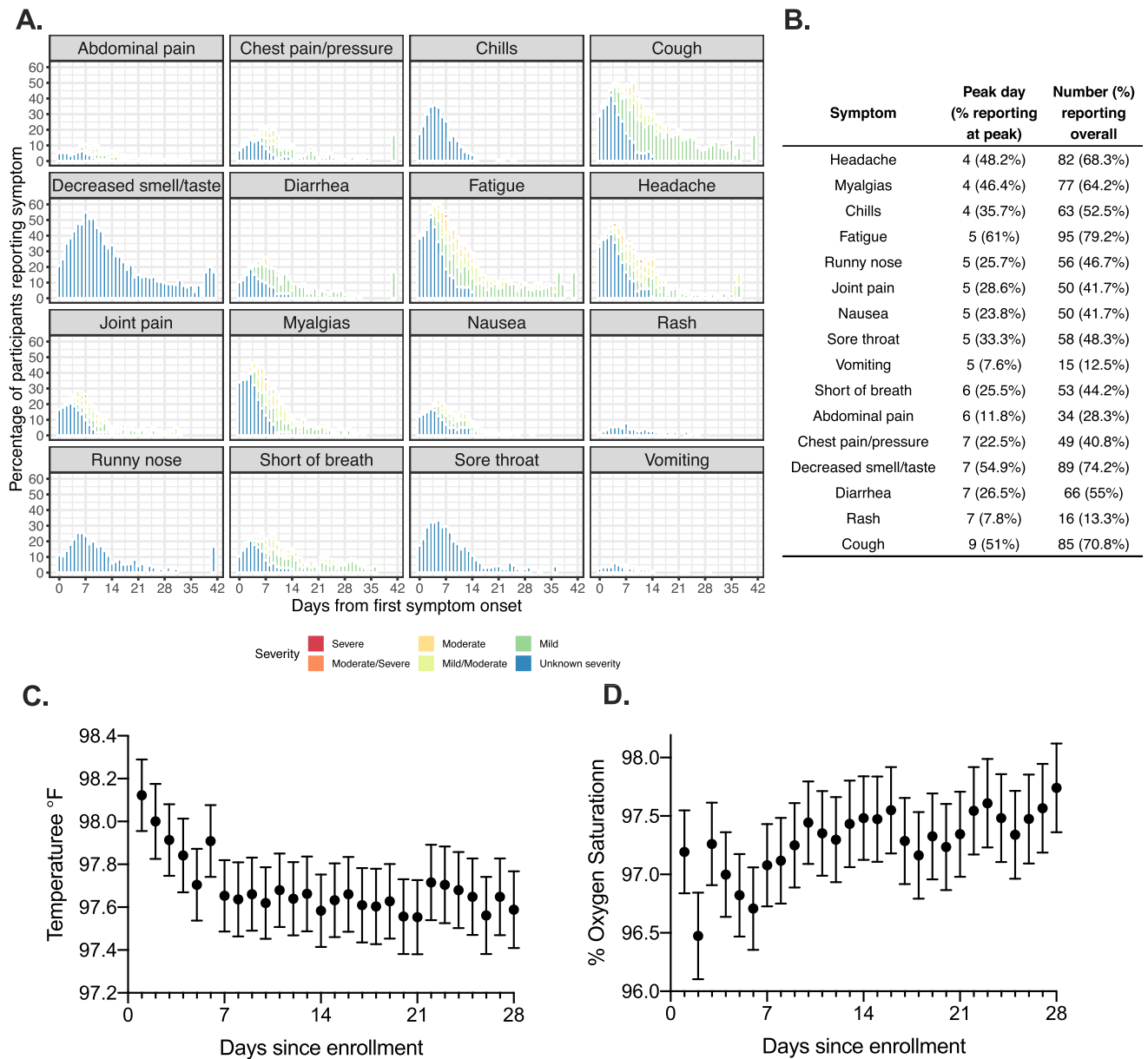
Fig. 1. Overall symptom summary and daily measurements of temperature and oxygen saturation. (A) Distribution of the percentage of participants reporting each symptom by day from symptom onset. Color represents the severity of the symptom reported. "Unknown severity" includes both symptoms in which severity was not asked and symptoms reported as starting prior to enrollment. (B) Summary of the peak day of which each symptom was reported with corresponding percentage (%) of participants reporting the symptom on the peak day, and the number and percentage of participants reporting each symptom at least once during the study period. For symptoms present prior to enrollment, severity data was not collected. Temperature (C) and oxygen saturation (D) was measured daily at home using study-provided equipment. Shown are mean temperature and mean percent oxygen saturation with 95% confidence intervals (marginal estimates from GEE models) on each day after enrollment.

(40.8%) were SARS-CoV-2 IgG seropositive. SARS-CoV-2 IgG seropositive participants had a significantly longer duration of symptoms prior to enrollment compared with seronegative participants (Fig. S2). Overall, 110 participants (91.7%) completed 28 days of follow-up, and the proportion of missing follow-up visits was 44/960 (4.6%).

3.2. Symptom prevalence and trajectories

The most prevalent symptoms over the course of 28 days of follow-up were fatigue (n = 95, 79.2%), decreased smell/taste (n = 89, 74.2%), and cough (n = 85, 70.8%, Fig. 1A). Headache, myalgias and chills were the first symptoms to peak at day 4, while cough did not peak until day 9 (Fig. 1B). In 18/120 (15%) of participants, symptoms persisted through day 28 follow-up, with fatigue (7/18), cough and decreased taste/smell (5/18), and shortness of breath (4/18) reported in participants.

There were no statistically significant differences in the proportion of participants experiencing each symptom at any point in the study by arm (Fig. S4A-D; Table S4). However, we found that the distributions over time of diarrhea, rash, runny nose, fatigue, myalgias, and chest pain/pressure differed between placebo and lambda, with these symptoms peaking later in Lambda vs. placebo (Wilcoxon rank sum test P < 0.05; Fig. S4A-D; Table S4). Therefore, while the overall prevalence of symptoms was similar between the 2 arms, there were some individual symptoms that lasted longer in the Lambda arm than the placebo arm.

Of 2730 at-home daily oral temperature measurements among 118 participants (average 23.1 measurements/participant), only 7 (0.3%) measurements in 6 participants were >100.4°F. However, oral temperatures decreased significantly after enrollment, with mean temperatures declining from 97.9°F (95% CI 97.8–98.0) between days 1 to 6 to 97.6°F (95% CI 97.5–97.7) between days 7 and 28 (coef 0.75,
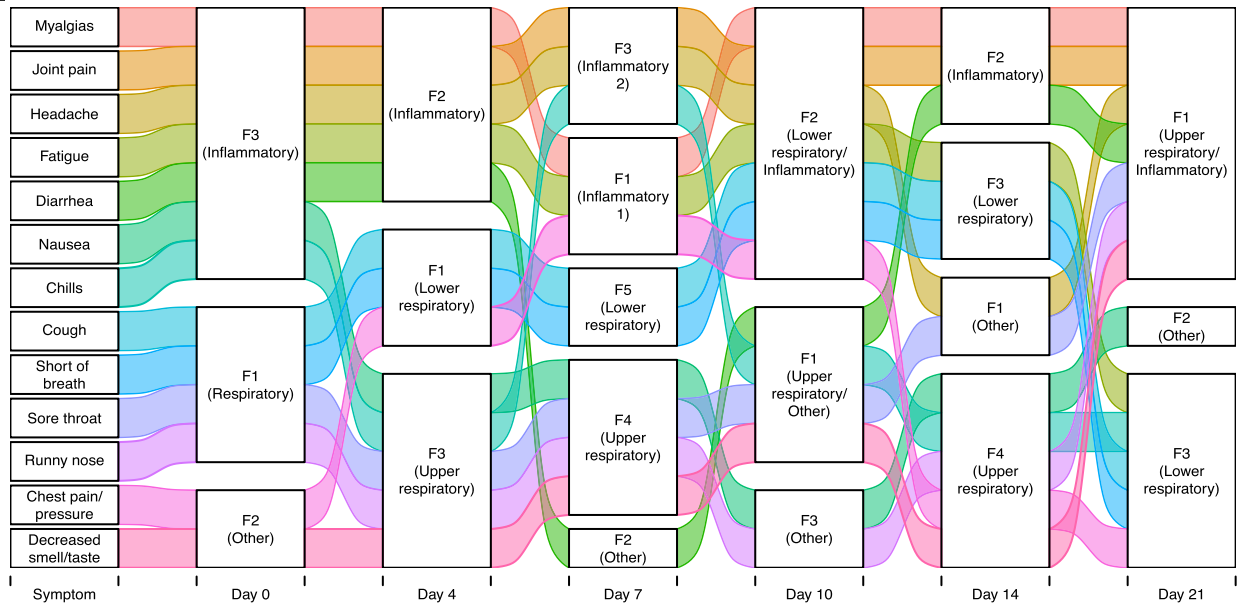
A.
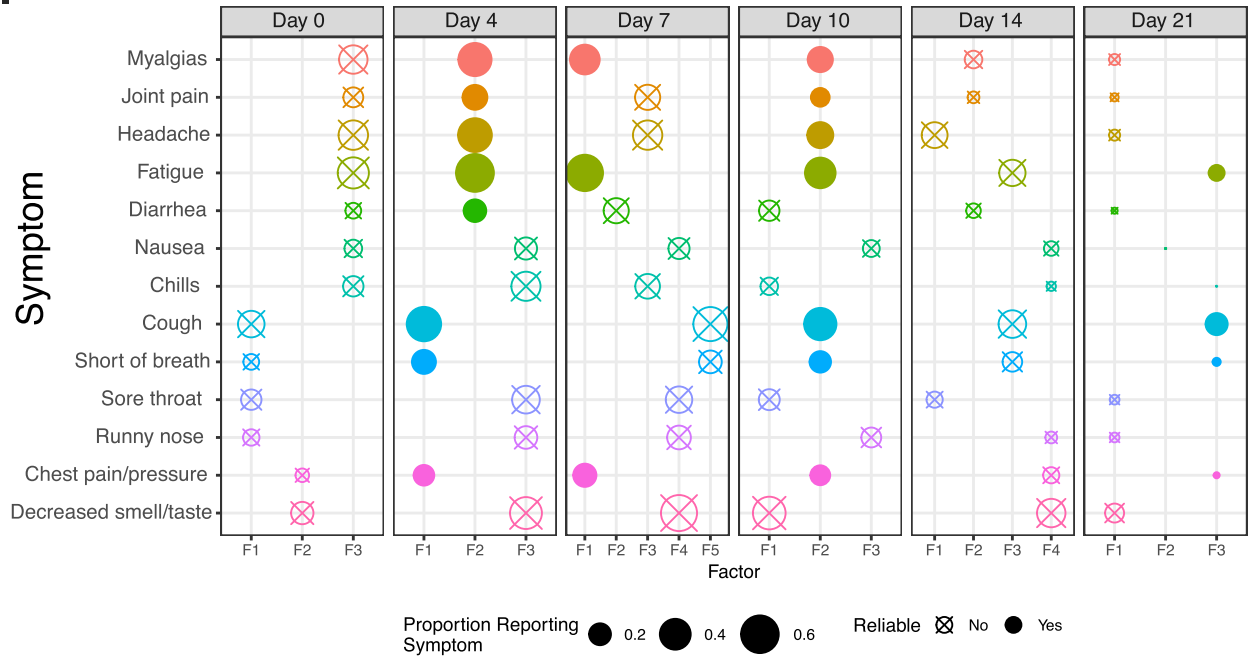
B.

Fig. 2. Symptom clusters by days from symptom onset as identified by exploratory factor analysis. (A) Dot plot of symptoms by days from symptom onset and resulting factors. Size of dot represents the proportion of participants reporting that symptom on that day. Symptoms that load on a factor are represented by a symbol (reliable vs not). Within-factor reliability is defined as a Cronbach's alpha of 0.70 and above. (B) Alluvial plot of how symptoms group into clusters/factors and how those groups change over time.

95% CI 0.66−0.84, *P* < 0.001, Fig. 1C). In parallel, at home oxygen saturation measurements increased from 96.9% (95% CI 96.6−97.2) from days 1 to <7 to 97.4% (95% CI 97.2−97.6) from days 7 to 28 (coef 0.46, 95% CI 0.21−0.72, *P* < 0.001, Fig. 1D).

3.3. Symptom clusters

On the day of symptom onset (day 0), 3 symptom clusters were identified (Fig. 2, Table S2, Fig. S5A-F)—inflammatory (myalgias, joint pain, fatigue, headache), respiratory (shortness of breath, runny nose), and other (decreased smell/taste, chest pain/pressure), although poor within-cluster reliability was found, in

which symptoms did not consistently load on the same factor (Fig. 2A). The inflammatory symptom cluster persisted and increased in reliability from day 4 to day 10 before decreasing (Fig. 2A,B). After day 0, 2 distinct respiratory clusters were identified, including upper (sore throat, runny nose, nausea) and lower (shortness of breath, cough, chest pain/pressure) respiratory tract symptoms. Interestingly, a larger cluster encompassing lower respiratory and inflammatory clusters emerged between days 7 and 10 of symptom onset.

We next assessed the joint trajectory of symptoms over time among 81 participants with symptom data, and 2 participant groups emerged (Fig. 3). Cluster B (n = 7) generally had greater symptom
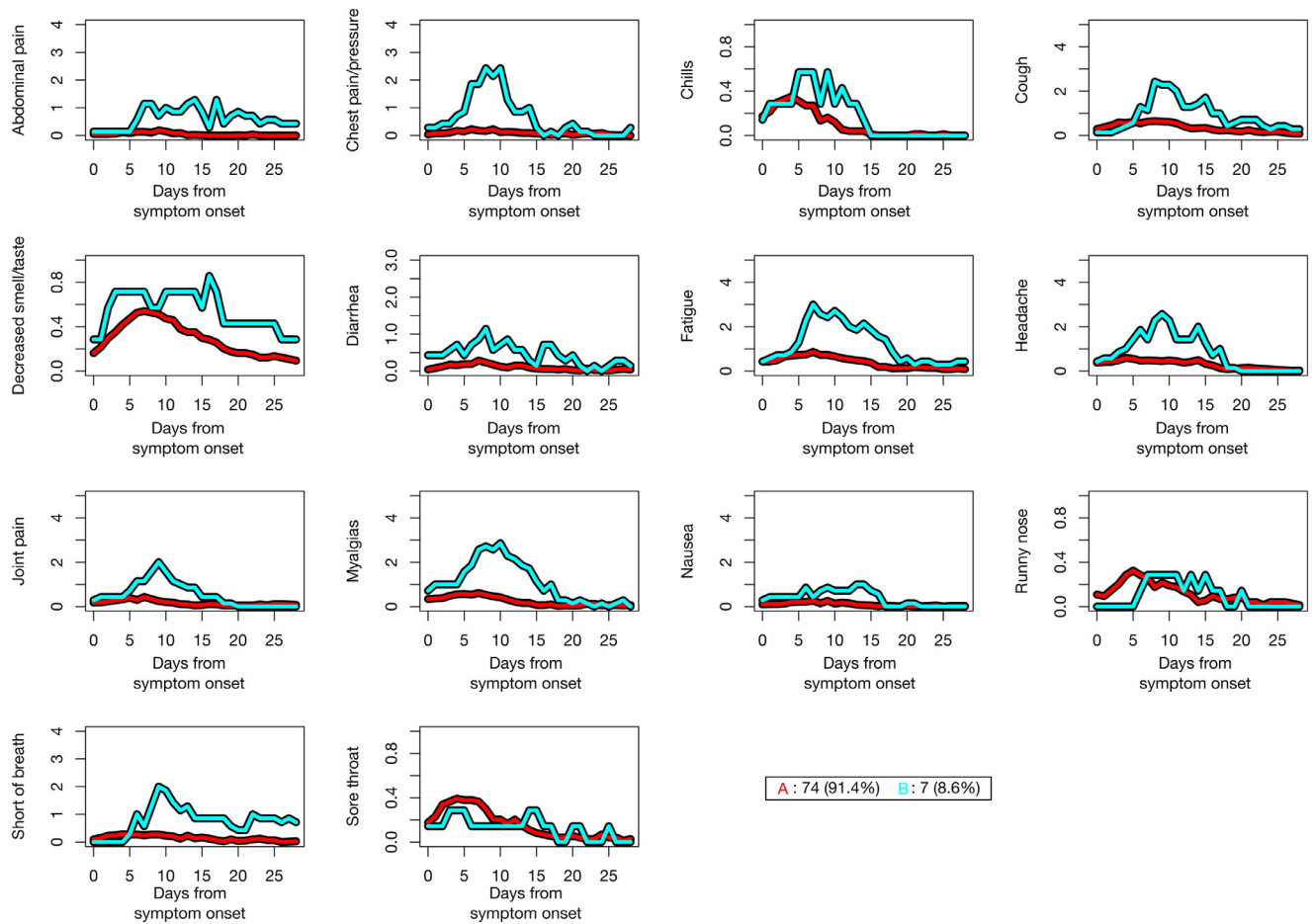
Fig. 3. Longitudinal symptom trajectories by participant cluster. Participant clusters identified by joint trajectory analysis (A and B). Cluster A (red, n = 74 participants) characterized by higher prevalence of runny nose and sore throat. Cluster B (teal, n = 7 participants) characterized by greater symptom severity and/or later peak severity (chest pain/pressure, fatigue, and myalgias.) Y-axis represents the severity of the symptom (0 = Not reported; 1 = Mild; 2 = Mild to Moderate; 3 = Moderate; 4 = Moderate to Severe; 5 = Severe for the scores ranging from 0 to 5 and 0 = Not reported to 1 = Reported for scores ranging from 0 to 1), while the x-axis represents days from symptom onset. Participants with more than 2 consecutive days of missing symptom data (n = 39) were excluded.

severity and/or later peak severity than cluster A, especially chest pain/pressure, fatigue, and myalgias. However, cluster A (n = 74) had slightly higher prevalence of runny nose and sore throat compared to cluster B. There were no differences between Clusters A and B in terms of demographics, BMI, initial lab values, or baseline seropositivity (Table S3). While participants in cluster B had slightly shorter time to viral shedding cessation, these differences were not statistically significant.

3.4. Predictors of symptom resolution

Median time to symptom resolution from earliest symptom onset was 17 days (95% CI 14−18). Participants with higher BMI were less likely to experience symptom resolution (hazard ratio [95% CI]: 0.92 [0.85−1.0, Fig. 4A). Participants identifying as LatinX had more rapid symptom resolution compared to those identifying as non-LatinX, white participants (hazard ratio [95% CI]: 2.10 [1.23−3.60]). When considering predictors of symptom resolution from the time of enrollment, for every 10 unit increase in alanine transaminase at enrollment, likelihood of symptom resolution increased by 10% (Fig. 4B). Neither enrollment seropositivity nor oropharyngeal swab cycle thresholds were significantly associated with symptom resolution (Fig. 4B). Treatment arm was not a predictor of symptom resolution.

3.5. Virologic trajectories and predictors of viral shedding cessation

The median time to cessation of oropharyngeal viral shedding was 10 days from first reported positive test (95% CI: 8−12), with 108 participants experiencing cessation of viral shedding during the study. SARS-CoV-2 IgG seropositivity (HR [95% CI]: 1.8 [1.1, 3.1]) at enrollment were associated with more rapid viral shedding cessation (Fig. 4C). Higher cycle threshold (Ct) values at enrollment were also associated with more rapid viral shedding cessation in an independent model (HR [95% CI]: 1.2 [1.1, 1.2], P < 0.001). Treatment arm, other baseline demographics, and other measured laboratory values were also not significantly associated with viral shedding cessation (Fig. 4C).

3.6. Associations between clinical symptoms and oropharyngeal viral shedding

We visually assessed whether time from enrollment until viral shedding cessation and symptom resolution were similar in our cohort (Fig. 5A). Half of participants included stopped shedding virus by 7 days after enrollment, while half of participants experienced symptom resolution 2 days later on study day 9. While most participants experienced shedding cessation before their symptoms resolved, the survival probability was similar over time for both outcomes.
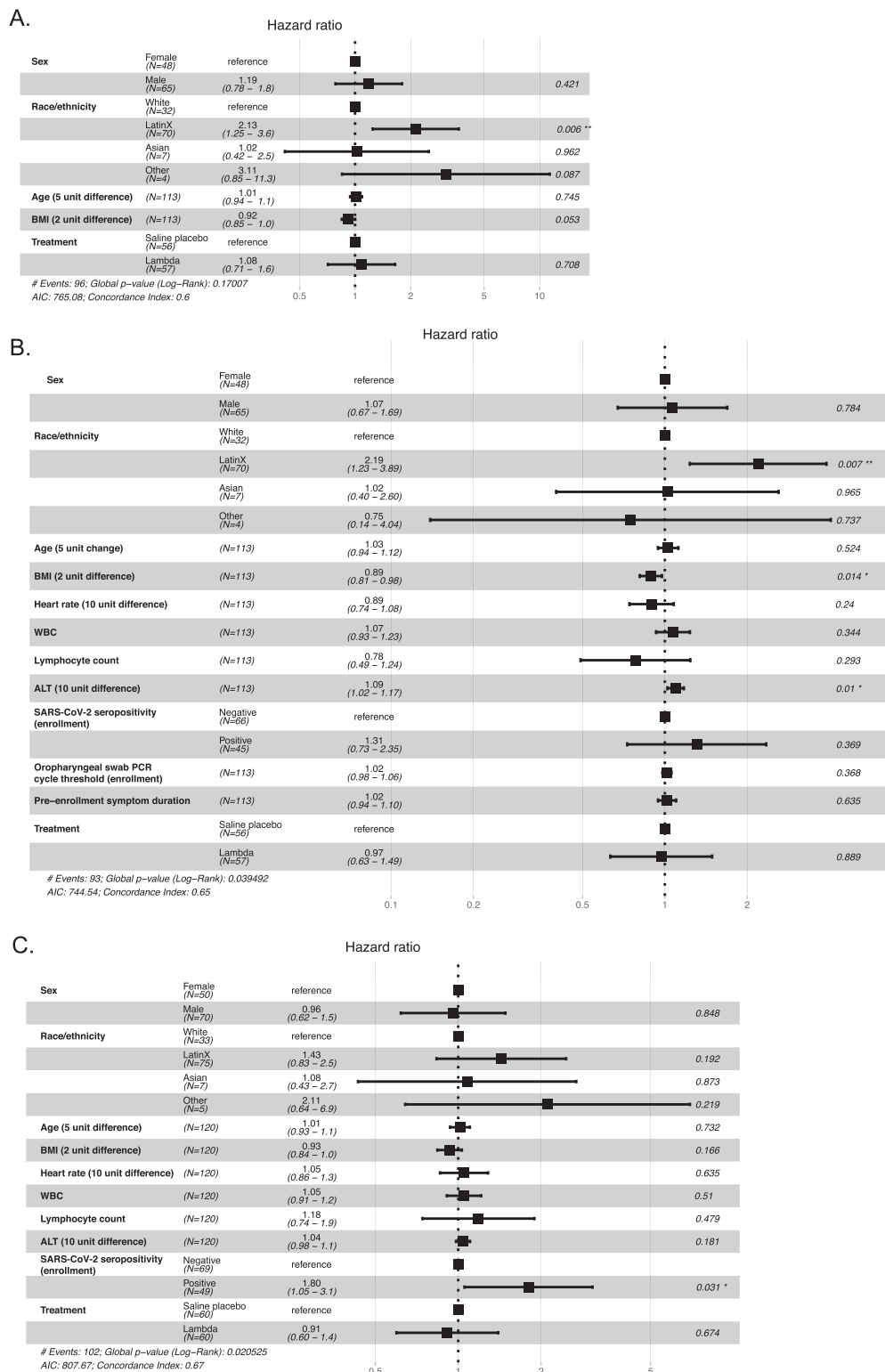
Fig. 4. Predictors of time to symptom resolution and time to viral shedding cessation. Forest plots of the multivariable Cox proportional hazards model for (A) time from symptom onset and (B) time from enrollment to first day of symptom resolution, and C) time from first positive PCR test to time to first of 2 consecutive negative PCR tests. Vital signs and clinical labs were measured at enrollment. Time from enrollment model additionally adjusted for sex, age, race/ethnicity, BMI and treatment arm. Visualizations of each hazard ratio are presented on the log-HR scale. ALT = alanine transaminase; WBC = white blood count. N = 111 (# events=96), N = 107 (# events=93), and N = 114, (# events = 102), respectively.

Finally, we assessed whether specific symptoms were associated with detection of oropharyngeal SARS-CoV-2 RNA. On each day, the majority of participants reporting symptoms had detectable oropharyngeal SARS-CoV-2 RNA (Fig. 5B). In multivariable analysis, joint pain (OR 2.88, 95% CI 1.39−5.99), myalgias (OR 2.71, 95% CI 1.51 −4.84), chills (OR 2.4, 1.16−4.99), and fatigue (OR 1.68, 95% CI 1.01 −2.81) were associated with significantly greater odds of oropharyngeal SARS-CoV-2 RNA detection (Fig. 5C). In contrast, there was no statistically significant association between presence or absence of upper respiratory symptoms (e.g., runny nose, shortness of breath,
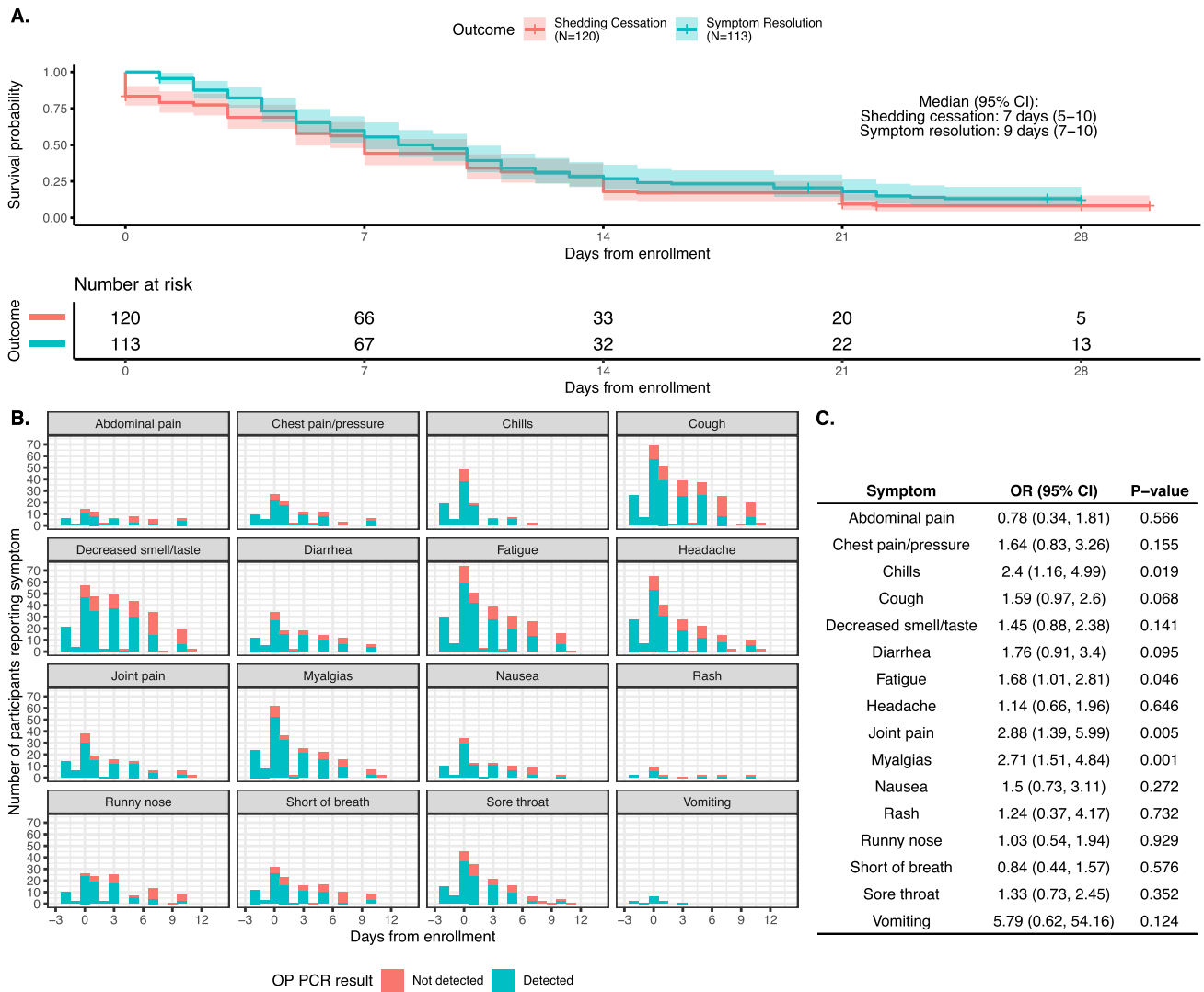
Fig. 5. Associations between clinical symptoms and oropharyngeal viral shedding. (A) Joint Kaplan-Meier survival plots of time to shedding cessation and symptom resolution from enrollment. Lines are not mutually exclusive. (B) Stacked bar plots of number of participants reporting symptoms on each day by symptom and oropharyngeal (OP) PCR result. Within each bar, color represents the proportion of those participants with either PCR detected or not detected. (C) Mixed effect logistic regression model results for odds of a positive PCR as a function of symptom reported (yes/no), age at enrollment, sex, treatment arm, and time from first positive result. Odds ratios (ORs) in each row correspond to a separate symptom model.

sore throat, anosmia) and odds of oropharyngeal SARS-CoV-2 RNA detection.

4. Discussion

In this study, we leveraged a comprehensive and detailed dataset among outpatients with uncomplicated COVID-19 enrolled in a Phase 2 clinical trial to carefully define symptom prevalence, longitudinal emergence and resolution of individual symptoms and symptom clusters, and associations between symptoms, viral shedding, and SARS-CoV-2 seropositivity. Although objective fever was uncommon, inflammatory symptoms (myalgias, chills, fatigue) were common and peaked early; these symptoms were also associated with ongoing viral shedding. In contrast, respiratory symptoms were not associated with viral shedding. Though SARS-CoV-2 seropositivity at enrollment was associated with more rapid viral shedding cessation, it was not associated with more rapid time to symptom resolution. Participants were enrolled early in the course of disease, with excellent participant retention and little missing data. Only 4 participants were hospitalized, and no deaths observed.

Importantly, though the most prevalent symptoms observed were consistent with previous reports, (Ferguson et al., 2020; Guan et al., 2020; Kim et al., 2020; Struyf et al., 2020; Wang et al., 2020) we observed different prevalence peaks per symptom. The most common initial symptoms were headache, myalgias and chills; these symptoms peaked at 4 days postsymptom onset. Shortness of breath and cough peaked at 6 and 9 days, respectively. These data differ from a prediction model which suggested that cough would precede headache and myalgias (Larsen et al., 2020). Anosmia was common and is likely specific for COVID-19 (Dixon et al., 2020), but was most prominent one week post symptom onset. Thus, patients may be shedding infectious virus for up to one week prior to the onset of "typical" COVID-19 symptoms such as cough, shortness of breath, and anosmia.

Only 3 participants had fever >100.4° F at enrollment, and 6 had fever at any timepoint during follow-up, consistent with other studies which show relative lack of fever in mild/moderate cases compared with severe/critical cases (Ferguson et al., 2020; Kim et al., 2020; Skipper et al., 2020; To et al., 2020; Wang et al., 2020). However, overall temperature did decrease in the first week after

enrollment, after which temperatures remained stable at a mean temperature of 97.6°F. These observations are consistent with recent reports suggesting that "normal" body temperatures are well below the established "normal" of 98.6°F, (Obermeyer et al., 2017; Protsiv et al., 2020) and suggest that temperatures above 97.6°F may represent clinically significant physiologic changes within the context of uncomplicated COVID-19.

LatinX participants were significantly more likely to have symptoms resolve at any point during the study compared to non-LatinX, white participants. This was after controlling for key demographic/clinical characteristics, including age, gender, and BMI. Although it is possible that biologic differences may underlie these differences in symptom resolution, prior reports have suggested that race or ethnic-based differences are not significant predictors of clinically relevant hospitalization outcomes such as mortality, ICU admission, or mechanical ventilation (McCarty et al., 2021; Ogedegbe et al., 2020). These differences may be driven by residual confounding, including the possibility of differential symptom recall bias and/or delays in testing/diagnosis prior to enrollment.

The median time to viral shedding cessation from enrollment was 10 days, consistent with other reports (Fang et al., 2020; Tirupathi et al., 2020). Though other studies have identified disease severity as a risk factor for longer duration of shedding (Fang et al., 2020), in this cohort, only SARS-CoV-2 seropositivity and oropharyngeal PCR cycle thresholds at enrollment were associated with more rapid viral shedding cessation. The majority of participants reporting symptoms on each day had detectable oropharyngeal virus by PCR, suggesting that ongoing presence of symptoms is an indicator of ongoing viral shedding. This supports CDC guidelines (Centers for Disease Control and Prevention, 2020) to continue isolating until symptoms are improved, though PCR positivity does not infer infectivity (Vetter et al., 2020). Myalgia and joint pain were the only symptoms significantly associated with oropharyngeal PCR positivity. These are also some of the earliest symptoms to appear, when viral loads are higher early in disease course and patients are most likely to be infectious. Therefore, screening for respiratory symptoms may miss the most infectious patients, who may attribute their symptoms to other causes.

There were limitations to this study. This cohort was part of a randomized, placebo-controlled trial, where half the cohort received Lambda and the other half received placebo. The duration of symptoms and viral shedding was similar between the 2 arms in the primary analysis (Jagannathan et al., 2021), so we included the entire cohort in order to improve statistical power to perform our analyses. In this analysis of individual symptoms, there were some symptoms that lasted longer in the Lambda vs. placebo arm, although adjustment for treatment arm did not significantly alter our time to event models. Only 4 (3%) participants in this cohort needed hospitalization and 10 (8.3%) went to the ED for evaluation, compared with an incidence of hospitalization of 2.9% to 11% in other outpatient trials (Davoodi et al., 2020; Skipper et al., 2020). This is likely related to study selection criteria, and that recruitment occurred during non-surge conditions when even moderately ill patients were being hospitalized. Median participant age was 36 years, and the cohort was predominantly LatinX, reflecting our local population of COVID-19 cases (Center CoSCEO); however, our findings may not be generalizable to other settings, including those with other circulating SARS-CoV-2 variants and/or post-vaccination infections. Though there was high retention in the study, 34 participants missed 2 consecutive daily symptom surveys and were excluded from the symptom cluster analysis. Though we collected symptom data daily for 28 days after enrollment, time of symptom onset was reported retrospectively by participants at enrollment and thus subject to recall bias. Finally, this is a secondary analysis of data from a clinical trial that was not designed for these analyses, so this study should be considered hypothesis-generating.

In this cohort of participants with uncomplicated COVID-19, distinct symptom clusters and trajectories were identified and

inflammatory symptoms were associated with ongoing viral replication. In contrast, cough, loss of taste/smell, and elevated temperature, which are often used for screening programs, are not always earliest to present and not associated with viral replication, and may therefore not be ideal for screening approaches. Data from this and other longitudinal studies will be critical in shaping our understanding of disease pathogenesis in patients, and for planning large, Phase 3 outpatient studies based on clinical and virologic endpoints.

Authors' contributions

KJ, NP, HH, and PJ designed the study. NP, HH, JP, VB developed study data instruments. KJ, JP, JA, KE, US, PJ collected data. NP, VB, MD, KJ, PJ, and HH prepared the statistical analysis plan and analyzed the data. All authors participated in data interpretation. KJ and PJ wrote the first draft and writing the manuscript and agreed on the decision to publish. There were no confidentiality agreements between the sponsors and authors.

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Declaration of competing interest

The authors have no conflicts of interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.diagmicrobio.2021.115612.

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