Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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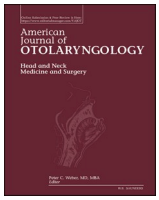

Temporal patterns of nasal symptoms in patients with mild severity SARS-CoV-2 infection

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ABSTRACT

Background: No study to date has analyzed the progression of sinonasal symptoms over time in COVID-19 patients. The purpose of this study is to analyze the progression of sinonasal symptoms and risk factors for olfactory dysfunction in the mild severity COVID-19 patient.

Methods: An internet survey was used to assess sinonasal symptoms in patients with COVID-19. Changes in rhinologic domain and symptom-specific Sinonasal Outcome Test (SNOT-22) scores were compared at five time points: two weeks before diagnosis, at diagnosis, two weeks after diagnosis, four weeks after diagnosis, and six months after diagnosis.

Results: 521 responses were collected. Rhinologic domain SNOT-22 scores increased significantly ($p < 0.001$) to 8.94 at the time of diagnosis, remained elevated two weeks post-diagnosis (5.14, $p = 0.004$), and decreased significantly four weeks post-diagnosis (3.14, $p = 0.004$). Smell-specific SNOT-22 scores peaked at the time of diagnosis (2.05, $p < 0.001$), remained elevated two weeks after diagnosis (1.19, $p < 0.001$), and returned to baseline four weeks post-diagnosis (0.64, $p > 0.999$). Taste-specific SNOT-22 scores also peaked at diagnosis (2.06, $p < 0.001$), remained elevated two weeks after diagnosis (1.19, $p < 0.001$), and returned to baseline four weeks after diagnosis (0.71, $p > 0.999$). There were no significant differences in sense of smell or taste between 1-month and 6-month timepoints.

Conclusion: Sinonasal symptoms, particularly loss of smell and taste, may be important presenting symptoms in the mild severity COVID-19 patient. Our findings support incorporating these symptoms into screening protocols.
Level of evidence: 4

1. Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 and continues to strain the healthcare system throughout the world [1,2]. Although SARS-CoV-2 shares significant genetic similarities with SARS-CoV-1 and the Middle East Respiratory Syndrome coronavirus (MERS), it has proven to spread more rapidly with a higher basic reproduction number despite a lower fatality rate [3]. Early studies in China, where it was first reported, described largely non-specific symptoms such as fever, cough, dyspnea, and fatigue, and more recent data have suggested that over 80% of patients have only mild symptoms [4–7].

Additionally, there is growing evidence in favor of an association between SARS-CoV-2 infection and loss of smell or taste, particularly among those with mild-to-moderate disease [8–11]. This phenomenon of post-viral olfactory dysfunction is not new to otolaryngology, and numerous viruses, including non-SARS-CoV-2 strains of coronavirus, have been implicated [12]. In March 2020, The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) recommended

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that the presence of smell or taste dysfunction, in those without underlying sinonasal or respiratory disease, should alert physicians to the possibility of COVID-19 [13]. Furthermore, the academy's "COVID-19 Anosmia Reporting Tool" was designed for clinicians and patients to gather data about such experiences, in an effort to learn more about this reported association [14]. Since that time, evidence in favor of this association has grown significantly, with a recent meta-analysis reporting a 47% prevalence of smell or taste loss among those with COVID-19 [15]. As a result, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) have endorsed new-onset smell or taste loss as symptoms of SARS-CoV-2 infection [16,17].

Although a strong association has been demonstrated between COVID-19 and chemosensory dysfunction, few studies have described the temporal progression of these symptoms [18,19]. To our knowledge, only early reports over short follow-up periods have been published [15,20–22]. Currently-available data suggests smell or taste loss is present early in the disease course and that majority of those who experience these symptoms recover function within one to two weeks [15]. However, these studies report that atleast 10% of those with smell or taste loss will have persistent symptoms beyond one month. Furthermore, little is known about the progression of these and other sinonasal symptoms beyond one month. Therefore, the purpose of this study is to characterize the long-term temporal progression of sinonasal symptoms, including smell and taste loss, among a diverse, urban SARS-CoV-2 population over six months. This information may aid in counseling infected persons on the expected recovery from sinonasal symptoms in COVID-19 and provide information in order to assess the feasibility of potential therapeutic approaches.

2. Materials and methods

2.1. Study design and subjects

This study is a prospective, internet-based survey analysis of patients with SARS-CoV-2 infection conducted at an urban, tertiary-care academic medical center within the Chicago region. The clinical research analytics team identified subjects based on the following inclusion criteria: adult patients (18 years and older) with an encounter between January 1, 2020 and April 15, 2020 with laboratory-confirmed SARS-CoV-2 infection. Contact information for these patients including email address and phone number, was provided to the study team. Only living adult patients diagnosed with COVID-19 and discharged to quarantine at home at the time of their evaluation were included, thus defining a "mild severity" cohort of COVID-19 patients. The study received approval from the Rush University Medical Center Institutional Review Board.

2.2. Survey distribution, data collection, and reporting of results

A two-part, internet-based survey was designed using SurveyMonkey and distributed electronically via email to all subjects with a valid email address on file. Survey responses were collected at two separate time points. The initial survey was sent in April and the follow-up survey was sent in September. These were "closed" surveys with each subject receiving a unique email survey invite. Subjects were not allowed to access the survey more than once, preventing multiple responses from a single subject. Survey responses were automatically collected anonymously and stored securely in SurveyMonkey's online database. Partial responses were accepted and included in the results. Survey results were reported according to the Journal of Medical Internet Research's Checklist for Reporting Results of Internet *E*-Surveys (CHERRIES) [23]. Survey completion rate was calculated as the number of surveys completed out of the total number started.

2.3. The sinonasal survey of COVID-19 patients

The initial survey consisted of eight questions to identify: patient demographics; relevant past medical problems, including history of smell or taste dysfunction, seasonal allergies, sinus disease, sinus surgery, asthma, and smoking; and the progression of sinonasal symptoms in relation to a patient's diagnosis of COVID-19. Importantly, the temporal progression of sinonasal symptoms was assessed using the rhinologic domain from a validated symptom-reporting tool widely used among otolaryngologists, the 22-item Sinonasal Outcome Test (SNOT-22) [24]. The rhinologic domain includes symptoms of decreased smell, decreased sense of taste, need to blow nose, sneezing, runny nose, and blockage or congestion of the nose. Initial survey participants were asked to rate the severity of each symptom on a Likert scale of 0–5 (0 – No problem, 5 – problem as bad as it can be) at four time points: two weeks prior to diagnosis of COVID-19, at the time of diagnosis by confirmatory testing, two weeks after diagnosis, and four weeks after diagnosis. Rhinologic-domain SNOT-22 scores were calculated by adding subjects' ratings of the six symptoms, with a minimum score of zero and a maximum of 30. A higher score indicates greater severity of sinonasal symptoms. A copy of this survey is attached as a supplemental material titled "Sinonasal Survey of COVID-19 Patients". Temporal progression of sinonasal symptoms was assessed based on responses to survey questions #5–8, which ask the subject to rate their symptoms at the four time points noted previously. In order to do so, respondents estimate the severity of their symptoms from two weeks, up to three months in the past. All respondents to the initial survey were sent an additional follow-up survey approximately six months later. In contrast to the initial survey, follow-up respondents were asked to rate the current severity of their rhinologic symptoms.

2.4. Data analysis

To characterize the temporal progression of symptoms, a one-way ANOVA with repeated measures was utilized to compare the rhinologic domain of the SNOT-22 score as well as responses to individual questions in the rhinologic domain across time points [25]. Post-hoc analysis with the Bonferroni correction was subsequently performed to assess pairwise comparisons between time points. Associations between rhinologic domain variables were assessed with bivariate Pearson's correlation. To compare mean sinonasal symptom scores between patients stratified by past medical history, an independent samples two-tailed Student's *t*-test was utilized. Statistical significance was established as $p < 0.05$. All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Statistics Version 26, IBM Corporation, Armonk, NY).

3. Results

A total of 2042 subjects met inclusion criteria, and 1346 subjects had sufficient contact information to participate in the initial survey. Over seven days, 521 (38.7% response rate) internet-based responses or were collected from the initial survey. The average age of participants was 43.5 ± 13.9 years and 65.1% of participants were female (Table 1). A history of seasonal allergies or allergic rhinitis was endorsed by 207 participants (39.7%), and 171 participants (32.8%) endorsed a history of prior smell taste loss. In addition, 81 subjects (15.9%) reported some abnormality in smell, taste, or both prior to their diagnosis of COVID-19.

Analysis of the temporal progression of sinonasal symptom scores is depicted in Table 2. The mean rhinologic domain SNOT-22 score reached a maximum of 8.94 at the time of COVID-19 diagnosis, representing a statistically significant increase from the baseline value two weeks before diagnosis ($p < 0.001$) (Fig. 1). The mean rhinologic domain SNOT-22 score remained above baseline beyond two weeks post-diagnosis (5.14, $p = 0.004$) but subsequently decreased below baseline values four weeks after diagnosis (3.14, $p = 0.004$).

Analysis of patient reported loss of smell scores demonstrated a significant increase at the time of diagnosis (2.05, $p < 0.001$); this elevation persisted two weeks after diagnosis (1.19, $p < 0.001$), but

Table 1
Patient demographics.

Demographics	Value (percentage or standard deviation)
Total sample size	521
Gender	
Male	181 (34.7)
Female	339 (65.1)
Average age	43.5 (13.9)
Medical history	
History of smell or taste loss	171 (32.8)
Seasonal allergies	207 (39.7)
Asthma	88 (16.9)
Chronic sinusitis	24 (4.6)
History of sinus surgery	20 (3.8)
History of cigarette smoking	21 (4.0)
Sense of smell and taste immediately before COVID-19 diagnosis	
Smell and taste were normal	438 (84.1)
Smell was not normal	21 (4.0)
Taste was not normal	12 (2.3)
Smell and taste were not normal	46 (8.8)

Table 2
Progression of mean sinonasal symptom scores.

Rhinologic SNOT	Mean (standard deviation)	*p*-Value
2 weeks before diagnosis	4.09 (5.45)	
At diagnosis	8.94 (6.93)	<0.001
2 weeks after diagnosis	5.14 (5.43)	0.004
4 weeks after diagnosis	3.14 (4.48)	0.004
Sense of smell		
2 weeks before diagnosis	0.64 (1.31)	
At diagnosis	2.06 (1.94)	<0.001
2 weeks after diagnosis	1.19 (1.53)	<0.001
4 weeks after diagnosis	0.71 (1.28)	>0.999
Sense of taste		
2 weeks before diagnosis	0.67 (1.38)	
At diagnosis	2.14 (1.90)	<0.001
2 weeks after diagnosis	1.16 (1.47)	<0.001
4 weeks after diagnosis	0.64 (1.19)	>0.999
Need to blow nose		
2 weeks before diagnosis	0.73 (1.12)	
At diagnosis	1.30 (1.37)	<0.001
2 weeks after diagnosis	0.74 (1.09)	>0.999
4 weeks after diagnosis	0.47 (0.88)	<0.001
Sneezing		
2 weeks before diagnosis	0.64 (1.03)	
At diagnosis	1.06 (1.24)	<0.001
2 weeks after diagnosis	0.63 (0.94)	>0.999
4 weeks after diagnosis	0.39 (0.75)	<0.001
Runny nose		
2 weeks before diagnosis	0.66 (1.08)	
At diagnosis	1.10 (1.32)	<0.001
2 weeks after diagnosis	0.66 (1.02)	>0.999
4 weeks after diagnosis	0.44 (0.88)	<0.001
Blockage/congestion		
2 weeks before diagnosis	0.81 (1.19)	
At diagnosis	1.43 (1.52)	<0.001
2 weeks after diagnosis	0.84 (1.18)	>0.999
4 weeks after diagnosis	0.54 (0.98)	<0.001

SNOT Sinonasal outcome test.

returned to baseline levels four weeks after diagnosis (0.71, $p > 0.999$) (Fig. 2). 78.3% of patients reported that four weeks post-diagnosis, their sense of smell returned to baseline.

Patient-reported taste dysfunction follows a similar course, peaking at diagnosis (2.06, $p < 0.001$), remains elevated two weeks after diagnosis (1.19, $p < 0.001$), and returns to baseline four weeks after diagnosis (0.71, $p = 0.999$). Four weeks after diagnosis, 80.8% of patients reported that their sense of taste was just as good as baseline. At six months, there was a significant improvement in taste scores compared to one month ($p < 0.001$). 80.8% reported that their sense of taste returned to baseline at four weeks. The remaining rhinologic domain symptoms, including the need to blow nose, sneezing, runny nose, and nasal congestion, were also most severe at the time of diagnosis and returned to baseline by two weeks post-diagnosis.

Data obtained six months after diagnosis from 343 patients are depicted in Table 3. There were no significant differences between 1-month scores and 6-month scores in any rhinologic domain. Additional analysis was performed to compare sinonasal symptom scores at the time of diagnosis based on the presence or absence of comorbidities in self-reported medical history (Table 4). Patients with a history of smell dysfunction had significantly higher rhinologic SNOT scores (8.30 vs. 11.45, $p < 0.001$), loss of smell (1.92 vs. 2.83, $p < 0.001$), and loss of taste (1.96 vs. 2.85, $p < 0.001$) compared to patients without prior smell dysfunction. Patients with asthma also had significantly higher rhinologic SNOT scores (8.99 vs. 11.06, $p = 0.010$), loss of smell (2.13 vs. 2.66, $p = 0.021$), and loss of taste (2.12 vs. 2.92, $p < 0.001$).

4. Discussion

Coronaviruses are traditionally implicated in the common cold but have also given rise to severe epidemics, including the SARS and MERS outbreaks in 2003 and 2012, respectively [26,27]. In the current COVID-19 pandemic, the literature has focused on lower respiratory system consequences, including pneumonia, need for ventilation, and acute respiratory distress syndrome. However, greater than 80% of patients present with mild rhinologic symptoms alone, underscoring the importance of characterizing the severity and progression of such symptoms [7]. To our knowledge, this investigation is the largest to date to evaluate the temporal progression of rhinologic symptoms in COVID-19 through a 6-month follow-up timepoint.

Current literature suggests that changes in sense of smell or taste may precede other COVID-19 symptoms [11,14,28–30]. Based on early results of the AAO-HNS "COVID-19 Anosmia Reporting Tool", Kaye et al. reported that nearly 75% of those with anosmia noted that it began before their COVID-19 diagnosis; in addition, smell loss was the initial symptom in over 25% of these patients [14]. In our analysis, patients reported some degree of smell or taste dysfunction and nasal congestion beginning as early as two weeks before having a positive test. Thus, one strategy for patients who develop new onset chemosensory dysfunction is to self-quarantine and seek medical advice. Recognizing smell or taste loss as a possible sign of infection offers an additional opportunity to prevent unintended viral transmission.

The persistence of smell loss in COVID-19 patients has been an active area of investigation that is particularly important for patient counseling. Our analysis demonstrates that sense of smell significantly worsens from baseline to 2-weeks after diagnosis but normalizes by 1-month after diagnosis. In addition, there was no significant difference in mean sense of smell scores from 1-month to 6-months after diagnosis. These findings are consistent with prior studies of smell loss in COVID-19: an analysis conducted by Hopkins et al. reports that the majority of patients with loss of smell had resolution of these symptoms within two weeks [15]. Additionally, an analysis of anosmic COVID-19 patients reports an eight-day median duration of smell loss [31].

Less characteristic rhinologic symptoms, including nasal congestion and runny nose, have not been well-studied in the context of COVID-19. Our investigation suggested that patients experienced a significant increase in the severity of nasal congestion, rhinorrhea, and the need to blow nose from baseline to the time of diagnosis; however, these symptoms resolved two weeks after diagnosis and remained normal through the 6-month time point. An analysis by Lechien et al. similarly noted that 46% and 33% of patients experienced worsening nasal obstruction and rhinorrhea, respectively, at the time of diagnosis, although the temporal progression of these symptoms was not analyzed [11].

Finally, our analysis also explored the relationship between severity of sinonasal symptoms and prior history of rhinologic comorbidities.

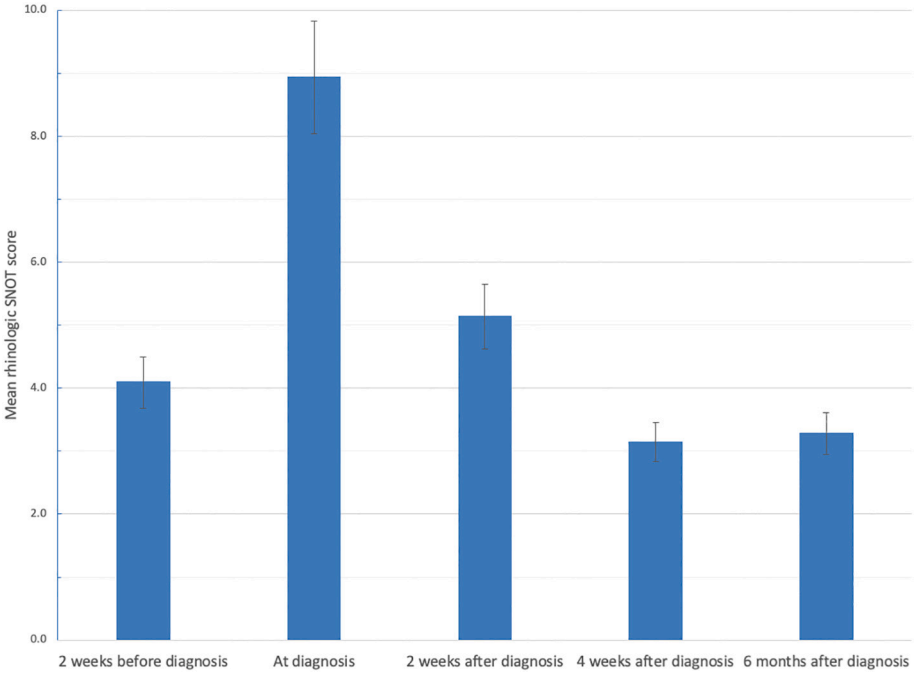

Fig. 1. Mean rhinologic SNOT-22 scores.

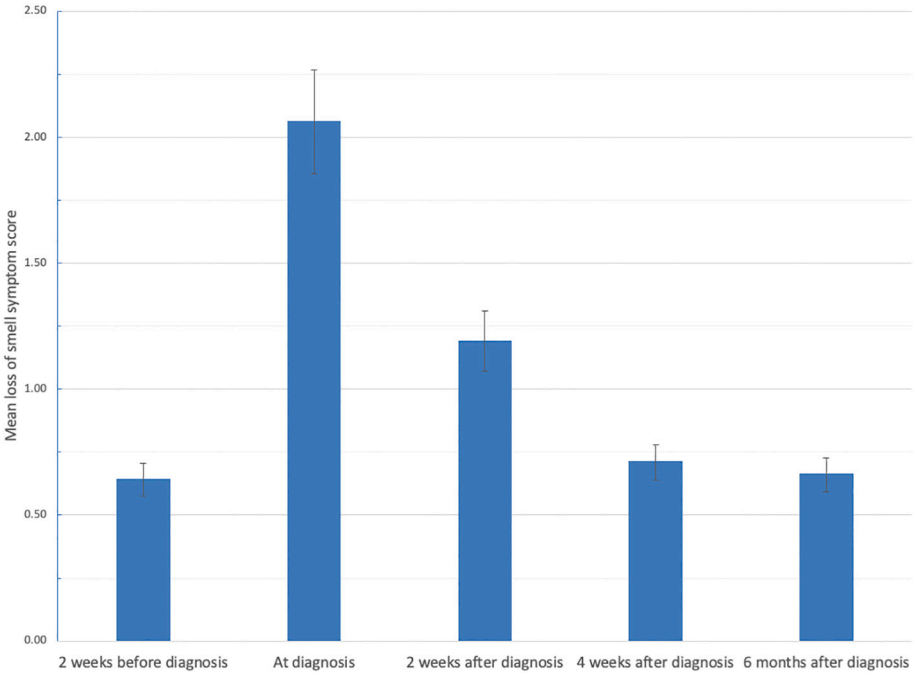

Fig. 2. Mean loss of smell symptom scores.

Table 3
Comparison of 6-month mean sinonasal symptom scores to 1-month scores.

Domain	6-month mean score (standard deviation)	*p*-Value
Rhinologic SNOT	3.28 (4.28)	0.708
Sense of smell	0.66 (1.19)	0.664
Sense of taste	0.47 (1.05)	0.058
Need to blow nose	0.55 (0.96)	0.218
Sneezing	0.50 (0.84)	0.064
Runny Nose	0.44 (0.84)	0.867
Blockage/congestion	0.64 (1.05)	0.202

SNOT Sinonasal outcome test.

Patients with a history of hyposmia, asthma, or chronic sinusitis experienced an exaggerated worsening of sinonasal symptoms, as measured by the rhinologic SNOT score at the time of diagnosis. Additionally, patients with a history of hyposmia and asthma experienced a more significant degree of smell loss at the time of diagnosis. The nasal cavity and nasopharynx are reservoirs for SARS-CoV-2, and it is believed that the virus causes sinonasal mucosal inflammation, resulting in subsequent nasal congestion [32]. Any underlying inflammation associated with pre-morbid asthma or chronic sinusitis, would likely be compounded by SARS-CoV-2, resulting in more severe symptoms.

The current study has several limitations. First, the study design

Table 4
Comparison of average sinonasal symptom scores at the time of diagnosis stratified by self-reported history of medical conditions.

History	Average rhinologic SNOT at time of diagnosis ($n = 517$)	Average loss of smell score at diagnosis ($n = 514$)	Average loss of taste score at diagnosis ($n = 511$)
Prior smell or taste loss			
Yes	11.45	2.83	2.85
No	8.30	1.92	1.96
p-Value	<0.001	<0.001	<0.001
Allergic rhinitis			
Yes	10.05	2.32	2.20
No	8.87	2.42	2.28
p-Value	0.053	0.323	0.647
Asthma			
Yes	11.06	2.66	2.92
No	8.99	2.13	2.12
p-Value	0.010	0.021	<0.001
Chronic sinusitis			
Yes	14.5	2.46	2.71
No	9.09	2.21	2.23
p-Value	<0.001	0.535	0.234
Sinus surgery			
Yes	10.95	1.85	1.65
No	9.27	2.23	2.28
p-Value	0.280	0.388	0.153
Tobacco use			
Yes	9.24	2.24	2.29
No	9.34	2.22	2.25
p-Value	0.946	0.961	0.935

SNOT Sinonasal outcome test.

introduces potential for recall bias: initial survey respondents were asked to retrospectively report symptoms at several previous time points. Respondents reported symptoms they experienced from weeks, up to three months in the past. In contrast, respondents to the follow-up survey were only asked to report their current severity of symptoms. Surveys were also sent on discrete dates, so there was variability as to where each patient was in their individual course of disease. These aspects of the study design may have adversely affected patient's ability to accurately recall and report true symptom severity. Second, there is no information on whether medical therapies were used by patients, which may affect severity of symptoms. Third, despite a 2% false negative rate for the screening test used in this study, the possibility of false positives is recognized; this is somewhat mitigated by the large sample size. Fourth, the current study is focused in one metropolitan area, although the results may be generalizable given its large population. Finally, the time points selected for assessment of symptoms were chosen based on intervals of incubation time and resolution of disease in mild cases; these may not apply consistently across all cases but serve as reasonable estimates for most cases.

5. Conclusion

This investigation is the largest to date to describe the temporal progression of sinonasal symptoms up to six months in the mild severity COVID-19 population. Overall, sinonasal symptoms, particularly loss of smell and taste, peak at the time of diagnosis, normalize by 1-month after diagnosis, and remain normal through 6-months after diagnosis.

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CRediT authorship contribution statement

Conceptualization: RR, PSB, BAT.
Data curation: RR, PSB, BAT.
Formal analysis: AG, MM.
Project administration: PP, PL, PSB, BAT.
Resources: PP, PL, PSB, BAT.
Software: AG.
Supervision: PP, PL, PSB, BAT.
Validation: PP, PL, MM, ECK, PSB, BAT.
Visualization: RR, AG.
Writing (Original Draft): RR, AG.
Writing (Reviewing and editing): RR, AG, KG, BML, PP, PL, MM, ECK, PSB, BAT

Declaration of competing interest

All authors declare that they have no relevant conflicts of interest.

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