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Discriminatory Ability of Gas Chromatography–Ion Mobility Spectrometry to Identify Patients Hospitalized With COVID-19 and Predict Prognosis

Joshua Nazareth,[1,2,*] Daniel Pan,[1,2,*] Jee Whang Kim,[1,3] Jack Leach,[4] James G. Brosnan,[4] Adam Ahmed,[4] Emma Brodrick,[5] Paul Bird,[6] Alfian Wicaksono,[7] Emma Daulton,[7] Julian W. Tang,[1,6] Caroline Williams,[1,2] Pranabashis Haldar,[1,3] James A. Covington,[7] Manish Pareek,[1,2,**] and Amandip Sahota[2,**]

[1]Department of Respiratory Sciences, University of Leicester, Leicester, United Kingdom, [2]Department of Infectious Diseases and HIV Medicine, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, [3]Respiratory Biomedical Research Centre, University of Leicester, Leicester, United Kingdom, [4]University of Leicester Medical School, Leicester, United Kingdom, [5]IMSPEX Diagnostics Ltd, Abercynon, United Kingdom, [6]Department of Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, and [7]School of Engineering, University of Warwick, Coventry, United Kingdom

Background. Rapid diagnostic and prognostic tests for coronavirus disease (COVID-19) are urgently required. We aimed to evaluate the diagnostic and prognostic ability of breath analysis using gas chromatography–ion mobility spectrometry (GC-IMS) in hospitalized patients with COVID-19.

Methods. Between February and May 2021, we took 1 breath sample for analysis using GC-IMS from participants who were admitted to the hospital for COVID-19, participants who were admitted to the hospital for other respiratory infections, and symptom-free controls, at the University Hospitals of Leicester NHS Trust, United Kingdom. Demographic, clinical, and radiological data, including requirement for continuous positive airway pressure (CPAP) ventilation as a marker for severe disease in the COVID-19 group, were collected.

Results. A total of 113 participants were recruited into the study. Seventy-two (64%) were diagnosed with COVID-19, 20 (18%) were diagnosed with another respiratory infection, and 21 (19%) were healthy controls. Differentiation between participants with COVID-19 and those with other respiratory tract infections with GC-IMS was highly accurate (sensitivity/specificity, 0.80/0.88; area under the receiver operating characteristics curve [AUROC], 0.85; 95% CI, 0.74–0.96). GC-IMS was also moderately accurate at identifying those who subsequently required CPAP (sensitivity/specificity, 0.62/0.80; AUROC, 0.70; 95% CI, 0.53–0.87).

Conclusions. GC-IMS shows promise as both a diagnostic tool and a predictor of prognosis in hospitalized patients with COVID-19 and should be assessed further in larger studies.

Keywords. COVID-19; diagnosis; respiratory virus; volatile organic compounds.

BACKGROUND

Coronavirus disease (COVID-19) continues to cause significant global morbidity and mortality. Rapid diagnosis and prognostic assessment of patients with COVID-19 are crucial to ensure that patients can be triaged and managed appropriately. Current diagnosis of COVID-19 is made by correlating clinical symptoms and collecting samples for reverse transcription polymerase

chain reaction (RT-PCR) by swabbing the anterior nares, nasopharynx, or oropharynx or collecting saliva from an oral rinse [1]. However, these samples have to be processed by trained laboratory staff and may be negative by the time a patient has symptoms severe enough to present to the hospital [2].

Exhaled breath analysis is an emerging approach to respiratory infection diagnosis. Volatile organic compounds (VOCs) measured in breath mirror metabolic processes both locally within the respiratory system and systemically. Techniques to measure VOCs for diagnosis of infection have the potential to be rapid, noninvasive, at point-of-care, and completed without the need for trained laboratory staff [3]. Breath analysis has already been shown to diagnose viral and bacterial respiratory infections, such as influenza and tuberculosis, with high accuracy [3, 4]. There is emerging evidence regarding the value of breath analysis in the diagnosis of patients with COVID-19; however, evidence pertaining to its ability to predict prognosis is still lacking.

We conducted a study to assess the ability of gas chromatography–ion mobility spectrometry (GC-IMS), a well-established method of rapid breath analysis, to differentiate hospitalized patients with COVID-19 from both symptom-free controls

and patients with other respiratory infections. We also assessed whether GC-IMS was able to predict prognosis in hospitalized patients with COVID-19.

METHODS

Study Settings

We undertook a prospective observational study between February 1, 2021, and May 24, 2021, that enrolled consecutive patients hospitalized for COVID-19, patients hospitalized for other respiratory tract infections, and symptom-free controls at Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. During this period, there was a transition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants in the United Kingdom from Alpha to Delta (98% of sequenced SARS-CoV-2 samples were classified as Alpha or Delta variants after May 10, 2021), and vaccinations were prioritized in the general population for older persons or those at risk of developing severe disease [5].

For COVID-19, we included participants who fulfilled the following criteria: age ≥16 years; hospitalized; positive for SARS-CoV-2 on RT-PCR using routine nasopharyngeal testing within the last 24 hours; no previously known positive SARS-CoV-2 RT-PCR or clinically diagnosed COVID-19 before the current admission. For the non-COVID-19 (other) respiratory tract infection group, we recruited participants: aged ≥16 years; hospitalized; negative for SARS-CoV-2 on both RT-PCR and rapid antigen test using routine nasopharyngeal testing within the last 24 hours; no positive test for SARS-CoV-2 on RT-PCR in the preceding 8 weeks before recruitment; and with a clinical, radiological, or microbiological diagnosis of another respiratory tract infection. Symptom-free controls were aged ≥16 years, with no respiratory symptoms and no positive test for SARS-CoV-2 on RT-PCR in the 8 weeks before recruitment. Patients who were unable to understand and comply with the protocol, or unable or unwilling to give informed consent, were not included in the study.

Clinical Data Collection

We collected the following demographic and clinical data: age, gender, ethnicity, comorbidities (specifically autoimmune disease, hypertension, diabetes, ischemic heart disease, chronic kidney disease, cancer, chronic lung disease, neurological disease, gastroenterological/liver disease, hematological disease), COVID-19 vaccination status, clinical symptoms at the time of sampling, duration between symptom onset and recruitment, radiology and laboratory findings on admission (white cell count, lymphocyte count, hemoglobin concentration, C-reactive protein [CRP], plasma concentrations of sodium, potassium, urea, and creatinine). Laboratory findings were from the same day as breath sampling. Clinical outcomes collected included requirement for noninvasive and invasive ventilation and death by June 30, 2021.

Patient Consent

The study had ethical approval from the West Midlands Research Ethics Committee (REC Reference 20/WM/0153). It was conducted in accordance with ICH-GCP, the Declaration of Helsinki, and the Data Protection Act 1998 and NHS Act 2006. All participants gave written, informed consent before any study procedures.

Breath Analysis Platform

For this study, a commercial GC-IMS instrument was used (BreathSpec, IMSPEX Diagnostics Ltd, Abercynon, UK). This instrument combines a gas-chromatograph (GC) front end, with a drift-tube ion mobility spectrometer (IMS) as the VOC detector. In use, the sample is injected into the GC, which separates the chemicals based on their interaction with the stationary phase within the column. As these chemicals elute from the column, they move into a drift-tube IMS, where the chemicals are ionized and then driven along the tube using a high electric field. A buffer gas flows against this "drift," which results in collisions between the ions and the buffer gas. Thus, the drift time becomes a function of the molecular interaction with the electric field and the number of collisions with the buffer gas. This generates a high dimensional data set based on the retention time of the column and the drift time of the IMS [6, 7]. Supplementary Table 1 provides the GC-IMS method and column used in the study.

This instrument is of relatively small size and is able to sit on a standard clinical trolley (Supplementary Picture 1). It requires a standard mains power supply and uses filtered room air as the carrier gas, provided by a circular gas flow unit (CGFU) fitted to the top of the unit.

Sample Collection

Once consented, participants provided 1 breath sample within 24 hours of an RT-PCR nasopharyngeal swab for SARS-CoV-2. All breath sampling equipment was supplied by IMSPEX Diagnostics Ltd (Abercynon, UK) and used as instructed. It was composed of a mouthpiece connected to an open-ended reservoir tube, with a 10-mL syringe attached to a hole at the side of the reservoir. For collection, the participants exhaled slowly through the mouth piece into the reservoir tube. Five seconds before the end of the breath, the syringe was used to aspirate 10 mL of end-tidal breath (Supplementary Picture 2). The breath-filled syringe was then resealed within the plastic bag it came originally packaged in and immediately taken to the BreathSpec machine for injection and processing. The syringes spent a maximum of 2 minutes in the sealed bag before injecting contents into the BreathSpec machine. Breath sample analysis was completed within 15 minutes, followed by flushing of the machine with room air for 1 minute before another sample could be analyzed. The data generated were then stored on the machine and sent to the University of Warwick (Coventry,

UK) for analysis. Although possible to transport the machine to the bedside, for infection control purposes the machine was located in a separate room from inpatients on the acute medical wards.

Statistical Analysis

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are displayed as numbers and percentages (%). Pearson's chi-square and the Fisher exact row test were used to compare categorical variables between groups. The Student t test and Kruskal-Wallis test were used to compare continuous variables between groups depending on the normality of distribution. Analyses were performed using STATA, version 14.2 (StataCorp, College Station, TX, USA), and Excel, version 2016 (Microsoft, Redmond, WA, USA).

The GC-IMS data were processed according to the in-house pipeline developed at Warwick University using R (version 3.6.2) [6, 7]. In brief, GC-IMS data are high dimensional but with low information content. Each sample consists of >10 million data points, making standard multivariate analysis difficult. For the pipeline, the data were first preprocessed to reduce their dimensionality. This was achieved by cropping the central section of the output data array, which contains the most useful information, followed by manual inspection of all the data files. The same settings were used for each file. A single line of data containing no chemical information was then subtracted to remove the reactive ion peak (RIP), that is, the output when no VOCs are present. A small threshold of twice the average background value was added to this value, with any value below this number set to 0. These steps reduce the number of data points by a factor of 1000. The data were then processed using a 10-fold cross-validation. Within each fold, discriminatory features were identified by a rank-sum test, and the 100 features with the lowest P value were used to construct 2 models (Gaussian Process and Neural network), which were applied to the test set. This generated probabilities from each of the test samples. The process was repeated until all the data had been a test sample, and the resultant probabilities were used to calculate statistical values such as sensitivity and specificity. A number of quality assurance and quality control checks were undertaken, including daily tests to ensure that the RIP location and magnitude were within specification; that temperature, flow rates, and other instrument settings were correct; and that each sample contained an appropriate concentration of acetone.

RESULTS

Participant Demographics and Clinical Features

Between February and June 2021, a total of 113 participants were recruited into the study: 72 were admitted to the hospital with COVID-19; 20 were admitted to the hospital with a respiratory tract infection other than COVID-19; and 21 were symptom-free controls (Figure 1). All participants successfully provided a breath sample for GC-IMS analysis without any difficulty.

Table 1 shows participant demographic and clinical data. In the "other respiratory infection" group, all 20 participants had 2 negative RT-PCR swabs for SARS-CoV-2. Twelve had radiological features on chest imaging suggestive of infection; 2 had a microbiological diagnosis of infection by respiratory PCR, sputum culture, or blood culture; 3 had both a radiological and microbiological diagnosis of respiratory tract infection; and 3 had no positive microbiology or radiology but were diagnosed by a respiratory physician based on clinical features. Symptom-free controls were younger, more likely to be female, and of White ethnicity compared with those who were admitted to the hospital with a respiratory infection. Participants with COVID-19 were more likely to have lower white cell counts compared with other respiratory infections. Approximately a quarter of participants (27%) with COVID-19 had had 1 dose of either the Oxford-AztraZeneca or Pfizer-BioNTech vaccine before hospitalization. Thirteen participants (18%) with COVID-19 required CPAP. There were 4 deaths in the 28 days following recruitment: 2 participants with COVID-19 and 2 with other respiratory infection.

Table 2 shows the demographics of participants with COVID-19, stratified by whether they received CPAP during hospitalization. Participants who required CPAP after sampling were more likely to have higher admission serum urea levels and a longer duration of symptoms before sampling compared with those who did not.

GC-IMS Results

Supplementary Figure 1 depicts the typical output from a breath sample of a COVID-19-infected participant. The output shows that there are numerous peaks, linked to different chemicals within both the breath and the environment. The output also indicates that the instrument is clean and providing good chemical differentiation. Supplementary Figure 2 shows the locations of the data points selected by the University of Warwick processing pipeline for the different comparisons. Here, the features are identified in red. The results show that different features are selected for each of the different comparisons.

Table 3 shows the results from an analysis of the GC-IMS data, comparing performance metrics for the ability of the instrument to distinguish between COVID-19 and symptom-free controls, between COVID-19 and other respiratory infections, and between varying levels of COVID-19 disease severity (as defined by requirement for CPAP). Overall, the machine was able to distinguish between all 3 states with highly significant P values across all groups.
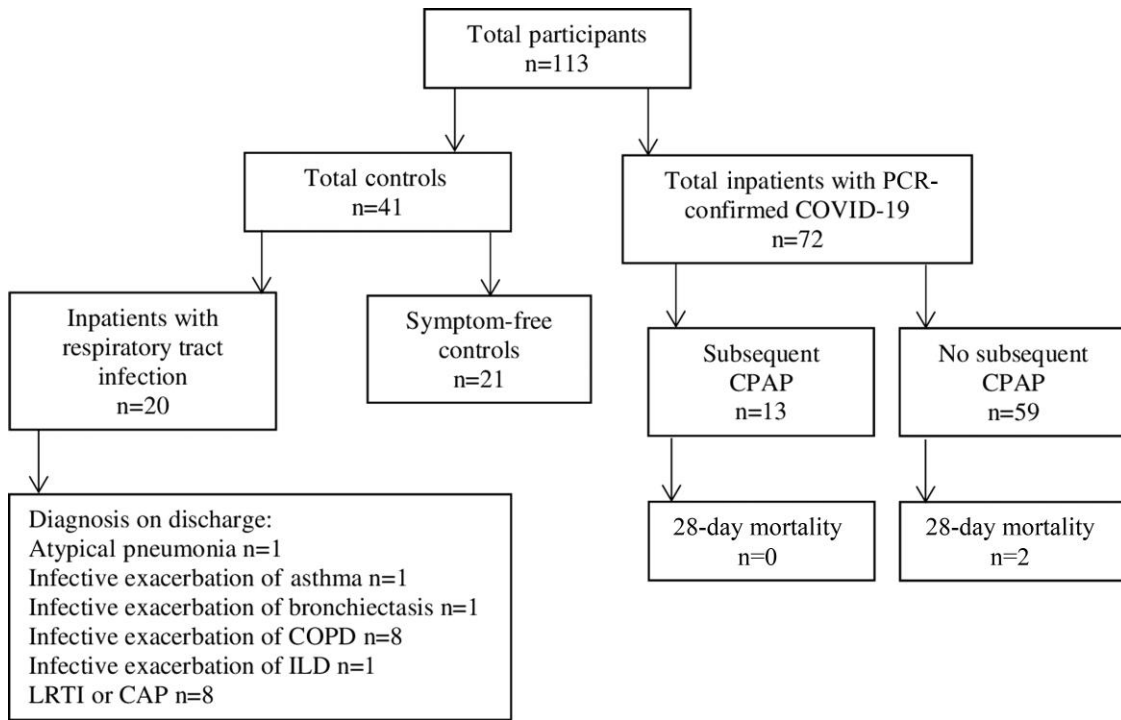
Figure 1. Details of participants recruited into the study. Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ILD, interstitial lung disease; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction.

Different classifiers generated the best distinguishing ability between groups, with Neural Network being the best to distinguish between COVID-19 and symptom-free controls, Gaussian Process being the best to distinguish between COVID-19 and other respiratory infections, and Neural Network being the best to distinguish between CPAP vs no CPAP. Within our small cohort, GC-IMS appeared to have high positive predictive values when distinguishing COVID-19 from hospitalized participants with other respiratory tract infections and high negative predictive values in distinguishing participants who would (and would not) go on to require CPAP during hospitalization. Receiver operating characteristic (ROC) curves using different classifiers for all analyses are shown in Supplementary Figure 3.

Multivariable Analysis of Predictors of Correct Identification of Participants With COVID-19 and Subsequent Requirement for CPAP

Table 3 shows adjusted logistic regression analyses of GC-IMS and other variables in relation to prediction of COVID-19 compared with other respiratory infections and prospective requirement for CPAP. In an adjusted analysis, both decreasing serum white cell count and increasing GC-IMS readings (using Gaussian Process) were independently related to a diagnosis of COVID-19 compared with other respiratory infections. Finally, despite univariable associations, we did not find GC-IMS to be associated with subsequent CPAP requirement on multivariable analysis.

DISCUSSION

There are 3 main findings from this study. First, exhaled breath collection and analysis by GC-IMS/Breathspec were feasible and well tolerated by acutely unwell patients admitted to the hospital with COVID-19 and other respiratory infections. Second, GC-IMS was strongly able to distinguish COVID-19 infection from other respiratory infections, as well as symptom-free controls. Third, we found a relationship between GC-IMS readings and worse prognosis in COVID-19, as evidenced by an association with prospective requirement for CPAP.

Three previous studies have evaluated the diagnostic potential of breath analysis for COVID-19 [8–10]. All showed specific breath metabolomic signatures in participants with COVID-19 compared with controls with other diseases (respiratory infection, acute respiratory distress syndrome, and chronic diseases that cause breathlessness), as well as symptom-free controls, with ROC curves comparable to those found in our study. In contrast to other studies, where participants had to be transported into a room housing the analysis machine, the BreathSpec machine we employed was portable and could be taken to the patients' bedside. This would allow

Table 1. Participant Demographics, Clinical and Laboratory Data, and Clinical Outcomes

Variables	COVID-19 (n = 72)	Other Respiratory Infection (n = 20)	Symptom-Free Controls (n = 21)	P Value
Demographic data				
Age, median (IQR), y	57 (49–66)	65 (52–77)	45 (38–51)	
Male, No. (%)	47 (66)	12 (60)	3 (14)	<.001
White ethnicity, No. (%)	46 (75)	18 (95)	16 (76)	.004
Asian ethnicity, No. (%)	14 (23)	1 (5)	2 (10)	
Black ethnicity, No. (%)	1 (2)	0	3 (14)	
Clinical data				
Autoimmune disease	13 (18)	6 (30)		.24
Hypertension	21 (29)	7 (35)		.61
Diabetes	16 (22)	4 (20)		.99
Ischemic heart disease	12 (17)	5 (25)		.40
Chronic kidney disease	3 (4)	3 (15)		.11
Cancer	1 (1)	0 (0)		.99
Chronic lung disease	13 (18)	15 (75)		<.001
Neurological disease	2 (3)	3 (15)		.07
Gastroenterological/liver disease	7 (10)	1 (5)		.68
Hematological	4 (6)	1 (5)		.99
No. of comorbidities	1.5 (0–2)	2.5 (1–3)		.04
Admission oxygen saturations, median (IQR), %	97 (95–98)	96 (94–97.5)	n/a	.35
White cell count, median (IQR), ×10⁹ cells/L	7.1 (5.3–9.1)	11.8 (10.3–14.0)		<.001
Lymphocyte, median (IQR), ×10⁹ cells/L	1.0 (0.7–1.5)	1.1 (0.9–2.3)		.34
Urea, median (IQR), mmol/L	5.3 (3.9–7.2)	5.7 (4.2–9.4)		.56
Creatinine, median (IQR), µmol/L	82.5 (66.5–99)	87.5 (68.5–115)		.15
CRP, median (IQR), mg/L	80.5 (35–138.5)	51 (13.5–140.5)		.59
Hemoglobin, median (IQR), g/L	142.5 (131.5–153)	124 (116.5–146)		.06
Duration of symptoms, median (IQR), d	7 (5–10)	7 (2.5–8)	…	.51
Treatment with dexamethasone, No. (%)	55 (78)	0	…	
Vaccinated, No. (%)	19 (27)	16 (80)	21 (100)	
Pfizer, No. (%)	12 (17)	9 (45)	5 (24)	
Astra Zeneca, No. (%)	7 (10)	7 (35)	16 (76)	
Clinical outcomes				
Need for supplemental oxygen during hospital admission, No. (%)	57 (79)	14 (70)	…	.39
Received CPAP following sampling, No. (%)	13 (18)	…	…	
28-d mortality, No. (%)	2 (3)	2 (10)	…	

11 Participants had missing ethnicity data; there were no other missing data.

Abbreviations: COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; CRP, C-reactive protein; IQR, interquartile range.

for use within routine hospital settings where patients may be too unwell to mobilize or transfer.

Though we were unable to identify specific biomarkers for the differences between disease groups, we found that a positive diagnosis could be made based on the cumulative array of chemical compounds found in the breath of a COVID-19-infected patient. This suggests that the disease may affect lung and/or other internal metabolic pathways differently compared with infection with other respiratory pathogens, which is in keeping with breath analysis studies completed on COVID-19 patients by Ruszkiewicz and colleageus [8].

Our findings support the use of exhaled breath analysis in COVID-19 diagnosis. Although in our clinical setup analysis time was 15 minutes in order to maximize the chemical information collected, when focusing on the detection of specific spectral markers, analysis time could be reduced to <5 minutes. This has logistical advantages over current RT-PCR testing, due to the rapidity of producing a result and the ability of non-laboratory staff to perform and interpret the test [11]. In the hospital, this could allow for faster identification and triage of patients with COVID-19 and differentiation from other respiratory infections, preventing nosocomial spread and leading to swifter commencement on appropriate medical therapy. Within primary care, application of such a test has the potential to distinguish bacterial from viral infections, helping clinicians decide whether antibiotic prescription would be necessary, and to rapidly direct ill patients who have COVID-19 to the hospital. Within other community settings, for example, schools and airports, such testing could offer significant benefits over

Table 2. COVID-19-Positive Participant Demographics, Clinical and Laboratory Data, and Clinical Outcomes by Future Requirement for CPAP

Variables	COVID-19 With Subsequent CPAP (n = 13)	COVID-19 With No Subsequent CPAP (n = 59)	P Value
Demographic data			
Age, median (IQR), y	56 (55–63)	57.5 (48–66)	
Male, No. (%)	9 (69)	39 (66)	.89
White ethnicity, No. (%)	9 (75)	37 (76)	.11
Asian ethnicity, No. (%)	2 (17)	12 (25)	
Black ethnicity, No. (%)	1 (8)	…	
Clinical data			
Autoimmune disease	3 (23)	10 (17)	.69
Hypertension	6 (46)	15 (25)	.14
Diabetes	5 (38)	11 (19)	.12
Ischemic heart disease	2 (15)	10 (17)	.99
Chronic kidney disease	0 (0)	3 (5)	.99
Cancer	0 (0)	1 (2)	.99
Chronic lung disease	1 (8)	12 (20)	.44
Neurological disease	0 (0)	2 (3)	.99
Gastroenterological/liver disease	1 (8)	6 (10)	.99
Hematological	2 (15)	2 (3)	.15
No. of comorbidities	2 (1–3)	1 (0–2)	.27
Admission oxygen saturations, median (IQR), %	96.5 (95.5–98)	97 (95–98)	.74
Need for supplemental oxygen during hospital admission, No. (%)	13 (100)	45 (78)	.20
28-d mortality, No. (%)	0 (0)	2 (3)	
White cell count, median (IQR), ×10^9 cells/L	7.2 (5.8–8.1)	6.9 (5.3–9.3)	.60
Lymphocyte, median (IQR), ×10^9 cells/L	1.1 (0.7–1.5)	1.0 (0.7–1.4)	.99
Urea, median (IQR), mmol/L	5.8 (4.2–9.5)	5.1 (3.8–7)	.03
Creatinine, median (IQR), μmol/L	78 (67–90)	83 (66–100)	.41
CRP, median (IQR), mg/L	140 (37–196)	79 (35–132)	.15
Hemoglobin, median (IQR), g/L	141 (129–155)	143 (132–151)	.73
Duration of symptoms, median (IQR), d	10 (6–15)	7 (4.5–10)	.01
Treatment with dexamethasone, No. (%)	10 (77)	45 (78)	.96
Vaccinated, No. (%)	3 (23)	16 (28)	.79
Pfizer, No. (%)	1 (8)	11 (19)	.33
Astra Zeneca, No. (%)	2 (15)	5 (9)	.46

11 Participants had missing ethnicity data; there were no other missing data.

Abbreviations: COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; IQR, interquartile range.

current methods of rapid detection and better tolerability than oropharyngeal swabbing.

To our knowledge, we are the first to demonstrate the potential of exhaled breath analysis to predict the need for CPAP. Grassin-Delyle and colleagues found that VOC concentrations were not correlated with severity of illness, as measured by concomitant severity scores (SAPS II and SOFA) [10]. However, one-off measurements of such scores underpredict disease severity in COVID-19, and the use of clinically important end points, such as CPAP, may be more accurate as an outcome [12, 13]. As only 2 participants died within our cohort, it remains unclear whether the differences we identified in exhaled breath metabolomics are a consequence of protective or deleterious immune responses within the lungs. Ruskiewicz and colleagues identified differences in exhaled breath metabolomics between those with mild COVID-19 compared with those who had fatal disease and those requiring intubation/intensive care, suggesting the latter hypothesis. In contrast to previous studies, we showed that GC-IMS has the potential to detect COVID-19 and predict disease trajectory in those who had been partially vaccinated. When comparing the exhaled VOC signals in those progressing to CPAP compared with those not progressing to CPAP, we found differing concentrations of similar signals in the 2 groups. This may indicate that different metabolic processes are occurring at the time of sampling in infected individuals who progress to more severe disease. Further research to characterize these metabolic processes could provide greater understanding of COVID-19 pathophysiology and be used as a tool to identify other markers that predict disease severity.

We did not perform SARS-CoV-2 genetic sequencing to examine for any differences in exhaled volatile compounds between different variants as this was not the intention of our study. However, it is likely that our technology can detect disease in multiple variants given the epidemiological transition from Alpha to Delta during the period of recruitment [5].

Table 3. Performance Metrics for the 3 Comparisons Made: COVID-19 vs Symptom-Free Controls; COVID-19 vs Other Respiratory Infection; COVID-19 Subsequently Requiring CPAP vs COVID-19 With No Subsequent Requirement for CPAP

	COVID-19 vs Symptom-Free Control	COVID-19 vs Other Respiratory Infection	COVID-19 Subsequent CPAP vs No Subsequent CPAP
Classifier	Gaussian Process	Neural Network	Neural Network
AUC (95% CI)	0.89 (0.81–0.96)	0.85 (0.74–0.96)	0.70 (0.53–0.87)
Sensitivity (95% CI)	0.85 (0.76–0.91)	0.80 (0.56–0.94)	0.62 (0.32–0.86)
Specificity (95% CI)	0.90 (0.68–0.99)	0.88 (0.79–0.94)	0.80 (0.69–0.89)
Positive predictive value	0.98	0.59	0.36
Negative predictive value	0.56	0.95	0.92
P value	<.001	<.001	.01
Threshold	0.66	0.06	0.06
Multivariable Analysis[a]	Adjusted OR (95% CI)	P Value	…
Outcome: COVID-19 vs respiratory control			…
Breath analysis Gaussian Process[b]	2.35 (1.55–3.57)	<.001	…
Admission white cell count	0.73 (0.58–0.91)	.01	…
No. of comorbidities	0.97 (0.56–1.69)	.92	…
Outcome: subsequent CPAP vs no subsequent CPAP			…
Breath analysis Neural Network[c]	1.13 (0.95–1.35)	.17	…
Admission urea	1.04 (0.93–1.17)	.47	…
Duration of symptoms[d]	1.15 (1.00–1.33)	.047	…

Abbreviations: AUC, area under the curve; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; OR, odds ratio.

[a]Analyses adjusted for all other variables in the table.

[b]Gaussian Process COVID + ve vs respiratory control analysis output was multiplied by 10 in order for multivariable regression to be completed.

[c]Neural network subsequent CPAP vs no subsequent CPAP analysis output was multiplied by 10 in order for multivariable regression to be completed.

[d]For each day increase in duration of symptoms.

Finally, despite univariable associations, we did not find GC-IMS to be associated with subsequent CPAP requirement on multivariable analysis. Given that COVID-19 in its most severe disease states results in multi-organ failure, it may be that sampling from the respiratory tract alone is insufficient to provide the full clinical picture or that the instrument does not have sufficient sensitivity. We note that a longer duration of symptoms before hospital admission was an independent predictor of prognosis; therefore, GC-IMS may have stronger diagnostic and predictive roles in the clinical assessment of COVID-19 in early disease.

Our study had limitations. The sample size was relatively small. The study population was highly diverse, comprising multiple comorbidities, differing vaccination statuses, and differing treatments within the hospital, which could have resulted in underestimation of the ability of GC-IMS to distinguish between specific subgroups.

Not all participants diagnosed with respiratory infection other than COVID-19 had positive microbiology. As nasopharyngeal tests for SARS-CoV-2 themselves have limited sensitivity, it is possible that this group's symptoms could be explained by SARS-CoV-2 infection. However, no significant differences existed in the duration of symptoms between those who had COVID-19 and those with other respiratory infection. This is the main factor relating to PCR positivity for COVID-19, with those early in infection most likely to have a positive test.

In conclusion, GC-IMS has a high capability to distinguish between acute COVID-19 infection and other disease states, including other respiratory infections. GC-IMS may also be able to predict subsequent requirement for CPAP in hospitalized patients with COVID-19, but in this study it was not an independent predictor of outcome when other variables were taken into account. Our study demonstrates the use of a novel technology that could be embedded within clinical practice, with workforce and economic implications that come with a reduced need for laboratory processing.

Supplementary Data

[Supplementary materials](#) are available at *Open Forum 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.

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