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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Original Research

Characteristics and outcomes of ambulatory patients with suspected COVID-19 at a respiratory referral center

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ABSTRACT

Rationale: SARS-CoV-2 continues to cause a global pandemic and management of COVID-19 in outpatient settings remains challenging. **Objective:** We sought to describe characteristics of patients with chronic respiratory disease (CRD) experiencing symptoms consistent with COVID-19, who were seen in a novel Acute Respiratory Clinic, prior to widely available testing, emergence of variants, COVID-19 vaccination, and post-vaccination (breakthrough) SARS-CoV-2 infections. **Methods:** Retrospective electronic medical record data were analyzed from 907 adults with presumed COVID-19 seen between March 16, 2020 and January 7, 2021. Data included demographics, comorbidities, medications, vital signs, laboratory tests, pulmonary function tests, patient disposition, and co-infections. The overdispersed data (aod) R package was used to create a logit model using COVID-19 diagnosis by PCR as the dichotomous outcome variable. Univariate, conventional multivariate and elastic net machine learning were used to analyze data. **Results:** Male gender, elevated baseline temperature, and respiratory rate predicted COVID-19 diagnosis. Eosinopenia, neutrophilia, and lymphocytosis were also associated with COVID-19 diagnosis. However, asthma and COPD diagnoses were not associated with SARS-CoV-2 PCR positive test. Male gender, low oxygen saturation, and lower forced expiratory volume in 1 s (FEV_1) were associated with higher hospital referral. **Conclusions:** CRD patients with acute respiratory symptoms in the ambulatory setting were more likely to have COVID-19 if male, febrile and tachypneic. Patients with lower premorbid FEV_1 and lower SPO_2 are more likely to be referred to the hospital. A composite of vitals sigs and WBC differential help risk stratify CRD patients seeking care for presumed COVID-19.

Author contributions

Acquisition of data: VPG, BDM, LAM, JJE, PZ. Conception and design: VPG, BDM, LAM, JJE, PZ, CAH, RCK, BJM, IP, MEW. Analysis and interpretation: VPG, BDM, LAM, JJE, SYL, NMG, PZ, BJM, IP, MEW. Writing of manuscript: VPG, BDM, LAM, JJE, SYL, NMG, PZ, BJM, IP, MEW. Editing and approval of manuscript: VPG, BDM, LAM, JJE, SYL, NMG, PZ, CAH, RCK, BJM, IP, MEW.

Subject Category: Diagnosis of Infections, Epidemiology.

1. Introduction

SARS-CoV-2 continues to cause a global pandemic that has overwhelmed emergency department (ED), hospital, and intensive care unit bed capacity [1]. Concerns regarding viral transmission at many ambulatory centers early in the pandemic resulted in diversion of

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patients suspected of acute SARS-CoV-2 infection (COVID-19) to hospitals. While understanding of COVID-19 continues to improve, best practices regarding ambulatory patient assessment and management during ongoing transmission and viral mutation remain unclear. We describe ambulatory assessment of patients with presumed COVID-19.

National Jewish Health (NJH) is a subspecialty academic medical center that cares for a population with high prevalence of underlying chronic respiratory disease (CRD) including asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD); all of which were initially presumed to be risk factors for severe COVID-19. CRD patients frequently experience respiratory exacerbations from many etiologies, often indistinguishable from COVID-19. Persons at risk of severe COVID-19 illness (older age, chronic medical conditions), displaying fever or signs of lower respiratory illness, met criteria for COVID-19 testing. To provide rapid assessment, early triage, and hospital decompression, we designed an Acute Respiratory Clinic (ARC) where presumed COVID-19 infections could be assessed. This unique resource allowed us to study patients with CRD suspected of COVID-19.

Although defining factors for COVID-19 severity in hospitalized patients were identified [2–13], the risks of developing COVID-19 amongst ambulatory patients with CRD, were less well appreciated. COPD and asthma were presumed to be associated with severe COVID-19 amongst the hospitalized, resulting in high healthcare utilization and morbidity/mortality [8,14,15]. However, others found that asthmatics actually may have lower likelihood of COVID-19 severity [16]. These discrepancies underscored our unawareness of associations between CRD and COVID-19.

Using a retrospective analysis of data collected during regular care in the ARC, we described easily identifiable clinical factors that could correlate with and predict COVID-19 infection and/or hospitalization in those with CRD. We report the demographic, clinical, and laboratory characteristics that distinguished COVID-19 from exacerbations of underlying CRD in an ambulatory patient cohort and their disposition.

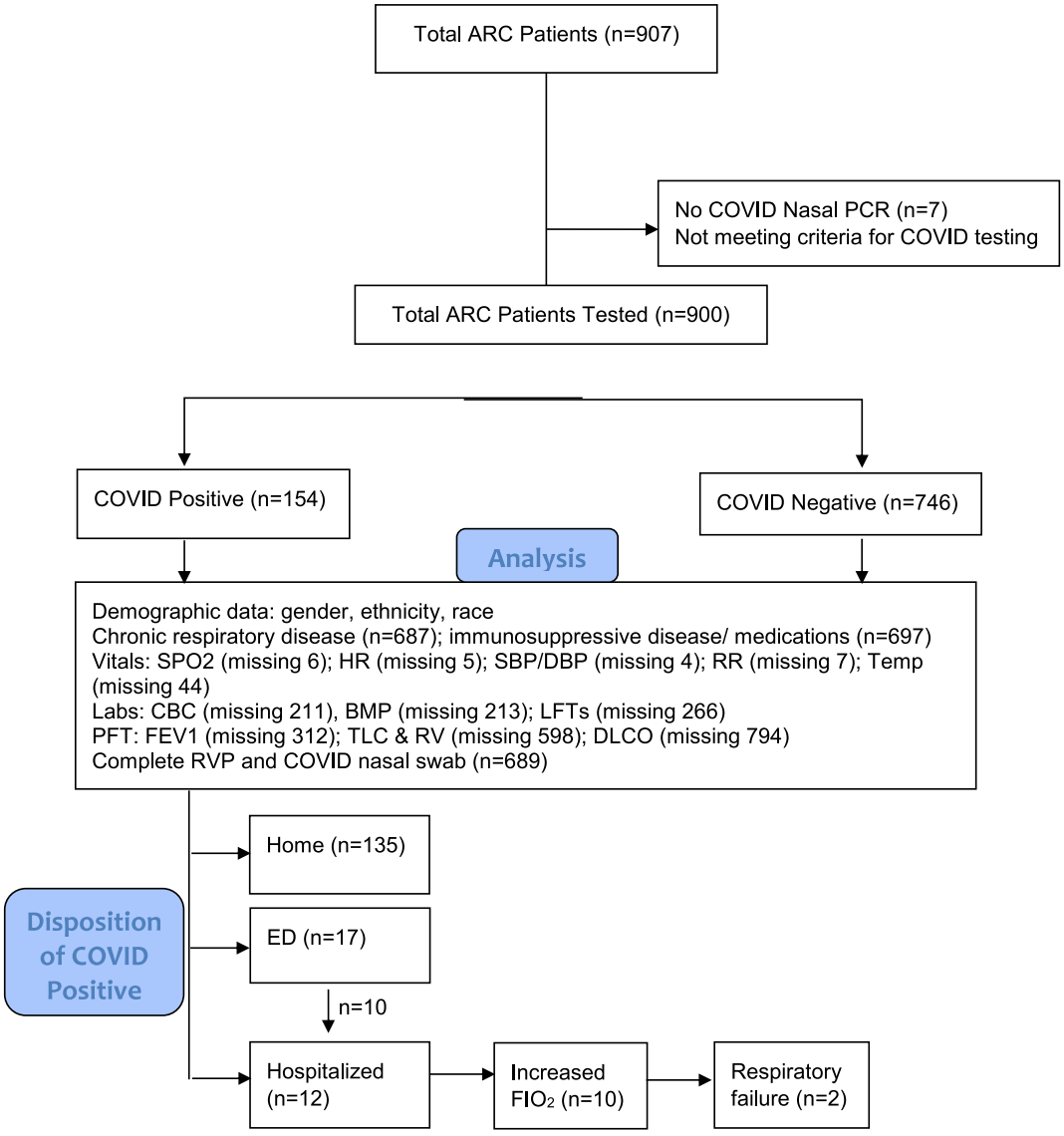

Fig. 1. ARC Patients Recruited and Analyzed (March 16, 2020–January 7, 2021). Data analyzed on all available values. Of all 907 ARC patients seen between March 16, 2020 and January 7, 2021, 154 were diagnosed with COVID-19, of whom 135 were discharged home. Fifteen were referred for ED evaluation and 10 hospitalized. There is overlap between disposition to ED and Hospital. Of the 10 patients hospitalized, 7 were admitted from the ED, 2 were directly admitted, and 1 patient we could not ascertain by which of these routes they were hospitalized. Additionally, one patient seen in the ED refused admission. Missing data is noted in the figure.

2. Methods

2.1. Study population, clinic design, disposition

This single-center retrospective cohort analysis was approved by the NJH institutional review board, who waived requirement for consent when approving the study. Study is retrospective review on electronic medical records (EMR) of 907 adult patients (≥18 years) seen in ARC between March 16, 2020 and January 7, 2021 (Fig. 1). Demographics, comorbidities, medications, vital signs, laboratory, and spirometry were collected. Data were assembled from the NJH Research Database, dataSCOUT™, containing discrete and validated EMR information.

The ARC, with negative pressure rooms and dedicated entry/exit points, was situated in a physically separate location from other clinical areas. Air exchanges between patients was ensured and PPE donned by patients and providers. Multidisciplinary providers with COVID-19 pandemic training attended to patients. History was obtained and charting performed outside clinic rooms to limit exposure. Disposition following initial ARC visit was decided by the treating clinician and defined as: a) discharge home for self-isolation until COVID-19 results were obtained or b) referral to higher level of care (local ED, direct hospital admission).

2.2. Laboratory testing

Laboratory data included blood analyses of complete blood count, metabolic panel, liver function tests, and SARS CoV-2 real-time Polymerase Chain Reaction (PCR) or end-point PCR followed by amplicon detection via mass-spectrometry. Other respiratory pathogens were tested with multiplex respiratory pathogen panels (RPPs; BioFire® RP, RP2, RP2.1) targeting adenovirus, coronavirus (KHU1, NL63, 229E, OC43), human metapneumovirus, rhinovirus/enterovirus, influenza A/B, parainfluenza virus 1–4, respiratory syncytial virus, Bordetella parapertussis, Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae. Respiratory secretions were collected via nasopharyngeal swabs. To preserve COVID-19 test kits when resources were sparse (March 2020), nasal swabs were submitted for SARS-CoV-2 PCR only if respiratory viral panel (RVP) negative first. By April 2020, both tests were simultaneously conducted on a single swab. As the pandemic progressed (June 2020) and influenza season ended, fewer patients were tested for endemic respiratory viruses beyond SARS-CoV-2.

2.3. Statistical analysis

EMR data wrangling was performed using the tidyr R software package. The analysis of overdispersed data (aod) R package was used to create a logit model using SARS-CoV-2 PCR positivity (COVID-19) as the dichotomous outcome variable. A limited set of predictor variables were used in the logit model based on those that were likely to predict positivity (e.g., temperature, SPO_2), respiratory rate (RR)). To compare COVID-19 positive vs. negative populations, between-group differences of continuous variables were tested by a pooled *t*-test or analysis of variance (JMP software, SAS Institute, Cary, NC). Associations between categorical variables were assessed by Pearson test, based on contingency tables. Tests and confidence intervals on odds ratio (OR) were based on the Wald Test. Multivariable analysis was performed using the *glmnet* algorithm. Candidate variables included 1) vital signs: heart rate (HR), SPO_2, RR, body temperature, systolic (SBP) and diastolic blood pressures (DBP); 2) medical comorbidities; and 3) laboratory values: total white blood count (WBC), neutrophils, lymphocytes, eosinophils, hemoglobin, blood urea nitrogen (BUN), creatinine, sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. We also applied the elastic net as the method for the variable selection [17], which addressed over-regularization by balancing between LASSO and ridge penalty. The subjects were divided into 80:20 ratio for training and testing sets. We first obtained the coefficients using the training set and calculated the area under the curve (AUC) using the test set. Acceptable discrimination was defined as AUC >0.70. The importance of the selected variable was estimated using the variable importance plots (VIP).

A subset of individuals having both RVP and SARS-CoV-2 testing was identified and stratified by SARS-CoV-2 status. RVP-positivity in the 2 groups was then compared with Chi-square and Fisher exact tests conducted in SAS® University Edition (SAS® Studio 3.8 with SAS® 9.4).

3. Results

3.1. Demographics

Subject characteristics are listed in Table 1. Of the 907 patients, 154 tested positive for SARS-CoV-2 (17%). Seven of the remaining 753 patients were not tested because COVID-19 was deemed unlikely by the treating clinician. There were no significant demographic differences between COVID-19 positive and negative groups. Race and ethnic analyses were limited due to unavailable data for 31.2% of subjects.

Table 1
Demographics and clinical characteristics of subjects seen in acute respiratory clinic (March 16, 2020 to January 7, 2021).

Characteristic	Total (N = 907)	COVID+ (N = 154)	COVID- or not tested (N = 753)
Age (years), mean ± SD	55.8 ± 16	56.2 ± 14	55.7 ± 16
Female, n (% total)	628 (69.2%)	99 (64.2%)	529 (70.2%)
Race, n (% total)			
White	563 (62.1%)	97 (63.0%)	466 (61.9%)
Black or African American	45 (5.0%)	10 (6.5%)	35 (4.6%)
American Indian or Alaska Native	3 (0.3%)	1 (0.6%)	2 (0.3%)
Asian	8 (0.9%)	1 (0.6%)	7 (0.9%)
Native Hawaiian, Pacific Islander	3 (0.3%)	0	3 (0.4%)
Declined	128 (14.1%)	18 (11.7%)	110 (14.4%)
Unknown	155 (17.1%)	26 (16.9%)	129 (16.9%)
Hispanic or Latino, n (% total)	80 (8.8%)	22 (14.3%)	58 (7.6%)
BMI (kg/m2), mean ± SD	29.8 + 7.4	29.4 + 6.5	29.9 + 7.5
Chronic respiratory disease, n (% total)			
COPD	226 (24.9%)	35 (22.7%)	191 (25.3%)
Asthma	441 (48.6%)	65 (42.2%)	374 (49.7%)
ILD	87 (9.6%)	11 (7.1%)	76 (10.1%)
Chronic immunosuppressive conditions, n (%total)			
Diabetes	83 (9.2%)	14 (9.1%)	69 (9.2%)
HIV, Cancer	2 (0.2%)	0	2 (0.3%)
Immunosuppressive medications, n (%total)			
Oral/systemic steroids	564 (62.2%)	82 (53.2%)	482 (64.0%)
Inhaled steroids	391 (43.1%)	52 (33.8%)	339 (45.0%)
Anti-neoplastic drugs	81 (8.9%)	16 (10.4%)	65 (8.6%)
Hypertension, n (%total)	263 (29.0%)	43 (27.9%)	220 (29.2%)
Chronic Kidney Disease, n (% total)	24 (2.6%)	3 (1.9%)	21 (2.8%)

SD = standard deviation, COVID=Coronavirus disease 2019, n = number, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease, HIV = human immunodeficiency virus.

3.2. Vital signs and laboratory analysis

Compared to SARS-CoV-2 negative patients, COVID-19 patients had higher median temperature, lower SPO_2, higher HR, higher RR, and lower SBP (Table 2). Group analysis combining all vital signs resulted receiver operating characteristic curve (ROC) AUC of 0.64 (Fig. 2A). Temperature had the greatest impact on COVID-19 positivity (likelihood ratio, LR, 10.27, $p = 0.0013$).

Univariate analysis demonstrated that COVID-19 patients had lower WBC and %eosinophils compared to patients without COVID-19; whereas no group differences were noted in %neutrophils and %lymphocytes. COVID-19 patients had higher AST compared with COVID-19 negative patients (Table 2). Multivariable group analysis of laboratory values resulted in AUC 0.69, with significant LR in WBC (LR 8.84, $p = 0.0029$), %neutrophils (LR 12, $p = 0.0005$), %lymphocytes (LR 12, $p = 0.0005$), and %eosinophils (LR 21, $p < 0.0001$). These laboratory values together with temperature, were used in a final multivariate model (Table 2).

3.3. Spirometry and Co-morbidities

Diagnosis of asthma, ILD, or COPD was not associated with testing positive for COVID-19. Use of systemic/inhaled corticosteroids at the time of visit was not correlated with COVID-19 diagnosis, nor was forced expiratory volume in first second (FEV_1) (Table 2).

3.4. Patient disposition

Of the 154 patients with COVID-19, 135 (87.7%) were discharged home, 17 (11%) were referred to ED, and 12 (7.8%) were hospitalized. Most (10/12) hospitalized subjects required supplemental oxygen above their baseline; two experienced respiratory failure requiring ventilator support; and all survived to hospital discharge (Fig. 1). There was no difference in age between those referred to the hospital compared to those discharged home from the ARC. Men were referred to the hospital at higher rates compared with women (LR $p = 0.05$) but not hospitalized at a higher rate ($p = 0.08$).

Patients referred to the hospital had 4.47% lower SPO_2 compared with those discharged home (*t*-test, $p = 0.0096$). While patients may have been referred for other reasons, this finding suggests that hypoxia was an important independent determinant for hospital referral. Although temperature, HR and RR were higher and SBP lower in hospital-referred patients, the differences were not significant. Laboratory values were similar between the two groups. Patients referred to hospital trended lower pre-morbid forced expiratory volume in 1 s to forced vital capacity ratio (FEV_1/FVC, by 13%, one-way *t*-test, $p = 0.035$) and lower pre-bronchodilator FEV_1 (by 23%, *t*-test, $p < 0.05$), suggesting that chronic airflow limitation may predict hospital referral for patients presenting with COVID-19.

Most COVID-19 patients, 111 of the 154 (72%), had CRD, since most of our patient population is represented by this group (Table 1). The most represented CRD was asthma, which was associated with higher likelihood of being referred to hospital (LR, $p < 0.05$). While COPD and ILD were not correlated with ED referral; the low number of patients with these diagnoses limited our analysis.

3.5. Respiratory viral co-infections

689 of the total 907 (75.96%) subjects had testing for other respiratory viruses. There was a relatively low prevalence of other viruses, with 6% of the COVID-19 group (6/96) and 8% of the COVID-19 negative group (47/593) demonstrating positive RVP. Chi-square and Fischer exact test were not significant between the two groups ($p = 0.500$ and $p = 0.684$, respectively). The lower prevalence of RVP positive results might be due to social distancing measures during the time of study, resulting in low overall transmission of other endemic viruses.

3.6. Multivariate analysis

Conventional multivariate analysis of vital signs resulted in AUC of 0.64 for discriminating between symptomatic individuals who were positive or negative for COVID-19 (ROC curve, Fig. 2). Chi-square analysis for vital signs was significant ($p < 0.0001$). Group analysis of blood count and differential data resulted in AUC 0.69 ($p < 0.0001$, Chi-square). A 5-variable composite of vital signs and laboratory values (temperature, WBC, neutrophils, lymphocytes, and eosinophils) resulted in AUC 0.71 ($p < 0.0001$ by Chi-square), thereby able to discriminate COVID-19 positive from COVID-19 negative status in similarly symptomatic individuals.

Combining vital signs, laboratory tests, demographics, and

Table 2
Linear regression analysis for COVID (+) status.

	Univariate			Multivariate[a]		
Variable	Δ COVID(−) - COVID(+)	95% CI	P Value	Odds Ratio	95% CI	P Value
Age (years)	−0.44	−3.27–2.38	0.76			
Temp (°C)	−0.22	−0.37 - (−0.08)	0.0023	2.55	1.6–4.0	<0.0001
HR (beats/min)	−5.78	−8.22- (−3.34)	<0.0001	–	–	–
SBP (mm Hg)	4.41	1.51–7.31	0.0031	–	–	–
RR (breaths/min)	−0.76	−1.36- (−0.15)	0.015	–	–	–
O2 Saturation	0.65	0.06–1.23	0.03	–	–	–
Total WBC (10^3/μL)	1.02	0.47–1.57	0.0003	0.90	0.81–0.99	0.021
%Neutrophils	1.24	−0.76–3.24	0.22	0.88	0.81–0.95	0.0006
%Lymphocytes	−0.47	−2.36–1.41	0.62	0.88	0.81–0.96	0.0015
%Eosinophils	0.68	0.24–1.13	0.0027	0.74	0.63–0.87	<0.0001
Hgb (g/dL)	0.05	−0.25–0.35	0.75	–	–	–
BUN (mg/dL)	−0.47	−1.77–0.84	0.48	–	–	–
Creatinine (mg/dL)	−0.04	−0.11–0.02	0.2	–	–	–
AST (units/L)	−4.11	−7.13 – (−1.1)	0.0078	–	–	–
ALT (units/L)	−4.16	−8.6–0.27	0.07	–	–	–
FEV_1 (L)	−4.18	−9.35–0.98	0.11	–	–	–

One-way ANOVA unless stated otherwise.
COVID=Coronavirus disease 2019, Δ = difference between COVID (−) and COVID (+), Temp = temperature, HR = heart rate, SBP = systolic blood pressure, RR = respiratory rate, O_2 = oxygen, WBC = white blood cells, Hgb = hemoglobin, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALT = alanine aminotransferase, FEV_1 = forced expiratory volume in first second, L = liters, dL = deciliters, μL = microliters, mm Hg = millimeters of mercury, min = minute.
[a] Based on optimized multivariate analysis with temperature, WBC, neutrophils, lymphocytes, and eosinophils as features in the model, per unit change in regressor. These 5 variables were chosen due to their significance within group analysis of a) vitals and b) laboratory parameters, not shown here.

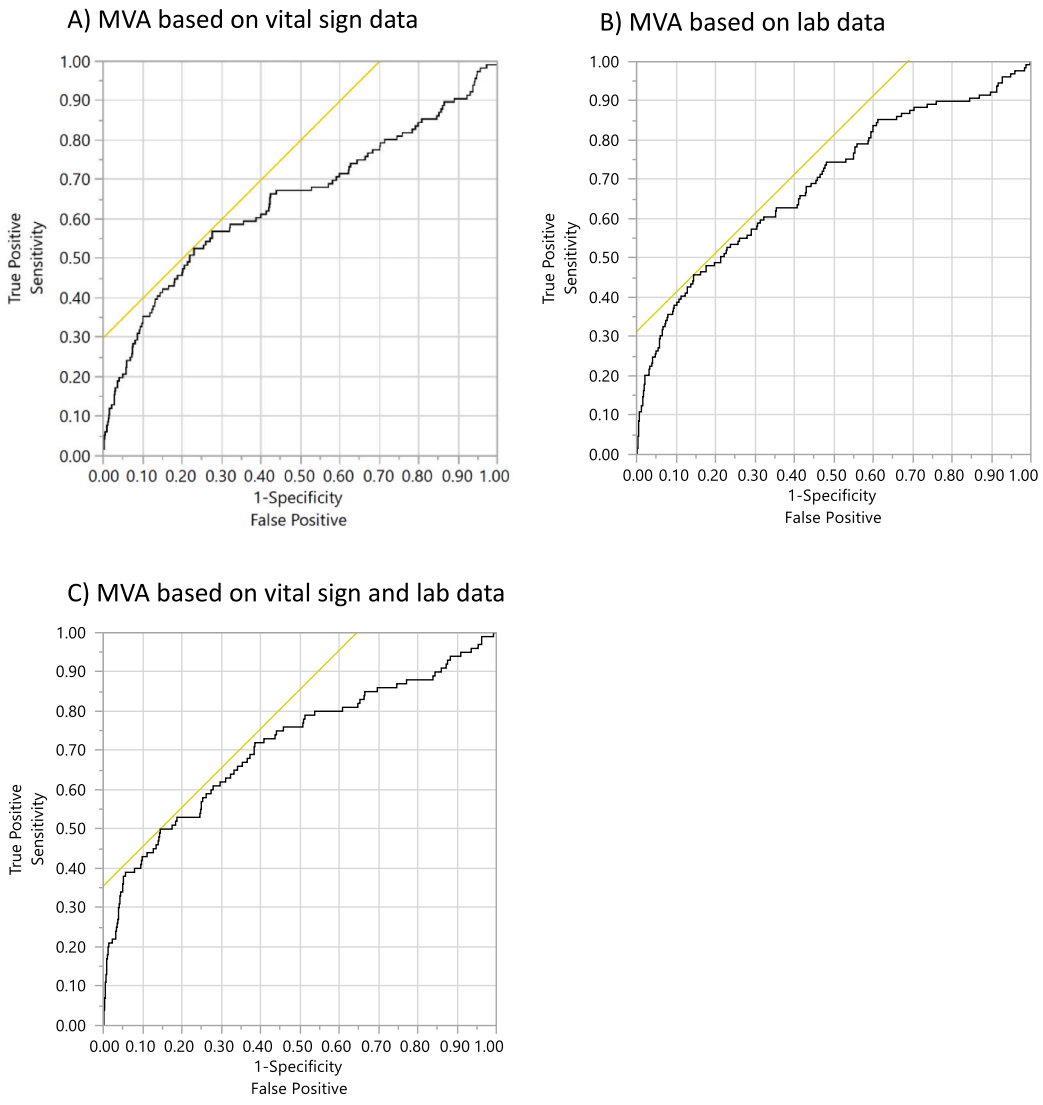

Fig. 2. A–C, Receiver operating characteristic curves (ROCs) for discrimination between COVID-19 positive (n = 154) and negative (n = 753) cases based on multiple variable analysis (MVA) of (**A**) vital sign data (AUC 0.64), which included SPO2, HR, SBP, DBP, RR, and temperature; (**B**) laboratory (lab) data (AUC 0.69), which included WBC, %neutrophils, %lymphocytes, and %eosinophils; and (**C**) vital sign and lab data (AUC 0.71), which included temperature, and labs described. Yellow line is logistic fit for positive cohort. Vital signs and labs individually and together correlated with COVID-19. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

comorbidities revealed similar information. 405 subjects (61 with COVID-19) with all candidate variables available were included in the elastic net analysis. Five variables including male sex, HR, RR, temperature, and ALT were selected as predictors for the COVID-19 susceptibility with AUC 0.80. All variables increased the likelihood of COVID-19 diagnosis, with OR ranging from 1.01 to 1.30 (Fig. 3). The VIP showed that temperature, RR, and male sex were the 3 most important predictive variables for COVID-19 in our cohort.

4. Discussion

Early in the COVID-19 pandemic, prior to widespread testing availability, patients with CRD experiencing acute respiratory symptoms sought medical care at our outpatient ARC. Symptoms of COVID-19 were non-specific and indistinguishable from endemic respiratory viruses or underlying CRD exacerbations. Although many attempted to identify distinguishing characteristics associated with severity of COVID-19 infections, few focused on identifying ambulatory clinical factors associated with SARS-CoV-2 PCR positive status [4,18–21]. Due to overtaxed EDs, outpatient centers are tasked with absorbing the burden of care for patients suspected of SARS-CoV-2 infections. We found a set of factors that are associated with testing positive for SARS-CoV-2 PCR and possibly risk factors associated with hospital referrals.

Less than 1 in 5 patients in this cohort tested positive for SARS-CoV-2 and few (12%) were referred to the ED and/or eventually hospitalized. Only 1% experienced respiratory failure. Hypoxia was the most important factor determining hospital referral. Those referred to the ED were more commonly male, non-Hispanic, had asthma diagnosis and independent of asthma diagnosis had lower FEV_1.

In our patient population of >60% with CRD, temperature, RR, WBC differentials and AST correlated with COVID-19, with elevated temperature and eosinopenia emerging as most influential. With increasing patient access to home monitoring of SPO_2, temperature and HR, an increase in median body temperature or HR could be considered potentially useful screening tools. Lower WBC or eosinophils, in the context of viral syndrome, could be useful in risk stratification if COVID-19 testing is limited. A more important inference from our study is that

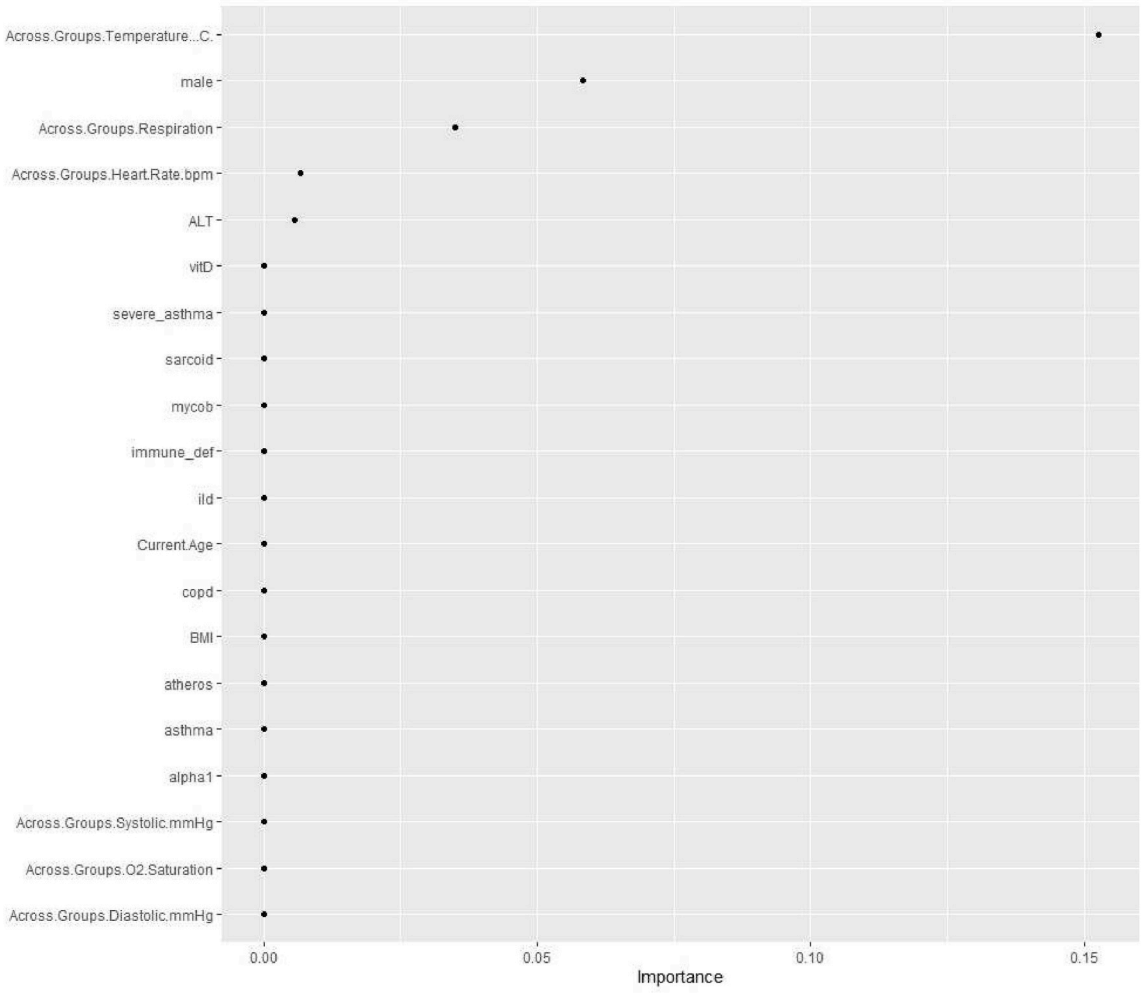

Fig. 3. Variable Importance Plot (VIP) for variables selected by the elastic net method for the prediction of testing positive for COVID in 405 subjects with complete data. Variables are located on the y-axis and relative importance to predicting COVID (+) status is located on the x-axis (the higher the number, the more important the variable). Temperature, male sex, and RR together may predict COVID-19 in subjects evaluated for acute respiratory symptoms.

CRD, in the absence of clinical immunosuppression, did not emerge as a risk factor for testing positive for SARS-CoV-2.

Asthma did not differentiate those who were eventually diagnosed with COVID-19, despite earlier studies predicting it to be a risk factor for viral disease based on rhinoviral studies [22]. In fact, asthmatics were represented in higher proportion in the COVID-negative group. An early small study at the Hospital of Wuhan University and a large multi-center heterogenous database in Israel also suggested that asthma is unlikely to be a risk for SARS-CoV-2 infection [23,24]. In fact, we found eosinopenia associated with SARS-CoV-2 infection (Table 2). Together, this suggests a possible protective effect of eosinophilia in SARS-CoV-2, as previously implied by studies of ACE2 and TMPRSS2 receptor expression in asthma [25–27]. The effect of COVID-19 in T2-high and T2-low asthma subtypes, as well as peripheral eosinophilia, needs further evaluation.

We did not observe higher associations of likelihood of SARS-CoV-2 infection or increased hospital referrals with obesity, race, or ethnicity in our cohort. However, our population was skewed towards higher White race reported, limiting our ability to detect differences. SPO_2 was lower in COVID-19 individuals but was not a key factor in predicting COVID-19 in our outpatients.

4.1. Study limitations

Inherent to the study design, retrospective analysis was limited by data collected in a real-world clinical environment, leading to information bias. Clinical judgment by the treating clinician drives data collected. This led to some missing data and incomplete analysis. However, the large number of subjects included in the study may overcome some of these limitations. Effects of mixed race was also difficult to assess with limited reporting. Objective data points would be less disparate between COVID-19 and non-COVID-19 subjects in the outpatient setting compared with a more severely symptomatic inpatient population. Therefore, detecting these differences is more difficult in the ambulatory setting. Additionally, the rapidly evolving nature of SARS-CoV-2 and demographics of affected patients, posed a particular challenge in the timing of data collection, analysis, and publication of this study aimed to assist with identification and prediction of COVID-19 in outpatient clinics at a time of limited testing. Over the 9 months of data collection, there were changes affecting diagnostic and treatment guidelines, prevalence in our community, and availability of rapid testing amongst others. All these factors likely resulted in a different patient population in the latter half of our data collection period. With the advent of COVID-19 vaccinations and the emergence of novel variants, the demographic factors, vital signs, and laboratory parameters associated with COVID-19 positive status may have changed further.

5. Conclusions

Strong associations and predictors of COVID-19 amongst ambulatory

patients with a high prevalence of chronic respiratory disease include male sex, increased baseline temperature, and respiratory rate. Male sex, lower SPO_2, and low FEV_1 were associated with hospital referrals. Asthma diagnosis did not emerge as a risk factor for COVID-19 diagnosis or severity of outcome in COVID-19 positive individuals. Relative eosinopenia, neutrophilia, and lymphocytosis were associated with COVID-19 diagnosis. Composite of vitals and WBC differential resulted in greatest impact in determining SARS-CoV-2 PCR positivity, in the setting of an unvaccinated population during emergence of the alpha-variant of SARS-CoV-2. Our results may help rapid clinical risk stratification of patients with CRD evaluated in ambulatory settings for COVID-19, particularly amongst the unvaccinated. This is especially important in areas with limited timely access to testing and the demonstrated benefits of early monoclonal antibody administration [28–32].

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Human subjects

Approval from institutional review board was obtained prior to initiation of the study.

Declaration of competing interest

No conflicts with this manuscript.

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