Late Diagnosis of COVID-19 in Patients Admitted to the Hospital

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BACKGROUND

Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is vital for identification of cases. Currently, the Centers for Disease Control and Prevention recommends that hospitalized patients with symptoms receive priority for testing.¹

Delayed testing could occur because patients have atypical presentations or the initial test is a false negative. Since test sensitivity depends on the site sampled² and hospital protocols usually rely on nasal samples, patients with lower respiratory tract infections can have a false-negative result.³

Understanding how often the diagnosis of SARS-CoV-2 is missed is essential for infection control. We describe the frequency and characteristics of hospitalized patients with COVID-19 diagnosed after admission.

METHODS

This retrospective cohort study included adults hospitalized before April 20, 2020, who tested positive for SARS-CoV-2. Testing became available for Cleveland Clinic Health System (CCHS) patients with suspected COVID-19 starting March 6 and was restricted to symptomatic, high-risk patients (e.g., hospitalized patients) on March 10. We identified patients with a positive SARS-CoV-2 test through CCHS's COVID-19 registry. We compared patients whose first positive SARS-CoV-2 test was on the day of admission versus later ("late diagnosis").

We collected demographic and health data from our electronic health record and the registry. We collected common symptoms of COVID-19. We also created a binary indicator of having none of the cardinal symptoms of COVID-19: cough, shortness of breath, or fever.

We report descriptive statistics. To identify factors associated with late diagnosis, we used a multivariable logistic regression model that included presenting symptoms,

comorbidities, age, and sex. We used model building techniques to identify variables that were associated with late diagnosis and picked the model with the lowest AIC and BIC. To assess the association between late diagnosis and length of stay, intensive care unit (ICU) admission, discharge disposition, and mortality, we conducted multivariable regressions that included age, sex, and the variables associated with late diagnosis. CCHS's IRB deemed this study exempt.

RESULTS

Our study included 356 patients; 86% with COVID-19 diagnosed on admission and 14% had a late diagnosis ($n = 49$). Patients diagnosed later presented without fever, shortness of breath, or cough 29% of the time (Table 1); 86% of the time they had ≥ 1 common symptom. They were similar in age, sex, and pre-existing comorbidities to patients diagnosed on admission. In the adjusted model, patients with late diagnosis presented less often with sputum (AOR 0.26, 95% CI 0.08–0.88) and more often with heart failure (AOR 2.36, 95% CI 1.15–4.84) and with none of the cardinal symptoms (AOR 2.89, 95% CI 1.30–6.43). Late diagnosis was not associated with length of stay, ICU admission, death, or discharge home (Table 2).

Eleven patients with late diagnosis had an initial negative result and 4 had two prior negative results. Four of 11 had their positive result collected from a non-nasal site. False negatives averaged 3.7 days to a positive result versus 2.2 days for others with late diagnosis ($P > 0.05$). False negatives were retested due to worsening symptoms (7/11), imaging suggestive of COVID-19 (2/11), and discharge protocol for skilled nursing facility (2/11).

DISCUSSION

Undiagnosed patients with COVID-19 can increase caregivers' risk of infection, as protective equipment may not be used. We found that 14% of COVID-19 patients were diagnosed after admission and most presented with ≥ 1 common symptom. Few late diagnoses were due to a false-negative test. Retesting of false negatives often occurred after clinical deterioration, but 2 patients were not diagnosed until discharge. This study is limited because we could only identify false negatives if a patient was retested. Further, we could only include routinely collected clinical data. In conclusion, routine

Elizabeth R. Pfoh and Essa H. Hariri contributed equally to this work.

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Table 1 Demographic and Presenting Characteristics of Hospitalized Patients with COVID-19

	At hospitalization	After hospitalization	P value ^a
N	307	49	
Demographics			
Race (%)			0.36
Asian	5 (2%)	0 (0%)	
Black	112 (36%)	22 (45%)	
Other	15 (5%)	4 (8%)	
White	175 (57%)	23 (47%)	
Male (%)	176 (57%)	27 (55%)	0.77
Hispanic (%)	11 (4%)	5 (11%)	0.03
Smoking (%)			0.05
Current smoker	25 (8%)	2 (4%)	
Former smoker	115 (38%)	20 (43%)	
Non-smoker	146 (49%)	25 (53%)	
Age (mean [SE])	66.0 (0.9)	67.9 (2.2)	0.47
Exposure history			
Exposed to COVID-19	82 (28%)	7 (16%)	0.35
Family member w/ COVID-19	38 (13%)	3 (7%)	0.23
Presenting symptoms			
Cough (%)	226 (74%)	27 (55%)	0.01
Fever (%)	158 (51%)	22 (45%)	0.39
Shortness of breath (%)	195 (64%)	23 (47%)	0.03
Two or more of cardinal symptoms of COVID-19 ^b	209 (68%)	29 (59%)	0.22
None of the cardinal symptoms of COVID-19 ^b	36 (12%)	14 (29%)	< 0.01
Fatigue (%)	167 (54%)	19 (39%)	0.04
Sputum production (%)	74 (23%)	4 (8%)	0.02
Flu-like symptoms (%)	164 (53%)	21 (43%)	0.17
Diarrhea (%)	92 (30%)	11 (22%)	0.28
Loss of appetite (%)	95 (31%)	12 (24%)	0.36
Vomiting (%)	37 (12%)	1 (2%)	0.04
At least one presenting symptom	287 (93%)	42 (86%)	0.06
Comorbidities			
BMI (mean [SE])*	30.4 (0.42)	30.2 (1.1)	0.85
COPD/emphysema	47 (17%)	6 (14%)	0.34
Asthma	63 (23%)	12 (30%)	0.35
Diabetes	125 (45%)	16 (36%)	0.26
Hypertension	227 (78%)	35 (78%)	0.94
Coronary artery disease	62 (23%)	11 (27%)	0.58
Heart failure	68 (25%)	16 (39%)	0.06
Cancer	53 (18%)	12 (27%)	0.19
Transplant history	13 (5%)	0 (0%)	0.15
Connective tissue disease	49 (18%)	8 (20%)	0.79
Inflammatory bowel disease	16 (6%)	3 (7%)	0.76
Immunosuppressive disease	69 (24%)	13 (30%)	0.29
Vaccination history			
Flu shot	158 (51%)	28 (57%)	0.46
Pneumovax shot	103 (34%)	20 (41%)	0.32
Home medications			
NSAIDs	105 (34%)	20 (41%)	0.37
Steroids	46 (15%)	10 (20%)	0.33
Carvedilol	17 (6%)	3 (6%)	0.87
ACE inhibitor	39 (13%)	11 (22%)	0.07
ARB	35 (11%)	5 (10%)	0.81
Melatonin	19 (6%)	13 (27%)	< 0.01
Hospital transfer			
Hospital transfer	3 (1%)	5 (10%)	< 0.01

*Body mass index (BMI) missing in 11 (3%) of respondents; presenting symptoms, comorbidities, vaccination history, and home medications are shown if they were positively identified

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^aP values were obtained using chi-square and Student's T tests

^bCardinal symptoms of COVID-19 include cough, shortness of breath, and fever

Table 2 Outcomes for Patients Hospitalized with COVID-19

	At hospitalization		After hospitalization		Adjusted <i>P</i> value ^a
	<i>N</i>	%/median (IQR)	<i>N</i>	%/median (IQR)	
Patient outcomes					
ICU admission	111	36%	23	47%	0.15
Died	46	16%	10	23%	0.51
Length of stay (median [IQR])	239	4 [2–8]	38	6 [3–12]	0.16
Discharge home (versus other)	153	63%	27	71%	0.09

Missing death information on 24 people (7%); missing length of stay and discharge destination on 79 people (22%)

IQR interquartile range

^a*P* values were obtained using an adjusted regression model including the following confounders: age, sex, heart failure, sputum on admission and binary indicator of no cough, shortness of breath, or fever on admission

testing on admission may reduce delayed identification of COVID-19. Retesting is also warranted.

Elizabeth R. Pfoh, PhD, MPH¹

Essa H. Hariri, MD²

Anita D. Misra-Hebert, MD, MPH³

Abhishek Deshpande, PhD, MD¹

Lara Jehi, MD⁴

Michael B. Rothberg, MD, MPH¹

¹Center for Value-Based Care Research, Cleveland Clinic Community Care,

9500 Euclid Avenue, Cleveland, OH 44195, USA

²Department of Internal Medicine, Cleveland Clinic Community Care, Cleveland, OH, USA

³Healthcare Delivery and Implementation Science Center, Cleveland Clinic, Cleveland, OH, USA

⁴Chief Research Information Officer, Cleveland Clinic, Cleveland, OH, USA

Corresponding Author: Elizabeth R. Pfoh, PhD, MPH; Center for Value-Based Care Research, Cleveland Clinic Community Care, 9500 Euclid Avenue, Cleveland, OH 44195, USA (e-mail: pfohe@ccf.org).

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Compliance with Ethical Standards:

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