

# Impact of COVID-19 on diagnosis of primary pulmonary coccidioidomycosis

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## Abstract

The COVID-19 pandemic has disrupted medical care worldwide and caused delays in care for many illnesses and procedures unrelated to COVID-19; however, less clear is how it may have affected diagnosis of conditions that present with similar symptoms, such as primary pulmonary coccidioidomycosis (PPC). We conducted an observational cohort study of patients diagnosed with PPC between March 1 and December 1 in 2 years: 2019 (before COVID-19) and in 2020 (after COVID-19) to compare the time from symptom onset to PPC diagnosis. Relevant demographic and clinical variables were collected, and statistical analyses were performed with the  $\chi^2$  test, Wilcoxon rank sum test, and Cox proportional hazards regression analysis. During 2019, 83 patients were diagnosed with PPC. During 2020, 113 patients were diagnosed with PPC. For both groups, the median time from symptom onset to diagnosis of PPC was 14 days ( $P = .13$ ). No significant differences in time to diagnosis existed between the 2 years for location of diagnosis (outpatient clinic, emergency department, or in hospital), for computed tomographic imaging performed before diagnosis, or for number of COVID-19 tests received before PPC diagnosis. In addition, there were no differences in the 2 years between the total number of clinical visits before diagnosis. However, patients in the post-COVID-19 group who had fever were diagnosed with PPC earlier than those without fever (hazard ratio, 1.77; 95% confidence interval, 1.15–2.73;  $P = .01$ ). Contrary to what we expected, no significant delay in diagnosis of PPC occurred during the COVID-19 pandemic.

**Abbreviations:** CAP = community-acquired pneumonia, CT = computed tomography, ED = emergency department, EIA = enzyme immunoassay, ICD-10 = international classification of diseases, tenth revision, IgM = immunoglobulin M, PPC = primary pulmonary coccidioidomycosis, STROBE = Strengthening the Reporting of Observational Studies in Epidemiology.

**Keywords:** community-acquired pneumonia, COVID-19, primary pulmonary coccidioidomycosis

## 1. Introduction

The COVID-19 pandemic has overwhelmed health care systems throughout the world. As hospitals and clinics attempted to respond to surges of COVID-19 cases, care had to be delayed for patients with other medical conditions. A survey conducted by the Centers for Disease Control and Prevention showed that 41% of patients delayed their medical care because of the pandemic, and up to 12% of those delays were classified as urgent or emergent care.<sup>[1]</sup> In 2020, health care facilities reported 45% fewer stroke admissions than in 2019.<sup>[2]</sup> Rates of percutaneous interventions in ST-segment elevation myocardial infarction decreased by 19% in 2020.<sup>[3]</sup> These types of reductions and delays were likely multifactorial, attributable partially to limited resources and to patients' fears of contracting COVID-19 at medical facilities.

The impact of COVID-19 on the diagnosis and management of community-acquired pneumonia (CAP) has not been

well investigated. Several studies assessed the low rates of concomitant bacterial and fungal infections and the use of appropriate antimicrobial regimens for hospitalized patients with COVID-19 pneumonia.<sup>[4–6]</sup> However, COVID-19 may also contribute to the delay or misdiagnosis of CAP, particularly for atypical pathogens such as *Coccidioides* species. In portions of the southwest United States, primary pulmonary coccidioidomycosis (PPC) may account for one-fourth of all cases of CAP.<sup>[7,8]</sup> The presenting symptoms of PPC, such as cough, fever, and dyspnea, overlap with presenting symptoms of COVID-19 pneumonia.<sup>[9]</sup> To evaluate whether the pandemic delayed time to PPC diagnosis, we conducted a retrospective observational study to compare the time from onset of symptoms to diagnosis of PPC in the year before and directly after the start of the pandemic. Given the high numbers of COVID-19 cases and the possible diagnostic confusion with other causes of pneumonia, we hypothesized that

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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the time to diagnosis of PPC within the coccidioidal-endemic region would have increased during the pandemic.

## 2. Methods

### 2.1. Inclusion and exclusion criteria

The study protocol was approved by the Mayo Clinic Institutional Review Board, and the requirement for written informed consent was waived for this minimal-risk study. The reporting of this study is in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.<sup>[10]</sup> We conducted a single-center retrospective review of electronic health records using the *International Classification of Diseases, Tenth Revision (ICD-10)* codes B38.0 (coccidioidomycosis) and B38.2 (pulmonary coccidioidomycosis, unspecified) as the primary search diagnoses. We included patients over the age of 18 years who were diagnosed with acute PPC between March 1 and December 1 in 2019 and 2020 at Mayo Clinic in Arizona.

Criteria for the diagnosis of invasive mycoses were published by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.<sup>[7]</sup> We used similar criteria for PPC diagnosis. Patients had to meet the definition for 1 of the following categories: *proven*, *probable*, or *possible* pulmonary coccidioidomycosis. Patients who met *proven* criteria had either a positive biopsy, culture, or polymerase chain reaction result for coccidioidomycosis. Patients who met *probable* criteria had a combination of symptoms, serologic findings, and imaging findings typical of pneumonia. Patients who met *possible* criteria had symptoms and positive serologic findings without imaging findings suggestive of PPC.<sup>[8]</sup> Only patients with symptomatic infection were included.

Serologic testing included enzyme immunoassay (EIA), immunodiffusion, and/or complement fixation. Those patients whose results were positive only by EIA immunoglobulin M (IgM) were not considered to meet the criteria for coccidioidal diagnosis unless they seroconverted to positive IgM results by ID or positive immunoglobulin G results by EIA, ID, or complement fixation on follow-up testing. In such cases, the diagnosis date was recorded as the date of EIA IgM positivity and not the date of seroconversion. Patients who did not seroconvert or were treated without repeat testing were excluded. Patients were excluded for 2 additional reasons: (1) insufficient documentation in the electronic health record (e.g., incomplete notes about symptoms, missing serologic test results); and (2) concomitant disease that could produce symptoms similar to those of coccidioidomycosis (e.g., fever, cough, and weight loss from pulmonary adenocarcinoma; cough and dyspnea from worsening heart failure).

The date of the positive serologic results was considered the date of diagnosis. The date of symptom onset was either documented or estimated on the basis of the timeframe provided in the notes in the health record.

### 2.2. Data collection

We collected the following demographic data: age at diagnosis, race, sex, and smoking status. We also collected data on comorbid conditions (diabetes, cancer, cardiovascular disease, and pulmonary disease); the number of symptomatic COVID-19 tests before diagnosis; the number of in-office and video visits; and the location where the diagnosis was made (in the outpatient clinic, emergency department [ED], or hospital). Patients who had serologic samples collected in the ED and were discharged the same day had the ED as the listed diagnosis location. Those who had serologic samples collected in the ED but were

subsequently hospitalized had their diagnosis location listed as in hospital. We also assessed for a difference in time from symptom onset to diagnosis in relation to location (outpatient clinic, ED, in hospital), specific symptoms, and use or absence of diagnostic computed tomography (CT) imaging.

To assess the effect of a COVID-19 surge on the time to PPC diagnosis, we compared the average time to diagnosis of PPC for 160 patients diagnosed before October 1, 2020, and 36 patients who were diagnosed on or after October 1, 2020.

### 2.3. Outcomes

The primary outcome of the study was the number of days from onset of symptoms to diagnosis of PPC. Secondary outcomes included time to diagnosis based on symptoms and the location where the diagnosis of PPC was made (including in the outpatient clinic, ED, and hospital), as well as whether CT imaging was performed before diagnosis.

### 2.4. Statistical analysis

Demographic and clinical results were reported as mean (standard deviation) for continuous variables and percentages for categorical variables. A  $\chi^2$  analysis was used to evaluate categorical variables. A Kruskal–Wallis test was used to compare continuous variables, such as age. A Wilcoxon rank sum test was used to calculate the significance between number of visits by year. Cox proportional hazards models were used to assess the outcome of days from onset of symptoms to diagnosis (covariates of diagnosis location and year of diagnosis); to evaluate time from symptom onset to diagnosis on the basis of specific symptoms including fever, cough, and shortness of breath; and to adjust for year and the use of CT scans before the diagnosis date. A *P* value of <.05 indicated significance.

## 3. Results

In 2019 (pre-COVID-19), 83 patients met the inclusion criteria, and in 2020, 113 patients met the inclusion criteria. Demographic characteristics, comorbid conditions, and characteristics of the patients' clinical course are summarized in Table 1. There was no significant difference between the 2 years in demographic data or comorbid conditions. The median time to diagnosis in both cohorts was 14 days (*P* = .13). In 2019, patients had slightly more in-person visits than in 2020 (2.0 vs 1.8, *P* = .05). There was no difference when video visits were included in the total number of health care visits. Those who were diagnosed in the hospital had shorter times to diagnosis than those diagnosed in an outpatient setting (hazard ratio (HR), 2.06; 95% confidence interval (CI), 1.52–2.80; *P* < .001). There was no difference in the time from symptom onset to diagnosis between the patients diagnosed in the ED and outpatient settings (*P* = .08). The symptoms of PPC for patients in the 2020 group are summarized in Table 2. Fever and cough were the most common presenting symptoms in patients with PPC.

Results of the Cox models for most comparisons were not significant. Patients with PPC who had a fever, however, had a 64% chance of being diagnosed earlier than patients without fever (HR, 1.77; 95% CI, 1.15–2.73; *P* = .01). In 2019, 43 patients (51.8%) had a chest CT scan before their PPC diagnosis compared with 62 patients (54.9%) in 2020, and the number of CT scans was not different between the 2 years (*P* = .67). Results of the Cox model adjusting for year and CT scans completed before the diagnosis date were not statistically significant (HR, 1.12; 95% CI, 0.85–1.49; and HR, 0.79; 95% CI, 0.60–1.06; *P* = .12).

The number of COVID-19 tests performed for symptomatic illness was analyzed for the 2020 group. Of the patients, 56 (49.6%) had 2 or more (0–5) tests, 44 patients (38.9%) had 1, and 13 patients (11.5%) had no tests. The number of COVID-19

**Table 1**  
Demographic and clinical characteristics of patients with primary pulmonary coccidioidomycosis before (2019) and after the pandemic (2020).

	No. (%) <sup>*</sup>		P value
	2019 (n = 83)	2020 (n = 113)	
Age at diagnosis, mean (SD), yr	57 (16.1)	55 (15.4)	.50†
Race			.37‡
White	72 (86.7)	93 (82.3)	
Asian	3 (3.6)	10 (8.8)	
Black or African American	2 (2.4)	5 (4.4)	
Pacific Islander	3 (3.6)	1 (0.9)	
Other	3 (3.6)	4 (3.5)	
Smoking status			.23‡
Never	52 (62.7)	82 (72.6)	
Former	29 (34.9)	27 (23.9)	
Current	2 (2.4)	4 (3.5)	
Sex			.68‡
Male	48 (57.8)	62 (54.9)	
Comorbid conditions§			
Cardiovascular disease or its risk factors	34 (41.0)	47 (41.6)	.93‡
Cancer	14 (16.9)	17 (15.0)	.73‡
Pulmonary disease	11 (13.3)	15 (13.3)	.99‡
Location of diagnosis			.60†
Outpatient setting	44 (53.0)	52 (46.0)	
ED	8 (9.6)	14 (12.4)	
In hospital	31 (37.3)	47 (41.6)	
Coccidioidomycosis diagnosis			
Proven¶	12 (14.5)	12 (10.6)	.42‡
Probable¶¶	63 (75.9)	96 (85.0)	.11‡
Possible#	8 (9.6)	5 (4.4)	.15‡
Onset of symptoms to PPC diagnosis, median (range)§	14.0 (2.0–225.0)	14.0 (0–227.0)	.13**
Visits, median (range), No.			
In-person	2.0 (1.0–5.0)	1.8 (0–5.0)	.05**
Video	NA	n = 112††	NA
Total	2.0 (1.0–5.0)	0 (0–2.0) n = 112††	.35**

ED = emergency department, NA = not applicable, PPC = primary pulmonary coccidioidomycosis.

<sup>\*</sup> Data are presented as No. (%) unless indicated otherwise.

† Kruskal–Wallis P value.

‡  $\chi^2$  P value.

§ No significant difference between the other comorbid conditions: diabetes, transplant, connective tissue disease, cancer, and HIV.

¶ Positive culture, pathologic findings, or polymerase chain reaction for *Coccidioides* species.

¶¶ Positive serologic and imaging studies and typical symptoms.

# Positive serologic findings without abnormal imaging in the presence of typical symptoms.

\*\* Wilcoxon rank sum P value.

†† One patient in the 2020 cohort had an unclear number of video visits.

tests did not appear to affect time to PPC diagnosis (>2 vs <2; P = .36). The median time to diagnosis of PPC was also not different before and after a surge of COVID-19 in the community (14 days before and 15 days after the surge; P = .74).

#### 4. Discussion

Although we hypothesized that patients with PPC would have increased time from symptom onset to diagnosis during the

**Table 2**  
Prevalence of symptoms in patients with primary pulmonary coccidioidomycosis in 2020 (post-COVID-19).

	Total, no. (%) (N = 113)
Cough	90 (79.6)
Fever	79 (69.9)
Fatigue/weakness	60 (53.1)
Pleuritic chest/back pain	44 (38.9)
Shortness of breath	42 (37.2)
Rash	41 (36.3)
Myalgia	34 (30.1)
Night sweats	31 (27.4)
Chills	29 (25.7)
Headache	22 (19.5)
Weight loss	15 (13.3)
Arthralgia	11 (9.7)
Nausea/vomiting	11 (9.7)
Hemoptysis	2 (1.8)

pandemic, our study showed no difference before and after the pandemic began. The median number of days to diagnosis was 14 for each cohort. In addition, we did not find any significant differences between the total number of clinical visits, whether or not CT imaging was used, or the time to diagnosis based on patient location (outpatient clinic, ED, in hospital). Within the 2020 group, the number of COVID-19 tests and time to diagnosis were also not significantly different. However, our data indicated that patients who had a fever were diagnosed sooner than those without a fever.

The consistent time to diagnosis in both years has a few possible explanations. First, the patient population was limited to our institution. Our patients are usually insured, and they already have an assigned practitioner whom they can access easily through the electronic health portal system. As a result, they may seek care sooner and thus shorten the time to a diagnostic work-up, which may be why the pandemic did not significantly affect CAP diagnosis and access to care in our patient population. Second, patients may have sought medical evaluation for possible COVID-19 infection and were subsequently diagnosed with PPC. Patients who had fever were diagnosed more quickly than those without fever. Both fever and fatigue are common presenting symptoms for patients with PPC (86% and 100% of patients, respectively).<sup>[11]</sup> In patients with COVID-19, fever is the most common symptom at illness onset, present in up to 55% of patients.<sup>[12]</sup> Therefore, patients with a fever could have asked for care sooner because of concern for COVID-19 infection, leading to a quicker diagnosis of PPC. Although we did not evaluate the time from symptom onset to diagnosis in patients with COVID-19, current literature suggests that the average time from onset of symptoms to diagnosis ranges from 3 to 10 days.<sup>[13]</sup>

A surprising finding of this study was the speed at which the diagnosis of PPC was reached after the onset of symptoms as compared with other previously published studies. Testing for coccidioidomycosis infection in patients who have CAP ranges anywhere from 2% to 13%.<sup>[14]</sup> Donovan et al<sup>[15]</sup> reported a median delay of 23 days from initial evaluation to laboratory diagnosis of coccidioidomycosis. A study by Blair et al<sup>[11]</sup> had similar findings, showing the average time from onset of symptoms to treatment was 21 days. As addressed previously, fever may have been an important factor for why some patients sought care earlier in 2020. However, this result does not explain why patients in 2019 had a similar median time to diagnosis. Another explanation could be that the ICD-10 codes we used preselected patients who were diagnosed quicker. We did

not include patients with the more general *ICD-10* code of *coccidioidomycosis, unspecified*. Our data also suggest that patients who were diagnosed with PPC in the hospital were diagnosed more quickly than those diagnosed in an outpatient setting. Possibly, a larger proportion of patients who were diagnosed in the hospital contributed to a shorter overall time to diagnosis than what is reported in the literature.

#### 4.1. Limitations

We acknowledge limitations to this study. First, the data may not be generalizable to hospitals or health care systems outside of the southwestern United States, where coccidioidomycosis is less prevalent. Second, our institution is a tertiary care center, and an inherent referral bias may exist because patients usually have undergone an initial work-up elsewhere and may have more severe illness than patients seeking care at nontertiary care centers. Third, our selection criteria had limitations. Using *ICD-10* codes B38.0 and B38.2, we selected patients with diagnosed *acute pulmonary coccidiomycosis* and *pulmonary coccidiomycosis, unspecified*. Therefore, we may have missed patients with PPC who were coded under other *ICD-10* codes such as *coccidiomycosis, unspecified*. We also did not account for the slight difference in the sample size between the 2 years.

#### 5. Conclusion

Our findings showed no delay in diagnosis of PPC in patients during the COVID-19 pandemic compared with a prepandemic cohort. With low overall rates of coccidioidomycosis testing in patients with CAP, it is encouraging to see that the COVID-19 pandemic may not have significantly delayed care for those with PPC. To achieve early diagnosis and management of PPC, we advise that providers in the *Coccidioides*-endemic area continue to keep a high level of suspicion and consider the diagnosis of PPC for patients with CAP.

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