Prevalence and risk factors for postinfectious cough in discharged patients with coronavirus disease 2019 (COVID-19)

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**Background:** Cough is one of the most common symptoms of coronavirus disease 2019 (COVID-19). However, the prevalence of persistent cough in recovered patients with COVID-19 during a longer follow-up remained unknown. This study aims to investigate the prevalence, and risk factors for postinfectious cough in COVID-19 patients after discharge.

**Methods:** We conducted a follow-up study for 129 discharged patients with laboratory-confirmed COVID-19 in two large hospitals located in Hubei Province, China from January 2020 to December 2020. Baseline demographics, comorbidities and smoking history were extracted from the medical record. Current symptoms and severity were recorded by a uniform questionnaire. Spirometry, diffuse function and chest computed tomography (CT) were performed on part of patients who were able to return to the outpatient department at follow-up.

**Results:** The median (interquartile range) follow-up time was 8.1 (7.9–8.5) months after discharge. The mean (standard deviation) age was 51.5 (14.9) years and 57 (44.2%) were male. A total of 27 (20.9%) patients had postinfectious cough (>3 weeks), 6 patients (4.7%) had persistent cough by the end of follow-up, including 3 patients with previous chronic respiratory diseases or current smoking. Other symptoms included dyspnea (6, 4.7%), sputum (4, 3.1%), fatigue (4, 3.1%), and anorexia (4, 3.1%) by the end of follow-up. Thirty-six of 41 (87.8%) patients showed impaired lung function or diffuse function, and 39 of 50 (78.0%) patients showed abnormal CT imaging. Patients with postinfectious cough demonstrated more severe and more frequent cough during hospitalization (P<0.001), and more chronic respiratory diseases (P=0.01). In multivariate logistic regression analysis, digestive symptoms during hospitalization [odds ratio (OR) 2.95, 95% confidence interval (CI): 1.10–7.92] and current smoking (OR 6.95, 95% CI: 1.46–33.14) were significantly associated with postinfectious cough of COVID-19.

**Conclusions:** A small part of patients developed postinfectious cough after recovery from COVID-19, few patients developed chronic cough in spite of a higher proportion of impaired lung function and abnormal lung CT image. Current smoking and digestive symptoms during hospitalization were risk factors for postinfectious cough in COVID-19.

**Keywords:** Coronavirus disease 2019 (COVID-19); respiratory infection; postinfectious cough; digestive symptoms; post-acute sequelae of SARS-CoV-2 infection
Introduction

Up to December 18, 2021, coronavirus disease 2019 (COVID-19) infection has been reported in more than two hundred million cases around the world. Given the epidemic has been going on for an extended period of time, an incredibly increasing number of studies (1-7) involving the epidemiology, transmission pattern, immune mechanism, clinical manifestation, radiological features and clinical drug trials, have been trying to reveal the whole picture of this novel disease. As more and more patients recovered from the acute infection of COVID-19, increasing attention has been directed to the long-term outcome of the disease, which is now referred to as “post-acute sequelae of SARS-CoV-2 infection” (PASC).

Numerous studies have confirmed that cough is one of the most common symptoms of COVID-19, which occurred in 40–80% of patients with COVID-19 during infectious period (8-11). Evidence from other viral infection caused by rhinovirus and adenovirus suggested that postinfectious cough was common (12,13), and some even developed into chronic cough (12,14,15). Another survey conducted on H1N1 influenza found that postinfectious cough occurred in 8.5% of patients and 2.8% of patients developed chronic cough (16). In online surveys, cough was reported in 20–64% of patients 2–6 months after the onset of symptoms of COVID-19 (17-23) and 2.5–23.3% after 6 months (24-27). The results of the prevalence of cough in the long-term follow-up are quite different. In addition, there is no study exploring the risk factors associated with postinfectious cough in patients with COVID-19. In this study, we conducted an 8-month follow-up with a uniform questionnaire in discharged patients with COVID-19, to clarify the prevalence and risk factors of postinfectious cough in COVID-19. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-876/rc).

Methods

Participants

This observational follow-up was based on our previous study conducted at First People’s Hospital of Jingzhou and Xiangyang Central Hospital from January 19, 2020, to May 22, 2020 (28). 129 patients with confirmed SARS-CoV-2 infection by real-time PCR in the previous study received a follow-up at about 8 months after discharge from October 2020 to December 2020. The age of patients ranged from 19 to 84 years. The inclusion and diagnosis procedure were described before and disease severity was categorized according to the WHO interim guidance. Patients were discharged after fulfilment of all standard criteria in Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial version 5 revised) released by China’s National Health Commission (29). Follow-up was conducted mainly by telephone since most patients were unable to revisit the hospital due to the epidemic. To reduce information bias, the telephone follow-up was performed by the same physician in each center. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First People’s Hospital of Jingzhou (42016803-T) and Xiangyang Central Hospital (2020-001). Only oral informed consent was obtained and recorded in electronic medical records from patients after a full explanation of this study.

Data collection

Baseline demographics, comorbidities, smoking history were extracted from the medical record. Patients returned to hospitals’ outpatient clinics or received telephone interview 8 months after discharge. All patients were asked to complete a uniform questionnaire including items on current symptoms, cough duration, Cough Visual Analog Scales (VAS), cough severity and cough frequency during hospitalization and after discharge. VAS is a 100 mm scale on which patients indicate the severity of cough. Cough severity level was scaled as mild, moderate, and severe and evaluated by patients. Cough frequency was categorized into four scales as scale 1 (a little of the time), scale 2 (some of the time), scale 3 (a good bit of the time) and scale 4 (most of the time). Cough severity and cough frequency were decided subjectively by patients. In this study, we defined postinfectious cough as a cough last for more than 3 weeks.
and persistent cough as a continuous cough from the onset of COVID-19 infection until the end of follow-up. Patients with a cough persistent for no more than 3 weeks or no cough throughout the disease were regarded as having no postinfectious cough.

Assessment

Spirometry and pulmonary diffusion capacity tests were performed following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines in a part of patients. Variables with values below the lower limit of normal (LLN) or <80% of predicted were considered abnormal (30). Chest CT imaging analysis was performed by two radiographers with over 10-year experience who were blind to clinical and laboratory findings.

Statistical analysis

Continuous data conformance to normal distribution was described by mean ± standard deviation and an independent t-test was used to compare differences between groups, otherwise median (interquartile range) and Manny-Whitney U-test were used. For categorical data, frequency counts and percentages were used in descriptive analysis. The Chi-square test and Fisher's exact test were used in group comparison. The association between postinfectious cough and clinical manifestations was assessed by binary logistic regression analysis corrected for age and sex. A two-sided P value <0.05 was considered statistically significant. For missing data, we deleted cases with missing data of a certain variable when analyzing the variable.

Results

Among 301 confirmed cases enrolled in the previous study, 129 were successfully followed up, the mean (standard deviation) age was 51.5 (14.9) years and 57 (44.2%) were male (Table 1). The reasons for loss of follow-up were inability to contact patients or patient refusal of follow-up. In 123 patients who have been classified according to disease severity, the numbers of mild, moderate, severe and critical cases on admission were 1 (0.8%), 107 (87.0%), 12 (9.8%) and 3 (2.4%) respectively, 6 patients were not classified due to lack of origin information on admission since they were transferred from other hospitals. The median (interquartile range) follow-up time was 8.1 (7.9–8.5) months after discharge (Table 1).

By the end of follow-up, 27 (20.9%) patients still had at least one symptom caused by COVID-19. The presenting symptoms included cough (6, 4.7%), dyspnea (6, 4.7%), sputum (4, 3.1%), fatigue (4, 3.1%), anorexia (4, 3.1%), chest tightness (3, 2.3%), myalgia (3, 2.3%), sore throat (2, 1.6%) and other symptoms (7, 5.4%) including anosmia, hypogeusia, insomnia and palpitation (Figure 1). Based on the duration of cough, 76 (58.9%) patients had acute cough (<3 weeks after cough onset), and 27 (20.9%) patients had postinfectious cough, among which 6 (4.7%) patients developed into persistent cough (Figure 2). In patients with postinfectious cough, 5 (18.5%) had a history of chronic respiratory disease including chronic obstructive pulmonary disease (COPD), chronic cough and pulmonary tuberculosis, and all of them complained of more severe cough during COVID-19 infection. Six (22.2%) were current smokers, including current second-hand smokers (Table 1). Of 6 patients with persistent cough, 3 had a history of chronic respiratory disease among which 2 were current smokers, while the other 3 patients had no history of respiratory disease and none of them were current smokers. Of these 3 patients with persistent cough caused by COVID-19, the median score of VAS was 30, and all of them presented occasional mild dry cough which could be evoked by cold air, cigarette, smoke or perfume (data not shown).

Compared with patients without postinfectious cough, the incidence of digestive symptoms including nausea (51.9% vs. 30.4%, P=0.044), vomit (51.9% vs. 28.4%, P=0.037) and diarrhea (51.9% vs. 29.4%, P=0.040) during hospitalization were higher in postinfectious cough group. In patients who had cough during hospitalization, the proportions of cough frequency were 48.1% and 84.0% on scale 1–2, 51.8% and 16.0% on scale 3–4 in patients with and without postinfectious cough respectively (P<0.001). For cough severity, 51.5% of patients had mild cough, 29.6% had moderate cough, 18.5% had severe cough in patients with postinfectious cough group, while the corresponding proportion were 85.3%, 13.3% and 1.3% in patients without postinfectious cough (P<0.001) (Table 2). The prevalence of a history of chronic respiratory disease was higher in the postinfectious cough group (18.5% vs. 2.9%, P=0.010). The proportion of current smoker was also higher in the postinfectious cough group (22.2% vs. 3.7%, P=0.016). In multivariate logistic regression analysis adjusted by age and gender, digestive symptoms on admission showed an odds ratio (OR) of 2.95 [95% confidence interval (CI): 1.10–7.92] and current...
smoking showed an OR of 6.95 (95% CI: 1.46–33.14) for postinfectious cough after COVID-19 infection (Figure 3). No significant association of age, gender, or history of chronic respiratory disease with postinfectious cough was observed.

Totally 41 patients received pulmonary function test at the follow-up, 36 (87.8%) patients had at least one abnormal variable. 13 (31.7%) and 3 (7.32%) patients had the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) below LLN, while 6 (14.63%) patients had decreased maximum mid expiratory flow (MMEF). 21 (51%) and 29 (70.7%) patients showed decreased total

| Clinical manifestation            | Total (n=129) | Postinfectious cough (n=27) | No postinfectious cough (n=102) | P value |
|----------------------------------|---------------|-----------------------------|---------------------------------|---------|
| Age (y), mean (SD)              | 51.5 (14.9)   | 47.4 (12.9)                 | 52.6 (15.3)                     | 0.106   |
| Gender, male                    | 57 (44.2)     | 11 (40.7)                   | 46 (35.7)                       | 0.828   |
| Duration of hospitalization (day)| 24.0 (11.0–32.0) | 26.0 (18.0–33.0)       | 23.0 (8.8–31.0)                 | 0.612   |
| Severity on admission            |               |                             |                                 |         |
| Mild                             | 1/123 (0.8)   | 0/26 (0.0)                  | 1/97 (1.0)                      | 0.622   |
| Moderate                         | 107/123 (87.0)| 25/26 (96.2)                | 82/97 (84.5)                    |         |
| Severe                           | 12/123 (9.8)  | 1/26 (3.8)                  | 11/97 (11.3)                    |         |
| Critical severe                  | 3/123 (2.4)   | 0/26 (0.0)                  | 3/97 (3.1)                      |         |
| Symptoms                         |               |                             |                                 |         |
| Fever                            | 107 (83.0)    | 23 (85.2)                   | 84 (82.4)                       | 0.999   |
| Cough                            | 102 (79.1)    | 27 (100.0)                  | 75 (73.5)                       | NA      |
| Sputum                           | 60 (46.5)     | 18 (66.7)                   | 42 (41.2)                       | 0.029   |
| Dyspnea                          | 52 (40.3)     | 12 (44.4)                   | 40 (39.2)                       | 0.663   |
| Headache                         | 43 (33.3)     | 12 (44.4)                   | 31 (30.4)                       | 0.126   |
| Fatigue                          | 66 (51.2)     | 16 (59.3)                   | 50 (49.0)                       | 0.391   |
| Myalgia                          | 52 (40.3)     | 11 (40.7)                   | 41 (40.2)                       | 0.999   |
| Rhinobyon                        | 41 (31.8)     | 11 (40.7)                   | 30 (29.4)                       | 0.352   |
| Sore throat                      | 44 (34.1)     | 13 (48.2)                   | 31 (30.4)                       | 0.110   |
| Chest tightness                  | 23 (17.8)     | 6 (22.2)                    | 17 (16.7)                       | 0.338   |
| Anorexia                         | 51 (39.5)     | 12 (44.4)                   | 39 (38.2)                       | 0.659   |
| Nausea                           | 45 (34.9)     | 14 (51.9)                   | 31 (30.4)                       | 0.044   |
| Vomit                            | 43 (33.3)     | 14 (51.9)                   | 29 (28.4)                       | 0.037   |
| Diarrhea                         | 44 (34.1)     | 14 (51.9)                   | 30 (29.4)                       | 0.040   |
| Chronic respiratory disease      | 8 (6.2)       | 5 (18.5)                    | 3 (2.9)                         | 0.010   |

Smoking history, n=108
| Smoking history | Total (n=108) | Postinfectious cough (n=27) | No postinfectious cough (n=81) | P value |
|-----------------|---------------|-----------------------------|---------------------------------|---------|
| Non-smoker      | 91/108 (84.3) | 20/27 (74.1)                | 71/81 (87.7)                    | 0.016   |
| Current smoker  | 9/108 (8.3)   | 6/27 (22.2)                 | 3/81 (3.7)                      |         |
| Ex-Smoker       | 8/108 (7.4)   | 1/27 (3.7)                  | 7/81 (8.6)                      |         |

Data are presented as mean (standard deviation), median (interquartile range) or n/N (%). N represents the number of patients with available data. COVID-19, coronavirus disease 2019; SD, standard deviation; NA, not available.
l lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (DLCO) respectively. No significant difference between the postinfectious cough group and the no postinfectious cough group in all indices mentioned above (data not shown). Chest CT was performed on 50 patients, 39 (78.0%) had at least one type of abnormality. The most common abnormality of chest CT at the follow-up was focal fibrosis (16, 32.0%). Compared to patients without postinfectious cough, more patients showed interstitial infiltration (8.3% vs. 2.6%) in the postinfectious cough group (data not shown).

**Discussion**

To our knowledge, this is the first study that analyses the prevalence of acute cough, postinfectious cough and persistent cough in COVID-19 with a follow-up of 8 months after discharge. Our study showed that symptoms of COVID-19 significantly reduced long after discharge, however, approximately one-fifth of patients still presented with at least one symptom, including cough, dyspnea, fatigue and anorexia at the follow-up. The incidence of symptoms in our study is significantly lower compared with previous studies (17,18,21-23,26,27). We attributed it to a longer period after discharge, which also implied that COVID-19 infection would rarely cause severe and long-term sequelae.

The prevalence of acute cough and persistent cough caused by COVID-19 in our study were 58.9% and 4.7% respectively. A previous study found that the prevalence of persistent cough was 18% (95% CI: 12–24%), with follow-up duration ranging from 6 weeks to 4 months (31). However, the prevalence varied widely among studies, and is presumably associated with patient characteristics. A recent study involving 1,950 hospitalized COVID-19 patients in Madrid showed that one year after discharge, the prevalence of post-COVID-19 cough was as low as 2.5%. However, in that study, only 28.1% of patients had cough at hospital admission (26) which was much lower than that in our study (79%) and other studies in China (8,32-35). Compared with studies from European and American countries, the prevalence of post-COVID-19 cough in Asian countries seemed to be lower (20–41.9%
vs. 27.5–29%) (20-27,36). It is unclear whether the ethnic difference contributed to the prevalence of cough. The prevalence of persistent cough in previous studies enrolling mild to moderate patients was less than 10%, while it was more than 30% in more critical severe patients (37-39). Therefore, besides the follow-up duration, the severity of disease on admission may be a non-negligible reason for the different outcomes. Due to the minority of severe patients in our study, we are not able to explore whether the severity of disease is an independent risk factor for persistent cough in COVID-19 infection. Overall, the prevalence of postinfectious cough especially persistent cough is relatively low compared with other COVID-19 symptoms. The C-fibers innervating conducting airways have been identified in inducing cough and reflex-mediated bronchospasm. However, some evidence implies the C-fibers innervating the distal airways may inhibit cough (11,40,41). Therefore, we speculate the possible reason for the low incidence of postinfectious and persistent cough post COVID-19 is that SARS-CoV-2 infection mainly damages distal airway and alveoli innervated by C-fibers preferentially regulating the bronchia contraction rather than cough upon activation (40,42). That may also explain the inconsistency of a relatively high incidence of decreased lung function and persistent abnormalities in chest CT but low prevalence of persistent cough.

Compared with those without postinfectious cough, patients with postinfectious cough showed more severe and frequent cough during hospitalization. Interestingly, our results also implicated that, patients with evident digestive symptoms including nausea, vomit and diarrhea during infection period are prone to developing postinfectious cough. Digestive symptoms have been reported in severe acute respiratory syndrome (SARS) and

### Table 2 Assessment of cough in patients with COVID-19 on admission

| Assessment of cough | Total (n=129) | Postinfectious cough (n=27) | No postinfectious cough (n=102) | P value |
|---------------------|--------------|-----------------------------|---------------------------------|---------|
| VAS (mm), n=89      | 21.0 (10.5–51.5) | 42.5 (20.0–72.0) | 19.0 (0.0–48.0) | 0.001   |
| Frequency of cough  | (n=102)      | (n=27)                      | (n=75)                          |         |
| A little of the time (scale 1) | 55 (53.9) | 6 (22.2) | 49 (65.3) | <0.001 |
| Some of the time (scale 2)     | 21 (20.6) | 7 (25.9) | 14 (18.7) |         |
| A good bit of the time (scale 3) | 21 (20.6) | 9 (33.3) | 12 (16.0) |         |
| Most of the time (scale 4)     | 5 (4.9) | 5 (18.5) | 0 |         |
| Severity of cough  | (n=102)      | (n=27)                      | (n=75)                          |         |
| Mild (scale 1)       | 78 (76.5) | 14 (51.9) | 64 (85.3) | <0.001 |
| Moderate (scale 2)   | 18 (17.6) | 8 (29.6) | 10 (13.3) |         |
| Severe (scale 3)     | 6 (5.9) | 5 (18.5) | 1 (1.3) |         |

Data are presented as median (interquartile range) or n (%). COVID-19, coronavirus disease 2019; VAS, Visual Analog Scales.

### Figure 3 Risk factors for postinfectious cough by using multivariable logistic regression model.

| Variables | OR (95% CI) | P value |
|-----------|-------------|---------|
| Male      | 1.14 (0.39–3.33) | 0.813   |
| Age       | 0.97 (0.94–1.01) | 0.140   |
| Chronic respiratory disease | 4.99 (0.93–26.71) | 0.061   |
| Ex-smoker | 1.54 (0.13–18.57) | 0.735   |
| Current smoker | 6.95 (1.46–33.14) | 0.015   |
| Digestive symptoms | 2.95 (1.10–7.92) | 0.032   |
COVID-19 patients during and after infection (43-45). Although the pathophysiology of SARS-CoV-2 infection in gastrointestinal tract remains unclear, it has been identified that the virus invades target cells by binding to the angiotensin-converting-enzyme 2 (ACE2) receptors expressed in airway epithelial and gastrointestinal tract, which shares the similar pattern with SARS and Middle East Respiratory Syndrome (MERS) (43,46). The ACE2 gene has also been reported in a subset of human dorsal root ganglion sensory neurons in the thoracic ganglia (47), suggesting the possibility of direct infection of SARS-CoV-2 to sensory nerve. A previous study found the convergence of vagal afferents from the esophagus and respiratory tract in the brain stem, which is the cause of an esophageal-bronchial reflex (48). It might be possible that the central sensitization caused by the interaction of vagal afferents contributes to the prone to postinfectious cough in patients with digestive symptoms. Since the questionnaire did not investigate the duration and treatment of digestive symptoms in our study, it is not clear if cough symptom was parallel to digestive symptoms during the last 8 months after discharge. Whether postinfectious cough after COVID-19 is related to gastroesophageal reflux disease (GERD) or shares a similar mechanism with gastroesophageal reflux-related cough (GERC) remains to be further investigated.

Cigarette smoking is regarded as a major risk factor for respiratory and cardiovascular disease including airway infection. Data had shown that the prevalence of influenza was five times higher in smokers than that in non-smokers (49). Several studies implicated that smoking was significantly associated with more severe and increased mortality of COVID-19 (50-52), however, some studies reported inconsistent results (53). In our study, only 6 patients with persistent cough were current smokers among which 4 patients had no history of respiratory disease. Therefore, we speculated smoking is an important risk factor for postinfectious cough in COVID-19.

Decreased diffusion capacity was presented in most patients who also have comorbid decreased TLC and RV, indicating the injury of alveolar interstitium and a restrictive ventilatory deficit in COVID-19. It was identified in several studies that 10% to 52% of COVID-19 patients had decreased DLCO which was associated with total CT score, dyspnea score and duration of oxygen supplementation during hospitalization (36,54-56). And the high prevalence of lung diffusion impairment could persist for 6 months and one year after discharge (57). However, there was no clear association between cough and decreased diffusion capacity, with regard to the similar DLCO between patients with and without postinfectious cough in our study and the previous study (58). Whether the decline of pulmonary function would persist for a long time needs further and larger cohort studies. With regard to chest CT, a part of patients still presented abnormalities at the follow-up, which was consistent with some previous studies (59,60). We noticed that the proportion of local patchy shadowing and interstitial infiltration were higher in patients with postinfectious cough, suggesting the impairment of parenchyma and interstitium of lung caused by COVID-19 infection may exist for a long time. The pathogenesis of cough in interstitial lung diseases (ILD) or parenchyma and interstitium damage remains unclear. Lung fibrosis could increase cough reflex sensitivity in response to capsaicin (61) and mechanical stimulation of the chest wall (62). A generalized neuronal hypersensitivity caused by neuroinflammatory and neuroimmune mechanisms after the elimination of SARS-CoV-2 might also be an important consideration (31). Thus, a functional up-regulation of sensory neurons of the lung and inflammatory changes could both probably get involved (63).

However, there are some limitations of our study. Firstly, the follow-up was conducted by telephone in a part of patients, so only parts of patients who were able to revisit in clinic received pulmonary function test and chest CT. Secondly, a timely follow-up had not been conducted regularly after discharge, so the duration and severity of postinfectious cough and treatment after discharge could not be reached. Thirdly, most of patients included in this study were moderate, therefore the results may not be applicable to severe and critical severe patients.

Conclusions

Our 8-months follow-up study demonstrated that about one-fifth of COVID-19 patients develop postinfectious cough, but persistent cough is uncommon in rehabilitated patients. Current smoking including second-hand smoking and digestive symptoms in acute phase are risk factors for postinfectious cough after recovery from COVID-19.

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Footnote

Provenance and Peer Review: This article was a standard submission for the series “Cough Section” published in Journal of Thoracic Disease. The article has undergone external peer review.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-876/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First People’s Hospital of Jingzhou (42016803-T) and Xiangyang Central Hospital (2020-001). Oral informed consent was obtained and recorded in electronic medical records from patients after a full explanation of this study.

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