Original Article

Association of persistent respiratory symptoms with severity of COVID-19

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ABSTRACT

Background: *Coronavirus disease 2019 (COVID-19) is a new and highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms and disease severity of COVID-19 vary from asymptomatic to severe or fatal illness. A major complication of those who survived from COVID-19 is the development of lung disease leading to persistence of respiratory symptoms. The objective of the present study was to find out the association of persistence of respiratory symptoms with severity of COVID-19.*

Methods: *This prospective observational study was carried out in the Department of Respiratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka during the period from July 2020 to December 2020. During follow-up around three months (90.62±2.21 days) after the onset of the first COVID-19 symptoms, 500 patients were taken as the study sample.*

Results: *Total patients were 500 with 206 (41.2%) severe cases. Two-fifths of the study participants had persistent respiratory symptom at 3 months. Persistence of respiratory symptoms was associated with severity of COVID-19 (p = <0.001). Among the respiratory symptoms, shortness of breath (34.72%) and cough (29.63%) were the most prevalent symptoms that was persisted in severe COVID-19 during follow-up.*

Conclusion: *This study has shown that persistent respiratory symptoms were common after COVID-19 that was about 40% and were associated with the severity of COVID-19.*

Key words: *Coronavirus disease 2019, severe acute respiratory syndrome coronavirus-2, acute respiratory distress syndrome.*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new and highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which presented a risk of infection from human to human.[1] At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world.

The spectrum of symptomatic infection ranges from mild to critical; most infections are not severe.[2] Specifically, in a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed cases with an estimation of disease severity: mild (no or mild pneumonia) was reported in 81 percent. Severe disease (eg, with dyspnea, hypoxia, or >50 percent lung involvement on imaging within 24 to 48

hours) was reported in 14 percent.[3] Critical disease (eg, with respiratory failure, shock or multi-organ dysfunction) was reported in 5 percent. The overall case-fatality rate was 2.3 percent. Among hospitalized patients, the proportion of critical or fatal disease is higher.[4] It might progress rapidly and some patients develop respiratory failure early in the disease. After SARS-CoV-2 infection, a major complication of those who survive, is the development of severe lung disease leading to persistent respiratory symptoms.[5] Persistent impairment of pulmonary function ranging from months to even years after discharge has been reported in other coronavirus infections, such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[6,7] Recent evidence has suggested that lung is the most affected organ in COVID-19.[8] The extent and severity of the long term respiratory complications of COVID-19 remain to be seen but emerging data indicate that many patients experience persistent respiratory symptoms months after their initial illness.[9] Recently published guidance by the National Health Survice (NHS), UK lays out the likely after care needs of patients recovering from COVID-19 and identifies potential respiratory problems including chronic cough, fibrotic lung disease, bronchiectasis and pulmonary vascular disease. The evidence for these possible sequelae is largely derived from acute manifestations of COVID-19, along with extrapolations from the 2003 outbreak of SARS and data on acute respiratory distress syndrome. In Italy, one study showed where patients were assessed a mean of 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom; at the time of the evaluation, only 18 (12.6%) were completely free of any COVID-19 related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more and a high proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%) and chest pain.[5] Persistent respiratory symptoms following COVID-19 may cause substantial morbidity and optimal management remains unclear. Prospective studies are under way to evaluate these complications further and to identify people at greatest risk. This study was done too see the association of persistent respiratory symptoms with severity of COVID-19.

METHODS

This prospective observational study was carried out in the Department of Respiratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka during the period from July 2020 to December 2020. Patients were recruited consecutively. All patients admitted in the COVID-19 ward, who were laboratory-confirmed SARS-CoV-2 infection by reverse transcription-polymerase chain reaction with respiratory symptoms were considered for this study. All patients who met the eligibility criteria were followed up. After discharge from the hospital, we kept their records. Patients were assessed around three months (90.62±2.21 days) after the onset of the first COVID-19 symptoms. Patients were asked or requested to attend the post-COVID clinic three months from the onset of their first symptoms. Then data were collected with a structured questionnaire. Those who could not attend the post-COVID clinic were contacted by telephone call and data were collected. The visual analog scale (VAS) was used to ask patients to score their quality of life from 0 (no symptoms) to 100 (worst symptoms imaginable) during COVID-19 and at the time of the visit. A difference of 10 points was defined as a worsened quality of life. Total 590 confirmed COVID-19 patients were primarily screened for the study. During follow-up around three months after the onset of the first COVID-19 symptoms, 33 died and 57 patients were unwilling to participate. Following then 500 patients were taken as the study sample.

RESULTS

Total patients were 500 with mean age of 52.69±12.81 (range 18-80) years. One hundred thirty two (26.4%) were over 60 years of age followed by 114 (22.8%) in 51-60 years. Only fifty (10.0%) patients were under age of group of 30 years (Table I). Majority (294, 58.8%) had non-severe disease while 206 (41.2%) had severe disease.

Table I. Age distribution of the study population (N=500)

Age in years	Frequency	Percentage
18- 30 years	50	10.0
31-40 years	114	22.8
41-50 years	90	18.0
51-60 years	114	22.8
> 60 years	132	26.4

Our study showed 334 (66.80%) were male and 166 (33.20%) patients were female. Cough and shortness of

breath were the two most prevalent respiratory symptoms during the infection and at follow-up (cough: 88.4% versus 26.8%; shortness of breath: 58.6% versus 22.6%) respectively. Other prevalent respiratory symptoms were during the infection and follow-up (sore throat: 22.6% versus 1.8%, sputum production: 11.4% versus 2.2%, anosmia: 30.8% versus 2.0%, chest pain: 15.4% versus 5.6%, rhinitis: 31.20% versus 2.0%), respectively (Figure 1).

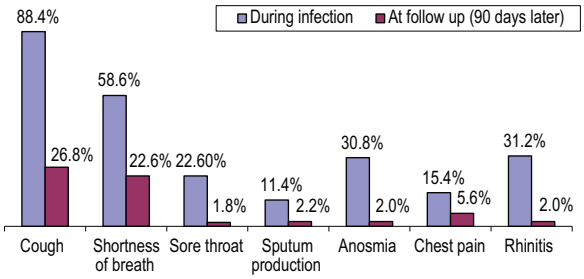

Figure 1. Bar graph showing the prevalence of respiratory symptoms during the infection and at follow-up (90 days later) of the study patients (N=500)

Majority of COVID-19 patients (300, 60%) were symptoms free during follow-up (three months later) and 40.0% had persistent respiratory symptoms. Persistent respiratory symptoms were more common in severe COVID-19 than non-severe cases and which was significant ($p<0.001$) (Table III).

In our study significant differences were found in respiratory symptoms during infection in non-severe cases with severe cases, which were shortness of breath (38.44% versus 87.96%), sore throat (26.53% versus 18.05%) and rhinosinusitis (2.38% versus 1.85%) ($p<0.05$) respectively (Table IV).

In Our study significant differences were also found in respiratory symptoms at follow-up (three months later) in non-severe cases with severe cases, which were shortness of breath (14.29% versus 34.72%) ($p<0.05$) respectively (Table V).

Table III. Association of severity of COVID-19 with the persistent respiratory symptoms (N=500)

Severity of COVID-19 during infection	Persistent respiratory symptoms		X^2	p value
	Present n=200	Absent n=300		
Non-severe	98 (49.0%)	196 (65.33%)		
Severe	102 (51.0%)	104 (34.67%)	13.21	<0.001

Table IV. Association of respiratory symptoms with the severity of COVID-19 during infection

Respiratory symptoms during infection	Severity of COVID-19		X^2	p value
	Non-severe n=294	Severe n=206		
Cough	266 (90.48%)	185 (85.64%)	2.83	0.09
Shortness of breath	113 (38.44%)	190 (87.96%)	126.66	<0.001
Sore throat	78 (26.53%)	39 (18.05%)	5.05	0.02
Sputum production	35 (11.60%)	26 (12.03%)	0.002	0.96
Anosmia	101 (34.35%)	58 (26.85%)	3.26	0.07
Chest pain	52 (5.78%)	26 (6.01%)	3.06	0.08
Rhinosinusitis	107 (2.38%)	56 (1.85%)	6.27	0.01

Table V. Association of respiratory symptoms with the severity of COVID-19 at follow-up after three months later

Respiratory symptoms at follow-up	Severity of COVID-19		X^2	p value
	Non-severe n=294	Severe n=206		
Cough	73 (24.83%)	64 (29.63%)	2.08	0.14
Shortness of breath	42 (14.29%)	75(34.72%)	29.41	<0.001
Sore throat	7 (2.38%)	2 (0.93%)	1.52	0.31
Sputum production	08 (2.72%)	03(1.39%)	1.04	0.36
Anosmia	08 (2.72%)	03 (1.39%)	1.04	0.36
Chest pain	19 (6.46%)	11 (5.09%)	0.42	0.51
Rhinosinusitis	04 (1.36%)	07 (3.24%)	2.08	0.14

DISCUSSION

In the present study maximum patients were found in the sixth and seventh decades for both males and females. Among the study population, the maximum number of patients were male. Our demographic findings are matched with a study done in Wuhan, China where their median age was 56.0 years and most patients were male.[10]

In one study conducted in Italy where patients were assessed a mean of 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom; at the time of the evaluation, only 18 (12.6%) were completely free of any COVID-19 related symptom, while 32% had one or two symptoms and the majority had three or more.[5] A living systematic review of five databases was performed in order to identify studies which reported the persistence of respiratory symptoms in COVID-19 patients after discharge. In the pooled analysis, they found a prevalence of 0.52 (CI 0.38–0.66, p < 0.01, I2 ¼ 97%), 0.37 (CI 0.28–0.48, p < 0.01, I2 ¼ 93%), 0.16 (CI 0.10–0.23, p < 0.01, I2 ¼ 90%) and 0.14 (CI 0.06–0.24, p < 0.01, I2 ¼ 96%) for fatigue, dyspnoea, chest pain, and cough, respectively. Fatigue, dyspnoea, chest pain, and cough were the most prevalent respiratory symptoms found in 52%, 37%, 16% and 14% of patients between 3 weeks and 3 months, after discharge in survivors of hospital admission by COVID-19, respectively.[11] All these results were quite similar to our result.

In the present study, we found a significant difference in respiratory symptoms during infection in non-severe cases with severe cases. Among them cough, sore throat and rhinosinusitis were found more in non-severe cases than severe cases. But shortness of breath was the commonest symptom in severe COVID-19 cases. During follow-up (three months later) shortness of breath was also the commonest symptom. These might be due to diffuse involvement of the lung, low SpO2, and thrombo-embolic manifestations due to SARS-CoV-2 infection. These results were consistent with a study where they reported the association between COVID-19 symptoms with severe and non-severe patients.[12] The majority had dyspnea in the severe group. Other features of fever, cough, myalgia or fatigue, and headache were also found higher in the severe COVID-19 patients. However, except for dyspnea, their meta-analysis did not find any statistically significant association with the severity of the disease.[12] In one study two hundred eighty-eight participants were recruited, and follow-up data were available for 183, 175, and 120 participants at days 30, 90, and 180 postsymptom onset, respectively. Symptoms related to COVID-19 were present in 31 (16.9%), 13 (7.4%), and 14 (11.7%) at days 30, 90, and 180. In a multivariable they found the severity of acute infection were associated with increased likelihood of persistent symptoms.[13] These results were quite similar to our result.

In our study, we found maximum COVID-19 survivors were free from respiratory symptoms during follow-up (three months later) but in case of severe COVID-19, we found respiratory symptoms were persisted more than in non-severe cases. In ne study they found recovered COVID-19 patients had elevated levels of proinflammatory interleukin (IL)-17A, stem cell factor, IL-12p70, and IL-1â and pro-angiogenic macrophage

inflammatory protein 1â, brain-derived neurotrophic factor, and vascular endothelial growth factor at day 180 compared with healthy controls.[13] Higher levels of monocyte chemoattractant protein-1 and platelet-derived growth factor-BB were detected in patients with persistent symptoms, versus symptom-free patients.[13]

The wide range of persistent respiratory symptoms seen in this study. The sequelae left by severe COVID-19 and the persistent symptoms after discharge agree with what was seen in previous years with Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), where it was reported that hospitalised patients presented physical and psychological sequelae up to 6 months and 1 year, respectively.[14] The follow-up of these patients is essential, not only in the physical field but also in the biopsychosocial field. It represents a tremendous logistical and economic challenge, as a follow-up implies; therefore, a rigorous selection of patients who benefit from these follow-up programmes are generally patients who developed more severe disease.

Conclusion

This study has shown that persistent respiratory symptoms were common after COVID-19 and were related to the severity of COVID-19. Identification of persistent symptoms requiring early intervention is critical to plan for and providing post-acute medical, psychological and physical services to enable recovery from COVID-19, ncluding the ability to return to work.

Limitations

Limitations of the study include the lack of information on symptoms and history before acute COVID-19 illness and the lack of details on symptom severity. Furthermore, this was a single-center study with a relatively small number of patients.

Recommendation

A more comprehensive study on a large scale of all patients should be conducted to confirm the results of our study.

Authors' contribution: MMR, AIK, RJ, SR, SMS, RCB, AKMMH were involved in diagnosis, patient management and manuscript writing. FBH was involved in patient diagnosis and manuscript writing.

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REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020 Feb 15;395 (10223):507-13.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020 Feb 15;395(10223):497-506.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 Apr 7;323(13):1239-42.
4. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. The Lancet 2020 Jun 6;395(10239):1763-70.
5. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020 Aug 11;324(6):603-5.
6. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clinic Proceedings 2020 Jun 1: 95(6):1138-47.
7. Hui DS, Wong KT, Ko FW, Tam LS, Chan DP, Woo J, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest 2005 Oct 1;128(4):2247-61.
8. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases 2020 Apr 1;20(4):425-34.
9. Haque MA. Pulmonary Fibrosis as Sequelae of Covid-19 Pneumonia. TAJ: Journal of Teachers Association 2020 Dec 31;33(2):i-ii.
10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020 Mar 28;395(10229):1054-62.
11. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et

al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Chronic Respiratory Disease 2021 Mar 16;18: 1479973 1211002240.

12. Talukder A, Razu SR, Alif S, Rahman MA, Islam SM. Association between symptoms and severity of disease in hospitalised novel coronavirus (COVID-19) patients: A systemic review and meta-analysis. J Multidiscip Healthc 2022 May 12;15:1101-10.

13. Ong SW, Fong SW, Young BE, Chan YH, Lee B, Amrun SN, et al. Persistent symptoms and association with inflammatory cytokine signatures in recovered coronavirus disease 2019 patients. Open Forum Infectious Diseases 2021 Jun: 8(6):156.

14. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurology 2011 Dec;11(1):1-7.