Double Trouble: Post COVID Pulmonary Sequelae

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Abstract
Background: Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial aetiology associated with Wuhan City, Hubei Province, China on 31 December 2019¹,². The first case was reported in India on 27th January 2020 and in Srikakulam on 25th April 2020. As per WHO, patients will recover with an incubation period of 10 to 14 days, sometimes COVID symptoms can remain for more than 20 days up to 45 days due to the long-term effect of COVID and patients develop Post COVID complications. Multi-organ involvement seen in patients who had a severe illness, lung being most commonly involved. Other organs involved are the heart, brain, vascular system, kidney, skin⁴. Here, we provide a comprehensive review on complications of the respiratory system arising in post-COVID patients depicted as post-COVID pulmonary sequelae

Aim of the Study: To evaluate the post COVID pulmonary complications, treat the cause and prevent disease progression

Materials & Methods: This is a prospective observational study conducted on 77 patients recovered from COVID-19 for a duration of 6 months, in Great eastern medical school & hospital, Srikakulam, Andhra Pradesh which was a District COVID hospital. The study was done in COVID patients after recovery, within a duration of 1 month to 6 months with a confirmed diagnosis of COVID-19 in the second wave in the year 2021. A register would be made for data collection for both out-patients and in-patients. Information will be collected regarding symptoms, history, personal history. HRCT chest, sputum bacterial culture, TRUENAAT is done to assess complications and prevent them. The study was conducted after obtaining consent from patients.

Results: Among 77 study populations, the analysis showed males were 71.43% and females were 28.57% with an age group of 41-60 years is most commonly involved. Most of the patients presented with a duration of symptoms >1 month i.e., 29.87%. Most common complication encountered was pulmonary fibrosis 23.37%, Fungal pneumonia 10.3%, Allergic rhinitis 10.3%, death 10.38%, pleural diseases 9%, diabetes 9%, pulmonary TB 6.49%, Extrapulmonary(pleural) TB- 5.19%, Extrapulmonary complications 2.59%.

Conclusion: The pulmonary sequelae of COVID-19 after the acute phase of COVID-19 is increasingly being appreciated. COVID-19 affects people of all age groups and gender. It neither spares people with comorbidities nor those without any comorbidities. Social distancing, proper mask and hand hygiene will be the long-lasting self-disciplinary measures to curtail the spread of the disease.

Keywords: Post COVID complications, COVID-19, Pulmonary sequelae
Introduction
Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial aetiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing.3

Pathogenesis

Post COVID
The mechanism of post-COVID conditions is not well understood, but is hypothesized to be secondary to virus-specific pathophysiologic changes, prolonged inflammatory response to the acute infection and sequelae of post-intensive care illness
Post-COVID conditions are referred to by a wide range of names, including “long COVID,” “post-COVID syndrome,” “post-acute COVID-19 syndrome,” as well as the research term “post-acute sequelae of SARS-CoV-2 infection” (PASC). Among the lay public, the phrase “long-haulers” is also used.7,9
Long COVID is used to describe signs and symptoms that last for longer than 4 weeks after getting COVID-19.8

Definition
A potentially severe acute respiratory infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical presentation is generally that of a respiratory infection with a symptom severity ranging from a mild common cold-like illness, to a severe viral pneumonia leading to acute respiratory distress syndrome that is potentially fatal. Characteristic symptoms include fever, dry cough, dyspnoea, and loss of taste/smell, although some patients may have mild upper respiratory tract symptoms or be asymptomatic. Complications of severe disease include, multi-organ failure, septic shock, and venous thromboembolism. Symptoms may be persistent and continue for more than 12 weeks in some patients.6

Fig 1: pathogenesis of COVID-19

Pathophysiology of COVID-19
There are two stages to what is commonly known as Long COVID⁵:

- Ongoing symptomatic COVID-19 – symptoms that last 4-12 weeks
- Post-COVID-19 syndrome – symptoms that last for more than 12 weeks and can’t be explained by another diagnosis

Materials & Methods

Objective of the Study

1. To study the clinical picture
2. To study the radiological pattern
3. To analyse the microbiological flora

Aim of the Study

To identify the post COVID complications, treat the cause and to prevent disease progression

Study Group: post COVID patients

Study Design: prospective observational study

Place Of Study: patients attending out-patient and In-patient of GEMS Hospital, Srikakulam.

Duration of Study: 6months

Study Sample: 77

Methodology: patients attending GEMS Hospital, srikakulam with cough, dyspnoea, fever, general malaise, cold with past history of COVID in 2ⁿᵈ wave and follow-up patients is included in our study.

The study was done in COVID patients after recovery within a duration of 1month to 6months. A register would be made for data collection for both out-patients and in-patients.

Information collected regarding symptoms, past history, personal history. HRCT chest, sputum bacterial culture, sputum TRUENAAT is done to assess complications and prevent it.

Inclusion Criteria

1. All patients who suffered from COVID recovered, discharged and tested negative for COVID with documented evidence.
2. Age >18years
3. Patients with comorbidities: Diabetes, Hypertension, Pulmonary TB, Bronchial asthma etc.,
4. Smokers & non-smokers

Exclusion Criteria

1. Age <18years
2. Active COVID infection.

The nature and purpose of the study was explained in detail to all the study Patients and written informed consent was obtained from all of them included in this study. Data collection was done as per the proforma

Study Procedure

Patients re-admitted with symptoms after recovery from COVID-19 from 1month to 6months duration were studied. Clinical presentation, comorbidities, personal history with CT CHEST, sputum bacterial and fungal culture, sputum TRUNAAT was done to analyse the complications and treat at the earliest. Patients admitted with post COVID were evaluated for study after inclusion and exclusion criteria analysis.

Results

Table 1: Age wise Distribution

| Age group | No. of patients | %    |
|-----------|-----------------|------|
| 18-20     | 3               | 3.90%|
| 21-30     | 6               | 7.79%|
| 31-40     | 13              | 16.88%|
| 41-50     | 21              | 27.27%|
| 51-60     | 20              | 25.97%|
| 61-70     | 9               | 11.69%|
| 71-80     | 3               | 3.90%|
| >80       | 2               | 2.60%|
| Total     | 77              | 100% |

The minimum age taken in the study was 18 and maximum age 85. Most common age group affected was between 41-60 years (53.34%).
Table 2: Sex Distribution

| Sex    | No. of patients | %     |
|--------|-----------------|-------|
| Male   | 55              | 71.43%|
| Female | 22              | 28.57%|
| Total  | 77              | 100%  |

Males are more commonly affected than females.

Table 3: Age wise sex distribution

| SEX    | N  | Mean age in years | Std. Deviation | Student independent t-test |
|--------|----|-------------------|----------------|----------------------------|
| Male   | 55 | 48.69             | 14.56          | t=0.13 p=0.90 (not-Significant) |
| Female | 22 | 49.18             | 15.36          |                            |

Males mean age is 48.69 years and females mean age is 49.18 years. Overall mean age is 48.83 years and SD is 14.70 years.

Table 4: Chief Complaints of Study Patients

| Chief complications    | No. of patients | %    |
|------------------------|-----------------|------|
| Asymptomatic           | 6               | 7.79%|
| Chest pain             | 10              | 12.99%|
| Cold                   | 8               | 10.39%|
| Dry cough              | 17              | 22.08%|
| Dyspnoea               | 12              | 15.58%|
| Fever                  | 17              | 22.08%|
| General malaise        | 2               | 2.60%|
| Headache               | 1               | 1.30%|
| Jerking of limbs       | 1               | 1.30%|
| Productive cough       | 3               | 3.90%|
| Total                  | 77              | 100% |

Majority of patients presented with dry cough 22.08% and fever 22.08%.

Table 5: Duration of symptoms

| Duration   | No. of patients | %    |
|------------|-----------------|------|
| Nil        | 6               | 7.79%|
| < 7 days   | 16              | 20.78%|
| 8-15 days  | 12              | 15.58%|
| 1 month    | 20              | 25.97%|
| >1 month   | 23              | 29.87%|
| Total      | 77              | 100% |

Majority of patients i.e., 55.84% having symptoms >1 month
Duration couldn’t be assessed in 7.79% patients.

Table 9: Comorbidities

| Comorbidities    | No. of patients | %    |
|------------------|-----------------|------|
| Diabetes         | 12              | 15.58%|
| Bronchial asthma | 2               | 2.59%|
| Hypertension     | 1               | 1.30%|
| No comorbidities | 61              | 79.22%|
| Pulmonary TB     | 1               | 1.29%|
| Total            | 77              | 100% |

Table 10: Smoking Status

| Smoking status  | No. of patients | %    |
|-----------------|-----------------|------|
| Non smoker      | 42              | 54.55%|
| Smoker          | 35              | 45.55%|
| Total           | 77              | 100% |
Table 11: Immunisation Status for COVID

| Vaccination status | No. of patients | %  |
|--------------------|----------------|----|
| Not Vaccinated     | 61             | 79.22% |
| Vaccinated         | 16             | 20.78% |
| Total              | 77             | 100%  |

Table 12: HRCT Chest

| HRCT FINDINGS | No. of cases | % |
|---------------|--------------|---|
| Aspergilloma  | 1            | 1.3 |
| Cavity with consolidation | 1 | 1.3 |
| Cavity with aspergilloma | 2 | 2.6 |
| Cavity with bronchiectasis | 1 | 1.3 |
| Consolidation | 4            | 5.2 |
| Destroyed lung | 1            | 1.3 |
| Empyema       | 1            | 1.3 |
| Hydropneumothorax | 2 | 2.6 |
| Normal        | 28           | 36.4 |
| Pleural effusion | 2             | 2.6 |
| Pneumomediastinum | 1          | 1.3 |
| Pneumothorax  | 7            | 9.0 |
| Pulmonary fibrosis | 21          | 27.3 |
| Pulmonary fibrosis with traction bronchiectasis | 1 | 1.3 |
| Pulmonary fibrosis with infiltrates | 1 | 1.3 |
| Pulmonary fibrosis with left pleural effusion | 1 | 1.3 |
| Subcutaneous emphysema | 1 | 1.3 |
| Subcutaneous emphysema with pneumomediastinum | 1 | 1.3 |
| Total          | 77           | 100% |

Table 13: Side of involvement

| SIDE OF INVOLVEMENT | No. of cases | %  |
|---------------------|--------------|----|
| Nil                 | 28           | 36.36 |
| Bilateral           | 26           | 33.7 |
| Left                | 12           | 13.0 |
| Right               | 11           | 14.28 |
| Total               | 77           | 100% |

28 patients had normal CT chest with no significant findings, side of involvement is mentioned as nil in 36.36% study population

Table 14: Sputum Culture

| Culture            | No. of cases | %  |
|--------------------|--------------|----|
| Aspergillus        | 7            | 9.09% |
| Candida            | 2            | 2.60% |
| E.coli             | 1            | 1.30% |
| Klebsiella         | 1            | 1.30% |
| H.influenza        | 8            | 10.39% |
| No growth          | 55           | 71.42% |
| Pseudomonas        | 1            | 1.30% |
| Streptococcus      | 2            | 2.60% |
| Total              | 77           | 100% |

Normal oropharyngial growth is observed in majority of patients 71.42%, H.influenza 10.39%, Aspergillus 9.09%, Candida 2.60%.
Table 15: Sputum Truenaat for Mycobacterium tuberculosis

| Sputum TRUENAAT | No. of cases | %   |
|-----------------|--------------|-----|
| Negative for MTB| 72           | 93.50% |
| POSITIVE        | 5            | 6.49%  |
| TOTAL           | 77           | 100%   |

Fig 2: Shows sputum TRUENAAT to detect Mycobacterium tuberculosis in post COVID patients

Table 16: Pleural Fluid Analysis

| PLEURAL FLUID   | No. of cases | %   |
|-----------------|--------------|-----|
| Nil             | 69           | 89.61% |
| Exudate         | 8            | 10.3%  |
| TOTAL           | 77           | 100%   |

Out of 77 study population Pleural effusion is seen in only 8 patients. Exudative type of pleural effusion is seen in all the 8 patients with raised ADA levels.

Fig 3: Showing exudative type of pleural effusion in 8 patients
Table 17: Complications

| S.no | Complications                  | No. of cases | %    |
|------|-------------------------------|--------------|------|
| 1.   | Allergic rhinitis             | 08           | 10.3%|
| 2.   | Asperilloma +Pulmonary TB -01 | 03           | 3.8% |
| 3.   | Fungal pneumonia +asperillus -06 +candida - 02 | 08           | 10.3%|
| 4.   | Diabetes +empyema-01 +aspergillus-01 | 07           | 9%   |
| 5.   | Hydro-pneumothorax +empyema -01 +TB pleural effusion-01 | 02           | 2.59%|
| 6.   | Myocardial infarction         | 01           | 1.29%|
| 7.   | Generalised tonic clonic seizures | 01           | 1.29%|
| 8.   | Pulmonary fibrosis            | 17           | 23.37%|
| 9.   | Pneumothorax +empyema -02 +BPF -02 +necrotizing pneumonia -01 | 06           | 7.79%|
| 10.  | Sub-cutaneous emphysema +pneumomediastinum -02 +pulmonary fibrosis -01 | 04           | 5.19%|
| 11.  | Pulmonary TB +bronchiectasis -01 +(diabetes+fibrosis)-01 | 04           | 5.19%|
| 12.  | Tubercular pleural effusion   | 03           | 3.38%|
| 13.  | No complication               | 13           | 16.8%|

Table 18: Mortality rate

| MORTALITY | No. of cases | %     |
|-----------|--------------|-------|
| Survived  | 69           | 89.61%|
| Death     | 8            | 10.38%|
| Total     | 77           | 100%  |

Table 19: Association between Outcome and age in post COVID patients

| Outcome | Yates corrected Chi-square test |
|---------|---------------------------------|
| Discharged | Death                         |
| n   | %    | n   | %    |
| < 40 years | 22 | 100.00% | 0 | 0.00% | χ²=2.18 p=0.14 (NS) |
| >40 years | 47 | 85.45% | 8 | 14.55% |

Statistical analysis was done using Chi-square test obtained P-Value of 0.14(Non-significant). Death observed in patients with age above 40 years, survival rate is seen in patients with age <40 years.

Table 20: Association between Outcome and sex in post COVID patients

| Outcome | Yates corrected Chi-square test |
|---------|---------------------------------|
| Discharged | Death                         |
| n   | %    | n   | %    |
| Male | 48 | 87.27% | 7 | 12.73% | χ²=0.42 p=0.52(NS) |
| Female | 21 | 95.45% | 1 | 4.55%   |

Among 48 males death observed in 7 patients, out of 21 females death occurred in 1 case.
Fig 4: CT chest showing a. coronal section with a cavity in left lower zone with a fungal ball b. axial section (mediastinal window) showing left lower lobe cavity with fungal ball

Fig 5: CT chest axial view showing left necrotising lung with pneumothorax

Fig 6: CT chest axial view showing right side pneumothorax with ground glass opacification in left lung

Fig 7: CT chest axial view showing left side hydropneumothorax

Fig 8: Chest x-ray showing right loculated hydropneumothorax
Discussion

1. Clustering of cases seen between age group of 41 to 60 years, least number of cases seen in extreme age groups.
2. Males were more commonly affected than females
3. Majority of the follow up cases presented with persistent dry cough 22.08%, fever 22.08% and 15.58% presented with dyspnoea.
4. 29.87% patients presented with duration of symptoms more than 1 month, 25.97% with duration of 1 month.
5. Most of the patients had no comorbidities, 15.58% presented with past history of diabetes mellitus, 2.59% with bronchial asthma, 1.29% with systemic hypertension, 1.29% with pulmonary tuberculosis.
6. None of the patients were vaccinated before contracting disease, 20.78% patients received only 1st dose of COVID vaccination after recovery.
7. 45.55% were smokers, 54.55% were non-smokers
8. Most of the patients presented with pulmonary fibrosis on CT chest i.e., 24 among 77 patients has pulmonary fibrosis with other findings like traction bronchiectasis, infiltrates, pleural effusion. 36.4% patients had normal CT chest which include stable, follow-up patients. Subcutaneous emphysema is seen in 1.3%, subcutaneous emphysema with pneumomediastinum in 1.3%, cavity with consolidation seen in 1.3%, consolidation 5.2%, empyema 1.3%, hydro pneumothorax 2.6%, pleural effusion 2.6%, pneumomediastinum 1.3%, pneumothorax 9%, aspergilloma 3.9%.
9. Bilateral lung involvement is most common in 33.7%, left lung 13%, right lung 11%.
10. Sputum analysis was done in admitted patients and stable OP patients, Sputum culture shows normal oropharyngeal flora in 71.72%, *H.influenza* 10.39%, *Aspergillus* 9.09%, *Candida* 2.60%, *Streptococcus* 2.60%, *E.coli* 1.3%, *Klebsiella* 1.3%, *Pseudomonas* 1.3%.
11. Sputum for TRUENAAT is done to rule out pulmonary tuberculosis out of 77 study patients 5 patients detected positive for TRUENAAT i.e., 6.49%.
12. Most common complication encountered was pulmonary fibrosis 23.37%, Fungal pneumonia 10.3%, Allergic rhinitis 10.3%, death 10.38%, pleural diseases 9%, diabetes 9%, pulmonary TB 6.49%, Extra pulmonary(pleural) TB- 5.19%, Extra pulmonary complications 2.59%.
13. Allergic rhinitis was seen in 10.3% of post COVID patients who never had an history of allergy in the past.¹⁰
14. Pleural fluid analysis shows exudative type among 8 (10.3%) patients in 77 study population.¹¹
15. Death occurred in 10.38% which include patients of necrotising pneumonia, massive pneumothorax, pneumomediastinum, empyema.
16. Fungal pneumonia is seen in patients with history of diabetes. 9% of patients had denovo diabetes in post COVID condition with no past history of diabetes mellitus.
17. A diabetic Patient with haemoptysis had Aspergilloma with persistently elevated Absolute eosinophil count and serum IgE levels.
18. Death rate was seen in 10.38% out of 77 study population.

Conclusion

Post COVID patients with continuous fever, shortness of breath, dry cough, productive cough, haemoptysis should be evaluated to rule out post COVID complications. The pulmonary sequelae of COVID-19 after the acute phase of COVID-19 is increasingly being appreciated. COVID-19 affects people of all age groups and gender. It
neither spares people with comorbidities nor those without any comorbidities. Social distancing, proper mask and hand hygiene will be long lasting self-disciplinary measure to curtail the spread of the disease.

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