CASE SERIES

AIR LEAK SYNDROME IN PATIENTS WITH SEVERE COVID PNEUMONIA

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There are number of emerging studies that link the air leak syndrome (ALS) with COVID 19 disease but still data to explain the association, incidence and outcome in these patients is lacking. We aim to understand the risk factors and clinical outcome of these air leakage events in COVID 19 patients admitted to our institution. **Methods.** This is a single-centered case series conducted at the COVID unit of the SMBBIT in Karachi, Pakistan. Data collection was done from April 24, 2020 to June 10, 2021. **Results:** There were 19 patients with severe COVID pneumonia who developed air leaks. Most common finding was subcutaneous emphysema 94%. Four patients (21%) didn't receive positive pressure ventilation in any form. Median time of developing air leak from admission is 5 [2-9] and from PPV is 2 [1-3] days. There was high percentage of mortality 84.5 % in these patients.

Keywords: Air leak syndrome; COVID pneumonia

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2). It was first reported in December 2019 in Wuhan, and has been globally spread.[1] Most common symptoms of COVID-19 are fever, cough and shortness of breath. The diagnosis is made by real time-reverse transcription polymerase chain reaction (r RT-PCR) from a nasopharyngeal swab.[2] It has been reported that computed tomography (CT) has high accuracy to determine lung infiltrate as compared to chest x-ray (CXR). However, in resource limited setting the transport of COVID-19 patients on various modes of oxygenation/ventilation is a demanding task and can be a source of disease spread.[3,10] Therefore in most of the healthcare facilities in Pakistan, portable CXR imaging is performed on admission and afterward.[4]

Development of Subcutaneous emphysema (SE), pnemomediastinum (PM) and pneumothorax (PT) are suspected to be the sequelae of injury to tracheobronchial tree or alveolar membrane rupture secondary to direct COVID infection.[5,6] Clark *et al*. reported that SE and PM can complicate severe acute respiratory syndrome (SARS), and indicate worsening of disease.[7] The coincidence of seeing this clinical manifestation in COVID-19 may indicate a similar viral pathogenesis.[8]

While a number of emerging studies have linked the air leak syndrome (ALS) with COVID 19 disease[4,8], there is still lack of data to explain the association, incidence and outcome in these patients. We aim to understand the risk factors and clinical outcome of these air leakage events in COVID 19 patients admitted to our institution.

This is a single-cantered case series conducted at the COVID unit of the SMBBIT in Karachi, Pakistan. Data collection was done from April 24, 2020 to June 10, 2021. Inclusion Criteria: All patients with severe COVID 19 disease who developed ALS were included.

Definitions:

Air Leak Syndrome (ALS): SE and/ or PM and/or PT with severe COVID 19 pneumonia[8]

Cytokine release syndrome (CRS)[7]:

1. Ferritin > 1000 mcg/L and rising in last 24 hours 2. Ferritin > 2000 mcg/L in patient requiring high-flow oxygen or ventilation 3. Absolute lymphocyte count < 800 cells/ml, or neutrophil to lymphocyte ratio of >5 and two of the following:

a. Ferritin > 700 mcg/mL and rising in the last 24 hours

b. Lactate dehydrogenase (LDH) > 300 IU and rising in the last 24 hours

c. D-dimer > 1000ng/mL (or >1 mcg/ml) and rising in the last 24 hours

d. C-reactive protein (CRP) > 70 mg/L rising in the last 24 hours,in the absence of bacterial infection

Disease Category: Categories were assigned as severe and non-severe as per National Guidelines.[9]

We retrospectively screened 756 COVID-19 patients out of which 450 were severe. Nineteen patients developed ALS; we collected detailed medical records, and CXR images complicated by air leaks. These charts were then thoroughly reviewed. Mode of oxygen therapy, clinical, laboratory and radiological parameters on admission and at the time of diagnosis of ALS were recorded retrospectively.

Standard COVID-19 management in our institute was antiviral medication, steroid therapy, anticoagulation, Tocilizumab (if patient developed Cytokine release syndrome (CRS). Antiviral (Remdesivir) was not available in Pakistan initially. We started giving Remdesivir from November 2020 onwards. All treatment was provided free of cost to all patients.

CASE SERIES

we described 19 cases of ALS (SE with or without PM and/or PT) detected on chest radiography during Intensive Care Unit (ICU) stay of COVID 19 patients with either severe or critical disease who were admitted to COVID unit of SMBB institute of Trauma, Karachi, Pakistan from April 24, 2020 to June 10, 2021.

Table-1 shows the demographic and clinical characteristics of the patients enrolled. The median age of patients was 57 [53–64] years and 10 (52.6%) were males. Of the 19 patients, 7 (36.8%) were obese had one or more coexisting medical conditions: cardiovascular disease in 5(26%) diabetes mellitus in 10(56%) and chronic respiratory disease in 3 (15.8%). As per institutional protocol we took consent of escalation of oxygen therapy to intubation and mechanical ventilation if needed on admission.

Attendants of two patients refused for intubation. As per inclusion criteria all were severe COVID pneumonia ALS. All the patients had shortness of breath (SOB), 14 (73.6%) had cough and 5(26.3%) had fever (defined as an axillary temperature of 37.5 °C or higher). All had CRS which was proven on lab investigation and all received standard treatment including oxygen therapy, steroids, anticoagulants, and tocizulamab 8mg/kg single dose within 24 hours of admission.

Mode of oxygenation/ventilation on admission time was face mask (FM) in 1 (5.3%) , non-rebreather mask (NRB) in 10 (52.6%) non-invasive ventilation (NIV) in 7 (36.8%) and mechanical ventilation (MV) in 1 (5.3%) . Sixteen patients (84.2) died out of which five patients had multiple organ dysfunction syndromes (MODS) while 11 died of hypoxemic arrest.

Table-1: Demographic and clinical characteristics of patients

Parameters	n= 19
Age (years)	57 [53-64]
Gender	
Male	10 (52.6)
Female	9 (47.4)
Obesity	7 (36.8)
Comorbid	
Lung disease	3 (15.8)
Cardiovascular	5 (26.3)
Diabetes Mellitus	10 (52.6)
Consent for intubation and ventilation	17 (89)
Disease category	
Severe	19 (100)
Symptoms	
SOB	5 (26.3)
cough	14 (73.6)
fever	5 (26.3)
CRS	18(100)
Treatment	
Steroids	
Anticoagulants	19 (100)
Tocizulamab	
Saturation at arrival	80 [77-86]
Mode of oxygenation/ventilation on arrival	
FM	1 (5.3%)
NRB	10 (52.6%)
NIV	7 (36.8%)
MV	1 (5.3%)

SOB=Shortness of breath, CRS=cytokine release syndrome, FM= face mask, NRB= non rebreather mask, NIV = noninvasive ventilation, MV= mechanical ventilation.

Table-2: Baseline laboratory investigation

Parameter	Median [IQR]
WBC count	20 [17–25.3]
Ferritin	1200[650–1800]
LDH	980 [827–304]
CRP	121 [93–304]
D dimer	3 [1.5–6]

WBC= white blood cell, LDH=lactate dehydrogenase, CRP=C-reactive protein

Table-3: Clinical data of patients at the time of diagnosis of air leak.

Parameter	Median [IQR]/ n (%)
Time to air leak from admission in days	5 [2–9]
Time to air leak from PPV in days	2 [1–3]
Type of leak	
SC	18 (94)
PT	9 (47.3)
PM	7 (36.8)
Chest tube	
Yes	6 (31.5)
Intubated	
Yes	15 (78.9)
No	4 (21.1)
Consent for intubation	
Yes	15 (78.9)
No	4 (21.1)
LOS (days)	10[4–15]
Outcome	
Survive	3(15.2)
Expire	16(84.2)

SC=subcutaneous emphysema, PM= Pneumomediastinum, PT=Pnemothorax, LOS= Length of stay

CASE REVIEWS

Case 1 to case 4 on admission were on FM or NRB and remained on NRB/ high flow nasal oxygen (HFNO) until they developed air leak. Case 1 developed pneumothax on day 5 and tube thoracostomy was done to which pneumothorax resolved subsequently. Case 2 had small pneumothorax with subcutaneous emphysema which was resolved spontaneously. Case 3 was the known case of chronic obstructive pulmonary disease (COPD) and was admitted in thoracic surgery ward for bullectomy where he contracted COVID-19 with increased oxygen requirement and later developed pneumothorax. He improved after chest tube insertion and ultimately discharged, all 3 of them survived and weaned from NRB/HFNO, Case 4 was shifted to private facility as per patient and family decision, later on intubated and thoracostomy was done and expired with MODS.

Case 5 to 11 also required NRB at admission to maintain saturation but switched to NIV/MV later on. However, cases 6-8 and 10 stayed on NIV continuously as they did not tolerate removal of NIV for NIV breaks while case 5 and 9 received NIV breaks for 1 hour after 4 hours of NIV. Case 11 deteriorated further and underwent intubation and MV.

Case 12–18 were those who were on NIV at admission and developed air leak subsequently. Case 19 was on MV at admission. Cases 4–7 and 9–18 were all eventually intubated and required MV. Case 8 was not intubated because of lack of consent. Of 16 cases who did not survive, 6 expired due to multi-organ failure; 10 expired due to refractory hypoxemia and eventually cardiorespiratory arrest. Case 4,5,6,11,12 and 15 were obese BMI >30 kg/m^2 that ultimately developed air leak and put on MV and expired.

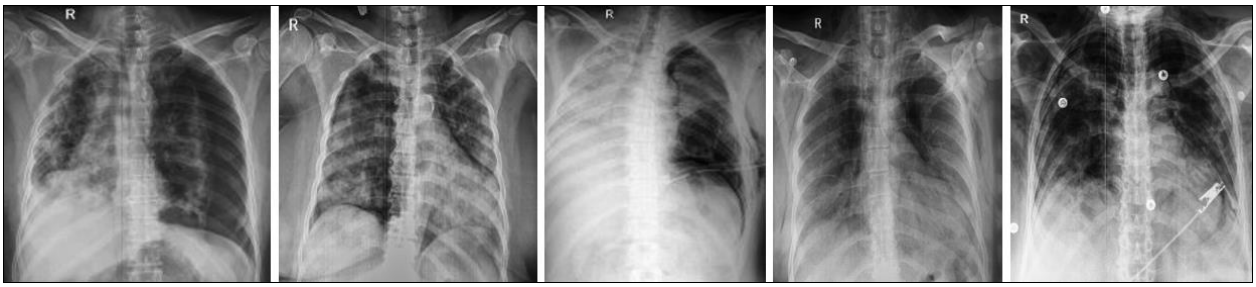
Table-4: Respiratory therapy during development of Air leak syndrome

	Age	Gender	Type of ventilation on admission	Day of Switch to NIV	NIV continuous or intermittent	Type of ventilation at the time of air leak	Day of detection of leak
1.	64	Male	FM	-	-	NRB/HFNO	D5
2.	50	Female	NRB	D5	-	NRB/HFNO	D5
3.	27	Male	NRB			NRB/HFNO	D4
4.	55	Male	NRB	-	-	NRB/HFNO	D10
5.	32	Female	NRB	D7	Intermittent	NIV/NRB	D10
6.	53	Female	NRB	D2	continuous	NIV	D2
7.	57	Female	NRB	D2	continuous	NIV	D4
8.	55	Male	NRB	D5	continuous	NIV	D5
9.	64	Male	NRB	D4	intermittent	NIV/NRB	D15
10.	70	Female	NRB	D5	continuous	NIV	D7
11.	62	Female	NRB	D7	continuous	MV	D9
12.	49	Female	NIV	-	continuous	NIV	D1
13.	59	Male	NIV	-	intermittent	NIV/NRB	D3
14.	60	Male	NIV	-	continuous	NIV	D2
15.	55	Male	NIV	-	continuous	NIV	D2
16.	65	Female	NIV	D1	continuous	NIV	D3
17.	65	Male	NIV	-	continuous	NIV	D1
18.	60	Female	NIV	-	continuous	MV	D8
19.	54	Male	MV	-	-	MV	D10

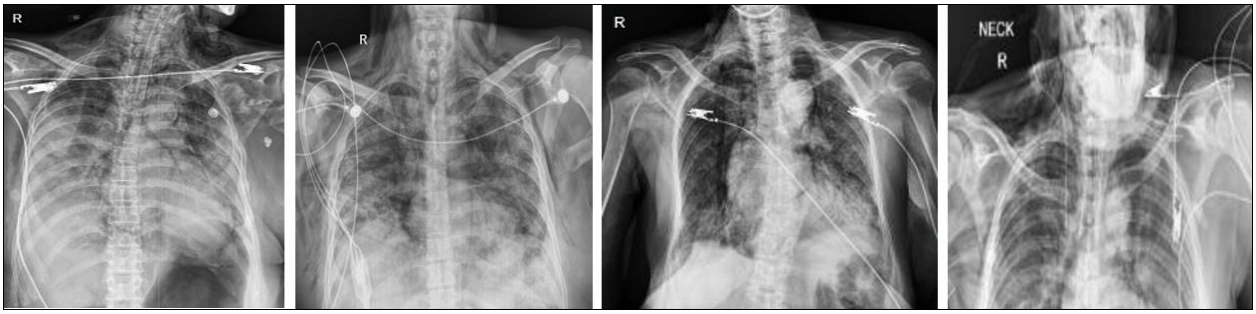
Table-5: Imaging and outcome

	PM	SC	PT	PPV to leak (Days)	Chest tube	LOS days	Day of intubation	outcome	Cause of death
1.	no	no	yes	-	yes	15	Not intubated	discharge	-
2.	no	yes	yes	-	no	13	Not intubated	discharge	-
3.	no	yes	yes	-	yes	19	Not intubated	discharge	-
4.	no	yes	no	-	yes	12*	Yes*	Shifted* & expired	MODS*
5.	no	yes	yes	D4	yes	13	D13	expired	Hypoxemia &arrest
6.	yes	yes	no	D2	no	5	D5	expired	Hypoxemia &arrest
7.	no	yes	no	D3	no	4	D4	expired	hypoxemia
8.	no	yes	no	D1	no	10	Not intubated	expired	Hypoxemic death
9.	no	yes	yes	D1		36	D9	expired	hypoxemia
10.	yes	yes	no	D1	no	17	D8	expired	MODS
11.	yes	yes	no	D1	no	4	D2	expired	Hypoxemia & arrest
12.	no	yes	yes	D1	no	3	D3	expired	hypoxemia
13.	yes	yes	no	D3	yes	10	D10	expired	MODS
14.	yes	yes	no	D2	no	4	D2	expired	MODs
15.	no	no	yes	D2	no	2	D2	expired	Hypoxemia
16.	yes	yes	no	D3	no	6	D5	Shifted *& expired	MODS
17.	no	yes	yes	D1	no	9	D9	expired	Hypoxemia & arrest
18.	yes	yes	no	D8	no	9	D8	expired	Hypoxemia & arrest
19.	no	yes	yes	D10	yes	20	Received intubated	expired	MODS

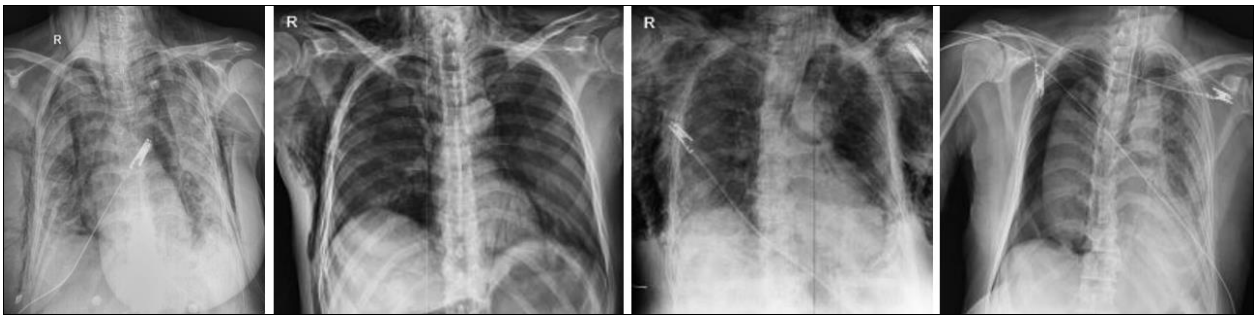
SC=subcutaneous emphysema, PM= Pneumomediastinum, PT=Pnemothorax, MODS=multi organ dysfunction syndrome, PPV=positive pressure ventilation, LOS=length of stay



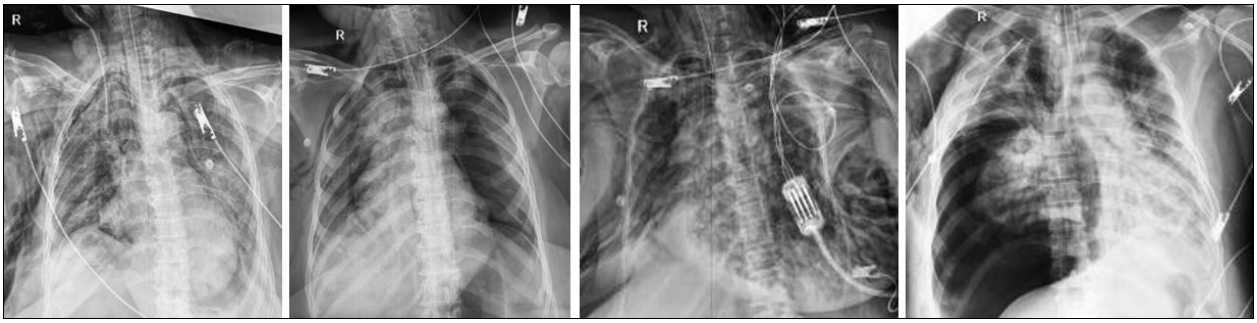
Case 1, 2, 3, 4 & 6



Case 7, 8, 10 & 11



Case 12, 13, 14 & 15



Case 16, 17, 18 & 19

DISCUSSION

Air leak syndrome comprises of pneumothorax, pneumomedistinum and subcutaneous emphysema.[7,8] In Different studies pathophysiology of airleak due to tracheobromchial or alveolar injury is explained by previous lung disease, consolidation, interstitial pneumonia and in situ thrombosis.[11,12] In our study cases too these findings were present even though thrombosis was not confirmed with CT Pulmonary angiography, but levels of d -dimer were monitored for the supportive of ongoing thrombosis.[13]

Lung protective strategies are used from long time to prevent barotrauma , atelecto-trauma or volutrauma in patients on ventilator support , but insufficiency of LPV in COVID pneumonia patients indicates that the pathology is more complicated.[8]

Reports about Air leak in patients who did not receive positive pressure also indicates that local ischemia, thrombosis ,inflammation and subsequent formation of inflammatory exudate in the airway rendering alveolar wall prone to rupture, played a role in causing trauma to trachea bronchial tree. Tarig Sami Elhakim *et al*, reported a patient who developed subcutaneous emphysema / pneumothorax, who didn't receive positive pressure ventilation.[14,15] In our case series we have 4 patients who didn't receive PPV but developed subcutaneous emphysema.

In a recent similar study authors believed that a cytokine release syndrome (CRS) could trigger parenchymal and microvascular inflammation with micro thrombosis and hyper coagulable states. This substantial increase in inflammatory response along with direct viral invasion of the pleura and provoking thromboembolic phenomena are the triple hit for the development of air leak.[15]

Large pneumothorax and subcutaneous emphysema are usually easy to diagnose on chest Xray , but small PX and pneumomedistinum sometime needs CT to confirm but transfer of such patients to CT scan suit is logistically difficult and risky for hypoxic patients and portable scan is mostly unavailable.[16] In our hospital CT scan facilities are not equipped to accommodate mechanically ventilated patient hence the diagnosis, management and outcome are based on serial CXR and clinical/biochemical perimeters.

Obesity is a known risk factor for severe COVID. Mechanism might involve increased expression of ACE which is high in adipose tissue which increase the susceptibility of obese to severe COVID which is itself a risk factor for air leak syndrome.[17] Seven of our patients in this case series were obese out of which 6 expired.

Cough has also been shown to be a risk factor to trigger a sudden increase in alveolar pressures inducing the formation of subpleural bullae and pnemothorax in COVID 19. Almost all of our patients had strong power full cough.[18] However, we did not find any supporting evidence from published data to suggest the use of anti-tussive agents to prevent air leak syndrome in COVID-19. In our patient population, pronounced cough may have promoted tracheo bronchial tree and alveolar rupture generating complications such as PT and SE.

Although rare, SE is usually considered a non-life-threatening condition and is usually self-limited requiring supportive treatment. Death from SE is rare and has been reported in the context of pneumothorax. However, clinical significance is important when the amount of air is large or rapidly inflating, as it can place severe pressure on the airway and becoming life-threatening. Most of the cases identified during the literature review showed spontaneous resolution with conservative management.[19,20] Conversely only 3 of our patients recovered with conservative management, and these cases had not received PPV at any time.

Over all patients who developed air leaks are more susceptible to die because these cases are mostly severe cases, especially those with increasing demands of oxygen.[21–24]

Further research and more case studies are needed in this area to better understand the association of outcome with air leak syndrome.

CONCLUSION

Our series presents a heterogeneous clinical scenario of air-leak syndrome. In a resource-limited setup where CT chest is not possible in all patients, clinical diagnosis is paramount to identify air-leak syndrome. A high level of alertness, clinical suspicion, and prompt action are mandatory to prevent fatal consequences.

This series highlights COVID-19-induced air-leak syndrome in terms of clinical presentation, day of illness from first symptom, mode of ventilation, and radiological features. Although, the laboratory values in all our patients point toward a state of severe inflammatory response, further studies are required to understand the pathophysiology and predictors of air-leak syndrome associated with COVID-19 for better management of these patients.

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