The clinical course of pneumomediastinum in patients with SARS-CoV-2 before invasive mechanical ventilation

Authors: Akshay Dwarakanath,[A] Laura Horgan,[A] Manika Jayawardena,[B] Muthu Thirumaran[A] and Owen Johnson[A]

ABSTRACT

Pneumomediastinum and pneumothorax are recognised complications encountered in COVID-19 before or during invasive mechanical ventilation (IMV). The clinical course of patients developing pneumomediastinum before IMV is yet to be evaluated.

Four-thousand, one-hundred and thirty-one patients hospitalised with COVID-19 over a 12-month period were retrospectively reviewed to evaluate for incidence, clinical characteristics and outcomes. A subgroup analysis was done to identify any clinical traits between survivors and non-survivors. The overall incidence of pneumomediastinum prior to IMV was 0.92% (n=38) and was seen at admission or during non-invasive respiratory support. Thirty-seven per cent had associated pneumothorax most commonly unilateral (right side). The median (interquartile range (IQR)) duration from admission to developing pneumomediastinum was 7 days (3–11) and complete resolution was seen in 53% of patients; median (IQR) duration to resolution was 8 days (4–17). The in-hospital mortality associated with pneumomediastinum in patients with SARS-CoV-2 (PneumoCoV) was 55%. Increasing age (68 ± 12 years vs 56 ± 14 years; p=0.01), higher body mass index (31 ± 5 kg/m^2 vs 28 ± 5 kg/m^2; p=0.04), lack of resolution of pneumomediastinum (67% vs 24%; p=0.01; odds ratio (OR) 6.5; 95% confidence interval (CI) 1.5–27.5), presence of concurrent pneumothorax (65% vs 14%; p=0.002; OR 11; 95% CI 2.2–53.1) and elevated procalcitonin levels (>0.5 ng/mL; 81% vs 41%; p=0.01; OR 6; 95% CI 1.4–26) were significant features in those who did not survive.

The incidence of PneumoCoV, despite being low, is associated with increased mortality. It is a hallmark of moderate to severe disease with multifaceted contributory factors. Both demographic and clinical factors predict survival.

KEYWORDS: SARS-CoV-2, pulmonary complication, pneumothorax, pneumomediastinum, respiratory failure

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Authors: [A]consultant respiratory physician, The Mid Yorkshire Hospitals NHS Trust, Wakefield, UK; [B]consultant radiologist, The Mid Yorkshire Hospitals NHS Trust, Wakefield, UK

Introduction

COVID-19 presents with various clinical phenotypes with hypoxaemia being a marker of severity.[1] Apart from specific supportive treatment strategies, high-flow oxygen therapy (HFOT) and non-invasive respiratory support (continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV)) are recommended early in the disease process for patients with acute hypoxaemic respiratory failure prior considering invasive mechanical ventilation (IMV) in appropriate patients.[2] This clinical syndrome is associated with both pulmonary and extra-pulmonary manifestations leading to increased morbidity and mortality.[3] Pneumothorax alone or associated with pneumomediastinum as a pulmonary complication have been described both prior to or as a consequence of invasive ventilation.[4–7] Development of pneumothorax did not seem to be an independent marker of poor prognosis but age >70 years and acidosis was.[5] However, data from the International Severe Acute Respiratory Infection Consortium (ISARIC) 4C study showed that men, smoking history, chronic pulmonary disease and invasive ventilation were associated with increased risk of pneumothorax and presence of pneumothorax was associated with increased mortality.[7]

Pneumomediastinum in the non-SARS-CoV-2 cohort is considered as a benign entity and is usually treated conservatively in the absence of significant cardiorespiratory compromise.[8,9] All the studies so far have favoured reporting the clinical course associated with pneumothorax and included patients who were mechanically ventilated. However, there is a paucity of data about clinical outcome in patients with SARS-CoV-2 who develop pneumomediastinum (PneumoCoV) alone pre-IMV. We have evaluated the incidence, clinical characteristics and outcomes in hospitalised patients and also assessed the difference in clinical traits between survivors and non-survivors.

Aims of the study

We aimed to evaluate the incidence, clinical characteristics and outcomes in hospitalised patients with SARS-CoV-2 who developed pneumomediastinum pre-IMV and to explore any difference in clinical traits between survivors and non-survivors.

Method

Patient selection

This was a single-centre retrospective sequential case series and all hospitalised patients with SARS-CoV-2 over a 12-month period

(April 2020 – March 2021) were included. Electronic records for baseline demographics, patient characteristics, clinical outcomes and all radiological images (chest X-ray, high-resolution computed tomography (CT), CT pulmonary angiography) were reviewed to identify patients with pneumomediastinum pre-IMV. Chest X-rays were reported either by a radiologist or an advanced radiographer practitioner and all the CT by a radiologist only. Patients with SARS-CoV-2 (n=4) who developed pneumomediastinum during IMV and patients (n=5) with isolated pneumothorax were excluded.

Statistical analyses

This was carried out with Prism version 9 (GraphPad, San Diego, USA) and patient data are presented as mean (standard deviation (SD)) or median (interquartile range (IQR)). Unpaired t-tests and Fisher's exact test were used for subgroup analysis with $p<0.05$ considered as statistically significant. Charlson Comorbidity Index (CCI) and ISARIC 4C mortality score were used to assess the morbidity burden and mortality prediction at admission, respectively.

Results

Incidence and patient characteristics

Four-thousand, one-hundred and thirty-one patients with SARS-CoV-2 were hospitalised over 12 months (3,197 in dedicated SARS-CoV-2 wards, 733 in the acute respiratory care unit (ARCU) and 201 in the intensive care unit (ICU)). Thirty-eight patients had pneumomediastinum pre-IMV and the overall incidence was 0.92%. The majority were men (66%), non-smokers (76%), had a body mass index (BMI) >25 kg/m^2 (76%) and had associated comorbidities. Diabetes mellitus and hypertension were the most common systemic comorbidities and specific respiratory comorbidities included asthma (21%), chronic obstructive pulmonary disease (11%) and obstructive sleep apnoea (5%; Table 1).

Table 1. Baseline demographics

Total number of patients, n	38
Age, years, mean ± SD	63 ± 16
Men, % (n)	66 (25)
Women, % (n), (1 pregnant)	34 (13)
Smoking history, % (n):	
non-smokers	76 (29)
ex-smokers	21 (13)
smokers	3 (1)
Body mass index, % (n):	
normal (<25 kg/m^2)	24 (9)
overweight (25–30 kg/m^2)	26 (10)
obese (>30 kg/m^2)	50 (19)
Charlson Comorbidity Index score, % (n):	
0	19 (7)
1	8 (3)
2	29 (11)
3	29 (11)
4	5 (2)
5	5 (2)
6	5 (2)
ISARIC 4C mortality score at admission, % (n):	
low: 0–3	0 (0)
intermediate: 4–8	40 (15)
high: 9–14	47 (18)
very high: >15	13 (5)
RT-PCR swab positive, % (n)	94.7 (36)
Clinical SARS-CoV-2 (symptoms + radiological features suggestive SARS-CoV-2 + positive contact + lymphopenia), % (n)	5.3 (2)

ISARIC = International Severe Acute Respiratory Infection Consortium; RT-PCR = real-time reverse transcriptase polymerase chain reaction.

PneumoCoV pre-invasive mechanical ventilation

PneumoCoV was encountered at three stages: at the time of admission (5%; n=2), incidental finding during routine clinical assessment (18%; n=7) and due to clinical suspicion in patients who had clinically deteriorated (77%; n=29). It was visible on plain film X-ray in all and 42% (n=16) needed CT for further characterisation. Thirty-seven per cent (n=14) had associated pneumothoraces, unilateral in the majority (six on the right side including one patient with tension pneumothorax; three on the left side including one patient with hydro-pneumothorax) and bilateral in five patients. The median (IQR) duration from admission to developing pneumomediastinum was 7 days (3–11). Resolution was seen in 53% (n=20) and the median (IQR) duration to resolution was 8 days (4–17).

Clinical outcome

The respiratory support before and after the onset of pneumomediastinum along with other supportive interventions are shown in Table 2. The use of CPAP significantly reduced after developing pneumomediastinum (87% vs 29%; $p<0.0001$; OR 19.26). The in-hospital mortality was 55% (n=21). Consideration of antibiotics for secondary infections was based on the level of procalcitonin levels (normal range <0.5 ng/mL) and 63% had elevated procalcitonin levels.

Subgroup analysis

On further subgroup analysis, increasing age (68 ± 12 years vs 56 ± 14 years; p=0.01), higher BMI (31 ± 5 kg/m^2 vs 28 ± 5 kg/m^2; p=0.04), lack of resolution of pneumomediastinum (67% vs 24%; p=0.01; OR 6.5; 95%CI 1.5–27.5), presence of concurrent pneumothorax (65% vs 14%; p=0.002; OR 11; 95% CI 2.2–53.1) and procalcitonin level of >0.5 ng/mL (81% vs 41%; p=0.01; OR 6; 95% CI 1.4–26) predicted prognosis. There was no difference in gender, smoking history, duration of respiratory support or the need for IMV between the two groups.

Discussion

Compared with non-SARS-CoV-2 cohorts, patients with COVID-19 were at increased risk for developing pneumothorax

Table 2. The clinical outcomes of patients with pneumomediastinum with SARS-CoV-2

Respiratory support pre-pneumomediastinum	
Conventional oxygen therapy (VM, NC or NRB), % (n)	5 (2)
HFOT, % (n)	8 (3)
CPAP (PEEP; 8–12 cm), % (n)	87 (33)
Duration of respiratory support, days, median (IQR)	4 (2–8)
Respiratory support post-pneumomediastinum	
HFOT, % (n)	3 (1)
CPAP (PEEP; 6–8 cm), % (n)	29 (11)
IMV, including one patient for ECMO, % (n)	45 (17)
Conventional oxygen therapy, % (n)	16 (6)
Palliation, % (n)	7 (3)
Supportive measures	
Chest-drain insertion, % (n)	13 (5)
Steroids (dexamethasone 6 mg once daily), % (n)	95 (36)
Awake proning, % (n)	89 (34)
Antibiotics (based on elevated procalcitonin >0.5 ng/mL), % (n)	63 (24)

CPAP = continuous positive airway pressure; ECMO = extra-corporeal membrane oxygenation; HFOT = high-flow oxygen therapy; IQR = interquartile range; PEEP = positive end-expiratory pressure; NC = nasal cannula; NRB = non-rebreather mask; VM = Venturi mask.

with or without pneumomediastinum. Table 3 summarises the studies that show an increased association but one of the limitations in these studies has been the lack of clarity about pneumomediastinum alone, especially before invasive ventilation, and this is largely due to limited numbers.[4–8] We evaluated this further and focused on three main clinical domains: potential predisposing factors, complication burden and clinical outcomes. Our data suggest that one in five patients hospitalised with COVID-19 had moderate to severe disease needing either non-invasive respiratory support and/or IMV. PneumoCoV was more common in men with a higher BMI (>25 kg/m^2) and the majority were non-smokers.[9] We used the Charlson Comorbidity Index to categorise the comorbidities' burden; a third of patients had airways disease (asthma and COPD) and none had any previous episode of pneumomediastinum.[10] Association of asthma is not specific to SARS-CoV-2 and has been reported in a quarter of patients with spontaneous pneumomediastinum in the non-SARS-CoV-2 cohort.[11] The ISARIC-developed risk stratification tool was used at admission, and majority of patients (60%) had a high to very high 4C score signifying poor outcomes.[12]

Despite excluding patients with SARS-CoV-2 with pneumothorax alone, our data are consistent with a recently published estimate.[4] PneumoCoV was encountered in patients predominately with moderate to severe disease requiring non-invasive respiratory support (HFOT, CPAP or NIV) and seldom seen in mild illness. Proper clinical assessment and a low threshold for chest X-rays are necessary as this complication can be seen at three stages: at admission, during the course of illness and as an incidental finding. The majority of patients who developed pneumomediastinum had clinical deterioration (worsening gas exchange, increased respiratory rate or unexplained desaturations) on non-invasive respiratory support but one in five patients had an incidental diagnosis, most commonly seen during nasogastric tube check prior to

Table 3. Summary of pneumothorax/pneumomediastinum studies in COVID-19

Author	Year	Patients, n	Study type	Respiratory support	Outcome	Comments
Marciniak *et al*[8]	2021	1,283	Prospective observational	NIV/IMV	Pneumothorax incidence 0.97%	Did not include pneumomediastinum
Martinelli *et al*[5]	2020	71	Multicentre retrospective	NIV/IMV	Pneumothorax incidence 1%, age >70 years and acidosis associated with poor prognosis	Limited patients with pneumomediastinum, n=11
Palumbo *et al*[4]	2021	14	Multicentre retrospective	NIV only	Rate of pneumothorax and pneumomediastinum was higher in wave 2	Limited patients with pneumomediastinum, n=8
Belletti *et al*[6]	2021	28	Single-centre observational	IMV only	Pneumothorax/ pneumomediastinum incidence 24.1%	Limited patients with pneumomediastinum, n=13
Lemmers *et al*[7]	2020	23	Single-centre retrospective	IMV only	Seven-fold increase in pneumothorax/ pnumomediastinum as compared with non-COVID-19 group	No data about pneumomediastinum alone

IMV = invasive mechanical ventilation; NIV = non-invasive ventilation.

initiating nutritional support, thus the severity of the illness matters. Following the evidence from the RECOVERY trial, dexamethasone (6 mg once per day for 10 days) was considered as the standard of care and we witnessed increased cases following this pharmacological implementation.[13] Two patients developed pneumomediastinum prior to steroids being a standard of care as compared with the remaining 36 patients. This observation was consistent with a recently reported study and, although an observational case series cannot establish the temporal contributory relation, the role of steroids needs to be evaluated further.[4] Procalcitonin as a biomarker for secondary infections was part of routine investigations and, as per local protocol, a level of >0.5 ng/mL was considered sufficient to suspect secondary bacterial infections and triggered a course of antibiotics. An interesting observational finding was that two-thirds of patients were initiated on antibiotics (5–7 days) and no positive yield from blood cultures was isolated. Increased procalcitonin levels predicted survival on subgroup analysis and further large-scale studies are needed to evaluate the temporal relationship of elevated procalcitonin as a contributory factor for developing PneumoCoV. We did not find any association with other parameters (C-reactive protein, D-dimer, lactate dehydrogenase, creatine kinase, troponin and ferritin).

Patients were managed as per national guidelines and we were biased towards CPAP.[2] This was mainly due to three reasons: inconsistent advice from different national societies and guidelines, some of which discouraged the use of HFOT; discordance between oxygen demand and supply with a risk of exhausting hospital oxygen supply; and the risk of aerosol generating procedure. Due to high patient burden leading to increased oxygen demand, HFOT was limited to those who were intolerant to CPAP and this provision was only available in ARCU and ICU. CPAP was provided with non-invasive ventilators (Trilogy100/202, V60 and Trilogy Evo) and the median duration of CPAP was 4 days. All patients were maintained on a positive end-expiratory pressure (PEEP) ranging from 8–12 cm of water depending on patient tolerance and targeted oxygen saturations (92%–96% as standard, and 88%–92% for those not suitable for IMV). The majority of patients underwent awake proning (full prone or semi-prone) that was carried out by a multidisciplinary proning team with constant monitoring to assess clinical stability or to identify the deteriorating patient.

Pneumomediastinum is not specific to SARS-CoV-2, with reported incidence of approximately 1 in 30,000 in the general population and may be either primary (idiopathic) or secondary to any underlying secondary disease or interventions.[10] Likely barotrauma, viral-associated tracheal oedema, recruitment manoeuvres and cytokine storm leading to Macklin's phenomenon (increased intra-alveolar pressure leading to alveolar rupture causing the air leak to pulmonary interstitial spaces with further extension of the air leak along the perivascular sheaths that dissect into the mediastinum leading to mediastinal emphysema) may all be plausible explanations for the development of PneumoCoV, shown in Fig 1 (chest X-ray and CT).[14,15] Following an episode of pneumomediastinum, 45% (n=17) of patients were transferred to ICU for IMV but a third of our patients were deemed unsuitable for escalation beyond ARCU due to poor performance status and or extensive comorbidities. A third of patients continued on CPAP but

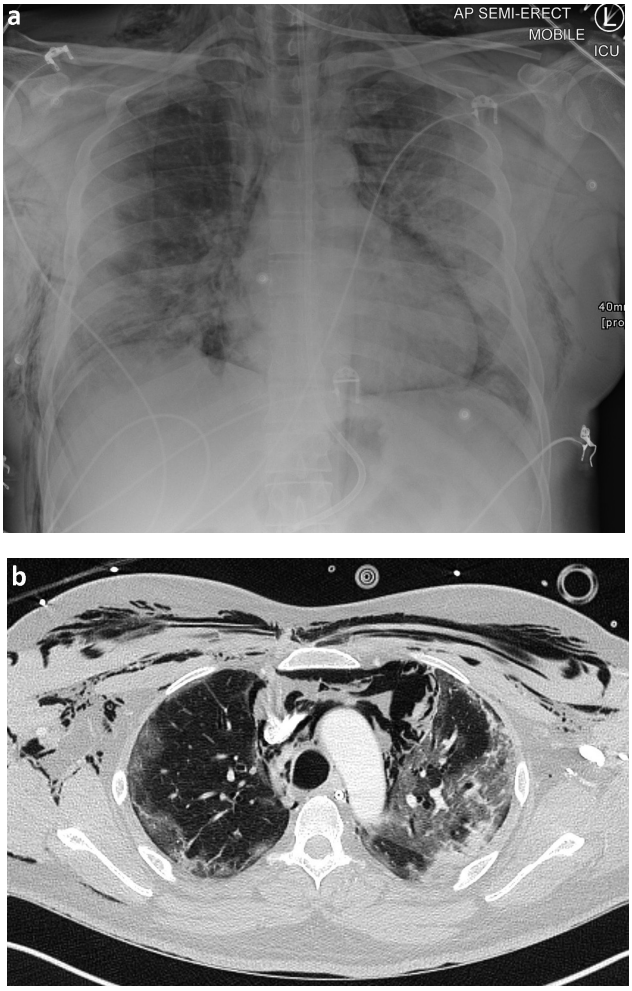

Fig 1. a) Chest X-ray showing pneumomediastinum and SARS-CoV-2 pneumonia. b) Computed tomography showing subcutaneous air leak and parenchymal changes of severe COVID-19.

with lesser PEEP (6–8 cm of water) and the rest had either conventional oxygen therapy or were considered for palliation due to poor clinical outcome. Close clinical monitoring, appropriate escalation plan and a patient-centred clinical decision about continuing respiratory support post-PneumoCoV may be beneficial for best outcomes.

Pneumothorax can be associated with pneumomediastinum and this is usually unilateral (more commonly on the right side). The preponderance is likely due to SARS-CoV-2 targeting the right more than the left lung.[16] Further evaluation with CT was not routinely considered due to patient haemodynamic instability and due to strict infection control measures limiting the safe transfer of patients from either ARCU or ICU to the radiology department. This was only considered when further characterisation of the complication was required at the clinician's discretion or prior to planning any specific invasive intervention, specifically chest drain. Seldinger chest drain insertion was required only in patients with significant pneumothorax (>2 cm) and five patients underwent this

intervention.[5] As per our data, the associated mortality rate in PneumoCoV was higher when compared with our overall mortality in patients requiring either ARCU and/or ICU (55% vs 43%). Thus, patients developing pneumomediastinum alone or with associated pneumothorax have a worse outcome. Additionally, on subgroup analysis, increasing age, higher BMI, lack of resolution of pneumomediastinum, presence of concurrent pneumothorax and the need for antibiotics for secondary infections based on procalcitonin predicted survival.

Our case series had limitations: data were from a single centre and, thus, an accurate estimate of the incidence and causal relationships cannot be extrapolated. PneumoCoV may have an impact on length of stay and we did not evaluate this but, at the time of reporting, two patients were still being managed as inpatients. We did not undertake multivariate analysis given the limited numbers. Further large-scale multicentre studies are needed for a better understanding of possible predisposing factors for PneumoCoV. Finally, a national registry to collate data and clinical characteristics may help in better understanding this complication.

Conclusion

The incidence of PneumoCoV, despite being low, is associated with increased mortality. It is a hallmark of moderate to severe disease with multifaceted contributory factors. A combination of demographic and clinical factors may aid the clinicians about prognosis.■

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Address for correspondence: Dr Akshay Dwarakanath, Department of Respiratory Medicine, Sleep and Ventilation, Pinderfields Hospital, The Mid Yorkshire Hospitals NHS Trust, Aberford Road, Wakefield, West Yorkshire WF1 4DG, UK.
Email: akshay.dwarakanath@nhs.net
Twitter: @ADwarakanath