Early View

Original research article

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JM is the guarantor and takes responsibility for the integrity of the work from inception to published article.

Author Contributions

J.M conceived and designed the study, collated and analysed data and drafted the manuscript. A.A and R.J.H contributed data, contributed to study design and data analysis and drafted the manuscript. F.C, E.T, E.S, N. P, J.D, P.N, B.V, M.T, C.D, G.L, V.A, T.J, A.A, B.I, A.H, V.K, E.R, A.Y.K.C.N, S.U, M.S, N.M, P.E, M.N, F.A, G.D, M.B, C.M, M.I, M.B, N.H, Y.M, R.H, H.B, A.A, K.J, G.T, I.Z, D.S, N.M, S.K, H.I, J.N, H.W, C.C, H.L, R.S, N.J, A.G, T.S, K.B, C.R, B.P, E.B, G.W, R.W, R,T, K.M, N.B, V.K, S.N, K.S, M.A.K, A.I.M, Y.M.M.M, H.G, B.L & A.R, contributed data and revised the manuscript for important intellectual content, W.L designed the figures and carried out statistical analyses and N.M.R helped design the study and revised the manuscript for important intellectual content

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'Take Home Message' / ERS Social Media

Roughly 0.6% of patients admitted with COVID-19 have pneumomediastinum identified. The finding is associated with severe COVID-19 and high mortality.

Plain Language Summary

Pneumomediastinum is air around the heart and structures in the middle of the chest. This survey of hospitals from around the UK found that roughly 1 in every 160 patients (0.6%) admitted to hospital with COVID-19 had pneumomediastinum identified. Most of these patients were not mechanically ventilated when pneumomediastinum was diagnosed. However, by the end of their admissions more than three quarters (76.5%) of all patients with COVID-19 and pneumomediastinum who were eligible for mechanical ventilation had been mechanically ventilated. Half of all patients with COVID-19 and pneumomediastinum died. Pneumomediastinum occurs in patients with severe COVID-19 pneumonitis but it is not clear if pneumomediastinum is a contributory factor to the high death rate. There was no difference in outcome associated with removing patients from CPAP treatment after pneumomediastinum was identified.

Abstract

Background

There is an emerging understanding that coronavirus disease 2019 (COVID-19) is associated with increased incidence of pneumomediastinum. We aimed to determine its incidence among patients hospitalized with COVID-19 in the United Kingdom and describe factors associated with outcome.

Methods

A structured survey of pneumomediastinum and its incidence was conducted from September 2020 to February 2021. United Kingdom-wide participation was solicited via respiratory research networks. Identified patients had SARS-CoV-2 infection and radiologically proven pneumomediastinum. The primary outcomes were to determine incidence of pneumomediastinum in COVID-19 and to investigate risk factors associated with patient mortality.

Results

377 cases of pneumomediastinum in COVID-19 were identified from 58,484 inpatients with COVID-19 at 53 hospitals during the study period, giving an incidence of 0.64%. Overall 120-day mortality in COVID-19 pneumomediastinum was 195/377 (51.7%). Pneumomediastinum in COVID-19 was associated with high rates of mechanical ventilation. 172/377 patients (45.6%) were mechanically ventilated at the point of diagnosis. Mechanical ventilation was the most important predictor of

mortality in COVID-19 pneumomediastinum at the time of diagnosis and thereafter (p < 0.001) along with increasing age (p < 0.01) and diabetes mellitus (p = 0.08). Switching patients from continuous positive airways pressure support to oxygen or high flow nasal oxygen after the diagnosis of pneumomediastinum was not associated with difference in mortality.

Conclusions

Pneumomediastinum appears to be a marker of severe COVID-19 pneumonitis. The majority of patients in whom pneumomediastinum was identified had not been mechanically ventilated at the point of diagnosis.

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Keywords: Pneumomediastinum, Mediastinal Emphysema, COVID-19, Subcutaneous Emphysema, Pneumothorax, Barotrauma

Glossary of terms

ARDS = acute respiratory distress syndrome; BiPaP = conscious non-invasive bi-level positive airways pressure ventilation; COVID-19 = coronavirus 2019 infection; CPAP = continuous positive airways pressure; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; HFNO = high flow nasal oxygen; Mechanical ventilation = invasive mechanical ventilation; PEEP = positive end expiratory pressure; PTM = pneumomediastinum; PPV = positive pressure ventilation; UK = United Kingdom

Introduction

Pneumomediastinum (PTM) is the abnormal presence of air or gas in the mediastinum. Spontaneous PTM is rare, appearing in approximately 1 in 33,000 hospital admissions [1]. PTM has a higher reported incidence among patients receiving positive pressure ventilation (PPV), particularly those with acute respiratory distress syndrome (ARDS) [2, 3].

The COVID-19 pandemic has seen a remarkable increase in the number of patients receiving PPV within a given period with many patients with COVID-19 pneumonitis meeting ARDS criteria [4, 5]. The publication of several case reports and small series of PTM in patients with COVID-19 could be viewed in this context [5-8]. There have however, been a number of reports of PTM occurring in COVID-19 pneumonitis without positive pressure ventilation [9-11]. The true incidence of PTM in COVID-19 and its relationship to PPV remains unclear. In addition, whether management should be altered after the identification of PTM is not known.

We report a multi-centre observational study of 377 cases of COVID-19 PTM from 53 hospitals in the United Kingdom between September 2020 and February 2021. We describe the incidence and risk factors associated with PTM in COVID-19 and associations with mortality.

Materials and methods

Study population

The study recruited across the United Kingdom (UK). It was advertised via national and regional trainee research networks including Pulmonary Research Inter-Site Matrix (PRISM) and North West Collaborative Respiratory Research (NCORR).

Participating institutions contributed cases of PTM in inpatients with COVID-19 identified between 01/09/2020 to 31/01/2021. The diagnosis of PTM was based on a computed tomography (CT) or plain radiograph of chest and the diagnosis of COVID-19 was based on a positive SARS-CoV-2 PCR result or evidence of COVID-19 pneumonitis on CT imaging and a clear clinical history. All participating institutions searched radiology reports using the keywords 'pneumomediastinum', 'pneumothorax' or 'subcutaneous emphysema', and patient lists from medical and respiratory wards and intensive care units to ensure all cases were identified. Anonymized data were collected for each case. These included; demographics; past medical history; radiological findings; clinical outcomes and respiratory settings from all respiratory support prior to and after diagnosis of PTM. Follow up at 120 days or more was recorded for all patients and all cases of interhospital transfer were cross-checked to ensure no duplication. In order to accurately estimate incidence data were collected on the total numbers of patients admitted during this period who were coronavirus positive on SARS-CoV-2 PCR testing and the proportion who underwent CT imaging of chest at each institution.

All data pertaining to fraction of inspired oxygen (FiO2) were normalized to a uniform scale prior to analyses. This is described in online supplementary table S2 (e.g., all patients receiving 15L of oxygen via a non-rebreather mask with reservoir were assigned an inspired FiO2 of 90%). A variety of devices were used to deliver high flow nasal oxygen (HFNO) and continuous positive airways pressure (CPAP). Positive end expiratory pressure (PEEP) and FiO2 for patients receiving CPAP were normalized to values based on data from the Association of Respiratory Technology and Physiology (2020). PEEP for patients on HFNO was estimated and normalized based on published physiological data from Groves & Tobin (2007) [12]. Details of this can be found in online supplementary Tables S3a and S3b and supplementary Figure S3c.

Ethical approval was obtained from the Oxford University Hospitals NHS Foundation Trust (UK) audit committee with additional ethical approval from local NHS Trusts where relevant. All data were collected retrospectively and entered by local physicians in anonymized fashion without linkage to patient identifiers.

Statistical methods

Patient data are presented as frequencies and percentages for categorical data and mean (±SD) for continuous data. Where data were not normally distributed the median and interquartile range (IQR) are presented. Differences in categorical data are presented using the chi-square test. For comparisons of continuous normally distributed data 2-sided independent t-tests were used. All outcomes quoted are outcomes at 120 days. Variable entry into regression models was performed

backward stepwise. Analyses were performed using SPSS 28 (SPSS, Chicago, IL, USA). Figures were created in R version 4.0.3.

We present the following article in accordance with the STROBE reporting checklist.

Results

A total of 377 cases of pneumomediastinum were detected of whom 98.4% had a positive SARS-CoV-2 PCR and the remainder were diagnosed clinically. The diagnosis of PTM was made or confirmed on CT-scan of chest in 318 cases (84.4%). For 147/318 (46.2%) of the cases diagnosed by CT scan, PTM had not been visible on a preceding chest radiograph. Outcome data were obtained for all patients and incidence data from all included hospitals. All other data was ≥ 95% complete for all parameters.

Incidence

There were 58,484 PCR positive inpatient admissions for the period 1st September 2020 to 31st January 2021 within the 53 participating hospitals (mean 1103 ± 611 COVID-19 inpatients per hospital). The incidence of PTM was 0.64% (95% CI 0.58%-0.71%) per COVID-19 inpatient admission with a mean number of PTM cases of 7.1 ± 4.8 per hospital. 12,703 of the 58,484 PCR positive inpatients (21.7%) underwent CT imaging of chest during admission with a mean number of CT scans performed per hospital of 240 ± 200. The relationship between the number of total inpatient admissions, use of CT imaging of chest and the number of cases of PTM across hospitals is presented in online supplementary Figure S4.

Demographics

The median age was 60 years (IQR 52-78). Male patients were over-represented with 277 (73.5%) male to 100 (26.5%) female patients. The most prevalent medical comorbidities were: hypertension (32.4%), diabetes mellitus (21.5%), asthma (19.4%), obesity (10.6%), ischaemic heart disease / left ventricular systolic dysfunction (8.8%) and chronic kidney disease (4.5%). Three patients were pregnant. The median duration of symptoms prior to admission to hospital was 7 days (IQR 5-10) while the median duration from admission to the identification of PTM on imaging was 7 days (IQR 5-12.3). Chest pain was a feature of the presenting complaint in 11.9% of patients.

315/377 (83.6%) patients were considered eligible for mechanical ventilation should it be required. Eligibility for mechanical ventilation was a clinical decision recorded in the notes. Treatment of the remaining 62 patients was limited to CPAP support should it be required. Given the differences in management between these two groups they are considered separately in our regression analyses examining factors linked to patient outcome.

Management

241/315 (76.5%) of patients considered eligible for escalation to mechanical ventilation were mechanically ventilated at some point during their admission. 172 of these 241 (71.4%) patients were mechanically ventilated prior to the diagnosis of PTM. PTM was detected within 24 hours following intubation in 38/241 (15.8%) of these patients. 24/241 (10.0%) of these patients went on to receive extracorporeal

membrane oxygenation (ECMO). Of the 377 patients eligible to receive CPAP 256/377 (67.9%) had received CPAP prior to the diagnosis of PTM. Conscious non-invasive bi-level positive airways pressure ventilation (BiPaP) was used at some point in the admissions of 9/377 (2.4%) patients, other than its use in weaning patients from mechanical ventilation. Four of these nine patients were in type two respiratory failure. The indication for use of BiPaP for the other five patients was not clear. Given the few patients who received BiPaP and the variation in its use we have excluded it from our analyses.

The maximum respiratory support provided to all patients before and after diagnosis of PTM is described in Figure 1. Four patients whose treatment was limited to non invasive respiratory support were switched from CPAP to Oxygen at the point of diagnosis of PTM as part of a decision to initiate palliative treatment. Two patients were managed on room air throughout.

Alteration of respiratory support at the time of diagnosis is illustrated in Figure 1. Most patients whose respiratory support was changed after diagnosis of PTM were on CPAP. At the point of diagnosis of PTM 93 patients eligible for mechanical ventilation were on CPAP. Fifty (53.8%) of these patients were switched immediately on diagnosis of PTM to either Oxygen or HFNO therapy creating two subgroups amenable to analysis; the 50 switched to Oxygen or HFNO and the 43 continuing on CPAP. These two subgroups were retrospectively well matched at the point of diagnosis by age (CPAP mean age 57.0 years vs Oxygen or HFNO 55.6 years, p = 0.51), by the maximum FiO2 they had received (CPAP mean FIO2 66% vs Oxygen

or HFNO 68%, p = 0.15) or by the maximum PEEP they had received (CPAP mean PEEP 10.4cmH$_2$0 vs Oxygen or HFNO 9.8cmH$_2$0, p = 0.19). The subsequent trajectory of these two subgroups is illustrated in Figure 2. Associations of change in mode of respiratory support and mortality for these patients was examined by ANOVA. There was no significant main effect of switching support from CPAP to Oxygen or HFNO on outcome. There was however, a main effect of mechanical ventilation as a factor associated with mortality for both subgroups (p < 0.001).

Co-occurrence of pneumothorax, subcutaneous emphysema and complications associated with pneumomediastinum

Pneumothorax was seen concurrently in 154/377 patients (40.8%) and subcutaneous emphysema was seen in 280/377 (74.3%) of patients. The co-occurrence of pneumomediastinum with pneumothorax, subcutaneous emphysema and tension phenomena and the use of intercostal drains are displayed in Figure 3. The number and frequencies of intercostal chest drains inserted are presented in online supplementary Figure S5. In cases associated with subcutaneous emphysema, subcutaneous drains were employed in 6 (1.6%) cases. In 5 of these 6 cases subcutaneous drains were inserted for threatened or actual tension subcutaneous emphysema. There were 4 (1.1%) instances of mediastinal drains being used. In 1 of these 4 cases the mediastinal drain was inserted as an emergency bedside procedure for suspected tension PTM and tension subcutaneous emphysema. In the other 3/4 cases the mediastinal drain was inserted to obviate possible tension PTM. These four mediastinal drains were inserted in patients at four different hospitals, each without on-site cardiothoracic services.

There were 14 cases of tension pneumothorax. During 10 cases of suspected tension phenomena bilateral intercostal drains were inserted as an emergency procedure. Seven of these 10 cases were performed without prior radiographic evidence of pneumothorax.

The development of pneumothorax was not associated with increased risk of death for our cohort (Table 1) including the subset of 16 patients who were mechanically ventilated before pneumothorax developed [11/116 (9.5%) were among those patients who subsequently died while 5/56 (8.9%) were among those discharged, p = 0.9] There were two cases of pneumoperitoneum. Both of these cases were in mechanically ventilated patients.

In 8 cases PTM appeared following an interventional procedure that could potentially represent a separate mechanism for occurrence e.g., tracheostomy, and these cases are included in the final analysis. Analyses were performed excluding these cases without any statistically significant deviation from the results presented.

Mortality

At 120 days from admission 175/377 (46.4%) patients had been discharged and 195/377 (51.7%) patients had died. Of the seven patients still in hospital at 120 days, at time of writing one patient had died on day 162 of their admission. Three patients remained mechanically ventilated on days 131, 146 and 150 of admission. One patient had been extubated but remained within intensive care on day 132 of

admission. These 5 patients were categorized with those who had died at 120 days in all outcome analyses. The remaining two patients were medically fit for discharge to rehab facilities at days 137 and 149 of admission. They were categorized with patients discharged at 120 days in all outcome analyses. A breakdown of mortality is provided in online supplementary Tables S6a and S6b according to whether patients were eligible for mechanical ventilation or limited to CPAP support.

Factors of the presentation and association with outcome are presented for all patients in Table 1. All factors significantly associated with mortality in univariate analyses were entered into binary regression prediction models with the exception of the use of ECMO which, was excluded as the direction of association for this variable was in favour of discharge rather than death. The variable 'radiographic progression of pneumomediastinum' was excluded where the model was conducted from the point of diagnosis.

A regression model comparing the predictive utility of variables for mortality at 120 days from the point of diagnosis for patients eligible for all treatment is presented in Table 2. Further models looking at the predictive utility of the same variables for mortality across the duration of hospital admission are presented for patients eligible for all treatment in online supplementary Table S7 and for those limited to CPAP in online supplementary Table S8.

Discussion

These data comprise the largest series of PTM in COVID-19 to date. In comparison with other series we sought to accurately represent the incidence of PTM in COVID-19 during the period of the survey – the United Kingdom's 'second wave' of the pandemic. Hospital records and radiology reports were systematically reviewed in each centre. Hospitals that did not observe cases of PTM but provided accurate incidence data were included. However, hospital participation was sought via trainee research networks and this may have resulted in inclusion bias.

Our estimate of incidence is also subject to diagnostic biases. We identified cases through radiology reports which, may not always reference a relevant finding. The main mode of diagnosis of PTM was CT imaging and there was considerable variation in the use of CT by participating hospitals (online supplementary Figure S4). Many CT scans of chest were pulmonary angiogram studies assaying for pulmonary emboli, not for PTM. For 46.2% of the patients diagnosed with PTM on thoracic CT the PTM was not visible on their preceding chest radiograph. As only 21.7% of our total denominator population of 58,484 COVID-19 positive inpatients had thoracic CT imaging performed during their admissions, there is likely to be a number of undetected cases of PTM in our denominator population. These unknown cases may have had a more benign disease trajectory than the cases identified.

With these caveats these data demonstrate an incidence of PTM in COVID-19 of 0.64% per inpatient admission and 3.0% per COVID-19 inpatients undergoing

thoracic CT. This incidence is similar to rates reported by two other studies of PTM in hospitalized COVID-19 populations from Brazil and Romania, of 0.51% and 0.67% respectively [13,14]. The incidence of 'spontaneous' PTM in COVID-19 in this cohort i.e., without any PPV via mechanical ventilation *or CPAP*, was 77/58,484 (0.13%). This is much higher than estimated background rates of non-COVID-19 'spontaneous' PTM. The largest study of non-COVID-19 'spontaneous' PTM in the literature with a defined denominator population, identified 41 cases of PTM from 1,824,967 emergency department admissions over 16 years (0.00002%) [15].

The mean age of the cohort (59.1 years) is consistent with inpatient international COVID-19 PTM cohorts from Brazil, Romania, Turkey, Pakistan and the USA [13, 16-19]. It is somewhat younger than the mean age of general COVID-19 inpatients in the UK, according to the largest epidemiological study (70.4 years) [20]. There could be pathophysiological reasons why COVID-19 inpatients who develop PTM are younger than the hospital population average (we note that background rates of non-COVID-19 PTM typically occur in younger adults) [1, 14-15]. It could reflect bias towards more frequent imaging in younger patients who are usually eligible for all treatments, with an artificial reduction in the identification of PTM in older patient groups. A younger mean age is also representative of trends in patients hospitalized with COVID-19 during the 'second wave' in the UK [21].

Pneumothorax was found to co-exist with PTM in 40.3% of cases. This compares to reported rates of between 20.0% and 72.7% in other series with more than 10 patients [6, 13, 16-18, 22]. There was no finding of an effect on mortality of

pneumothorax within this cohort, nor specifically for those patients who were mechanically ventilated when pneumothorax occurred. This contrasts with the findings of Marciniak et al [23] who report an increased risk of mortality with COVID-19 pneumothorax in a large dataset of UK inpatients, and Chopra et al [24] who found increased mortality in mechanically ventilated patients across four intensive care units in the USA. As concurrent PTM was not reported in the Marciniak et al study and was relevant to 30% of the patients in the Chopra et al study it is not clear how comparable these patient groups are to our cohort. The extent to which pneumothorax and PTM are manifestations of barotrauma in COVID-19 underwritten by a pathophysiological process and the extent to which they are distinct entities remains to be determined.

Subcutaneous emphysema was seen in 77.9% of COVID-19 PTM patients. Subcutaneous emphysema has been documented at rates of between 63.6% and 90.5% in other COVID-19 PTM series with more than 10 patients [13, 16-17]. This result is in keeping with high reported rates of subcutaneous emphysema in spontaneous non-COVID PTM of up to 100% [1] and in excess of lower rates of co-occurrence between subcutaneous emphysema and non-COVID-19 pneumothorax of up to 20% [25]. It would suggest that subcutaneous emphysema is a feature strongly associated with PTM and not specifically to COVID-19 PTM. It is acknowledged however, that co-occurrence of subcutaneous emphysema and PTM may be subject to diagnostic bias with patients presenting with subcutaneous emphysema more likely to have CT imaging and subsequent revealing of a diagnosis of PTM.

It is not possible to determine the effect of different ventilatory strategies on outcome within an observational study such as this. However, we examined this for those patients eligible for mechanical ventilation who were on CPAP when PTM was diagnosed. The role of CPAP in patients with PTM is a clinically important question: Analysis of changes in respiratory support after diagnosis of PTM permits an exploration of physician preferences regarding respiratory support, and by inference use of PEEP, in PTM. Those patients who remained on CPAP immediately after diagnosis of PTM were retrospectively well matched with those patients who were switched immediately to Oxygen or HFNO by age, maximum FiO2 and maximum PEEP. There was no difference in survival at 120 days between these subgroups. Thus, the current data do not support a policy of taking patients off CPAP when PTM is diagnosed, although we acknowledge potential confounders.

The 120-day mortality rate for patients with COVID-19 PTM of 51.7% is in keeping with reported mortality rates of 47.7% - 72.2% in other COVID-19 PTM cohorts [13, 16-17]. The severity of COVID-19 illness is demonstrated by the high mean levels of FiO2 and PEEP before and after the diagnosis of PTM was made (Figure 1). Only two patients (0.5%) were managed on room air throughout admission. The number of patients who were mechanically ventilated at some point during their admission was remarkable at 76.5% of those eligible, in comparison to the UK average for mechanical ventilation of COVID-19 inpatients of 8.8% [20]. Mechanical ventilation was unsurprisingly an important prognostic factor and dominant variable in outcome prediction models (Table 2). It is a ubiquitous event in the trajectory of a deteriorating patient eligible for this support. Only one eligible patient in our cohort died without having been mechanical ventilated.

High rates of mechanical ventilation in COVID-19 PTM have been reported in other general hospital inpatient COVID-19 studies [13,16]. This may reflect a confounding relationship between more severe illness and higher rates of CT scanning and detection in high-care environments. It may also indicate an important role for mechanical ventilation in the development of PTM in COVID-19. However, the majority of this cohort, 205/377 patients (54.4%), were not mechanically ventilated at the point the diagnosis of PTM was made. Mechanical ventilation was therefore not a sufficient or necessary mechanism of PTM for the majority of patients.

Different mechanisms of PTM are described in the literature, including posterior membrane tracheal lesion or rupture due to coughing [26]. The 'Macklin effect' [27] describes PTM secondary to the rupture of marginal alveoli due to a steeply increased pressure gradient between the alveolus and the interstitial space. After rupture of the alveolus air dissects centripetally along the sheaths of the broncho-vascular bundles into the mediastinum. Depending on volume and pressure, air can be decompressed along cervical fascial planes into the subcutaneous tissues of the chest wall, neck or face. Air may rupture the relatively thin mediastinal pleura to enter the pleural space causing unilateral or bilateral pneumothorax and /or pneumopericardium / pneumoperitoneum. Macklin and Macklin believed the effect could be benign or result in circulatory collapse if air directly compressed the pericardium or venous return – a tension PTM or pneumothorax . Air in the broncho-vascular bundles could also have a pernicious splinting effect leading to hyperinflation and low compliance with vascular compression and poor gas exchange, 'malignant interstitial emphysema'. The 'Macklin effect' was inspired by physician descriptions of 'pulmonary interstitial emphysema' in patients suffering

severe respiratory illness during the 1918-20 influenza pandemic, [28, 29] the pathophysiology of which may bear comparison with the COVID-19 pandemic.

The 'Macklin effect' offers a plausible mechanism for PTM in COVID-19 whereby the pneumonitis creates an altered diathesis for the rupture of alveoli and the emergence of PTM. The proposition that COVID-19 PTM patients have severe pneumonitis is supported by cohort studies that describe high radiological scores of pneumonitis in COVID-19 PTM [10,16-18]. The complimentary findings in our cohort of; high levels of respiratory support (taken to represent severe pneumonitis); high rates of subcutaneous emphysema; episodes of tension phenomena, and low rates of chest pain (compared to spontaneous PTM) support the Macklin effect as the likely mechanism of PTM in COVID-19. The previous 2002-4 SARS epidemic also saw an increase in case reports of PTM [30] and this may reflect similar pathophysiology.

Future studies among mechanically ventilated patients with COVID-19 may elucidate whether strategies which modify trans-alveolar pressure have any association with development or progression of PTM. We notice that the 40/377 (10.6%) patients in our cohort with obesity were not at increased risk of death compared to other patients with PTM and speculate whether this could relate to mass loading around the chest wall and/or abdomen with reduction of alveolar compliance and/or trans-alveolar gradients. Propensity matched cohort analyses may address whether the development of PTM confers increased mortality risk, beyond severe pneumonitis, or whether development of PTM is affected by disease modifying drugs such as

dexamethasone (standard of care for our cohort) or different variants of coronavirus 2019.

In summary this study is the largest reported series of PTM in COVID-19 disease. PTM appears to be a marker of severe pneumonitis, and not necessarily as a result of the use of PPV. There was no evidence of increased harm by continuing CPAP in COVID-19 patients who developed PTM.

Data Sharing

De-identified participant data from the study will be made available with publication to medical researchers on a not for profit basis by email request to the corresponding author for the purposes of propensity matching or meta-analysis.

Declaration of Interest

The authors declare no conflicts of interest.

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Figure Legends

Figure 1. Sankey Plot charting the maximum respiratory support given to all patients four hours before the diagnosis of Pneumomediastinum and then following the diagnosis of Pneumomediastinum (n = 374). The mean fraction of inspired oxygen (FiO2) and positive end expiratory pressure (PEEP) received on these levels of support is given in the tables below. HFNO = high flow nasal oxygen; CPAP = continuous positive airways pressure.

Figure 2. Alluvial Plot describing the trajectory of 93 patients eligible for mechanical ventilation who were on continuous positive airways pressure (CPAP) at the point of diagnosis of pneumomediastinum. At point of diagnosis there was no statistical difference in age, maximum fraction of inspired oxygen (FiO2) or maximum positive end expiratory pressure (PEEP) received between those patients subsequently maintained on CPAP and those subsequently switched to Oxygen or high flow nasal oxygen (HFNO).

Figure 3. UpSet Plot illustrating the co-occurrence of pneumomediastinum with subcutaneous emphysema, pneumothorax and tension phenomena and the use of intercostal chest drains (n = 377). Bilateral pneumothorax was ascribed to pneumothoraces occurring on both sides of the thorax within the same admission

Tables

Table 1. Univariate analyses: Factors of the presentation and their association with outcome at 120 days (n = 377). HFNO = high flow nasal oxygen; CPAP = continuous positive airways pressure; ECMO = extracorporeal membrane oxygenation; MV = mechanical ventilation

	Outcome Dead	Outcome Discharged	N	Univariant analysis: Odds ratio for death with 95% CI	p
	Mean value (±SD) or N and %	Mean values (±SD) or N and %			
Mechanically ventilated at any time (of those eligible)	160 / 161 (99.8)	81 / 154 (52.6)	315	144.2 (19.7 – 1056)	< 0.001

Respiratory support at time of diagnosis:					
Oxygen (ref group)	24 / 199 (12.1)	44 / 176 (25.0)	375		
HFNO	4 / 199 (2.0)	6 / 176 (3.4)		1.2 (0.3 – 4.8)	0.77
CPAP	55 / 199 (27.6)	70 / 176 (39.8)		1.4 (0.8 – 2.7)	0.24
Mechanical ventilation	116 / 199 (58.3)	56 / 176 (31.8)		3.8 (2.1 – 6.9)	< 0.001
Age (mean years)	62.1 (11.4)	55.8 (13.1)		----	< 0.001
Subcutaneous emphysema	167 / 200 (83.5)	113 / 177 (63.8)		2.9 (1.8 – 4.6)	< 0.001

Ischaemic heart disease or left ventricular systolic dysfunction	26 / 200 (13.0)	7 / 177 (4.0)		3.6 (1.5 – 8.6)	< 0.01
Hypertension	76 / 200 (38.0)	46 / 177 (26.0)		1.9 (1.2 – 2.9)	0.01
Diabetes mellitus	53 / 200 (26.5)	28 / 177 (15.8)		1.9 (1.2 – 3.2)	0.01
Radiographic progression of pneumomediastinum	58 / 200 (29.0)	31 / 177 (17.5)		1.9 (1.2 – 3.2)	0.01
ECMO (those eligible)	11 / 160 (6.9)	13 / 81 (16.0)	241	0.4 (0.2 – 0.9)	0.03

Male sex	140 / 200 (70.0)	137 / 177 (77.4)		0.7 (0.4 – 1.1)	0.11
Chest pain at presentation	19 / 193 (9.8)	26 / 172 (15.1)	365	0.6 (0.3 – 1.2)	0.13
Chronic kidney disease	11 / 200 (6.0)	5 / 177 (2.8)		1.7 (0.6 – 4.6)	0.21
Asthma	43 / 200 (21.5)	30 / 177 (16.9)		1.3 (0.8 – 2.3)	0.27
Tension phenomena	13 / 200 (6.5)	7 / 177 (4.0)		1.7 (0.7 – 4.3)	0.28

Obesity (BMI ≥35)	23 / 200 (11.5)	17 / 177 (9.6)		1.2 (0.6 - .4)	0.55
Pneumothorax (at anytime)	84 / 200 (42.0)	70 / 177 (39.5)		1.1 (0.7 – 4.7)	0.63

Table 2.Binary Logistic Regression Model of factors predictive of death at 120 days *from the point of diagnosis of pneumomediastinum* (all patients eligible for mechanical ventilation, n=315). All variables significantly associated with mortality in univariate analyses were entered into the model stepwise, backwards. The model produces prediction accuracy for outcome of 68.4% versus a 51.1% default accuracy.

	B(SE)	Odds Ratio or % increase per unit (95% CI)	p
Mechanically ventilated (at diagnosis)	1.40 (0.26)	4.0 (2.4 - 6.7)	< 0.001
Age	-0.38 (0.12)	3.7 % per year (1.4 - 5.9)	< 0.01

Diabetes mellitus	0.59 (0.34)	1.8	(0.9 - 3.5)	0.08

Model R^2 = 0.251 Nagelkerke χ^2 (6) = 65.2 p < .001. Constant B(SE) = 2.38 (0.79) Variables in the regression but not listed, subcutaneous emphysema (p = .12), Hypertension (p = .35), ischaemic heart disease / left ventricular systolic dysfunction (p = .50).

Figures

Figure 1.

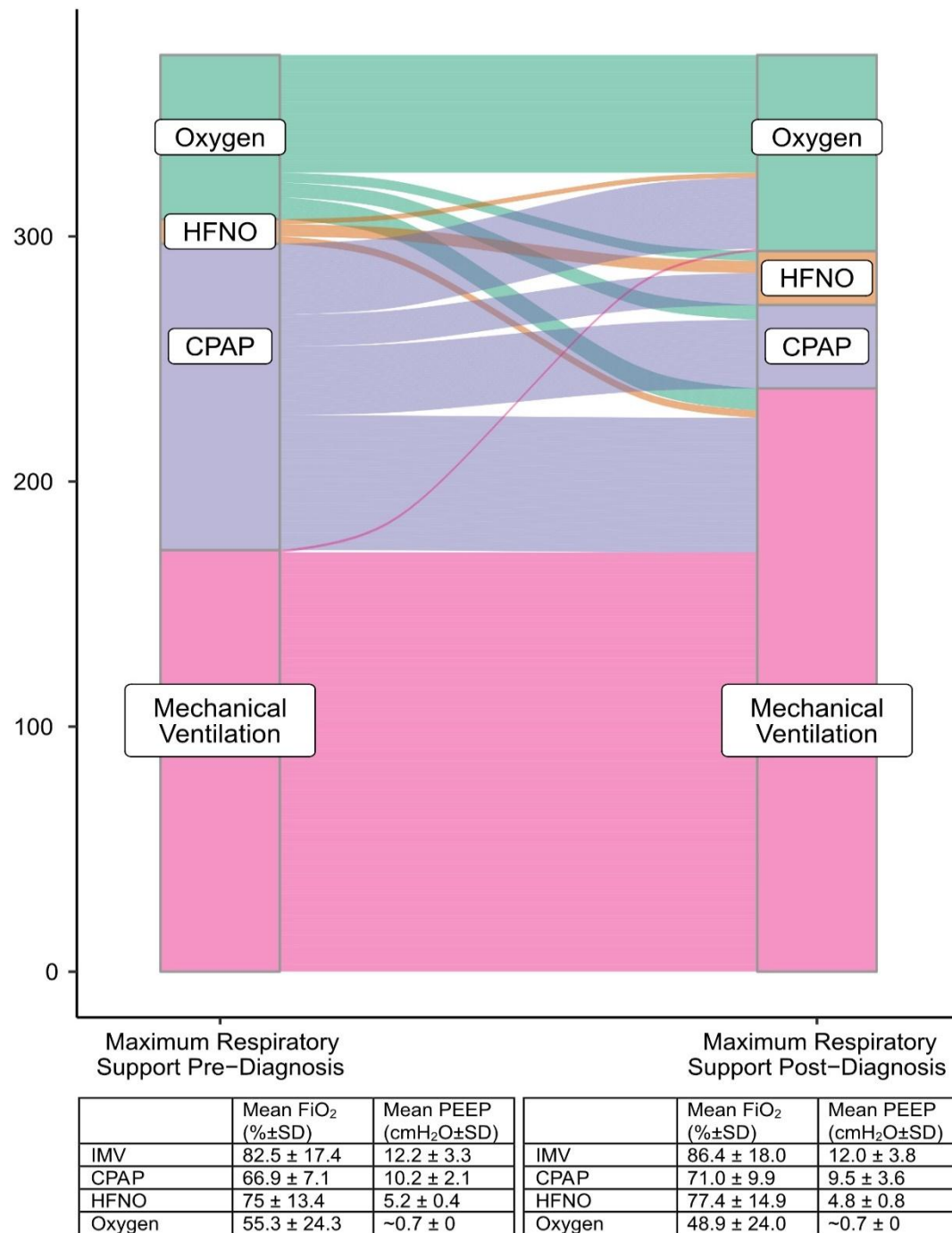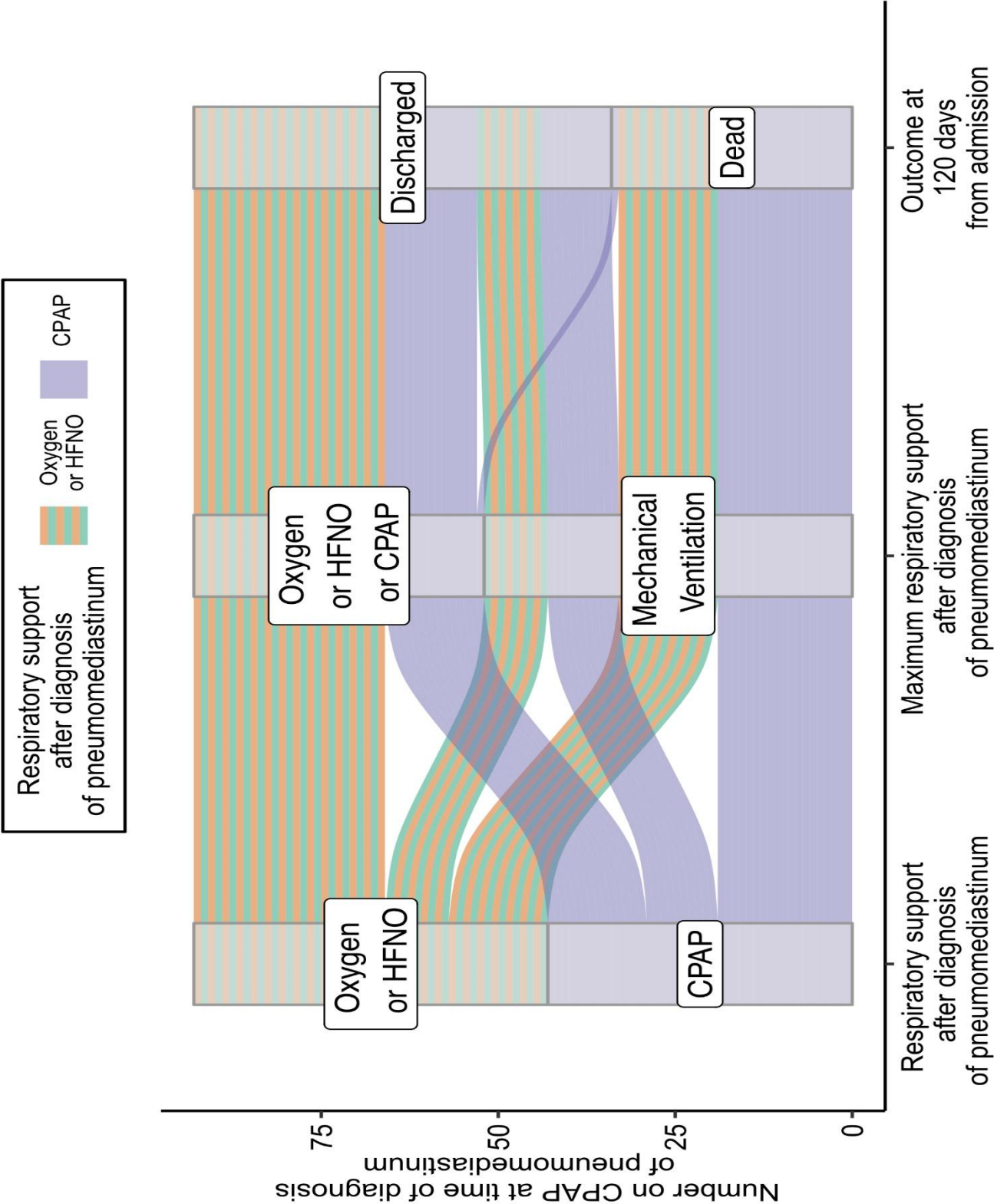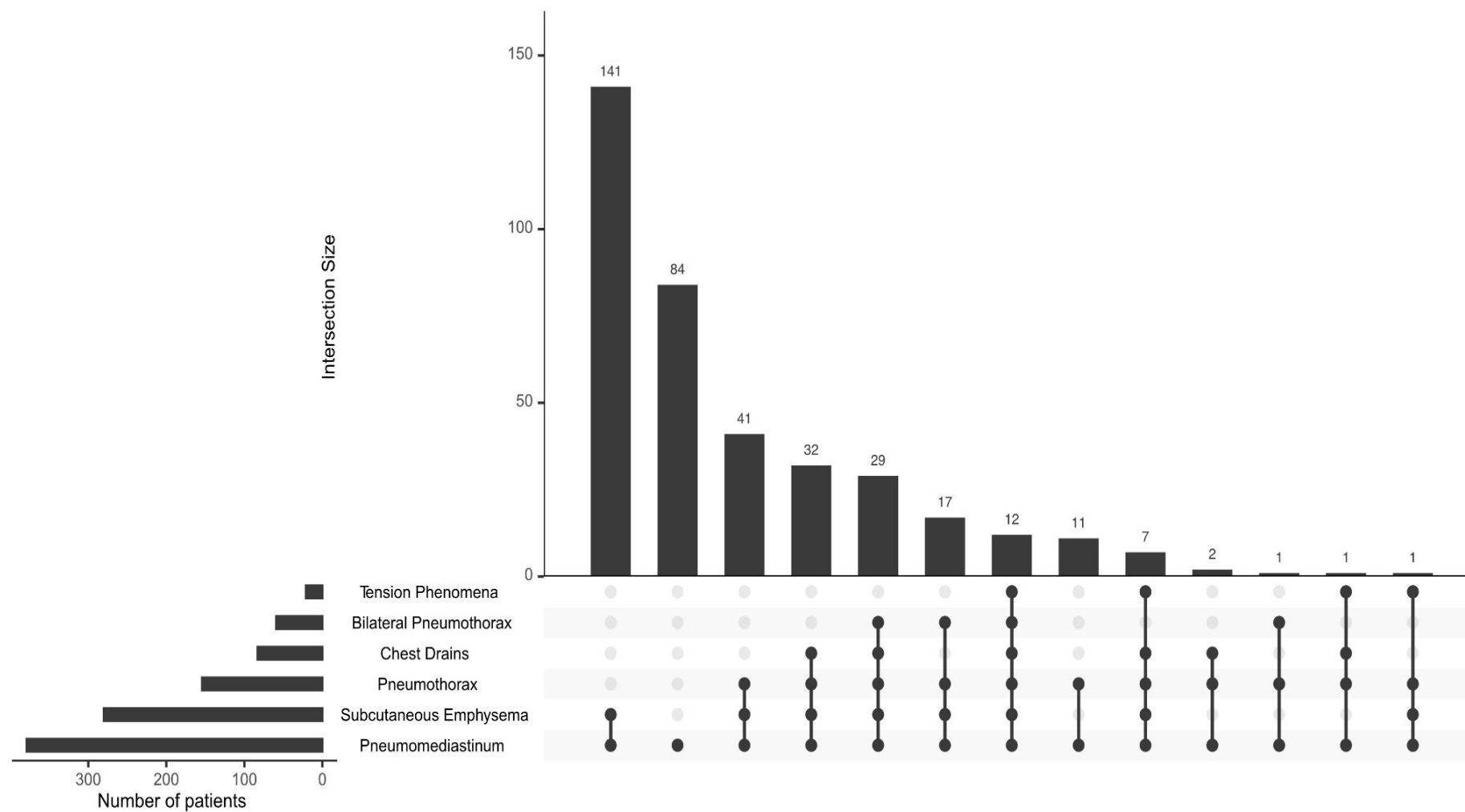|	Mean FiO$_2$ (%±SD)	Mean PEEP (cmH$_2$O±SD)		Mean FiO$_2$ (%±SD)	Mean PEEP (cmH$_2$O±SD)
IMV	82.5 ± 17.4	12.2 ± 3.3	IMV	86.4 ± 18.0	12.0 ± 3.8
CPAP	66.9 ± 7.1	10.2 ± 2.1	CPAP	71.0 ± 9.9	9.5 ± 3.6
HFNO	75 ± 13.4	5.2 ± 0.4	HFNO	77.4 ± 14.9	4.8 ± 0.8
Oxygen	55.3 ± 24.3	~0.7 ± 0	Oxygen	48.9 ± 24.0	~0.7 ± 0

Figure 2.

Figure 3.

Pneumomediastinum in COVID-19: a phenotype of severe COVID-19 pneumonitis? The results of the United Kingdom (POETIC) survey

Online Data Supplement
(S1 – S9)

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Glossary of terms used

ARDS = acute respiratory distress syndrome
BiPaP = conscious non-invasive bi-level positive airways pressure
COVID-19 = coronavirus 2019 infection
CPAP = continuous positive airways pressure
CT = computed tomography
CXR = chest radiograph
ECMO = extracorporeal membrane oxygenation
FiO2 = fraction of inspired oxygen
IHD = ischaemic heart disease
HFNO = high flow nasal oxygen
LVSD = left ventricular systolic dysfunction
MV = invasively mechanically ventilated
PEEP = positive end expiratory pressure
PPV = positive pressure ventilation
PTM = pneumomediastinum
UK = United Kingdom

Prior to performing the current study we conducted a literature search of evidence on the subject. We searched MEDLINE and PubMed for original peer-reviewed cohort studies describing the incidence of pneumomediastinum in COVID-19 between March 2020 and June 2021. Search terms were "Pneumomediastinum" AND "COVID-19" OR "Barotrauma" AND "COVID-19" OR "Pneumothorax" AND "COVID-19". Only reports published in English that included at least 5 cases and with estimates of a background population were included. Our search yielded 15 studies. These are detailed in table S1 below

Table S1. Previously published cohort studies with ≥5 cases of pneumomediastinum (PTM) and an identified denominator population.

Study and country of origin	Single or Multicentre	Date Published	Number of cases of PTM	% cases diagnosed by thoracic CT	PTM with concurrent PTX	PTM with concurrent SCE	Number of denominator population	Denominator patient population	% cases in denominator PCR positive
McGuiness et al (USA)[1]	Single	Nov 2020	59	CXR diagnoses	Not stated	Not stated	601	Mechanically Ventilated	100%
Kangas-Dick et al[2] (USA)	Single	Mar 2021	34	CXR diagnoses	35.3%	Not stated	346	Mechanically Ventilated	Unclear
Housman et al[3] (USA)	Single	Sep 2020	29	CXR diagnoses	6.9 - 24%	100%	171	Mechanically Ventilated	100%**

Wong et al[4] (USA)*	Multi (2)	Nov 2020	27	CXR diagnoses	100%	Not stated	1822	ARDS	Unclear
Chopra et al[5] (USA)*	Multi (4)	May 2021	24	Not stated	100%	Not stated	842	Critical Care (594 MV)	100%
Lemmers et al[6] (Italy)	Single	Sep 2020	23	CXR/CT	0%	100%	169	ARDS	100%
Rajdev et al[7] (USA)	Single	May 2021	21	CXR/CT	Not stated	Not stated	353	Oxygen / PPV (121 MV)	100%
Brito et al[8] (Brazil)	Single	April 2021	21	100%	33%	90.5%	4087	Hospital Inpatients	100%**
Martinelli et al[9] (UK)	Multi (16)	Sep 2020	17	CXR/CT	35.3%	Not stated	6574	Hospital Inpatients	Clinical Diagnoses
Belletti et al[10] (Italy)	Single	Feb 2021	13	38.5%	53.8%	Not stated	116	ARDS Criteria	100%
Cut et al[11] (Romania)	Single	Mar 2021	11	100%	72.7%	63.6%	1648	Hospital Inpatients	Unclear
Edwards et al[12] (USA)	Single	Nov 2020	10	CXR diagnoses	20%	90%	574	Mechanically Ventilated	100%

Talan et al[13] (Turkey)	Single	Dec 2020	7	71.4%	57.1%	57.1%	161	Critical Care (96 MV)	Unclear
Udi et al[14] (Germany)	Single	Aug 2020	5	Not stated	40%	40%	20	ARDS	100%
Eperjesiova et al[15] (USA)	Single	Jul 2020	5	Not stated	20%	80%	976	Hospital Inpatients	Unclear

Studies marked with an asterix (*) focused on identifying COVID-19 pneumothorax (PTX) rather than COVID-19 pneumomediastinum (PTM) therefore all cases were PTM/PTX overlap with likely underestimation of incidence of COVID-19 PTM. Studies marked with (**) describe 'confirmed COVID-19 infection' rather than SARS-CoV-2 PCR positivity.

S2

Hospitals within the POETIC consortium were a representative mix of secondary and tertiary hospitals throughout the UK including those within areas of high index of multiple deprivation. They are listed below in alphabetical order:

Addenbrooke's Hospital, Cambridge
Andover War Memorial Hospital
Barnet Hospital
Basingstoke and North Hampshire Hospital, Basingstoke
Bedford Hospital
Burnley General Teaching Hospital
Chelsea and Westminster Hospital
Glangwilli Hospital, Carmarthen
Gloucester Royal Hospital
Grange University Hospital, Newport
Great Western Hospital, Swindon
John Radcliffe Hospital
Kettering General Hospital
Lister Hospital, Stevenage
Luton & Dunstable University Hospital, Luton
Musgrove Park Hospital, Taunton
Neville Hall Hospital, Abergavenny
Newham University Hospital, London
Norfolk and Norwich University Hospital, Norwich
Northumbria Specialist Emergency Care Hospital
Nottingham City Hospital
Prince Philip Hospital, Llanelli
Prince of Wales Hospital, Bridgend
Princess Alexandria Hospital, Harlow
Queen Alexandra Hospital, Portsmouth
Queen Elizabeth University Hospital, Glasgow
Royal Berkshire Hospital, Reading
Royal Blackburn Teaching Hospital
Royal Brompton Hospital, London
Royal Cornwall Hospital, Truro
Royal Derby Hospital , Derby
Royal Devon & Exeter Hospital
Royal Free Hospital, London
Royal Glamorgan Hospital, Llantrisant
Royal Gwent Hospital, Newport
Royal Hampshire County Hospital, Winchester
Royal London Hospital
Royal Stoke University Hospital
Royal United Hospitals, Bath
Saint Bartholomew's Hospital, London
Southend University Hospital
Southport & Ormskirk District General Hospital
Stoke Mandeville Hospital

Sunderland Royal Hospital
University Hospital of Coventry and Warwickshire, Coventry
University Hospital of North Durham
University Hospital of North Tees, Stockton on Tees
University Hospital of Wales, Cardiff
Watford General Hospital
Wexham Park Hospital, Wexham
Whipps Cross Hospital, London
Wythenshawe Hospital, Manchester
Ysbyty Glan Clwyd, Rhyl

S3

Table S3a. Normalization of FiO2 received by patients. The assigned FiO2 we ascribed as received by patients on differing devices.[16,17]

Device	Flow Rate (L)	Estimated FiO2 received (%)
Nasal cannulae	1	24
Nasal cannulae	2	28
Nasal cannulae	3	32
Nasal cannulae	4	36
Nasal cannulae	5	40
Nasal cannulae	6	44
Venturi Mask '28%'	4-6	28
Venturi Mask '35%'	8-10	35
Venturi Mask '40%'	10-12	40
Venturi Mask '60%'	12-15	60
Non Rebreathe Mask with Reservoir	10	62
Non Rebreathe Mask with Reservoir	11	68
Non Rebreathe Mask with Reservoir	12	72

S3

Non Rebreathe Mask with Reservoir	13	78
Non Rebreathe Mask with Reservoir	14	84
Non Rebreathe Mask with Reservoir	15	90

Table S3b. The estimated PEEP received by patients on HFNO. This is extrapolated from expiratory pharyngeal readings for (Table 2, male subjects with their mouth closed) Groves and Tobin 2020.[18]

Nasal Flow (L/min)	0	10	20	30	40	50	60	70	80
PEEP (cmH20)	0.7	1.2	2.2	3.2	4.1	4.8	5.4	5.8	6.1

Domiciliary devices which entrain room air have been widely used during the pandemic. Such devices lack an oxygen blender and could result in an unreliable fraction of inspired oxygen (FiO_2).[19] Using a series of "bench" studies the ARTP COVID Group[20] have identified that amount of oxygen delivered (FiO_2) is influenced by the amount of CPAP pressure used by the patient. Ultimately increasing CPAP pressure exerts a dilutional effect on FiO_2.[20] Aware that many subjects in our data set did not have documented FiO_2 values we derived an estimate of FiO_2 for patients based upon data from ARTP COVID Group bench studies.

Using data from the ARTP Guidance for Oxygen Utilisation document,[20] we replicated a graph representing FiO_2 for varying CPAP pressure across 4 commonly used domiciliary devices at a flow rate of 15 L/min; Resmed Lumis 100, Resmed Lumis 150, Breas Vivo2 and Resmed AS10. In the figure below mean values of FiO2 for given CPAP pressures across these devices are plotted with a non-linear regression curve of best fit derived using GraphPad Prism version 9 (adapted from ARTP Guidance for Oxygen Utilisation, 2020).[20] Using the equation of this regression curve of mean values we estimated FiO_2 values for subjects in our dataset based on the assumption of 15L/min oxygen entrainment.

Measured FiO$_2$ for 15 L/min entrained oxygen
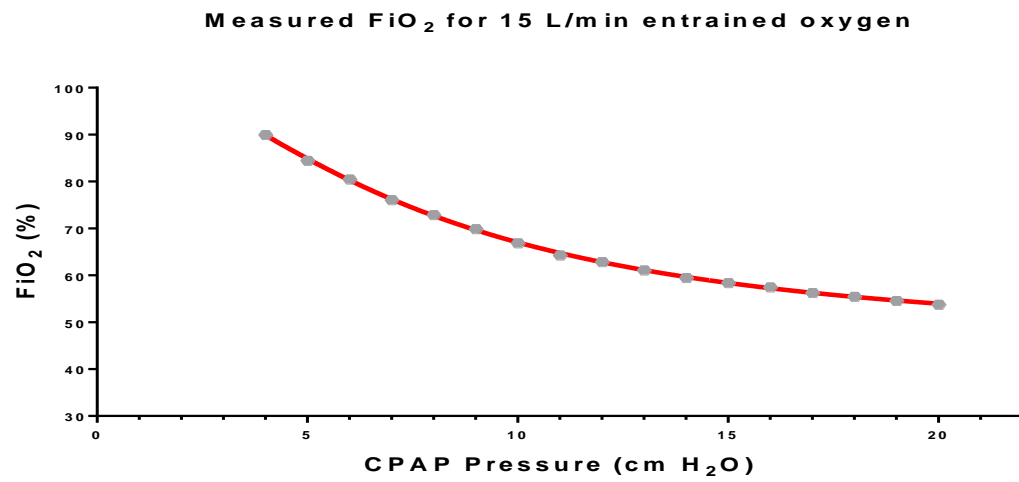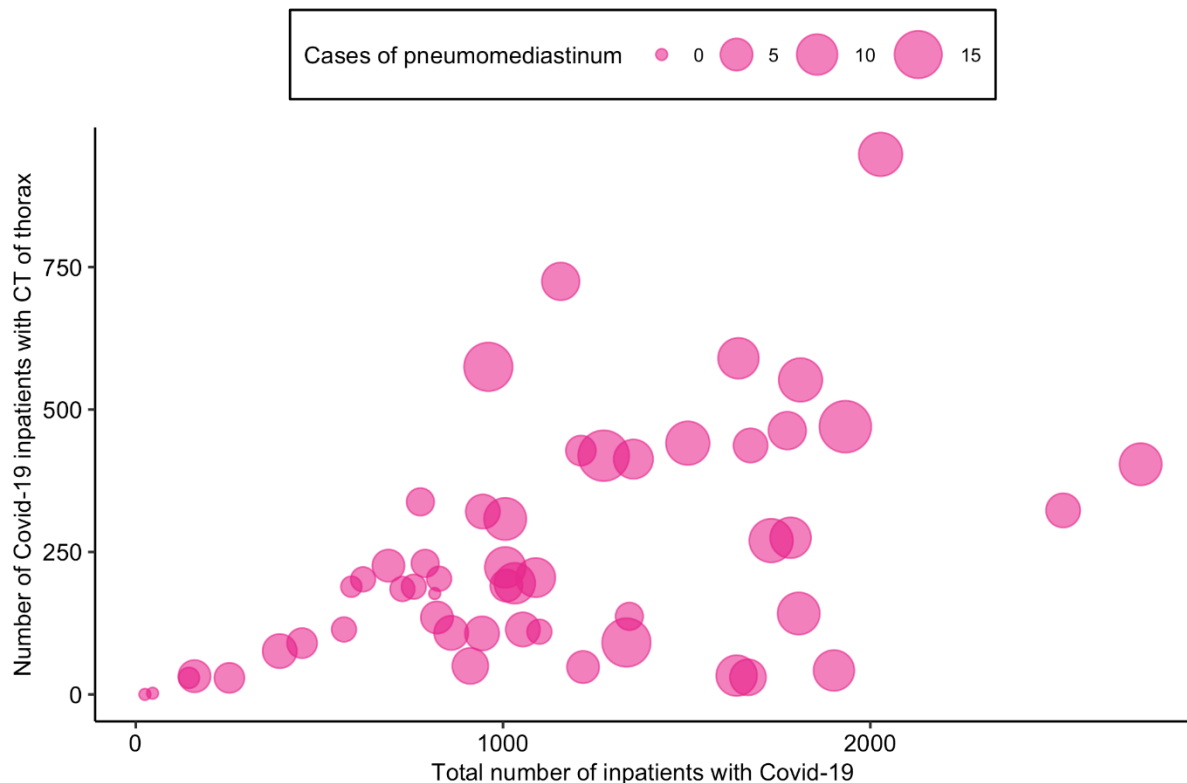
S4

Figure S4. Bubble Plot depicting the relationship between (i) the number of inpatient admissions with COVID-19 (ii) the number of these patients who had a thoracic CT scan and (iii) the number of cases of pneumomediastinum detected.*

*Results from the tertiary ECMO centre the Royal Brompton Hospital are not presented within Figure S4 given the highly selective patient intake. There were 17 cases of pneumomediastinum from 87 patients admitted to the Royal Brompton Hospital with COVID-19 of whom 67 had thoracic CT scans.

Three participating hospitals had no cases of pneumomediastinum but supplied incidence data and are included. There was a strong significant correlation between the number of COVID-19 inpatients and the number of cases identified $r(50) = 0.61$ $p < .001$ and a strong correlation between the number of COVID-19 inpatients who had CT Thoraces performed and the number of cases identified $r(50) = 0.49$ $p < .001$. The number of COVID-19 inpatients having CT-scans is an inferior predictor of the number of pneumomediastinum cases than the total number of COVID-19 inpatients at a hospital (3-way ANOVA; COVID-19 inpatients $t(50) = 3.885$ $p < .001$; CT-scans $t(50) = 1.888$ $p < 0.65$).

We believe these results reflect the alternate indications for CT imaging in our COVID-19 inpatient cohort during this period which, were likely to assay for

thromboembolism and prognostication, not for pneumomediastinum. As illustrated above, there is wide variation in the amount of CT scanning in COVID-19 pneumonitis inpatients among our hospitals. This could reflect physician opinion on the utility of CT scanning in COVID-19 and possibly the varying availability of this resource at this time during the pandemic.

S5

Figure S5. Bar chart illustrating the number and frequencies of intercostal chest drains employed according to whether pneumothoraces were unilateral or bilateral (n=154). Bilateral pneumothorax was ascribed to pneumothoraces occurring on both sides of the thorax within the same admission.
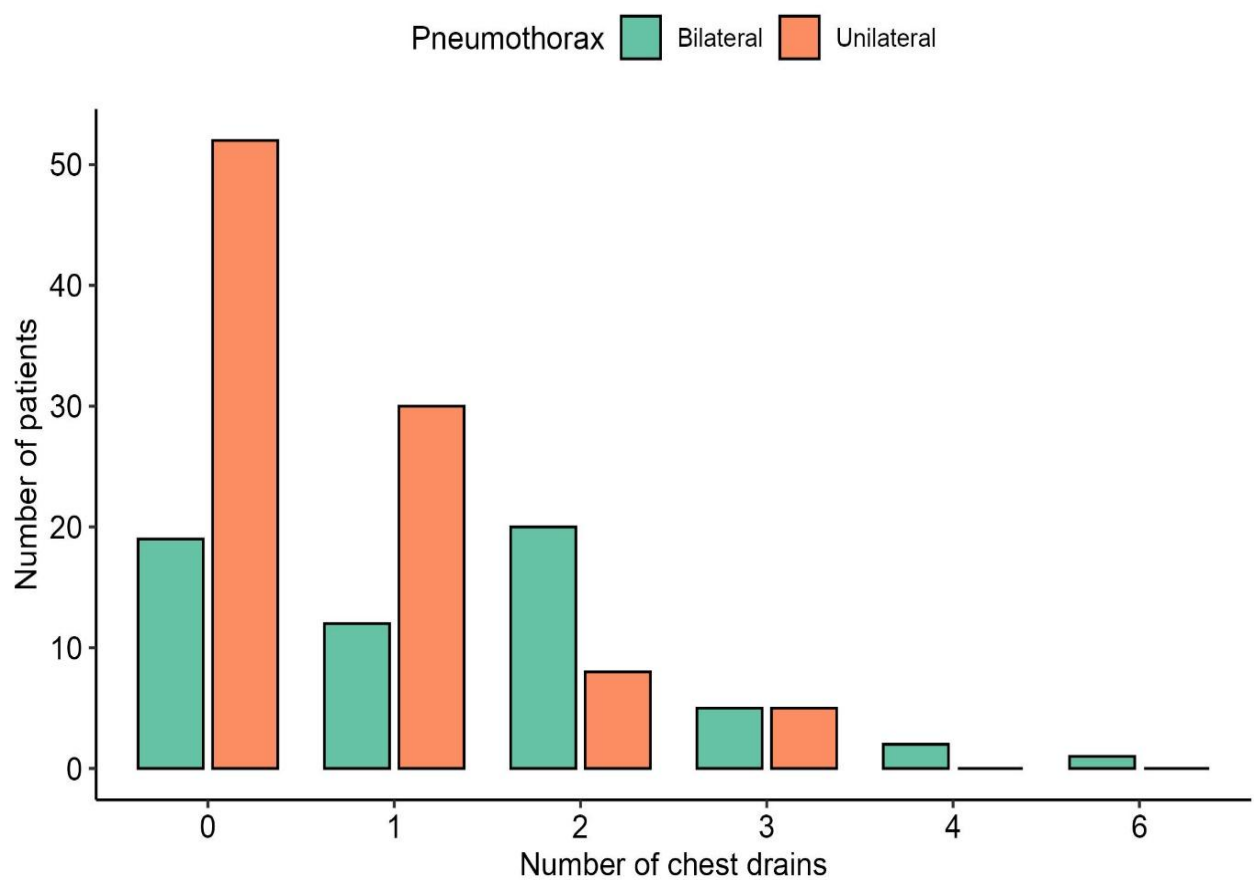
S6

Table S6a. Mortality data of patients deemed eligible for mechanical ventilation (whether mechanically ventilated or not), n = 315, Median Age = 58, (IQR 50 – 65)

	Outcome 28 Days Number (%)		Outcome 120 Days Number (%)	
Dead	114	(36.2)	156	(49.5)
Discharged Home	55	(17.5)	136	(43.2)
Discharged Rehab	1	(0.3)	16	(5.1)
Still Inpatient	145	(46.0)	7	(0.2)

	Number of Patients (%)	
Received MV anytime	241	(76.5)
Received ECMO	24	(10.0)

	Median and IQR (Days)	
Length of Admission	26	(16 – 47)
Duration of MV (dead)	14	(9 – 22)
Duration of MV (discharged)	24	(14 – 38)

Table S6b. Mortality data for patients limited to CPAP support, n = 62, Median Age = 72, (IQR 61.8 – 79.3)

	Outcome 28 Days Number (%)		Outcome 120 Days Number (%)	
Dead	32	(51.6)	39	(62.9)
Discharged Home	15	(24.2)	23	(37.1)
Discharged Rehab	0		0	
Still Inpatient	15	(24.2)	0	
Median Length of Admission	18	(13 – 29)		

<u>S7</u>

A binary logistic regression model of factors predictive of death at 120 days constructed for patients for full escalation *from the point of diagnosis of pneumomediastinum* is presented in Table 2 of the main manuscript. A similar model examining the predictive utility of variables *over the course of admission* is presented below. Presenting this model separately is done (i) to include *radiographic progression* in predictive modelling as this variable is not available at the point of diagnosis and (ii) to demonstrate the dominance of mechanical ventilation as a predictor of mortality when considered across patients' admissions.

<u>Table S7.</u> Binary Logistic Regression Model of factors most predictive of death at 120 days *over the course of admission* for patients eligible for mechanical ventilation (n=315). All variables significantly associated with mortality in univariate analyses were entered into the model stepwise, backwards. The model produces prediction accuracy for outcome of 75.2% versus a 51.1% default accuracy.

	B (SE)	Odds Ratio or % increase per unit with 95% CI		p
Mechanical ventilation	5.01 (1.03)	150.3	(20.1 - 1125.0)	< .001
Age	-0.54 (0.14)	5.3 % per year	(2.7 – 7.8)	< .001
Diabetes mellitus	0.71 (0.38)	2.0	(1.0 – 4.3)	0.06

Variable entry into model stepwise backward. Model R^2 = 0.484 Nagelkerke χ^2 (4) = 142.1   p < .001. Constant B(SE) = 1.46 (0.88) Variables in the regression model but not listed, Radiographic Progression (p = .103). Variables not included in the model hypertension, IHD/LVSD and subcutaneous emphysema

62 patients whose treatment was limited to CPAP support were analyzed separately with respect to factors associated with outcome. The following four factors were associated with increased risk of death at 120 days in univariate analysis for this group: HFNO (OR in favor of death versus oxygen 22.2, 95% CI 1.2 – 408.1, p = .04); CPAP (OR versus oxygen 4.2 , 95% CI 1.0 – 17.7, p = .05); IHD/LVSD (OR 9.8, 95% CI 1.2 – 81.2, p = 0.03) and subcutaneous emphysema (OR 3.8, 95% CI 1.3 – 11.3, p = 0.02). Notably, increasing age was *not* one of the variables associated with increased risk of death in this older subgroup. The four significantly associated variables in the univariate analyses (listed above) were entered into the regression model below.

Table S7. Binary Logistic Regression Model of factors most predictive of death at 120 days *over the course of admission* for patients whose treatment was limited to CPAP support. (n = 62). This model produces prediction accuracy for outcome of 78.3% versus a 65.0% default accuracy.

	B (SE)	Odds Ratio or % increase per unit with 95% CI		p
Subcutaneous emphysema	1.66 (0.74)	5.2	(1.2 – 22.2)	0.03

Variable entry into model stepwise backward. R^2 = 0.533 Nagelkerke. Model χ^2 (1) = 29.36, p < .001. Constant B(SE) = - 0.23 (0.47) Variables in the regression but not listed CPAP (p = .09). Variables not included in the model HFNO, IHD/LVSD.

Figures 9a and 9b. Axial and coronal slice of thoracic CT of a mechanically ventilated patient from the cohort with COVID-19 pneumonitis, pneumomediastinum and massive subcutaneous emphysema
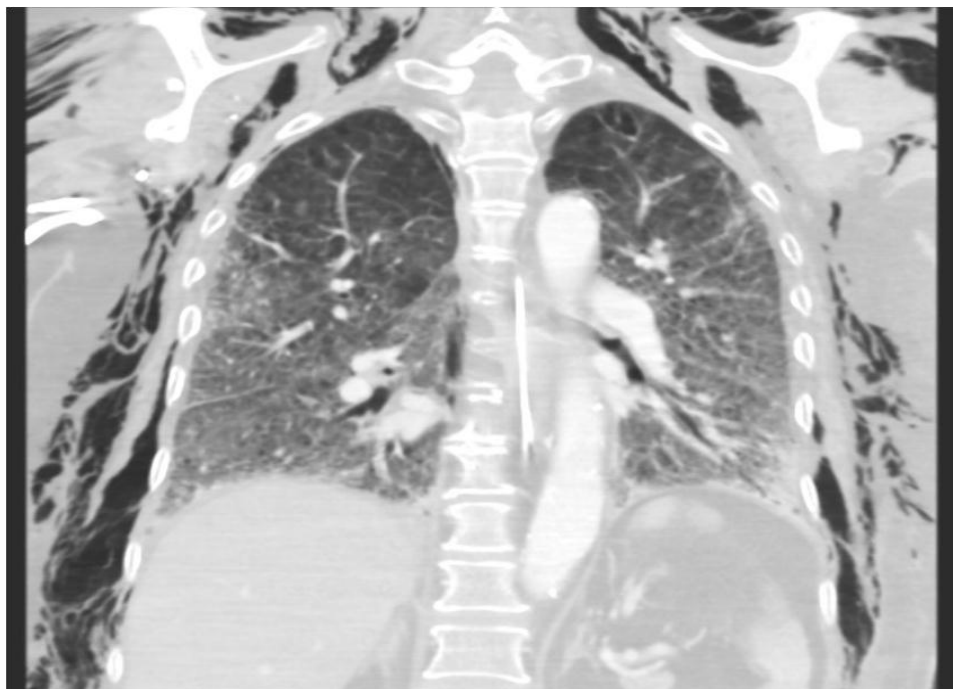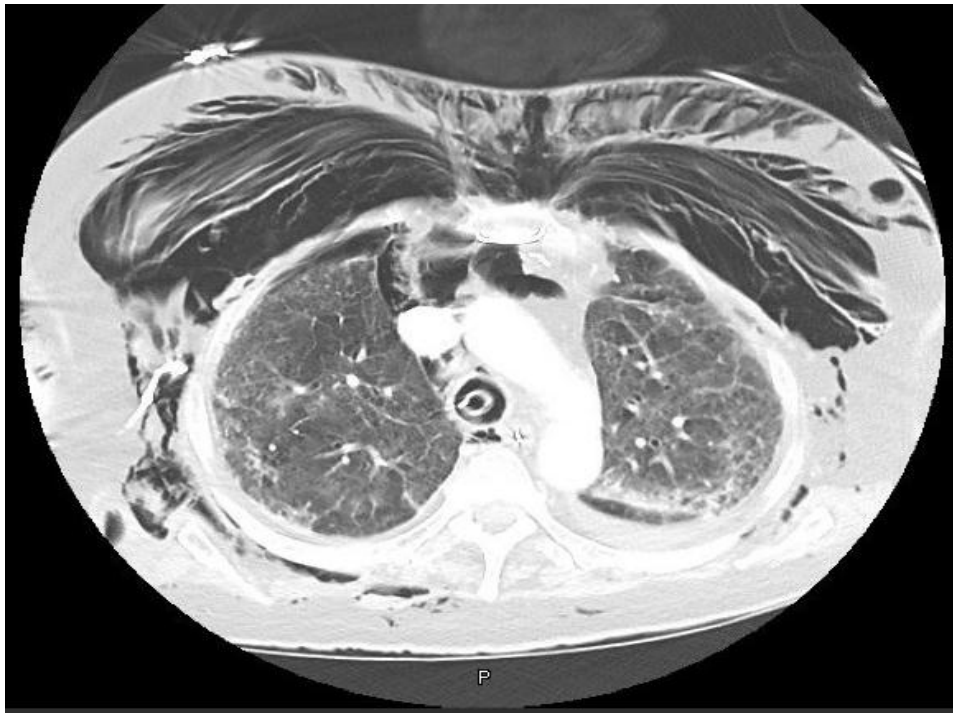
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