

COVID-19 Pneumothorax in the United Kingdom: a prospective observational study using the ISARIC WHO clinical characterisation protocol

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Take home message: Population level data from 131,679 patients show that COVID-19 pneumothorax occurs in 0.97% of admitted patients, especially males and smokers, and is associated with increased mortality.

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50 *To the Editor:*

51 Pneumothorax is an important complication of COVID-19 (1, 2). Based on a series of 60 individuals,
52 we previously estimated that 0.91% of people admitted to hospital with COVID-19 develop
53 pneumothorax (1). Males accounted for three quarters of those affected, and patients requiring non-
54 invasive or invasive ventilatory support appeared at elevated risk. In a separate series of ventilated
55 patients with COVID-19, barotrauma, defined as pneumothorax or pneumomediastinum, was found
56 to be an independent risk for death (2). During the pandemic, treatment strategies have evolved,
57 influenced by large randomised controlled trials and clinical experience. Following the landmark
58 results from the RECOVERY trial (3), dexamethasone became standard of care for patients
59 requiring supplemental oxygen. Following the first UK wave between March to June 2020, use of
60 non-invasive respiratory support became more common (4, 5). Such changes could plausibly alter
61 the incidence of pneumothorax caused by COVID-19. Indeed, a recent small study reported an
62 increase in pneumothoraces in the second wave of COVID-19 in Italy, speculating that
63 dexamethasone use might have been causal (6).

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65 To examine COVID-19 pneumothorax at a population level during the first and second waves in the
66 UK, we analysed data from the International Severe Acute Respiratory and emerging Infections
67 Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK). The study is being
68 performed by the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C) in 311
69 hospitals across England, Scotland, and Wales (National Institute for Health Research Clinical
70 Research Network Central Portfolio Management System ID 14152)(7). Approval was granted by
71 the following Ethics Committees: South Central-Oxford (Ref 13/SC/0149), Scotland (Ref
72 20/SS/0028), and WHO (RPC571, RPC572). Routine health data collation did not require consent.

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74 From its activation on 17th January 2020 to 15th February 2021, 131,679 patients aged ≥18 years
75 were recruited to CCP-UK if they were admitted to hospital with a positive SARS-CoV-2 PCR or
76 were considered highly clinically likely to have COVID-19. Of these, 1,283 (0.97%) had a
77 pneumothorax at some stage during their admission; 68.5% (879/1,283) of those with a

pneumothorax were male (Fig 1A). Taking 15th August as the boundary between the first and second waves of the pandemic, 56.1% (720) of pneumothoraces occurred during the first wave with an overall incidence of 1.01% (720/70,969). During the first 6 months of the second wave, the incidence of pneumothorax was not significantly different at 0.93% (563/60,710, $p=0.12$).

The incidence of pneumothorax differed between groups defined by the level of respiratory support they received. In patients requiring no supplemental oxygen, only 0.16% (60/37,030) had a pneumothorax; of those requiring oxygen without pressure support 0.56% (396/70,609) had pneumothoraces; treatment with non-invasive respiratory support alone was associated with an incidence of 0.96% (137/14,251); while significantly more patients (6.1%, 195/3,182) who received invasive ventilation also had a pneumothorax ($p=0.004$)(Fig 1B). Patients who received both non-invasive respiratory support and invasive ventilation had the highest incidence of pneumothorax at 8.5% (491/5,749, $p<0.0001$). It is noteworthy that despite an overall similar incidence of pneumothoraces during the first and second waves, the incidence of pneumothorax in patients who received both non-invasive respiratory support and invasive ventilation during their admission was lower in the first than the second wave (6.9% vs 11.2%, $p<0.001$)(Fig 1B). Among patients who did not receive corticosteroid treatment, 0.70% (598/85,961) developed a pneumothorax versus 1.46% (609/41,798) in those who did ($p<0.001$). Without steroids, pneumothoraces occurred in 4.94% (89/1,800) of patients who received invasive ventilation vs 6.31% (149/2,363) of patients who received both non-invasive respiratory support and invasive ventilation. Of patients treated with steroids, 7.57% (86/1,136) treated with invasive ventilation vs 10.36% (309/2,983) who received non-invasive respiratory support and invasive ventilation suffered pneumothoraces (Fig 1C). However, after adjusting for respiratory severity on admission (respiratory rate and peripheral oxygen saturation) and co-morbidities, corticosteroid therapy was not independently associated with increased incidence of pneumothorax either in critical care (intensive care unit, ICU, or high dependency unit, HDU) or non-critical care populations ($p = 0.20$ and 0.65 respectively).

In patients on non-critical care wards, asthma was not associated with pneumothorax after adjustment for age, sex and respiratory severity on admission, although “chronic pulmonary disease” (which includes chronic obstruction pulmonary disease, interstitial lung disease, and sarcoidosis) was associated with pneumothorax with an odds ratio (OR) of 1.80 (1.37-2.36, $p<0.001$)(Fig 1D). Former and current smokers were at increased risk: OR 1.44 (1.10-1.90, $p=0.009$) and 2.28 (1.60-3.22, $p<0.001$) respectively (Fig 1D). These associations did not translate to the critical care population where respiratory co-morbidities and smoking were not significant predictors of pneumothorax (Fig 1D). Restricting the analysis to patients not on pressure support, respiratory severity was not associated with increased risk of pneumothorax in both non-critical care and critical care populations.

In this series, pneumothorax with COVID-19 was associated with a worse prognosis. Adjusted for age, sex, and comorbidities, the OR for death was 2.94 (2.26-3.81; $p<0.001$) in non-critical care patients with pneumothorax compared to those without (Fig 1E). For critical care patients, the adjusted OR for death was 2.98 (2.47-3.60; $p<0.001$)(Fig 1F). Further analysis in both non-critical care and critical care populations showed that the OR of interaction terms between pneumothorax, age, sex and co-morbidities were not significant in predicting death. This suggests that the increased risk of death from pneumothorax was similar across subgroups.

There are several limitations to this study. The data collected from three London sites are excluded after 15th November 2020 due to unreliable classification of ICU patients. Inevitably, there are missing data, but the relatively low numbers are unlikely to impact the results. The case report form (CRF) of ISARIC does not request information on the timing of pneumothoraces and so we are unable to establish whether pneumothoraces occurred following the introduction of ventilatory support or if the presence of a pneumothorax resulted in respiratory deterioration requiring intubation. The CRF does not include history of previous pneumothorax nor treatment of pneumothorax. The CRF does not include pneumomediastinum, so we are unable to comment on this related complication. The lack of randomisation in any observational study makes attribution of

causality impossible. Therefore, we are unable to determine whether the increased incidence of pneumothorax in ventilated patients reflects severity of disease or is iatrogenic. In this regard, the RECOVERY-RS (Respiratory Support) trial may shed light on the relationship between ventilatory support and pneumothorax (8). The place of non-invasive respiratory support requires further study, since those who failed to respond to this and then required invasive ventilation appeared at greater risk of pneumothorax than those who underwent early intubation and mechanical ventilation.

Pneumothorax and pneumomediastinum have emerged as important complications of COVID-19 (1, 2, 9). Our previous smaller series suggested an incidence of 0.91% (1), similar to the 1.7% reported for SARS caused by SARS-CoV-1 (10). We now confirm using ISARIC data, which covers 40-45% of patients hospitalised for COVID-19 in England, Wales and Scotland, that 0.97% suffer a pneumothorax, but there are marked differences between subgroups. These may reflect disease severity, but we are unable to exclude an iatrogenic component. We report a clear association between incident pneumothorax and invasive mechanical ventilation. Pneumothorax had also been reported in patients with Middle East Respiratory Syndrome (MERS)-related coronavirus infection, and as with SARS, pneumothorax was a marker of poor prognosis (10, 11). Although in our previous small study we observed increased mortality only in patients >70 years of age, our current large series reveals that pneumothorax is independently associated with mortality over a wider age range.

In summary, we report data from the ISARIC4C study of 131,679 patients admitted with COVID-19 that reveal an overall incidence of pneumothorax of 0.97%. Male sex, smoking, chronic pulmonary disease and invasive ventilation were associated with increased risk of pneumothorax. Pneumothorax is associated with increased mortality in COVID-19.

Legend: COVID-19 pneumothorax in the ISARIC4C dataset.

(A) Histogram of incidence of pneumothoraces over time (absolute numbers, light grey females, dark grey males); line graph of pneumothorax incidence (percentage \pm 95% confidence interval). (B) Incidence of pneumothorax by age, ventilatory support and pandemic wave. (C) Incidence of

pneumothorax by age, ventilatory support and steroid therapy: NIV = non-invasive respiratory support. IMV = invasive respiratory support. (D) Demographics and risk factors for pneumothorax in non-critical care and critical care patients. Critical care patients include those admitted to an intensive care unit (ICU) or high dependency unit (HDU). Sample size for multivariable analysis was n = 61,046 and 10,719 for non-critical care and critical care populations respectively. (E) Risk factors for death in patients in non-critical care patients. (F) Risk factors for death in critical care patients.

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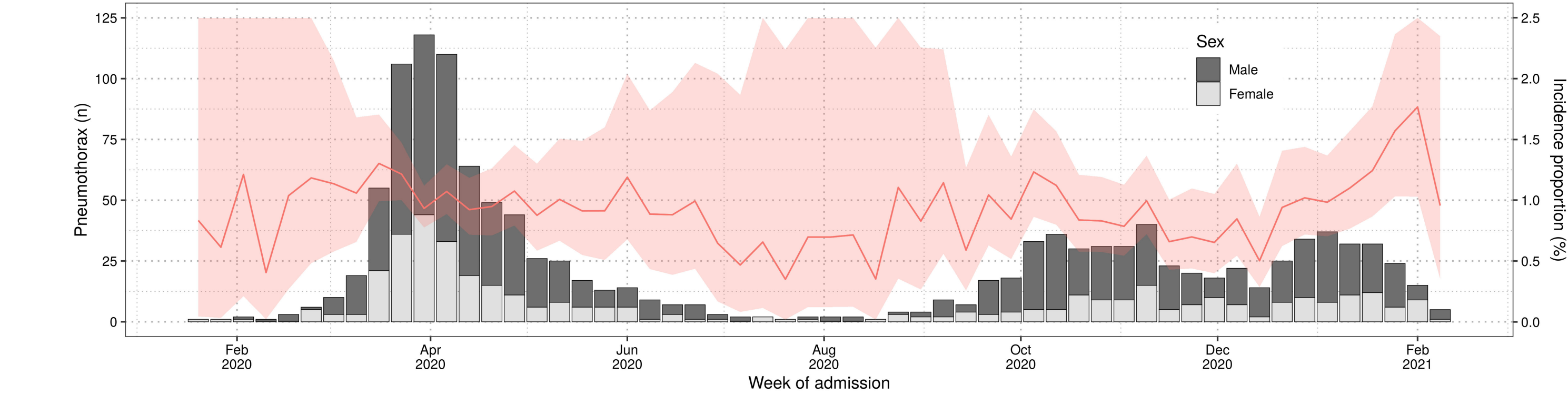
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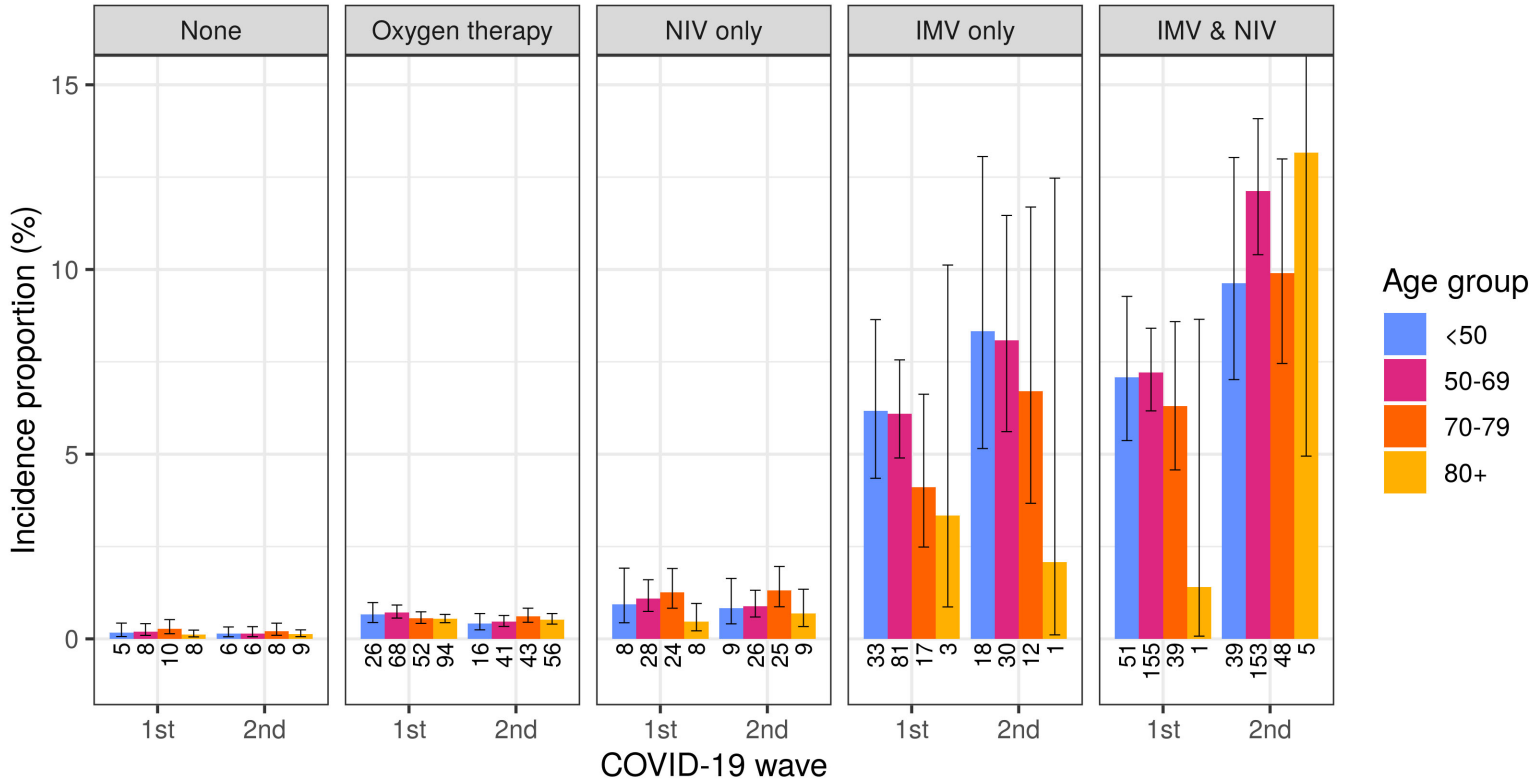
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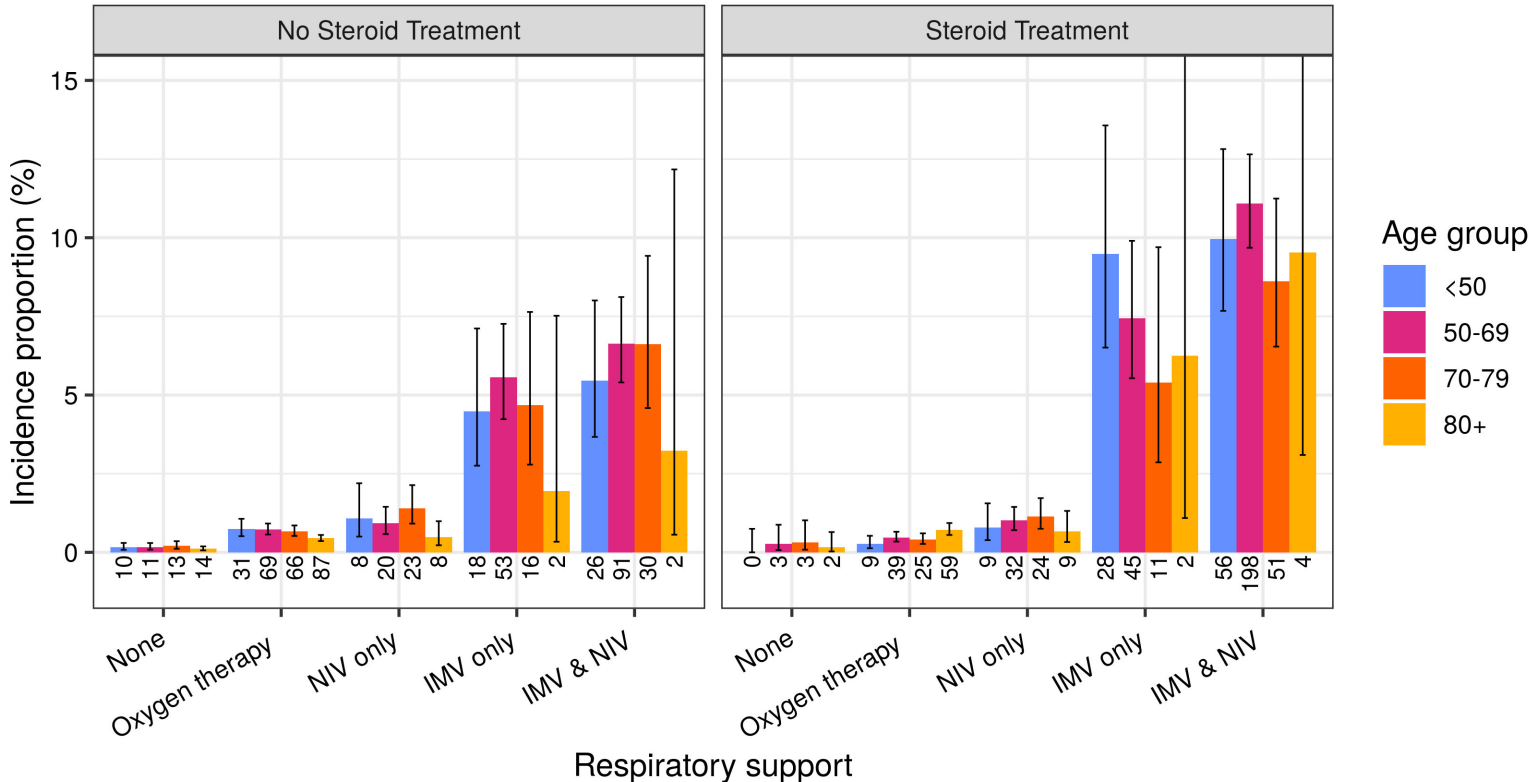
A Number of weekly pneumothorax cases and incidence



B Incidence of pneumothorax stratified by age group, respiratory support and COVID-19 wave
Numbers indicate pneumothorax cases



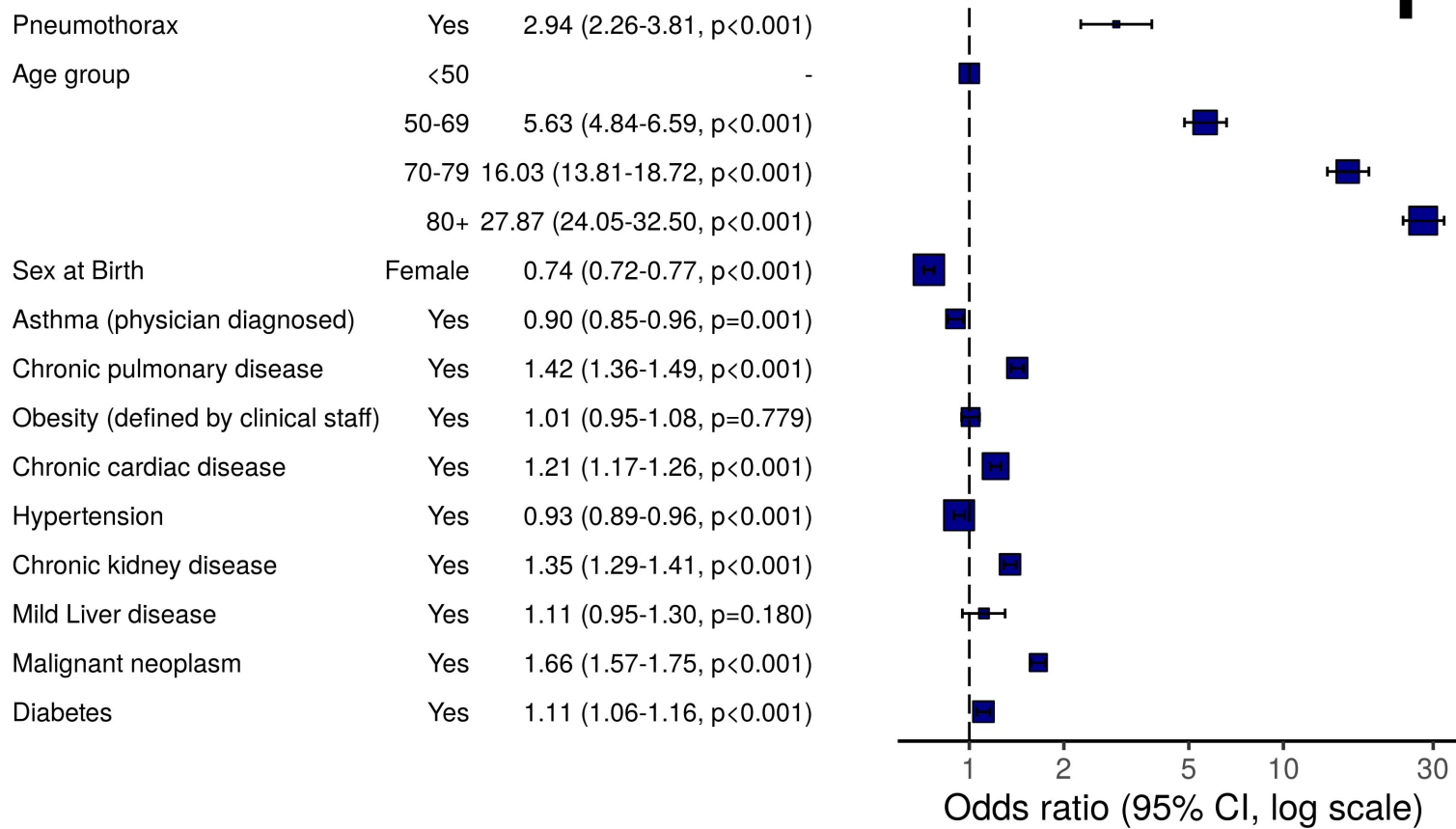
C Incidence of pneumothorax stratified by age group, respiratory support and steroid treatment
Numbers indicate pneumothorax cases



D Demographics and risk factors for patients with pneumothorax

		Non-Critical Care Patients				Critical Care Patients (ICU/HDU)			
Variable		Pneumothorax / Total	Incidence (%)	p-value	Multivariable OR (95% CI, p-value)	Pneumothorax / Total	Incidence (%)	p-value	Multivariable OR (95% CI, p-value)
Age group	< 50	43 / 15,162	0.28	0.011	-	168 / 3,689	4.55	<0.001	-
	50-69	124 / 28,153	0.44		1.32 (0.88-2.03, p=0.185)	472 / 9,039	5.22		1.23 (0.97-1.57, p=0.096)
	70-79	127 / 25,894	0.49		1.10 (0.71-1.73, p=0.688)	151 / 3,654	4.13		0.97 (0.72-1.31, p=0.852)
	80+	173 / 44,574	0.39		1.08 (0.71-1.67, p=0.735)	23 / 1,271	1.81		0.63 (0.36-1.04, p=0.083)
Sex at Birth	Male	300 / 60,417	0.50	<0.001	-	577 / 11,824	4.88	0.017	-
	Female	167 / 53,366	0.31		0.66 (0.51-0.84, p=0.001)	237 / 5,829	4.07		0.83 (0.67-1.01, p=0.069)
Asthma (physician diagnosed)	No	377 / 95,306	0.40	0.554	-	636 / 14,303	4.45	0.197	-
	Yes	64 / 14,798	0.43		1.03 (0.73-1.42, p=0.859)	143 / 2,849	5.02		1.01 (0.79-1.29, p=0.912)
Chronic pulmonary disease	No	291 / 90,583	0.32	<0.001	-	709 / 15,311	4.63	0.085	-
	Yes	155 / 19,781	0.78		1.80 (1.37-2.36, p<0.001)	67 / 1,807	3.71		0.89 (0.65-1.20, p=0.464)
Smoking	Never Smoked	115 / 34,531	0.33	<0.001	-	297 / 6,515	4.56	0.404	-
	Former Smoker	136 / 24,141	0.56		1.44 (1.10-1.90, p=0.009)	206 / 4,128	4.99		1.13 (0.93-1.38, p=0.223)
	Smoker	60 / 6,428	0.93		2.28 (1.60-3.22, p<0.001)	36 / 882	4.08		1.02 (0.70-1.45, p=0.910)
Respiratory rate (breaths/min)	< 20	160 / 44,855	0.36	0.004	-	146 / 3,463	4.22	0.029	-
	20-29	226 / 52,794	0.43		1.03 (0.80-1.34, p=0.806)	374 / 8,527	4.39		0.89 (0.70-1.14, p=0.336)
	30+	71 / 12,522	0.57		1.06 (0.70-1.55, p=0.790)	259 / 4,915	5.27		0.98 (0.75-1.28, p=0.865)
Peripheral oxygen saturation (%)	92+	356 / 91,980	0.39	0.003	-	473 / 10,644	4.44	0.090	-
	< 92	99 / 18,189	0.54		0.96 (0.70-1.30, p=0.803)	313 / 6,227	5.03		1.04 (0.86-1.26, p=0.685)

E Death (non-critical care): OR (95% CI, p-value, n = 73,832)



F Death (critical care): OR (95% CI, p-value, n = 11,174)

