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COVID-19 associated pneumothorax - A multicentre critical care experience from Qatar.

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Title: COVID-19 associated pneumothorax - A multicentre critical care experience from Qatar.

Running Title: COVID-19 associated pneumothorax.

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Abbreviations:

ALT - alanine transaminase, APACHE II - Acute Physiology and Chronic Health Evaluation II, ARDS - Acute respiratory distress syndrome, AST - aspartate aminotransferase, BiPap - bilevel positive airway pressure, BMI – Body Mass Index, CAD - Coronary Artery Disease, COPD - Chronic Obstructive Pulmonary Disease, COVID-19 - Coronavirus disease of 2019, CPAP - Continuous positive airway pressure, CPAP with PS - Continuous positive airway pressure with pressure support, CRP - C-reactive protein, CT - computerized tomography, CVA - Cerebrovascular accident, ECCO 2 R - Extracorporeal carbon dioxide removal, ECMO - extracorporeal membrane oxygenation, gm/dl- grams per deciliter, gm/L – gram per liter, HFNC - High-flow nasal cannula, HGH - Hamad General Hospital, HMC - Hamad Medical Corporation, HMGH - Hazm Mebaireek General Hospital, HTN – Hypertension, ICU - Intensive care Unit, IL-6 - Interleukin 6, Interquartile range -IQR, IV - Invasive ventilation, MENA - Middle East and North Africa, mg/dL - milligrams per liter, mmol/L - millimoles per liter, n- number, NC - Nasal Cannula, ng/ml - nanograms per milliliter, NGT - Nasogastric

tube, NIV - Non-invasive ventilation, NRBM - Non-re-breather mask, PaO2/FIO2 - Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration, PEEP - Positive End-Expiratory Pressure, pg/ml - picograms per milliliter, PTB - Pulmonary Tuberculosis, RT-PCR - reverse transcriptase polymerase chain reaction, SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2, SOFA - Sequential Organ Failure Assessment, Standard deviation – SD, T2DM – Type 2 Diabetes Mellitus, TV - Tidal volume, U/L – Units per liter, uL – millimeter, umol/L - micromoles per liter, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, WBC - white blood count, XR – X-ray

Abstract

objectives:

To study the prevalence, incidence, characteristics, treatment, associated risk factors, and outcome of COVID-19 associated pneumothorax in ICU.

design:

Retrospective observational data review.

setting:

Multicentre study, including intensive care unit of three tertiary care hospitals in Qatar.

participants:

1788 patients with COVID-19 pneumonia requiring ICU admission from 01/03/2020 to 01/11/2020 were enrolled in this study.

interventions:

not applicable.

primary and secondary outcome measures:

The primary endpoint was to identify the incidence and prevalence of COVID-19 associated pneumothorax in patients requiring ICU admission. Secondary endpoints were to determine the associated risk factors, treatment, mortality, and morbidity.

results:

1788 patients from 3 centers were reviewed in the study. The total episodes of pneumothorax were 85. The incidence rate of COVID-19 related pneumothorax in ICU patients was 4.6%, whereas the prevalence was calculated as 4.7%. The majority of the subjects were male (n=82, 96.5%). The mean age was 54.5years (+/-12.4years). The majority of the subjects were nationals of South Asian countries and the Middle East and North Africa (MENA) regions. 51.7% (n=44) of the patients had no comorbidities before ICU admission. The recurrence rate was 8.2%. The median length of ICU stay was 28 days (21.5-46 days). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 35 days, with a median of 13 days. 43.5 % of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID-19 related pneumothorax was 55.3% (n= 47). The Odds of mortality in patients with COVID-19 pneumonia with pneumothorax were 10.14% (92% confidence interval 6.4-16.4, P<0.05) compared to those who did not develop pneumothorax.

conclusions:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission. It is associated with poor prognosis and outcome.

Trial registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Strengths and limitations:

- This is an extensive multicentre observational study with total cohort of 1788 patients, including subjects from MENA region.
- It provides extensive data on risk factors, ventilatory parameters, incidence, and prevalence of COVID-19 associated pneumothorax in a critical care setting.
- The limitations of our study stem from the study design being retrospective, observational.
- Despite an extensive review, there was some missing information when screening for risk factors of pneumothorax such as smoking history.

Background:

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can affect multiple organs of the body.[1] The most commonly involved organ system

is the respiratory system. The spectrum of pulmonary complications ranges from alveolar damage leading to pneumonia, acute respiratory distress syndrome (ARDS), or an effect on the coagulation cascade causing pulmonary infarction via thrombi and emboli [2].

Pneumothorax is one of the known pulmonary complications of COVID-19. The incidence of pneumothorax in COVID-19 is approximately 1% in patients requiring hospital admission and 2% in ICU admissions. [3–6]. The risk factors predisposing to the development of pneumothorax include advanced age, pre-existing lung disease, and mechanical ventilation. [6]

The underlying pathophysiology is unclear, but cyst formation in the diseased areas of the lungs may be a precipitating factor as the cysts can progress to bullae associated with the development of pneumothorax. [6] Cyst formation also occurs with barotrauma and is seen as a late consequence of ARDS [7]. Barotrauma is reported in 15% of patients with COVID-19 requiring invasive mechanical ventilation. [7] Barotrauma is considered an independent risk factor for death and is associated with a more extended hospital stay in patients with COVID-19. [7]

Some previous studies report that the development of pneumothorax is not an independent marker of poor prognosis. [8,9] The mortality rate of COVID-19 patients admitted to ICU is reported up to 39%.[7] There is a higher incidence of pneumothorax in critically ill COVID-19 patients with ARDS. This combination of patients with ARDS developing pneumothorax results in a prolonged hospital stay length and a high mortality rate of up to 80%. [10]

We carried out a multicentre retrospective study to establish the prevalence of pneumothorax in patients with COVID-19 requiring ICU admission in Qatar. The study also describes the characteristics, treatment, associated risk factors, and outcome of COVID-19 associated pneumothorax in Qatar.

Study Design and Methods:

This is a multicentre, retrospective study. Patients admitted to the ICU of Hamad General Hospital (HGH), Hazm Mebaireek General Hospital (HMGH), and Cuban hospital diagnosed with COVID-19 associated pneumothorax between 01/03/2020-01/11/2020 were identified from the patient registry and included in this study. Data was gathered retrospectively from the electronic health record system (Cerner™.)

Inclusion Criteria:

1. All patients 14 years and older were admitted to ICU with a diagnosis of COVID-19 and pneumothorax.
2. Confirmed COVID-19 status by a positive nasopharyngeal/oropharyngeal or tracheal aspirate positive for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR.)
3. Confirmation of pneumothorax by at least one imaging modality, including chest X-ray, point of care ultrasound, or chest CT scan.

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Exclusion Criteria:

1. Age less than 14 years old.
2. Indeterminate or negative RT-PCR for SARS-CoV-2.
3. COVID-19 diagnosis based on rapid antigen testing.
4. Any patient with a presumptive diagnosis of COVID-19 based on clinical diagnosis.
5. No clear evidence of pneumothorax on imaging.
6. Patients not admitted to ICU.

Outcomes:

Primary Outcome

1. To identify the incidence and prevalence of pneumothorax in patients with COVID-19 admitted to ICU in Qatar.

Secondary Outcome

1. To assess the risk factors associated with the development of pneumothorax in COVID-19 patients.
2. To assess the treatment of the disease.
3. To assess mortality and morbidity associated with developing pneumothorax.

Statistical analyses

Descriptive and summary statistics were used to describe the study cohort's socio-demographic parameters, with continuous variables presented as means (± standard deviation) or median (interquartile range) as appropriate. Categorical variables were presented as numbers (percentages). The Shapiro-Wilk tests analyzed the normality of the data. We used One-Way ANOVA (Welch's) for the parametric variables and Kruskal-Wallis for the non-parametric variables for the comparison. All data were analyzed using Jamovi version 1.2 (created in 2020, Sydney, Australia) (15)

Clinical Trial Registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient and public statement:

This is retrospective data review, so it was not possible to involve the patients or public in the design, or conduct or dissemination plans of our research.

Results:

Prevalence of pneumothorax in COVID-19 patients admitted to ICU:

Our cohort consisted of 1788 patients with COVID-19 requiring ICU admission from Mar 1, 2020, to Nov 1, 2020. 75 out of 1788 subjects developed pneumothorax. The total number of events was 85 due to recurrent episodes. Each episode was considered a separate event. Three of the episodes were post-traumatic and were incidentally found to have COVID-19,

so they were excluded from the analysis. Pneumothorax occurred in 4.7 % of the patients with COVID-19 pneumonia requiring ICU admission.

Demographic and Clinical Characteristics:

Majority of the subjects were male (n=82, 96.5%), with 3.35 %(n=3) female. The mean age was 54.5years (+/-12.4years). Majority of the subjects were of South East Asian ethnicity (Nepalese n=16/18.8%, Bangladeshi n=14/16.5%, Pakistani n=10/11.8%, Indian n=10/11.8% and Filipino n=10/11.8%). 17.6 % belonged to Middle East and North Africa (MENA) regions (Qatari n= 6/7.1%, Syrian n=4/4.7%, Sudan n=3/3.5% and Iranian n=2/2.4%) and 11.7% belongs to other ethnicities. [table.1]

The median height was 166cm and the mean body mass index (BMI) was 27. 51.7% (n=44) of the patients had no comorbidity prior to ICU admission. 25.9% (n=22) had type 2 diabetes mellitus (T2DM), another 25.9% (n=22) had hypertension (HTN), 3.5 % (3) had cerebrovascular accident (CVA) or coronary artery disease (CAD). Prior respiratory diseases were found in only 9.3 % (n=8) of patients. 5.9% (n=5) had asthma, 1.2% (n=1) had pulmonary tuberculosis (PTB) and 2.4 % (n=2) had chronic obstructive pulmonary disease (COPD). Only 5.9 % (n=5) of patients had malignancy. [**Table 1**]

Upon admission to ICU, the mean respiratory rate was 31.6 breaths/minutes; median FiO2 requirement was 75% (51-90%), median sequential organ failure assessment (SOFA) score was 2 (2-4), mean acute physiology and chronic health evaluation II (APACHE II) score of 8.8 (+/- 2.9) and the median pneumonia severity index was 76 (65-96). All patients had abnormal chest X-ray (XR) findings suggestive of COVID-19 pneumonia upon admission. 80% of the patients required inotropic support at some point during ICU stay. [**Table 1**]

97.6 % of patients required respiratory support before developing pneumothorax. This included supplemental oxygen, non-invasive ventilation (NIV), and invasive ventilation. 2.3% (n=2) patients were on room air when they developed pneumothorax, and they were shifted to ICU after the development of pneumothorax. Thus, pneumothorax incidence in patients with COVID-19 pneumonia requiring ICU admission was calculated as 4.6%, whereas the prevalence was 4.7%. [**Table 2**]

Respiratory support:

Most patients required more than one form of respiratory support, with bilevel positive airway pressure (BiPAP) (26.3%, n=20) being the most used form of non-invasive ventilation. 4.7% (n=4) were on NIV, and 80% (n=68) were mechanically ventilated when they developed pneumothorax. [**Table 3**]

The median tidal volume (tidal volume of 6 to 8ml per ideal body weight was used for each patient) was 400ml (350-420ml), mean plateau pressure was 26.4cm H2O (+/- 7.27cmH2O), median PEEP was 8 cm H2O (6-10cmH2O) and mean driving pressure was 17.3 cm H20 (+/- 5.19cm H2O). [**Table 4**]

The median time to develop pneumothorax from ICU admission was 15 days (6-23days) and was 23 days (14-34days) from the first Covid-19 PCR. Patients who were on NIV developed

pneumothorax between 1 to 5 days, with the median being 1. Whereas patients on invasive ventilation developed pneumothorax between 4 to 22 days, the median was 10 days. [**Table 4**]

After developing pneumothorax, all the patients required respiratory support, with 85.9% patients requiring invasive ventilation. Other 14.1% of patients required a different form of respiratory support [table.3]. The median Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration (PaO2/FiO2) at the time of admission to ICU was 81 (67.5-115), while median PaO2/FiO2 before developing pneumothorax was 122 (85.8 to 179). [**Table 4**]

Risk factors:

40% (n 34) of patients had one or more procedures (known to be associated with pneumothorax) done within 24hours of the development of pneumothorax. The most commonly performed procedure was internal jugular line insertion in 35.3%, intubation in 35.3%, followed by nasogastric tube (NGT) insertion in 16.2%, in 3%, subclavian venous line insertion in 3%, Veno-venous extracorporeal membrane oxygenation (VV-ECMO) cannulation in 1.5%, Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation in 1.5%, post-extubation while on extracorporeal membrane oxygenation (ECMO) in 1.5% and pleural tapping in 1.5% of patients. [**Table 5**]

Investigations done upon admission revealed mean neutrophil count of 9.8 x 10 3/uL(+/- 4.93), median neutrophil/lymphocyte ratio 10 (5.4-18), median platelets 237x10 3/uL, median haemoglobin 13.2 gm/dL(12.1-14.5 gm/dL), median D dimer 1.47 mg/L (0.68-6.47), mean fibrinogen 5.89 gm/L (SD+/-1.82gm/L), median IL6 94 pg/ml (21-96), CRP 145 mg/L (89.5-223), procalcitonin 0.4 ng/ml (0.13-1), lactic acid 1.7 mmol/L (1.2-2.3), median urea 6.1 mmol/L (4.1-8.5), median creatinine 75umol/L (64-96), median Sodium 136mmol/L (133-139), aspartate aminotransferase (AST) 49 U/L (35-77), alanine transaminase (ALT) 47U/L (32-77) and median bilirubin 10.5umol/L (8-19). [**table.6]**

Characteristics of the pneumothorax:

Pneumothorax occurred more on the right side (55.3%) than on the left side (28.2%). 16.5% of the pneumothoraxes occurred bilaterally. A chest tube was inserted for 81.2% (n 69), and others were managed conservatively. None of the patients required surgical intervention. When the chest tube was inserted, it was removed at a median of 8 days (4-17 days). The recurrence rate was 8.2%. The median length of ICU stay was 28 days (21.5-46 days). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 35 days, with a median of 13 days. After developing pneumothorax, the length of NIV ranged from 3.5 to 15 days, with a median of 4 days. Almost 43.5 % of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID 19 related pneumothorax was 55.3% (n47). [**table7]**

Mortality:

We compared both parametric and non-parametric variables based on mortality. The analysis found statistically significant difference in mortality on the basis of SOFA score. (f= 8.9062, p= 0.004), respiratory rate (f=7.1853, p=0.009), PEEP (f=4.3158, p=0.044), length of

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NIV before developing pneumothorax (f=13.1002, p=0.003), D-Dimer (f=4.05921, p=0.049), fibrinogen (f=5.35264, p=0.023), blood urea Nitrogen (f=6.1109, p= 0.016), developing pneumothorax while on invasive ventilation (f=8.5717, p=0.003) and use of vasopressor/inotropes during ICU stay (f=10.7830, p=0.001). **[Supplementary Table A and Table B]**

Discussion:

COVID-19 is a multiorgan disease, but respiratory involvement is the most common in severe disease. Any phenomenon that strains the respiratory system further can contribute to morbidity and mortality. Pneumothorax is a source of morbidity and mortality. This retrospective study is the most extensive to date on COVID-19 associated pneumothorax and, to the best of our knowledge, the only one with a sizable cohort from the Middle-East North Africa (MENA) region.

In our study, pneumothorax occurred in 4.9 % of the critically ill COVID-19 patients as 2.3% (n 2) patients were on room air when they developed pneumothorax and were shifted to ICU after developing pneumothorax. Therefore, the incidence rate of COVID-19 related pneumothorax is 4.6%, whereas the prevalence is 4.7%. The incidence rate of 4.6% is more than twice the previously reported rates. [3-6]

Most of the patients were male, similar to other studies [6]. Our population had diverse nationalities.

Most of our patient population was previously healthy. The median SOFA score of COVID-19 patients who developed pneumothorax was 2 (2-4) compared to a mean of 4.4 (+/- 4) in COVID-19 patients without pneumothorax. **[table. 8]** There was also a reported statistically significant difference in mortality based on the SOFA score. APACHE II score of 8.8 (+/- 2.9) in patients with pneumothorax compared to APACHE II score of 13.5 (+/-6.4) in patients without pneumothorax**. [table. 8]** This indicates that patients with COVID-19 can develop pneumothorax even in the presence of lower estimated mortality and even without evidence of multiorgan failure upon ICU admission. However, the mortality of patients who developed pneumothorax was higher than the comparison group.

All patients had abnormal chest XR findings, most of them having bilateral ground glass shadows upon admission to ICU. Most of the patients were on some form of respiratory support when they developed pneumothorax. The ventilatory setting was not available for all patients. However, the available data review indicates that except for the slightly higher driving pressure (17.3 cm H20 (+/-5.19cm H2O), other lung-protective ventilation strategies were not violated. This indicates that the risk of barotrauma in these patients is high even when lung-protective strategies were being applied while positively ventilating the patients. Multiple mechanisms can contribute to it, such as cyst formation due to barotrauma or as a late consequence of ARDS may play an important role. [6-7] Authors postulate that the elevated driving pressure may cause increased shear pressure on the alveolar wall, leading

to barotrauma.[10] The exact mechanism is still unclear and needs further investigation. There was also a statistically significant difference in mortality based on PEEP.

Procedures that are known to cause pneumothorax preceded 43.5% of the episodes within 24hrs of the event. Most of the pneumothorax occurred on the right side after right internal venous catheter insertion. This high number of possibly iatrogenic pneumothorax may reflect the poor performance under stressful conditions or limited operator expertise, given the pandemic's overwhelmed situation.

The neutrophil/lymphocyte ratio was found to be high in these patients indicating high physiological stress. Mean fibrinogen and median interleukin-6 (IL-6) were also elevated, most likely due to activation of the coagulation cascade and cytokine storm. To determine the association of this phenomenon with the development of pneumothorax needs further investigation.

A chest tube was inserted for most patients to manage pneumothorax, as seen in previous studies. [10] We demonstrated that in patients with COVID-19, associated pneumothorax requiring chest tube placement was not associated with higher mortality.

Almost 8.2% of the patients developed recurrent episodes, with one patient developing as many as four distinct episodes during ICU stay.

Median stay in ICU for all COVID-19 patients was reported as 5 days (2–9) by Eleanor M. Rees et al. [11]. This study showed that the length of ICU stay was longer than patients without pneumothorax (median of 28 days (21.5-46 days) vs. mean of 14 ± 20.5).**[table.8]** This reflects a prolonged ICU stay due to COVID-19 related pneumothorax. It may also indicate that patients with COVID-19 pneumonia are more prone to develop pneumothorax with prolonged ICU admission.

All patients required respiratory support after developing pneumothorax. The tracheostomy rate was 43.5 % compared to 29.72% in overall COVID-19 patients requiring ICU admission, as reported by Jesus Sancho [12].

In-hospital mortality in the patients with COVID-19 related pneumothorax was 55.3% compared to 0.28% of overall mortality associated with COVID-19 reported in Qatar [13]. The mortality rate in patients with COVID-19 pneumonia requiring ICU who did not develop pneumothorax is calculated as 13% (n=236). **[table 8]** The odds of mortality in patients with COVID-19 pneumonia with pneumothorax are 10.14 (92% confidence interval 6.4 to 16.4, P<0.05) compared to those who did not develop pneumothorax. This indicates pneumothorax as an independent risk factor associated strongly with mortality in patients with COVID-19 pneumonia requiring ICU admission.

This study indicates that the pneumothorax rate is higher in-patient requiring ICU admission, with associated higher mortality and prolonged hospital stay.

Our study does have some limitations. The limitations of our study stem from the study design being retrospective, observational. Despite an extensive review, there was some missing information when screening for risk factors of pneumothorax.

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Pneumothorax is a well-recognized complication of COVID-19 in critically ill patients, and it is related to poor prognosis. Therefore, all possible efforts should be made towards prevention and prompt recognition. The patient that is at risk includes male, those of southeast Asian origin, with abnormal chest XR findings upon admission, those requiring respiratory support upon admission, mechanically ventilated, prolonged ICU admission, those with high neutrophil/lymphocyte ratio, high CRP with evidence of cytokine storm and those undergoing procedures that may cause pneumothorax.

Xiao-hui Wang et al. demonstrated that protective ventilation strategies, use of neuromuscular blockers, and timely use of ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) combined with ultra-protective ventilation might play an essential role in the prevention of pneumothorax in critically ill patients with severe ARDS [10].

Interpretation/Conclusion:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission. It is associated with poor prognosis and outcome. Prevention, early recognition, and prompt treatment may improve survival.

Ethical statement:

This work is original, has not been, and is not considered for publication in any other Journal. All authors have reviewed and approved the final version of the manuscript. The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient consent:

As this study is retrospective data review, taking patient consent was not applicable.

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Data sharing statement:
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Guarantor statement:
Dr. Zohaib Yousaf takes responsibility for (is the guarantor of) the manuscript's content, including the data and analysis.

Contributorship statement:

JA: Principal investigator, conceptualization, methodology, literature review, data collection and interpretation, manuscript writing.

ZY: Literature review, methodology, conceptualization, data analysis and interpretation, manuscript writing, and critical review.

YM, MI: Literature review and data collection

AS: Data retrieval.

NK: Critical review and revisions in the manuscript.

All authors: Review and approval of the final manuscript.

References:

[1] Vishwajit Deshmukh, et al. Histopathological observations in COVID-19: a systematic review. Journal of Clinical pathology.

http://orcid.org/0000-0002-2002-5198

[2] Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020 Dec;69(12):1181-1189. doi: 10.1007/s00011-020-01401-6. Epub 2020 Sep 12. PMID: 32918567; PMCID: PMC7486586

[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513. doi:10.1016/S0140-6736(20)30211-7

[4] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475–481. doi:10.1016/S2213-2600(20)30079-5

[5] Yang F, Shi S, Zhu J, et al. analysis of 92 deceased patients with COVID-19. J Med Virol 2020. doi:10.1002/jmv.25891

[6] Anthony W. Martinelli, et al. COVID-19 and Pneumothorax: A Multicentre Retrospective Case Series. European Respiratory Journal 2020; DOI: 10.1183/13993003.02697-2020

[7] Georgeann McGuinness, et al. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. Jul 2 2020https: //doi.org/10.1148/radiol.2020202352

[8] Semagn Mekonnen Abat, et al. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis. PloS one, Published: Jul 10, 2020https://doi.org/10.1371/journal.pone.0235653

[9] Massa Zantah, Pneumothorax in COVID-19 disease- incidence and clinical characteristics, Respiratory Research volume 21, Article number: 236 (2020)

[10] Xiao-hui Wang, et al. High incidence and mortality of pneumothorax in critically Ill patients with COVID-19. Heart Lung. 2021 January-February; 50(1): 37–43. doi: 10.1016/j.hrtlng.2020.10.002

[11] Eleanor M. Rees, et al. COVID-19 length of hospital stays: a systematic review and data synthesis. BMC Medicine volume 18, Article number: 270 (2020)

[12] Sancho, J., Ferrer, S., Lahosa, C. *et al.* Tracheostomy in patients with COVID-19: predictors and clinical features. *Eur Arch Otorhinolaryngol* (2021). https://doi.org/10.1007/s00405-020-06555-x

[13] Ali S. Omrani, et al. The first consecutive 5000 patients with Coronavirus Disease 2019 from Qatar; a nation-wide cohort study. BMC Infectious Diseases volume 20, Article number: 777 (2020)

Tables:

Baseline characteristics	**Total (*N*=85)**
Age (Mean +/- SD) years	54.5+/- 12.4
Gender n (%) Male	 82 (96.5 %)

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Female	3 (3.35%)
Ethnicities n (%) Nepalese Bangladeshi Pakistani Indian Filipino Qatari Syrian Sudani American Indonesian Irani Others	 16 (18.8%) 14 (16.5%) 10 (11.8%) 10 (11.8%) 10 (11.8%) 6 (7.1%) 4 (4.7%) 3 (3.5%) 2 (2.4%) 2 (2.4%) 2 (2.4%) 6 (7.0%)
Height (Median IQR) cm	166 (165 to 170)
Weight (Median IQR) Kg	75 (65 to 85)
BMI (Mean +/- SD)	27 +/- 3.8
Comorbidities n (%) HTN T2DM CVA CAD COPD Asthma TB CKD HIV Malignancy	 22 (25.9%) 22 (25.9%) 3(3.5%) 3(3.5%) 2(2.4%) 5 (5.9%) 1 (1.2%) 3 (3.5%) 0 5 (5.9%)
Vitals at admission to ICU Temperature (Median IQR) Heart rate (Mean +/-SD) bpm MAP (Mean +/- SD) mmHg Respiratory rate (Median IQR) breaths/min Sofa score (Median IQR) Pneumonia severity index (Median IQR) APACHE II score (Mean +/-SD)	 36.9 (36.6 to 37.8) 102 +/- 20.7 93.2 +/- 13.5 31 (28 to 35) 2 (2 to 4) 76 (65 to 96) 8.8 (+/- 2.9)
Pneumonia on Chest XR N (%)	80 (94.1%)

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Inotrope use during ICU stay N (%)	74 (87.1)

Table 1. Demographics and clinical characteristics of patients with COVID-19 associated pneumothorax in ICU.

(n- number, MENA - Middle East and North Africa, BMI – Body mass index, T2DM – Type 2 diabetes mellitus, CVA – Cerebrovascular accident, CAD - Coronary artery disease, TB – Tuberculosis, COPD - Chronic obstructive pulmonary disease, SOFA - Sequential organ failure assessment, APACHE II - Acute physiology and chronic health evaluation II)

Supplementary oxygen uses before pneumothorax n (%)	83 (97.6%)
Types of oxygen delivery except for mechanical ventilation before pneumothorax	N 76
NC	10 (13.1%)
Face mask	4 (5.3%)
NRBM	27 (35.5%)
Venturi mask	2 (2.6%)
HFNC	7 (9.2%)
CPAP	2 (2.6%)
CPAP with PS	4 (5.3%)
BiPap	20 (26.3%)
Patient on IV who developed a pneumothorax n (%)	68 (80%)
Patients on NIV (BiPap) who developed pneumothorax n (%)	4 (4.7%)

Table 2. Respiratory support before developing pneumothorax

(NC – Nasal Cannula, NRBM - Non-re-breather mask, Venturi mask, HFNC - High-flow nasal cannula, CPAP - Continuous positive airway pressure, CPAP with PS - Continuous positive airway pressure with pressure support, NIV – Non-invasive ventilation, IV – Invasive ventilation, BiPap - bilevel positive airway pressure.)

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Supplementary oxygen uses after pneumothorax N (%)	85 (100%)
Types of oxygen delivery except for mechanical ventilation after pneumothorax NC NRBM HFNC CPAP	N 12 (14.1%) 6 (7.0%) 3 (3.5%) 1 (1.1%) 2 (2.3%)
Number of patients requiring IV after developing pneumothorax N (%)	73 (85.9%)

Table 3. Respiratory support after developing pneumothorax

(NC – Nasal Cannula, NRBM - Non-Re-Breather Mask, Venturi mask, HFNC - High-flow nasal cannula, CPAP - Continuous positive airway pressure)

Ventilatory setting in intubated patients before developing pneumothorax TV (Median IQR) Plateau pressure (Mean +/- SD) PEEP (Median IQR) Driving pressure (Mean +/-SD)	 400 (350 to 420) ml 26.4 +/- 7.27cmH2O 8 (6 to 10) cm H2O 17.3 +/-5.19 cm H2O
Length NIV before developing pneumothorax (Median IQR)	1 (1 to 5.5) days
Length of IV before developing pneumothorax (Median IQR)	10 (4 to 22) days
PaO2/FiO2 ratio on admission (Median IQR)	81 (67.5 to 115)

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PaO2/FiO2 before pneumothorax (Median IQR)	122 (85.8 to 179)

Table 4. Ventilator setting and PaO2/FiO2 before developing pneumothorax

(TV- Tidal volume, PEEP - positive end-expiratory pressure, PaO2/FIO2 - Pressure of arterial oxygen to fractional inspired oxygen concentration)

Number of patients who underwent procedures preceding pneumothorax	40% (n 34)
Number of procedure preceding pneumothorax	65
AV ECMO	1 (1.5%)
VV ECMO	1 (1.5%)
NGT insertion	11 (16.2%)
Tracheostomy	2 (3%)
internal jugular line insertion	23 (35.3%)
intubation	23 (35.3%)
post-extubation, while on ECMO	1 (1.5%)
subclavian central venous line insertion	2 (3 %)
therapeutic /diagnostic Pleural tapping	1 (1.5%)

Table 5. Procedures preceding pneumothorax in the last 24hrs

(NGT – Nasogastric tube, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, ECMO - extracorporeal membrane oxygenation)

Lab parameter	**Value**
WBC x 10 3/uL (mean +/- SD)	11.1 +/- 5.31

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Neutrophil x 10 3/uL (mean +/- SD)	9.81 +/- 4.93
Lymphocyte x 10 3/uL (median IQR)	0.8 (0.8-1.2)
Neutrophil/Lymphocyte (median IQR)	10.2 (5.4-18)
Platelets x 10 3/uL (median IQR)	237 (174-331)
Hemoglobin gm/dL (median IQR)	13.2 (12.1-14.5)
INR (median +IQR)	1.1 (1-1.2)
D dimer mg/L (median IQR)	1.47 (0.68-6.47)
Fibrinogen gm/L (mean +/- SD)	5.89 +/- 1.82
IL6 pg/ml (median IQR)	94 (21-96)
CRP mg/L (median IQR)	145 (89.5-223)
Procalcitonin ng/ml (median IQR)	0.4 (0.138-1)
Lactic acid mmol/L (median IQR)	1.7 (1.2-2.3)
Urea mmol/L (median +IQR)	6.1 (4.1-8.5)
Creatinine umol/L (median IQR)	75 (64-96)
Sodium mmol/L (median IQR)	136 (133-139)
AST U/L (median +IQR)	49 (35-77)
ALT U/L (median +IQR)	47 (32-77)
Bilirubin U/L (median IQR)	10.5(8-19)

Table 6. Investigations upon admission to ICU

(WBC – white blood count, AST - aspartate aminotransferase, ALT - alanine transaminase, IL6 – Interleukin-6, CRP – C-reactive protein, uL – millimeter, gm/dL- grams per deciliter, mg/dL - milligrams per liter, gm/L – gram per liter, IL-6 - Interleukin 6, pg/ml - picograms per milliliter, ng/ml - nanograms per milliliter, mmol/L - millimoles per liter, umol/L - micromoles per liter, U/L – Units per liter)

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Side of pneumothorax N (%) Bilateral Left Right	 14 (16.5%) 24 (28.2%) 47 (55.3%)
Chest tube insertion n (%)	69 (81.2%)
Duration of a chest tube (median IQR)	8 (4-17)
Recurrences n (%)	7 (8.2%)
Length of ICU stay (days) (median +IQR)	28 (21.5-46) days
Length of NIV after developing pneumothorax (days) (median IQR)	4 (3.5-15) days
Length of IV before developing pneumothorax (median IQR)	13 (6-35) days
Need for tracheostomy n (%)	37 (43.5 %)
Number of days in ICU before a pneumothorax (median IQR)	15 (6-23) days
Time elapsed from first COVID-19 PCR to development of pneumothorax (days) (median IQR)	23 (14-34) days
Time to negative COVID-19 PCR (days) (median IQR)	28 (24-42) days (maximum 138)
In-hospital mortality n (%)	47 (55.3%)

Table 7. Treatment and outcome of COVID-19 associated pneumothorax

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SOFA score	4.3 +/- 4
APACHE II score	13.5+/-6.4
Length of ICU stay (days) (mean +/- SD)	14+/- 20.5 days
In-hospital mortality n (%)	236 (13.1%)

Table 8. The outcome of patients with COVID-19 without pneumothorax

Supplementary tables

Variable	F	df1	df2	p
Age	2.58	1	81.95	0.112
Weight	1.25	1	82.05	0.266
Height	0.084	1	66.70	0.773
BMI	0.013	1	60.29	0.907
Vitals at admission to ICU				
Temperature	1.2503	1	72.72	0.267
Heart rate	0.6050	1	80.66	0.439
MAP	0.2757	1	82.20	0.601
Respiratory rate	0.0187	1	69.52	0.892
Pneumonia severity index	3.7453	1	82.97	0.056
Sofa score	8.9062	1	82.65	0.004
Vitals prior to developing pneumothorax				
Temperature	0.4178	1	38.46	0.522
Heart rate	3.5670	1	82.35	0.062
MAP	1.8560	1	81.64	0.177
Respiratory rate	7.1853	1	77.77	0.009
Ventilatory setting in intubated patients prior to developing pneumothorax				
TV	1.7641	1	41.87	0.191
Plateau pressure	0.5220	1	10.77	0.485
PEEP	4.3158	1	44.96	0.044
Driving pressure	1.0033	1	7.24	0.349
length of NIV before developing pneumothorax	13.1002	1	14.72	0.003

length of IV before developing pneumothorax	1.3650	1	40.88	0.249
PaO2/FiO2 ratio on admission	0.88810	1	65.9	0.349
PaO2/FiO2 before pneumothorax	3.30052	1	77.6	0.073
WBC x 10 3/uL	1.87817	1	83.0	0.174
Neutrophil x 10 3/uL	2.42496	1	82.9	0.123
Lymphocyte x 10 3/uL	0.10569	1	82.6	0.746
Neutrophil/Lymphocyte	0.02758	1	52.7	0.869
Platelets x 10 3/uL	0.58941	1	72.3	0.445
Hemoglobin gm/dL	0.03114	1	81.6	0.860
INR	1.90530	1	65.6	0.172
D dimer mg/L	4.05921	1	51.8	0.049
Fibrinogen gm/L	5.35264	1	73.9	0.023
IL6 pg/ml	1.15572	1	44.3	0.288
CRP mg/L	0.07510	1	80.3	0.785
Procalcitonin ng/ml	0.01634	1	77.4	0.899
Lactic acid mmol/L	2.85955	1	58.0	0.096
Urea mmol/L	6.11094	1	69.8	0.016
Creatinine umol/L	2.12994	1	46.9	0.151
Sodium mmol/L	0.00322	1	81.8	0.955
AST U/L	1.64645	1	48.4	0.206

ALT U/L	0.66233	1	53.4	0.419
Bilirubin U/L	0.22281	1	59.9	0.639
time of removal of chest tube	0.506	1	30.4	0.482
length of ICU stay	0.213	1	77.5	0.646
length of mechanical ventilation after developing pneumothorax	0.760	1	54.9	0.387
number of episodes of pneumothorax	0.809	1	60.0	0.372
Number of days in ICU before developing pneumothorax	0.213	1	69.9	0.646
Time elapsed from first COVID-19 PCR to development of pneumothorax (days	1.31	1	66.8	0.991
Time to negative COVID-19 PCR (days)	1.280	1	21.7	0.27

Table A. One-Way ANOVA (Welch's) for compared parametric variables based on mortality.

variable	χ^2	df	p
Ethnicity	0.8997	1	0.343
Supplementary oxygen requirement before developing pneumothorax	2.5035	1	0.114
Number of patients requiring non-invasive ventilation before developing pneumothorax	1.5247	1	0.217
Number of patients requiring invasive ventilation before developing pneumothorax	8.5717	1	0.003
Number of patients requiring non-invasive ventilation before developing pneumothorax	0.1608	1	0.688
Number of patients requiring invasive ventilation after developing pneumothorax	17.0786	1	< .001
Inotrope use during ICU stay	10.7830	1	0.001
side of pneumothorax	2.1571	1	0.142
Comorbidities			
HTN	0.8258	1	0.363
T2DM	1.9709	1	0.160
CVA	0.1608	1	0.688
CAD	0.5996	1	0.439
COPD	2.5035	1	0.114
Asthma	0.0470	1	0.828

TB CKD Malignancy	1.2368 0.1608 0.0470	1 1 1	0.266 0.688 0.828
Treatment of pneumothorax	1.0501	1	0.305
need for tracheostomy	0.4545	1	0.500
recurrent	0.0444	1	0.833

Table B. One-Way ANOVA (Kruskal-Wallis) for compared non-parametric variables based on mortality.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-8
		(*b*) Report category boundaries when continuous variables were categorized	5-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiological and outcome analysis of COVID-19 associated pneumothorax - A multicentre retrospective critical care experience from Qatar.

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1

Title: Epidemiological and outcome analysis of COVID-19 associated pneumothorax - A multicentre retrospective critical care experience from Qatar.

Running Title: COVID-19 associated pneumothorax.

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Abbreviations:

ALT - alanine transaminase, APACHE II - Acute Physiology and Chronic Health Evaluation II, ARDS - Acute respiratory distress syndrome, AST - aspartate aminotransferase, BMI – Body Mass Index, CAD - Coronary Artery Disease, COPD - Chronic Obstructive Pulmonary Disease, COVID-19 - Coronavirus disease of 2019, CRP - C-reactive protein, CT - computerized tomography, CVA - Cerebrovascular accident, ECCO 2 R - Extracorporeal carbon dioxide removal, ECMO - extracorporeal membrane oxygenation, gm/dl- grams per decilitre, gm/L – gram per litre, HGH - Hamad General Hospital, HMC - Hamad Medical Corporation, HMGH - Hazm Mebaireek General Hospital, HTN – Hypertension, ICU - Intensive care Unit, IL-6 - Interleukin 6, Interquartile range -IQR, IV - Invasive ventilation, MENA - Middle East and North Africa, mg/dL - milligrams per litre, mmol/L - millimoles per litre, n- number, ng/ml - nanograms per millilitre, NGT - Nasogastric tube, NIV - Non-invasive ventilation, PaO2/FIO2 - Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration, PEEP - Positive End-Expiratory Pressure, pg/ml - picograms per millilitre, PTB - Pulmonary Tuberculosis, RT-

PCR - reverse transcriptase polymerase chain reaction, SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2, SOFA - Sequential Organ Failure Assessment, Standard deviation – SD, T2DM – Type 2 Diabetes Mellitus, TV - Tidal volume, U/L – Units per litre, uL – millimetre, umol/L - micromoles per litre, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, WBC - white blood count, XR – X-ray

Abstract

Objectives:

To study the incidence, characteristics, treatment, associated risk factors and outcome of COVID-19 associated pneumothorax in ICU.

Design:

Retrospective observational data review.

Setting:

Multicentre study, including intensive care units of three tertiary care hospitals in Qatar.

Participants:

1788 patients with COVID-19 pneumonia requiring ICU admission from 01/03/2020 to 01/11/2020 were enrolled in this study.

Interventions:

Not applicable.

Primary and secondary outcome measures:

The primary endpoint was to identify the incidence of COVID-19 associated pneumothorax in patients requiring ICU admission. Secondary endpoints were to determine the associated risk factors, treatment, mortality, and morbidity.

Results:

1788 patients from 3 centres were reviewed in the study. The total episodes of pneumothorax were 75. Pneumothorax occurred in 4.1 % of the patients with COVID-19 pneumonia requiring ICU admission. The majority of the subjects were male (n=72, 96%).

The mean age was 55.1 (+/- 12.7 years). Majority of the subjects were nationals of South Asian countries and the Middle East and North Africa (MENA) regions. 52% (n=32) of the patients were previously healthy without co-morbidities before ICU admission. The recurrence rate was 9.3%. The median length of ICU stay was 28 days (20.5-45.8 days). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 32 days, with a median of 13 days. 44% of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID-19 related pneumothorax was 53.3% (n= 40). The odds of mortality in patients with COVID-19 pneumonia with pneumothorax is 7.15 (95% confidence interval 4.45 to 11.48, P<0.0001) compared to those who did not develop pneumothorax. This indicates pneumothorax is a potential independent risk factor associated with mortality in patients with COVID-19 pneumonia requiring ICU admission.

conclusions:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission. It is associated with poor prognosis and outcome.

Trial registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Strengths and limitations:

- This is an extensive multicentre observational study with total cohort of 1788 patients, including subjects from MENA region.
- It provides extensive data on the demographics, risk factors, morbidity and mortality of pneumothorax in critically ill COVID-19 patients.
- The limitations of our study stem from the study design being retrospective, observational study.
- It is not a comparative study between critically ill COVID-19 patients with or with out pneumothorax.
- Despite an extensive review, there was some missing information when screening for risk factors of pneumothorax such as smoking history.

Background:

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can affect multiple organs of the body.[1] The most commonly involved organ system is the respiratory system. The spectrum of pulmonary complications ranges from alveolar damage leading to pneumonia, acute respiratory distress syndrome (ARDS), or an effect on the coagulation cascade causing pulmonary infarction via thrombi and emboli [2].

Pneumothorax is one of the known pulmonary complications of COVID-19. The incidence of pneumothorax in COVID-19 is approximately 1% in patients requiring hospital admission and 2% in ICU admissions. [3–6]. The risk factors predisposing to the development of pneumothorax include advanced age, pre-existing lung disease, and mechanical ventilation. [6]

The underlying pathophysiology is unclear, but cyst formation in the diseased areas of the lungs may be a precipitating factor as the cysts can progress to bullae associated with the development of pneumothorax. [6] Cyst formation also occurs with barotrauma and is seen as a late consequence of ARDS [7]. Barotrauma is reported in 15% of patients with COVID-19 requiring invasive mechanical ventilation. [7] Barotrauma is considered an independent risk factor for death and is associated with a more extended hospital stay in patients with COVID-19. [7]

We have conflicting data regarding association of pneumothorax with mortality in COVID-19 patients, with older studies reporting that the development of pneumothorax is not an independent marker of poor prognosis, but evolving evidence is in the favour of association of pneumothorax with high mortality. [8,9,10] The mortality rate of COVID-19 patients admitted to ICU is reported up to 39%.[7] There is a higher incidence of pneumothorax in critically ill COVID-19 patients with ARDS. This combination of patients with ARDS developing pneumothorax results in a prolonged hospital stay length and a high mortality rate of up to 80%. [11] Data from ISARIC4C study concludes that pneumothorax is associated with increased mortality in COVID-19. [10]

We carried out a multicentre retrospective study to establish the prevalence of pneumothorax in patients with COVID-19 requiring ICU admission in Qatar. The study also describes the characteristics, treatment, associated risk factors, and outcome of COVID-19 associated pneumothorax in Qatar.

Study Design and Methods:

This is a multicentre, retrospective study. Patients admitted to the ICU of Hamad General Hospital (HGH), Hazm Mebaireek General Hospital (HMGH), and Cuban hospital diagnosed with COVID-19 associated pneumothorax between 01/03/2020-01/11/2020 were identified from the patient registry and included in this study. Data was gathered retrospectively from the electronic health record system (Cerner™.)

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Inclusion Criteria:

1. All patients 14 years and older were admitted to ICU with a diagnosis of COVID-19 and pneumothorax.
2. Confirmed COVID-19 status by a positive nasopharyngeal/oropharyngeal or tracheal aspirate positive for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR.)
3. Confirmation of pneumothorax by at least one imaging modality, including chest X-ray, point of care ultrasound, or chest CT scan.

Exclusion Criteria:

1. Age less than 14 years old.
2. Indeterminate or negative RT-PCR for SARS-CoV-2.
3. COVID-19 diagnosis based on rapid antigen testing.
4. Any patient with a presumptive diagnosis of COVID-19 based on clinical diagnosis.
5. No clear evidence of pneumothorax on imaging.
6. Patients not admitted to ICU.

Outcomes:

Primary Outcome

1. To identify the incidence and prevalence of pneumothorax in patients with COVID-19 admitted to ICU in Qatar.

Secondary Outcome

1. To assess the risk factors associated with the development of pneumothorax in COVID-19 patients.
2. To assess the treatment of the disease.
3. To assess mortality and morbidity associated with developing pneumothorax.

Statistical analyses

Descriptive and summary statistics were used to describe the study cohort's socio-demographic parameters, with continuous variables presented as means (± standard deviation) or median (interquartile range) as appropriate. Categorical variables were presented as numbers (percentages). The Shapiro-Wilk tests analyzed the normality of the data. We used One-Way ANOVA (Welch's) for the parametric variables and Kruskal-Wallis for the non-parametric variables for the comparison. All data were analyzed using Jamovi version 1.2 (created in 2020, Sydney, Australia) (15)

Clinical Trial Registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient and public statement:

No Patient and Public Involvement

This is retrospective data review, so it was not possible to involve the patients or public in the design, or conduct or dissemination plans of our research.

Results:

Prevalence of pneumothorax in COVID-19 patients admitted to ICU:

Our cohort consisted of 1788 patients with COVID-19 requiring ICU admission from Mar 1, 2020, to Nov 1, 2020. 75 out of 1788 subjects developed pneumothorax. Three of the episodes were post-traumatic and were incidentally found to have COVID-19, so they were excluded from the analysis. Pneumothorax occurred in 4.1 % of the patients with COVID-19 pneumonia requiring ICU admission.

Demographic and Clinical Characteristics:

Majority of the subjects were male (96%) with 4% female. The mean age was 55.1 years (+/- 12.7 years). Majority (72%) of the subjects were of Southern and Southeast Asian ethnicity. 17.3 % belonged to Middle East and North Africa (MENA) regions and 10.7% belongs to other ethnicities. [**table.1**]

The median height was 168cm (164 to 170cm) and the mean body mass index (BMI) was 27.2kg/m2 (+/- 3.9kg/m2). Majority (52%) of the patients had no comorbidity prior to ICU admission. 29.3% had type 2 diabetes mellitus (T2DM), another 21% had hypertension (HTN), 4% had cerebrovascular accident (CVA) or coronary artery disease (CAD). Prior respiratory diseases were found in only 9.3% of patients. 6.7% had asthma, 1.3% had pulmonary tuberculosis (PTB) and 1.3 % had chronic obstructive pulmonary disease (COPD). Only 6.7 % of patients had malignancy. [**Table 1**]

Upon admission to ICU, the median respiratory rate was 30 breaths/minutes, median Pao2/FiO2 was 81 (67.5 to 130), median sequential organ failure assessment (SOFA) score was 2 (2-4), mean acute physiology and chronic health evaluation II (APACHE II) score of 8.8 (+/- 2.9) and the median pneumonia severity index was 76 (65-96). All patients had abnormal chest X-ray (XR) findings suggestive of COVID-19 pneumonia upon admission. 97.3% of the patients required inotropic support at some point during ICU stay. All patient received intra venous antibiotics, steroids and anti-viral therapy during their ICU stay. [**Table 1**]

97.3 % of patients required respiratory support before developing pneumothorax. This included supplemental oxygen, non-invasive ventilation (NIV), and invasive ventilation. 2.% (n=2) patients were on room air when they developed pneumothorax, and they were shifted to ICU after the development of pneumothorax. Thus, pneumothorax incidence in patients with COVID-19 pneumonia requiring ICU admission was calculated as 4.08%. [**Table 2**]

Respiratory support:

Most patients required more than one form of respiratory support. 13.3% (n=10) were on NIV, where as 80% (n=60) were mechanically ventilated when they developed pneumothorax. [**Table 2**]

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After developing pneumothorax, all the patients required respiratory support, with 86.7% patients requiring invasive ventilation. Remaining 13.3% of patients required different forms of respiratory support [table.3]. The median Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration (PaO2/FiO2) before developing pneumothorax was 122 (84 to 179). [**Table 3, 4**]

The median tidal volume (tidal volume of 6 to 8ml per ideal body weight was used for each patient) was 400ml (358-420ml), mean plateau pressure was 26.4cm H2O (+/- 4.27cmH2O), median PEEP was 8 cm H2O (6-10cmH2O) and mean driving pressure was 17.3 cm H20 (+/- 5.19cm H2O). [**Table 4**]

The median time to develop pneumothorax from ICU admission was 15 days (6-23 days) and was 21 days (13.5-32 days) from the first Covid-19 PCR. Patients who were on NIV developed pneumothorax between 3.5 to 15 days, with the median being 4. Whereas patients on invasive ventilation developed pneumothorax between 6 to 32 days, the median was 13 days. [**Table 4**]

Risk factors:

45.3% (n=34) of patients had one or more procedures (known to be associated with pneumothorax) done within preceding 24hours of the development of pneumothorax. The most commonly performed procedures were internal jugular line insertion and intubation with a frequency of 35.3% each. Detailed list of the procedures is provided in table 5. **[Table 5]**

Investigations done upon admission revealed mean neutrophil count of 9.68 x 10 3/uL(+/- 5.13), median neutrophil/lymphocyte ratio 10 (5.25-18), median platelets 236x10 3/uL (174-325), median haemoglobin 13.2 gm/dL(12.1-14.5 gm/dL), median D dimer 1.47 mg/L (0.69-6.65), mean fibrinogen 5.89 gm/L (+/-1.82), median IL6 97 pg/ml (31.5-33), CRP 146 mg/L (87-232), procalcitonin 0.45 ng/ml (0.145-1), lactic acid 1.7 mmol/L (1.2-2.3), median urea 6.1 mmol/L (4.2-8.7), median creatinine 75 umol/L (64-99), median Sodium 136 mmol/L (133-139), aspartate aminotransferase (AST) 49 U/L (34-76), alanine transaminase (ALT) 47 U/L (32-74) and median bilirubin 10 umol/L (8-17.6). **[table.6]**

Characteristics of the pneumothorax:

Pneumothorax occurred more on the right side (56%) than on the left side (28%). Whereas pneumothorax occurred bilaterally in 16% of patients. Chest tube was inserted for 78.7%% (n=59) and others were managed conservatively. None of the patients required surgical intervention. When the chest tube was inserted, it was removed at a median of 8 days (4-18 days). The recurrence rate was 9.3%. The median length of ICU stay was 28 days (20.5-45.8). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 35 days, with a median of 13 days. After developing pneumothorax, the length of NIV ranged from 3.5 to 15 days, with a median of 4 days, with length of IV ranging from 6 to 32 days, with median of 13 days. Almost 44 % of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID 19 related pneumothorax was 53.3% (n=40). **[table7]**

Mortality:

We compared both parametric and non-parametric variables based on mortality in patients with COVID 19 related pneumothorax requiring ICU admission. The analysis found statistically significant difference in mortality on the basis of SOFA score (f= 6.32, p= 0.014), respiratory rate (f=7.26, p=0.008), PEEP (f=5.234, p=0.027), D-Dimer (f=4.1, p=0.049), fibrinogen (f=5.358, p=0.023), blood urea Nitrogen (f=5.714, p= 0.020), developing pneumothorax while on invasive ventilation (f=5.2857, p=0.022), need for invasive ventilation after developing pneumothorax (f=13.01, p=<0.001), use of vasopressor/inotropes during ICU stay (f=8.5893, p=0.003) and when procedures known to cause pneumothorax were being performed within 24hrs preceding development of pneumothorax. **[Supplementary Table A and Table B]**

Outcome parameters of patient with critically ill COVID-19 patients without pneumothorax

Although our study is primarily not a comparative study. Some of the outcome parameters for the critically ill COVID-19 patients who did not develop pneumothorax were calculated for a comparison and better understanding of the association. For the patients who were admitted to ICU with COVID-19 and they did not develop pneumothorax, the mean SOFA score was 4.3 (+/-4), APACHE II score 13.5 (+/-6.4), mean length of ICU stay was 14days (+/-20.5 days) and in hospital mortality was 13.1% (n=236). **[Table. 1, 7]**

Discussion:

COVID-19 is a multiorgan disease, but respiratory involvement is the most common in severe disease. Any phenomenon that strains the respiratory system further can contribute to morbidity and mortality. Pneumothorax is a source of morbidity and mortality. This is an extensive retrospective study on COVID-19 associated pneumothorax in critically ill patients and to the best of our knowledge, one of the very few studies with a sizable cohort from the Middle-East North Africa (MENA) region.

In our study, pneumothorax occurred in 4.1 % of the critically ill COVID-19 patients. As 2.6% (n=2) patients were on room air when they developed pneumothorax and were shifted to ICU after developing pneumothorax. Therefore, the incidence rate of COVID-19 related pneumothorax was calculated as 4.08%, which is almost twice as high as previously reported incidence rates. [3-6]

Most of the patients were male, similar to other studies [6]. Our population had diverse nationalities.

Most of our patient population was previously healthy. The mean SOFA score of COVID-19 patients who developed pneumothorax was 2.92 (+/-1.75) compared to a mean of 4.3 (+/-4) in COVID-19 patients without pneumothorax. **[table. 1]** Whereas, the mean APACHE II score of 8.8 (+/- 2.9) in patients with pneumothorax compared to mean APACHE II score of

13.5 (+/-6.4) in patients without pneumothorax**. [table. 1]** This indicates that patients with COVID-19 can develop pneumothorax even in the presence of lower estimated mortality and even without evidence of multiorgan failure upon ICU admission. However, the mortality of patients who developed pneumothorax was higher than the comparison group.

All patients had abnormal chest XR findings, most of them having bilateral ground glass shadows upon admission to ICU. Most of the patients were on some form of respiratory support when they developed pneumothorax. The ventilatory setting was not available for all patients. However, the available data review indicates that except for the slightly higher driving pressure (17.3 cm H20 (+/-5.19cm H2O), other lung-protective ventilation strategies were not violated. This indicates that the risk of barotrauma in these patients is high even when lung-protective strategies were being applied while positively ventilating the patients. Multiple mechanisms can contribute to it, such as cyst formation due to barotrauma or as a late consequence of ARDS may play an important role. [6-7] Authors postulate that the elevated driving pressure may cause increased shear pressure on the alveolar wall, leading to barotrauma.[10] The exact mechanism is still unclear and needs further investigation. There was also a statistically significant difference in mortality based on PEEP.

Procedures that are known to cause pneumothorax preceded 45.3% of the events within 24hrs of the event. Most of the pneumothorax occurred on the right side after right internal venous catheter insertion. This high number of possibly iatrogenic pneumothorax may reflect the poor performance under stressful conditions or limited operator expertise, given the pandemic's overwhelmed situation.

The neutrophil/lymphocyte ratio was found to be high in these patients indicating high physiological stress. Mean fibrinogen and median interleukin-6 (IL-6) were also elevated, most likely due to activation of the coagulation cascade and cytokine storm. Further studies are needed to determine the association of this phenomenon with the development of pneumothorax.

Chest tube was inserted for most patients to manage pneumothorax, as seen in previous studies. [10] We demonstrated that in patients with COVID-19, associated pneumothorax requiring chest tube placement was not associated with higher mortality.

Almost 9.3% of the patients developed recurrent episodes, with one patient developing as many as four distinct episodes during ICU stay.

Median stay in ICU for all COVID-19 patients was reported as 5 days (2–9) by Eleanor M. Rees et al. [12]. Our study showed a longer median length of stay of 28 days (20.5 to 45.8) for critically ill patients with COVID 19 related pneumothorax. When compare to patients without pneumothorax the length of ICU stay was longer in patients who developed pneumothorax (mean of 39.2 +/- 32.9 days vs. mean of 14 +/- 20.5 days). [**table. 7]** This reflects a prolonged ICU stay due to COVID-19 related pneumothorax. It may also indicate that patients with COVID-19 pneumonia are more prone to develop pneumothorax with prolonged ICU admission.

All patients required respiratory support after developing pneumothorax. The tracheostomy rate was 44% compared to 29.72% in overall COVID-19 patients requiring ICU admission, as reported by Jesus Sancho [13].

In-hospital mortality in the patients with COVID-19 related pneumothorax was 53.3%. The mortality rate in patients with COVID-19 pneumonia requiring ICU who did not develop pneumothorax was calculated as 13% (n=236). **[table. 7]** The odds of mortality in patients with COVID-19 pneumonia with pneumothorax are 7.15 (95% confidence interval 4.4 to 11.4, P<0.0001) compared to those who did not develop pneumothorax. This indicates pneumothorax as a potential independent risk factor associated with mortality in patients with COVID-19 pneumonia requiring ICU admission.

This study indicates that the pneumothorax rate is higher in-patient requiring ICU admission, with associated higher mortality and prolonged hospital stay.

Our study does have some limitations. The limitations of our study stem from the study design being retrospective and observational study. Despite an extensive review, there was some missing information when screening for risk factors of pneumothorax.

Pneumothorax is a well-recognized complication of COVID-19 in critically ill patients, and it is related to poor prognosis. Therefore, all possible efforts should be made towards prevention and prompt recognition. The patient that is at risk includes male, those of southeast Asian origin, with abnormal chest XR findings upon admission, those requiring respiratory support upon admission, mechanically ventilated, prolonged ICU admission, those with high neutrophil/lymphocyte ratio, high CRP with evidence of cytokine storm and those undergoing procedures that may cause pneumothorax.

Xiao-hui Wang et al. demonstrated that protective ventilation strategies, use of neuromuscular blockers, and timely use of ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) combined with ultra-protective ventilation might play an essential role in the prevention of pneumothorax in critically ill patients with severe ARDS [11].

Interpretation/Conclusion:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission. It is associated with poor prognosis and outcome. Prevention, early recognition, and prompt treatment may improve survival.

Ethical statement:

This work is original, has not been, and is not considered for publication in any other Journal. All authors have reviewed and approved the final version of the manuscript. The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient consent:

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As this study is retrospective data review, taking patient consent was not applicable.

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Data sharing statement:
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Guarantor statement:
Dr. Zohaib Yousaf takes responsibility for (is the guarantor of) the manuscript's content, including the data and analysis.

Contributorship statement:

Dr Jaweria Akram (JA): Principal investigator, conceptualization, methodology, literature review, data collection and interpretation, manuscript writing.

Dr Zohaib Yousaf (ZY): Literature review, methodology, conceptualization, data analysis and interpretation, manuscript writing, and critical review.

Dr Yasir Mustafa Alabbas (YM) and Dr Mustafa Ibrahim Abdullah Almoyaaf (MI): Literature review and data collection

Dr Abdus Salam Saif Ibrahim (AS): Data retrieval.

Dr Nadir Kharma (NK): Critical review and revisions in the manuscript.

All authors: Review and approval of the final manuscript.

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References:

[1] Vishwajit Deshmukh, et al. Histopathological observations in COVID-19: a systematic review. Journal of Clinical pathology.

http://orcid.org/0000-0002-2002-5198

[2] Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020 Dec;69(12):1181-1189. doi: 10.1007/s00011-020-01401-6. Epub 2020 Sep 12. PMID: 32918567; PMCID: PMC7486586

[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513. doi:10.1016/S0140-6736(20)30211-7

[4] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475–481. doi:10.1016/S2213-2600(20)30079-5

[5] Yang F, Shi S, Zhu J, et al. analysis of 92 deceased patients with COVID-19. J Med Virol 2020. doi:10.1002/jmv.25891

[6] Anthony W. Martinelli, et al. COVID-19 and Pneumothorax: A Multicentre Retrospective Case Series. European Respiratory Journal 2020; DOI: 10.1183/13993003.02697-2020

[7] Georgeann McGuinness, et al. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. Jul 2 2020https: //doi.org/10.1148/radiol.2020202352

[8] Semagn Mekonnen Abat, et al. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis. PloS one, Published: Jul 10, 2020https://doi.org/10.1371/journal.pone.0235653

[9] Massa Zantah, Pneumothorax in COVID-19 disease- incidence and clinical characteristics, Respiratory Research volume 21, Article number: 236 (2020)

[10] Stefan J. Marcinia, et al. COVID-19 pneumothorax in the UK: a prospective observational study using the ISARIC WHO clinical characterisation protocol. European Respiratory Journal Sep 2021, 58 (3) 2100929; DOI: 10.1183/13993003.00929-2021

[11] Xiao-hui Wang, et al. High incidence and mortality of pneumothorax in critically Ill patients with COVID-19. Heart Lung. 2021 January-February; 50(1): 37–43. doi: 10.1016/j.hrtlng.2020.10.002

[12] Eleanor M. Rees, et al. COVID-19 length of hospital stays: a systematic review and data synthesis. BMC Medicine volume 18, Article number: 270 (2020)

[13] Sancho, J., Ferrer, S., Lahosa, C. *et al.* Tracheostomy in patients with COVID-19: predictors and clinical features. *Eur Arch Otorhinolaryngol* (2021). https://doi.org/10.1007/s00405-020-06555-x

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Tables:

	COVID-19 associated pneumothorax	**COVID-19 not associated with pneumothorax**
Baseline characteristics	**Total *N*=75**	**N= 1713**
Age (Mean +/- SD) years	55.1 (+/- 12.7)	NA
Gender n (%) Male Female	 72 (96%) 3 (4%)	NA
Ethnicities n (%) Nepalese Bangladeshi Pakistani Indian Filipino Qatari Syrian	 14 (18.7%) 10 (13.3%) 9 (12%) 10 (13.3%) 10 (13.3%) 6 (8%) 2 (2.6%)	NA

Sudani American Indonesian Irani Others	3 (4%) 2 (2.7%) 1 (1.3%) 2 (2.7%) 6 (8%)	
Height (Median IQR) cm	168 (164 to 170)	NA
Weight (Median IQR) Kg	75 (65 to 85)	NA
BMI (Mean +/- SD) kg/m2	27.2 (+/- 3.9)	NA
Comorbidities n (%) HTN T2DM CVA CAD COPD Asthma TB CKD HIV Malignancy	 22 (29.3%) 21 (28%) 3 (4%) 3 (4%) 1 (1.3%) 5 (6.7%) 1 (1.3%) 3 (4%) 0 (0%) 5 (6.7%)	NA
Vitals at admission to ICU Temperature (Median IQR) Heart rate (Mean +/-SD) bpm MAP (Mean +/- SD) mmHg Respiratory rate (Median IQR) breaths/min Sofa score (Median IQR) Sofa score (Mean +/-SD) Pneumonia severity index (Median IQR) APACHE II score (Mean +/-SD)	 36.9 (36.6 to 37.8) 101 (+/- 21.3) 93.1 (+/- 14.1) 30 (26 to 34) 2 (2 to 4) 2.92 (+/-1.75) 77 (65 to 96) 8.8 (+/- 2.9)	 NA NA NA NA NA 4.3 (+/- 4) NA 13.5 (+/-6.4)
Pneumonia on Chest XR n (%)	70 (93.3%)	NA
Inotrope use during ICU stay n (%)	73 (97.3%)	NA

Table 1. Demographics and clinical characteristics of patients with COVID-19 associated pneumothorax in ICU and without pneumothorax.

(n- number, MENA - Middle East and North Africa, BMI – Body mass index, T2DM – Type 2 diabetes mellitus, CVA – Cerebrovascular accident, CAD - Coronary artery disease, TB – Tuberculosis, COPD - Chronic obstructive pulmonary disease, SOFA - Sequential organ failure assessment, APACHE II - Acute physiology and chronic health evaluation II)

Supplementary oxygen uses before pneumothorax n (%)	73 (97.3%)
Patient on IV who developed a pneumothorax n (%)	60 (80%)
Patients on NIV who developed pneumothorax n (%)	10 (13.3%)

Table 2. Respiratory support before developing pneumothorax

(NIV – Non-invasive ventilation, IV – Invasive ventilation)

Supplementary oxygen uses after pneumothorax N (%)	75 (100%)
Number of patients requiring NIV after developing pneumothorax N (%)	3 (4%)
Number of patients requiring IV after developing pneumothorax N (%)	65 (86.7%)

Table 3. Respiratory support after developing pneumothorax

Ventilatory setting in intubated patients before developing pneumothorax	

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TV (Median IQR) Plateau pressure (Mean +/- SD) PEEP (Median IQR) Driving pressure (Mean +/-SD)	400 (358 to 420) ml 26.4 (+/- 4.27) cmH2O 8 (6 to 10) cm H2O 17.3 (+/-5.19) cm H2O
Length NIV before developing pneumothorax (Median IQR)	1 (1 to 2) day
Length of IV before developing pneumothorax (Median IQR)	9 (4 to 21) days
PaO2/FiO2 ratio on admission (Median IQR)	81 (67.5 to 130)
PaO2/FiO2 before pneumothorax (Median IQR)	122 (84 to 179)

Table 4. Ventilator setting and PaO2/FiO2 before developing pneumothorax

(TV- Tidal volume, PEEP - positive end-expiratory pressure, PaO2/FIO2 - Pressure of arterial oxygen to fractional inspired oxygen concentration)

Number of patients who underwent procedures with in preceding 24hrs before developing pneumothorax n (%)	34 (45.3%)
Number of procedure preceding pneumothorax	65
AV ECMO VV ECMO NGT insertion Tracheostomy internal jugular line insertion intubation post-extubation, while on ECMO subclavian central venous line insertion	1 (1.5%) 1 (1.5%) 11 (16.2%) 2 (3%) 23 (35.3%) 23 (35.3%) 1 (1.5%) 2 (3 %)

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therapeutic /diagnostic Pleural tapping	1 (1.5%)

Table 5. Procedures preceding pneumothorax in the last 24hrs

(NGT – Nasogastric tube, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, ECMO - extracorporeal membrane oxygenation)

Lab parameter	Value
WBC x 10 3/uL (mean +/- SD)	11.1 (+/- 5.53)
Neutrophil x 10 3/uL (mean +/- SD)	9.68 (+/- 5.13)
Lymphocyte x 10 3/uL (median IQR)	0.8 (0.5-1.2)
Neutrophil/Lymphocyte (median IQR)	10 (5.25-18)
Platelets x 10 3/uL (median IQR)	236 (174-325)
Hemoglobin gm/dL (median IQR)	13.2 (12.1-14.5)
INR (median +IQR)	1.1 (1-1.2)
D dimer mg/L (median IQR)	1.47 (0.69-6.65)
Fibrinogen gm/L (mean +/- SD)	5.89 +/- 1.89
IL6 pg/ml (median IQR)	97 (31.5-33)
CRP mg/L (median IQR)	146 (87-232)
Procalcitonin ng/ml (median IQR)	0.45 (0.145-1)
Lactic acid mmol/L (median IQR)	1.7 (1.2-2.3)
Urea mmol/L (median +IQR)	6.1 (4.2-8.7)
Creatinine umol/L (median IQR)	75 (64-99)
Sodium mmol/L (median IQR)	136 (133-139)
AST U/L (median +IQR)	49 (34-76)
ALT U/L (median +IQR)	47 (32-74)

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Bilirubin U/L (median IQR)	10 (8-17.6)

Table 6. Investigations upon admission to ICU

(WBC – white blood count, AST - aspartate aminotransferase, ALT - alanine transaminase, IL6 – Interleukin-6, CRP – C-reactive protein, uL – millimeter, gm/dL- grams per deciliter, mg/dL - milligrams per liter, gm/L – gram per liter, IL-6 - Interleukin 6, pg/ml - picograms per milliliter, ng/ml - nanograms per milliliter, mmol/L - millimoles per liter, umol/L - micromoles per liter, U/L – Units per liter)

Outcome/treatment	**COVID-19 associated pneumothorax**	**COVID-19 not associated with pneumothorax**
Side of pneumothorax N (%) Bilateral Left Right	 12 (16%) 21 (28%) 42 (56%)	NA
Chest tube insertion n (%)	59 (78.7%)	NA
Duration of a chest tube (Median IQR)	8 (4-18)	NA
Recurrences n (%)	7 (9.3%)	NA
Length of ICU stay (days) (Median +IQR) (Mean+/-SD)	 28 (20.5-45.8) days 39.2 (+/-32.9) days	 14(+/- 20.5) days
Length of NIV after developing pneumothorax (days) (Median IQR)	4 (3.5-15) days	NA
Length of IV after developing pneumothorax (Median IQR)	13 (6-32) days	NA
Need for tracheostomy	33 (44%)	NA

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n (%)		
Number of days in ICU before developing pneumothorax (median IQR)	15 (6-23) days	NA
Time elapsed from first COVID-19 PCR to development of pneumothorax (days) (Median IQR)	21 (13.5-32) days	NA
Time to negative COVID-19 PCR (days) (Median IQR)	28 (24-42) days (maximum 138)	NA
In-hospital mortality n (%)	40 (53.3%)	236 (13.1%)

Table 7. Treatment, outcome of COVID-19 associated pneumothorax and outcome of patients with COVID-19 without pneumothorax

Supplementary tables

Variable	F	df1	p
Sofa score	6.32	1	0.014
Respiratory rate prior to developing pneumothorax	7.26	1	0.008
PEEP in intubated patients prior to developing pneumothorax	5.234	1	0.027
D dimer mg/L	4.1	1	0.049
Fibrinogen gm/L	5.358	1	0.023
Urea mmol/L	5.714	1	0.020

Table A. One-Way ANOVA (Welch's) for compared parametric variables based on mortality.

variable	χ^2	df	p
Number of patients requiring invasive ventilation before developing pneumothorax	5.2857	1	0.022
Number of patients requiring invasive ventilation after developing pneumothorax	13.0110	1	< .001
Inotrope/ vasopressor use during ICU stay	8.5893	1	0.003
Procedures known to cause pneumothorax preceding pneumothorax	7.9488	1	0.005

Table B. One-Way ANOVA (Kruskal-Wallis) for compared non-parametric variables based on mortality.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-8
		(*b*) Report category boundaries when continuous variables were categorized	5-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiological and outcome analysis of COVID-19 associated pneumothorax - A multicentre retrospective critical care experience from Qatar.

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Title: Epidemiological and outcome analysis of COVID-19 associated pneumothorax - A multicentre retrospective critical care experience from Qatar.

Running Title: COVID-19 associated pneumothorax.

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COVID-19, incidence, mortality, critical care unit, pneumothorax

Abbreviations:

ALT - alanine transaminase, APACHE II - Acute Physiology and Chronic Health Evaluation II, ARDS - Acute respiratory distress syndrome, AST - aspartate aminotransferase, BMI – Body Mass Index, CAD - Coronary Artery Disease, COPD - Chronic Obstructive Pulmonary Disease, COVID-19 - Coronavirus disease of 2019, CRP - C-reactive protein, CT - computerized tomography, CVA - Cerebrovascular accident, ECCO 2 R - Extracorporeal carbon dioxide removal, ECMO - extracorporeal membrane oxygenation, gm/dl- grams per decilitre, gm/L – gram per litre, HGH - Hamad General Hospital, HMC - Hamad Medical Corporation, HMGH - Hazm Mebaireek General Hospital, HTN – Hypertension, ICU - Intensive care Unit, IL-6 - Interleukin 6, Interquartile range -IQR, IV - Invasive ventilation, MENA - Middle East and North Africa, mg/dL - milligrams per litre, mmol/L - millimoles per litre, n- number, ng/ml - nanograms per millilitre, NGT - Nasogastric tube, NIV - Non-invasive ventilation, PaO2/FIO2 - Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration, PEEP - Positive End-Expiratory Pressure, pg/ml - picograms per millilitre, PTB - Pulmonary Tuberculosis, RT-

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PCR - reverse transcriptase polymerase chain reaction, SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2, SOFA - Sequential Organ Failure Assessment, Standard deviation – SD, T2DM – Type 2 Diabetes Mellitus, TV - Tidal volume, U/L – Units per litre, uL – millimetre, umol/L - micromoles per litre, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, WBC - white blood count, XR – X-ray

Abstract

Objectives:

To study the incidence, characteristics, treatment, associated risk factors, and outcome of COVID-19 associated pneumothorax in ICU.

Design:

Retrospective observational data review.

Setting:

A multicentre study from intensive care units of three tertiary care hospitals in Qatar.

Participants:

1788 patients with COVID-19 pneumonia requiring ICU admission from 01/03/2020 to 01/11/2020 were enrolled in this study.

Interventions:

Not applicable.

Primary and secondary outcome measures:

The primary endpoint was to identify the incidence of COVID-19 associated pneumothorax in patients requiring ICU admission. Secondary endpoints were to determine the associated risk factors, treatment, mortality, and morbidity.

Results:

1788 patients from 3 centers were reviewed in the study. The total episodes of pneumothorax were 75. Pneumothorax occurred in 4.2 % of the patients with COVID-19 pneumonia requiring ICU admission. The majority of the subjects were male (n=72, 96%).

The mean age was 55.1 (+/- 12.7 years). The majority of the subjects were nationals of South Asian countries and the Middle East and North Africa (MENA) regions. 52% (n=39) of the patients were previously healthy without comorbidities before ICU admission. The recurrence rate was 9.3%. The median length of ICU stay was 28 days (20.5-45.8 days). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 32 days, with a median of 13 days. 44% of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID-19 related pneumothorax was 53.3% (n= 40). The odds of mortality in patients with COVID-19 pneumonia with pneumothorax is 7.15 (95% confidence interval 4.45 to 11.48, P<0.0001) compared to those who did not develop pneumothorax. This indicates pneumothorax is a potential independent risk factor associated with mortality in patients with COVID-19 pneumonia requiring ICU admission.

conclusions:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission, associated with poor prognosis and outcome.

Trial registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Strengths and limitations:

- This multicentre study provides detailed demographics, risk factors, morbidity and mortality of pneumothorax in critically ill COVID-19 patients.
- Multiple outcome assessments are performed.
- The retrospective, observational nature of the study is the major limitation.
- Data on some variables like smoking could not be extracted from the electronic medical records.
- The absence of data on comparative controls is a limitation.

Background:

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can affect multiple organs of the body.[1] The most commonly involved organ system is the respiratory system. The spectrum of pulmonary complications ranges from alveolar damage leading to pneumonia, acute respiratory distress syndrome (ARDS), or an effect on the coagulation cascade causing pulmonary infarction via thrombi and emboli [2].

Pneumothorax is one of the known pulmonary complications of COVID-19. The incidence of pneumothorax in COVID-19 is approximately 1% in patients requiring hospital admission and 2% in ICU admissions. [3,4,5,6]. The risk factors predisposing to the development of pneumothorax include advanced age, pre-existing lung disease, and mechanical ventilation. [6]

The underlying pathophysiology is unclear, but cyst formation in the diseased areas of the lungs may be a precipitating factor as the cysts can progress to bullae associated with the development of pneumothorax. [6] Cyst formation also occurs with barotrauma and is seen as a late consequence of ARDS [7]. Barotrauma is reported in 15% of patients with COVID-19 requiring invasive mechanical ventilation. [7] Barotrauma is considered an independent risk factor for death and is associated with a more extended hospital stay in patients with COVID-19. [7]

We have conflicting data regarding the association of pneumothorax with mortality in COVID-19 patients, with older studies reporting that the development of pneumothorax is not an independent marker of poor prognosis. However, evolving evidence is in favour of the association of pneumothorax with high mortality. [8,9,10] The mortality rate of COVID-19 patients admitted to ICU is reported up to 39%.[7] There is a higher incidence of pneumothorax in critically ill COVID-19 patients with ARDS. This combination of patients with ARDS developing pneumothorax results in a prolonged hospital stay and a high mortality rate of up to 80%. [11] Data from the ISARIC4C study concludes that pneumothorax is associated with increased mortality in COVID-19. [10]

We carried out a multicentre retrospective study to establish the incidence of pneumothorax in patients with COVID-19 requiring ICU admission in Qatar. The study also describes the characteristics, treatment, associated risk factors, and outcome of COVID-19 associated pneumothorax in Qatar.

Study Design and Methods:

This is a multicentre, retrospective study. Patients admitted to the ICU of Hamad General Hospital (HGH), Hazm Mebaireek General Hospital (HMGH), and Cuban hospital diagnosed with COVID-19 associated pneumothorax between 01/03/2020-01/11/2020 were identified from the patient registry and included in this study. Data was gathered retrospectively from the electronic health record system (Cerner™.)

Inclusion Criteria:

1. All patients 14 years and older were admitted to ICU with a diagnosis of COVID-19 and pneumothorax.
2. Confirmed COVID-19 status by a positive nasopharyngeal/oropharyngeal or tracheal aspirate positive for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR.)

3. Confirm pneumothorax by at least one imaging modality, including chest X-ray, point of care ultrasound, or chest CT scan.

Exclusion Criteria:

1. Age less than 14 years old.
2. Indeterminate or negative RT-PCR for SARS-CoV-2.
3. COVID-19 diagnosis based on rapid antigen testing.
4. Any patient with a presumptive diagnosis of COVID-19 based on clinical diagnosis.
5. No clear evidence of pneumothorax on imaging.
6. Patients not admitted to ICU.

Outcomes:

Primary Outcome

1. To identify the incidence of pneumothorax in patients with COVID-19 admitted to ICU in Qatar.

Secondary Outcome

1. To assess the risk factors associated with the development of pneumothorax in COVID-19 patients.
2. To assess the treatment of the disease.
3. To assess mortality and morbidity associated with developing pneumothorax.

Statistical analyses

Descriptive and summary statistics were used to describe the study cohort's socio-demographic parameters, with continuous variables presented as means (± standard deviation) or median (interquartile range) as appropriate. Categorical variables were presented as numbers (percentages). The Shapiro-Wilk tests analyzed the normality of the data. We used One-Way ANOVA (Welch's) for the parametric variables and Kruskal-Wallis for the non-parametric variables for the comparison. All data were analyzed using Jamovi version 1.2 (created in 2020, Sydney, Australia) (15)

Clinical Trial Registration:

The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient and public statement:

No Patient and Public Involvement

This is a retrospective data review, so it was not possible to involve the patients or public in our research's design, conduct, or dissemination plans.

Results:

Incidence of pneumothorax in COVID-19 patients admitted to ICU:

Our cohort consisted of 1788 patients with COVID-19 requiring ICU admission from Mar 1, 2020, to Nov 1, 2020. 75 out of 1788 subjects developed pneumothorax. Three episodes were post-traumatic and were incidentally found to have COVID-19, so they were excluded from the analysis. Pneumothorax occurred in 4.2 % of the patients with COVID-19 pneumonia requiring ICU admission.

Demographic and Clinical Characteristics:

The majority of the subjects were male (96%), with 4% female. The mean age was 55.1 years (+/- 12.7 years). The majority (72%) of the subjects were of Southern and Southeast Asian ethnicity. 17.3 % belonged to the Middle East and North Africa (MENA) regions, and 10.7% belonged to other ethnicities. [**Table 1**]

The median height was 168cm (164 to 170cm) and the mean body mass index (BMI) was 27.2kg/m2 (+/- 3.9kg/m2). The majority (52%, n=39) of the patients had no comorbidity before ICU admission. 29.3% had type 2 diabetes mellitus (T2DM), another 21% had hypertension (HTN), 4% had cerebrovascular accident (CVA) or coronary artery disease (CAD). Prior respiratory diseases were found in only 9.3% of patients. 6.7% had asthma, 1.3% had pulmonary tuberculosis (PTB), and 1.3 % had the chronic obstructive pulmonary disease (COPD). Only 6.7 % of patients had malignancy. [**Table 1**]

Upon admission to ICU, the median respiratory rate was 30 breaths/minutes, median Pao2/FiO2 was 81 (67.5 to 130), median sequential organ failure assessment (SOFA) score was 2 (2-4), mean acute physiology and chronic health evaluation II (APACHE II) score of 8.8 (+/- 2.9) and the median pneumonia severity index was 76 (65-96). All patients had abnormal chest X-ray (XR) findings suggestive of COVID-19 pneumonia upon admission. 97.3% of the patients required inotropic support at some point during ICU stay. All patients received intravenous antibiotics, steroids and anti-viral therapy during their ICU stay. [**Table 1**]

97.3 % of patients required respiratory support before developing pneumothorax. This included supplemental oxygen, non-invasive ventilation (NIV), and invasive ventilation. 2.% (n=2) patients were on room air when they developed pneumothorax, and they were shifted to ICU after the development of pneumothorax. Thus, pneumothorax incidence in patients with COVID-19 pneumonia requiring ICU admission was calculated as 4.08%. [**Table 2**]

Respiratory support:

Most patients required more than one form of respiratory support. 13.3% (n=10) were on NIV, whereas 80% (n=60) were mechanically ventilated when they developed pneumothorax. [**Table 2**]

After developing pneumothorax, all the patients required respiratory support, with 86.7% of patients requiring invasive ventilation, remaining 13.3% required different forms of respiratory support [table 3]. The median Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration (PaO2/FiO2) before developing pneumothorax was 122 (84 to 179). [**Table 2, 3**]

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The median tidal volume (tidal volume of 6 to 8ml per ideal body weight was used for each patient) was 400ml (358-420ml), mean plateau pressure was 26.4cm H2O (+/- 4.27cmH2O), median PEEP was 8 cm H2O (6-10cmH2O) and mean driving pressure was 17.3 cm H20 (+/- 5.19cm H2O). [**Table 3**]

The median time to develop pneumothorax from ICU admission was 15 days (6-23 days) and was 21 days (13.5-32 days) from the first Covid-19 PCR. Patients who were on NIV developed pneumothorax between 3.5 to 15 days, with the median being 4. Whereas patients on invasive ventilation developed pneumothorax between 6 to 32 days, the median was 13 days. [**Table 3**]

Risk factors:

45.3% (n=34) of patients had one or more procedures (known to be associated with pneumothorax) done within the preceding 24hours of the development of pneumothorax. Out of the total procedures (n=65), the most commonly performed procedures were internal jugular line insertion and intubation with a frequency of 35.3% each. A detailed list of the procedures is provided in table 4. **[Table 4]**

Investigations done upon admission are summarized in supplementary table A. **[Supplementary Table A]**

Characteristics of the pneumothorax:

Pneumothorax occurred more on the right side (56%) than on the left side (28%). At the same time, pneumothorax occurred bilaterally in 16% of patients. A chest tube was inserted for 78.7%% (n=59), and others were managed conservatively. None of the patients required surgical intervention. When the chest tube was inserted, it was removed at a median of 8 days (4-18 days). The recurrence rate was 9.3%. The median length of ICU stay was 28 days (20.5-45.8). After developing pneumothorax, the length of mechanical ventilation ranged from 6 to 35 days, with a median of 13 days. After developing pneumothorax, the length of NIV ranged from 3.5 to 15 days, with a median of 4 days, with a length of IV ranging from 6 to 32 days, with a median of 13 days. Almost 44 % of patients eventually ended up with tracheostomy. In-hospital mortality in the patients with COVID 19 related pneumothorax was 53.3% (n=40). **[table 5]**

Mortality:

We compared both parametric and non-parametric variables based on mortality in patients with COVID 19 related pneumothorax requiring ICU admission. The analysis found statistically significant difference in mortality on the basis of SOFA score (f= 6.32, p= 0.014), respiratory rate (f=7.26, p=0.008), PEEP (f=5.234, p=0.027), D-Dimer (f=4.1, p=0.049), fibrinogen (f=5.358, p=0.023), blood urea Nitrogen (f=5.714, p= 0.020), developing pneumothorax while on invasive ventilation (f=5.2857, p=0.022), need for invasive ventilation after developing pneumothorax (f=13.01, p=<0.001), use of vasopressor/inotropes during ICU stay (f=8.5893, p=0.003) and when procedures known to

cause pneumothorax were being performed within 24hrs preceding development of pneumothorax. **[Supplementary Table B and Table C]**

Outcome parameters of the patient with critically ill COVID-19 patients without pneumothorax:

Although our study is primarily not a comparative study, some of the outcome parameters for the critically ill COVID-19 patients who did not develop pneumothorax were calculated to compare and better understand the association. For the patients who were admitted to ICU with COVID-19 and did not develop a pneumothorax, the mean SOFA score was 4.3 (+/-4), APACHE II score 13.5 (+/-6.4), mean length of ICU stay was 14days (+/-20.5 days), and in-hospital mortality was 13.1% (n=236). **[Table. 1, 5]**

Discussion:

COVID-19 is a multiorgan disease, but respiratory involvement is the most common in severe disease. Any phenomenon that strains the respiratory system further can contribute to morbidity and mortality. Pneumothorax is a source of morbidity and mortality. This is an extensive retrospective study on COVID-19 associated pneumothorax in critically ill patients and one of the few studies with a sizable cohort from the Middle-East North Africa (MENA) region.

In our study, pneumothorax occurred in 4.2 % of the critically ill COVID-19 patients. As 2.6% (n=2) patients were on room air when they developed pneumothorax and were shifted to ICU after developing pneumothorax. Therefore, the incidence rate of COVID-19 related pneumothorax was calculated as 4.08%, higher than some studies but similar to a study by Stefan J. Marciniak. [3,4,5,6,10]

Most of the patients were male, similar to other studies [6]. Our population had diverse nationalities.

Most of our patient population was previously healthy. The mean SOFA score of COVID-19 patients who developed pneumothorax was 2.92 (+/-1.75) compared to a mean of 4.3 (+/-4) in COVID-19 patients without pneumothorax. **[table 1]** Whereas, the mean APACHE II score of 8.8 (+/- 2.9) in patients with pneumothorax compared to the mean APACHE II score of 13.5 (+/-6.4) in patients without pneumothorax**. [table 1]** This indicates that patients with COVID-19 can develop pneumothorax even in the presence of lower estimated mortality and even without evidence of multiorgan failure upon ICU admission. However, the mortality of patients who developed pneumothorax was higher than the comparison group.

All patients had abnormal chest XR findings, most of them having bilateral ground glass shadows upon admission to ICU. Most of the patients were on some form of respiratory support when they developed pneumothorax. The ventilatory setting was not available for all patients. However, the available data review indicates that other lung-protective ventilation strategies were not violated except the slightly higher driving pressure (17.3 cm H20 (+/-5.19cm H2O). This indicates that the risk of barotrauma in these patients is high

even when lung-protective strategies were being applied while positively ventilating the patients. Multiple mechanisms can contribute to it, such as cyst formation due to barotrauma or as a late consequence of ARDS may play an important role. [6,7] Authors postulate that the elevated driving pressure may cause increased shear pressure on the alveolar wall, leading to barotrauma.[10] The exact mechanism is still unclear and needs further investigation. There was also a statistically significant difference in mortality based on PEEP.

Procedures that are known to cause pneumothorax preceded 45.3% of the events within 24hrs of the event. Most of the pneumothorax occurred on the right side after right internal venous catheter insertion. This high number of possibly iatrogenic pneumothorax may reflect the poor performance under stressful conditions or limited operator expertise, given the pandemic's overwhelmed situation.

The neutrophil/lymphocyte ratio was found to be high in these patients indicating high physiological stress. Mean fibrinogen and median interleukin-6 (IL-6) were also elevated, most likely due to activation of the coagulation cascade and cytokine storm. **[Supplementary Table A]** Further studies are needed to determine the association of this phenomenon with the development of pneumothorax.

A chest tube was inserted for most patients to manage pneumothorax, as seen in previous studies. [10] We demonstrated that in patients with COVID-19, associated pneumothorax requiring chest tube placement was not associated with higher mortality.

Almost 9.3% of the patients developed recurrent episodes, with one patient developing as many as four distinct episodes during ICU stay.

Median stay in ICU for all COVID-19 patients was reported as 5 days (2–9) by Eleanor M. Rees et al. [12]. Our study showed a longer median length of stay of 28 days (20.5 to 45.8) for critically ill patients with COVID 19 related pneumothorax. Compared to patients without pneumothorax, ICU stay was longer in patients who developed a pneumothorax (mean of 39.2 +/- 32.9 days vs mean of 14 +/- 20.5 days). **[table 5]** This reflects a prolonged ICU stay due to COVID-19 related pneumothorax. It may also indicate that patients with COVID-19 pneumonia are more prone to develop pneumothorax with prolonged ICU admission.

All patients required respiratory support after developing pneumothorax. The tracheostomy rate was 44% compared to 29.72% in overall COVID-19 patients requiring ICU admission, as reported by Jesus Sancho [13].

In-hospital mortality in the patients with COVID-19 related pneumothorax was 53.3%. The mortality rate in patients with COVID-19 pneumonia requiring ICU who did not develop pneumothorax was calculated as 13% (n=236). **[table 5]** The odds of mortality in patients with COVID-19 pneumonia with pneumothorax are 7.15 (95% confidence interval 4.4 to 11.4, P<0.0001) compared to those who did not develop pneumothorax. This indicates pneumothorax as a potential independent risk factor associated with mortality in patients with COVID-19 pneumonia requiring ICU admission.

This study indicates that the pneumothorax rate is higher in-patient requiring ICU admission, with associated higher mortality and prolonged hospital stay.

Our study does have some limitations. The limitations of our study stem from the study design being retrospective and observational study. Despite an extensive review, there was some missing information when screening for risk factors of pneumothorax.

Pneumothorax is a well-recognized complication of COVID-19 in critically ill patients, and it is related to poor prognosis. Therefore, all possible efforts should be made towards prevention and prompt recognition. The patient that is at risk includes male, those of southeast Asian origin, with abnormal chest XR findings upon admission, those requiring respiratory support upon admission, mechanically ventilated, prolonged ICU admission, those with high neutrophil/lymphocyte ratio, high CRP with evidence of cytokine storm and those undergoing procedures that may cause pneumothorax.

Xiao-hui Wang et al. demonstrated that protective ventilation strategies, neuromuscular blockers, timely ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) combined with ultra-protective ventilation might play an essential role in the prevention of pneumothorax in critically ill patients with severe ARDS [11].

Interpretation/Conclusion:

Pneumothorax is a common complication in patients with COVID-19 requiring ICU admission. It is associated with poor prognosis and outcome. Prevention, early recognition, and prompt treatment may improve survival.

Ethical statement:

This work is original, has not been, and is not considered for publication in any other Journal. All authors have reviewed and approved the final version of the manuscript. The study was approved by the Medical Research Centre (MRC) Qatar. (MRC-01-20-1116)

Patient consent:

As this study is a retrospective data review, taking patient consent was not applicable.

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Dr Zohaib Yousaf takes responsibility for (is the guarantor of) the manuscript's content, including the data and analysis.

Contributorship statement:

Dr Jaweria Akram (JA): Principal investigator, conceptualization, methodology, literature review, data collection and interpretation, manuscript writing.

Dr Zohaib Yousaf (ZY): Literature review, methodology, conceptualization, data analysis and interpretation, manuscript writing, and critical review.

Dr Yasir Mustafa Alabbas (YM) and Dr Mustafa Ibrahim Abdullah Almoyaaf (MI): Literature review and data collection

Dr Abdus Salam Saif Ibrahim (AS): Data retrieval.

Dr Nadir Kharma (NK): Critical review and revisions in the manuscript.

All authors: Review and approval of the final manuscript.

References:
[1] Vishwajit Deshmukh, et al. Histopathological observations in COVID-19: a systematic review. Journal of Clinical pathology.

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[2] Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020 Dec;69(12):1181-1189. doi: 10.1007/s00011-020-01401-6. Epub 2020 Sep 12. PMID: 32918567; PMCID: PMC7486586

[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513. doi:10.1016/S0140-6736(20)30211-7

[4] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475–481. doi:10.1016/S2213-2600(20)30079-5

[5] Yang F, Shi S, Zhu J, et al. analysis of 92 deceased patients with COVID-19. J Med Virol 2020. doi:10.1002/jmv.25891

[6] Anthony W. Martinelli, et al. COVID-19 and Pneumothorax: A Multicentre Retrospective Case Series. European Respiratory Journal 2020; DOI: 10.1183/13993003.02697-2020

[7] Georgeann McGuinness, et al. Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. Jul 2 2020https: //doi.org/10.1148/radiol.2020202352

[8] Semagn Mekonnen Abat, et al. Rate of Intensive Care Unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis. PloS one, Published: Jul 10, 2020https://doi.org/10.1371/journal.pone.0235653

[9] Massa Zantah, Pneumothorax in COVID-19 disease- incidence and clinical characteristics, Respiratory Research volume 21, Article number: 236 (2020)

[10] Stefan J. Marciniak, et al. COVID-19 pneumothorax in the UK: a prospective observational study using the ISARIC WHO clinical characterisation protocol. European Respiratory Journal Sep 2021, 58 (3) 2100929; DOI: 10.1183/13993003.00929-2021

[11] Xiao-hui Wang, et al. High incidence and mortality of pneumothorax in critically Ill patients with COVID-19. Heart Lung. 2021 January-February; 50(1): 37–43. doi: 10.1016/j.hrtlng.2020.10.002

[12] Eleanor M. Rees, et al. COVID-19 length of hospital stays: a systematic review and data synthesis. BMC Medicine volume 18, Article number: 270 (2020)

[13] Sancho, J., Ferrer, S., Lahosa, C. et al. Tracheostomy in patients with COVID-19: predictors and clinical features. Eur Arch Otorhinolaryngol (2021). https://doi.org/10.1007/s00405-020-06555-x

Tables:

	COVID-19 associated pneumothorax	**COVID-19 not associated with pneumothorax**
Baseline characteristics	**Total *N*=75**	**N= 1713**
Age (Mean +/- SD) years	55.1 (+/- 12.7)	NA

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Gender n (%) Male Female	 72 (96%) 3 (4%)	NA
Ethnicities n (%) Nepalese Bangladeshi Pakistani Indian Filipino Qatari Syrian Sudani American Indonesian Irani Others	 14 (18.7%) 10 (13.3%) 9 (12%) 10 (13.3%) 10 (13.3%) 6 (8%) 2 (2.6%) 3 (4%) 2 (2.7%) 1 (1.3%) 2 (2.7%) 6 (8%)	NA
Height (Median IQR) cm	168 (164 to 170)	NA
Weight (Median IQR) Kg	75 (65 to 85)	NA
BMI (Mean +/- SD) kg/m2	27.2 (+/- 3.9)	NA
Comorbidities n (%) HTN T2DM CVA CAD COPD Asthma TB CKD HIV Malignancy	 22 (29.3%) 21 (28%) 3 (4%) 3 (4%) 1 (1.3%) 5 (6.7%) 1 (1.3%) 3 (4%) 0 (0%) 5 (6.7%)	NA
Vitals at admission to ICU Temperature (Median IQR) Heart rate (Mean +/-SD) bpm MAP (Mean +/- SD) mmHg Respiratory rate (Median IQR) breaths/min Sofa score (Median IQR) Sofa score (Mean +/-SD) 	 36.9 (36.6 to 37.8) 101 (+/- 21.3) 93.1 (+/- 14.1) 30 (26 to 34) 2 (2 to 4) 2.92 (+/-1.75) 77 (65 to 96)	 NA NA NA NA NA 4.3 (+/- 4) NA

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Pneumonia severity index (Median IQR) APACHE II score (Mean +/-SD)	8.8 (+/- 2.9)	13.5 (+/-6.4)
Pneumonia on Chest XR n (%)	70 (93.3%)	NA
Inotrope use during ICU stay n (%)	73 (97.3%)	NA

Table 1. Demographics and clinical characteristics of patients with COVID-19 associated pneumothorax in ICU and without pneumothorax.

(n- number, MENA - Middle East and North Africa, BMI – Body mass index, T2DM – Type 2 diabetes mellitus, CVA – Cerebrovascular accident, CAD - Coronary artery disease, TB – Tuberculosis, COPD - Chronic obstructive pulmonary disease, SOFA - Sequential organ failure assessment, APACHE II - Acute physiology and chronic health evaluation II)

Supplementary oxygen uses before pneumothorax n (%)	73 (97.3%)
Patient on IV who developed a pneumothorax n (%)	60 (80%)
Patients on NIV who developed a pneumothorax n (%)	10 (13.3%)
Supplementary oxygen used after pneumothorax N (%)	75 (100%)
Number of patients requiring NIV after developing pneumothorax N (%)	3 (4%)

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Number of patients requiring IV after developing pneumothorax N (%)	65 (86.7%)

Table 2. Respiratory support before and after developing pneumothorax

(NIV – Non-invasive ventilation, IV – Invasive ventilation)

Ventilatory setting in intubated patients before developing pneumothorax TV (Median IQR) Plateau pressure (Mean +/- SD) PEEP (Median IQR) Driving pressure (Mean +/-SD)	 400 (358 to 420) ml 26.4 (+/- 4.27) cmH2O 8 (6 to 10) cm H2O 17.3 (+/-5.19) cm H2O
Length NIV before developing pneumothorax (Median IQR)	1 (1 to 2) day
Length of IV before developing pneumothorax (Median IQR)	9 (4 to 21) days
PaO2/FiO2 ratio on admission (Median IQR)	81 (67.5 to 130)
PaO2/FiO2 before pneumothorax (Median IQR)	122 (84 to 179)

Table 3. Ventilator setting and PaO2/FiO2 before developing pneumothorax

(TV- Tidal volume, PEEP - positive end-expiratory pressure, PaO2/FIO2 - Pressure of arterial oxygen to fractional inspired oxygen concentration)

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Number of patients who underwent procedures within the preceding 24hrs before developing pneumothorax n (%)	34 (45.3%)
Number of procedures preceding pneumothorax	65
AV ECMO	1 (1.5%)
VV ECMO	1 (1.5%)
NGT insertion	11 (16.2%)
Tracheostomy	2 (3%)
internal jugular line insertion	23 (35.3%)
intubation	23 (35.3%)
post-extubation, while on ECMO	1 (1.5%)
subclavian central venous line insertion	2 (3 %)
therapeutic /diagnostic Pleural tapping	1 (1.5%)

Table 4. Procedures preceding pneumothorax in the last 24hrs

(NGT – Nasogastric tube, VA ECMO - Veno-arterial extracorporeal membrane oxygenation, VV ECMO – Veno-venous extracorporeal membrane oxygenation, ECMO - extracorporeal membrane oxygenation)

Outcome/treatment	**COVID-19 associated pneumothorax**	**COVID-19 not associated with pneumothorax**
Side of pneumothorax N (%)		NA
Bilateral	12 (16%)	
Left	21 (28%)	
Right	42 (56%)	
Chest tube insertion n (%)	59 (78.7%)	NA
Duration of a chest tube (Median IQR)	8 (4-18)	NA
Recurrences	7 (9.3%)	NA

n (%)		
Length of ICU stay (days) (Median +IQR) (Mean+/-SD)	 28 (20.5-45.8) days 39.2 (+/-32.9) days	 14(+/- 20.5) days
Length of NIV after developing pneumothorax (days) (Median IQR)	4 (3.5-15) days	NA
Length of IV after developing pneumothorax (Median IQR)	13 (6-32) days	NA
Need for tracheostomy n (%)	33 (44%)	NA
Number of days in ICU before developing pneumothorax (median IQR)	15 (6-23) days	NA
Time elapsed from first COVID-19 PCR to development of pneumothorax (days) (Median IQR)	21 (13.5-32) days	NA
Time to negative COVID-19 PCR (days) (Median IQR)	28 (24-42) days (maximum 138)	NA
In-hospital mortality n (%)	40 (53.3%)	236 (13.1%)

Table 5. Treatment, the outcome of COVID-19 associated pneumothorax and outcome of patients with COVID-19 without pneumothorax

Supplementary tables

Lab parameter	Value
WBC x 10 3/uL (mean +/- SD)	11.1 (+/- 5.53)
Neutrophil x 10 3/uL (mean +/- SD)	9.68 (+/- 5.13)
Lymphocyte x 10 3/uL (median IQR)	0.8 (0.5-1.2)
Neutrophil/Lymphocyte (median IQR)	10 (5.25-18)
Platelets x 10 3/uL (median IQR)	236 (174-325)
Hemoglobin gm/dL (median IQR)	13.2 (12.1-14.5)
INR (median +IQR)	1.1 (1-1.2)
D dimer mg/L (median IQR)	1.47 (0.69-6.65)
Fibrinogen gm/L (mean +/- SD)	5.89 +/- 1.89
IL6 pg/ml (median IQR)	97 (31.5-33)
CRP mg/L (median IQR)	146 (87-232)
Procalcitonin ng/ml (median IQR)	0.45 (0.145-1)
Lactic acid mmol/L (median IQR)	1.7 (1.2-2.3)
Urea mmol/L (median +IQR)	6.1 (4.2-8.7)
Creatinine umol/L (median IQR)	75 (64-99)
Sodium mmol/L (median IQR)	136 (133-139)
AST U/L (median +IQR)	49 (34-76)
ALT U/L	47 (32-74)

(median +IQR)	
Bilirubin U/L (median IQR)	10 (8-17.6)

Supplementary Table A. Investigations upon admission to ICU

(WBC – white blood count, AST - aspartate aminotransferase, ALT - alanine transaminase, IL6 – Interleukin-6, CRP – C-reactive protein, uL – millimetre, gm/dL- grams per deciliter, mg/dL - milligrams per litre, gm/L – gram per litre, IL-6 - Interleukin 6, pg/ml - picograms per millilitre, ng/ml - nanograms per millilitre, mmol/L - millimoles per litre, umol/L - micromoles per litre, U/L – Units per litre)

Variable	**F**	**df1**	**p**
Sofa score	6.32	1	0.014
Respiratory rate prior to developing pneumothorax	7.26	1	0.008
PEEP in intubated patients prior to developing pneumothorax	5.234	1	0.027
D dimer mg/L	4.1	1	0.049
Fibrinogen gm/L	5.358	1	0.023

Urea mmol/L	5.714	1	0.020

Table B. One-Way ANOVA (Welch's) for compared parametric variables based on mortality.

variable	χ^2	df	p
Number of patients requiring invasive ventilation before developing pneumothorax	5.2857	1	0.022
Number of patients requiring invasive ventilation after developing pneumothorax	13.0110	1	< .001
Inotrope/vasopressor use during ICU stay	8.5893	1	0.003
Procedures known to cause pneumothorax preceding pneumothorax	7.9488	1	0.005

Table C. One-Way ANOVA (Kruskal-Wallis) for compared non-parametric variables based on mortality.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5-8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*5-8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-8
		(*b*) Report category boundaries when continuous variables were categorized	5-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.