Air leak syndromes (Pneumomediastinum, pneumothorax, and subcutaneous emphysema) in Critically ill COVID – 19 patients – Prevalence, risk factors, and outcome.

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Research Article

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Abstract

BACKGROUND: A high incidence of air leak syndromes (ALS) has been reported in critically ill COVID-19 patients. This not only prolongs the hospital stay of patients but also affects the disease outcome.

OBJECTIVE: Our objective is to evaluate the incidence, clinical outcome, and risk factors associated with ALS in critically ill COVID-19 patients receiving invasive or non-invasive positive pressure ventilation.

RESULT: Out of 79 patients, 16(20.2%) patients had ALS. The mean age of the ALS group was 48.6±13.1 years as compared to 52.8±13.1 (p = 0.260) years in the non-ALS group. The ALS group had a lower median BMI (25.9 kg/m2 vs 27.6 kg/m2 , p = 0.096), a higher D-dimer value at presentation (1179.5 vs 762.0, p = 0.024) , lower saturation (74% vs 88%, p = 0.006) and lower PF (134 vs 189, p = 0.028) ratio at presentation as compared to the ALS group. Patients who developed ALS were found to have received a higher median PEEP (10 cm vs 8 cm of water, p = 0.005). Pressure support, highest driving pressure, and peak airway pressure were not significantly different in the two groups. ALS group was seen to have a significantly longer duration of hospital stay (17.5 days vs 9 days, p = 0.003). Multiple Logistic Regressions analysis indicated patients who received Inj. Dexamethasone was less likely to develop ALS (OR: 12.6 (95% CI 1.6-95.4), p=0.015).

CONCLUSION: A high incidence of ALS is present in critically ill COVID 19 patients. High inflammatory parameters, severe hypoxia at presentation, and use of high PEEP are significant risk factors associated with the development of ALS. The risk of developing ALS was observed to be lower in patients who received Inj. Dexamethasone. ALS is associated with a longer duration of hospital stay.

Introduction

The corona virus disease (COVID 19) has affected millions of people worldwide. As of December 2020, COVID 19 was the leading cause of death in USA.1 Nearly 1 in 10 patients suffering from COVID 19 progress to develop acute respiratory distress syndrome(ARDS) with 72% of them requiring mechanical ventilation.2 High mortality is associated with critically ill patients requiring ICU care.3

Air Leak Syndromes (ALS) have been reported to be a common problem in mechanically ventilated patients which affects disease outcome.4–7 The high incidence of air leak in critically ill COVID 19 patients makes understanding the risk factors leading to it in the critical care setting all the more important.8–10 Furthermore, ALS in COVID 19 patients has been shown, in some settings, to be associated to longer hospital stay and increased mortality in patients more than 70 years of age.11 The higher incidence of air leak in COVID-19 ARDS independent of transpulmonary pressure and various cases of spontaneous air leaks without any previous risk factors suggest pathogenesis beyond pulmonary barotrauma. Macklin effect has been considered as a possible explanation for the curious and disproportionate development of pneumomediastinum in COVID 19 patients (compared to pneumothoraces).12–14
Understanding the risk factors leading to air leak syndromes in critically ill COVID-19 patients will help in identifying high risk patients who would benefit from early specific interventions. Impact of ALS on outcome will aid in the prognostication of patients which is crucial in an intensive care setting.

**Methodology**

**Study design and participants**

This was a retrospective, observational cohort study conducted in a single center, a tertiary health care center located in South India. Patients admitted in the Intensive care unit (ICU) from 25/07/2020 to 31/10/2020 with a confirmed diagnosis of COVID 19 (defined by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR)) with mild to severe ARDS based on Berlin criteria and on any form of oxygen therapy (invasive or non-invasive) were included.

Ethical approval was obtained from the Institutional Review Board IRB Min. No. 13594 [Retro] dated: 25.11.2020.

**Data Collection**

Inpatient medical records of the patients who were admitted in the intensive care unit from 25/07/2020 to 31/10/2020 were reviewed. All patients that were to be included would be evaluated for occurrence of air leak syndromes (pneumo-mediastinum, pneumothorax and subcutaneous emphysema) on chest x-rays or computed tomographic (CT) scan by a team of two radiologists. Only the study authors would be permitted access to the data collected which would be stored in a secure manner. Patients who would meet the inclusion criteria would be studied in detail to collect information pertaining to their age, gender, body mass index (BMI), co-morbidities, baseline inflammatory parameters, acute respiratory distress syndrome (ARDS) severity, ventilator, and NIPPV settings, duration of ventilation, intervention for barotrauma, mortality, and hospital length of stay in ICU and hospital. Highest values of tidal volumes, pressure support (PS), positive end expiratory pressure (PEEP) and driving pressure delivered for at least 2 hours would be documented. For patients who developed air leak syndrome (ALS), the highest value of PS, PEEP and peak inspiratory pressure delivered on the day prior to the onset of ALS for at least 2 hours would be documented. Telephonic follow up would be done to assess the mortality at 6 months.

**Statistical analysis**

Continuous variables would be summarized using the descriptive statistics. We would use mean and standard deviation for variables with a gaussian distribution and median and inter-quartile range for variables with a skewed distribution. Normally distributed continuous variables would be analysed using Independent sample T test while non-normally distributed variables would be analysed using Mann-Whitney U test. The risk factors for ALS would be analysed in three steps. Firstly, the association of potential risk factors with observed ALS (yes/no) would be examined. Secondly, three most significant variables with a p-value <0.05 in bivariate analysis would be entered in a stepwise logistic-regression.
model. Thirdly, only the risk factors with significant p-value will be studied. The result of multiple logistic regression analysis was to be presented with adjusted odds-ratio, 95% confidence intervals (95% CI) and p-value. Significance levels were defined at 0.05. Survival analysis will be done using Kaplan-Meir analysis and Log-rank test. All analyses were conducted in IBM SPSS Statistics 25 and RStudio (Version 1.4.1717).

Results

Patient characteristics and Prevalence of ALS

Out of the 100 patients who were admitted in the intensive care unit during the study period, a total of 89 patients tested positive for COVID-19 out of whom 79 patients met the inclusion criteria. Ten patients did not satisfy the inclusion criteria as their PF ratio was more than 300 and were admitted in intensive care unit for complications other than ARDS and were incidentally tested positive for COVID-19.
Radiological images of these patients were assessed by a team of two radiologists and a total of 16 (20.2%) patients were detected to have air leak syndromes. Isolated pneumo-mediastinum was detected in 13 patients, isolated pneumothorax was seen in 1 patient and a combination of the two was seen in 2 patients. Seven patients had subcutaneous emphysema along with pneumo-mediastinum or pneumothorax. Spontaneous pneumo-mediastinum was noticed in 3 patients at presentation prior to administration of positive pressure ventilation. None of the patients in the study developed air leak syndrome secondary to procedural complications (e.g. central line insertion). ALS developed after a mean of 12.6±3.8 days since the onset of symptoms. Only one patient required chest tube insertion for management of pneumothorax. Patients who did not succumb to the illness showed spontaneous resolution of ALS following conservative management after a median of 4 days (IQR = 1.75-9.5).

The mean age of the ALS group was 48.6±13.1 years as compared to 52.8±13.1 years in the non-ALS group. The ALS group had lesser median BMI as compared to the non-ALS group (25.9 kg/m\(^2\) vs 27.6 kg/m\(^2\)). However, these two correlations were not statistically significant. The other baseline characteristics are mentioned in Table 1.

**Risk factors**

A total of 18 possible risk factors were studied and analysed. Three inflammatory makers (ferritin, D-dimer, CRP) were studied. Out of the three only D-dimer value at presentation showed a statistical significant correlation, with patients who developed ALS having a higher D-dimer value at presentation (1179.5 vs 762.0, \(p = 0.024\)). The patients who developed ALS were found to be more hypoxic at presentation which was assessed in terms of saturation at presentation (74% vs 88%, \(p = 0.006\)) and PF ratio at presentation (134 vs 189, \(p = 0.028\)).

Ventilatory settings were compared between the two groups (Table 2). The overall duration of ventilation was significantly longer in the ALS group. Invasive ventilation was more prevalent as compared to Non-invasive ventilation in the ALS group (43.8%) as compared to non-ALS group (37.5%). Patients who developed ALS were found to have received a higher median positive end expiratory pressure (10 cm of water vs 8 cm of water, \(p = 0.005\)). Pressure support, higher driving pressure and peak airway pressure were not significantly different in the ALS and non-ALS groups. Tidal Volume values were not reliably recorded for most patients and therefore were not taken for analysis.

As per institutional treatment protocol, patients either received Inj. Dexamethasone 6mg once daily or Inj. Methylprednisolone 1mg/kg once daily for a total of 10 days from the onset of oxygen therapy (invasive or non-invasive). Patients who received Inj. Dexamethasone during their ICU stay were less likely to develop ALS with protective Odds ratio of 17.6 (95% CI – 3.86-80.54, \(p < 0.001\)).

The three most significant variables were included in the multiple logistic regression analysis (Table 4). Only type of steroid given was observed to have a statistically significant relation with adjusted OR – 12.57 (95% CI -1.63-96.41, p-value – 0.015) after eliminating possible confounders.
Outcomes

ALS group was seen to have a significantly longer duration of ICU stay (17.5 days vs 9 days, \( p = 0.003 \)). A greater percentage of patients in the ALS group developed secondary bacterial pneumonia (50% vs 20.6%, \( p = 0.023 \)). A total of 9 (56.3%) patients died or were terminally discharged in the ALS group as compared to 24 (38.1%) patients in the non-ALS group. These findings are summarized in Table 3. Kaplan-Meir analysis (Figure 1) showed a trend towards increased mortality in patients with ALS. However, this was not statistically significant.

Seven patients were discharged against medical advice in view of financial constraints. Out of these 5 patients succumbed to illness within maximum of 3 weeks following discharge and 2 patients were lost to follow up.

Discussion

In our study, we observed a high incidence of air leak syndromes in patients with COVID 19 related ARDS requiring intensive care. We prefer the terminology ‘Air leak syndrome’ over ‘Barotrauma’ as not all patients were on positive pressure ventilation when they were found to have pneumo-mediastinum, pneumothorax or subcutaneous emphysema. A total of 16 (20.2%) patients developed ALS, which is significantly higher when compared with ALS incidence in other ARDS patient populations (5-8%).\(^{16,17}\)

Out of the 16 patients, 6 patients were on non-invasive ventilation, 7 patients were on invasive mechanical ventilation were as 3 patients were found to have spontaneous pneumo-mediastinum.

Multiple cases have reported spontaneous pneumo-mediastinum in patients with COVID-19.\(^{18-22}\) Many of these reports indicate that patients were not on mechanical ventilation and did not have history of prior pneumothorax. Thus, the cause of spontaneous air leak syndromes and specifically pneumo-mediastina in the realm of Covid-19 ARDS remains an enigma. The predominant mechanism of air leak may not be barotrauma or related to ventilatory pressures, although positive pressure may be contributory to their development. The high incidence of ALS in critically ill COVID 19 patients may be related to excessive lung inflammation. Indeed high plasma levels of inflammatory mediators like IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF\(\alpha\) have been observed in ICU patients as compared to non-ICU patients with COVID-19.\(^{23}\) It is plausible that excessively inflamed lung tissue may be friable and prone to lung tears. Alternatively, there also may be a predisposition to fibrosis and worsening of swings in transpulmonary pressures with respiratory efforts of mechanical ventilation. Macklin and Macklin first noticed that air released from alveolar rupture centripetally dissects through the interstitium of the lungs, along the broncho vascular sheaths toward the pulmonary hila and into the mediastinum.\(^{24}\) Macklin effect is commonly seen in patients with blunt chest trauma.\(^{12}\) The Macklin effect has been observed in COVID-19 patients and could explain the high incidence of spontaneous pneumo-mediastinum often leading to pneumothorax.\(^{13,14,25,26}\) We studied D-dimer, CRP and Ferritin at admission to assess the role of inflammation. Admission D-dimer in ALS group was observed to be higher and reached statistical
significance. Both baseline hypoxia and low PF ratio at presentation were significantly lower in ALS group, which may indicate that severity of disease has a role in the tendency for air leak.

Prior to COVID 19, air leak syndromes in ARDS have been known not only to increase hospital stay but also be associated with morbidity and mortality. In our cohort of patients, the requirement of prolonged ventilation in the ALS group was associated with higher incidence of ventilator associated pneumonia in these patients which may have adversely impacted their outcome.

Ventilatory management of COVID-19 patients has been a tough challenge throughout the pandemic. Different ventilatory management has been suggested based on the COVID phenotypes: L-type pneumonia and H-type pneumonia. Some previously done studies have found relationship between PEEP and barotrauma, whereas others have found no relation between airway pressures and barotrauma. In our study, higher PEEP was observed in the ALS group which was statistically significant. The pressure support, driving pressures and peak airway pressures were found to be higher in the ALS group. However, this trend was not found to be statistically significant. The higher PEEP settings in the ALS group may have set by clinicians in order to tackle poorer oxygenation and severity of disease in that group relative to the non-ALS group (and therefore may be a confounder)

Use of corticosteroids has shown reduction in severity of ARDS, increase in ventilator free days and reduction in mortality. An observational study showed better results with high dose methylprednisolone as compared with conventional dose dexamethasone in COVID 19 patients in terms of progression of ARDS. In our study we observed that patients who received Inj. Dexamethasone were less likely to develop ALS as opposed to patients who received Inj. methylprednisolone. Although this could be chance finding, it is possible that fluid retention associate with the mineralocorticoid properties of methylprednisolone may have rendered the lung more friable or amenable to injury as opposed to Dexamethasone. Further studies need to be done to understand difference in effect of dexamethasone and methylprednisolone on outcome in COVID 19 patients.

Limitations:

A limitation of our study is a small sample size from a single center, however our study adds to the volume of data available on this topic as well as supports results from other settings. Another key limitation was out inability to capture tidal volume data from our cohort appropriately. However, the classic teaching is that pressure is the chief variable involved in air leak. Also other studies have not demonstrated that volume is a predictor of ALS. The unique incidence and pattern of ALS in Covid-19 patients, such as predisposition to pneumomediastina, gives us a window into understanding the pathophysiology and course of COVID 19 ARDS. Prospective studies need to continue to look into how to mitigate ALS so as to improve outcomes. With early recognition and emerging treatment options there could be reduced level of inflammation and severity of disease leading to less incidence of ALS and perhaps better outcomes.
Conclusion

COVID 19 is still an evolving disease which is still not entirely understood. Air leak syndromes are disproportionately higher in COVID ARDS as compared to other causes of ARDS with a preponderance to form pneumomediastina. Inflammatory markers like D-dimer and severity of hypoxemia may help in predicting the predisposition to ALS and eventual outcomes of patients. Patients with ALS tend to have increased duration of hospital stay, high incidence of secondary respiratory tract infections and poorer long-term outcomes. Dexamethasone may be more protective than methylprednisolone with regards to ALS although more prospective studies are required to confirm this.

Declarations

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DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest.

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**Tables**

Table 1: Baseline Characteristics
|                                | ALS (n=16) | No ALS (n=63) | P value |
|--------------------------------|------------|---------------|---------|
| **Age (years)**                | 48.6±13.1  | 52.8±13.1     | 0.260   |
| **Gender**                     |            |               | 0.625   |
| Males                          | 12(75%)    | 47(74.6%)     |         |
| Females                        | 4(25%)     | 16(25.4%)     |         |
| **BMI (kg/m²)**                | 25.9(23.4-27.6) | 27.6(24.5-32.7) | 0.096   |
| **Comorbidities**              |            |               | 0.735   |
| Diabtes                        | 11(68.8%)  | 33(52.4%)     |         |
| HTN                            | 8(50%)     | 33(52.4%)     |         |
| Overweight or Obese (BMI > 24.9 kg/m²) | 13(81.3%)  | 51(81%)       | 0.531   |
| **Inflammatory markers at admission** |         |               |         |
| Ferritin (ng/ml)               | 684.0(276.3-1047.0) | 668.6(280.4-833.7) | 0.394   |
| D-Dimer (ng/ml)                | 1179.5(836.7-9718.0) | 762.0(481.7-1876.2) | **0.024** |
| CRP (mg/L)                     | 140.0(115.9-190.7) | 108.0(43.4-117.0) | 0.547   |
| SpO2 at presentation (%)       | 74(44-87)  | 88(76-94)     | **0.006** |
| PF ratio at presentation       | 134(72-190) | 189(89-254)   | **0.028** |
| **Steroid therapy**            |            |               | <0.001  |
| Dexamethasone                  | 8(50%)     | 53(84.1%)     |         |
| Methylprednisolone             | 8(50%)     | 3(4.8%)       |         |
| Duration of anticoagulation (days) | 15.5(12.25-19) | 13(10-20.75) | 0.372   |
| Remdesivir                     | 13(81.3%)  | 36(57.1%)     | 0.065   |

* Mean and standard deviation
# Median and interquartile range
@ At least 1 comorbidity

$ BMI values were occasionally calculated based on approximate body weight values in Kgs

Table 2 – Ventilatory support
|                            | ALS (n=16) $ | Not ALS (n=61) | P value |
|---------------------------|-------------|----------------|----------|
| **Mode of Ventilation**   |             |                | 0.189    |
| Non-invasive              | 6 (37.5%)   | 39 (61.9%)     |          |
| Invasive                  | 7 (43.8%)   | 22 (34.9%)     |          |
| **Highest PEEP (cm of H₂O)** # | 10 (10-12) | 8 (8-10) | **0.005** |
| **Highest PS (cm of H₂O)** # | 15 (0-23)  | 8 (5-15)      | 0.769    |
| **Highest Driving pressure (cm of H₂O)** # | 25 (10-34) | 17 (13-24) | 0.533    |
| **Highest Peak airway pressure (cm of H₂O)** # | 33 (16-38) | 19 (15-30) | 0.111    |

$ 3$ patients developed spontaneous pneumomediastinum

# Median and interquartile range

**Table 3 – Outcome**

|                            | ALS (n=16) | Not ALS (n=61) | P value |
|---------------------------|------------|----------------|----------|
| **Length of ICU stay (days)** # | 17.5 (10-19) | 9 (5-13) | **0.003** |
| **Length of Hospital stay (days)** # | 19.5 (16.25-23.25) | 16 (13-26) | 0.285    |
| **ICU free days** $ \$ | 7.3 ± 2.3 days | 12.1 ± 1.3 days | 0.085    |
| **Secondary Bacterial Pneumonia** | 8 (50%) | 13 (20.6%) | **0.023** |
| **Outcome**                |            |                | 0.151    |
| Alive and well at discharge | 7 (43.8%)  | 39 (61.9%)     |          |
| Discharged against medical advice | 1 (6.3%) | 6 (9.5%) |          |
| In-hospital mortality      | 8 (50%)    | 18 (28.6%)     |          |
| 28-day survival*           | 5 (35.7%)  | 38 (67.8%)     | 0.18     |
| 6-month survival*          | 5 (35.7%)  | 29 (51.7%)     |          |

$ \$ Median and interquartile range

*9 patients from the non-ALS group and 2 patients from the ALS group were lost to follow up.

$ Mean and SD
Table 4 – Multiple logistic regression analysis

|                                | Adjusted values     |           |     |
|--------------------------------|---------------------|-----------|-----|
|                                | OR                  | 95% CI    | P   |
| SpO2 at presentation (\%)      | 0.964               | 0.925-1.005 | 0.088 |
| Steroid therapy (Dexamethasone vs Methylprednisolone) | 12.572              | 1.639-96.418 | 0.015 |
| Highest PEEP (cm of H\textsubscript{2}O) | 1.447               | 0.870-2.406 | 0.154 |

Figures

Figure 1

Kaplan Meier graph showing survival probability in ALS vs Non-ALS group.
