Risk factors associated with barotrauma in patients with COVID-19

Original Article

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Abstract— Introduction: Barotrauma in mechanical ventilation is defined as lung damage attributable to the application of high airway pressure. In patients with COVID-19, the incidence of this complication is more common than in other ARDS patients with no clear pathophysiological path. **Aim:** The aim of this study was to determine the risk factors for developing barotrauma in patients under MV with COVID-19 associated ARDS. Secondary objectives were to determine the incidence of barotrauma and its association with mortality. **Patients and methods:** A case-control nested in a cohort study was performed in patients with SARS-CoV2 infection under MV, admitted in a Hospital in Mexico City from April 2020 to January 2021. Cases were defined as patients with barotrauma and controls were selected from a COVID-19/ARDS cohort. Demographic, ventilatory and clinical variables were analyzed. Prognostic univariate and multivariate modeling were carried out through logistic regression. **Results:** A total of 267 patients were included in the cohort, 15 patients developed barotrauma (5.6%) and 252 were controls. Significant differences between groups in ventilatory parameters such as PEEP (13±2 cmH_2O vs. 11±3 cmH_2O, p=0.04), tidal volume (431±49 mL vs 452±57 mL, p=0.05), PaO_2 (52±13mmHg vs. 62±15mmHg, p=0.05), and PaO_2/FiO_2 (56±18 vs. 66±16, p=0.05) were found. Barotrauma was more common in men (80% vs. 67%, p=0.05) and smokers (20% vs. 7.2%, p=0.05). The prognostic risk factors were smoking, higher PEEP, Hypotension, non-ICU hospitalization and SOFA score. **Conclusion:** This case control study provides insights on the risk factors for COVID-19/ARDS barotrauma development; smoking history, higher PEEP, hypotension, and non-ICU hospitalization. **Rev Med Clin 2021;5(3):e01092105024**

Keywords—Barotrauma, COVID-19, SARS-CoV2, ARDS.

Resumen— Factores de Riesgo Asociados a Barotraumata en Pacientes COVID-19. Introducción: El barotrauma por ventilación mecánica se define como el daño pulmonar atribuible a la aplicación de una presión elevada en las vías respiratorias. En los pacientes con COVID-19, la incidencia de esta complicación es más frecuente que en otros pacientes con SDRA, sin que exista una fisiopatología clara. **Objetivos:** El objetivo de este estudio fue determinar los factores de riesgo para desarrollar barotrauma en pacientes bajo VM con SDRA asociado a COVID-19. Los objetivos secundarios fueron determinar la incidencia de barotrauma y su asociación con la mortalidad. **Pacientes y Métodos:** Se realizó un estudio de casos y controles anidado en una cohorte en pacientes con infección por SARS-CoV2 bajo VM, ingresados en un Hospital de la Ciudad de México de abril de 2020 a enero de 2021. Los casos se definieron como pacientes con barotrauma y los controles se seleccionaron de una cohorte COVID-19/ARDS. Se analizaron variables demográficas, ventilatorias y clínicas. Se realizaron modelos pronósticos univariados y multivariados mediante regresión logística. **Resultados:** Un total de 267 pacientes fueron incluidos en la cohorte, 15 pacientes desarrollaron barotrauma (5,6%) y 252 fueron controles. Se encontraron diferencias significativas entre los grupos en los parámetros ventilatorios, como la PEEP (13±2 cmH_2O frente a 11±3 cmH_2O, p=0,04), el volumen tidal (431±49 mL frente a 452±57 mL, p=0,05), la PaO_2 (52±13mmHg frente a 62±15mmHg, p=0,05) y la PaO_2/FiO_2 (56±18 frente a 66±16, p=0,05). El barotrauma fue más frecuente en los hombres (80% vs. 67%, p=0,05) y en los fumadores (20% vs. 7,2%, p=0,05). Los factores de riesgo pronósticos identificados fueron el tabaquismo, PEEP elevada, hipotensión, hospitalización fuera de la UCI y la puntuación SOFA. **Conclusiones:** Este estudio de casos y controles proporciona información sobre los factores de riesgo para el desarrollo de barotrauma por COVID-19 con SDRA: antecedentes de tabaquismo, PEEP elevada, hipotensión y hospitalización fuera de la UCI. **Rev Med Clin 2021;5(3):e01092105024**

Palabras clave—Barotrauma, COVID-19, SARS-CoV2, SDRA.

INTRODUCTION

Barotrauma in mechanical ventilation (MV) is defined as lung damage attributable to the application of high airway pressure and is one of the potential mechanisms of ventilator-induced lung injury (VILI).[1] Previous studies have shown an increased mortality in patients with barotrauma under MV;[2] pneumothorax (PTX) being the most common presentation, but it can also present as pneumomediastinum (PM) with or without PTX, with extension to soft tissue as subcutaneous emphysema or even as pneumo-retroperitoneum and pneumo-scrotum.

Traditionally, underlying lung disease or age are known risk factors for non-trauma related barotrauma.[3] However, in patients with novel coronavirus disease (COVID-19), the incidence of this complication is more common than in non-infected patients, as recently reported.[4] Since little is known regarding which are the main risk factors for these events to develop, most pathophysiological mechanisms remain unexplained.

The aim of this study was to determine the risk factors for developing barotrauma in patients under MV with COVID-19 associated Acute Respiratory Distress Syndrome (ARDS). Secondary objectives were to determine the incidence of barotrauma and its association with mortality.

PATIENTS AND METHODS

Study Design and Population. From April 2020 to January 2021 a case-control nested in a cohort study was performed in patients with diagnosis of severe SARS-CoV2 infection and mechanical ventilation, admitted in a single-center community Hospital in Mexico City. Inclusion criteria for the COVID-19/ARDS cohort population were patients under MV fulfilling the Berlin definition for ARDS,[5] with positive SARS-CoV2 real time polymerase chain reaction aged between 18-90 years. Exclusion criteria included incomplete clinical records and other causes of extrapulmonary air such as trauma or evidence of PM/PTX before intubation. Cases were defined as patients with barotrauma consulted with the Surgery Department. Controls were selected from a random sample of the COVID-19/ARDS cohort. A simple randomization strategy was used matching by sex and age, with a case-control ratio of 1:6. Barotrauma was defined as a clinical and radiological finding of air outside the lungs associated with mechanical ventilation. According to imaging, barotrauma was defined as intrapleural (PTX) or extra pleural (PM, soft tissue emphysema, pneumoperitoneum).

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The cohort's time-zero was considered the day the patient was intubated and put under MV. The primary outcome variable was intra-hospital mortality. Other variables of interest determined as risk factors were ventilatory parameters such as positive end-expiratory pressure (PEEP), tidal volume, PaO_2/FiO_2 ratio and whether the patient received care in an intensive care unit (ICU) ward or not. Clinical variables were comorbidities, smoking history, laboratory results, D-Dimer (DD), C-reactive protein (CRP), sequential organ failure assessment (SOFA) score and infection history. All patients signed consent upon hospitalization. The study was approved by the Hospital's Ethics and Research Department.

Statistical analysis. Normality tests were performed for quantitative variables, expressing them with central tendency measures (mean or median) and dispersion (standard deviation and interquartile ranges). Qualitative variables were expressed in absolute frequencies and percentages. Bivariate analysis in qualitative variables was performed among subjects with and without barotrauma with chi-square or Fisher's exact test; while quantitative variables were analyzed with the Mann Whitney T or U test. Statistical significance was established for an alpha value of 0.05.

Prognostic modeling was carried out through logistic regression with an entry criterion of both biological plausibility and a value of $p<0.1$. Variables included in the final model used the B-coefficient value to estimate the individual probability of each patient with the following formula: P=e(constant+B1+B2 ...)/1-e. The area under the curve (AUC) of each of the probabilities along with the r^2 value was calculated for the model. All the analysis was made with SPSS version 25 for Mac.

RESULTS

From April 2020-January 2021, a total of 22,497 patients with COVID-19 received medical attention in our Hospital. A total of 1,190 patients were hospitalized of which 785 met the inclusion criteria. After exclusion, 267 patients were included in the cohort. During this period, a total of 15 patients developed barotrauma and 252 patients were randomized/matched as controls.

	No Barotrauma n= 85		Barotrauma n= 15		
Variable	**Mean**	**±SD**	**Mean**	**±SD**	**p**
Age (year)	58	12	55	12	NS
Weight (kg)	73	18	77	18	NS
Tidal Volume (mL/kg)	6.6	1.6	6.6	2.2	NS
Comorbidities	2	0.4	2	0-5	NS
PEEP (cmH_2O)	11	3	13	3	0.04
Total Volume (mL)	452	57	431	49	0.05
FiO_2	96	10	94	13	NS
PaO_2	62	30	52	13	0.05
$Sat0_2$ (%)	83	15	80	13	NS
PaO_2/FiO_2	66	36	56	18	0.05
Platelets (cel/mm^3)	272,929	88,842	296,400	92,146	0.03
Creatinine (mg/dL)*	0.9	0.7-1.2	0.5	0.8-1.3	0.02
Bilirubin (mg/dL)*	0.7	0.4-1.2	0.7	0.6	NS
SOFA score	5	2	5	1	NS
Admission DD (ng/mL)	3,499	2,944	3,386	1,200	NS
Highest DD (ng/mL)	2,120	1,855	1,616	1,091	0.01
Admission CRP (mg(dL)	31.09	9.74	31.81	11.7	NS
Highest CRP (mg(dL)	21.9	10.89	18.68	14.44	NS
Hospital Stay (days)*	18	11-25	12	19-35	0.03

Note: *Median (interquartile range, p25-p75); Stastical test: X^2, Mann Whitney U test, SD: standard deviation; NS: non-significant.

TABLE 1: QUANTITATIVE VARIABLES COMPARISON BETWEEN GROUPS.

The initial cohort of patients with ARDS and MV had a mean age of 56±13 years, 189 of them (75%) were men, and the overall mortality was 83%. The control group consisted of patients who were randomly selected from the cohort according to the matching criteria.

When comparing the quantitative variables between groups (Table 1), there were no statistically significant differences in the anthropometric values. In contrast, ventilatory parameters such as PEEP (13±2 cmH_2O vs. 11±3 cmH_2O, p=.04), total volume (431±49 mL vs 452±57 mL, p=0.05), PaO2 (52±13mmHg vs. 62±15mmHg, p=0.05), and the PaO_2/FiO_2 ratio (56±18 vs. 66±16, p=0.05) were statistically significant. As well, significant differences in biochemical parameters were found in platelet values, serum creatinine and DD upon hospital admission.

Qualitative variables shown in Table 2, revealed that men had a higher proportion of barotrauma patients (80% vs. 67%, p=0.05) along with a higher presence of smoking history (20% vs. 7.2%, p=0.05); there were no differences between both groups regarding comorbidities and mortality.

The prognostic model included ventilatory (PEEP, tidal volume, PaO_2 and PaO_2/FiO_2 ratio), clinical (hypotension, smoking, SOFA score, ICU hospitalization) and biochemical variables (platelets, creatinine, CRP and DD). These were initially tested in a categorized manner. The final resulting variables were smoking history, PEEP, Hypotension, non-ICU hospitalization and SOFA score, as shown in Table 3, with a value of r^2=0.78 and an AUC of 0.82 (Figure 1).

	No Barotrauma n= 85		Barotrauma n= 15		
Variable	**n=**	**%**	**n=**	**%**	**p**
Gender					NS
Female	28	32.9	3	20	
Male	57	67.1	12	80	
Diabetes Mellitus 2	25	30.1	6	40	NS
Hypertension*	24	28.6	3	20	NS
Smoking history*	6	7.2	3	20	NS
Death	69	82.1	13	86.7	NS

Note: Statistical test: X^2, *Fisher exact test; NS: non-significant.

TABLE 2: COMPARISON OF QUALITATIVE VARIABLES BETWEEN GROUPS.

In patients with barotrauma, the most common clinical presentation was extra-pleural air with PM and subcutaneous emphysema in 7 patients (46.7%), four patients had isolated PTX (26.7%) and four had both intra and extra-pleural air in imaging studies (26.7%) as seen in Figure 2. Most of the patients with barotrauma were males (80%), with an age of 54.5±12.3 years. No significant differences were found in their pre-post barotrauma ventilatory parameters. Only one required a thoracotomy for closure of a bronco-alveolar fistula. The median hospital stay for barotrauma patients was 12 (19-35) days vs 18 (11-25) days in the control group. Detailed clinical records are described in Table 4.

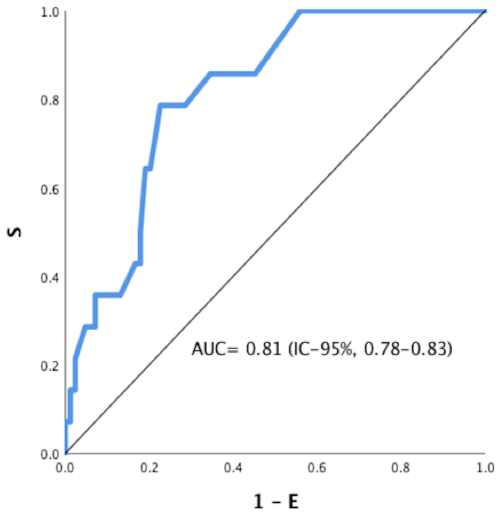

Figure 1: AUC prognostic model for developing 287 barotrauma in SARS-COV2 patients under mechanical ventilation.

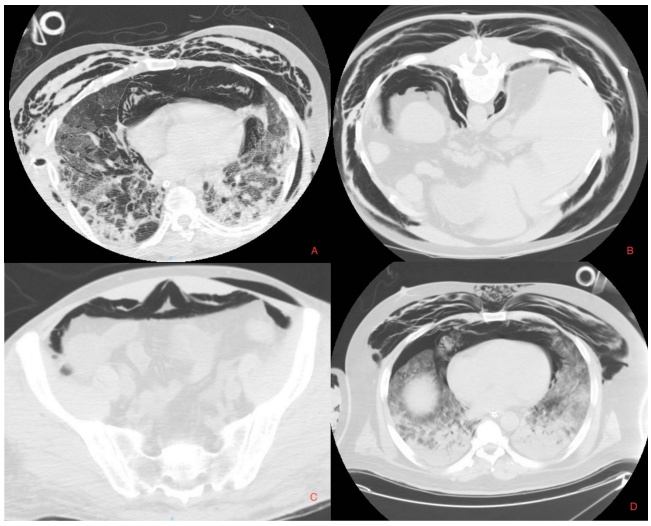

Figure 2: Imaging studies of different presentations of 302 Barotrauma in COVID19. **A.** Patient with pneumomediastinum and extension to subcutaneous planes; **B.** Patient with pneumo-retroperitoneum and soft subcutaneous emphysema; **C.** Patient with pneumothorax, pneumomediastinum and subcutaneous emphysema; **D.** Patient with pneumoperitoneum and subcutaneous emphysema.

DISCUSSION

The incidence of PTX and PM in COVID-19 has been difficult to document. From the initial case series, the incidence varies between 0.66% and 56%.[6,7] These differences respond to mixed data between intubated and non-intubated patients. Previously studied COVID-19 ARDS cohorts have shown increased incidence in this specific population of nearly 6.5%,[8] consistent with our study population, where incidence was 5.6% in only-ventilated patients.

Gattinoni et. al. have compared the mortality of patients under MV with ARDS to be increased when PTX is present compared to when it is not (66% vs. 46%),[2] further corroborated by Anzueto et al. (51 vs. 39).[8] However, these studies date from before Berlin criteria were established and thus may represent a great patient heterogeneity inside the ARDS cohorts studied. Although initial COVID-19 studies with very small samples have found differences in survival between barotrauma and non-barotrauma patients with COVID-19 associated ARDS,[9,10] other recent studies[11] including our own, have not been able to find differences in mortality, this discordance between both incidences and mortality can be explained by study heterogeneity (mostly case reports) and small samples currently published.

Barotrauma is mostly attributed to lung damage due to supra-physiological stress and strain, which can pro-

	Beta coefficient	OR	IC95%		p
Smoking history	0.54	1.60	1.10	1.80	**0.05**
PEEP (cmH_2O)	0.19	1.40	1.10	1.70	**0.04**
Hypotension severity*	1.73	5.66	1.62	19.74	**0.007**
SOFA score	-1.08	0.34	0.16	0.71	**0.004**
Non-ICU hospitalization	1.15	3.1	2.1	5.2	**0.0001**
Constant	4.14				

Note: PEEP: Post Expiratory End Pressure, SOFA: Sequential Organ Failure Assessment
*Modified from SOFA score: 0=no hypotension, 1=hypotension, 2=norepinephrine or dopamine infusion
Included variables: age, SatO2%, DD, CPR, PaO2/FiO2

TABLE 3: PROGNOSTIC MODEL FOR DEVELOPING BAROTRAUMA IN SARS-COV2 PATIENTS UNDER MECHANICAL VENTILATION.

mote proinflammatory cytokines and migration of white cells provoking acute pulmonary inflammation known as biotrauma.[12,13] This is explained due to uneven elasticity and stiffness in consolidated parenchymas, such as in patients with SARS-CoV2 pneumonia. In our study, PM with soft tissue involvement was the most common diagnosis in over half of these patients (46.7%).

It has been hypothesized that alveolar rupture during ARDS is explained by structural damages during the recruitment and de-recruitment of the lung. The abnormal and heterogeneous alveolar pressure along with the counter-wise negative pleural pressure induces an increased transpulmonary pressure that stretches cellular junctions between pneumocytes.[7] This is why the use of neuromuscular blockers in ARDS, which nullify the patient's pleural pressure, has been related with a decrease in PTX incidence in these populations.[14] Since the most common complication of COVID-19 is pneumonia, with a further requirement of mechanical ventilation and consequently ARDS, it is natural to extrapolate previous studies from ARDS cohorts to these patients. Specifically, McGuiness et al. found a difference in barotrauma incidence between COVID-19 and a previous ARDS cohort (15% vs 10%; p=0.04).[4]

Despite this, there is no clear evidence regarding the pathophysiology of barotrauma in patients with COVID-19. Early ARDS studies have stated that ventilatory parameters like peak pressure (PIP), plateau pressure (PP), positive end-expiratory pressure (PEEP), and tidal volume (TV) are correlated with barotrauma.[15] However, two previous COVID-19 studies have shown that ventilatory parameters do not correlate with barotrauma development,[11,16] or are even temporally discordant with barotrauma development.[3] In our study, PEEP values did show significance as a risk factor for barotrauma as Elsaaran et al. have also reported.[17] In this study, PEEP as a risk factor can be explained by another risk factor identified such as non-ICU stay. Unlike a controlled-ICU setting where ventilatory parameters are carefully monitored, general wards reconverted during the pandemic can lack strict control and propitiate more barotrauma-prone environment.

An additional explanation for the increased incidence of PTX and PM in COVID-19 patients can come from the fact that the intubation procedure alone in these patients has a 5.9% incidence of PTX as a complication.[18] Some studies have hypothesized that increased tracheal edema or procedural manipulation of the airway might account for these findings.[10] However, it contrasts with the fact that PTX and PM have been both found in non-intubated patients with COVID-19.[11] This opens the door to hypothesize that other phenomena like cystic or fibrotic structural changes in the lung parenchyma, mucus impaction, and alveolar heterogeneity, or intrathoracic pressure increase due to cough could be the underlying mechanisms for an increased incidence of PTX and PM in COVID-19 patients.[6,10]

Moreover, our patients with barotrauma had a mean of 8.4 days of mechanical ventilation prior to intrathoracic air findings, which corresponds to previous evidence that shows that the incidence of pneumothorax in ARDS is higher in patients with > 2 weeks of mechanical ventilation vs. < 1 week (87% vs. 30%)[2] and also correlates with longer ICU stay.[8]

Patient No.	Gender	Age (yr)	MV prior BT (days)	SOFA* score	PEEP* (cmH_2O)	FiO_2*	TV* (mL)	PaO_2 /FiO2*	Diagnosis	Treatment	Death (y/n)
1	F	60	10	4	12	80	380	55	PTX, PMT, EMP	Chest tube	Y
2	M	42	1	9	12	100	520	36	PTX bilateral	Bilateral Chest tube	N
3	M	56	10	6	15	100	450	65	PMT, EMP	Chest tube	Y
4	M	46	8	4	13	100		60	PMT, EMP	Chest tube, Fasciotomy	Y
5	M	51	11	7	10	100	450	162	PTX	Chest tube	Y
6	M	67	17	3	12	30	265	127	PMT, EMP	Chest tube	Y
7	M	34	4	6	16	90	450	104	PMT, EMP	None	Y
8	F	63	8	4	10	100	400	53	PTX bilateral	Bilateral Chest tube	Y
9	M	70	1	4		100			PTX	Chest tube	Y
10	M	48	9	4	14	75	490	55	PTX, PMT, EMP	Chest tube, Fasciotomy	Y
11	M	52	7	5	18	100	450	94	PMT, EMP	Chest tube	Y
12	F	39	1	8	12	100	400	56	PTX, PMT	Chest tube, Lobectomy	N
13	M	80	20	7	12	35	410	82	PMT, EMP	Fasciotomy	Y
14	M	52	14	4	14	65	450	85	PTX, PMT, EMP	Chest tube	Y
15	M	59	6	8	20	100	360	37	EMP	Fasciotomy	Y
Median ±SD	54.6±12.3	8.4±5.6	5.5±1.8	13.5±2.8	83±24	421±64	76±35				
Range	34-80	1-20	3-9	10-20	30-100	265-520	36-162				
Total n=(%)											13(86.7)

Note: MV: mechanical ventilation, BT: barotrauma, SOFA: Sequential Organ Failure Assessment, PEEP: Post Expiratory End Pressure, FiO2: Inspiratory oxygen fraction, PTX: pneumothorax, TV: total volume, PMT: pneumomediastinum, EMP: subcutaneous emphysema.
*Day of barotrauma

TABLE 4: CLINICAL AND VENTILATORY CHARACTERISTICS OF PATIENTS WITH BAROTRAUMA.

Further analyzing risk factors that might predispose to barotrauma beyond ventilatory parameters, traditional risk factors for PTX development such as male sex and smoking history are consistent in this study. While previous publications have shown that acidosis in this subgroup of patients correlated with mortality,[11] this study identified other specific risk factors for mortality such as hypotension, SOFA score, smoking, and treatment in an non-ICU ward. All these variables, along with PEEP values build up a prognostic model that, although requiring further validation in prospective cohorts, sheds some light regarding both pathophysiology and clinical management of these patients. Specifically, both SOFA and hypotension speak of disease severity which correlates with the previously mentioned pH decrease as a risk factor for barotrauma. As also previously mentioned, staying in a controlled environment such as an ICU is another relevant protective factor for barotrauma development.

Despite its retrospective design being this study's main limitation, a robust randomized control selection nested inside a COVID-19-ARDS cohort with a 6:1 matching strategy, offers validity to the results compared to previous publications. Furthermore, even when pre-post barotrauma ventilatory values were not significant, our findings gear pathophysiology hypothesis more towards lung-specific features than to ventilatory-parameter originated barotrauma.

Conclusions

In conclusion, this case-control study provides insights into the risk factors for COVID-19-ARDS barotrauma development. Although further prospective studies are required to validate these findings, they currently aid in explaining the pathophysiological mechanisms that might be involved in this patient population.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

ClinicalTrials.gov Identifier

NCT04859881

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