Original Article

A Retrospective Observational Study to Analyze Recruitment Paradigms in the Treatment of Hypoxemic COVID-19 Patients Admitted in the Intensive Care Unit of a Tertiary Care Institute in India

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Abstract

Introduction: This retrospective study attempted to assess the recruitability of the lungs that were affected by acute respiratory distress syndrome (ARDS) due to COVID-19. This was done with the combined use of transpulmonary pressure monitoring (to limit the stress), measurement of end-expiratory lung volume (EELV) (to measure the actual volume gain and be within limits of strain), electrical impedance tomography (EIT), and compliance (to diagnose overdistension). Recruitment was judged clinically by an increase in the SpO_2 values. **Methods:** Retrospective data from the charts and progress sheets were collected from 27 patients admitted to the intensive care unit (between February 2021 and June 2021) with a ratio of arterial Partial pressure of oxygen (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2) <150 (i.e., PaO_2/FiO_2 <150) with a diagnosis of ARDS. The esophageal pressure was monitored using the polyfunctional nasogastric tube (Nutrivent™). The end-expiratory volume was measured using the Carescape R860 (GE Healthcare) by the nitrogen multiple breath wash-out/wash-in (EELV) at a positive end-expiratory pressure of 5. EIT measurements were performed using the Pulmo Vista 500. We performed a recruitment maneuver using the "staircase maneuver." **Results:** As per the results of our study, we found that almost 2/3rd (66.7%) of the patients affected with COVID lungs affected with ARDS were recruitable. **Conclusion:** The results of our study again make us believe that majority of COVID-19 lungs affected with ARDS may be recruitable in the earlier stage of the illness (within the 1st week of ARDS). Thus, in such patients, safe, monitored lung recruitment should be attempted to improve oxygenation rather than directly proning the patient, which is fraught with its own set of complications.

Keywords: Acute respiratory distress syndrome, COVID-19, electrical impedance tomography, transpulmonary pressure

INTRODUCTION

One of the most interesting and intriguing pathologies in critical care has been acute respiratory distress syndrome (ARDS). The mortality of this pathology has been nearly the same at 30%–40% in the past 15 years. Apart from lung-protective ventilation and prone positioning, not many interventions have convincingly improved mortality in ARDS.[1] As per the results from the RECOVERY trial, mortality at 28 days was lower among hypoxic patients who received dexamethasone than among those who received the standard of care. The pooled estimated mortality for COVID-19 ARDS as per the data from March to July 2020 was 39%, with some countries such as China reporting 69%–72% (95% confidence interval [CI]: 67%–72%) and others like Germany reporting as low mortality as 13% (95% CI: 2%–29%).[2] Hypoxia is an independent predictor of mortality.[3] It is also known that alveolar recruitment improves oxygenation.[4] Investigators have studied the recruitability of COVID patients, with the

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majority of these concluding that the COVID-19 lungs are largely nonrecruitable. This was a retrospective study including COVID-19 patients who developed ARDS. We attempted to determine whether these patients' lungs were recruitable with the combined use of transpulmonary pressure monitoring (to limit the stress) and measurement of end-expiratory lung volume (EELV) (to measure the actual volume gain and be within the limits of strain). The strain is the volume applied by the ventilator (tidal volume [VT]) relative to the volume within the lung available for gas exchange (EELV, i.e., EELV or the, i.e., functional residual capacity [FRC]). Hence, strain is VT/EELV.[5] Patients with acute lung injury and a strain >0.27 are known to produce significantly more inflammatory cytokines, measured in bronchoalveolar lavage fluid, contributing to biotrauma and ventilator-induced lung injury.[6] Hence, to limit the strain, the VT was kept at 25% of the measured EELV, a combination of electrical impedance tomography (EIT) and compliance (to diagnose overdistension). Recruitment was judged clinically by an increase in the SpO_2 (oxygen saturation) values.

METHODS

After ethics committee approval (ECR/70/Inst/MH/2013/RR-19), retrospective data from the charts and progress sheets were collected from 27 patients admitted to the intensive care unit (ICU) (between February 2021 and June 2021) with a PaO_2/FiO_2 ratio <150 with a diagnosis of ARDS. Patients who had respiratory insufficiency due to pulmonary edema from the cardiac origin, pneumothorax, chronic obstructive pulmonary disease, pulmonary embolism, and those who required vasopressors to maintain hemodynamics were not included. All patients were paralyzed with nondepolarizing neuromuscular blocker vecuronium bromide and sedated using dexmedetomidine and fentanyl to a Richmond agitation sedation scale of 0 to − 1.

We monitored the absolute values of the esophageal pressures to determine the pleural pressure. The measurement of the pleural pressure by measuring the esophageal pressure (Pes) determines the fraction of airway pressure (Paw) applied to overcome lung and chest wall elastance. The difference between Paw and Pes is the transpulmonary pressure (Ptp) which is the distending pressure of the lung. Pes is often elevated in patients with ARDS. Often, it is noticed that the transpulmonary pressure can be negative at the end-expiration. This may indicate closed airways, fluid overload, or collapsed lungs. At this stage, positive end-expiratory pressure (PEEP) could be increased gradually until Ptp becomes positive at end-expiration to keep airways open.[7] Conversely, Pes could also determine whether the applied peep is too high, thus causing increased lung "stress" (for example, during excessive recruitment).[8] Measuring the FRC or the EELV will help determine the aerated lung available for ventilation and help monitor ventilation strategies. The EELV can be measured on some modern ventilators with the help of inbuilt wash-out/wash-in techniques using nitrogen or oxygen. This technique has been used for many years and has been described extensively elsewhere.[9,10]

In short, in this technique, the ventilator calculates the aerated lung volume (EELV) by continuously measuring end-tidal oxygen and end-tidal carbon dioxide during a small change in the FiO_2 (Fraction of inspired oxygen) using a gas exchange module of the ventilator. This technique is sufficient to detect EELV change >200 mL accurately.[11]

EIT is a validated noninvasive, radiation-free real-time imaging method to assess ventilation distribution, measure changes in lung volumes, pick up overdistension of lung zones, and assess regional respiratory mechanics.[12] This is done by placing a 16 electrode belt around the thorax 5 cm above the xiphoid level, sending data to the bedside monitor. The bedside monitor displays a real-time cross-sectional image of the lung. Further, the EIT data, with the help of software, measure the regional compliance per pixel of the image. This colored pixel map helps find the optimal PEEP and show the regional areas of overdistension in real-time.[13] The measured regional lung volume changes correlate well with volume changes detected on computed tomography (CT).[14]

We monitored Pes using the polyfunctional nasogastric tube (Nutrivent™, Sidam, Italy). Correct positioning was tested with a "dynamic occlusion test."[7]

The EELV was measured using the Carescape R860 (Carescape R860; GE Healthcare, Chicago, IL, USA). The Carescape R860 performs EELV measurements based on monitoring the change of N_2 (nitrogen) concentration measured in the airway (modified nitrogen dilution method). The concentration of inspired N_2 is changed by changing the delivered FiO_2 concentration.

EIT measurements were performed using the PulmoVista 500 (Dräger Medical, Lübeck, Germany). An EIT electrode belt with 16 electrodes was placed around the thorax 5 cm above the xiphoid level.

We used a combination of EIT and EELV to differentiate between the true anatomical recruitment of collapsed alveoli or overdistension of already open alveoli.[15]

Lung recruitment is generally provided as a rescue intervention in those patients whose PaO_2/FiO_2 ratio is < 150 and other methods of open lung approach like high PEEP. These maneuvers are known to cause an improvement in oxygenation and lung compliances. However, an unmonitored excess increase in transpulmonary pressure may result in barotrauma and hemodynamic compromise.[16] Hence, recruitment maneuvers are contraindicated when there is hemodynamic instability, pneumothorax, or raised intracranial pressure. As described above, the Ptp (to limit "stress") and EIT (which demonstrated overdistension) was monitored to know the limits of pressure that could be increased for safe and optimal recruitment. Recruitment could be provided by many methods, such as sustained inflation, applying sigh breath, and a stepwise increase in airway pressure/PEEP.[17-19]

All patients included in this study had a PaO2/FiO2 ratio of <150 were hemodynamically stable, and thus qualified for using a recruitment maneuver. We performed a recruitment maneuver using the stepwise increase in airway pressure called the "staircase maneuver," as this form would recruit lung units as effectively as sustained inflation. Moreover, the lower mean airway pressure would lead to less hemodynamic compromise and lesser hyperinflation.[20]

The patients were ventilated with a pressure-controlled mode at a FiO_2 of 80% and with the driving pressure (pressure control – PEEP) maintained at 15. The PEEP was progressively increased in steps of 5. 2 min were spent at each PEEP setting since most of the EELV changes are known to occur in 2 min.[21] The inspiratory transpulmonary pressure was noted at each step. The PEEP increase was continued until the transpulmonary pressure reached 25 or the PEEP reached 40 (whichever occurred earlier). At each step, the ventilator calculated the static compliance after performing an inspiratory hold maneuver for 3 sec. The EELV was measured using the nitrogen wash-out technique using the Carescape R860 FRC maneuver. At each step, the change in the EIT was measured at four different quadrants to pick up overdistension, as indicated by a disproportionate change in the values measured in the quadrants. At any given moment, if there was a drop in the mean arterial pressure by 10%, the maneuver was abandoned and attempted again later within the same day. Anatomical recruitment was inferred by a combination of improved EELV, improved compliance, and improved air distribution with the absence of overdistension as measured by EIT.[22] Clinical recruitment was defined as a combination of anatomical recruitment and an increase in SPO_2 by 3% at the end of 2 h and 4 h. Furthermore, PEEP was set to maintain the expiratory transpulmonary pressure of 5 as per the EPVent 2 study protocol (as the FiO_2 was set at 80%).[23]

Statistical analysis

The categorical variables are presented as frequency and percentage (%), and continuous variables are presented as mean and standard deviation. The comparison between pre- and postrecruitable was tested using a *t*-test, whereas repeated-measures ANOVA was used to test follow-ups such as 2 h and 4 h. Statistical significance is assumed at a value of $P < 0.05$.

RESULTS

The details of the patients with laboratory markers are tabulated in Table 1, and the severity of illness parameters and comorbidity status is shown in Table 2.

The majority of the patients had a moderate CT severity score (66.7%) with comorbidities (74.1%).

Respiratory parameters

Table 3 and Figure 1 show the average plateau pressure (cm of H20), mean compliance, FRC, and SPO_2 noticed before the attempt at recruitment and after recruitment, and 2 h and 4 h postrecruitment. Figure 2 shows the average plateau pressure in our study. Various other studies have reported the plateau pressure value to be between 20.5 and 31 cm H2O.[24-26] The mean compliance in our study is shown in Figure 3. Other studies have reported wide variability in compliances ranging from 24 to 49 ml/cmH2O.[25-27] The EELV or FRC is the absolute lung volume most commonly monitored at the bedside. The mean prerecruitment FRC in our patients is shown in Figure 4. After conducting the staircase maneuver, the plateau pressure remained at 25.56, with a standard deviation of 3.641. However, the mean compliance rose to 31.926 (from 26)

Table 1: Patient details with laboratory markers

	Mean±SD
Age	61.04±10.48
Hemoglobin	13.06±2.00
WBC	13.92±8.13
Platelets	2.53±0.99
CRP	95.12±68.64
PCT	0.49±1.04
LDH	545.93±343.64
D-DIMER	1.47±1.73
Creatinine	1.39±1.45
IL6	225.29±267.93
Serum Ferritin	832.08±631.56

WBC: White blood cells, CRP: C-reactive protein, PCT: Procalcitonin, LDH: Lactate dehydrogenase, IL6: Interleukin-6, SD: Standard deviation

Table 2: Patient details with comorbidities and severity of illness scores

	Frequency (%)
Sex	
Male	22 (81.5)
Female	5 (18.5)
Comorbidities	
No	7 (25.9)
Yes	20 (74.1)
CT severity score	
10-15 - moderate	18 (66.7)
>15 - severe	9 (33.3)
APACHE II score	
<10	2 (7.4)
11-20	17 (63.0)
>20	8 (29.6)
SOFA score	
0-6	11 (40.7)
7-9	7 (25.9)
10-12	8 (29.6)
>12	1 (3.7)

CT: Computed tomography, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment

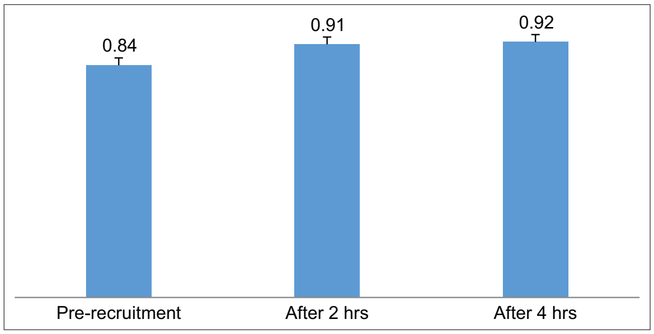

Figure 1: Average plateau pressure (prerecruitment plateau pressure) and compliance (prerecruitment C) *Pre recruitment is significantly different from after 2 h and 4 h at $P = 0.000$. FRC: Functional residual capacity

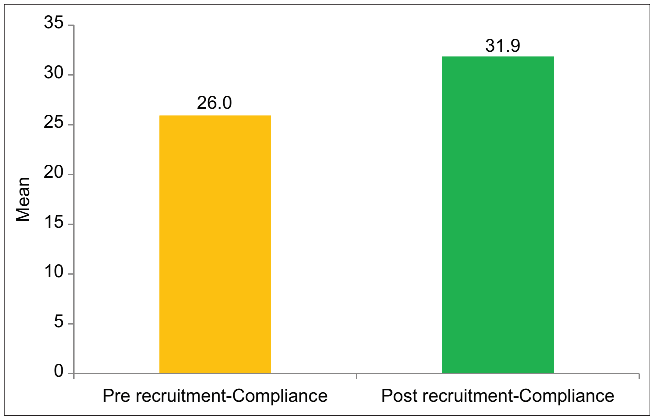

Figure 3: Difference between prerecruitment and postrecruitment in terms of compliance

with a standard deviation of 10.099. Postrecruitment, there was a marked rise of FRC to 1581.778 with a standard deviation of 311.049 ml. Prerecruitment, the means SPO2 was 83.6%, with a standard deviation of 3.9%. Postrecruitment at 2 h, the SPO2 had reached 91.1% with a standard deviation of 5.4% and remained the same at 91.9% with a standard deviation of 7.5% after 4 h. Among the 27 patients' clinical recruitment (rise in spo2 maintained at 2 and 4 h along with the absence of overdistension as seen on EIT with an increase in FRC and compliance) was seen in 18 patients (66.7%) [Figure 5].

DISCUSSION

ARDS occurs due to a dysregulated or hyperregulated innate cell-mediated immune response that causes damage to the alveoli of the lungs.[28] Lung protective ventilation strategy and prone ventilation stand tall among all the methods which have demonstrated a reduction in the mortality of ARDS patients. A classically prone position is attempted when the PaO_2/FiO_2 ratios are below 150 with a FiO_2 of 60% or more with the intention of "homogenization" of the lung fields and improving the ventilation of the dorsal part of the lung.[29,30] PEEP has been employed to reduce atelectrauma and to recruit the collapsed alveoli to improve hypoxemia (one of the reasons for which

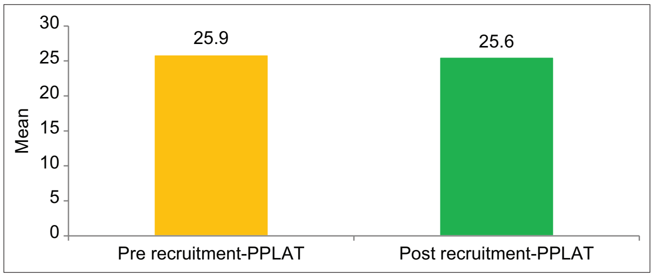

Figure 2: Difference between prerecruitment and postrecruitment in terms of PPLAT: plateau Pressure

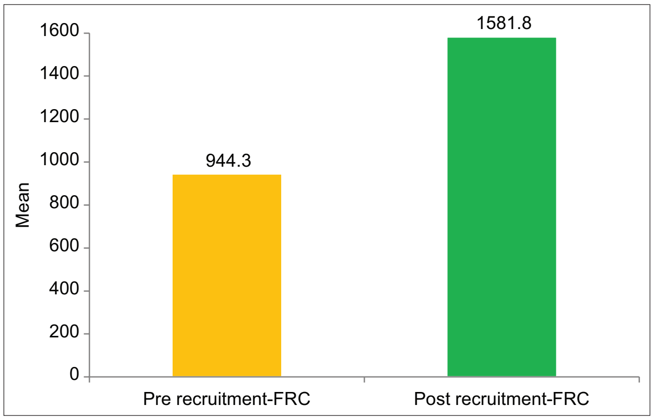

Figure 4: Difference between prerecruitment and postrecruitment in terms of FRC. FRC: Functional residual capacity

prone ventilation is performed). Subgroups analysis of large, well-conducted trials seems to suggest improved survival among those ARDS patients who objectively responded by increased oxygenation to an increased PEEP.[31]

Recent trials such as the ICU ROX trial- Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy trial, the oxygen ICU trial, and the Improving Oxygen Therapy in Acute-illness (IOTA) trial have called for a conservative oxygen strategy largely targeting a saturation between 90% and 96% with advice to avoid extremely low (<88% SpO_2 levels) and high (>96% SpO_2 levels).[32-34] However, a recent multicenter randomized, liberal, or conservative oxygen therapy for ARDS trial, the LOCO-2 trial in ARDS patients, showed no difference in mortality in patients at 28 days with increased 90-day mortality in the conservative group (SpO_2 target 88%–92%) compared to the liberal oxygen (SpO_2 > 96%).[35] Thus, targeting a SpO_2 of 92%–96% in the COVID ARDS patients seems to be at least without harm. Death from COVID-19 ARDS is due to respiratory failure (53%) followed by respiratory failure combined with cardiac failure (33%) with myocardial damage and circulatory failure and unknown causes contributing to the remaining.[36] Studies have shown hypoxia to be an independent predictor of mortality in COVID-19.[3] In this regard, no single ventilation strategy has been convincingly found to be the ideal one. The open lung approach with individualization of PEEP is one such approach that would also be of help in understanding

Table 3: Average plateau pressure (prerecruitment plateau pressure) and compliance (prerecruitment C)

	Prerecruitment	Postrecruitment	After 2 h	After 4 h	*t*
PPLAT	25.89±2.47	25.56±3.64			0.427
Compliance	26±7.54	31.93±10.09			−6.37***
FRC	944.26±196.9	1581.78±311.05			−12.63***
SPO_2	84%±3.9%^{a}		91%±5.4%	92%±7.5	16.94***
SPO_2/FIO_2			158.38±45.120		

***P=0.000; ^{a}Significantly different from after 2 h and 4 h at P=0.000. PPLAT: Average plateau pressure, FRC: Functional residual capacity, SPO_2: Arterial oxygen partial pressure, FIO_2: Fractional inspired oxygen

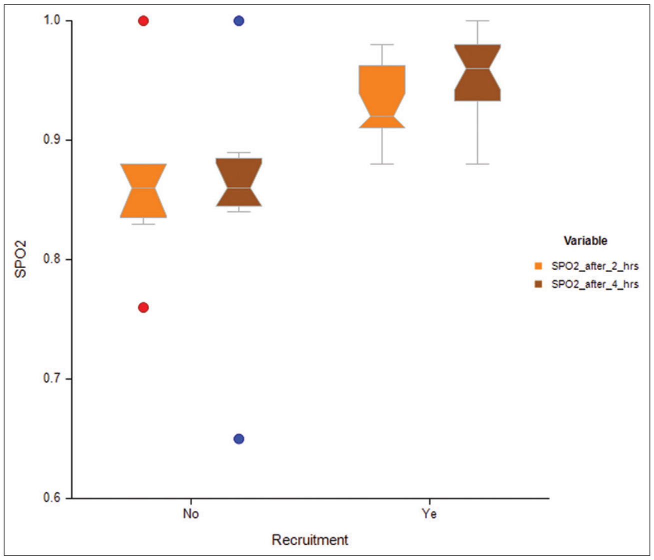

Figure 5: Average SPO_2 at 2 and at 4 h gained in those that were anatomically recruitable (based on EIT and EELV) and anatomically not recruitable (based on EIT and EELV). EIT: Electrical impedance tomography, EELV: End-Expiratory Lung Volume

whether the lungs are recruitable. Numerous studies have been done to assess the lung recruitability and individualization of PEEP. Some of these studies have concluded that the majority of COVID-19 ARDS lungs were nonrecruitable.[37,38] However, the results of this study and, in the author's opinion, this statement may not be true. There are many recruitment methods, and there is no single method that is superior to the other. Some studies in COVID-19 have reported recruitability of lungs when there was a rise in the PaO_2 and static compliance with a decrease of $PaCO_2$ (partial pressure of carbon dioxide in arterial blood) after PEEP was increased to 15 from 5 after a baseline period of ventilation at 6 ml/kg VT and PEEP of 5 min.[37] Others have tried using the recruitability to inflation ratio as a means to judge the potential for recruitment.[38] Common to all strategies is the use of "lung-protective" ventilation, including limited VT, and low end-inspiratory plateau pressures while maintaining sufficiently high PEEP. At present, all the pressures monitored (airway opening pressure, plateau, and PEEP) reflect a combination of alveolar distending pressure and chest wall distending pressure. In respiratory failure patients, the chest wall mechanical properties often contribute substantially and unpredictably to total respiratory impedance. Hence, the plateau or airway opening pressure may not adequately predict lung distension.[39] The pleural pressure or chest wall pressure can be measured from the esophageal pressure surrogate.[40] The actual distending pressure would thus be the difference between the plateau and esophageal pressure.

Recruitment would involve a maneuver to open up collapsed units. The limits of recruitment could be guided by measuring the inspiratory transpulmonary pressure. It is important to avoid negative expiratory transpulmonary pressure to keep the lung open. After a recruitment maneuver, few methods can be used to determine actual recruitment (opening of closed alveoli) or just overdistension of the existing alveoli.[41-45]

Method 1

Superimposing pressure-volume curves recorded from PEEP and zero end-expiratory pressure on a common volume axis. This could be achieved by using a prolonged expiration from PEEP to zero end expiratory pressure. The volume difference between the curve recorded from PEEP and the curve recorded at zero expiratory pressure for a given airway pressure would correspond to alveolar recruitment.[41]

Method 2

By the measurement of the difference in expired volumes during two test cycles preceded by ventilation in zero end-expiratory pressure and PEEP.[42]

Method 3

By analyzing the shape of the pressure trace in the volume-controlled mode of ventilation with a constant inspiratory flow.[41]

Method 4

By studying the volume of gas penetrating the nonaerating or poorly aerated lung regions when peep was applied.[43]

Method 5

Bedside assessment of regional lung ventilation using electric impedance tomography during the application of the recruitment maneuver.[44]

Method 6

By studying the intrapulmonary gas at the end of expiration, which is the EELV or the FRC, the nitrogen washout technique with the rationale that the higher the FRC, the alveoli recruited.[45]

Our method of studying recruitment involved method 5 and method 6 along with the use of a staircase maneuver to recruit the lung with the use of transpulmonary pressure monitoring to limit the stress delivered during the recruitment, thus, making recruitment "safer."

As per the results of our study, we found that almost 2/3rd (66.7%) of the COVID ARDS lungs were recruitable safely. As shown in Figure 6, earlier this year in January 2021, Sang *et al.* studied lung recruitability by assessing the improvement of PaO2, PaCO2, and static respiratory system compliance as PEEP was increased from 5 to 15 in 20 patients. This study demonstrated that the ability to recruit COVID 19 ARDS was only 20%.[37] However, there was no measurement of EELV or any way to study whether there was overdistension. The method of recruitment was not a standardized method and the sudden rise of PEEP from 5 to 15 would have potentially led to overdistension rather than homogenization of the lung. Owing to these reasons, the results of this study could be doubtful. In another study, Pan *et al*. used the recruitablity/inflation ratio to judge the potential for recruitment. This study concluded that only 83% (10/12 patients) of patients in COVID 19 induced ARDS were poorly recruitable (R/I ratio, 0.21 ± 0.14) on the 1st day of observation.[38] However, this recently studied new mechanics-based index to assess recruitability (R/I ratio) needs further validation and may not be ready for real-time till further studies.

Limitation

Our study has a few limitations, including the fact that this was a single-center nonrandomized observational study. However, this study would lay the impetus to conduct a larger well conducted randomized control trial in this regard to study the validity of our results.

CONCLUSION

Our study is the first study to comprehensively study recruitment in COVID-19 ARDS patients with the best available techniques in the present era. As per the results of our study, almost 2/3rd of COVID-19 patients were recruitable.

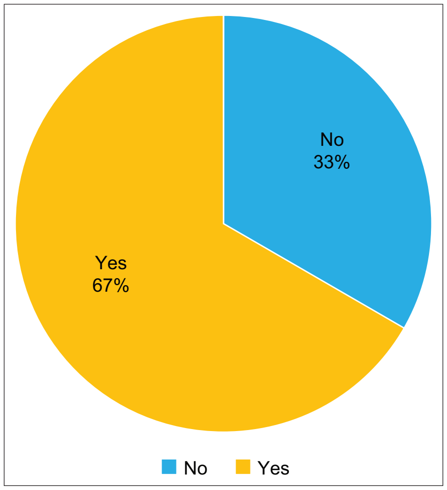

Figure 6: Frequency of recruitable

This result is rather contrasting to what earlier results have shown. However, the discrepancy in the results may be because the few published studies on this subject may not have been as comprehensive as the study from our center. The results of our study again make us believe that majority of COVID-19 affected patients in ARDS may be recruitable in the earlier stage of the illness (within the 1st week of ARDS and mechanical ventilation) and thus warrant a trial of a safe monitored recruitment strategy to improve oxygenation rather than directly proning the patient which in itself is fought with its own set of complications.

Financial support and sponsorship

Nil.

Conflicts of interest

This is a retrospective study based upon the routine practice of ICU care, and data collected from the available information of the routine protocols; therefore, no consent was obtained. Ethics committee approval has been taken for the same.

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