SYSTEMATIC REVIEW/META-ANALYSIS

Prognostic Significance of Driving Pressure for Initiation and Maintenance of ECMO in Patients with Severe ARDS: A Systematic Review and Meta-analysis

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Received on: 07 September 2024; *Accepted on:* 21 December 2024; *Published on:* 31 January 2025

Abstract

Introduction: In life-threatening conditions like severe acute respiratory distress syndrome (ARDS), rescue interventions like extracorporeal membrane oxygenation (ECMO) should be initiated urgently to resolve an otherwise potentially adverse clinical outcome. Driving pressure (DP) is an independent prognosticator of the survival of ARDS during mechanical ventilation. We conducted this review with the objective to identify the optimal DP for initiating ECMO in severe ARDS and to study the change in DP during ECMO strategy in survivors and non-survivors.

Materials and methods: A systematic search of EMBASE, PubMed, Cochrane Library, and SCOPUS databases was conducted from their inception to January 2024. Two investigators independently carried out the processes of literature search, study selection, data extraction, and quality assessment. The analysis was conducted using comprehensive meta-analysis software (CMA).

Results: For meta-analysis, six studies comprising 668 patients were included. In survivors, the DP at ECMO initiation was lower (mean DP = 14.56 cm H_2O, 95% CI: [11.060–18.060]) than non-survivors (mean DP = 17.77 cm H_2O, 95% CI: [12.935–22.607]). During ECMO, the survivors had lower DP (mean DP = 11.63 cm H_2O, 95% CI: [10.070–13.195]) than non-survivors (mean DP = 14.67 cm H_2O, 95% CI: [12.810–15.831]).

Conclusion: The optimum DP to initiate ECMO in severe ARDS patients on MV is 15 cm H_2O. Extracorporeal membrane oxygenation reduces the intensity of MV, as reflected by a reduction in DP in both survivors and non-survivors during the ECMO by 3 cm H_2O. The DP ≤ 12 cm H_2O during ECMO strategy is a predictor of survival, and DP persisting ≥ 15 cm H_2O on ECMO prompts the search for strategies to reduce DP.

Trial Registration: PROSPERO CRD42022327846.

Keywords: Acute respiratory distress syndrome, Driving pressure, Extracorporeal membrane oxygenation, Mortality.

Indian Journal of Critical Care Medicine (2025): 10.5005/jp-journals-10071-24893

Highlights

Extracorporeal membrane oxygenation (ECMO) in severe acute respiratory distress syndrome (ARDS) is a rescue strategy used to rest lungs and reduce the stress, strain, and intensity of MV. Of late driving pressure (DP) is considered a paramount ventilator variable in the management of severe ARDS patients on invasive MV and prognosticating mortality. Being a potential guiding factor, the utility of DP in patients receiving ECMO is least explored. Therefore, this systematic review is conducted to study the utility of DP in severe ARDS patients on invasive MV with ECMO.

Introduction

Severe ARDS has a high mortality rate of more than 40%.[1,2] mechanical ventilation (MV) with lung protective ventilation (LPV) strategies remains a cornerstone in the treatment of severe ARDS. Approximately 10–15% of mortality in severe ARDS is due to refractory hypoxemia, defined as "persistent or worsening hypoxemia unresponsive to conventional MV with LPV strategies."[3] Clinicians utilize rescue/adjunct therapies for treating life-threatening refractory hypoxemia. In severe ARDS, when all the rescue measures of optimizing ventilation/perfusion (V/Q) mismatch to alleviate hypoxemia fail, ECMO, which provides external oxygenation of the blood, serves as a rescue therapy.[4]

Over the past decade, ECMO has been increasingly used as a rescue option for severe ARDS.[5,6] The initiation of ECMO can substantially reduce the intensity of MV by reducing the tidal volume (V_T), the DP, the plateau pressure (Pplat), and the requirement for

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How to cite this article: Todur P, Nileshwar A, Chaudhuri S, Nagendra D, Shanbhag V, Vennila J. Prognostic Significance of Driving Pressure for Initiation and Maintenance of ECMO in Patients with Severe ARDS: A Systematic Review and Meta-analysis. Indian J Crit Care Med 2025;29(2):177–185.

Source of support: Nil

Conflict of interest: None

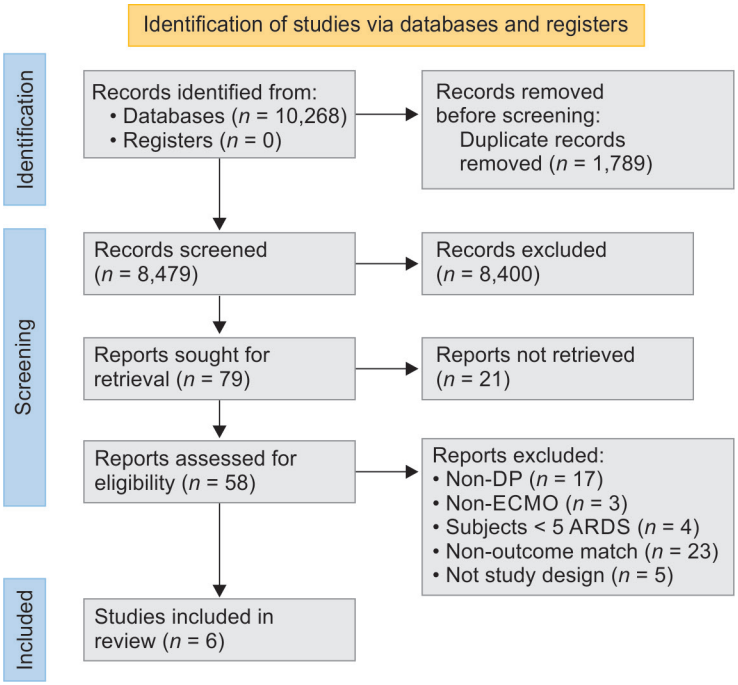


Fig. 1: PRISMA chart

a fraction of inspired oxygen (FiO_2). This reduction results in better outcomes by preventing additional ventilator-induced lung injury (VILI).[7,8] Among patients with severe ARDS, studies have investigated the indications, techniques, and outcomes of ECMO. However, there are limited studies on the timing that may be optimal for initiation of ECMO in patients receiving MV and the prognosticators of ECMO success or futility.

Once ECMO is initiated, the value of the most common indicator of pulmonary gas exchange namely the PaO_2/FiO_2 ratio (PF ratio), is lost. This occurs because the majority of oxygenation takes place extracorporeally in the membranes rather than across the alveolar-capillary membranes. In this context, pulmonary mechanics serves as a better clinical guide for measuring the severity of lung injury, assessing the response to ECMO strategies, and prognosticating mortality during ECMO. Pulmonary mechanics is the functioning of the lung in terms of the flow and pressure of air during the respiratory phases.[9] From the pressure and flow variables, other indices like resistance and compliance of the lung, the work of breathing can be calculated. Monitoring pulmonary mechanics can provide insight into the patient's response to treatment rescue therapy such as ECMO.

The DP is calculated as the "difference between Pplat and PEEP" and is also defined as "ratio of V_T to compliance (C_{RS})."[10] Thus, from the definition, it is evident that the DP is a ventilator variable that is physiologically and mathematically coupled with other factors like Pplat, PEEP, $C_{RS,}$ and V_T which are components of pulmonary mechanics. Amato et al., found DP to be a predictor of mortality in ARDS, with higher values of DP associated with higher risks of death.[10,11] An epidemiological study of 2000 patients from 50 countries emphasized that DP is a factor that influences mortality in ARDS patients on MV.[2] Additionally, DP serves as a marker of severity in ARDS, as it emphasizes the need to ventilate the lung to its functional size. Driving pressure is "the pressure applied to support the delivery of V_T and can, therefore, be a measure of the stress as well as the strain applied to the respiratory system during ventilation."[12] Consequently, this parameter can be a useful guide in titrating MV parameters to avoid VILI.[13,14]

Therefore, we hypothesize that the DP can be a significant measure of the pulmonary mechanics in patients with severe ARDS who are on MV and receiving ECMO. However, to the best of our knowledge, there is no SRMA identifying the DP for the commencement of ECMO in severe ARDS patients to ensure mortality benefit.

The objectives of this study were to:

- Identify the optimal DP for initiating ECMO in severe ARDS patients receiving invasive MV as a prognostic ventilator index for predicting survival.
- To study the change in DP during the ECMO strategy and the lowest DP achieved during ECMO in survivors and non-survivors of ARDS.

Materials and Methods

PROSPERO registration was done (CRD42022327846), and the study followed Preferred Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) (Fig. 1).

Search Strategy for the Identification of Relevant Studies

Relevant literature was searched electronically using PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), Embase (https://www.embase.com/), and Cochrane Library (https://www.cochranelibrary.com) databases from inception to January 2024, employing a sensitive search strategy. A search was completed with the vocabulary terms and keytext words. Blocks of terms per concept were created [Driving pressure (with related synonyms) AND ARDS (with related synonyms) AND ECMO (with related synonyms)]. No restrictions were applied for

article selection. Additional records were identified through a bibliography search of the relevant articles.

Inclusion and Exclusion Criteria

We included all interventional and observational studies that mentioned the details of DP values in ECMO-dependent ARDS patients receiving MV, along with outcomes in terms of mortality, ECMO days, and length of ICU stay.

We excluded the following study types: Case reports, editorials, reviews, abstracts, conference proceedings, and commentaries. Studies involving non-human participants, those published in languages other than English, studies with unrelated outcomes or interventions, and studies with fewer than five participants were also excluded. Additionally, studies that provided inadequate information for data extraction, even after contacting the first author or corresponding author, were excluded.

Participants

Patients with age >18 years with ARDS receiving ECMO treatment along with MV, were admitted to the ICU.

Index/Prognostic factor: Values of DP.

Comparator: Survivors vs non-survivors on ECMO.

Outcome Measures: Mortality, ECMO days, and length of ICU stay.

Definitions

Acute respiratory distress syndrome is defined by Berlin Criteria as "acute onset within a week of primary insult or new/worsening symptoms in one week, with bilateral opacities in chest imaging, not fully attributed cardiac failure or volume overload, with a PaO_2/FiO_2 ratio < 200 mm Hg with PEEP > 5 cm H_2O."[1]

Driving pressure is defined as "the difference between the Pplat and PEEP, and can also be expressed as the ratio of V_T to compliance (C_{RS})."[11]

Extracorporeal membrane oxygenation: "A form of life support that supports the heart and/or lungs outside the body. Extracorporeal membrane oxygenation may support the body for a period (days, or sometimes, months) to allow the heart and/or lungs time to rest and heal."

Study Selection and Data Extraction

After the initial screening of titles and abstracts, the full-length articles were retrieved and assessed for eligibility, and the resulting studies were included in the final analysis. Two reviewers (Pratibha Todur and Souvik Chaudhuri) independently extracted data from the studies. In cases of conflict between the two reviewers, the third reviewer (Anitha Nileshwar) was consulted. The extracted data included study characteristics and variables from each eligible study, such as the authors, publication year, country, study design and settings, and patient characteristics including age, gender, sample size, DP values, timing of DP measurement, number of survivors and non-survivors, and outcomes like mortality, which was assessed over 28 days as the primary outcome. If 28-day mortality data were unavailable, the latest reported time point for mortality was used. Other extracted outcomes included the number of ECMO days and length of ICU stay, wherever reported.

Quality Evaluation

The Quality in Prognosis Studies (QUIPS) tool was used to assess the risk of bias (RoB) in the studies. This tool evaluates six key domains essential for appraising the validity and bias of prognostic studies. QUIPS tool categorizes the risk of bias into three levels: low, moderate, or high.

Statistical Analysis

The statistical software Comprehensive Meta-Analysis (CMA) version 4 was used for the statistical analysis, and the results were presented as forest plots.[15]

Continuous outcomes were represented as differences in means (D) with 95% CI.

For the outcomes of interest, a meta-analysis of pooled estimates was performed, and the *p*-values were reported. A *p*-value of < 0.05 was deemed statistically significant. Heterogeneity was evaluated using the I^2 statistic, which quantifies the proportion of variability in the meta-analysis attributable to differences between studies rather than sampling error. An I^2 value of <50% was interpreted as low heterogeneity, 50–70% as moderate, and >75% as high, defining the thresholds for heterogeneity. A fixed-effect (FE) model was applied in cases of low heterogeneity, whereas a random-effects (RE) model was used for moderate and high heterogeneity. The analysis of the difference in mean of outcome of interest between survivors and non-survivors groups, and data conversion of the respective studies was done from median and interquartile range to mean and standard deviation.

Using mean difference as the measure of outcome, the analysis was performed, and the RE model was used to fit the data. A restricted maximum-likelihood estimator was used to estimate the amount of heterogeneity, (i.e., tau^2). For the test of heterogenicity, the Q-test and I^2 have also been reported. If there is any heterogenicity ($Tau^2 > 0$), a prediction interval for the particular outcomes is shown. To determine if any study is an outlier, Cook's distances and Studentized Residuals were utilized. Probable outliers are defined as "studies with a studentized residual larger than the $100 \times (1 - 0.05/(2 \times k))$th percentile of a typical normal distribution." If there were studies with a total Cook's distance greater than six times IQR of the Cook's distances and also the median added to it, such studies were categorized to be influential studies. The rank correlation test, along with the regression test, were utilized to determine the symmetry of the funnel plot.

Publication Bias

A visual inspection of the funnel plot was conducted to assess potential publication bias, which was created using CMA. Additionally, publication bias was statistically analyzed using Egger's test, with a *p*-value of ≤ 0.05 considered statistically significant.[16]

Results

Study Selection

Using electronic search, we retrieved 10,268 studies. After removing duplicates and title screening, 820 original studies were taken for full-text screening. The inclusion and exclusion criteria were thoroughly applied, resulting in the consideration of nine studies on ARDS patients receiving ECMO with DP measurements. Of these, three studies did not have survivor/non-survivor groups, leaving six studies for the meta-analysis (Fig. 1).[8,17–21]

Characteristics of the Included Studies

We included six observational cohort studies of which five were retrospective and one was a prospective published between

2013 and 2021.[8,17–21] The characteristics of the included study are depicted in Table 1. All six studies were conducted in the intensive care units (ICUs) and involved adult patients with severe ARDS, with ages ranging from 29 to 69 years; the mean age was 48.07 years with a standard error of 2.35 years. The studies predominantly included male patients, with males comprising over 50% of the sample.

The sequential organ failure assessment (SOFA) score was used in all the studies, with a mean SOFA score of 10.7 and a standard error of 0.442. The sample size of the included studies varied from 35 to 203 patients, totaling 668 patients with severe ARDS on ECMO (Table 1). All six studies included both survivor and non-survivor groups. The meta-analysis had 364 survivors and 304 non-survivors. Regarding the timing of DP measurement, all studies measured DP before ECMO initiation, and four studies measured DP both before ECMO initiation and during ECMO therapy.[8,17,18–22]

The primary outcome of all six studies was mortality, assessed at 28 days. Other outcomes included ECMO days, reported in three studies, length of stay in the ICU, reported in four studies, and length of MV days, reported in one study.[8,17–21,23]

Risk of Bias Assessment

QUIPS tool was employed to evaluate the risk of bias (RoB) in the included studies. Two independent reviewers (PT and SC) assessed the quality of the studies, with any disagreements resolved through consultation with a third reviewer (AN). Among the studies, four showed a low risk of bias, while two showed a moderate risk. Overall, the studies were determined to have a low risk of bias, as illustrated by the traffic light plot and summary plot presented in Figure 2.

Optimal DP to Initiate ECMO in Patients with Severe ARDS Receiving Invasive MV

In the meta-analysis, among the included studies all six studies reported DP before initiation of ECMO in patients with severe ARDS and were already on invasive MV.[8,18–24] Among the survivors, the DP at ECMO initiation was lower (mean DP = 14.56 cm H_2O, 95% CI: [11.060–18.060) than non-survivors (mean DP = 17.77 cm H_2O, 95% CI: [12.935–22.607] (Fig. 3). The difference between the pooled mean values of DP before ECMO initiation was – 2.7 cm H_2O, 95% CI: [–4.60 to –0.947], *p*-value 0.003. I^2 value 75.9%, random model used.

There were six studies that were incorporated for statistical analysis. The range of the observed mean was from –8.7000 to 1.5000, and the majority of the estimates were negative (83%). The average standardized mean difference estimated using the RE model was = –2.6255 (95% CI: –4.5888 to –0.6623). The average outcome was found to be significantly different from zero (z = –2.6212, *p* = 0.0088). The Q-test depicted that the true outcomes were heterogeneous (Q(5) = 18.6923, *p* = 0.0022, tau^2 = 3.9438, I^2 = 75.9449%). A value of the 95% prediction interval for the true outcomes was –6.9850 to 1.7339. The Studentized Residuals depicted that there were no studies with a value greater than ± 2.6383, and therefore there was no specific indication of any outliers in the model. As per Cook's distance calculations, there were no studies that were found to be very influential. Rank correlation as well as the regression test did not depict any asymmetry in the funnel plot (*p* = 1.0000 and *p* = 0.6487, respectively).

The DP during ECMO Strategy Among Survivors vs Mortality Group

In the meta-analysis, of the six included studies only four studies that reported the values of DP during the ECMO strategy were

Table 1: Characteristics of included study

S. No.	*Author, publication year*	*Study design*	*Severity of ARDS*	*Sample size*	*Age (years)*	*Male (%)*	*Groups*	*Timepoint of DP measurement*	*Primary outcome*	*Other outcomes*	*Scores*	*SOFA score*	*APACHE II score*
1.	Pham T, 2013	Prospective observational cohort study	Severe ARDS	123	42 ± 13	61 (50%)	Survivor vs Non-survivor	Before and during ECMO	ICU mortality	MV d, ICU stay	SOFA at admission	9.5 ± 4	–
2.	Magunia H, 2020	Retrospective observational cohort study	Severe ARDS	56	54 ± 10	41 (73.2%)	Survivor vs Non-survivor	Before and during ECMO	ICU mortality	ECMO d, ICU stay	APACHE II SOFA	11.3 ± 2.7	26.05 ± 10.55
3.	Belliato M, 2021	Retrospective multicenter observational cohort study	Severe ARDS	35	53 (40–64)	24 (68%)	Survivor vs Non-survivor	Before and during ECMO	ICU mortality	ECMO d, ICU stay	SOFA at admission	12 (9–17)	–
4.	Schmidt M, 2015	Retrospective international multicenter study	severe ARDS	168	41 ± 14	105 (62%)	Survivor vs Non-survivor	Before and during ECMO	ICU mortality	–	APACHE II SOFA	10.9 ± 3.3	20 ± 8
5.	Schmidt M, 2018	Retrospective international multicenter study	Severe ARDS	203	51 (38–59)	127 (63%)	Survivor vs Non-survivor	Before ECMO	120 d mortality	MV d, ECMO d, ICU stay	APACHE II SOFA	12 (8–15)	28 (20–33)
6.	Spinelli E, 2020	Retrospective multicenter observational study	Severe ARDS	83	51 ± 14	53 (63.85%)	Survivor vs Non-survivor	Before ECMO	Hospital mortality	–	SOFA	9 (6–12)	–

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; DP, driving pressure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; SOFA, sequential organ failure assessment

Fig. 2: Risk of bias assessment

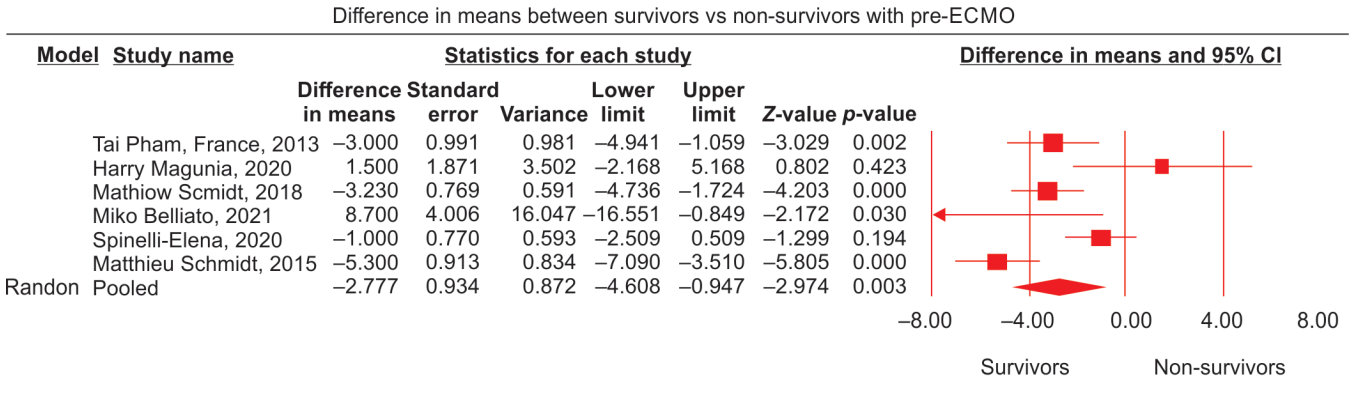
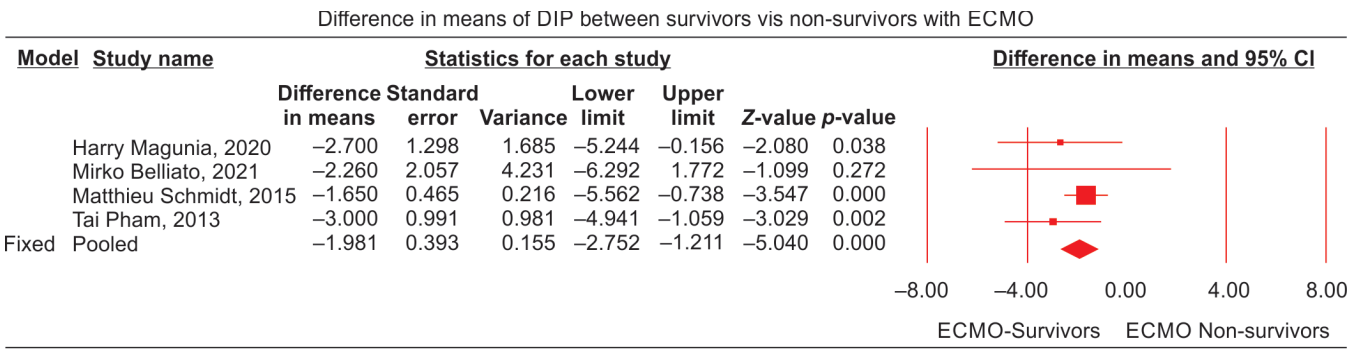


Fig. 3: Forest plot of DP before initiation of ECMO (comparison between the ECMO survivors and non-survivors at the time of initiation of ECMO)
CI, confidence interval; DP, driving pressure; ECMO, extracorporeal membrane oxygenation

considered.[8,18,21] One study measured DP at 12 hours of ECMO strategy, another study measured DP on the first day of ECMO, and another study measured DP within 48 hours of ECMO initiation, and one study reported DP measured on day 3 of ECMO.[8,18,19,24] During the ECMO strategy, the DP decreased in both survivors and non-survivors by 3 cm H_2O.

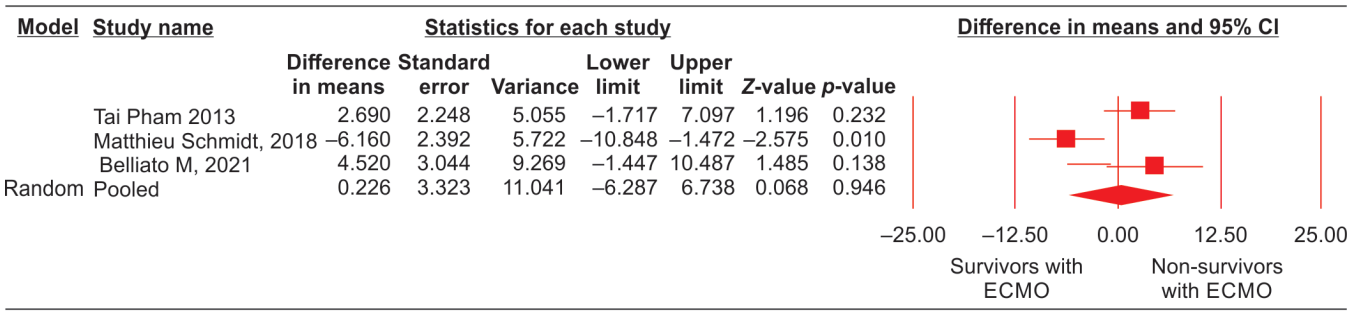
During ECMO strategy, in survivors the DP was lower (mean DP = 11.63 cm H_2O, 95% CI: [10.070–13.195]) than that of the non-survivors (mean DP = 14.67 cm H_2O, 95% CI: [12.810–15.831]) (Fig. 4) The difference between the pooled mean values of the DP between the survivors and non-survivors was –1.98 cm H_2O, 95% CI: [–2.75 to –1.211], *p*-value 0.001. I^2 value 0%, fixed model used.



Meta-analysis

Fig. 4: Forest plot of DP during the ECMO strategy (comparison between the ECMO survivors and non-survivors of ECMO in severe ARDS)

CI, confidence interval; DP, driving pressure; ECMO, extracorporeal membrane oxygenation



Meta-analysis

Fig. 5: Forest plot length of ECMO days (comparison between the ECMO survivors and non-survivors of ECMO in severe ARDS)

CI, confidence interval; DP, driving pressure; ECMO, extracorporeal membrane oxygenation

Length of EMCO Days and Length of ICU Stay

Only three studies were included that reported the length of ECMO days and it was observed that there was no difference in the mean ECMO days between the survivors and non-survivors (mean ECMO days 11.25 vs 11.15 and 95% CI: [7.701–14.814] vs [5.944–16.372], respectively) (Fig. 5). The difference between the pooled mean values of the ECMO days between the survivors and non-survivors was 0.22 days, 95% CI: [−6.28–6.73, *p*-value 0.94. I^2 value 80.9%, RE model used.

There were three studies that were incorporated for statistical analysis. The range of the observed mean was from −0.3946 to 0.5282, and the majority of the estimates were positive (67%). The average standardized mean difference that was estimated using the RE model was 0.0570 (95% CI: −0.4731–0.5871). The average outcome was found not to be significantly different from zero (z = 0.2108, p = 0.8331). The Q-test depicted that the true outcomes were heterogeneous (Q(2) = 9.4172, p = 0.0090, tau^2 = 0.1637, I^2 = 80.966%). A value of the 95% prediction interval for the true outcomes was −0.8969–1.0109. The Studentized Residuals depicted a single study with a value greater than ± 2.3940, and therefore there was an outlier in the model. As per the calculation of Cook's distances, there were no studies that were found to be very influential. Rank correlation as well as the regression test did not depict any asymmetry in the funnel plot (p = 1.0000 and p = 0.1756, respectively).

Four studies were included that reported the length of ICU to stay and it was observed that the survivors had increased length of ICU stay (Mean LOS ICU 32.16 ± 5.21 days, 95% CI: [21.953–42.380], then the non-survivors (Mean LOS ICU 19.47 ± 4.25 days, 95% CI: [11.388–27.559] (Fig. 6), which could be fallacy due to the fact that the non-survivors would have expired early. The difference between the pooled mean values of the length of stay between the survivors and non-survivors was 12.67 days, 95% CI: [1.27–24.4], *p*-value 0.030. I^2 value 81.89%, random model used.

There were four studies that were incorporated for statistical analysis. The range of the observed mean was from 0.1121 to 1.2184, and the majority of the estimates were positive (100%). The average standardized mean difference that was estimated using the RE model was 0.6467 (95% CI: 0.0835–1.2099). Thus, the average outcome was found to be significantly different from zero (z = 2.2504, p = 0.0244). The Q-test depicted that the true outcomes were heterogeneous (Q(3) = 18.1333, p = 0.0004, tau^2 = 0.2576, I^2 = 81.89%). A value of the 95% prediction interval for the true outcomes was −0.4964–1.7898. The Studentized Residuals depicted that there was a single study with a value greater than ± 2.4977, and therefore there were no outliers in the model. As per the calculation of Cook's distances, there were no studies that were found to be very influential. Rank correlation as well as the regression test did not depict any asymmetry in the funnel plot (p = 1.0000 and p = 0.8860, respectively).

Funnel Plot

The funnel plot depicts publication bias visually (Fig. 7).

In this case, the intercept (B0) is 2.62283, 95% confidence interval (−3.32034, 8.56601), with t = 1.22530, df = 4. The 1-tailed *p*-value (recommended) is 0.14384, and the two-tailed *p*-value is 0.28768, which shows no significant publication bias.

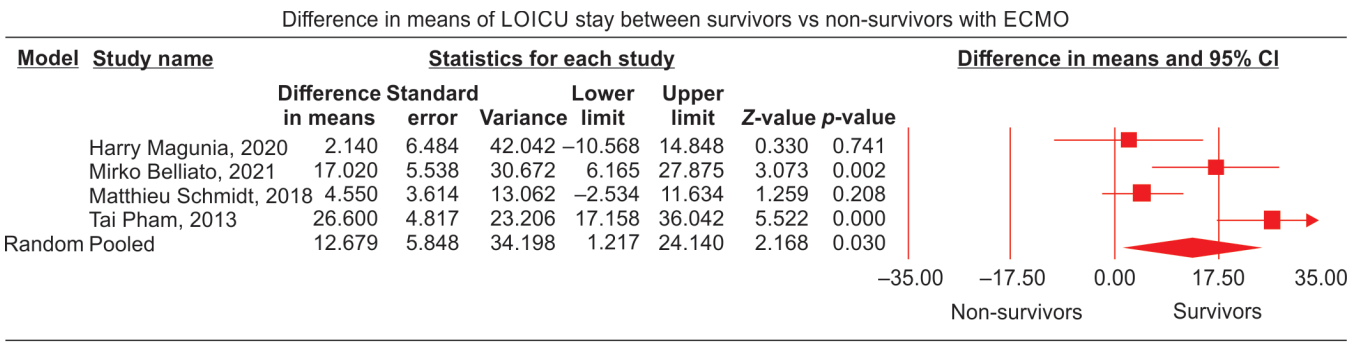


Fig. 6: Forest plot length of ICU stay (comparison between the ECMO survivors and non-survivors of ECMO in severe ARDS)
CI, confidence interval; DP, driving pressure; ECMO, extracorporeal membrane oxygenation

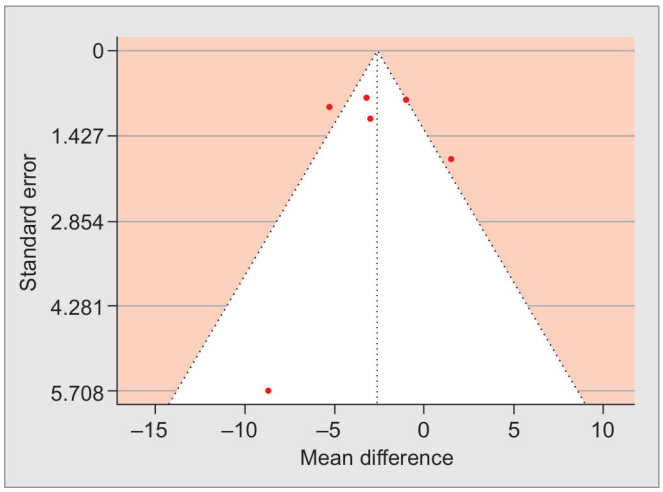


Fig. 7: Funnel plot

Discussion

The key to the success of ECMO is based on the optimal timing of initiation, when the critical balance is maintained, wherein the patient has the benefits of early initiation, without the risks of futility of delayed ECMO initiation. Prior to the initiation of ECMO, various ventilator parameters are available in the armamentarium of the clinicians to adjudicate the need for ECMO in cases of severe ARDS. Driving pressure has been a critical parameter in MV for patients with ARDS to predict survival however, there is no hard evidence of RCT that DP is a reliable predictor of survival in ARDS patients receiving ECMO.

However, identification of the cut-off of such a reliable parameter/variable is the need of the hour in guiding the clinicians, as to when to offer ECMO and prognosticate survival in such patients. The ECMOVIBER study conducted in 24 countries of the Iberian peninsula on COVID-19 ARDS patients mentioned DP prior to ECMO was one of the factors associated with a higher risk of mortality.[25] In ARDS, as decreased C_{RS} and hypoxia are hallmark signs, they play a major role in the decision of indication for treatment, evaluate the effects of treatment, and prognosticate mortality. PF ratio is the most accepted measure of hypoxia and DP is a measure of C_{RS} however the utility of the latter is yet to be incorporated in the guidelines for treatment of severe ARDS patients on ECMO.

This is the first meta-analysis that studied the literature on DP in severe ARDS patients on ECMO strategy along with invasive MV. In this review, we investigated the prognostic significance of DP for the initiation of ECMO and its change during the ECMO strategy among survivors and mortality groups in severe ARDS and predicted the prognosticators of survival during the ECMO strategy. Our main findings were that the optimal DP for initiation of the ECMO strategy is DP >14.56 cm H_2O (rounded off to 15 cm H_2O), and the change in DP during the ECMO strategy was reduced by 3 cm H_2O in both survivors and non-survivors. We also found that the DP during ECMO strategy in survivors was 11.63 cm H_2O (rounded off to 12 cm H_2O) and in non-survivors 14.67 cm H_2O (rounded off to 15 cm H_2O).

Previous meta-analysis conducted on DP in severe ARDS by Aoyama et al. concluded that the safe range of DP is 13–15 cm H_2O, and Chen et al., in their review observed the desired range of DP exists between 13 and 21 cm H_2O and hence it is evident that the higher value of DP is associated with mortality.[11,22] Individual studies reported that the DP ≥ 15 cm H_2O is a prognosticator of mortality.[10,25,26] Our meta-analysis found that the optimum timing for ECMO initiation is DP ≥ 15 cm H_2O. This suggests that despite conventional MV using LPV or other rescue therapy like higher PEEP levels, recruitment manures, prone ventilation, and yet the patient's DP ≥ 15 cm H_2O, that point EMCO strategy must be offered for better outcomes.

Extracorporeal membrane oxygenation is considered to reduce the intensity of MV which is reflected by the DP and mechanical power (MP). In the present meta-analysis, it was noted that the DP reduced by 3 cm H_2O in both the survivors and the non-survivors. In survivors, the DP ≤ 12 cm H_2O, and in non-survivors, the DP ≥ 15 cm H_2O. This infers that the DP ≤ 12 cm H_2O during ECMO strategy on IMV is a prognostic marker of survival. The DP persisting ≥ 15 cm H_2O on ECMO prompts the clinicians to opt for alternate strategies such as prone position ventilation during ECMO that might decrease DP during ECMO for reduction of adverse outcomes.

The present review did not find any difference in ECMO days between the survivors and non-survivors and, therefore, we were unable to find out if the DP was associated with ECMO days. The length of ICU stay was higher in survivors compared to the non-survivors (32 vs 19 days). Death on ECMO can be due to numerous non-pulmonary complications such as bleeding, stroke, thromboembolism, secondary infections, etc., and early death may be reflected as decreased ICU stay when compared to the survivors. Since DP is calculated as the difference between the Pplat and PEEP. Therefore, targeting either Pplat or the PEEP can alter the DP values. All the six studies included in this review targeted the lung protection ventilation strategy with Pplat <30 cm H_2O.

Huang Pin et al. compared the role of changes in DP vs MP in predicting mortality in ARDS and concluded that the predictive capacity of both changes in DP and MP were comparable.[27] Due to the ease of bedside calculation, the authors of the study concluded that DP was the best choice of all respiratory parameters to predict mortality in ARDS. Another study comparing the ventilatory variables and MP in ARDS patients found that the DP and RR were significant predictors of mortality in ARDS.[28] Therefore, for ease of calculation and bedside ready utility, we considered DP than the MP in this study.

Strength and Limitations of the Study

We used the robust method for the systematic review and meta-analysis that is in accordance with the recommendation by Cochrane Collaboration and our results are reported as PRISMA guidelines. In this, we could identify the mean level of DP for initiation of ECMO in severe ARDS for survival benefit. The meta-analysis of the study was conducted on a relatively better sample size of severe ARDS patients on IMV and on ECMO strategy (n = 668). To our knowledge, this is the first meta-analysis that studied the role of an eminent ventilator variable, DP at initiation, and its changes on outcomes of severe ARDS receiving ECMO treatment strategy.

The study had several limitations. Firstly, the included studies were all observational studies and the majority were retrospectively conducted. Second, the timepoint of DP measurement during the ECMO strategy was not uniform. It varied from 12 to 72 hours on ECMO strategy, and therefore difficult to conclude whether the reduction of DP at the exact timepoint on the ECMO strategy prognosticates survival or futility of treatment. The DP measurement has a challenge in which the values vary in patients who are obese or external factors contributing to chest wall resistance such as ascites. The accuracy of DP measurement still needs to be further studied.

Future Recommendations

At present, the results of DP in ECMO are only hypothesis-generating and future data from multicentered studies are required to confirm the findings of our study. Prospective studies are required to study the predictive capacity of DP in severe ARDS patients on ECMO. A safe and feasibility trial is also required with DP as an indicator of ECMO strategy and the mortality had to be evaluated.

Conclusion

The optimum DP to initiate ECMO in a severe ARDS patient who is already on MV is 15 cm H_2O. Extracorporeal membrane oxygenation reduces the intensity of MV, and the DP is reduced in both survivors and non-survivors during the ECMO strategy by 3 cm H_2O. The DP ≤ 12 cm H_2O during ECMO strategy is a predictor of survival, and DP persisting ≥ 15 cm H_2O on ECMO prompts the search for strategies to reduce DP during ECMO for reduction of adverse outcomes.

Acknowledgment

Sincere gratitude to the certificate course on "Meta-analysis and Meta-Synthesis- Unlock the power of Evidence synthesis" organized by the Center for Toxicovigilance and Drug Safety, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal.

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