BMJ Open Respiratory Research

Comparing the impact of targeting limited driving pressure to low tidal volume ventilation on mortality in mechanically ventilated adults with COVID-19 ARDS: an exploratory target trial emulation

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To cite: Tanios M, Wu TT, Nguyen HM, *et al*. Comparing the impact of targeting limited driving pressure to low tidal volume ventilation on mortality in mechanically ventilated adults with COVID-19 ARDS: an exploratory target trial emulation. *BMJ Open Respir Res* 2024;**11**:e002439. doi:10.1136/bmjresp-2024-002439

Received 19 March 2024
Accepted 9 September 2024

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ABSTRACT

Background An association between driving pressure (ΔP) and the outcomes of invasive mechanical ventilation (IMV) may exist. However, the effect of a sustained limitation of ΔP on mortality in patients with acute respiratory distress syndrome (ARDS), including patients with COVID-19 (COVID-19-related acute respiratory distress syndrome (C-ARDS)) undergoing IMV, has not been rigorously evaluated. The use of emulations of a target trial in intensive care unit research remains in its infancy. To inform future, large ARDS target trials, we explored using a target trial emulation approach to analyse data from a cohort of IMV adults with C-ARDS to determine whether maintaining daily Δp<15 cm H_2O (in addition to traditional low tidal volume ventilation (LTVV) (tidal volume 5–7 cc/PBW+plateau pressure (P_{plat}) ≤30 cm H_2O), compared with LTVV alone, affects the 28-day mortality.

Methods To emulate a target trial, adults with C-ARDS requiring >24 hours of IMV were considered to be assigned to limited ΔP or LTVV. Lung mechanics were measured twice daily after ventilator setting adjustments were made. To evaluate the effect of each lung-protective ventilation (LPV) strategy on the 28-day mortality, we fit a stabilised inverse probability weighted marginal structural model that adjusted for baseline and time-varying confounders known to affect protection strategy use/adherence or survival.

Results Among the 92 patients included, 27 (29.3%) followed limited ΔP ventilation, 23 (25.0%) the LTVV strategy and 42 (45.7%) received no LPV strategy. The adjusted estimated 28-day survival was 47.0% (95% CI 23%, 76%) in the limited ΔP group, 70.3% in the LTVV group (95% CI 37.6%, 100%) and 37.6% (95% CI 20.8%, 58.0%) in the no LPV strategy group.

Interpretation Limiting ΔP may not provide additional survival benefits for patients with C-ARDS over LTVV. Our results help inform the development of future target trial emulations focused on evaluating LPV strategies, including reduced ΔP, in adults with ARDS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies showed that high driving pressure (ΔP) predicts mortality and suggested targeting a protective limited ΔP of 13–15 cm H_2O.

⇒ However, studies have not addressed whether a ventilator setting using limited ΔP is superior to the low tidal volume ventilation strategy.

WHAT THIS STUDY ADDS

⇒ This study proposes that a strategy of targeting ΔP may not add survival benefits when employed in a community hospital setting in the absence of a validated limited ΔP protocol.

⇒ In addition, it presents the target trial emulation approach as a feasible approach to advance the understanding of the various protective lung ventilation and inform future trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study provides a novel example of using the target trial emulation approach as an important initial step to inform future research on the importance of examining interventions targeting a limited ΔP on intensive care unit outcomes.

INTRODUCTION

During the pandemic, the surge in severe COVID-19-related acute respiratory distress syndrome (C-ARDS) raised important questions about the optimal ventilator strategy(s) that should be used for patients with acute respiratory distress syndrome (ARDS).[1–4] Using low tidal volume (V_T) invasive mechanical ventilation (IMV) lung tidal volume ventilation (LTVV) strategies (ie, plateau pressure (P_{plat}) ≤30 cm H_2O and maintaining the V_T at 5–7 mL/kg/PBW) in the early stages of ARDS to limit ventilator-induced lung injury (VILI)

has provided a survival benefit in multiple well-designed randomised controlled trials (RCTs).[5 6]

Additional lung-protective ventilation (LPV) strategies, such as limited driving pressure (ΔP) (ie, the difference between P_{plat} and positive end-expiratory pressure (PEEP) in patients on controlled mechanical ventilation (MV) without spontaneous breathing efforts) have also been suggested to reduce VILI and improve outcomes in patients with ARDS.[6–10] The studies demonstrating improved survival when a ΔP-limiting strategy was used were observational and thus susceptible to multiple sources of bias, analysed patients only from the first day of IMV and did not include patients with C-ARDS.[11–14] The reduction in the intensity of MV during extracorporeal membrane oxygenation (ECMO) likely reduces VILI[15–17] and may explain the lower adjusted mortality, particularly in patients with a Δp>15 cm H_2O early in the course of MV.[18]

Despite the high mortality associated with COVID-19, our understanding of its pathophysiology, particularly in relation to C-ARDS, remains incomplete.[13 19–22] The nature of C-ARDS poses a challenge for conducting large, prospective randomised trials to understand the effects of different ventilator strategies on mortality. Moreover, there is no validated approach for ventilator adjusting ventilator settings to achieve protective ΔP. Adjusting ventilator parameters to lower ΔP could inadvertently affect other variables,[23] such as increasing the respiratory rate to accommodate a reduction in V_T, which could augment the mechanical power of ventilation and cause iatrogenic harm.[24 25] In addition, clinicians should be cautious about the risks of using very low tidal volumes in patients with lower lung elastance, given the possibility of refractory hypercapnia when strategies to limit ΔP are employed in the absence of extracorporeal CO_2 removal.[26] Furthermore, the impact of ventilator setting adjustments on outcomes such as mortality may vary among different ARDS subsets.[27–30]

Observational analyses are subject to several sources of bias.[31] Emulation of a target trial using routinely collected clinical data[32] represents an established statistical approach to measuring the causal effects of specific treatments under 'real-world' conditions, but it is just starting to be used in the critical care setting.[33–35] To inform future large ARDS target trials, we explored using a target trial emulation approach. We analysed data from a cohort of IMV adults with C-ARDS to determine whether aiming for a limited ΔP, compared with LTVV alone, affects the 28-day mortality.

METHODS

Study design

We designed a target trial[34 36] that would randomise IMV intensive care unit (ICU) patients with C-ARDS to receive limited ΔP, LTVV or neither on the first day of IMV and then at least 75% of the time until extubation (table 1). The target trial would follow up participants until 28 days after the first initiation of IMV to assess all-cause 28-day mortality.

Study subjects

This study examined adults (≥18 years old) with C-ARDS who received IMV between March 2020 and March 2021 in a 32-bed medical-surgical ICU at a 389-bed regional teaching hospital. We included consecutive patients who required IMV for at least 24 hours. We excluded patients with severe acute neurological injury, given the effect on

Table 1 Comparison between the target trial and the observational study of the effect of limited ΔP or LTVV vs no protection in patients with C-ARDS

Approach	Target trial specification	Target trial emulation
Eligibility	Adults (≥18 years old) with C-ARDS who were anticipated to require invasive MV for at least 24 hours and had a ΔP measurement at baseline.	Consecutive adults admitted between March 2020 and March 2021 meeting these criteria.
Treatment strategies	1. Limited ΔP: both protective low ΔP (≤15 cm H_2O)+low P_{plat} (≤30 cm H_2O) on the first day of MV and then for at least 75% of the time until extubation. 2. LTVV: only low P_{plat} (≤ 30 cm H_2O) on the first day of MV and then for at least 75% of the time until extubation. 3. No protection: neither protective ΔP nor P_{plat} on the first day of MV and then for at least 75% of the time until extubation.	Same as for target trial.
Treatment assignment	Individuals would be randomly assigned to a strategy at the time of initiation of MV.	Patients were assigned to one of the three treatment strategy groups at the time of initiation of MV.
Outcome	All-cause mortality 28 days after first MV initiation.	Same as for target trial.
Follow-up	From first day of MV to 28 days after first MV initiation.	Same as for target trial.
Causal estimand	Intension-to-treat and per-protocol (assigned) effects.	Observational analogue of the per-protocol effect.

C-ARDS, COVID-19-related acute respiratory distress syndrome ; LTVV, low tidal volume ventilation; MV, mechanical ventilation.

mortality, and also patients who died within the first 24 hours of IMV. Study day 0 was defined as the calendar day on which IMV was first initiated. For patients with multiple ventilation episodes during the same ICU admission, we only used data from their first eligible IMV episode. Any reintubation that occurred <24 hours after extubation was deemed to represent the same IMV period. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[36]

Ventilator procedures

Patients were managed with PB 840 ventilators according to an existing LPV institutional protocol (the initial V_T was set to 6 cc/PBW on a volume-controlled mode; respiratory rate and PEEP selection were deferred to the managing intensivist). Further adjustments in V_T and PEEP were conducted according to ARDnet guidelines.[5 37] During the COVID pandemic, lung mechanics were measured at least twice a day and also when a significant event occurred (eg, any ventilator setting change, sedation adjustment, neuromuscular blocker initiation). The P_{plat} was routinely measured by trained Respiratory Care Practitioners (RCPs), and unreadable measures were discarded and repeated with the assistance of the intensivists. To obtain P_{plat} measurement, RCPs introduced a 0.5-second pause during volume-controlled ventilation mode to schedule an automatic pause at the end of inspiration. For patients on pressure-support mode, the settings were briefly changed to a volume-controlled mode. The manoeuvre was performed regardless of whether the patient was triggering the ventilator or not.[38] No additional sedation or neuromuscular blockers were used during the procedure. Expiratory pauses and auto-PEEP measurements were obtained at the request of the managing team. All RCPs were educated on the above practices. No protocol was used to adjust the ventilator setting for limiting ΔP.

The treatment strategies in our hypothetical target trial are based on the patient receiving one of two different ventilator protection strategies during the first 24 hours of IMV: (1) limited ΔP: both protective low ΔP (≤15 cm H_2O)+low P_{plat} (≤30 cm H_2O) on the first day of MV and then for at least 75% of the time until extubation or (2) LTVV: only low P_{plat} (≤30 cm H_2O) on the first day of MV and then for at least 75% of the time until extubation. When neither limited ΔP nor LTVV was delivered in the first 24 hours of IMV, the patient was assigned to a non-protective ventilation group. In our target trial, we were interested in estimating the per-protocol effect, which refers to the impact that would have been observed if patients had strongly adhered to first-day treatment strategy.[39] We defined strong adherence as the cumulative daily adherence to the first-day treatment strategy ≥75% during their first period of IMV. We estimated 75% compliance to be a realistic, pragmatic and achievable daily adherence goal that would influence MV outcomes in patients with ARDS.[40 41]

Outcomes

The study outcome was all-cause mortality 28 days after the first initiation of IMV, as certified and recorded in the electronic health record by the physician. We chose all-cause 28-day mortality rather than ICU mortality as our outcome to avoid ICU discharge becoming a competing event.

We also considered other primary outcomes, including ventilator-free days (VFDs), but preferred all cause 28-day mortality as we considered it a more pragmatic, clearly defined outcome of strong interest to both clinicians and patients, and it has been the commonly used outcome when evaluating different LPV strategies.[5 7 12 42–45] The VFDs represent a composite outcome for both mortality and ventilation duration and can be influenced by the variability of MV practices during the epidemic. In addition, the time to event (ie, mortality) would provide us with the most power to show a difference between the study groups when the patient is adherent to ventilation strategies until they are censored (due to death or not adherent), whereas, for patients who ever became non-adherent to ventilation strategies, VDFs cannot be used and therefore we lose sample size.[46]

Analysis

We characterised the three patient groups by collecting the following variables at ICU admission (age, SOFA score, sex, non-white race, body mass index (BMI) and oxygenation use before intubation) and initiation of IMV (days from ICU admission to MV, P_aO_2/F_iO_2 ratio and VT). Through literature review and expert consensus, we identified those collected variables known to either affect choice or adherence to the ventilator protective strategies or survival: (1) ICU admission or initiation of MV baseline (age, Sequential Organ Failure Assessment (SOFA) score, days from hospital admission to IMV); and (2) time-varying (IMV day #, presence of coma (Richmond Agitation-Sedation Scale (RASS) = −4 or −5) on the previous day).[6 26 47]

We applied a stabilised inverse probability cumulative adherence weighted (IPW) marginal structural model controlling for baseline and time-varying confounders known to affect protection strategy use or survival to evaluate the effect of each protective strategy on 28-day mortality. First, we calculated the daily stabilised IPW (ie, the time-varying IPW) by dividing the daily marginal probability of protection strategy adherence adjusted for baseline covariates by the estimated propensity score adjusted for both baseline and time-varying covariates. This means that when a patient was censored on an IMV day due to non-adherence in the protective group strategy, we up-weighted other patients based on the inverse probability of them remaining adherent. This approach creates a pseudo-population where each patient is adherent to

their assigned treatment strategy until extubation or day 28. We removed the first day from the IPW calculation because, by definition, patients are always adherent to the assigned protection strategy on the first IMV day.[34]

Second, we censored patients the first time their cumulative adherence to the assigned protection strategy was <75%. We then used a pooled logistic regression model with the time-varying IPW, directly adjusting for baseline confounders, to estimate the HR for 28-day all-cause mortality in the pseudo-population. Third, we standardised the survival estimates from the step 2 model, allowing our survival estimates to be interpreted as marginal causal effects, representing the survival outcomes if everyone had adhered to one of the three treatment strategies for 28 days. We plotted the causal survival curves and computed 95% CIs via a bootstrap with resampling. Missing model variables were addressed using simple imputation with the median. We performed all the data analyses using R, V.4.0.3 (R Foundation for Statistical Computing, 2020).

Patient and public involvement statement

Our study was conducted using deidentified data. There was no direct interaction with any individual participant, and therefore, members of the public were not involved in the study design, recruitment or conduct.

RESULTS

Patient characteristics

Among the 92 included patients, 27 (29.3%) were assigned to the limited ΔP lung protection group, 23 (25.0%) were assigned to the LTVV lung protection and 42 (45.7%) were assigned to the no protection group (table 2). No patient died within 24 hours of IMV initiation. Across the three groups, the median age was approximately 70 years, and the median baseline SOFA score was 5. The median days from ICU admission to MV initiation were 3.0, 0 and 2.5 days in the limited ΔP, LTVV and no lung protection groups, respectively.

Mortality

The 28-day causal survival curves by protection type are presented in figure 1. The adjusted estimated 28-day survival was 47% (95% CI 23% to 76%) in the limited ΔP group, 70.3% in the LTVV group (95% CI 37.6% to 100%) and 37.6% (95% CI 20.8% to 58.0%) in the no lung protection group. This corresponds to a 28-day survival difference of 9% (95% CI −19 to 41%) between the limited ΔP and no protection groups, 33% (95% CI −6% to 63%) between the LTVV versus no protection groups, and −23% (95% CI −58% to 18%) between the dual protection and single protection groups.

DISCUSSION

Our study represents one of the first published ARDS studies to use target trial emulation. In our exploratory investigation, we used data from a 'real world' setting to emulate a clinical trial comparing the effect of adding limited ΔP to conventional LTVV protective lung ventilation on mortality in adults with C-ARDS. This approach serves as a reliable method to estimate the causal effect of an intervention when only observational data are available, given it accounts for daily intervention adherence and both baseline and daily factors affecting both intervention adherence and primary outcome occurrence.[34 35 48]

Table 2 Patient characteristics on the day of initiation of mechanical ventilation

	Limited ΔP* (n=27)	LTVV† (n=23)	No protection (n=42)
ICU baseline			
Age, years‡	70.0 (61.0–76.5)	70.0 (65.5–80.0)	66.5 (57.0–72.0)
SOFA at ICU admission‡	5.0 (3.0–7.0)	5.0 (3.5–10.0)	5.0 (2.0–9.0)
Female sex	9 (33.3%)	14 (60.1%)	13 (31.0%)
Non-white	15 (55.6%)	14 (60.9%)	26 (61.9%)
Body mass index	29.6 (25.1–33.8)	23.3 (21.2–27.9)	29.0 (24.9–34.7)
Use of HFNC at ICU admission	9 (33.3%)	3 (13.0%)	15 (35.7%)
Initiation of mechanical ventilation			
Days from ICU admission to MV initiation‡	3.0 (1.5–8.0)	0.0 (0.0–2.0)	2.5 (0.0–11.5)
PaO_2/FiO_2 at intubation	77.0 (64.0–100.6)	96.0 (72.5–128.5)	78.9 (55.7–124.0)
Tidal volume/ideal body weight at intubation	6.4 (5.9–7.0)	6.8 (6.6–8.0)	6.5 (6.1–7.9)

*Low P_{plat} (≤30 cmH_2O) + low ΔP (≤15 cmH_2O) on ≥75% of MV days.
†LTVV: low P_{plat} (≤30 cmH_2O) on ≥75% of MV days.
‡Used in the inverse probability weighted (IPW) marginal structural model.
HFNC, high-flow nasal cannula; ICU, intensive care unit; LTVV, low tidal volume ventilation; MV, mechanical ventilation; SOFA, sequential organ failure assessment .

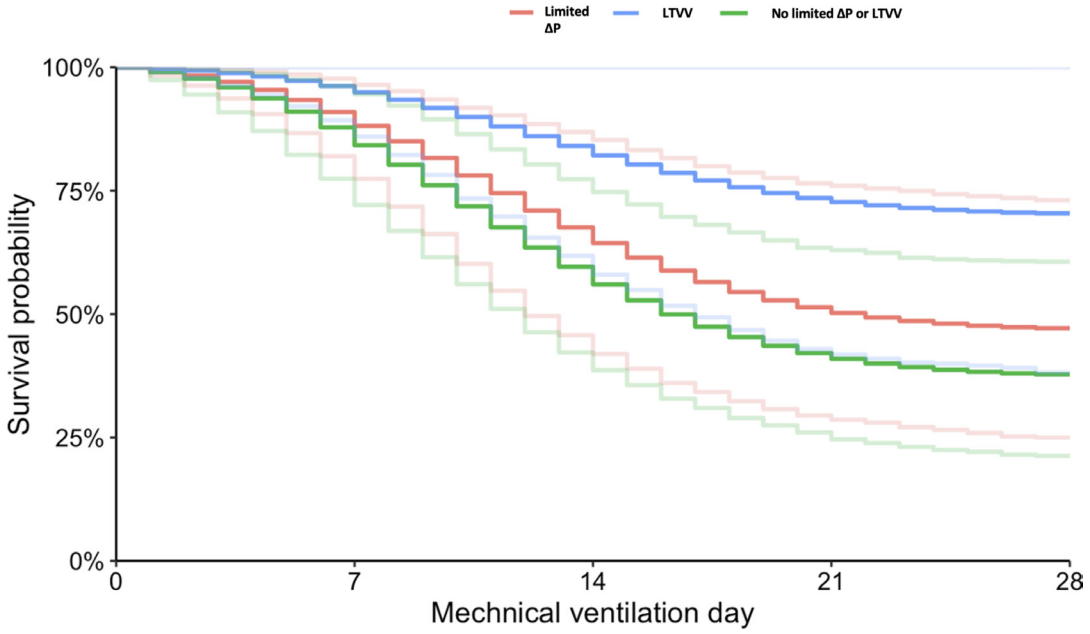

Figure 1 Comparison of the 28-day survival curves standardised for baseline covariates and weighed for time-varying confounders following invasive mechanical ventilation among patients using limited ΔP, LTVV, or no limited ΔP or LTVV. LTVV, low tidal volume ventilation.

While our sample is relatively small, our exploratory results suggest that limiting ΔP when LPV is already employed may not improve survival in patients C-ARDS. Our results highlight the need to conduct future prospective RCTs comparing limited ΔP to LTVV in IMV adults with ARDS. This study also demonstrates that target trial emulation approaches are feasible to use, particularly where RCTs are lacking and data are collected prospectively and rigorously.

Results from published studies evaluating the association between a limited ΔP and survival among adults with non-COVID ARDS have varied. Calls to limit ΔP are derived from studies that have associated ΔP with increased mortality from VILI, lung stress, strain or biotrauma.[7 17 49 50] In one study, an initial ΔP of >15 cm H_2O was shown to be a stronger predictor of mortality than the traditional LPV approach.[7] However, ΔP data were evaluated only once in the first 24 hours of IMV and only in patients without any respiratory efforts; the effect of a sustained ΔP over time on survival remained unclear. A secondary analysis of two previous trials demonstrated the limited prognostic value of IMV day 1 Δp≤13 cm H_2O on survival.[44] The SIESTA Investigators reported a ΔP cut-off ≤19 cm to be a slightly better predictive value of mortality than P_{plat},[51] whereas the results from the Lung Safe study showed a linear increase in mortality with an increase with ΔP with no threshold value identified.[52] The alveolar recruitment for acute respiratory distress syndrome trial (ART) has raised concerns about limiting ΔP.[53] An emulated pragmatic clinical trial using a large observational registry of patients without COVID ARDS posited that early and sustained ΔP reduction is associated with survival benefit.[6] However, this benefit was primarily influenced by adherence to protective lung ventilation rather than maintenance of a low ΔP.

The recent ESICM ARDS guidelines[26] highlight the trade-off between adjusting V_T and respiratory rate in attempting to control the overall intensity of MV[23] and emphasise the need for further examination of the merits of additional lung-protective strategies (eg, ΔP) and personalised ventilator targets. Clinicians often consider the initial ΔP to reflect the initial lung compliance and adjust ΔP in response to changes in lung compliance over time. Our results explored mortality outcomes with static ΔP for the duration of the IMV period.

Multiple studies have compared patient characteristics, treatments and outcomes between patients with and without C-ARDS .[54–57] While patients with C-ARDS are generally older, heavier and more likely to have diabetes, the respiratory mechanics and response to treatment have been similar.[26 54 56] Bain *et al* found key demographic and physiological parameters, biomarkers and clinical outcomes between C-ARDS and non-coronavirus 19 viral ARDS, but the delivered minute ventilation to be lower C-ARDS compared with bacterial and culture-negative ARDS.[54] In the study by Brault *et al*, the driving pressures, respiratory system compliance and oxygenation responses to recruitment manoeuvres and prone position therapies were similar between C-ARDS and non-C-ARDS.[56] However, there was heterogeneity in ventilator response, which underscores the importance of considering a personalised ventilator strategy that is independent of the underlying ARDS phenotype. This highlights the importance of future research on LPV strategy, for example, limited ΔP and the role of personalised ventilator targets.[26]

Our data suggest that in the routine care of spontaneously breathing patients with ARDS, maintaining LPV using low P_{plat} should be prioritised over limiting ΔP. Our exploratory findings inform the feasibility of conducting future target trial emulation studies in larger cohorts to inform ARDS management strategies. Our results will also help inform the design of future prospective randomised trials evaluating a ΔP limitation strategy and offer insights into the real-world experiences for different ARDS subphenotypes where the application of typical syndromic definitions is challenging.[19 21 22 58–62] The misclassification of ARDS subphenotypes in the LIVE trial was reported to be a large factor in the lack of demonstrable benefit associated with the use of personalised treatment strategy.[58] Our results urge the need to examine the role of personalised LPV on outcomes among the various ARDS phenotyping.[26 58] It remains unclear whether selecting different ventilatory strategies or precision treatment strategies based on ARDS subphenotypes will influence outcomes.[63]

While our data were not derived from a prospective RCT, and our study cohort was relatively small, our results suggest that when variables that influence ICU survival are considered,[26 47] limiting ΔP may not improve survival. It is unclear if limiting ΔP derives benefits from the adjustment of its individual components or is linked to the total driving force.[64 65] The effect of modulating ΔP by adjusting tidal volume and PEEP may vary based on disease progression, the nature of the underlying lung and chest wall compliance,[65–69] and the possibility of the potentially harmful effect of mechanical power.[24 25]

In our cohort, the initial V_T and PEEP were adjusted according to the current guidelines,[26 37] but further interventions to limit ΔP varied and were at the clinicians' discretion. The absence of the benefit of limited ΔP can be related to the variability in adjusting V_T, PEEP or the respiratory rate to limit ΔP and compensate for the low-minute ventilation offsetting potential benefits[51 70] and a validated approach to guide ventilator adjustment for a ΔP limitation strategy is needed. A certain ΔP may not have the same protective effects across all ARDS subsets nor across all disease subgroups due to different phenotypical features, specifically in compliance and recruitability.[6 20–22 60 69 71 72] The misclassification of ARDS subphenotypes in the LIVE trial was reported to be a large factor in the lack of demonstrable benefit associated with the use of personalised treatment strategy.[58] Our results urge the need to examine the role of personalised LPV on outcomes among the various ARDS phenotyping.[26 58] Certain subphenotypes have been shown to benefit from certain therapeutics,[55 57] but it remains unclear whether selecting different ventilatory strategies or precision treatment strategies based on ARDS subphenotypes will influence outcomes.[63] Current literature describes a similar pathophysiology for C-ARDS and ARDS from other etiologies,[54 56 57] and recent recommendations for non-pharmacological respiratory support do not recommend the use of a specific ventilatory strategy but recommend implementing evidence-based strategies for patients with ARDS, including ARDS due to COVID-19.[26 55] Our findings can be extended to ARDS from other aetiologies, considering the similarities in phenotypes and lung mechanics. While some baseline differences were reported (eg, higher BMI, socioeconomic status, gender, etc), these differences do not merit deviation from evidence-based respiratory support strategies of ARDS from any cause.[26]

Our exploratory study has several limitations. Emulation analysis provides a novel approach to ARDS research, but it also has inherent limitations. This modelling approach relies on the correct weight specification and the consistency assumption that the weights are correctly specified.[73] The stabilised IPW marginal structure model relies on the consistency assumption that the weights are correctly specified and can be sensitive to violations of the positivity assumption (ie, non-zero probability of receiving any treatment sequence).[73] While our small sample limited our ability to consider all variables that could influence survival in patients with ARDS (eg, sedation choice and depth or neuromuscular blocker use) and may limit inference, we provided the needed real-world data to explore the use of target trial emulation in patients with ARDS. We included a convenience cohort of patients with C-ARDS and formally evaluated the sample size needed to show a benefit with limiting ΔP's, should one exist. Although there were missing Pplat, ΔP and covariate values, the incidences were low, and we used a formal approach to address the missingness. Factors such as short inspiratory pauses or auto-PEEP and chest wall stiffness were not collected; thus, misinterpretation of the ΔP may have occurred.[74] We made extensive efforts to control for confounders and collected data that were routinely available to clinicians. Our data were prospectively collected, but the computation of pulmonary mechanics was not independently verified. The presence of spontaneous breathing may result in underestimating transpulmonary ΔP, thus limiting its accuracy. Lastly, the lack of observed benefit from limiting ΔP might be related to the variability in ΔP adjustment approaches in the absence of a validated institutional strategy.

CONCLUSION

In summary, our exploratory emulated target trial analysis suggests that in the absence of a validated limited ΔP protocol, a strategy of targeting ΔP may not confer additional survival benefits. Our findings help guide future ARDS research, particularly in the context of ARDS from infectious aetiologies, and demonstrate the potential of using emulated target trial approach in critical care studies. This work underscores the pressing need for large, controlled trials to investigate personalised ventilator strategies for patients with ARDS.

Since the targeting limited ΔP strategy was not found to be inferior to LTVV, it remains a viable option in clinical

practice. However, it should be used with caution and not prioritised until further studies confirm its benefits.

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Contributors MT was responsible for the overall content (as guarantor), accepted full responsibility for the finished work and/or the conduct of the study, has access to the data and controlled the decision to publish. MT, TTW, HN, LS, RM and JWD were involved in the conception and design of the study. MAT and HN acquired the data. MT, TTW, HN, LS and JWD analysed the data. MAT, TTW, HN, LHS, RM and JWD drafted the manuscript and approved the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Dignity Health CA/NV Institutional Review Board (IRB) #00006573, project number GR13-0102. The need for informed consent was waived due to the large number of patients involved in the study and the retrospective nature of the research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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