Low Tidal Volume Ventilation for Emergency Department Patients: A Systematic Review and Meta-Analysis on Practice Patterns and Clinical Impact

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OBJECTIVES: Data suggest that low tidal volume ventilation (LTVV) initiated in the emergency department (ED) has a positive impact on outcome. This systematic review and meta-analysis quantify the impact of ED-based LTVV on outcomes and ventilator settings in the ED and ICU.

DATA SOURCES: We systematically reviewed MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, references, conferences, and ClinicalTrials.gov.

STUDY SELECTION: Randomized and nonrandomized studies of mechanically ventilated ED adults were eligible.

DATA EXTRACTION: Two reviewers independently screened abstracts. The primary outcome was mortality. Secondary outcomes included ventilation duration, lengths of stay, and occurrence rate of acute respiratory distress syndrome (ARDS). We assessed impact of ED LTVV interventions on ED and ICU tidal volumes.

DATA SYNTHESIS: The search identified 1,023 studies. Eleven studies ($n = 12,912$) provided outcome data and were meta-analyzed; 10 additional studies ($n = 1,863$) provided descriptive ED tidal volume data. Overall quality of evidence was low. Random effect meta-analytic models revealed that ED LTVV was associated with lower mortality (26.5%) versus non-LTVV (31.1%) (odds ratio, 0.80 [0.72–0.88]). ED LTVV was associated with shorter ICU (mean difference, −1.0; 95% CI, −1.7 to −0.3) and hospital (mean difference, −1.2; 95% CI, −2.3 to −0.1) lengths of stay, more ventilator-free days (mean difference, 1.4; 95% CI, 0.4–2.4), and lower occurrence rate (4.5% vs 8.3%) of ARDS (odds ratio, 0.57 [0.44–0.75]). ED LTVV interventions were associated with reductions in ED (−1.5-mL/kg predicted body weight [PBW] [−1.9 to −1.0]; $p < 0.001$) and ICU (−1.0-mL/kg PBW [−1.8 to −0.2]; $p = 0.01$) tidal volume.

CONCLUSIONS: The use of LTVV in the ED is associated with improved clinical outcomes and increased use of lung protection, recognizing low quality of evidence in this domain. Interventions aimed at implementing and sustaining LTVV in the ED should be explored.

KEY WORDS: emergency department; low tidal volume; lung injury; lung protective ventilation; mechanical ventilation

Critically ill, mechanically ventilated patients experience high mortality and survivor morbidity (1–3). Lung-protective ventilation improves outcome among patients with acute respiratory distress syndrome (ARDS) by mitigating ventilator-associated lung injury (VALI), and there is increasing recognition that benefit may be afforded to those without ARDS as well (4–7). Low tidal volume ventilation (LTVV) is a critical aspect of a

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lung-protective strategy, and the primary intervention associated with improved outcome in mechanically ventilated ICU and operating room patients (5, 7, 8).

The use of LTVV in the emergency department (ED) could be especially beneficial for several reasons. Lengths of stay in the ED are long enough for VALI to occur, and longer ED mechanical ventilation duration has been associated with worse outcome and lower compliance with lung-protective ventilation (9–12). Mechanical ventilator settings during the early course of respiratory failure have been shown to be especially impactful on outcome in patients with ARDS, as well as those at risk for the syndrome (6, 13, 14). In addition, initial ventilator settings in the ICU tend to persist over time and change little during the first several days of respiratory failure (15). This is critical when considering that several studies have shown that ventilator settings in the ED directly influence ICU ventilator settings, and a before-after clinical trial demonstrated that ED-based lung protection was associated with improved outcome (6, 16, 17). The ED could therefore be a high-impact arena to target LTVV to improve outcome.

It has been almost a decade since publications documented that LTVV was rarely implemented in ED patients (16, 18). To explore the depth of the literature and to inform the potential to conduct of a systematic review, we conducted a scoping review of the literature, which indicated an increase in publications regarding mechanical ventilation in the ED over the last several years (19). Based on this scoping review, we decided to quantify the existing literature in order to inform clinicians and researchers about clinical outcomes and practice patterns regarding LTVV use in the ED. The objectives of this study were to perform a comprehensive systematic review of the global biomedical literature to evaluate LTVV use in mechanically ventilated ED patients. We hypothesized that tidal volumes in the ED have decreased over time and that LTVV in the ED is associated with improved clinical outcomes.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was registered in the PROSPERO international prospective register of systematic reviews (CRD42021256631). The final results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and Meta-analysis of Observational Studies in Epidemiology guidelines (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H41; and **Supplemental Digital Content 2**, http://links.lww.com/CCM/H42) (20, 21). This study did not require ethical approval.

Study Identification

An electronic search included the following databases: MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Each database was searched from the beginning of the database through May 2021 (**Supplemental Digital Content 3**, http://links.lww.com/CCM/H43). The search was designed in cooperation with a trained medical librarian who performed the electronic search.

The reference lists of included articles were manually screened to identify additional studies. A manual search of abstracts from the following meetings (2016–2021) was also conducted: American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, and CHEST. An online search of ClinicalTrials.gov was conducted to identify completed, but not yet published, studies. Study investigators were contacted via electronic mail for additional data as needed.

Eligibility Criteria

Inclusion was restricted to adults receiving invasive positive-pressure mechanical ventilation during the study period. There was no language restriction. Recognizing that it may impact study quality and heterogeneity, the inclusion of nonrandomized studies was decided a priori for the following reasons: 1) a high likelihood that the clinical question could not be investigated strictly with randomized trials, due to a lack of their existence, 2) to provide a comprehensive evaluation of strengths and weaknesses of the existing literature, and 3) to assess evidence of effects (benefit and harm) (22). Case studies, reviews, correspondences, or editorials were not eligible.

We compared outcomes between patients receiving ED LTVV versus non-LTVV. For the purposes of this

work, our definition of LTVV was that used for "LTVV" or "lung-protective ventilation" in the included studies. This was typically tidal volume less than or equal to 8-mL/kg predicted body weight (PBW). The primary outcome was hospital mortality. Secondary outcomes included mechanical ventilation duration, ICU length of stay, hospital length of stay, and the occurrence rate of ARDS after admission. For interventional studies (i.e., before-after clinical trials), we assessed the impact of the ED LTVV intervention on: 1) frequency of ED LTVV and tidal volumes and 2) frequency of ICU LTVV and tidal volumes.

Study Selection and Data Abstraction

Two independent reviewers (K.D.M., E.T.) screened abstracts of identified studies for eligibility. In the cases of uncertainty or disagreement, a third reviewer arbitrated consensus. Study characteristics, including author, publication year, number of patients, outcomes, quality assessment, study design, and tidal volume data, were extracted using a standardized approach. Although the overall eligibility criteria were identical, to be considered for the descriptive objective (i.e. to assess tidal volume changes over time), studies had to report delivered ED tidal volume settings; to be considered for the meta-analysis, studies had to report on clinical outcomes of interest.

Study Quality Assessment

Since all studies were cohort or before-after design, the Newcastle Ottawa Scale was used to assess quality, assigning up to 9 points, with less than or equal to 5 indicating poor quality (**Supplemental Digital Content 4**, http://links.lww.com/CCM/H44) (23).

Data Analysis

Qualitative descriptives were used for study characteristics and quality. Tidal volume was reported in mL/kg PBW and reported as mean (SD). For studies that reported median values, means and standard deviations were estimated per prior approach (24). Independent sample *t* test was used to compare tidal volumes.

A meta-analytic approach analyzed the data, using Review Manager (RevMan, Version 5.3; The Cochrane Collaboration, Copenhagen, Denmark). Random effects models calculated pooled effect sizes and 95% CIs, comparing the LTVV and non-LTVV groups. Odds ratios were calculated for binary outcomes; continuous variables were reported as mean differences, and overall effect estimates were generated using a *Z* test. The I^2 statistic was used to calculate between-study heterogeneity (25). Publication bias was assessed using a funnel plot of the size of treatment effect against study precision.

An a priori subgroup analysis was conducted on patients with ARDS. Upon completion of data abstraction, a post hoc "leave-one-out" analysis was conducted (26, 27). This was done to explore heterogeneity and address an influential outlier study with respect to mortality (28). In this study, mortality was 8.6% in the non-LTVV group versus 31.1% in the other included studies. In addition, contrary to the extensive amount of literature in the field, this outlier was the only study demonstrating a mortality increase with ED LTVV. We felt this lacked biological plausibility given the known contribution of tidal volume to VALI and outcome (29–34). It also contributed virtually all of the heterogeneity seen in the pooled analysis.

RESULTS

Search and Selection

The electronic search yielded 1,023 results. Three hundred seventy-one duplicates were deleted, resulting in 652 unique citations, of which 31 were given full-text review. In the final analysis, 21 studies were included. Eleven studies provided outcome data and were meta-analyzed (6, 11, 28, 35–42); 10 studies provided descriptive tidal volume data (16–18, 43–49). **Supplemental Digital Content 5** (http://links.lww.com/CCM/H45) displays the study flow diagram at each stage of the review.

Study Characteristics

Table 1 displays the 10 studies that provided descriptive tidal volume data from the ED but did not report clinical outcome data. The studies were published between 2009 and 2020, conducted in four different countries, and were all cohort studies. Three were rated as good quality on the Newcastle-Ottawa Scale, and seven were poor quality (Supplemental Digital Content 4, http://links.lww.com/CCM/H44). The total number of patients was 1,863.

TABLE 1.
Characteristics of Included Studies With Only Descriptive Tidal Volume Data Available (No Outcome Data)

Author, yr (No. of Patients)	Sites	Country	Quality Assessment	Study Design	Emergency Department Low Tidal Volume Ventilation, *n* (%)	Mean (SD) Tidal Volume (mL/kg Predicted Body Weight)	Comments
Rose, 2009 (307)	Twenty-four	Australia	Poor	Prospective cohort	82 (66.1)[a]	8.0 (1.8)	Abstract only
Fuller, 2013 (251)	One	United States	Good	Retrospective cohort	68 (27.1)	8.9 (1.6)	Severe sepsis and septic shock cohort
Wood, 2014 (509)	One	United States	Poor	Retrospective cohort	160 (31.4)	9.0 (1.6)	Abstract only
Dettmer, 2015 (97)	One	United States	Good	Retrospective cohort	Not reported	8.0 (1.5)	
Fuller, 2015 (219)	Four	United States	Good	Prospective cohort	122 (55.7)	7.8 (1.5)	
Cretallaz, 2017 (80)	Two	France	Poor	Retrospective cohort	56 (70.7)	7.0 (1.0)	Abstract only
Tran, 2017 (181)	One	United States	Poor	Retrospective cohort	Not reported	7.0 (1.5)	Abstract only intracranial hemorrhage cohort
Rasheed, 2019 (41)	One	Australia	Poor	Retrospective cohort	17 (41.5)	6.5 (1.0)	Abstract only
Tang, 2019 (71)	Not reported	Singapore	Poor	Retrospective cohort	67 (94.4)	7.0 (1.0)	Abstract only
Isenberg, 2020 (107)	One	United States	Poor	Retrospective cohort	72 (67.3)	8.0 (1.8)	Convenience sample of patients

[a]Out of 124 patients for which these data were available (direct communication with author).

Table 2 displays the 11 studies with outcome data that were eligible for meta-analysis. The studies were published between 2016 and 2021. There were three quasi-experimental, before-after studies, two retrospective before-after studies, and six cohort studies. Eight were rated as good quality on the Newcastle-Ottawa Scale, and three were rated as poor quality (Supplemental Digital Content 4, http://links.lww.com/CCM/H44). Eight were published as peer-reviewed articles and three presented as abstracts. The total number of patients was 12,912.

Meta-Analysis

The Impact of ED LTVV on Ventilator Settings. The before-after studies demonstrated an increase in ED LTVV with implementation of ED-based ventilator protocols (odds ratio, 7.29 [3.19–16.66]; $p < 0.001$) and significant reduction in ED tidal volume (−1.5-mL/kg PBW [−1.9 to −1.0]; $p < 0.001$). The use of LTVV in the ED was associated with an increase in ICU LTVV (odds ratio, 4.41 [1.90–10.26]; $p < 0.001$) and significant reduction in ICU tidal volume (−1.0-mL/kg PBW [−1.8 to −0.2]; $p = 0.01$) (**Supplemental Digital Content 6**, http://links.lww.com/CCM/H46).

Figure 1 displays ED tidal volume trend over time for studies that reported tidal volume values ($n = 15$ studies, conducted over 10-yr period). To more accurately approximate ED tidal volumes in use at the time, studies are ordered in the figure according to when the study was conducted (not published) or the period from which data were obtained, in the case of retrospective cohort studies. ED tidal volume decreased by approximately 2-mL/kg PBW over the 10-year period.

TABLE 2.
Characteristics of the Included Studies that Provided Outcome Data

Author, yr (No. of Patients)	Sites/ Country	Primary Outcomes Assessed	Secondary Outcomes Assessed	Study Design	ED LTVV, *n* (%)	Mean (SD) Tidal Volume (mL/kg Predicted Body Weight)	Comments
Wilcox, 2016 (433)	Three/ United States	Mortality, ventilator duration, and ICU and hospital LOS	None stated	Prospective cohort	261 (60.3)	8.0 (2.1)	Study conducted from July, 2011, to March, 2013
Fuller (LOV-ED Trial), 2017 (1,705)	One/ United States	Pulmonary complications (ARDS and ventilator-associated conditions)	Ventilator-, hospital-, and ICU-free days; and receipt of LTVV in ICU	Quasi-experimental, before-after trial	[a]Before: 1,202 (47.8) After: 731 (96.2)	Before: 8.3 (1.5) After: 6.4 (0.8)	Before phase, 2009–2014; after phase, 2014–2016
Fuller (ARDS Cohort), 2017 (229)	One/ United States	Hospital mortality	Ventilator-, hospital-, and ICU-free days; and receipt of LTVV in ICU	Quasi-experimental, before-after trial	[a]Before: 12 (11.1) After: 24 (61.5)	Before: 8.1 (1.6) After: 6.4 (0.4)	Was a priori substudy of LOV-ED trial
Skitch, 2019 (126)	One/ Canada	Hospital mortality	Duration of mechanical ventilation	Retrospective cohort	76 (60.3)	Not reported	Published as abstract only
Owyang, 2019 (446)	One/ United States	Final ED tidal volume	None specifically stated, but did report ICU and hospital LOS, and mortality	Retrospective cohort	256 (57.4)	7.8 (1.5)	Conducted from 2012 to 2015
Foley, 2020 (500)	One/ United States	Between-group tidal volume difference	Change in Sequential Organ Failure Assessment, vent- and hospital-free days, mortality, ARDS, and ventilator-associated pneumonia	Retrospective before-after cohort	Before: 235 (87.7) After: 213 (94.3)	Before: 6.6 (1.2) After: 6.2 (1.4)	Study conducted from March 2016 to July 2018
Prekker, 2020 (2,959)	One/ United States	Between-group tidal volume difference	% of ED patients with LTVV, duration of vent, ICU LOS, mortality, and ICU tidal volume	Quasi-experimental, before-after trial	Before: 501 (23.0) After: 560 (72.0)	Before: 9.0 (1.4) After: 7.2 (0.9)	Before phase, 2007–2014; after phase, 2015–2016; outlier-only study showing higher mortality

(*Continued*)

TABLE 2. (*Continued*).
Characteristics of the Included Studies that Provided Outcome Data

Author, yr (No. of Patients)	Sites/ Country	Primary Outcomes Assessed	Secondary Outcomes Assessed	Study Design	ED LTVV, *n* (%)	Mean (SD) Tidal Volume (mL/kg Predicted Body Weight)	Comments
Rolston, 2020 (297)	Two/ United States	Ventilator-free days and hospital mortality	None stated	Retrospective cohort	79 (25.9)	Not reported	Study conducted in 2017 Abstract only (outcome data provided by authors)
Sullivan, 2020 (217)	One/ United States	Mortality, vent duration, lengths of stay, and ARDS	None stated	Retrospective cohort	135 (62.2)	Non LTVV group: 9.0 (1.0) LTVV group: 6.9 (0.6)	Published as abstract only (outcome data provided by authors)
Tallman, 2020 (1,826)	One/ United States	Provision of LTVV	None stated	Retrospective before-after cohort	Before: 1,332 (84.5) After: 232 (93.9)	Not reported	Study conducted from 2015 to 2019. No patient-centered clinical outcomes reported
Fernando, 2021 (4,174)	Eight/ Canada	Hospital mortality	Development of ARDS, duration of mechanical ventilation, extubation failure, ICU LOS, hospital LOS, and cost	Retrospective cohort	2,437 (58.4)	Non LTVV group: 10.1 (1.4) LTVV group: 6.4 (1.3)	Study conducted between 2011 and 2017. LTVV also associated with reduced cost

ARDS = acute respiratory distress syndrome, ED = emergency department, LOS = length of stay, LTVV = low tidal volume ventilation.
[a]Reported as *n* (%) of ventilator settings.

Mean (SD) tidal volume during the first 5 years was 8.3 (1.6)-mL/kg PBW, compared with 6.8 (1.1)-mL/kg PBW during the last 5 years, $p < 0.001$.

The Impact of ED LTVV on Clinical Outcomes. The meta-analysis for binary outcomes is in **Figure 2**. Ten studies ($n = 11,086$) were included in the pooled analysis for mortality, which was 24.5% in the LTVV group, compared with 23.1% in the non-LTVV group (odds ratio, 0.87 [0.69–1.09]; $p = 0.23$). The "leave-one-out" subgroup analysis (nine studies, $n = 8,127$), which excluded the influential outlier study by Prekker et al (28), demonstrated mortality of 26.5% in the LTVV group, compared with 31.1% in the non-LTVV group (odds ratio, 0.80 [0.72–0.88]; $p < 0.001$). Heterogeneity was reduced from 76% to 0% in this subgroup analysis. The occurrence rate of ARDS after admission was

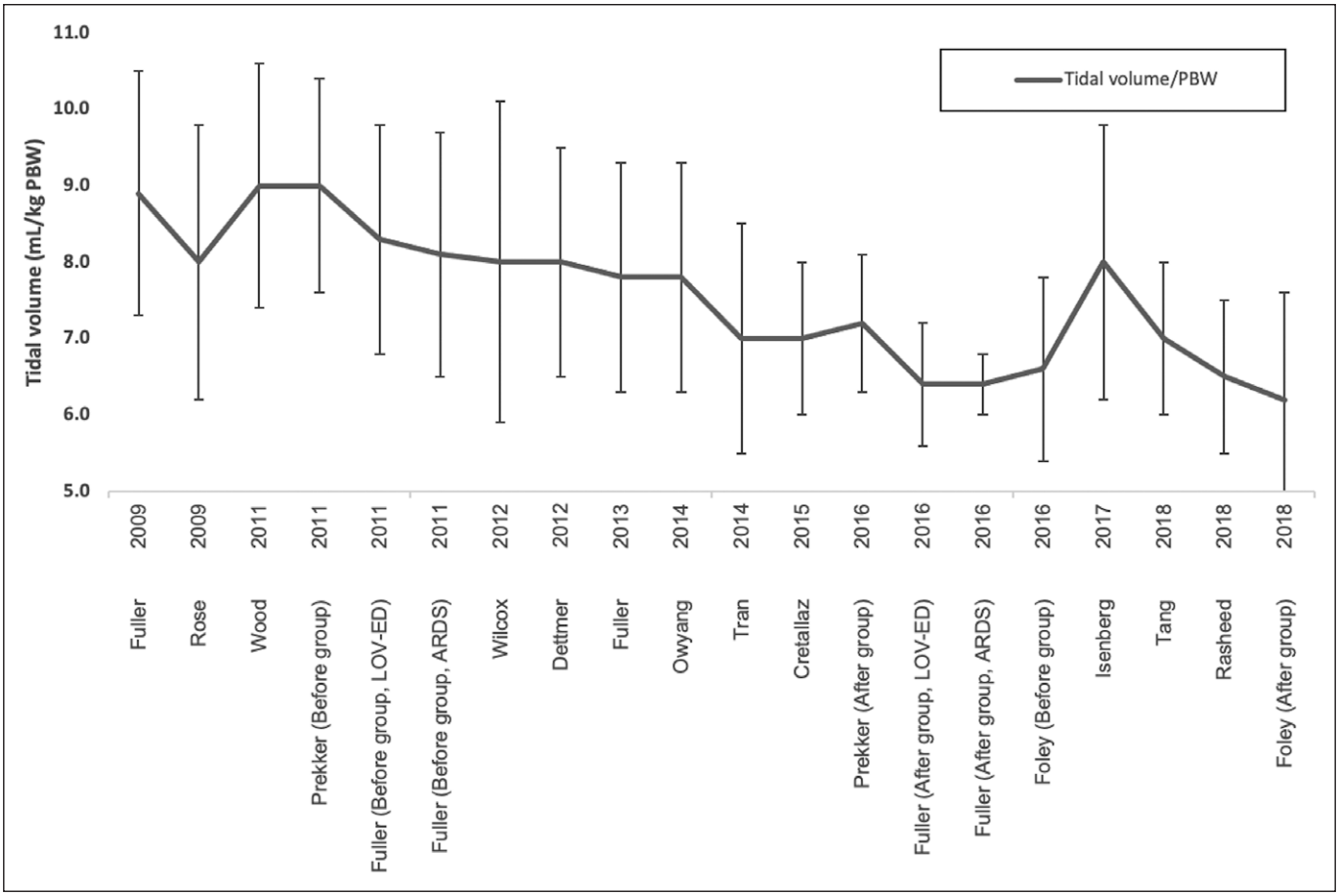

Figure 1. Emergency department (ED) tidal volume trend over time. *Error bars* represent SD. To better reflect tidal volumes in use at the time, the year on the *x*-axis corresponds to when the study was conducted (not published), or the time period from which the data was obtained (for retrospective cohort studies). ARDS = acute respiratory distress syndrome, PBW = predicted body weight.

reported in five studies (n = 7,042) and was 4.5% in the ED LTVV group versus 8.3% in the non-LTVV group (odds ratio, 0.57 [0.44–0.75]; $p < 0.001$). Funnel plot analysis for mortality (**Supplemental Digital Content 7**, http://links.lww.com/CCM/H47) revealed asymmetry, with lack of studies in the bottom-right, potentially indicating lack of publication of smaller, more positive studies.

Results for continuous outcomes are in **Figure 3**. ED LTVV was associated with shorter hospital length of stay (seven studies, n = 10,163; mean difference, −1.2 d [95% CI, −2.3 to −0.1 d]; p = 0.03) and ICU lengths of stay (seven studies, n = 10,163; mean difference, −1.0 d [95% CI, −1.7 to −0.3 d]; p = 0.004). There was an increase in ventilator-free days associated with ED LTVV (six studies, n = 7,122; mean difference 1.4 d [95% CI, 0.4–2.4 d]; p = 0.005). Two studies (n = 3,392) reported ventilator duration in days, but not ventilator-free days; there was no significant difference in the ED LTVV cohort compared with the non-LTVV cohort (mean difference, 0.2 d [95% CI, −0.04 to 0.5 d]; p = 0.09).

Statistical heterogeneity, described by the I^2 test, ranged from 0% to 82%, and there was moderate or high heterogeneity for all outcomes, except ARDS and ventilator duration (**Supplemental Digital Content 8**, http://links.lww.com/CCM/H48).

Subgroup Meta-Analysis in Patients With ARDS. Two studies (n = 633; **Supplemental Digital Content 9**, http://links.lww.com/CCM/H49) analyzed the impact of ED LTVV in patients with ARDS while in the ED. Mortality was 33.6% in the LTVV group versus 47.9% in the non-LTVV group (odds ratio, 0.68 [0.47–0.97]; p = 0.03). ED LTVV was associated with shorter ICU lengths of stay (mean difference, −1.8 d [95% CI, −3.2 to −0.4 d]; p = 0.010) and an increase in ventilator-free days (mean difference, 2.2 d [95% CI, 0.2–4.2 d]; p = 0.03). Hospital length of stay was lower by a mean difference of 1.7 days (95% CI, −5.1 to 1.7 d; p = 0.32), which was not statistically significant.

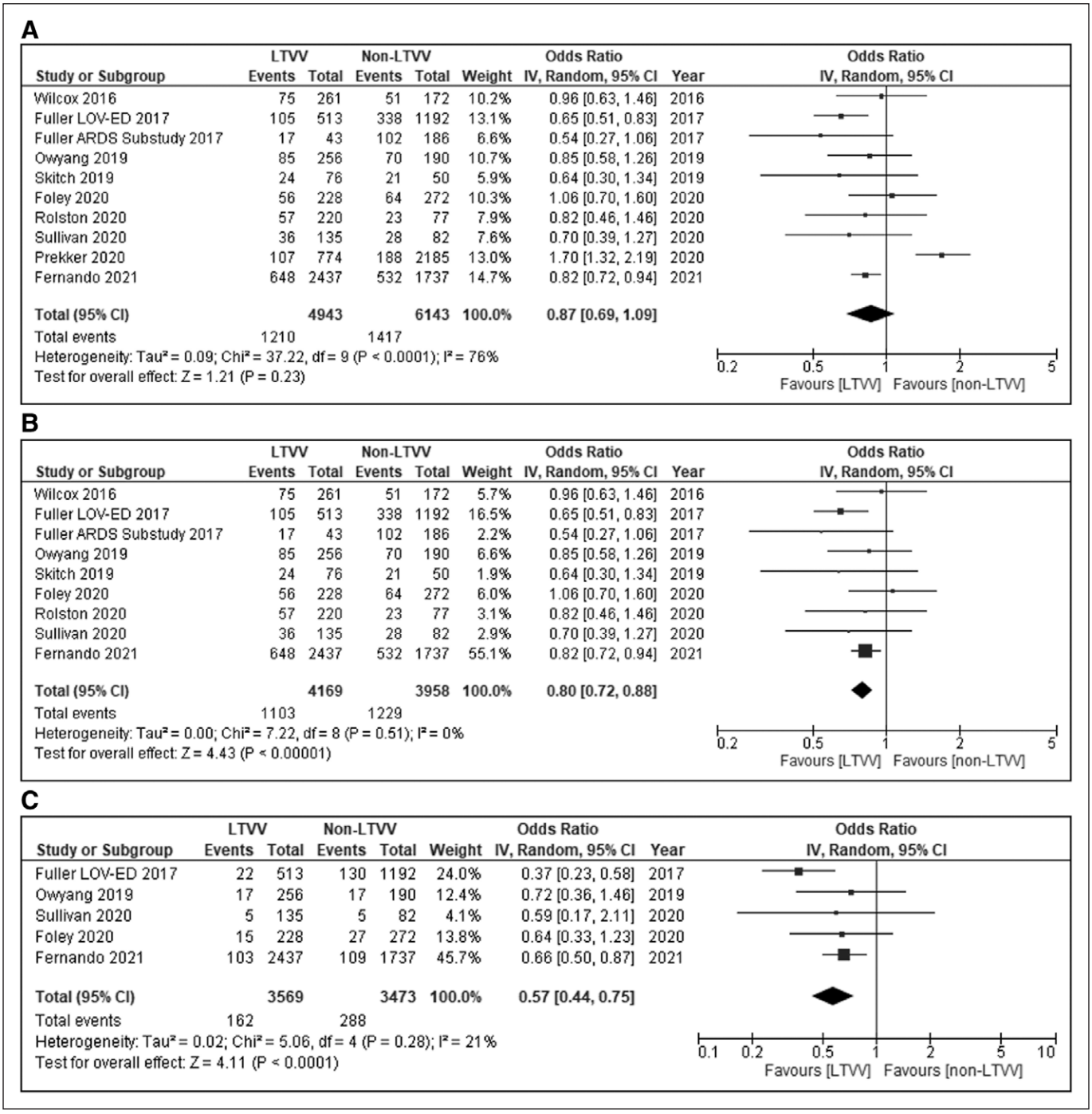

Figure 2. Forest plots displaying the impact of emergency department (ED) low tidal volume ventilation (LTVV) on mortality (**A**), mortality in the leave-one-out subgroup analysis (**B**), and acute respiratory distress syndrome (ARDS) (**C**).

DISCUSSION

The need for mechanical ventilation is a common indication for critical care services in the ED and ICU (50, 51). Major randomized clinical trials, large observational studies, systematic reviews, and meta-analyses have shown clinical benefit of LTVV in patients with ARDS, as well as those at risk for the syndrome (4, 5, 8, 13, 14, 52, 53). Despite this, a lack of adherence to this proven therapy is common in the ICU and associated with worse outcome (13, 14, 54). Initial tidal volume settings seem especially impactful in the early course of respiratory failure, both in terms of improving outcome and overall adherence to LTVV (6, 13, 14). Therefore, the ED could be an important arena in which to target LTVV to improve downstream adherence to

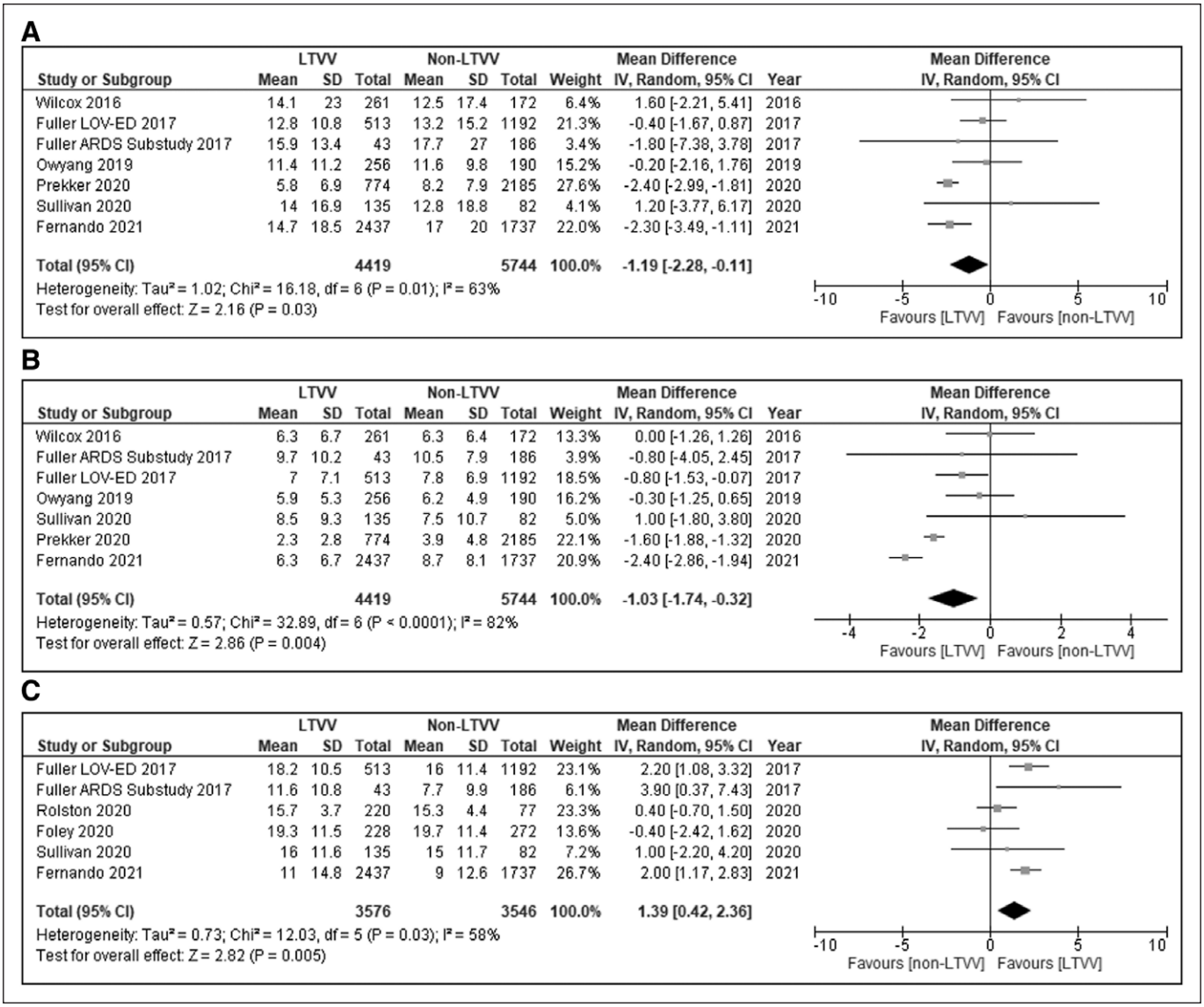

Figure 3. Forest plots displaying the impact of emergency department (ED) low tidal volume ventilation (LTVV) on hospital length of stay (**A**), ICU length of stay (**B**), and ventilator-free days (**C**). ARDS = acute respiratory distress syndrome.

LTVV and clinical outcomes. Initial observational data from the ED demonstrated that the use of high tidal volumes was common [8.8-mL/kg PBW (7.8–10.0)], and LTVV use was rare (27.1%) (16). On account of these data, subsequent published ED-based interventional studies, and nearly a decade of elapsed time, we undertook this systematic review and meta-analysis to characterize ED-based tidal volume trends over time and assess the potential impact of ED LTVV on clinical outcomes. There were several important findings.

Our main finding was an association between LTVV in the ED and improved clinical outcomes. ED LTVV was associated with decreased mortality, frequency of ARDS development after ICU admission, lengths of stay in the ICU and hospital, and an increase in ventilator-free days. These results were consistent in the subgroup analysis in patients with ARDS. Acknowledging that a "one-size-fits-all" approach should not be employed for all patients on a mechanical ventilator, our results suggest that LTVV should be the default approach to initial ventilator settings in the ED. Further, these data suggest that widespread implementation of LTVV in the ED could be a low-cost and rapidly scalable intervention to improve outcome and reduce healthcare utilization in mechanically ventilated patients.

Second, our systematic review demonstrated a decrease in ED tidal volume over time and the impact that ED tidal volume settings have on those delivered in the ICU. Data from five before-after implementation

studies (n = 8,705 patients) demonstrate that a protocolled approach to initial ED ventilator settings is feasible and associated with a decrease in tidal volume of approximately 1.5-mL/kg PBW. Additionally, multiple studies have demonstrated the influence that ED ventilator settings hold on subsequent ICU care (6, 16, 17, 36, 37). Our current results demonstrate that ED LTVV will improve adherence to LTVV in the ICU, with a decrease in tidal volume by approximately 1.0-mL/kg PBW. This represents a critical finding to support implementation of ED LTVV, considering the static nature of early ICU ventilator settings, high heterogeneity in ventilator settings and poor adherence to LTVV in the ICU, and data showing higher mortality with an increase of only 1-mL/kg PBW in initial ventilator settings in ARDS (13, 15, 54, 55).

Another important finding is the demonstration that ED tidal volume has decreased by approximately 2-mL/kg PBW in just over a decade, with less variability (i.e., more narrow SD over time). While we cannot pinpoint the reasons why, this translation from research evidence to clinical practice is in line with the typically slow adoption of evidence into real-world practice (56). Larger longitudinal studies will be needed to assess the penetrance and sustainability of LTVV in the ED and its ongoing impact on mechanical ventilation practices in the ICU. Utilizing dissemination and implementation science principles to develop strategies for systemic implementation of what appears to be an effective therapy is an important next step. Additionally, the sustainability of ED LTVV will need to be assessed, along with dissemination and implementation strategies for what appears to be an effective therapy.

There are important limitations to consider. First, there are no randomized clinical trials comparing LTVV in the ED with non-LTVV or usual care, necessitating the inclusion of cohort studies and before-after studies in the meta-analysis. Given the existing body of literature, a "classic" individually randomized, parallel group clinical trial comparing LTVV with non-LTVV raises ethical concerns. Additionally, the LOTUS-FRUIT Study estimated that between 66,000 and 107,000 patients (at a cost of $14–23 million) would need to be enrolled in a stepped-wedge cluster-randomized controlled trial in order to demonstrate a 3% improvement in mortality, comparing LTVV (6-mL/kg PBW) with usual care (7.1-mL/kg PBW, comparable to our current findings from the last 5 yr of ED data) (15). Recognizing that our reliance on observational and quasi-experimental studies with moderate-to-high statistical heterogeneity increases the risk of bias in our results, the current data are likely the most precise estimate of the benefit of ED LTVV for the foreseeable future. Second, our aggregate mortality estimate showed discordance when compared with the leave-one-out subgroup analysis, which was conducted after identification of an influential outlier that showed an increase in mortality associated with LTVV. Given the high volume of literature supporting LTVV in mechanically ventilated patients, the unusually low mortality, and a lack of face validity and biological plausibility of this outlier, we believe the leave-one-out analysis to be a more accurate reflection of the real estimate of effect. Third, our review focused solely on tidal volume and not on other mechanical ventilator settings that can be important aspects of lung protection (i.e., setting of positive end-expiratory pressure, limiting plateau pressure, and avoidance of hyperoxia). However, this approach was thought to be the most pragmatic and feasible with respect to collating the data. Fourth, excluding the subgroup analyses (leave-one-out subgroup, I^2 of 1%; ARDS subgroup I^2 of 0%), statistical heterogeneity was moderate-to-high, given the use of nonrandomized studies. As mechanically ventilated ED patients are clinically quite heterogeneous as well, statistical heterogeneity was not unexpected and should not prevent meta-analysis of the data. Fifth, the majority of our included studies were conducted in the United States and Canada and primarily in academic medical centers where dissemination of data may be more active. Therefore, these data may not reflect practices and outcomes in other regions of the world or in community settings. Sixth, our results (especially those regarding the impact on ICU LTVV) may reflect general changes over time with respect to the use of LTVV, as opposed to location-specific interventions in the ED. Finally, although our clinical outcomes were patient-centered, there were no longer-term outcomes assessed, such as physical, cognitive, and psychosocial outcomes. Given the survivor burden associated with mechanical ventilation, assessing longer term outcomes in survivors of ED mechanical ventilation is an important research priority going forward (3, 57).

CONCLUSIONS

This comprehensive systematic review collated the global biomedical literature regarding tidal volume during mechanical ventilation in the ED. The use of an LTVV approach in the ED is associated with improved clinical outcomes and an increase in lung protection in both the ED and ICU. Interventions aimed at implementing and sustaining LTVV in the ED should be explored further.

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REFERENCES

1. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693
2. Rubenfeld GD, Herridge MS: Epidemiology and outcomes of acute lung injury. *Chest* 2007; 131:554–562
3. Needham DM, Sepulveda KA, Dinglas VD, et al: Core outcome measures for clinical research in acute respiratory failure survivors. An International Modified Delphi Consensus Study. *Am J Respir Crit Care Med* 2017; 196:1122–1130
4. Brower RG, Matthay MA, Morris A; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. *N Engl J Med* 2000; 342:1301–1308
5. Serpa Neto A, Cardoso SO, Manetta JA, et al: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. *JAMA* 2012; 308:1651–1659
6. Fuller BM, Ferguson IT, Mohr NM et al: Lung-protective ventilation initiated in the emergency department (LOV-ED): A quasi-experimental, before-after trial. *Ann Emerg Med* 2017; 70:406–418.e404
7. Determann RM, Royakkers A, Wolthuis EK, et al: Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: A preventive randomized controlled trial. *Crit Care* 2010; 14:R1
8. Futier E, Constantin JM, Paugam-Burtz C, et al; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013; 369:428–437
9. Rose L, Gray S, Burns K, et al: Emergency department length of stay for patients requiring mechanical ventilation: A prospective observational study. *Scand J Trauma Resusc Emerg Med* 2012; 20:1–7

10. Angotti LB, Richards JB, Fisher DF, et al: Duration of mechanical ventilation in the emergency department. *West J Emerg Med* 2017; 18:972–979
11. Owyang CG, Kim JL, Loo G, et al: The effect of emergency department crowding on lung-protective ventilation utilization for critically ill patients. *J Crit Care* 2019; 52:40–47
12. Hung S-C, Kung C-T, Hung C-W, et al: Determining delayed admission to the intensive care unit for mechanically ventilated patients in the emergency department. *Critical Care* 2014; 18:1–9
13. Needham DM, Yang T, Dinglas VD, et al: Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome. A prospective cohort study. *Am J Respir Crit Care Med* 2015; 191:177–185
14. Needham DM, Colantuoni E, Mendez-Tellez PA, et al: Lung protective mechanical ventilation and two year survival in patients with acute lung injury: Prospective cohort study. *BMJ* 2012; 344:e2124
15. Lanspa MJ, Gong MN, Schoenfeld DA, et al; The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network: Prospective assessment of the feasibility of a trial of low-tidal volume ventilation for patients with acute respiratory failure. *Ann Am Thorac Soc* 2019; 16:356–362
16. Fuller BM, Mohr NM, Dettmer M, et al: Mechanical ventilation and acute lung injury in emergency department patients with severe sepsis and septic shock: An observational study. *Acad Emerg Med* 2013; 20:659–669
17. Fuller BM, Mohr NM, Miller CN, et al: Mechanical ventilation and ARDS in the ED: A multicenter, observational, prospective, cross-sectional Study. *Chest* 2015; 148:365–374
18. Wood SL, Papacostas NC, Lamb M, et al: Tidal volume in patients undergoing mechanical ventilation in the emergency department. *Ann Emerg Med* 2014; 64:S40
19. Peters MDJ, Marnie C, Tricco AC, et al: Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth* 2020; 18:2119–2126
20. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6:e1000097
21. Stroup DF, Berlin JA, Morton SC, et al: Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283:2008–2012
22. Reeves BC, Deeks JJ, Higgins JPT, et al; on behalf of the Cochrane Non-Randomised Studies Methods Group: Including non-randomised studies. *In*: Cochrane Handbook for Systematic Reviews of Interventions. Higgins JPT , Green S (Eds). London, United Kingdom, The Cochrane Collaboration, 2008
23. Wells G, Shea B, O'Connell D et al: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. The Ottawa Hospital Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed July 15, 2021
24. Wan X, Wang W, Liu J, et al: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol* 2014; 14:1–13
25. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–1558
26. Higgins JP: Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008; 37:1158–1160
27. Patsopoulos NA, Evangelou E, Ioannidis JP: Sensitivity of between-study heterogeneity in meta-analysis: Proposed metrics and empirical evaluation. *Int J Epidemiol* 2008; 37:1148–1157
28. Prekker ME, Donelan C, Ambur S, et al: Adoption of low tidal volume ventilation in the emergency department: A quality improvement intervention. *Am J Emerg Med* 2020; 38:763–767
29. Bshouty Z, Ali J, Younes M: Effect of tidal volume and PEEP on rate of edema formation in in situ perfused canine lobes. *J Appl Physiol (1985)* 1988; 64:1900–1907
30. Dreyfuss D, Soler P, Basset G, et al: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988; 137:1159–1164
31. Hernandez LA, Peevy KJ, Moise AA, et al: Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *J Appl Physiol (1985)* 1989; 66:2364–2368
32. Carlton DP, Cummings JJ, Scheerer RG, et al: Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. *J Appl Physiol (1985)* 1990; 69:577–583
33. Corbridge TC, Wood LD, Crawford GP, et al: Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990; 142:311–315
34. Hickling KG, Henderson SJ, Jackson R: Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990; 16:372–377
35. Fernando SM, Fan E, Rochwerg B, et al: Lung-protective ventilation and associated outcomes and costs among patients receiving invasive mechanical ventilation in the ED. *Chest* 2021; 159:606–618
36. Foley TM, Philpot BA, Davis AS, et al: Implementation of an ED-based bundled mechanical ventilation protocol improves adherence to lung-protective ventilation. *Am J Emerg Med* 2021; 43:186–194
37. Fuller BM, Ferguson IT, Mohr NM, et al: A quasi-experimental, before-after trial examining the impact of an emergency department mechanical ventilator protocol on clinical outcomes and lung-protective ventilation in acute respiratory distress syndrome. *Crit Care Med* 2017; 45:645–652
38. Ives Tallman CM, Harvey CE, Laurinec SL, et al: Impact of providing a tape measure on the provision of lung-protective ventilation. *West J Emerg Med* 2021; 22:389–393
39. Skitch S, Rochwerg B: A quality assurance study assessing mechanical ventilation practices in the emergency department. *Can J Anaesth* 2019; 66:S7–S8
40. Wilcox SR, Richards JB, Fisher DF, et al: Initial mechanical ventilator settings and lung protective ventilation in the ED. *Am J Emerg Med* 2016; 34:1446–1451
41. Johnson S, Li T, Libov D et al: The effects of initial emergency department ventilator settings on ventilator free days and in-hospital mortality. *Acad Emerg Med* 2020, 27:S227

42. Sullivan N, Quan T, Panda A, et al: Do initial tidal volumes matter in the setting of the emergency department? *Crit Care Med* 2020; 48:719
43. Cretallaz P, Mermillod-Blondin R, Richard JC, et al: Analysis of invasive mechanical ventilation as managed by French pre-hospital emergency physicians. *Ann Intensive Care* 2017; 7:25–26
44. Dettmer MR, Mohr NM, Fuller BM: Sepsis-associated pulmonary complications in emergency department patients monitored with serial lactate: An observational cohort study. *J Crit Care* 2015; 30:1163–1168
45. Isenberg DL, Bloom B, Gentile N, et al: Males receive low-tidal volume component of lung protective ventilation more frequently than females in the emergency department. *West J Emerg Med* 2020; 21:684–687
46. Rasheed A: Lung protective ventilation in the emergency department. *Intensive Care Med Exp* 2019; 7
47. Rose L, Gerdtz MF: Use of invasive mechanical ventilation in Australian emergency departments: Original Research. *Emerg Med Australas* 2009; 21:108–116
48. Tang J: Initiation of lung protective ventilation in the emergency department. *Emerg Med Australas* 2019, 31:33
49. Tran QK, Strong J, Al Rebh H, et al: Emergency providers adequately manage mechanical ventilation in critically ill patients with spontaneous intracranial hemorrhage and elevated intracranial pressure. *Ann Emerg Med* 2017; 70:S50
50. Wunsch H, Linde-Zwirble WT, Angus DC, et al: The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010; 38:1947–1953
51. Easter BD, Fischer C, Fisher J: The use of mechanical ventilation in the ED. *Am J Emerg Med* 2012; 30:1183–1188
52. Laffey JG, Bellani G, Pham T, et al; LUNG SAFE Investigators and the ESICM Trials Group: Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: The LUNG SAFE study. *Intensive Care Med* 2016; 42:1865–1876
53. Fuller BM, Mohr NM, Drewry AM, et al: Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: A systematic review. *Critical care* 2013; 17:R11
54. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 Countries. *JAMA* 2016; 315:788–800
55. Grasselli G, Cattaneo E, Florio G, et al: Mechanical ventilation parameters in critically ill COVID-19 patients: A scoping review. *Critical Care* 2021; 25:1–11
56. Wensing M, Grol R: Knowledge translation in health: How implementation science could contribute more. *BMC Med* 2019; 17:88
57. Dinglas VD, Faraone LN, Needham DM: Understanding patient-important outcomes after critical illness: A synthesis of recent qualitative, empirical, and consensus-related studies. *Curr Opin Crit Care* 2018; 24:401–409