Research Square

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Mortality Associated With Acute Respiratory Distress Syndrome 2009-2019: A Systematic Review and Meta-regression

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is a common occurrence in an intensive care unit. The reported mortality in studies evaluating acute respiratory distress syndrome is highly variable. The adherence to ventilatory specific and adjunctive therapies is also highly variable. We investigated the mortality of ARDS since the 2009 H1N1 pandemic and examined the adherence to ventilatory specific and adjunctive therapies.

Methods: We performed a systematic search in MEDLINE and EMBASE using a highly sensitive criterion from January 2009 to May 2019. We then ran a proportional meta-analysis for mortality and a meta-regression analysis using certain variables to address heterogeneity.

Results: We screened 5361 citations, of which 85 fully met inclusion criteria. The weighted pooled mortality of all 85 studies published from 2009 to 2019 was 38% (95% CI 35,40). Mortality was higher in observational studies [40% (95% CI 37, 42)] compared to RCTs [35% (95% CI 30,39)], (p=0.04) Significant variability exists in literature of reported tidal volumes, positive end expiratory pressures, plateau pressures, and use adjunctive therapies. The tidal volumes in our systematic review ranged from 5.8 to 8.9 ml/kg with a mean of 7.2 ml/kg. PEEP ranged from 4.6 to 16.1 cm H2O at the time of enrollment with a mean of 10.2 cm H2O. Reported plateau pressures ranged from 21.0 to 35.1 cm H2O, with a mean of 25.6 cm H2O. Higher reported initial PaO2/FiO2 ratios were associated with decreased mortality. A trend towards decreased mortality was seen with lower reported tidal volumes in the included studies.

Conclusions: Over the last decade, the mortality in ARDS has marginally improved and there exists significant heterogeneity in the utilization of low tidal volume strategies, application of PEEP and the adoption of adjunctive therapies in the management of these patients in published literature.

Background

Acute respiratory distress syndrome (ARDS) accounts for approximately 10 percent of intensive care unit (ICU) admissions, with a mortality rate ranging from 35-45 percent(1). Phua et al showed that the mortality among observational studies and randomized controlled trials remained static from the implementation of the 1994 AECC definition for ARDS to 2006(2). Since the publication of that meta-analysis, an influenza pandemic with a high prevalence of ARDS occurred, a new definition of ARDS was developed(3) and several landmark randomized controlled trials evaluating various interventions were published(4–9).

Over the last two decades lung-protective ventilation (LPV) strategies [tidal volume (Vt) 6-8 mL/kg predicted body weight and low plateau airway pressures (Pplat) (<30cmH2O)] remains the mainstay of ARDS management. Adherence to LPV strategies has consistently shown to improve patient survival(10). Use of Prone Position ventilation (PP)(9) in patients with moderate-severe ARDS is the only other therapeutic intervention that has been associated with improved survival. Use of continuous neuromuscular blocking agents (NMBA)(4,11) has been disparate results amongst the two major trials that have evaluated this question. Other interventions including use of higher positive end expiratory pressure (PEEP)(12,13), inhaled pulmonary vasodilators(14,15) and diuretics(16) improve oxygenation and duration of mechanical ventilation respectively, but their use has not been associated with a mortality benefit. Based on the current evidence early, consistent use of extracorporeal membrane oxygenation (ECMO) cannot be justified, and this therapy needs to be considered after failure of conventional mechanical ventilation(5,17,18). But more importantly independent of the quality or strength of evidence the application of all these therapies in ARDS remains inconsistent and is predominantly influenced by physician comfort and discretion(1). As a result, significant heterogeneity is seen in the adoption and application of these evidence-based therapies in the published literature.

We conducted a systematic review and meta-analysis to investigate mortality associated with ARDS since the 2009 H1N1 pandemic. We evaluated temporal changes in mortality over the study period. Due to the presence of heterogeneity in application of conventional and adjunctive management strategies in ARDS patients, we also evaluated the impact of specific

intervention such as reported tidal volume, PEEP and use of adjunctive therapies on the reported mortality in the included studies.

Methodology

Search strategy

We electronically searched MEDLINE and EMBASE (January 2009 to May 2019) using a highly sensitive strategy to identify the relevant studies. For potentially relevant articles the full text was obtained for review; for these articles, all references were inspected to supplement our search. Details of the search strategy are reported in the supplementary files. We limited our search strategy to articles published in English.

Study selection

We included both randomized controlled trials (RCT) and observational studies for the purpose of this systematic review. Using standardized criteria, two reviewers (DS and KS) reviewed titles and abstracts identified by the search strategy independently and in duplicate, retrieving studies that either reviewer thought relevant for full-text review. Disagreements between reviewers in study selection and data extraction were resolved by the senior author (AD). We selected observational studies and RCTs enrolling at least 50 adults with acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) and reporting mortality. We only included studies where 100% of the sample met any criteria for ARDS. We excluded reports available only in abstract form, duplicate reports and animal studies.

Data extraction

Two authors (DS and KS) independently extracted all the data. Extracted data included: geography (county, continent, institutions); duration of study (months, years); ARDS definition used [Berlin, American European Consensus Conference (AECC), or other]; patient characteristics [age, severity (Pa/FiO2 ratio, APACHE II, SAPS, SOFA)]; ventilator specific variables (Vt, PEEP, Pplat); adjunctive therapy [inhaled vasodilators, NMBA, High Frequency Oscillatory Ventilation (HFOV), PP, and ECMO]; and all reported mortality. Driving pressure was calculated using the reported PEEP and Pplat(19). The data from RCTs and observational studies that contained multiple arms were combined for analysis (if reported in means and standard deviation). If a study contained an arm dedicated to investigating an adjunctive therapy versus control, only the control arm from that study was included, so as to pertain to all ARDS patients. Any missing data is reported in the study table in the supplementary appendix. The primary outcome was short term mortality. Short term mortality was defined as hospital mortality where reported, as it was the most often reported. If not reported then ICU mortality, 90-day mortality, 60-day mortality, and 28/30-day mortality were substituted, in this order of preference.

Risk of bias assessment

To assess for risk of bias, two authors independently reviewed all included studies. The tool Cochrane RoB-2 was utilized to assess RCTs(20). Using this tool we evaluated five different domains for each RCT and determined an overall risk of bias. The ROBINS-1 tool was utilized for observational studies(21). Using this tool we evaluated seven different domains for each observational study and determined an overall risk of bias. The overall risk of bias for both RCTs and observational studies was determined by the highest risk allotment in any of the categories.

Data analysis

Baseline characteristics between observational studies and RCTs were compared using student's *t* test and chi squared tests, for continuous and categorical variables respectively. We performed a proportion meta-analysis using random-effects models to obtain pooled estimates of mortality and 95% confidence intervals (CIs) for all observational studies and all RCTs separately(22). We used Cochran's Q statistic and I2 to test for heterogeneity among studies(23). To further explore heterogeneity among studies we formed logistic meta-regression models to evaluate the association between selected

variables (PaO2/FiO2 ratios, Vt, PEEP, Pplat, driving pressure, mean age, APACHE II, SOFA, NMBA, PP, and ECMO) and mortality(24). We also ran a cumulative mortality analysis using median year of enrollment to evaluate the trend of mortality from our literature collection from 2009 to 2019(25). A *p* value of £ 0.05 was considered to be statistically significant. Funnel plot analysis and Egger's test were done to investigate for publication bias(26,27). The statistical analysis was conducted using Stata Version 15.1 (StataCorp LP, College Station, TX.). Two sensitivity analysis were also conducted to address certain aspects of our study and their effects on our findings. One focusing on combining both the intervention and control arms of studies which focused on one adjunctive therapy and another including only on studies reporting hospital mortality.

Results

Study Selection

Our search strategy yielded 5361 citations after de-duplication. We reviewed full texts for 1523 articles for a detailed evaluation and included 85 articles in our qualitative assessment **(Figure 1).** The final selection of 85 articles included 30 RCTs (35.3%) and 55 observational studies (64.7%). 19,963 patients were enrolled in the included studies. Among the 85 included studies, 9 studies investigated an adjunctive therapy versus control, and thus only the control arm was included in the primary analysis. But we included both arms of the 9 studies in a sensitivity analysis which consisted of 21,328 patients. We also performed a sensitivity analysis of studies reporting hospital mortality. This analysis consisted of 15 RCTs (32.6%) and 31 observational studies (67.4%), totaling 12,168 patients.

Study Characteristics

46 (54.2%) studies used the AECC criteria to diagnose ARDS, 36 studies (42.3%) used Berlin Criteria, 2 (2.3%) studies used either criteria, and 1 study (1.2%) used the Chinese critical care medicine definition. The mean age was reported in 70 studies (82.4%). The mean baseline PaO_2/FiO_2 ratio was reported in 72 studies (84.7%), mean APACHE II score was reported in 38 studies (44.7%), and mean SOFA score was reported in 32 studies (37.6%). Tidal volume in ml/kg was reported in 56 studies (65.9%), PEEP was reported in 60 studies (70.6%), Pplat was reported in 49 studies (57.7%), and we were able to calculate the driving pressure in 44 studies (51.8%). The use of inhaled vasodilators, NMB, HFOV, PP, and ECMO was reported in 23 (27%), 22 (25.8%), 9 (10.7%), 25 (29.4%), 20 (23.5%) studies, respectively (**Table 1).** There were no differences in the baseline characteristics, severity of initial illness and use of ventilatory strategies between the RCT's and observational studies (**Table 1**). The lack of asymmetry on the Funnel plot and the result of the Egger's test imply that publication bias did not alter the results (**e-Figures 5-6**).

Quality assessment

The risk of bias for RCTs was low in twelve studies, moderate in fourteen RCTs, and high in four RCTs (**e-Table 2**). The high risk of bias was driven mainly by deviation from intended intervention. For observational studies the risk of bias low in two studies, moderate in forty-one studies, and high in twelve studies (**e-Table 3**). The high and moderate risk of bias was driven mainly by confounding given the nature of study design.

Mortality

Hospital mortality (46 studies) was most commonly reported in the included studies. In the remaining 39 studies it was substituted with ICU mortality (8 studies), 90-day mortality (3 studies), 60-day mortality (9 studies), and 28/30-day mortality (19 studies). The weighted pooled mortality of all 85 studies published from 2009 to 2019 was 38% (95% CI 35,40). Mortality was higher in observational studies [40% (95% CI 37, 42)] compared to RCTs [35% (95% CI 30,39)], (p=0.04) (**Figure 2 and Table 1**). There was significant heterogeneity among the included studies (I^2 = 92.23%, p<0.01). This heterogeneity persisted across both observational studies (I^2 = 90.21%, p<0.01) and RCTs (I^2 = 93.87%, p<0.01) (**Figure 2**). Figure 2 depicts the reported mortality from the included studies listed in chronological order according to publication year. The continent where the study was performed failed to show a statistically significant different in mortality as determined by an one-way ANOVA [F(5,79) = 1.5, p=0.20].

The reported mortality did not change based on the sensitivity analysis. The first sensitivity analysis which included both the interventional and control arm of the 9 studies evaluating a particular adjunctive therapy resulted in a pooled mortality of 37% (95% CI 33,40) (**e-Figure 7**). The weighted pooled mortality was similarly higher in observational studies [40% (95% CI, 37,43)] compared to RCTs [33% (95% CI 29,37)] (p<0.01). The second sensitivity analysis which only included studies reporting hospital mortality (46 studies) resulted in a pooled mortality of 39% (95% CI 36,42) (**e-Figure 8**). Mortality again remained higher in observational studies [41% (95% CI 37,44)] compared to RCTs [34% (95% CI 28,39)] (p=0.05). The cumulative mortality analysis, which we conducted using the median year of enrollment, displays the evolution of mortality in studies published from 2009 to 2019, excluding one study which did not mention enrollment dates(28) (**Figure 3**). The median year of enrollment ranges from 2000 to 2018 and on visual inspection the mortality suggests an initial decrease after which it stabilizes around the mean with little change.

Meta-regression

In our meta-regression analysis, the initial PaO_2/FiO_2 ratio in the included studies was strongly associated with the reported mortality [b coef. -0.0041 (95% CI -.0023, -.0005); p<0.01] (**Figure 4**). We found significant variability in the reported ventilatory strategies and utilization of adjunctive therapies. The tidal volumes in our systematic review ranged from 5.8 to 8.9 ml/kg with a mean of 7.2 ml/kg. Though not statistically significant, a very clear trend towards a mortality benefit was observed in studies with lower reported tidal volumes [b coef. 0.0337 (95% CI -.0009, .0680); p=0.06], see **Figure 5**. PEEP ranged from 4.6 to 16.1 cm H2O at the time of enrollment with a mean of 10.2 cm H2O. Reported plateau pressures ranged from 21.0 to 35.1 cm H2O, with a mean of 25.6 cm H2O. Driving pressure ranged from 12.4 to 22.8 with a mean of 15.4. Neither PEEP [b coef. -0.0048 (95% CI -.0200, .0103); p=0.53], Pplat [b coef. 0.0046 (95% CI -.0077, .0169); p=0.45], nor driving pressure [b coef. 0.01382 (95% CI -.0030, .0307); p=0.11] appeared to impact mortality (**e-Figures 9-11**). Mean age, APACHE II, and SOFA also did not have any impact on mortality in our meta-regression (**e-Figures 12-14**). Reported adjunctive therapies were significantly variable in the included studies and did not have any impact on the mortality reported in our meta-regression (**e-Figures 15-18**). In the sensitivity analysis, which only included studies that reported hospital mortality, repeating meta-regression analysis for the same variables mentioned above produced identical results (**e-Table 4**).

Discussion

Our meta-analysis demonstrates a minor reduction in ARDS associated mortality since 2009. Compared to results reported by Phua et al, the cumulative reported mortality has dropped 6.9% from 44.3% to 38%(2) over the last decade. Similar to other studies, the mortality is consistently higher in observational studies compared to RCTs. The well described impact of initial severity of hypoxemia is seen in our meta-analysis and is strongly associated with mortality among the included studies.

Our study also shows that there remains significant heterogeneity and inconsistency in the reporting of key therapeutic interventions, markers of severity of illness and ventilatory strategies for patients with ARDS. This inconsistency in reporting makes the comparison of outcomes amongst these studies very difficult. Despite the development of the Berlin Definition(3) and a call for consistent reporting, this remains a problem among the studies that we evaluated. As seen in the LUNG SAFE study, ARDS still remains an underdiagnosed disease process and 40% of patients meeting ARDS criteria are never diagnosed(1). These findings suggest that diagnosis of ARDS is often delayed, with a high likelihood of delay in treatment for this diagnosis. This is especially concerning given that many of the ARDS treatments with proven benefit have only demonstrated a benefit in early ARDS(4,9,29).

The significant variability in use of evidence-based interventions in studies evaluating patients with ARDS is of concern. The use of ventilator specific variables, such as low tidal volume and PEEP, and adjunctive therapies, such as inhaled vasodilators, NMBAs, HFOV, PP, and ECMO, exhibit great inconsistency amongst the studies. This non-adherence to therapies with proven benefit(4,9,30) among the included studies might be a significant driver to the differences in outcomes reported by different studies independent of the severity of included patients. Similar to findings in LUNG SAFE few studies mentioned the plateau pressures for the patients included in their studies and the use of adjunctive therapies is inconsistent and highly variable outside of studies evaluating a specific intervention. LUNG SAFE study revealed that less than two-thirds of patients received

low tidal volume ventilation, 82.6% of patients received a PEEP < 12 cm H_2O, 37.8% of patients with severe ARDS received NMBAs, and only 16.3% of patients with severe ARDS were proned(1). The absence of standardization in the implementation of these therapies makes it difficult to discern their impact on outcomes. The low implementation of these therapies is surprising given a mean PaO_2/FiO_2 ratio of 132.5 mm Hg at baseline. The overall lack of standardization and implementation of best practices observed in our study highlights the need for protocol driven ARDS management that allow the clinicians to select the most appropriate adjunctive therapies for their patient. Personalization of care to patients with ARDS may be indicated in the future as suggested by colleagues Constantin et al(31), but not before therapies with proven benefit have been systematically standardized and adopted universally. Implementation of standardized ARDS management may help to further decrease ARDS associated mortality.

Over the last decade the overall mortality reported among RCTs has remained static since the last meta-analysis(2), and remains much higher than the suggested benchmark for ARDS trials(32). Significant mortality benefit has only been seen with isolated interventions such as PP in PROSEVA(9). The reported mortality among large epidemiologic studies in ARDS over the last two decades has not changed much. The lower reported mortality in RCTs compared to observational studies is not surprising as RCTs usually ensure strict adherence to protocols, with the probable exclusion of patients with a poor prognosis(33,34). Cumulative mortality for all ARDS studies shows a less than 7% change in reported mortality across time. With the application of evidence based ventilatory and non-ventilatory therapeutic interventions we had expected to see a much larger impact on mortality in the current meta-analysis. But a lack of reporting key variables and a wide variability in the reported numbers for these variables, brings to light a significant problem that the application of these therapies are not as widely consistent as we would hope when we are caring for ARDS patients. In many cases the intervention being studied, or co-interventions of interest are tightly accounted for in individual studies, but the complex care of these patients is not nearly enough a protocolized consistent approach that we would hope for.

Our systematic review and meta-analysis has several strengths. We conducted a comprehensive literature search using broad search terms. We included studies from institutions across five continents, and report an international evaluation of the trend in ARDS mortality, as opposed to the recent findings by Zhang et al(35). The inclusion criteria were carefully predefined and carried out in a methodological fashion. Additionally, we only included studies which exclusively evaluated ARDS patients. This is the first meta-analysis evaluating ARDS mortality trends to include a meta-regression analysis evaluating ARDS treatment modalities and their association with ARDS mortality.

Despite the strengths of our meta-analysis, there are potential limitations. First, we used hospital mortality as the primary mortality in our analysis as it was most frequently reported (46 of 85 studies). With a reported incidence of mortality of 3-15% in ARDS after discharge from the ICU(36,37), utilization of hospital mortality as our primary mortality type may have impacted our overall reported ARDS-related mortality. When hospital mortality was not available it was substituted with ICU, 90 day, 60 day, and 28/30 day mortality, in that order of preference. However, to tackle this potential inadequacy, we conducted a sensitivity analysis only including those studies reporting hospital mortality which produced identical results. Another limitation is the reporting of ventilator specific variables only at the time of patient enrollment in the majority of included studies. Although this may not represent the overall ventilator management strategy received by patients, it provides an insight into the initial management strategy, which is associated with the greatest mortality benefit. Not all studies may have reported the use of adjunctive therapies, possibly accounting for the low numbers we discovered. Finally, we included all diagnoses criteria for ARDS in our systematic review and meta-analysis and we did not stratify results based on ARDS severity. This unlikely impacted overall mortality results, however, as there was no difference in the PaO_2/FiO_2 ratio or severity scores at baseline for included studies.

Conclusions

Our systematic review and meta-analysis observed a minimal decline in ARDS related mortality over the last decade. We also saw that there remains a significant heterogeneity in reporting of both ventilator strategies and adjunctive therapies amongst the published literature. Despite established guidelines there is variability in the overall management of ARDS. Increased

clinician education regarding the importance of early recognition and implementation of best practices may help to reduce ARDS related mortality(38). Future studies should evaluate standardized ARDS treatment protocols, which implement evidence-based best practices, and their impact on mortality.

Abbreviations

ARDS – acute respiratory distress syndrome
ICU – intensive care unit

LPV – lung-protective ventilation

Vt – tidal volume

Pplat – plateau pressure

PP – prone position

NMBA – neuromuscular blocking agents

PEEP – positive end expiratory pressure

ECMO – extracorporeal membrane oxygenation

RCT – randomized controlled trials

ALI – acute lung injury

HFOV – high frequency oscillatory ventilation

APACHE II – Acute; Physiology and Chronic Health Evaluation

SOFA – Sequential Organ Failure Assessment

Declarations

Guarantor: AD is the guarantor for this original research manuscript and takes full responsibility for the data and analysis.

Author Contribution:

Study concept and study design – DS/KS/AD

Data acquisition – DS/SK/KS/VA/HT

Data interpretation – DS/SK/KS/KB/MS/VA/HT/SG/SK2/AD

Statistical analysis – DS/KS/KB/AD

Drafting/critical revision of manuscript – DS/SK/KS/KB/MS/VA/SG/HT/SK2/AD

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Tables

Table 1: Study Characteristics

Characteristics	All (% reporting)	RCT (% reporting)	Observational (% reporting)	*p* value
ARDS Criteria^				
Berlin	36 (42.4%)	8 (9.5%)	28 (33.3%)	
AECC	46 (54.0%)	21 (24.7%)	25 (30.0%)	
Berlin or AECC	2 (2.4%)	0	2 (2.4%)	
Other	1 (1.2%)	1 (1.6%)	0	
Mortality	38%	35%	40%	**0.04[a]**
Age, years*	55.9 ± 7.4 (82.4%)	56.2 ± 4.5 (34.1%)	55.7 ± 9.1 (48.2%)	0.84[a]
PaO_2/FiO_2, mm Hg*	131.7 ± 31.0 (84.7%)	133 ± 28.3 (34.1%)	130.8 ± 33.0 (50.6%)	0.77[a]
APACHE II*	22.1 ± 3.4 (44.7%)	21.0 ± 3.0 (16.5%)	22.8 ± 3.5 (28.2%)	0.10[a]
SOFA*	9.4 ± 1.8 (37.6%)	9.2 ± 1.8 (14.1%)	9.6 ± 1.8 (23.5%)	0.58[a]
Tidal Volume, ml/kg*	7.19 ± 0.85 (65.8%)	7.10 ± 0.90 (32.9%)	7.29 ± 0.81 (32.9%)	0.39[a]
PEEP, cm H_20*	10.2 ± 2.0 (71.8%)	10.9 ± 2.2 (30.6%)	9.7 ± 1.6 (41.2%)	**0.02[a]**
Plateau Pressure, cm H_20*	25.7 ± 2.8 (58.8%)	26.0 ± 2.6 (29.4%)	25.4 ± 3.0 (29.4%)	0.46[a]
Driving Pressure, cm H_20*	15.4 ± 2.2 (52.9%)	15.4 ± 2.1 (27.1%)	15.5 ± 2.2 (25.8%)	0.77[a]
Inhaled Vasodilators^	23 (27.1%)	7 (8.2%)	16 (18.9%)	0.18[a]
NMBA^	22 (26%)	10 (11.8%)	12 (14.2%)	0.50[a]
HFOV^	9 (10.6%)	4 (4.7%)	5 (5.9%)	0.40[a]
Prone Positioning^	25 (29.4%)	9 (10.6%)	16 (18.8%)	0.48[a]
ECMO^	20 (23.5%)	5 (5.9%)	15 (17.6%)	**0.07[a]**
Continent^				
Europe	34 (40.0%)	14 (16.4%)	20 (23.5%)	
North America	19 (22.3%)	6 (7.1%)	13 (15.3%)	
Asia	25 (29.4%)	6 (7.1%)	19 (22.3%)	
Australia	1 (1.2%)	0	1 (1.2%)	
South America	1 (1.2%)	0	1 (1.2%)	
Global	5 (5.9%)	4 (4.7%)	1 (1.2%)	

Table 1 – ^Number of studies (%); *Mean ± SD (% studies reporting); [a] by t-test; RCT: randomized controlled trial; AECC: American European Consensus Conference; APACHE II: Acute; Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; PEEP: positive end-expiratory pressure; NMBA: neuromuscular blocking agent; HFOV: high frequency oscillatory ventilation; ECMO: extracorporeal membrane oxygenation. Statistically significant variables are bolded.

Figures

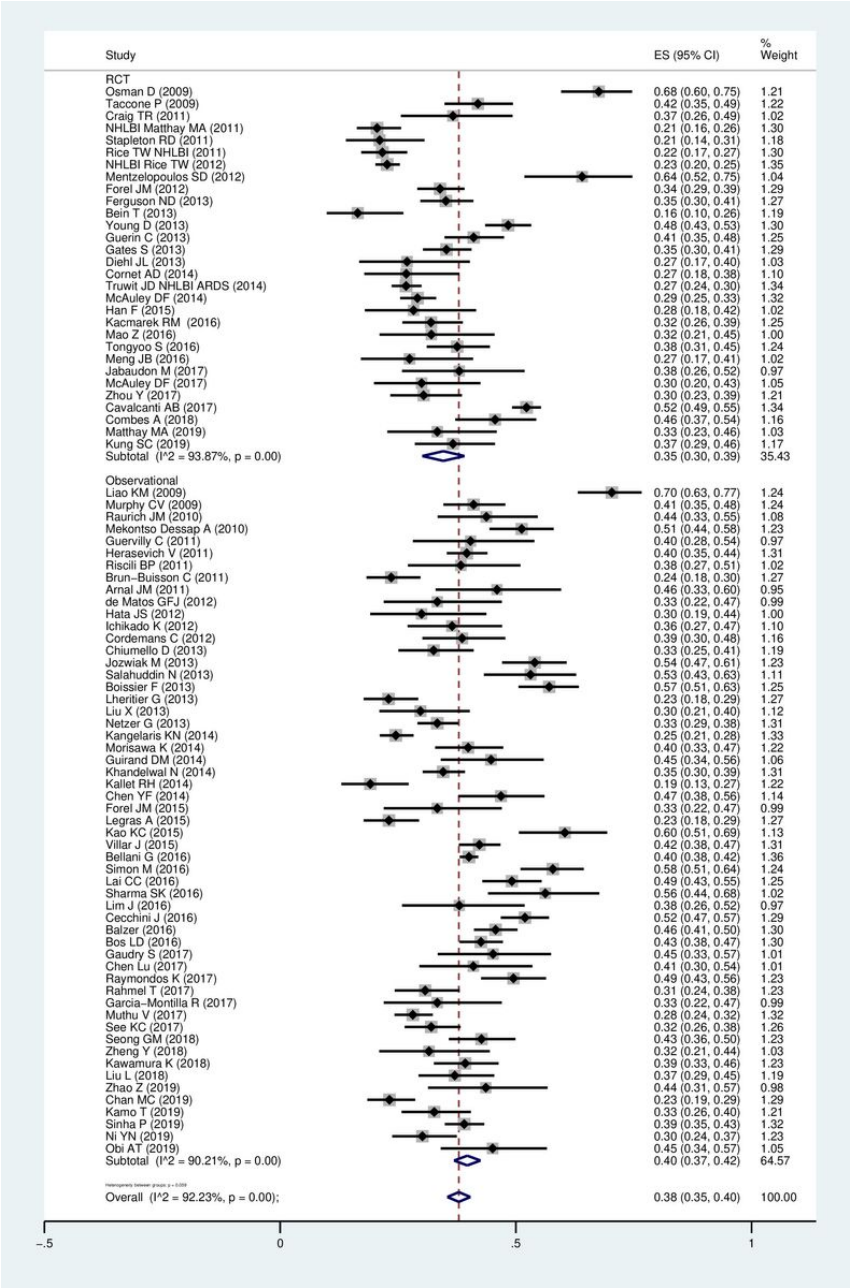

Figure 1

Study selection process Legend - Study selection process. More than one reason possible for study for study exclusion. Details on included studies available further in supplementary data.

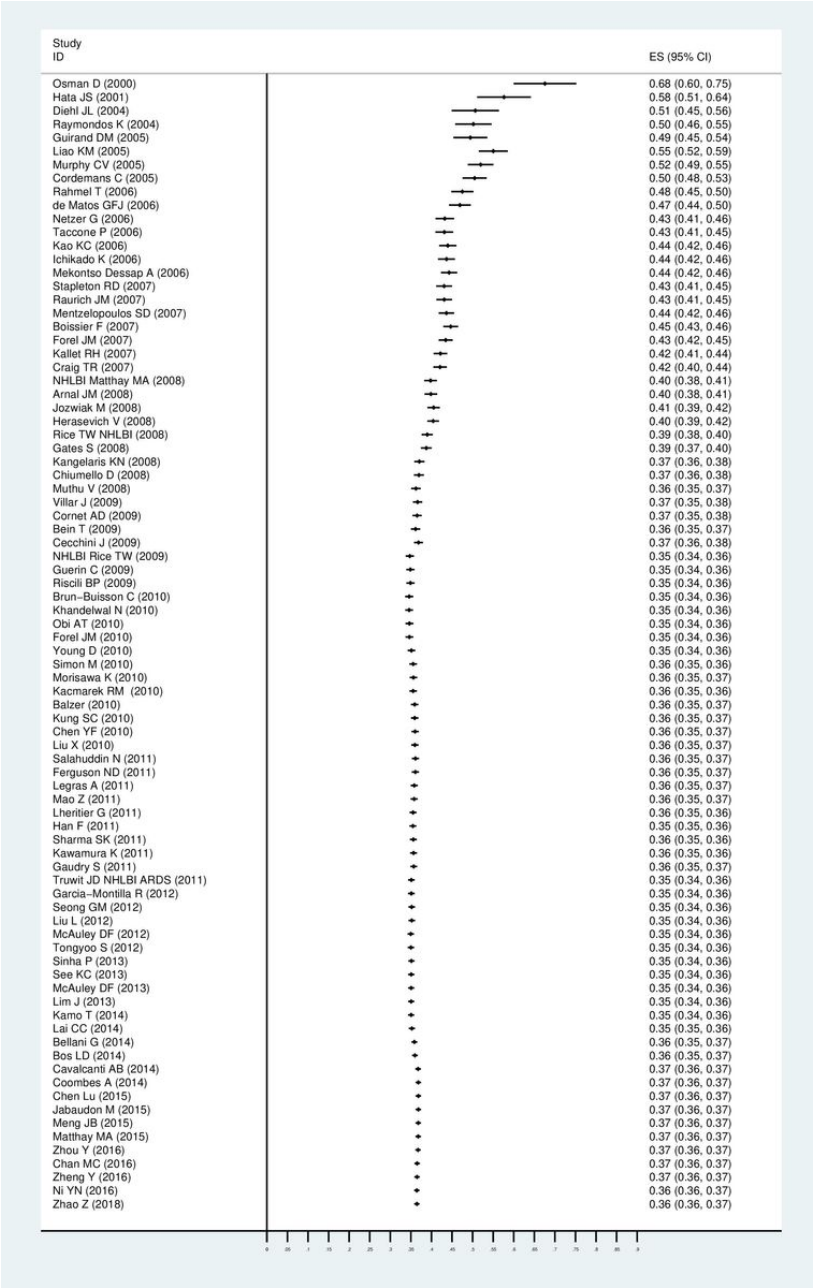

Figure 2

Forest plot of mortality for all studies included Legend - Forest plot of mortality for all studies included organized by RCT vs Observational study design. Listed in chronological order by year of publication (in parenthesis). 95% CI listed with point estimate of each individual study (vertical lines) and pooled estimate in observational studies, RCT, and in totality (vertical line and diamond).

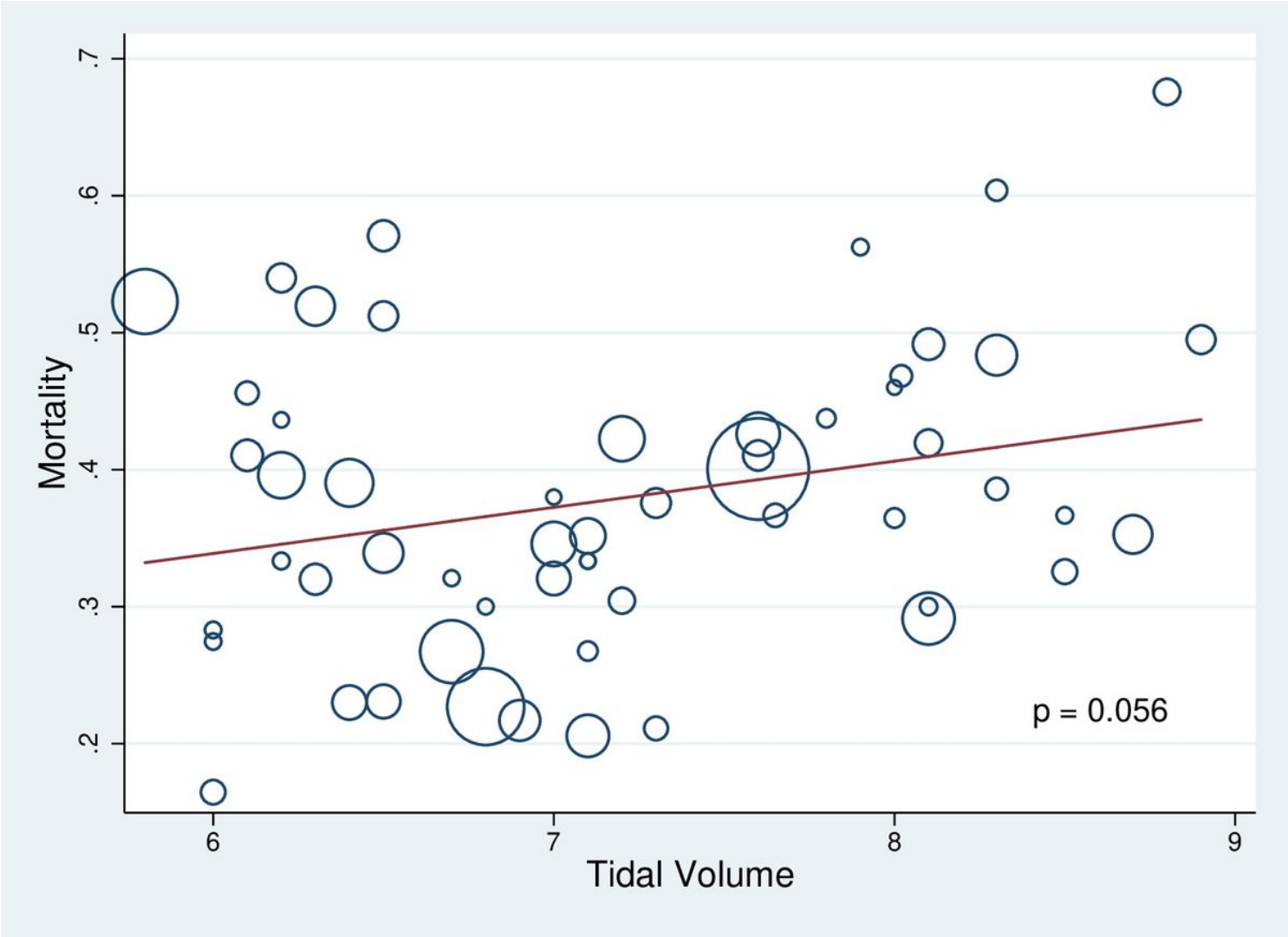

Figure 3

Cumulative mortality analysis Legend - Cumulative mortality analysis from 2000 – 2018 including each individual study. Listed in chronological order by median year of enrollment (in parenthesis).

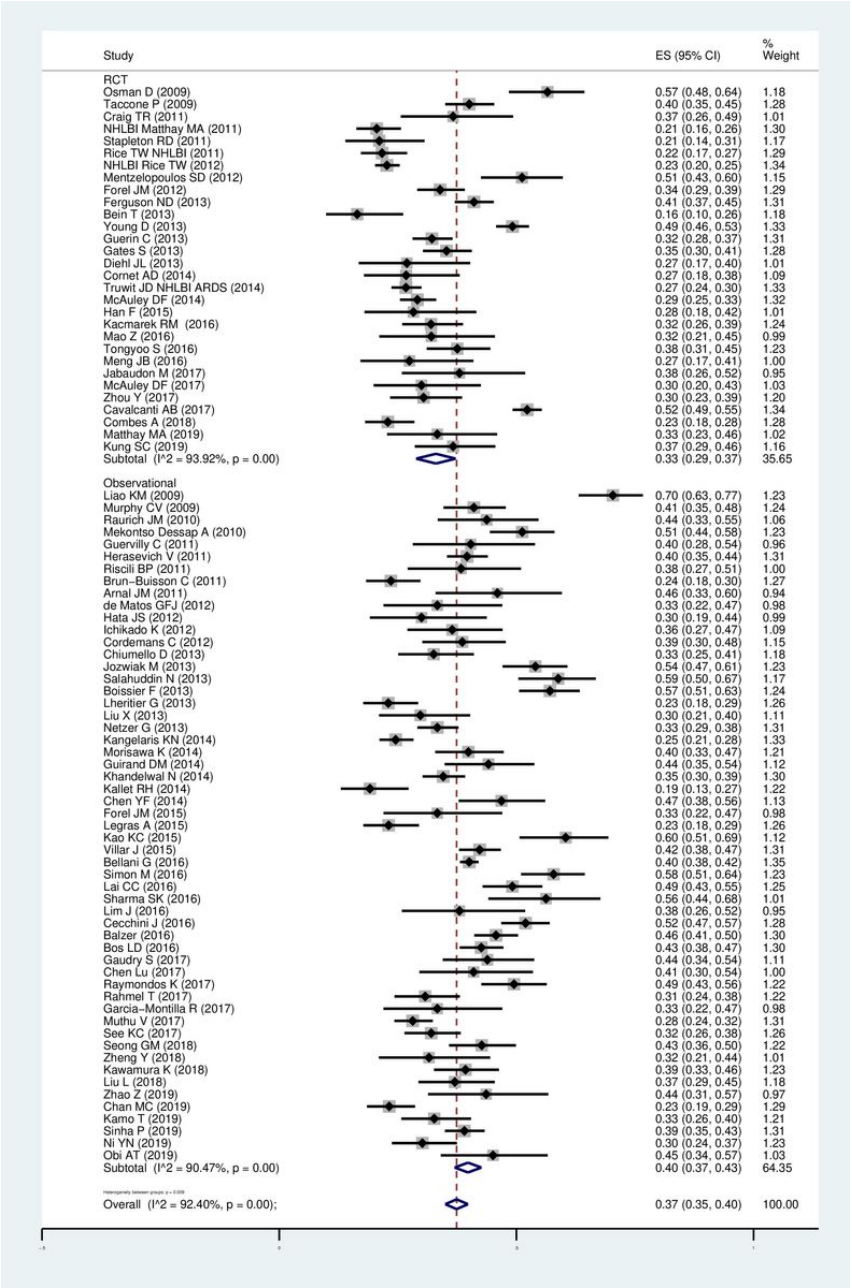

Figure 4

Meta-regression analysis of PaO2/FiO2 Legend - Meta-regression analysis of PaO2/FiO2 (mmHg). Mortality listed on y axis and PaO2/FiO2 on x axis. Circles represent each individual study and vertical line represents meta-regression line. The p value is reported on bottom right.

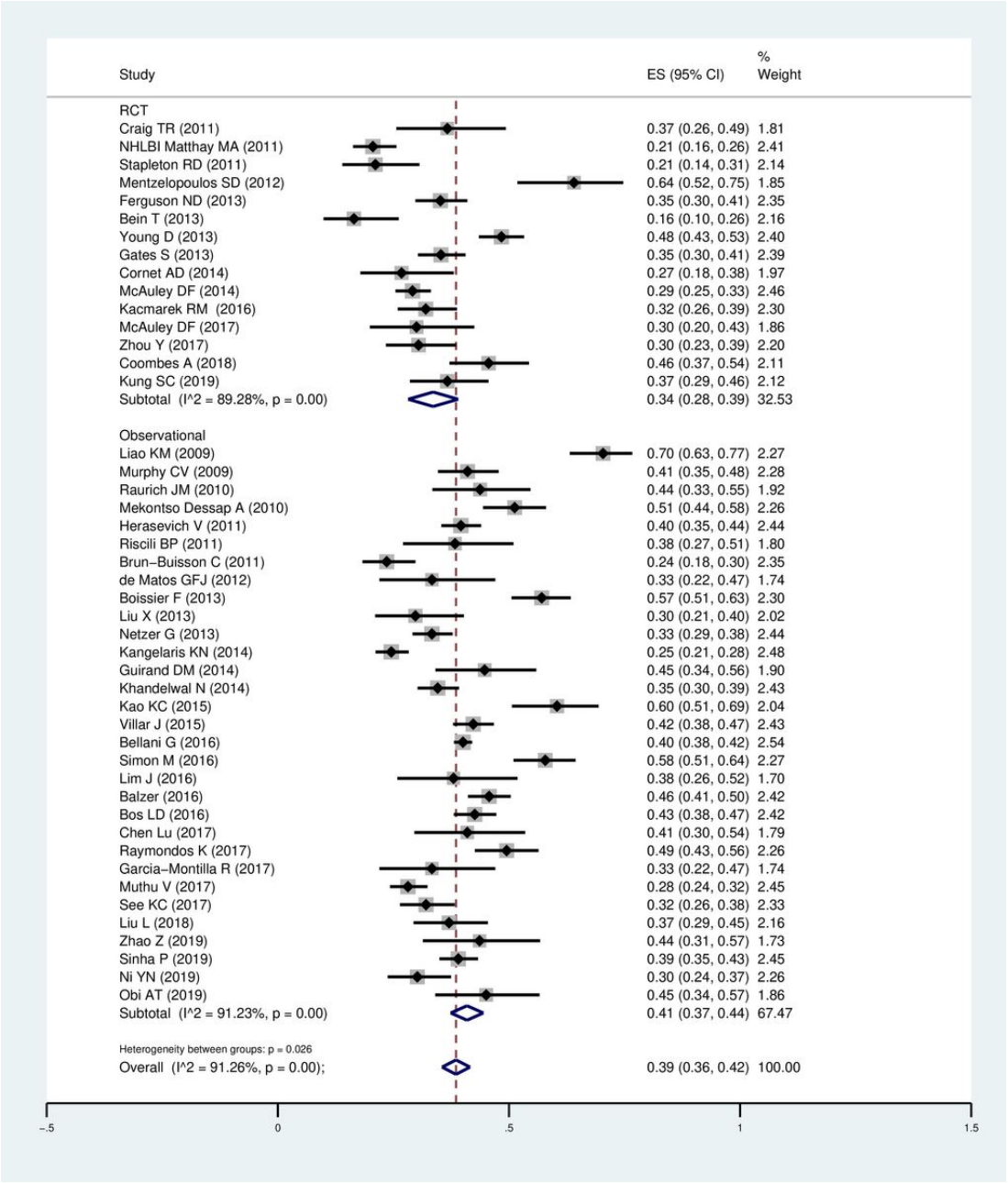

Figure 5

Meta-regression analysis of Tidal Volume Legend - Meta-regression analysis of Tidal Volume (ml/kg). Mortality listed on y axis and Tidal Volume on x axis. Circles represent each individual study and vertical line represents meta-regression line. The p value is reported on bottom right.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryAppendixUpdated.docx