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Review Article

Efficacy of high-frequency ventilation in adult patients with acute respiratory distress syndrome: a meta-analysis with trial sequential analysis of randomized clinical trials

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Abstract: High frequency oscillation ventilation (HFOV), which is sometimes used to treat patients with acute respiratory distress syndrome (ARDS), is an alternative to conventional mechanical ventilation (CMV) with uncertain effects on mortality and adverse clinical outcomes. The aim of this meta-analysis was to evaluate the efficacy of HFOV in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Trial sequential analyses (TSA) was applied to estimate whether the current result was enough to draw the conclusion. We searched the online databases of MEDLINE, Embase, Cochrane and other several databases for eligible randomized controlled trials (RCTs) of HFOV in adult patients with ALI and ARDS. Relative risk (RR) and standardized mean difference (SMD) with 95% confidence intervals (CIs) were pooled with fix-effects model. TSA was employed to indicate the credibility of pooled estimate. Seven trials met the inclusion criteria. Pooled analyses showed that there was no difference of in-hospital/28-day/30-day mortality between the HFOV and CMV group (RR 1.04; 95% CI 0.93, 1.16; $P > 0.05$). Duration of intensive care unit (ICU) stay (SMD 0.097; 95% CI -0.005, 0.200; $P = 0.062$) and incidence of barotraumas (RR 1.129; 95% CI 0.808, 1.577; $P = 0.476$) was similar between two groups. HFOV was associated with increased incidence of hypotension (RR 0.585; 95% CI 0.366, 0.934; $P = 0.025$) and prolonged the duration of mechanical ventilation (SMD 0.095; 95% CI 0.001, 0.189; $P < 0.05$). However, TSA did not provide conclusive evidence. This systematic review indicated that improved therapeutic effect of ARDS in patients treated with HFOV compared with CMV. Consequently, large randomized clinical trials are warranted.

Keywords: High-frequency oscillation ventilation, conventional mechanical ventilation, acute respiratory distress syndrome, acute lung injury, meta-analysis, trial sequential analysis

Introduction

The acute respiratory distress syndrome (ARDS) is characterized by life-threatening impairment of pulmonary gas exchange, resulting in hypoxemia, hypercapnia, and respiratory acidosis and requiring acute rescue measures. Oxygen delivery to the tissues is necessary for all aerobic life, and tissue hypoxia will result in various deleterious effects including altered vascular reactivity, inflammation, cell apoptosis, and organ dysfunction or failure [1]. CMV is still considered the cornerstone of treatment for these patients. However, although CMV can initially sustain life, it may cause further lung injury [2, 3]. In HFOV, a high mean airway pressure combined with extremely small tidal volumes, limiting peak inspiratory pressures [4, 5] is used to prevent atelectasis. It is characterized by rapid oscillation of a reciprocating diaphragm, leading to a high frequency-from 3 to 9 Hz in adults-and very low tidal volume. HFOV seems to be a promising technique for reducing rate of ventilator-associated lung injury in animals and death or bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome [6-8]. In recent years, new evidence has been reported on the feasibility, oxygenation and lung protection benefits of HFOV in ARDS [9-12]. Three previous trials comparing HFOV with CMV

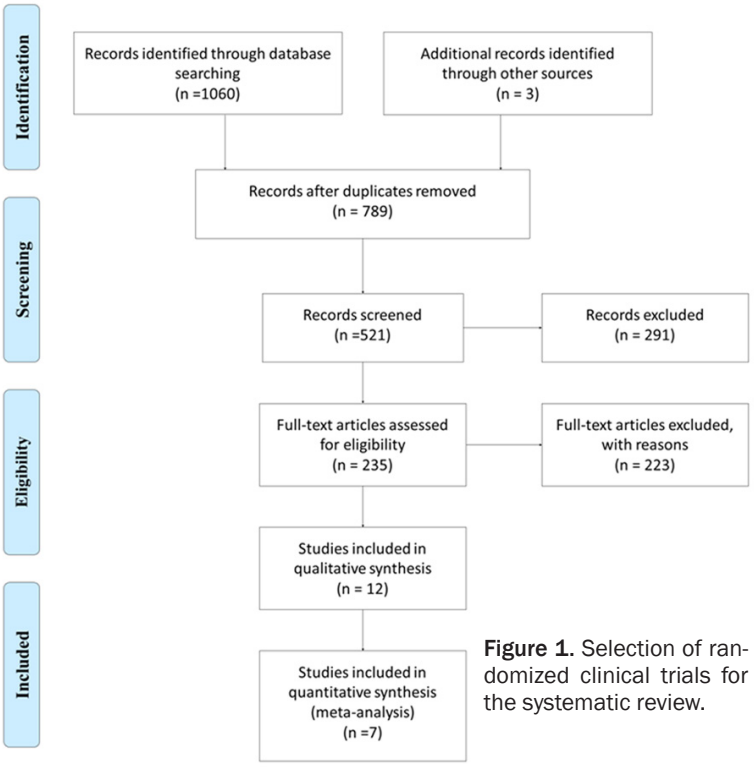

Figure 1. Selection of randomized clinical trials for the systematic review.

suggested that HFOV improved both oxygenation and survival in adults with ARDS [11, 13, 14]. However, two well-designed large RCTs indicated no benefit of HFOV in reducing in-hospital mortality in patients with ARDS [15, 16]. Therefore, its beneficial effects remain controversial and some authors suggested HFOV could only be treated as a rescue therapy [10]. When dealing with negative results, it is important to evaluate the statistical reliability of the finding, i.e., the power of the analysis. TSA is a tool which has been increasingly used [17] to assess whether optimal sample sizes-and benefit or harm boundaries-have been reached by an available sample of patients assuming a minimal clinically significant difference [18]. Therefore, the aim of this study was to determine whether HFOV is equal to or more beneficial than CMV in patients with ALI and ARDS. TSA was applied to estimate whether the current available evidence was enough conclusive.

Materials and methods

We reported this systematic review and meta-analysis based on the methodology recommended by the Cochrane Collaboration and according to the Preferred Reporting items for Systematic Review and Meta-analysis (PRISMA) statement [19] .There was no formal protocol for this meta-analysis.

Search strategy and selection criteria

We searched the online databases of MEDLINE (through PubMed), Embase, Scopus, and Central Register of Clinical Trials of the Cochrane Collaboration for eligible controlled trials using the following search words: “high frequency oscillation”, “high-frequency ventilation”, “conventional mechanical ventilation”, “acute respiratory distress syndrome” and “acute lung injury” from 1985 to April 2016. This search was conducted through July 2015, with no additional time limits. We did not restrict our search to studies published in any particular language. The reference lists of the identified primary studies and relevant meta-analyses were also searched for additional studies.

To be included in the present meta-analysis, trials had to be RCTs that compared HFOV with CMV, enrolled ALI/ARDS patients, and reported at least one of the following outcomes of interest: in-hospital mortality/28-day/30-day mortality; duration of ICU stay; duration of mechanical ventilation; and the incidence of barotraumas or hypotension. We did not consider studies on children, in contrast to the previous meta-analysis and Cochrane review. Studies involving a secondary respiratory adjunct therapy along with high-frequency oscillation, such as tracheal gas insufflation or recruitment maneuvers, were also included in this meta-analysis. Two investigators (HJ Jiang and Y Song) independently performed the study selection. Disagreements between the two investigators were resolved through discussion. We neither sought for unpublished studies nor contacted the authors for unpublished data. Data from previous meta-analyses and reviews was included.

Table 1. Essential characteristics of the included trials

Source	Mean Age (years)	No. of patients (Intervention/Control)	Details of lung injury	Overall risk of bias
Derdak et al, 2002	49	148 (75/73)	ARDS; PEEP > 10 cm H_2O	Low
Bollen et al, 2005	53	61 (37/24)	ARDS	Unclear
Demory et al, 2007	49	28 (13/15)	ARDS; $PaO_2/FiO_2 \leq 150$, PEEP $\geq$ 5 cm H_2O	Low
Mentzelopoulos et al, 2007	57	54 (27/27)	ARDS; $PaO_2/FiO_2 < 150$, PEEP 8 cm H_2O	Low
Mentzelopoulos et al, 2012	54	125 (61/64)	ARDS; $PaO_2/FiO_2 < 150$, PEEP $\geq$ 8 cm H_2O	Low
Ferguson et al, 2013	54	548 (275/273)	ARDS; $PaO_2/FiO_2 \leq 200$, $FiO_2 \geq 0.5$	Low
Lall et al, 2015	55	795 (398/397)	ARDS; $PaO_2/FiO_2 \leq 200$, PEEP $\geq$ 5 cm H_2O	Low

ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PaO_2, arteral oxygen tension; PEEP, positive end expiratory pressure.

Data collection and extraction

Two authors (HJ Jiang and Y Song) independently read the abstract of the potentially eligible studies. Both of them selected eligible studies by inclusion criteria. HJ Jiang and AH Hu initially extracted data from the eligible studies and the extracted data were cross-checked independently by YZ Qiu and AL Ding. Statistical analyses were performed by HJ Jiang. When encountering differences in opinions, the third author's opinion (AH Hu) was considered to be final. The data included first author, year of publication, study design, number of patients, patient characteristics, definition of ALI or ARDS used and overall risk of bias. The primary outcomes were ICU mortality/28-day/30-day mortality, duration of ICU stay and duration of mechanical ventilation. Secondary outcomes included hypotension and barotraumas.

Quality assessment

We assessed the studies in six domains according to the Cochrane Collaboration's tool for assessing risk of bias [20]: (I) random sequence generation, (II) allocation concealment, (III) blinding of participants and personnel, blinding of outcome assessment, (IV) incomplete outcome data, (V) selective reporting, and (VI) other bias; for other bias. Each item was answered by "Low" (low risk of bias), "Unclear" (either lack of information or uncertainty over the potential for bias), and "High" (high risk of bias). Two reviewers independently assessed the quality of the evidence for each meta-analysis according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, with inconsistency resolved through discussion and consensus [21].

Statistical analyses

We calculated relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes. The Z-test and chi-square test were used to generate the *p*-value for the continuous outcomes and for the binary outcomes, respectively. $P < 0.05$ was considered statistically significant. We evaluated the heterogeneity using a Cochran Q test, with a threshold *p*-value of 0.1, and an I^2 test, with a value > 50% indicating high heterogeneity; 95% confidence intervals for I^2 values were calculated [22]. We also quantified the effects of heterogeneity by using the I^2 test (ranges from 0% to 100%), which represents the proportion of inter-study variability that can be contributed to heterogeneity rather than to chance [23]. The fixed-effects model (Mantel-Haenszel method) was used except when a significant Q-test ($P < 0.05$) or $I^2 > 50\%$ indicated the existence of heterogeneity among studies; in that case, the random effects model (DerSimonian-Laird method) was applied for the meta-analysis. Subgroup analysis was conducted to investigate potential source of between-study heterogeneity. Sensitivity analysis was performed through omitting each study in turn to assess the quality and consistency of the results. Begg's funnel plots were used to detect publication biases. Egger's linear regression test was also used to evaluate the publication biases [23]. All statistical analyses were performed with Stata software (version 12.0; StataCorp, College Station, TX) using two-sided

Table 2. Details of HFOV and CMV in trials included in systematic review

	Derdak [10]	Bollen [12]	Demory [13]	Mentzelopoulos [26]	Mentzelopoulos [27]	Ferguson [14]	Lall [15]
HFOV							
Frequency (HZ)	5	5	5	4	3~7	3~12	10
mPaw (cmH_2O)	CMV+5	CMV+5	CMV+5	3 above mean tracheal pressure measured distal to endotracheal tube	CMV+(8~9)	30	CMV+5
ΔP (cmH_2O)	Achieve vibration from chest wall to mid-thigh	According to $PaCO_2$; achieve chest wall vibration	Same $PaCO_2$ as during CMV	30 above baseline $PaCO_2$ during CMV	30 above baseline $PaCO_2$ during CMV	90	According to $PaCO_2$
Criteria for transition to CMV	FiO_2 < 50%, mPaw < 24 cm H_2O	FiO_2 < 40%, PaO_2 > 60 mmHg,tolerating suctioning	After 12 hours of HFOV	After 6-24 hours of HFOV	After 12-24 hours of HFOV	After 24 hours of HFOV	FiO_2 < 40%, PaO_2 > 60 mmHg, mPaw ≤ 25 cm H_2O
CMV							
Mode	Pressure control	Pressure control	Volume assist control	Volume assist control	Volume assist control	Pressure control	Pressure control
Tidal volume	6-10 ml/kg actual body weight	Mean 8-9 ml/kg ideal body weight	6-7 ml/kg predicted body weight	6-7 ml/kg predicted body weight	6 ml/kg ideal body weight	6 ml/kg ideal body weight	6-8 ml/kg ideal body weight
Adjustment of PEEP (cm H_2O)	≥ 10	15	According to ARDS Network Protocol	According to ARDS Network Protocol	5-20	≥ 10	According to ARDS Network Protocol

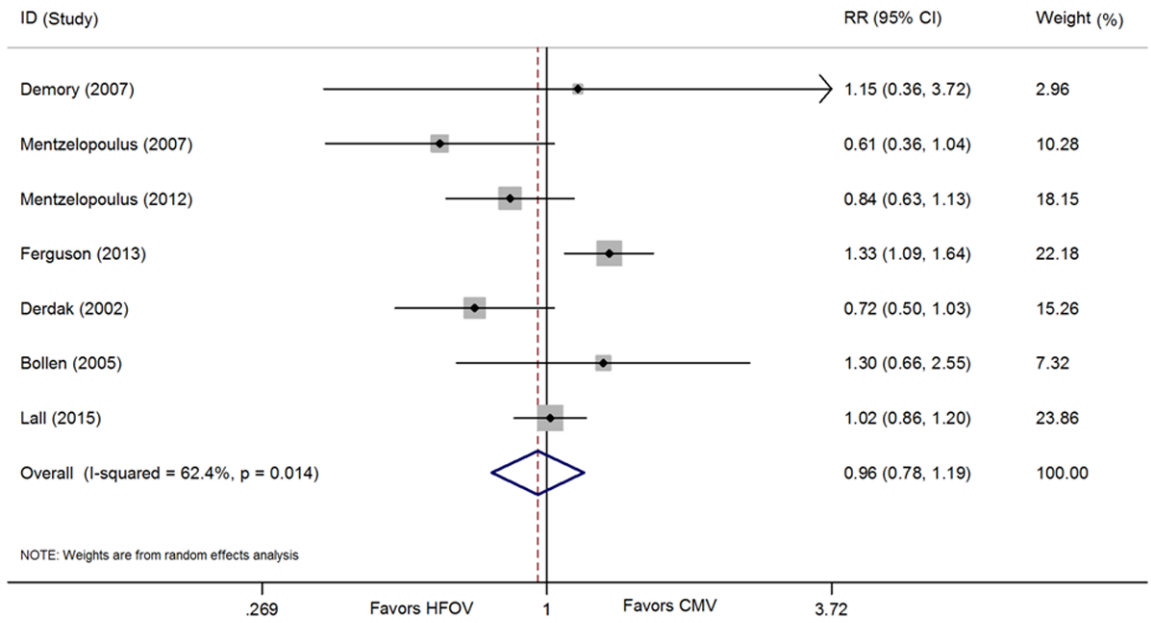

Figure 2. Forest plot of HFOV versus CMV on mortality.

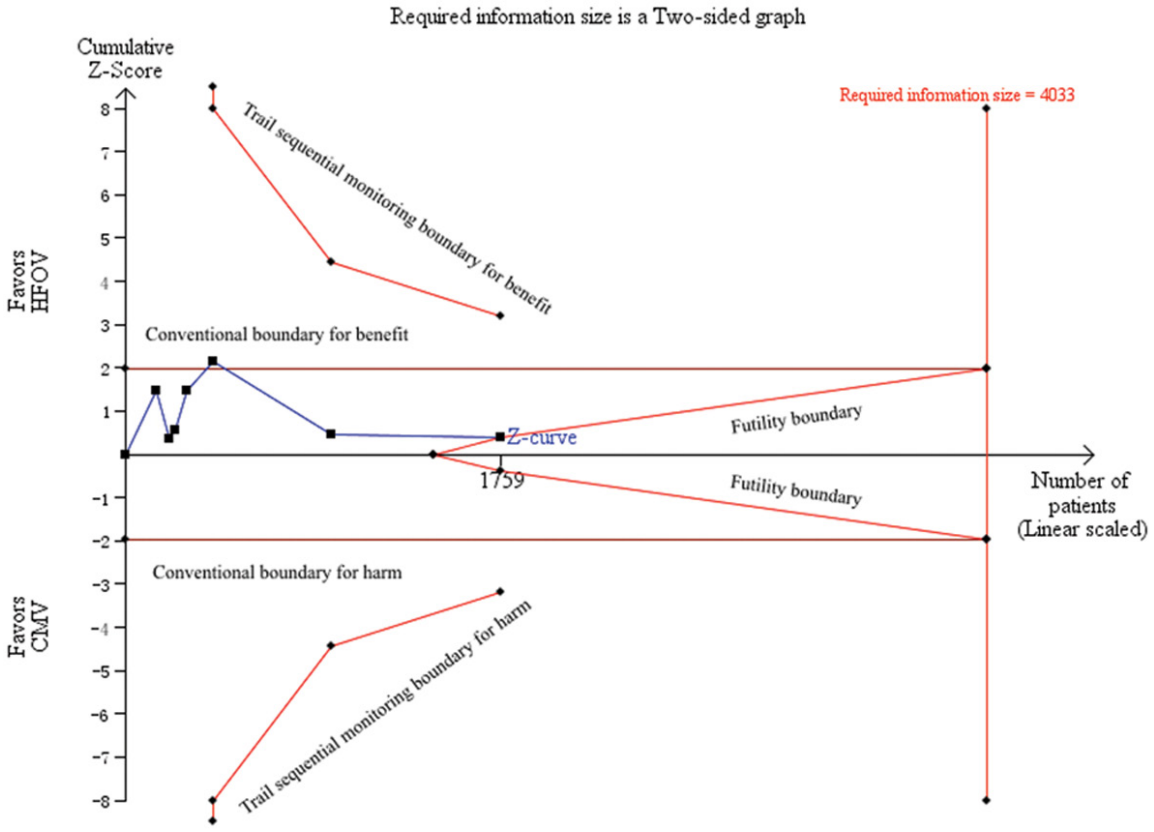

Figure 3. TSA of mortality in patients with ALI or ARDS. TSA of 7 trials comparing HFOV with CMV on mortality. The a priori heterogeneity adjusted information size (4033 patients) is estimated by assuming a 20% relative risk reduction (RRR). The cumulative *z* curve (blue line with solid circularity) at the current accrued information size of 1759 patients does not cross the trial sequential-monitoring boundaries constructed for an a priori heterogeneity adjusted required information size of 4033 patients (indicated by the right vertical red line). A diversity adjusted required information size of 4033 patients was calculated using $\alpha = 0.05$ (two sided), $\beta = 0.20$ (power 80%), and empirical estimation from TSA software.

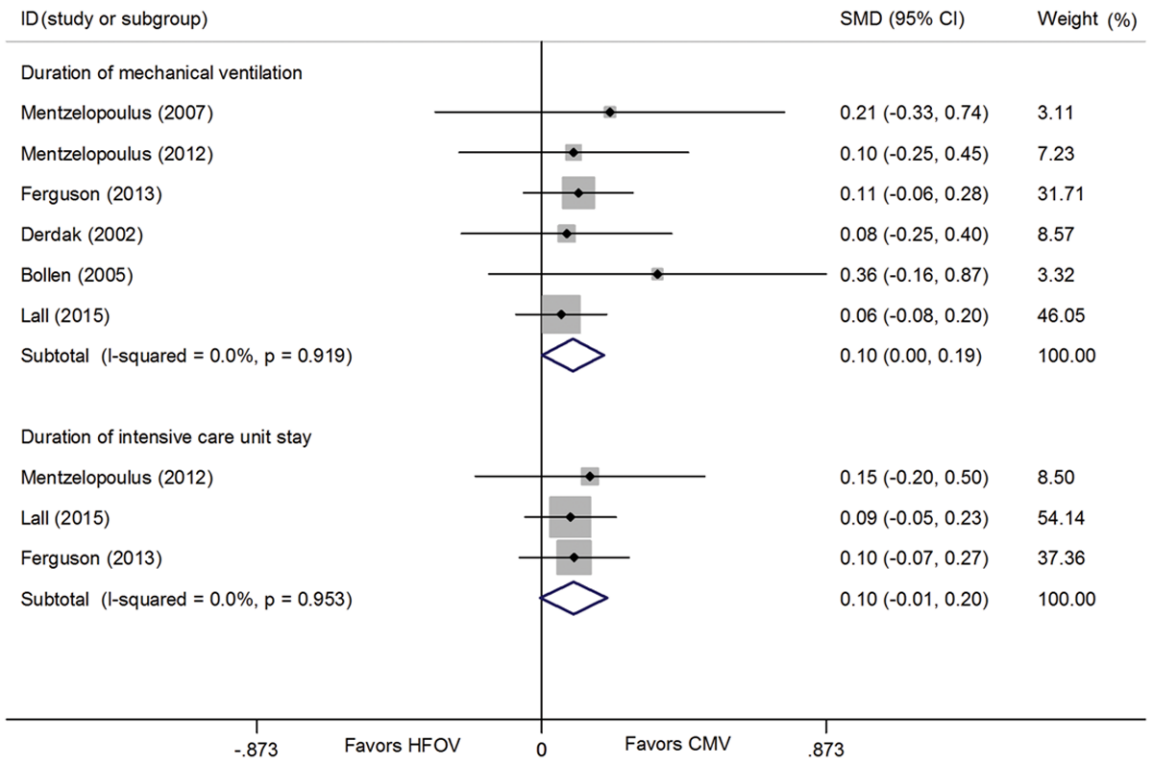

Figure 4. Forest plot of duration of mechanical ventilation and duration of ICU stay in patients with ALI/ARDS. Size of squares for relative risk reflects weight of trial in pooled analysis. Horizontal bars represent 95% CI. SMD, standardized mean difference.

p values. $P < 0.05$ was considered statistically significant.

Trial sequential analysis

Conventional meta-analyses may result in type I errors due to an increased risk of random error when sparse data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials [18, 23-25]. To avoid an increase of overall type I error, monitoring boundaries can be applied to decide whether a single randomized trial could be ended early if a *P* value is sufficiently small to show the anticipated effect [18, 24]. Therefore, we conducted TSA to reduce the risk of random error. TSA combines information-size estimation for a meta-analysis with the adaptation of monitoring boundaries to evaluate the accumulated evidence [18]. When the cumulative Z-curve crosses the trial sequential monitoring boundary, a sufficient level of evidence for an intervention is deemed achieved and no further trials are needed. If the trial sequential monitoring boundary is not crossed, then there is insufficient evidence to support a conclusion, and more trials are needed to confirm the results. TSA depends on the quantification of the required information size. A diversity adjusted required information size (RIS) is calculated through estimating the effect of type I error, type II error, the control event proportion, and the effect size in TSA. For our TSA, we estimated RIS using $\alpha = 0.05$ (two sided), $\beta = 0.20$ (power 80%) for all the variables of interest, the control event proportions calculated from the CMV group, an anticipated intervention effect of 20% RR reduction for dichotomous outcomes, and empirical estimation from TSA software for continuous outcomes. TSA version 0.9 beta (http://www.ctu.dk/tsa) was used for all these analyses.

Results

Search results and risk of bias

We identified 1063 documents through database searching and other sources (**Figure 1**). After excluding duplicate reports, we screened the titles and abstracts of 521 documents and rejected 291 as irrelevant. After full-text review,

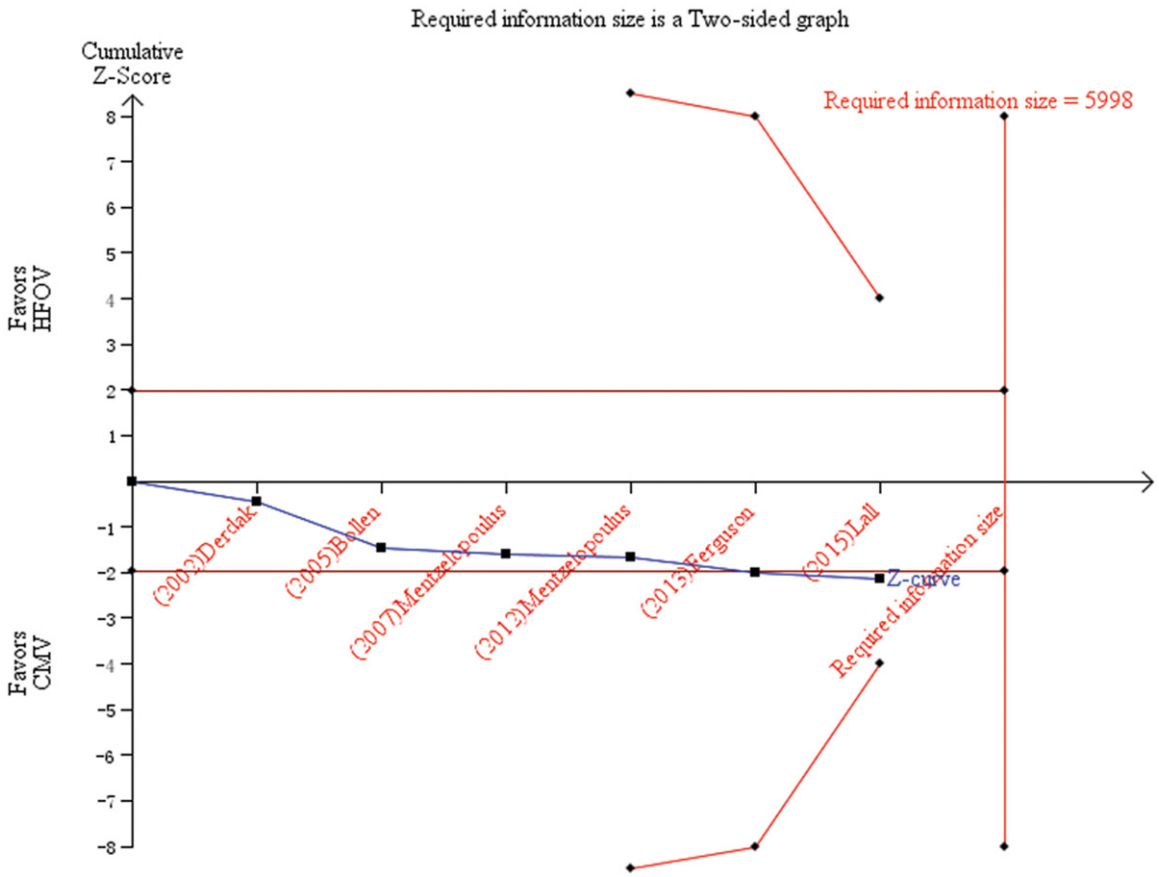

Figure 5. TSA of six randomized trials reporting duration of mechanical ventilation. The priori heterogeneity adjusted information size (5998 patients) is estimated by assuming a 20% relative risk reduction (RRR). The cumulative z curve (blue line with solid circularity) crossed the conventional boundary for harm ($P < 0.05$), but not the trial sequential monitoring boundary for harm. A diversity adjusted required information size of 5998 patients(indicated by the right vertical red line) was calculated using $\alpha = 0.05$ (two sided), $\beta = 0.20$ (power 80%), and empirical estimation from TSA software.

a further 223 reports were excluded because they did not meet our criteria. Finally, a total of 1759 adult patients were included in this meta-analysis, which compared in-hospital mortality/28-day/30-day mortality between HFOV and CMV in adult patients with ALI and ARDS. The publication years of the involved studies ranged from 2002 to 2015. All trials studied HFOV as an initial ventilation strategy for ALI or ARDS, but not a rescue treatment for refractory hypoxemia. All studies used a lung-protective ventilation strategy by targeting a tidal volume of 6 ml/kg or a plateau pressure of 30 to 35 cm H_2O or both. Among all trials, six had high methodological quality and a low risk of bias [11, 14-17, 26, 27] one had unclear risk of bias [13]. Patient characteristics in the individual studies and details of ventilation strategy of the included studies have been provided in **Tables 1**, **2**. The methodological qualities of all included studies are presented in **Figure 1**.

Clinical outcomes

Mortality

The mortality of patients in the standard HFOV and CMV group was 43.7% (387/886) and 42.2% (368/873), respectively [11, 12, 26, 27] The pooled results indicated that there was no significant difference in hospital/28-day/30-day mortality rate between study group and control group, and the pooled risk ratio was 1.038 (95% CI; 0.932, 1.157; $P = 0.496$) in the fixed effect model. However, there was significant heterogeneity between studies ($P = 0.014$, $I^2 = 62.4\%$), so the random effects model was used. The meta-analysis results showed that

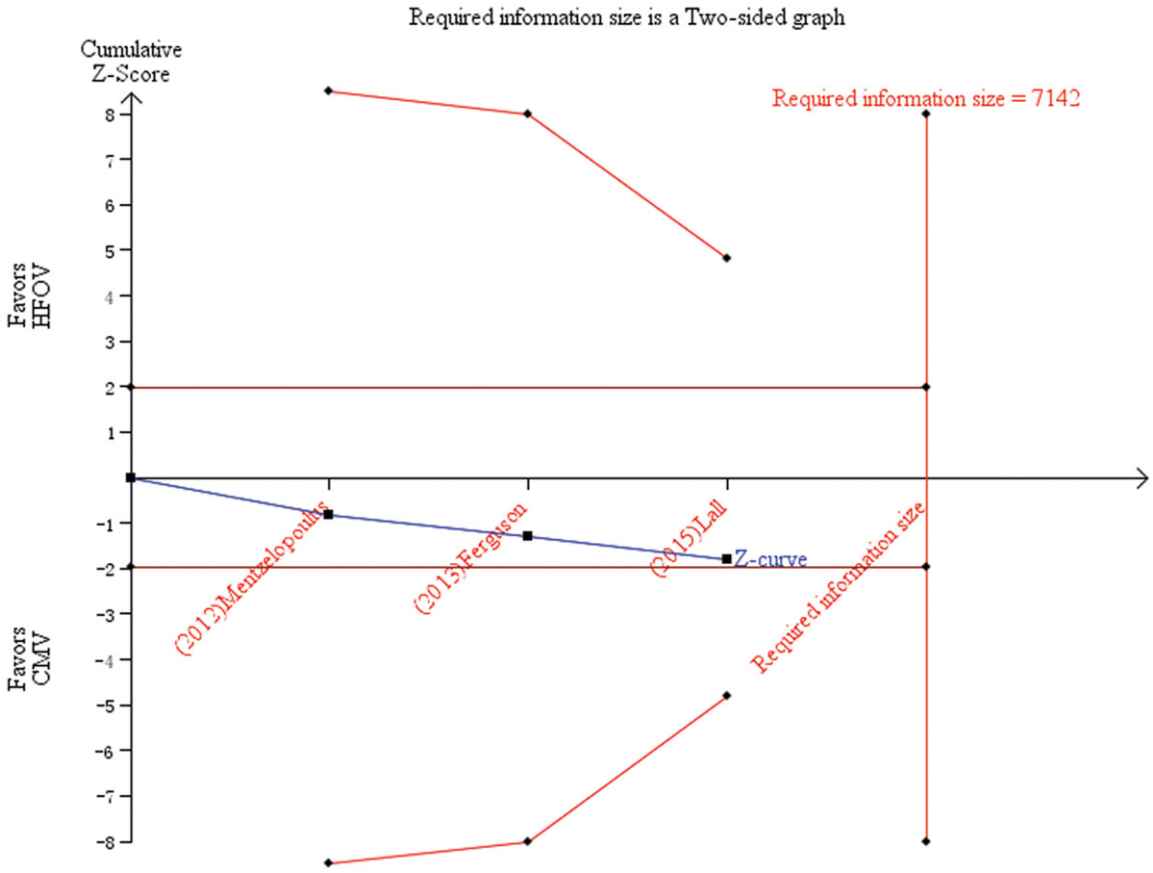

Figure 6. TSA of three randomized trials reporting duration of ICU stay. The a priori heterogeneity adjusted information size (7142 patients) is estimated by assuming a 20% relative risk reduction (RRR). The cumulative z curve (blue line with solid circularity) does not cross both the conventional boundary and the trial sequential monitoring boundary. A diversity adjusted required information size of 7142 patients(indicated by the right vertical red line) was calculated using α = 0.05 (two sided), β = 0.20 (power 80%), and empirical estimation from TSA software.

HFOV did not significantly reduce mortality at 28 or 30 days in adult ARDS patients (risk ratio 0.960; 95% CI 0.776 , 1.187; *P* = 0.705; **Figure 2**). In searching for potentially active factors, we performed subgroup analyses by the tidal volume (≤ 8 ml/kg predicted body weight) as well as the plateau airway pressure (≤ 35 cm H_2O). Subgroup analyses with two addtional factors indicated that HFOV failed to reduce mortality at 28 or 30 days in adult ARDS patients. TSA was performed for all 7 studies. The TSA adjusted 95% CI was 0.78-1.19 (diversity D2 = 74%). The diversity adjusted information size was 4033. The cumulative Z-curve did not surpassed the conventional boundary and trial sequential monitoring boundary for benefit or harm and also did not achieve the optimal information size which indicated the current results were not robust, and further clinical trials were required (**Figure 3**).

Duration of mechanical ventilation and ICU stay

Six trials (1731 patients) evaluated duration of mechanical ventilation. Compared with HFOV, CMV was associated with a shorter duration of mechanical ventilation (SMD, 0.095; 95% CI 0.001, 0.189; *P* = 0.048; **Figure 4**) in the fixed effect model, and no significant heterogeneity was found (Chi2 = 1.44, degrees of freedom (df) = 5, *P* = 0.919; I^2 = 0.0 %). The TSA adjusted 95% CI was 0.09-2.19 (diversity D2 = 0%). The diversity adjusted information size was 5998. The cumulative Z-curve crossed the conventional boundary for harm (*P* < 0.05), but not the trial sequential monitoring boundary for harm, and also did not achieve the optimal information size which indicated the current results were not robust, and further clinical trials were required (**Figure 5**). Three trials (with

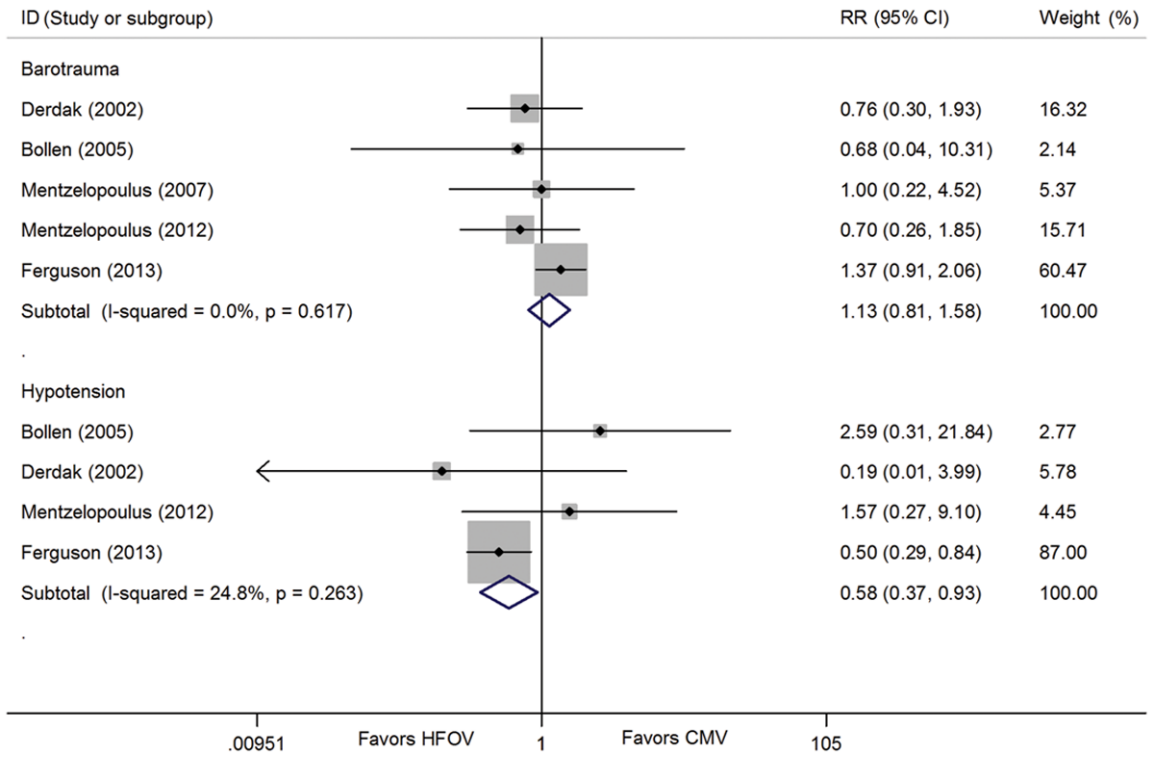

Figure 7. Forest plot of adverse events in patients with ALI/ARDS. Size of squares for relative risk reflects weight of trial in pooled analysis. Horizontal bars represent 95% CI. SMD, standardized mean difference.

1467 patients) evaluated duration of ICU stay. The pooled results showed that the HFOV did not significantly reduce the duration of ICU stay (SMD 0.097, 95% CI -0.005, 0.200; *P* = 0.062) in the fixed effect model, and no significant heterogeneity was found (Chi2 = 0.10, degrees of freedom (df) = 2, *P* = 0.953; I^2 = 0.0 %) (**Figure 4**). The TSA adjusted 95% CI was -0.11-2.53 (diversity D2 = 0%). The diversity adjusted information size was 7142. The cumulative Z-curve did not surpassed the conventional boundary and trial sequential monitoring boundary for benefit or harm and also did not achieve the optimal information size which indicated the current results were not robust, and further clinical trials were required (**Figure 6**).

Adverse events

Barotraumas

The incidences of barotraumas were reported in 5 studies [13-15, 26, 27]. The pooled results showed that the HFOV would not significantly increase the risk of barotraumas compared with CMV (RR 1.129; 95% CI 0.808, 1.577; *P* = 0.476; **Figure 7**) in the fixed effect model, and no significant heterogeneity was found (Chi2 = 2.65, degrees of freedom (df) = 4, *P* = 0.617; I^2 = 0.0%). The TSA adjusted 95% CI was 0.81-1.58 (diversity D2 = 0%). The diversity adjusted information size was 4986. The cumulative Z-curve did not surpassed the conventional boundary and trial sequential monitoring boundary for benefit or harm and also did not achieve the optimal information size which indicated the current results were not robust, and further clinical trials were required (**Figure 8**).

Hypotension

The incidences of hypotension were reported in 4 studies [13, 15, 27]. The pooled results showed that the HFOV significantly reduced the risk of hypotension compared with CMV (RR 0.585; 95% CI 0.366, 0.934; *P* = 0.025; **Figure 7**). For acceptable heterogeneity (Chi2 = 3.99, degrees of freedom (df) = 3, *P* = 0.263; I^2 = 24.8%), the fixed-effect analytical model was used to pool the results. The TSA adjusted 95% CI was 0.31-1.63 (diversity D2 = 66%). The diversity adjusted information size was 19159. The cumulative Z-curve crossed the conventional boundary for benefit (P < 0.05), but not

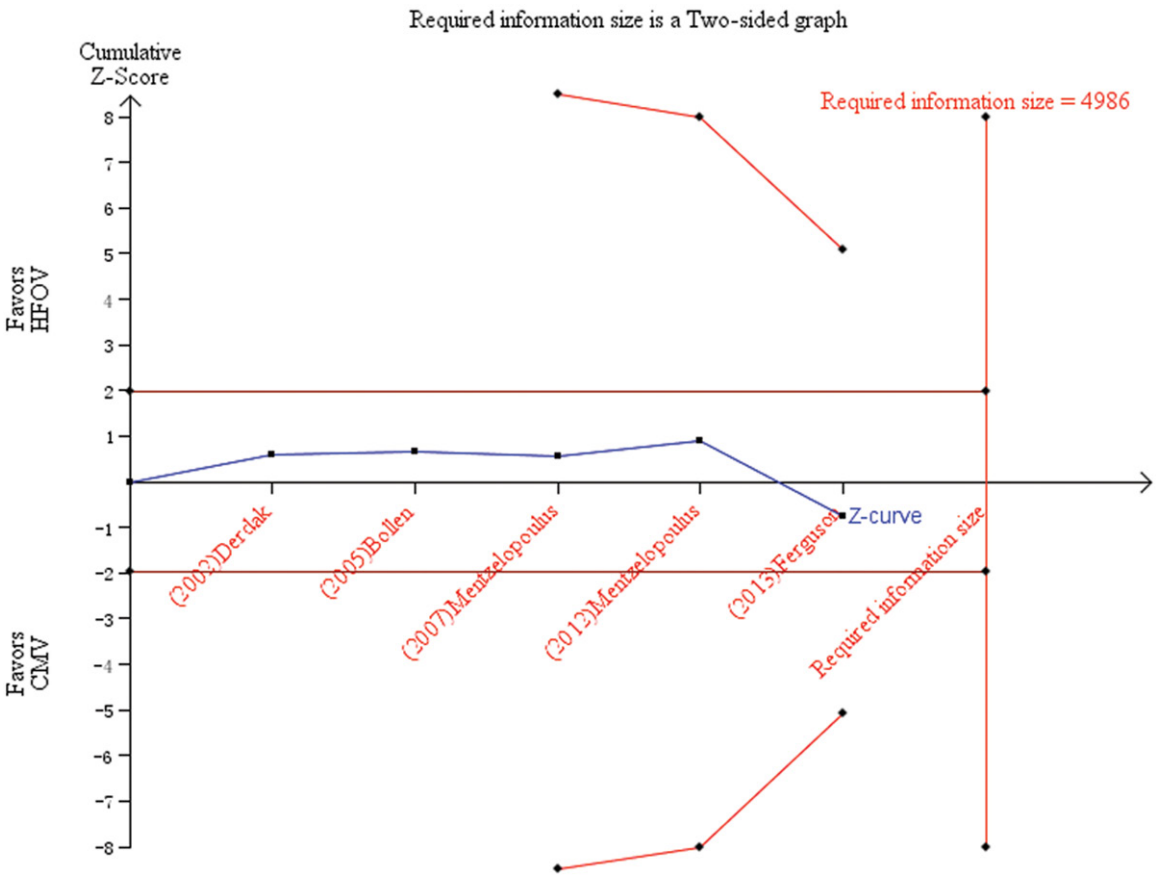

Figure 8. TSA of five randomized trials reporting the incidence of barotraumas. The priori heterogeneity adjusted information size (4986 patients) is estimated by assuming a 20% relative risk reduction (RRR). The cumulative *z* curve (blue line with solid circularity) does not cross both the conventional boundary and the trial sequential monitoring boundary. A diversity adjusted required information size of 4986 patients(indicated by the right vertical red line) was calculated using α = 0.05 (two sided), β = 0.20 (power 80%), and empirical estimation from TSA software.

the trial sequential monitoring boundary for benefit and also did not achieve the optimal information size which indicated the current results were not robust, and further clinical trials were required (**Figure 9**).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled RRs by omission of individual studies. The analysis results suggested that no individual studies significantly affected the pooled RR (**Figure 10**), indicating a statistically robust result. We assessed the potential publication bias for the primary outcomes of mortality (P = 1.000 for the Begg test, P = 0.467 for the Egger test). No potential publication bias was observed among the included trials (**Figure 11**). Tests were not available for all subgroup datasets with small sample sizes.

Discussion

This systematic review with meta-analysis and TSA included 7 randomized trials with 1759 patients. The present meta-analysis showed that there was no difference in hospital/28-day/30-day mortality rate of patients between the HFOV group and CMV group, which was confirmed by TSA [9]. As moderate degree of between-study heterogeneity revealed in the overall meta-analysis of mortality as well as the fact that the tidal volume and plateau airway pressure might be the sources of heterogeneity, we performed subgroup analysis according to the tidal volume and the plateau airway pressure in the control group. The results from these subgroup analyses all suggest that HFOV did not significantly reduce mortality at 30 or 28 days in adult ARDS patients. This indicates that the results of this meta-analysis are sta-

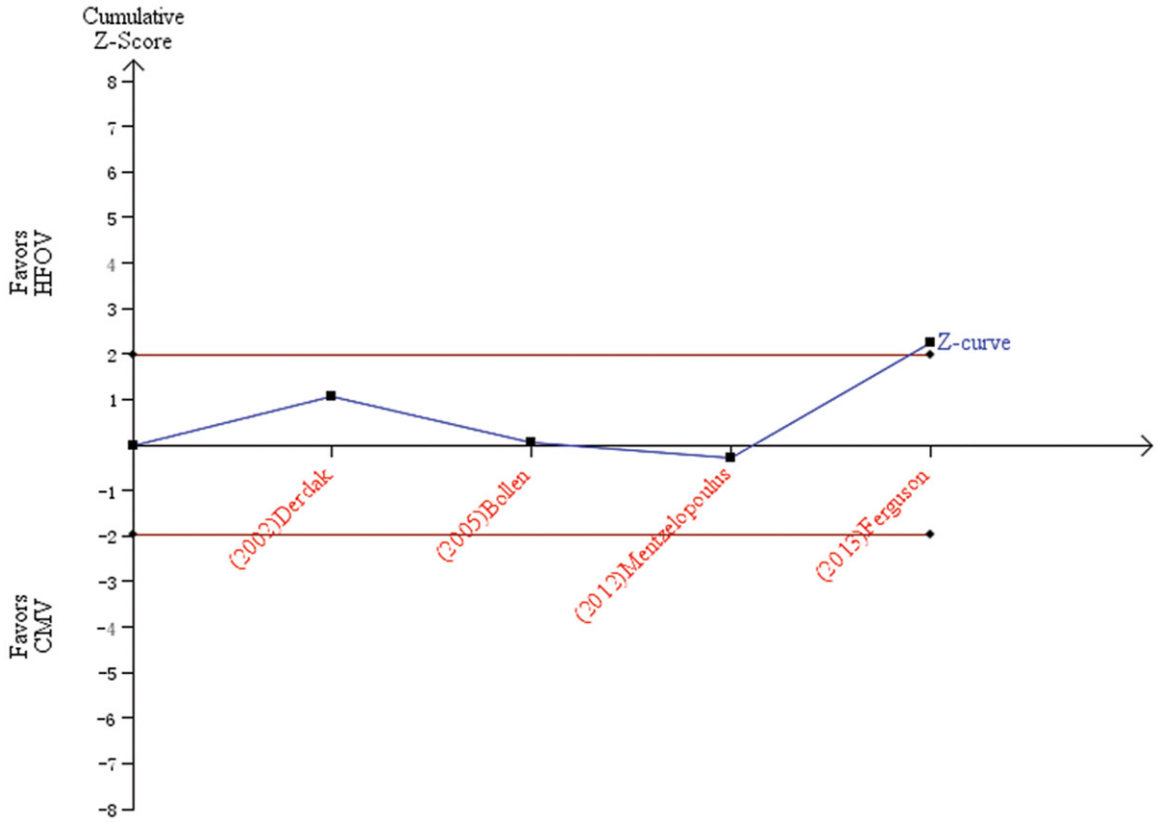

Figure 9. TSA of four randomized trials reporting the incidence of hypotension. The priori heterogeneity adjusted information size (19159 patients) is estimated by assuming a 20% relative risk reduction (RRR). The cumulative *z* curve (blue line with solid circularity) crossed the conventional boundary for benefit ($P < 0.05$), but not the trial sequential monitoring boundary for benefit. A diversity adjusted required information size of 19159 patients(indicated by the right vertical red line) was calculated using $\alpha = 0.05$ (two sided), $\beta = 0.20$ (power 80%), and empirical estimation from TSA software.

ble. Moreover, in spite of inadequate information size (1,759 out of 4,033 patients), TSA showed a evidence for this association. At this regard, a possible advantage of this methodological tool is that it may prevent the initiation of unnecessary trials when firm evidence has been gained. Several previous meta-analyses evaluating this topic have been published. Some of the major outcomes were reported by Sud et al [28] and Huang et al [29] in their relevant meta-analysis. However, the optimal ventilator setting for HFOV in adults remains unclear. Sud et al reported that in patients with ALI or ARDS, HFOV reduced hospital and 30-day mortality and decreased the risk of treatment failure compared with CMV [28]. Huang et al reported that HFOV does not confer any in-hospital mortality benefit over conventional lung-protective ventilation strategy in ARDS, and suggested that HFOV should not be a routine practice in ARDS [29]. Ferguson et al [3]. Reported a higher in-hospital mortality and Lall et al [16] reported equal mortality with the use of HFOV in patients with ARDS. There are substantial differences between our study and previous meta-analyses. First, this meta-analysis included two additional large scale studies and recruited more than three times the number of patients recruited in the previous meta-analyses. Second, TSA could provide more conservative estimates and establish more sufficient and conclusive evidence. Third, we evaluated the quality of evidence for outcomes based on GRADE Working Group criteria. Physicians could make clinical decisions with the aid of these evidence.

Although we did not find any increase in the mortality with the use of HFOV, subsequent trials may also change our findings because a large well-designed RCT [3, 15] has already found more harm with the use of HFOV. Despite

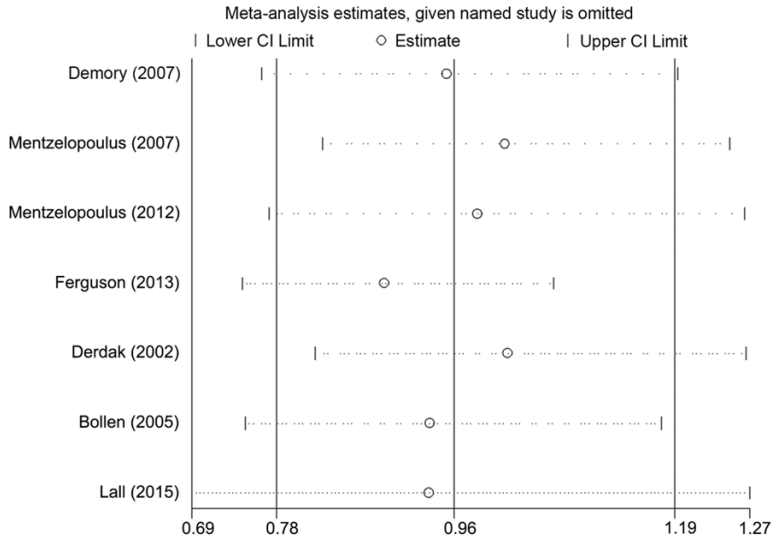

Figure 10. Sensitivity analysis of the summary relative risk (RR) for the primary outcomes of mortality. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95% confidence interval.

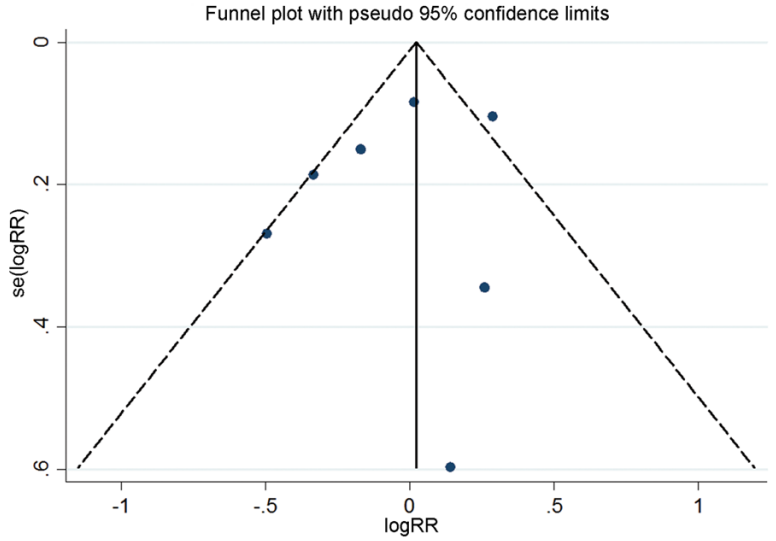

Figure 11. Begg's funnel plot for the primary outcomes of mortality. Each point represents a separate study for the indicated association. LogRR, natural logarithm of RR; SE, standard error. Horizontal line, mean magnitude of the effect.

a less incidence of hypotension, duration of mechanical ventilation is prolonged with the use of HFOV, and the result was confirmed by TSA. Another important finding of our study is that HFOV does not reduce the duration of ICU stay, which is consistent with the findings of the previous meta-analysis [29]. In addition, there was no significant difference in the incidence of barotrauma between HFOV group and CMV group. Current evidence did not support the routine use of HFOV for ARDS patients because of its potential harm.

Similar to other meta-analyses, our study also bears some limitations and shortages. First, the sample size is still relatively small and may not provide sufficient power to compare o estimate the standard HFOV with CMV. Therefore, more studies with larger sample size are needed to accurately provide a more representative statistical analysis. Second, we did not ask the authors of the included trials for unpublished data and did not include ongoing trials. Because the protocol of HFOV used in different studies is variable, there might be possibilities of biases. Two recent large multicentric studies influenced the primary outcome significantly. As both of these studies were multicentric, probability of heterogeneity in study protocol exists. Third, although further subgroups analyses, sensitive analyses, and TSA proved the robustness of pooled effect estimates, heterogeneity across studies cannot be neglected because of the inherent differences of baseline data. Finally, although all cases and controls of each study were well defined with similar inclusion criteria, there may be other potential factors that were not taken into account, which may have influences on our results. Our result may change with publications of further large RCTs. The inclusion criteria and patient population are variable in different studies. The primary causes of ARDS may influence ultimate outcomes. Timing of initiation of HFOV and duration of treatment may also influence mortality. In spite of these limitations, however, to our best knowledge, the present meta-analysis was the first to systematically evaluating the standard HFOV versus CMV in patients with ALI

or ARDS with TSA. Two multicenter RCTs were included [3, 15, 16]. This analysis explores the possibility of a false negative result and evaluates the statistical reliability of the present data. Another strength was that we conducted this systematic review with methodology following the recommendations of the Cochrane Collaboration. Finally, the sensitivity analysis indicated that the results are statistically robust.

Conclusions

In conclusion, in this systematic review with meta-analyses and TSA, we did not find any statistically significant beneficial effect that could support routine use of HFOV in place of CMV in adult patients with ARDS. On the contrary, the duration of mechanical ventilation may even be increased. In TSA, we did not find any statistically significant beneficial effect that could support the use of HFOV for ARDS. Further, our TSA suggests that many thousands of randomized patients are needed in order to change this perspective. As well as focusing on hard outcomes, future trials should assess both quality of life for survivors and cost-effectiveness.

Disclosure of conflict of interest

None.

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