# Effect of Dexmedetomidine on Duration of Mechanical Ventilation in Septic Patients: A Systematic Review and Meta-Analysis

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**Research article**

**Keywords:** sepsis, duration of mechanical ventilation, dexmedetomidine, systematic review and meta-analysis

**Posted Date:** June 25th, 2019

**DOI:** https://doi.org/10.21203/rs.2.10571/v1



**Version of Record:** A version of this preprint was published on February 17th, 2020. See the published version at https://doi.org/10.1186/s12890-020-1065-6.

# Abstract

Background Because of its analgesic and light sedative properties, the highly selective alpha-2 adrenergic receptor agonist dexmedetomidine (DEX) has been suggested for the treatment of septic patients, but its effect on the duration of mechanical ventilation remains unclear. The present study was conducted to review the extant literature in DEX and determine its influence on ventilation time in adult septic patients. Methods We searched the databases of PubMed, Cochrane, and EMBASE until 20 January 2019 using a strategy without language restriction. Two researchers independently reviewed the titles and abstracts and then selected potentially relevant randomized controlled trials that evaluated the influence of DEX on ventilation time in adult septic patients. Two authors independently extracted data from the included studies and performed a meta-analysis using Review Manager. Results Four studies with a total of 349 patients were included. The trials conducted in these studies indicated that DEX was associated with significantly different durations of mechanical ventilation (MD 0.65, 95% CI, -0.13 to 1.42, P = 0.10). However, there were significant differences in ventilator-free days (MD 3.57, 95% CI, 0.26 to 6.89, P = 0.03) and 28-day mortality (RR 0.61, 95% CI, 0.49 to 0.94, P = 0.02) in the septic patients. Conclusion Although the administration of DEX did not improve the duration of mechanical ventilation, it increased the number of ventilator-free days and 28-day mortality in the adult septic patients in this study.


# Introduction

Sepsis has been reported to be the final common pathway to death from infection [1] and is thus a major public health problem worldwide [2]. The cascade of sepsis may lead to single or multiple organ dysfunctions, such as acute respiratory distress syndrome (ARDS). A previous study showed that 4,827,769 cases of sepsis were identified from 2009 to 2011 in the United States among which 21.38% required mechanical ventilation[3]. Patients with prolonged mechanical ventilation were shown to have longer hospital stays, higher mortality, and increased costs [4, 5].

Septic patients on mechanical ventilation often require sedation. Appropriate sedation reduces the anxiety and stress caused by tracheal intubation and improves tolerance to endotracheal or tracheostomy tubes [6]. Early deep sedation was associated with increased ventilation time and increased mortality[7]. Furthermore, dexmedetomidine (DEX) was similar to midazolam and propofol in maintaining light to moderate sedation and reduced ventilation time compared with midazolam[8]. Thus, a non-benzodiazepine sedation strategy that includes DEX and propofol is recommended [9, 10].

As a highly selective and potent α2 agonist, DEX is used to achieve light sedation [8], and it has been highly rated because of its sedative and analgesic properties [11]. Compared with propofol, midazolam, benzodiazepine, and lorazepam, DEX improved patients' ability to communicate pain, and it provided safe and efficacious sedation in ICU patients [12, 13]. A previous trial showed that septic patients sedated with DEX required less mechanical ventilation time compared with those sedated with lorazepam [14]. In contrast, a recent multi-center randomized clinical trial demonstrated that the administration of DEX compared with no DEX (propofol, midazolam) resulted in neither a reduction in ventilator days nor an

increase in the number of ventilator-free days [15]. Hence, based on previous clinical trials, it remains controversial whether sedation with DEX improves ventilation time in adult septic patients. Therefore, in the present review study, we perform a meta-analysis to determine whether sedation with DXM shortens the duration of mechanical ventilation in adult septic patients.

# Methods

The present review study was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), which is the preferred system for reporting items for conducting systematic reviews and meta-analyses [16] .

# Eligibility criteria

The definition of sepsis was revised in February, 2016 [17]. Hence, the studies included in this review involved adults with sepsis and/or septic shock and at least two systemic inflammatory response syndrome (SIRS) criteria due to infection, which was defined by the investigators. All studies were prospective randomized control trials (RCTs), contained data on ventilation duration and/or ventilator-free duration. The exclusion criteria were as follows: pediatric; patients with SIRS by other causes, such as burn or trauma; and studies without a clear sepsis subgroup.

# Identification of studies

We searched the following databases: PubMed (1993 to 20 January 2019), Cochrane (2007 to 20 January 2019), and EMBASE (1990 to 20 January 2019). There was no language restriction. The search term “Clinical Trial” was used in searching the databases. The Endnote X8 citation manager was used to compile the references. Duplicates were filtered using the “Find Duplicates” feature, and then the data were searched manually. Two groups of search terms were combined in this study. The first group included “sepsis,” “septic shock,” “systemic inflammatory response,” and “SIRS.” The second group included “Alpha-2 agonists” and “dexmedetomidine” (additional file 1). When they were identified using the above search strategies, the references list of RCTs and the relevant review articles were manually checked to include other potentially eligible trials.

# Analysis of outcomes

The primary outcome of this study was the duration of mechanical ventilation. The secondary outcomes were 28-day mortality and ventilator-free days, which was defined as the number of days alive and successfully weaning from mechanical ventilation in the first 28 days after enrollment in the trials [18].

We also evaluated the methodological quality of this meta-analysis separately by using the “risk of bias table” tool in Manager (Revman) (Version 5.3. Copenhagen: The Nordic Cochrane Center, the Cochrane

Collaboration, 2014).

## Study selection and data extraction

Two reviewers (i.e., Chen and Zhang) independently screened the titles and abstracts yielded by the search strategies and selected the potentially relevant trials. Then the full texts of relevant trials were assessed according to the eligibility criteria. Chen and Jiang extracted the data from the included studies independently. The details about the study designs and outcomes were entered in Microsoft Office Excel 2007 and then checked by the third author (Hu). Any discrepancy was resolved by either discussion or according to advice from other authors. The original authors were contacted if data were not present in the relevant articles.

## Quality assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to assess the quality of the studies[19]. In brief, the quality of the evidence was analyzed and then categorized in one of four domains: “very low,” “low,” “moderate,” or “high.” All studies included in this meta-analysis were RCTs that provided high-quality evidence. In some cases, the quality of the evidence was decreased for several reasons, including reporting bias, imprecision, inconsistency, indirectness of evidence, and publication limitations.

## Statistical analysis

The mean values and standard deviation (SD) of the duration of mechanical ventilation and 28-day ventilator-free days were extracted for the outcome analysis. Because Tasdogan [20] and Kawazoe [15] expressed the data in the form of median and interquartile range, we emailed the first and corresponding authors but failed to obtain the raw data; therefore, we followed the recommendations of Wan et al [21]. and Luo et al [22] to estimate the mean values and SD of Tasdogan and Kawazoe’s data.

An inverse variance model with a 95% confidence interval was used to analyze the continuous outcome. The risk ratio (RR) and 95% confidence interval (CI) were used to analyze the dichotomous outcomes. A *P* value of less than 0.05 was considered significant. Significant heterogeneity was identified when the *P* value determine by the chi-square test was less than 0.10 and $I^2$ was greater than 50%. A fixed-effect model was employed to calculate the pooled effect when there was no statistically significant heterogeneity. Otherwise, a random-effects model was used. Publication bias was evaluated by a funnel plot. All statistical analyses were performed using the Review Manager software.

# Results

## Study selection

The comprehensive search yielded 42 titles in Cochrane, 849 in EMBASE, and 958 in PubMed. After removing duplicates, 1,836 citations were selected as potentially relevant. The titles and abstracts were screened, and then 33 full-text articles were selected for further analysis. Twenty-nine articles were excluded, six of which were duplicated, 11 did not include ventilator duration, four did not include sepsis, three were based on the same data, two were reviews, two were retrospective studies and one did not include DEX. Finally, four randomized clinical trials with 349 patients were included in this meta-analysis [14, 15, 20, 23] (Figure 1).

## Study characteristics and quality

Among the four trials, one was published in Chinese, and three were published in English. One study was double-blinded[14] and one was blinded-endpoint[15], while others were not blinded [20, 23]. All patients were adults. The experimental group was DEX, and the control included propofol[15, 20, 23], lorazepam[14], and midazolam[23]. The doses of DEX ranged from 0.1 μg /kg/hr to 2.5 μg /kg/hr. In one study, the patients were maintained at a Ramsay sedation score < 2[20]. In other studies, the target sedation levels were RASS score of 1[14], -1 to -2[23], and 0 during the day and -2 during the night[15]. The characteristics of the included studies and a summary of the durations of mechanical ventilation and/or 28-day ventilator-free days are shown in Table 1. Two studies reported the number of ventilator-free days [14, 15], but the other two did not [20, 23]. The duration of mechanical ventilator was available in three studies [15, 20, 23]. Figure 2 and Figure 3 show summaries of the risk of bias.

The quality of evidence in the included studies ranged from moderate to high (Table 2).

## Primary outcome

Three trials reported the duration of mechanical ventilation as an outcome [15, 20, 23]. Tasdogan et al. expressed the duration of mechanical ventilation in 37 survivors as a median (min–max) and in three non-survivors as the number of days requiring mechanical ventilation [20]. Because we were unable to obtain raw data, we only pooled the data on the survivors in our meta-analysis. Among three trials, DEX was compared with propofol[20] and propofol and midazolam [15]. However, Guo's study used two control groups (i.e., a propofol group and a midazolam group) [23], so we pooled the data accordingly. When the data were pooled in the propofol group, the fixed-effects analysis indicated that the use of DEX was not associated with a short duration of mechanical ventilation (MD 0.65, 95% CI, -0.13 to 1.42, $P$ = 0.10; $P$ for heterogeneity = 0.15, $I^2$ = 47%) (n = 268) (Figure 4). When the data were pooled in the midazolam group, the meta-analysis also indicated that the sedation of DEX did not shorten the duration of mechanical ventilation (MD 0.07, 95% CI, -1.58 to 1.72, $P$ = 0.94; $P$ for heterogeneity = 0.08, $I^2$ = 60%.) (n = 267) (Figure 5).

## Secondary outcome

Data on 28-day ventilator-free days were available in two RCTs [16, 18], but the outcomes were opposite. Pandharipande et al. reported that the septic patients who received DEX had more ventilator-free days than those who did not receive DEX [14], whereas Kawazoe et al. concluded that DEX did not increase the number of ventilator-free days in septic patients[15]. Our meta-analysis yielded a fixed-effect estimate of less ventilator-free days in patients who were not given DEX than those who were given DEX (MD 3.57, 95% CI, 0.26 to 6.89, $P = 0.03$; $P$ for heterogeneity = 0.45, $I^2 = 0\%$) (n = 264) (Figure 6).

Data on 28-day mortality were available in all the RCTs included in our meta-analysis. Pandharipande et al. [14] reported that septic patients sedated with DEX had a lower risk of death than those who did not receive DEX, whereas Tasdogan [20] and Guo [23] reported DEX did not improve the mortality rate. Kawazoe et al. [15] showed that DEX resulted in an 8% reduction in 28-day mortality even though the results were not statistically significant. Our meta-analysis indicated that compared with no DEX sedation, DEX improved short-term mortality (RR 0.61, 95% CI, 0.49 to 0.94, $P = 0.02$; $P$ for heterogeneity = 0.67, $I^2 = 0.$) (n = 334) (Figure 7).

## Sensitivity analysis and publication bias

The tests conducted to determine heterogeneity in the duration of mechanical ventilation revealed outliers in the results of Guo et al. (2016). We removing this study to eliminate heterogeneity, but the results were unchanged (MD 0.77, 95% CI, -0.02 to 1.56, $P = 0.06$;$P$ for heterogeneity = 0.30, $I^2 = 7\%.$) (n = 238) (Figure 8). The funnel plot showed no evidence of significant publication bias in the results of the duration of ventilator-free days and mortality (Figure 9 and Figure 10).

## Discussion

To the best of our knowledge, this meta-analysis is the first to assess the effects of sedation with DEX on the duration of mechanical ventilation in adult septic patients. A previous meta-analysis of critically ill patients, including medical, surgical, and trauma patients, revealed that compared with traditional sedative agents, DEX reduced the geometric mean duration of mechanical ventilation [24]. It included four studies and did not focus on an independent septic group. In the present meta-analysis, we identified four clinical trials involving 349 septic adult participants, and we compared the effects of sedation with DEX with the effects of no sedation with DEX. All patients in the included studies were enrolled before February, 2016, when the definition of sepsis was revised. So the change in sepsis definition did not cause significant differences in the patient population of the studies. Our results showed that sedation with DEX resulted in an improvement in the number of ventilator-free days and in 28-day mortality, but it did not reduce the duration of mechanical ventilation in septic patients.

Sedation is essential for improving the survival rates of ICU patients and their tolerance of mechanical ventilation [6, 25]. According to the Canadian Agency for Drugs and Technologies in Health, DEX was related to a shorter duration of mechanical ventilation compared with midazolam and propofol [26]. The

most recent meta-analysis also revealed that DEX reduced the geometric mean respiratory support time by 22% in critically ill patients compared with traditional sedative agents [24]. Two multi-center RCTs revealed that the median breathing support time was shorter with DEX than with midazolam but not with propofol in ICU patients [8]. All trials included in the present study and our meta-analysis showed that sedation with DEX did not reduce the duration of mechanical ventilation in adults compared with no sedation with DEX. The subgroup analysis indicated that compared with propofol, DEX did not shorten the duration of mechanical ventilation. We did not perform the subgroup analysis based on midazolam because of insufficient data. The results of the meta-analysis were contrary to that of Chen [24]. The difference in results may be attributable to differences in the participants (sepsis or septic shock patients vs. critically ill patients). Thus, in considering reductions in the ventilator duration in ICU patients, DEX could be better than other sedative agents, but it may not be the preferred agent in septic patients.

Ventilator-free day was defined as the number of days alive and free of mechanical ventilation in the first 28 days after enrollment [18]. The concept combines both mortality and duration of mechanical ventilation. It includes two aspects: a binary variable of whether the patient is alive or not in the first 28 days and a continuous variable of the patient requiring mechanical ventilaton[27]. A previous meta-analysis included two clinical trials involving 103 septic patients and the number of mechanical ventilation free days during the 28-day period. The authors concluded that DEX had no significant effect on the duration of mechanical ventilation [28]. However, the authors did not distinguish between mechanical ventilation free days and the duration of mechanical ventilation. Thus, we considered that this article did not show whether sedation with DEX affected the duration of mechanical ventilation. Our results suggested that DEX increased the number of ventilator-free days and reduced 28-day mortality, but it did not reduce the duration of mechanical ventilation. Because the number of ventilator-free days includes both mortality and the duration of mechanical ventilation, we may infer that the reduction in 28-day mortality contributed to the increase in the number of ventilator-free days.

The present meta-analysis has the following limitations. First, because of the limited number of available trials, we included only four studies that focused on sepsis patients. Therefore, it was not possible to use the Egger test or the arcsine test to create funnel plots or evaluate publication biases. Furthermore, it is possible that the small number of included studies might not have been sufficient to explore and eliminate heterogeneity. Second, Kawazoe[15] et al's study included patients on invasive and non invasive mechanical ventilation. The different mode of mechanical ventilation in the study may have an impact on the overall outcome of the meta-analysis. Third, the absence of duration of mechanical ventilation in three non-survivors [20] may have led to a publication bias. Finally, because Tasdogan [20] and Kawazoe's [15] data were described as medians in the interquartile range, we estimated the means using medians because of the lack of individual patient data. Because estimating the sample mean and variance from the median, range, and size of the sample is a widely accepted practice in meta-analyses, we did not consider that this estimation would significantly affect the results of this meta-analysis.

# Conclusion

The results of our meta-analysis suggest that sedation with DEX in mechanically-ventilated adult sepsis or septic shock patients did not improve the duration of mechanical ventilation, but it increased the number of ventilator-free days and 28-day mortality. Because of the limitations of the available studies and sample sizes, a large prospective study is needed to evaluate the influence of DEX on the duration of mechanical ventilation and ventilator-free days in septic patients.

## Declaration

## Disclosure

All authors declare no conflict of interest here.

## Acknowledgments

We thank all authors for allowing their work to be cited in the present article. This work was collectively supported by the Shenzhen Health Planning Commission Fund (Grant No. 20140611040) and National Natural Science Foundation of China (Grant No. 81701885). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the work.

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# Table

Due to technical limitations the tables could not be inserted here. They can be found in the supplemental files.

# Figures

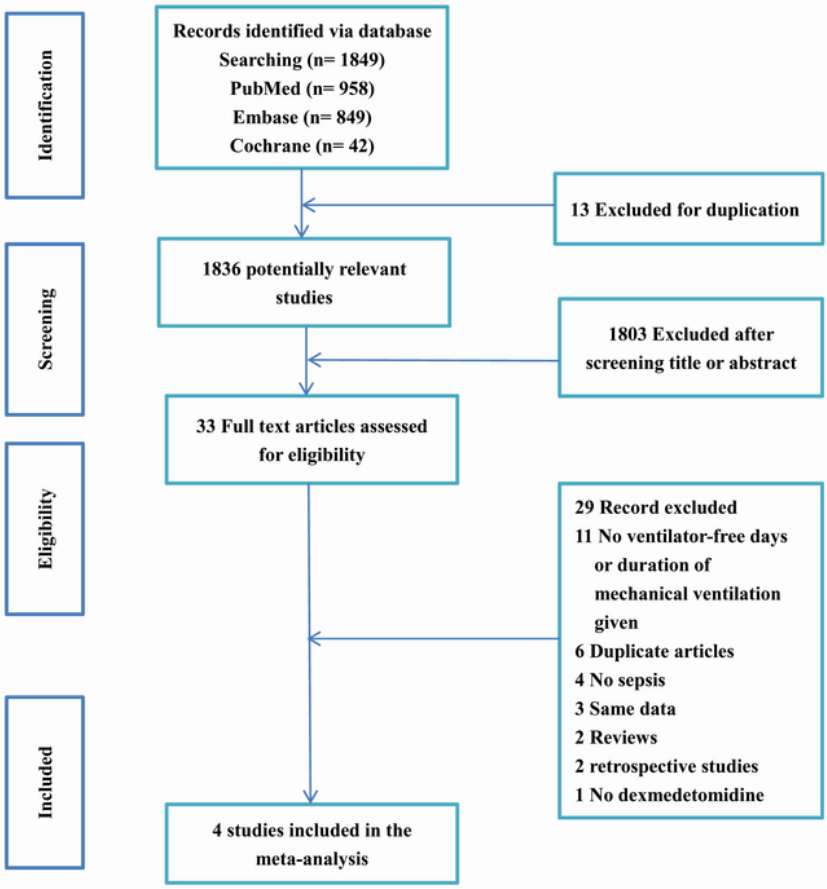



Fig. 1 Flow diagram of the study retrieved, excluded, assessed and included.

**Figure 1**

Flow diagram of the study

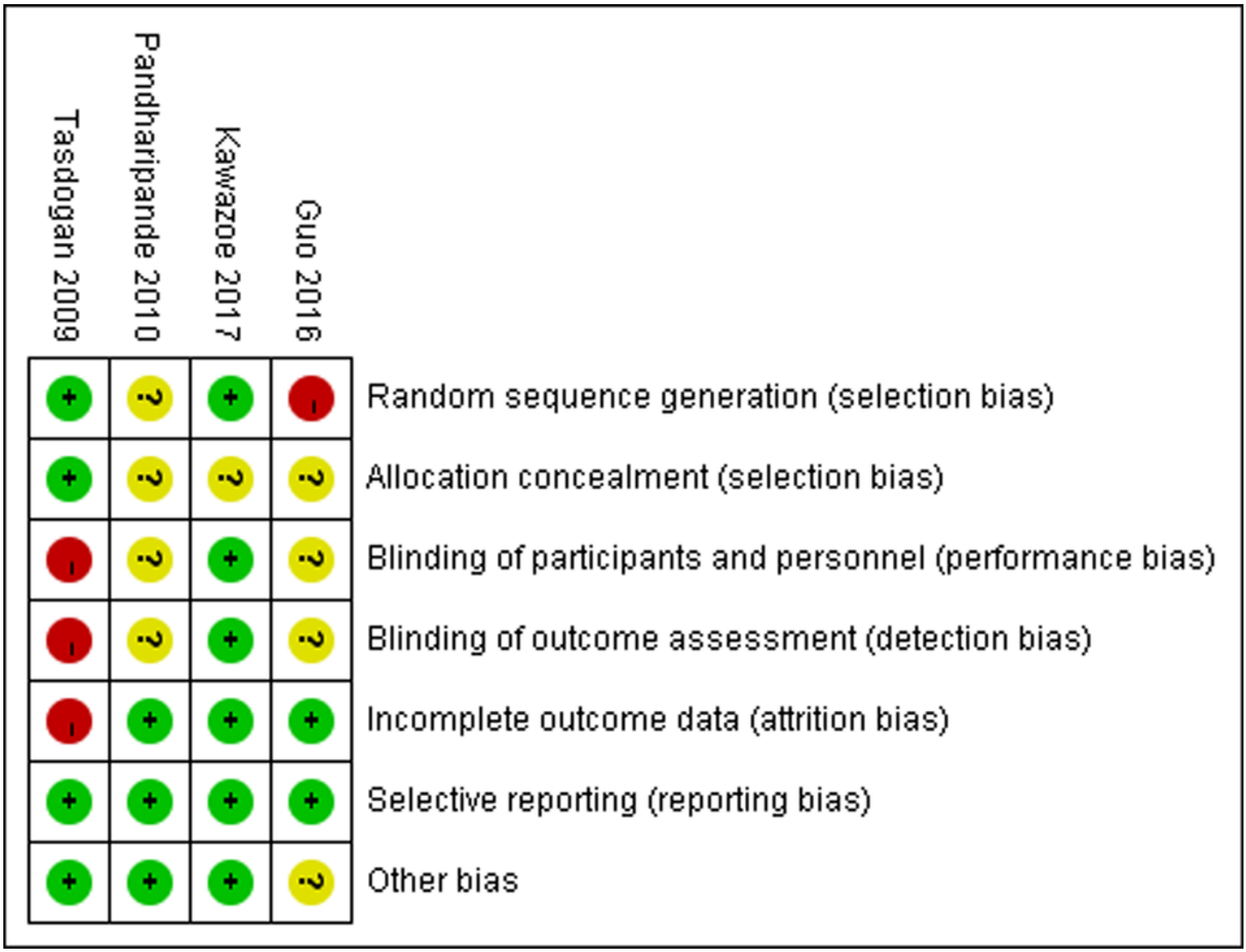
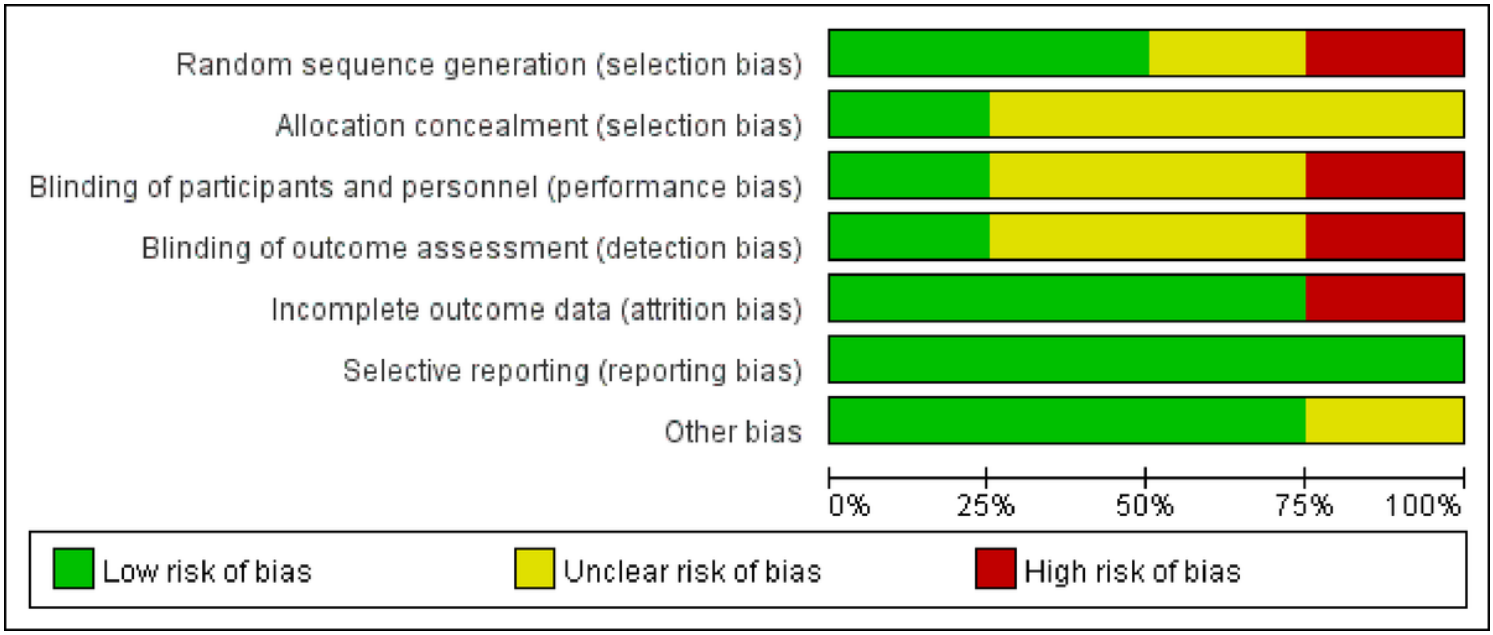


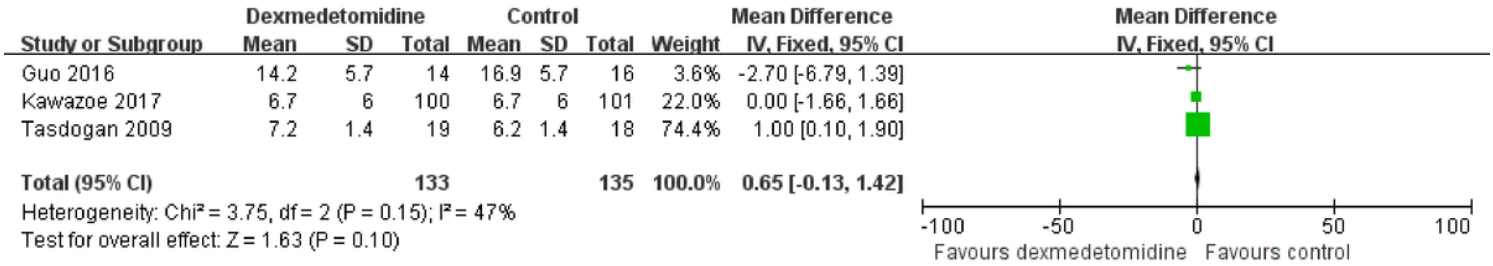

**Figure 2**

Risk of bias summary



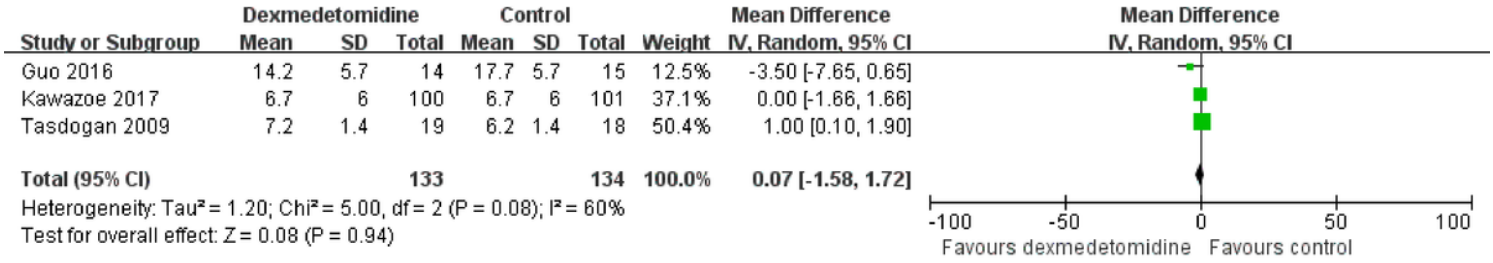

## Figure 3

Risk of bias graph



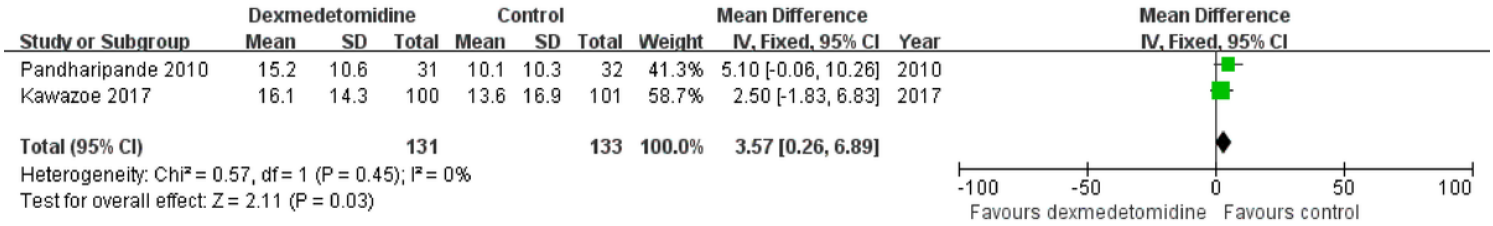

## Figure 4

Comparison of duration of mechanical ventilation



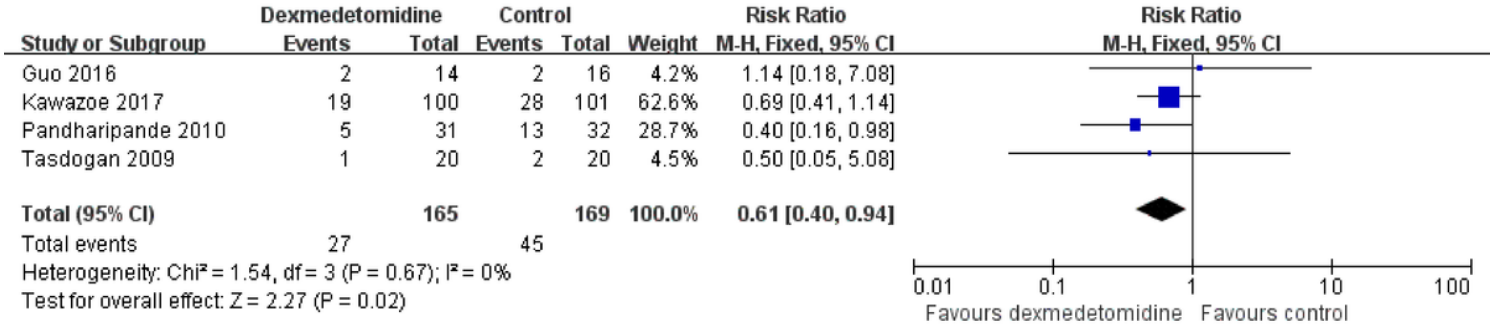

## Figure 5

Comparison of duration of mechanical ventilation



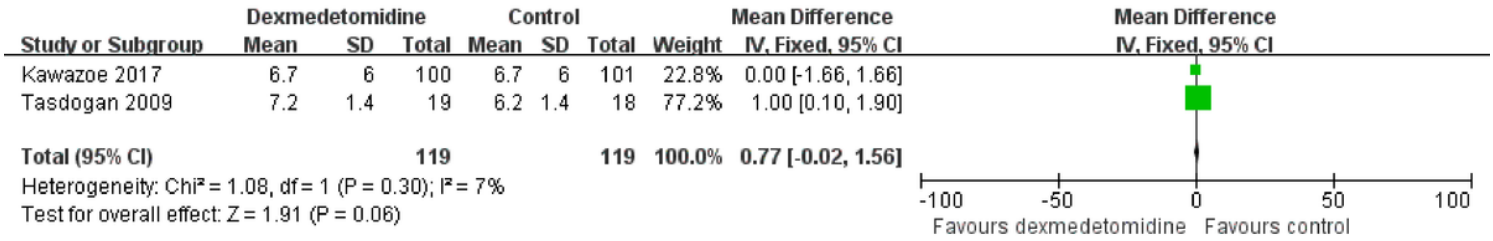

## Figure 6

Our meta-analysis yielded a fixed-effect estimate of less ventilator-free days in patients who were not given DEX than those who were given DEX (MD 3.57, 95% CI, 0.26 to 6.89, P = 0.03; P for heterogeneity = 0.45, I2 = 0%) (n = 264)




## Figure 7

Our meta-analysis indicated that compared with no DEX sedation, DEX improved short-term mortality (RR 0.61, 95% CI, 0.49 to 0.94, P = 0.02; P for heterogeneity = 0.67, I2 = 0.) (n = 334)




## Figure 8

The tests conducted to determine heterogeneity in the duration of mechanical ventilation revealed outliers in the results of Guo et al. (2016). We removing this study to eliminate heterogeneity, but the results were unchanged (MD 0.77, 95% CI, -0.02 to 1.56, P = 0.06; P for heterogeneity = 0.30, I2 = 7%.) (n = 238) figs 9 & 10: The funnel plot showed no evidence of significant publication bias in the results of the duration of ventilator-free days and mortality

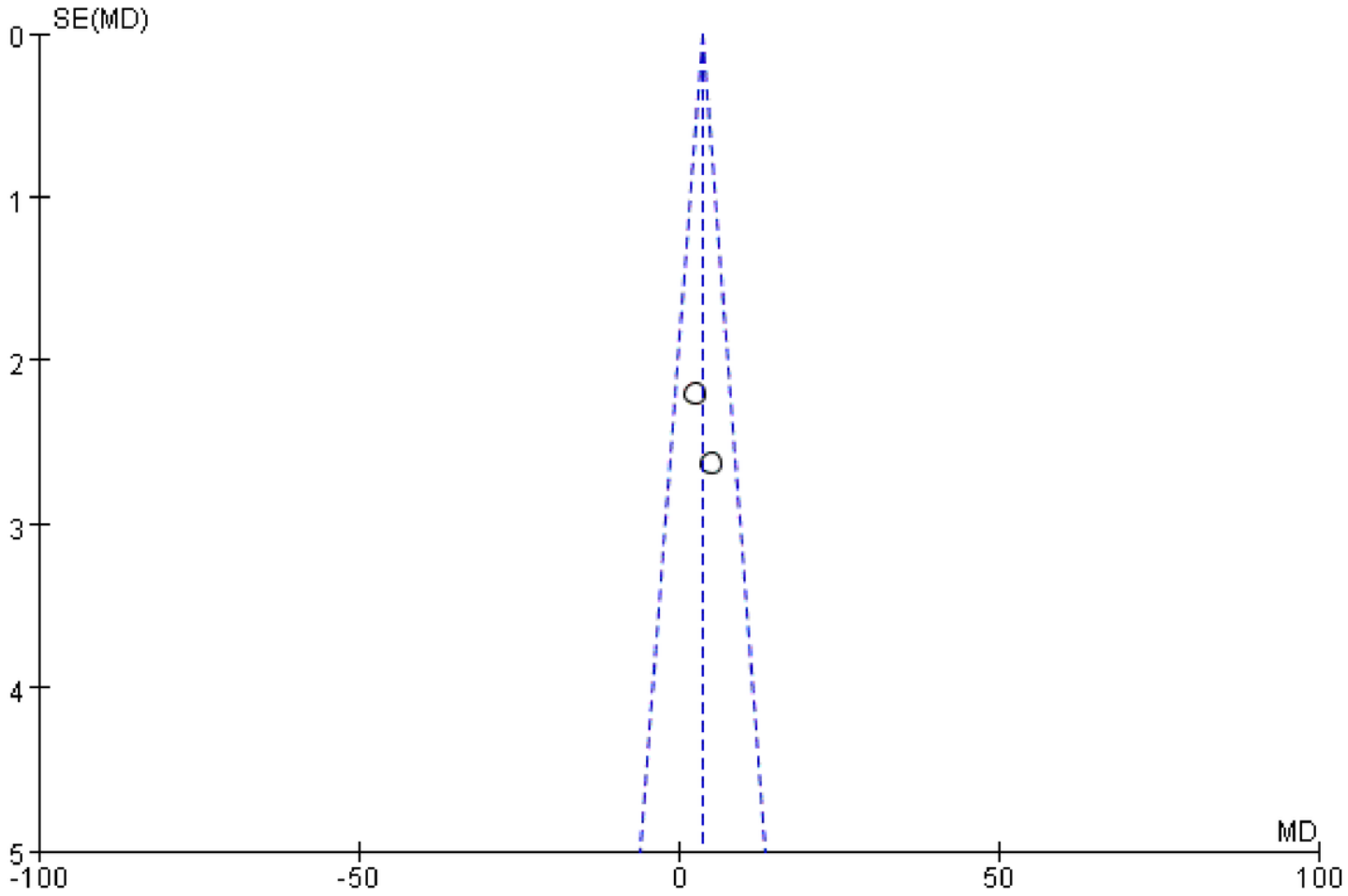



**Figure 9**

The funnel plot showed no evidence of significant publication bias in the results of the duration of ventilator-free days and mortality

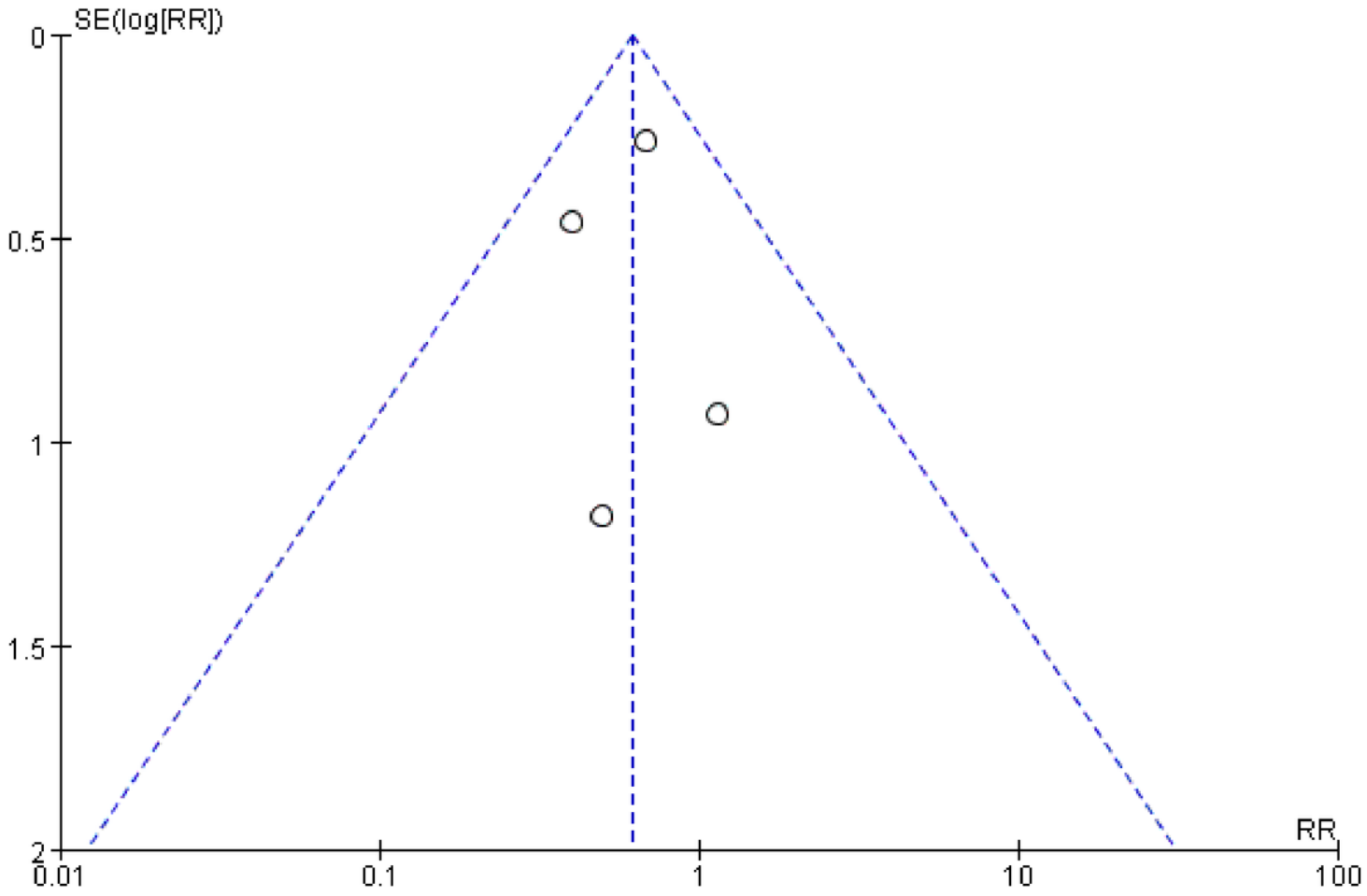



**Figure 10**

The funnel plot showed no evidence of significant publication bias in the results of the duration of ventilator-free days and mortality

# Supplementary Files

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

- supplement1.docx
- supplement2.pdf
- supplement3.pdf