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The effect of conservative oxygen therapy in reducing mortality in critical care patients: A systematic review and meta analysis

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Abstract
Background Conservative oxygen therapy can avoid both the hypoxemia and hyperoxemia, but the effect of it on the prognosis of patients admitted to intensive care unit (ICU) remains controversial.

Methods The Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL) as well as the Information Sciences Institute (ISI) Web of Science were searched for all the controlled studies comparing conservative oxygen therapy and conventional oxygen therapy in adult patients admitted to ICU. The primary outcome was the mortality and the secondary outcomes were length of ICU stay (ICU LOS), length of hospital stay (hospital LOS), length of mechanical ventilation (MV) hours, new organ failure during ICU stay, new infection during ICU stay.

Results Six trials with a total of 2250 patients were pooled in our final studies. No statistical heterogeneity was found in all the analysis. Compared with conventional oxygen therapy, conservative oxygen therapy could not reduce overall mortality (Z=0.96, P=0.34), ICU LOS (Z=0.29, P=0.77), hospital LOS (Z=1.98, P=0.05) and new infection during ICU stay (Z=0.94, P=0.35). However conservative oxygen therapy was associated with lower MV time (Z=5.03, P<0.001) and new organ failure during ICU stay (Z=2.05, P=0.04).

Conclusions Conservative oxygen therapy could not reduce the mortality but did lower the MV time and new organ failure in critically ill patients.

Background
Hypoxemia is life threatening and related to increasing intensive care units (ICU) mortality. Oxygen administration is a life saving treatment commonly used in the patients admitted to the ICU. Unfortunately, although oxygen administration in ICUs was recommended by a lot of guidelines, the most suitable oxygenation target remains unknown.

Studies presented that excess oxygen delivery was very common and about 50% of the patients showing hyperoxemia, among which 4% with severe hyperoxemia. As we all know, hyperoxia was related to adverse events such as histopathological injury, interstitial fibrosis, atelectasis, tracheobronchitis, alveolar protein leakage and infiltration by neutrophils. Moreover, it could also lead to decline of cardiac output, generate free radical-mediated in various organs and a marked
reduction in coronary blood flow and myocardial oxygen consumption. Studies showed that the ICU mortality of patients was independently associated with hyperoxia in mechanical ventilation patients (odds ratio[OR ]1.22, 95% confidence interval[CI] 1.12 – 1.33).\textsuperscript{15}

Thus, in order to prevent patients from hypoxemia and avoid the adverse events led by hyperoxemia, some researchers studied on the conservative oxygen therapy, which means adhering to a goal that pulse oxygen saturation(SpO\(_2\))is between 88–92% with lowest fraction of inspired oxygen (FiO\(_2\)). But the results remained controversial. In the study of Girardis, which included in 434 patients, conservative oxygen therapy can reduce about 19% of the ICU mortality (p=0.01).\textsuperscript{16}

However, in the study of Mackle et al., conservative oxygenation targets did not show any advantages in ICU mortality over the conventional oxygenation target (35.7%% vs. 34.5%).\textsuperscript{17}

Therefore, based on the controversial findings of the effect of conservative oxygen therapy, we conducted a systematic review and meta-analysis of all published trials aiming for identifying the roles of conservative oxygen therapy in improving the outcomes of patients admitted into ICU.

Methods

Search strategies

From 1946 to February 2020, a comprehensive computer search was conducted in Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trails (CENTRAL) and Information Sciences Institute (ISI) Web of Science using the keywords of “conservative oxygen therapy” or “conservative oxygenation target” or “oxygenation target” and “critically ill” or “ICU” or “intensive care unit” without limitation in the publication type or language. We also reviewed the references listed in each identified article and manually searched the related articles to identify all eligible studies and minimize the potential publication bias.

Inclusion and exclusion criteria

Eligible clinical trials were identified based on the following criteria: 1) the subjects enrolled in each study included patients admitted into ICU; 2) patients were divided into experimental group, in which conservative oxygen therapy was applied; and control group; 3) outcomes contained but not limited to mortality, length of ICU stay (ICU LOS), length of hospital stay (hospital LOS), length of mechanical
ventilation (MV) hours, new infection and new organ failure during ICU. We excluded studies if they were performed in animals or in patients less than 18 years old, or published as reviews or case reports.

Study selection
Two independent investigators performed the study selection in two phases. (Y-NN and Y-MW) Firstly, they discarded duplicated and non-controlled studies by screening titles and abstracts. Secondly, eligible studies were extracted by reviewing full texts in accordance with the previously designed study inclusion criteria. Any disagreement was solved by mutual consensus in the presence of a third investigator. (B-ML)

Data extraction
Independently, two data collectors extracted and recorded desirable information of each enrolled study in a standard form recommended by Cochrane18 which consisted of authors, publication year, study design, country, NCT No., population, demographic characteristics (age, gender, etc.), disease conditions (The Acute Physiologic and Chronic Health Evaluation III (APACHE III) and Simplified Acute Physiologic Score II (SAPS II)), outcome measures, and study results. For any missing data information, corresponding authors were contacted by email to request the full original data. Different opinions between the two collectors were determined by reaching a consensus or consulting a third investigator.

Quality assessment
For the assessment of risk of bias in estimating the study outcomes, we used the Cochrane risk of bias tool.18 Each study was assessed for: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of related outcomes assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other biases. Two investigators conducted the quality assessment for the study methodology, independently and separately. Any divergence was resolved by mutual consensus in the presence of a third investigator.

Statistical analysis
Statistical analysis of our study was accomplished by an independent statistician using Cochrane
systematic review software Review Manager (RevMan; Version 5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). We used Mann-Whitney U-test to verify hypothesis and rendered statistical significance as a Z-value and P-value < 0.05, and the results were displayed in Forest plots. Continuous variables were reported as mean and standard derivation (SD), while dichotomous variables were shown as frequency and proportion. An initial test for clinical, methodological and statistical heterogeneities was conducted, and we used the χ² test with P < 0.1 and I² > 50% to indicate significance. We also performed the sensitivity analysis to substitute alternative decisions or ranges of values for decisions that were arbitrary or unclear. Random-effects model was applied in the presence of statistical heterogeneity; for continuous data we calculated mean difference (MD) and 95% CI, while for dichotomous data we calculated OR and 95% CI.

Results
Initially 1154 records were identified, of which 1151 were extracted from electronic databases and 3 were extracted from reference lists review. (Fig. 1) By screening the titles and abstracts, 1146 studies were discarded for duplication (n = 973), animal experiments (n = 124) and non-adult patients (n = 49). We researched the full-text articles for the remaining 8 studies, and eventually 6 trials were enrolled in our final analysis due to 1 studies did not reporting related outcomes, and 1 did not designed as expected. (Supplemental Fig. 2s)

Study description
All 6 studies compared the outcomes of conservative oxygen therapy alone with those of conventional oxygen therapy.16,17,19–22 Three studies were randomized controlled trials (RCTs),16,17,21 1 studies was retrospective nest cohort analysis,19 and the other 2 studies was prospective before-after study.20,22 Mortality was reported in 6 studies, among which hospital mortality and ICU mortality was reported in 3 studies,16,19,20 28 day mortality was reported in 2 studies,19,22, 30 day mortality was reported in 1 study,20 90 day mortality was reported in 2 studies,17,21 180 day mortality was reported in 1 study.17 ICU LOS was presented in 5 studies,16,17,19–21 Hospital LOS was reported in 5 studies.16,17,19–21 MV hours was reported in 3 studies,17,19,20 The rate of new organ failure was
recorded in 2 studies, \(^{16,22}\) the rate of new infection was recorded in 2 studies. \(^{16,22}\) Details of each study were summarized in Table 1.

### Table 1
Characteristics of included studies

| Author(Year) | Study design | NCT No. | Country | Population | Diagnosis | Conservative group | Conditional group | Target conservative | Target conventional |
|--------------|--------------|---------|---------|------------|-----------|---------------------|-------------------|--------------------|---------------------|
| Eastwood 2015 | Retrospective nested cohort study | NCT 01684124 | Australia | 100 | Cardiac arrest | SpO\(_2\) 88%-92% | Oxygenation target was prescribed by their doctors | Hyperoxemia time (>120 mmHg): 28% |
| Esatwood 2019 | Uncontrolled before-and-after study | ACTRN12 61300132 2729 | Australia | 543 | Cardiac surgery | SpO\(_2\) 88%-92% | Oxygenation target was prescribed by their doctors | Mean PaO\(_2\): 88 mmHg (81–96) |
| Girardis 2015 | Randomized controlled trial | NCT0131 9643 | Italy | 434 | Cardiovascular, gastrointestinal, neurological, respiratory, sepsis, others | SpO\(_2\) 94%-98% | SpO\(_2\) 97%-100% | Mean PaO\(_2\): 87 mmHg (79–97) |
| Mackle 2019 | Randomized controlled trial | ACTRN12 61500095 7594 | Australia and New Zealand | 965 | Mixed | Least FiO\(_2\) to guarantee SpO\(_2\) > 90% | FiO\(_2\) > 0.3, no upper limit | Median number of hours per patient SpO\(_2\) ≥ 97%: 27 [11–63.5] |
| Panwar 2015 | Multicenter randomized controlled trial | ACTRN12 61300050 5707 | Australia, New Zealand, and France | 103 | Trauma, medical, surgical | SpO\(_2\) 88%-92% | SpO\(_2\) ≥ 96% | Mean PaO\(_2\): 72 mmHg (10) |
| Suzuki 2014 | Pilot prospective before-and-after study | NCT 01684124 | Australia | 105 | Medical, surgical | SpO\(_2\) 90%-92% | Oxygenation target was prescribed by their doctors | Mean PaO\(_2\): 83 mmHg (71–94) |

FiO\(_2\), fraction of inspired oxygen; NR, not reported; SpO\(_2\), pulse oxygen saturation

A total of 2250 patients were pooled from all the included trials in our final systematic review and meta-analysis, among which 1154 patients were treated with conservative oxygen therapy, 1096 patients received conventional oxygen therapy. Details of baseline characteristics of patients in each enrolled study were shown in Table 2.
Table 2
Baseline characteristics of patients

| Author(Year) | Conservative oxygen therapy | Conventional oxygen therapy |
|--------------|-----------------------------|-----------------------------|
|              | Age, Years Mean (SD) | Male n, (%) | SAPS II Mean (SD) | APACHE III Mean (SD) | Age, Years Mean (SD) | Male n, (%) | SAPS II Mean (SD) | APACHE III Mean (SD) |
| Eastwood 2015| 65(55–71)b | 34(68%)c | NR | 125(107–141)b | 67(59–77)b | 29(58%)c | NR | 121(105–142)b |
| Eastwood 2019| 65(56–73)b | 209(70.1%)c | NR | NR | 67(59–74)b | 179(73.1%)c | NR | NR |
| Girardis 2016| 63(51–74)b | 121(56%)c | 37(26–49)b | NR | 65(52–76)b | 93(57.3%)c | 39(28–55)b | NR |
| Mackle 2019 | 58.1(16.2)a | 306(63.2%)c | NR | 23.6(9.3)(APACHEII) | 57.5(16.1)a | 302(62.8%)c | NR | 23.3(9.4)(APACHEII) |
| Panwar 2015 | 62.4(14.9)a | 32(62%)c | NR | 79.5(61-92.5)b | 62.4(17.4)a | 33(65%)c | NR | 70(50–84) |
| Suzuki 2014 | 56(16)a | 32(59%)c | NR | 62(49-92)b | 59(17)a | 38(75%)c | NR | 68(42–94) |

APACHE The Acute Physiologic and Chronic Health Evaluation; IQR, interquartile range; NR, not report; SAPS Simplified Acute Physiologic Score; SD, standard derivation; a mean(SD) b median(IQR) c n(%) 

Quality assessment

Quality assessment of the 6 enrolled studies showed that there was no bias in attrition or reporting in 6 studies, but high bias existed in performance in 6 studies and in selection and detection in 3 studies. No studies were excluded for low quality or dubious decisions in the sensitivity analysis. (Supplemental Fig. 2s and Fig. 3s)

Heterogeneity

No significant statistical heterogeneity was found in overall mortality between conservative and conventional group ($I^2 = 39\%, \chi^2 = 8.23, P = 0.14$), ICU LOS ($I^2 = 28\%, \chi^2 = 5.55, P = 0.24$), hospital LOS ($I^2 = 0\%, \chi^2 = 3.39, P = 0.49$), length of MV hours($I^2 = 55\%, \chi^2 = 4.46, P = 0.11$), new organ failure during ICU stay ($I^2 = 0\%, \chi^2 = 0.00, P = 0.96$) nor new infection during ICU stay ($I^2 = 25\%, \chi^2 = 1.33, P = 0.25$).

Mortality

No significant difference in the overall mortality was found in conservative oxygen therapy compared with conventional oxygen therapy (RR 0.94, 95% CI 0.82 – 1.07; $Z = 0.96, P = 0.34$), (Fig. 1) nor in ICU mortality (RR 0.78, 95% CI 0.57 – 1.06; $Z = 1.60, P = 0.11$), (Supplemental Fig. 4s) hospital mortality(RR 0.90, 95% CI 0.59 – 1.39; $Z = 0.46, P = 0.65$), (Supplemental Fig. 5s) 28 day mortality(RR 0.80, 95% CI 0.41 – 1.55; $Z = 0.67, P = 0.50$) (Supplemental Fig. 6s) and 90 day mortality(RR 1.07,
95% CI 0.90 ~ 1.26; Z = 0.77, P = 0.44. (Supplemental Fig. 7s)

Icu Los
Figure 2 showed that differences of ICU LOS were not significant between conservative oxygen therapy and conventional oxygen therapy (MD -0.07, 95%CI -0.52 ~ 0.38, Z = 0.29, P = 0.77).

Hospital LOS
No significant role of conservative oxygen therapy in hospital LOS was found (MD -0.77, 95%CI -1.52 ~ -0.01, Z = 1.98, P = 0.05). (Fig. 3)

MV hours
Conservative oxygen therapy could reduce the MV hours when compared with conventional oxygen therapy (MD -2.38, 95%CI -3.31 ~ -1.45, Z = 5.03, P < 0.001). (Fig. 4)

New organ failure during ICU stay
Figure 5 showed that differences of ICU LOS existed in comparison between conservative oxygen therapy and conventional oxygen therapy (RR 0.74, 95%CI 0.55 ~ 0.99; Z = 2.05, P = 0.04).

New infection during ICU stay
No significant differences of new infection during ICU stay existed between conservative oxygen therapy and conventional oxygen therapy (OR 0.88, 95%CI 0.68 ~ 1.15; Z = 0.94, P = 0.35). (Fig. 6)

Discussion
In our meta-analysis, we found that conservative oxygen therapy could not decrease the rate of mortality, ICU LOS, and hospital LOS and new infection during ICU stay in critically ill patients. But conservative oxygen therapy could reduce the MV time and the new organ failure during ICU stay. The advantages of conservative oxygen therapy could not be denied. Conventional therapy would put 44.5% of the patients exposed to hyperoxemia, which is only about 11.4% in conservative oxygen group. The disadvantages of hyperoxemia have been well demonstrated by many researches. First of all, high inspired oxygen concentrations would inhibit immune system: compromising the ability of macrophages, suppressing the production of cytokine, causing structural changes within alveolar macrophages and leading to serious impairment of their antimicrobial activity. Secondly, pulmonary injury would be induced by hyperoxemia As mentioned above, hyperoxemia can result in decreased mucociliary clearance, atelectasis, inflammation, pulmonary edema, and eventually
interstitial fibrosis.\textsuperscript{27,28} The combination of the injury of immune system and pulmonary was related with higher risk of ventilator associated pneumonia (VAP). A retrospective observational study on 503 enrolled patients showed that both hyperoxemia at ICU admission (OR = 1.89, 95% CI 1.23 – 2.89, p = 0.004), and percentage of days with hyperoxemia (OR = 2.2, 95% CI 1.08 – 4.48, p = 0.029) were independently associated with VAP.\textsuperscript{29} As studies showed, the rate of VAP is associated with longer MV period.\textsuperscript{30} Moreover, two of enrolled studies showed a trend to lower use of mandatory MV mode in conservative oxygen group,\textsuperscript{19,21} which might indicate earlier attempts to wean patients in response to lower FiO\textsubscript{2} requirement. This explains the significant shorter MV hours in conservative oxygen therapy group. Third, every organ not just the lung would be damaged by production of reactive oxygen species (ROS) resulted from high concentration oxygen. ROS-mediated stress can lead to cellular necrosis and apoptosis.\textsuperscript{31} In addition, oxidative stress is responsible for direct damage to biological molecules and indirect injury through the release of cytotoxic products and mutagenic effects of lipid oxidation.\textsuperscript{32} ROS-mediated stress and oxidative stress caused by high inspired oxygen concentrations would promote the systemic organ failure; otherwise the decline of ROS in the conservative oxygen therapy group would lead to less new organ failure during the ICU stay. However, despite the advantages of conservative oxygen therapy, lower mortality, shorter ICU LOS and shorter hospital LOS were not been found in our study. We think the following reasons might explain. First of all, there were many factors contributes to the mortality of patients. Although conservative oxygen therapy could bring some benefit to patients, but other many factors such as the severity of baseline disease et al. also contributes significantly to mortality, ICU LOS and hospital LOS.\textsuperscript{33} Thus, the benefit of conservative oxygen therapy could be not strong enough to show a significant statistic significant when combined with so many factors. Secondly, conservative oxygen therapy actually puts patients in a higher risk of hypoxia at the same time when avoiding the hyperoxemia. Hypoxia was also related with higher mortality,\textsuperscript{34} which might offset the advantages of conservative oxygen therapy.
In addition, we did not found any advantages of conservative oxygen therapy in new infection during ICU stay compared with conventional oxygen therapy. As we all know, the incidence of new infection might have been underestimated because only those ascertained by microbiological samples were recorded. Moreover, only two of enrolled studies reported the data about new infection during ICU stay. Thus, the small sample might also be one of the reasons.

There are also several limitations in our study, which need to be addressed. First, high clinical heterogeneity existed in our analysis: 1) the primary disease of patients included in our enrolled studies was mixed, conservative oxygen therapy might have more benefit in hypoxic ischemic encephalopathy, but we could not do the subgroup analysis due to lack of data; 2) the severity of patients who admitted into ICU was also varies in included studies; 3) although all the studies divided participated into conservative and conventional groups, the actual oxygenation level in each group were varies in included studies. Second, because of the limit of FiO₂ titration, there were episodes when the oxygenation level of patients was out of the range of target oxygenation level, which might influence the application of our conclusions.

Conclusions
Compared with conventional oxygen therapy, conservative oxygen therapy has no effect on mortality, ICU LOS and hospital LOS in critically ill patients, but could reduce the length of MV hours and new organ failure.

Declarations

**Abbreviations List**

APACHE, The Acute Physiologic and Chronic Health Evaluation; CENTRAL, Cochrane Central Register of Controlled Trails; CI, confidence interval; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; ISI, Information Sciences Institute; LOS, length of stay; MD, mean difference; MV, mechanical ventilation; PaO₂, partial pressure of arterial oxygen; RCT, randomized controlled trial; OR, odds ratio; ROS, reactive oxygen species; SpO₂, pulse oxygen saturation; SAPS, Simplified Acute Physiologic Score; SD, standard derivation.

**Ethics approval and consent to participate**
Each enrolled trial was approved by the corresponding institutional ethical committee, and all participants provided written informed consent.

**Consent for publication**

Not applicable

**Availability of data and material**

Not applicable

**Competing interests**

None of all authors have any financial or non-financial competing interests in this manuscript.

**Guarantor**

B-ML takes responsibility for the content of the manuscript, including the data and analysis.

**Author contributions**

YNN and BML designed the study, drafted the manuscript, conducted literature search and data analysis; YNN and Y-MW revised the manuscript critically for important intellectual content; B-ML and Z-AL made the decision to submit the report for publication. All authors read and approved the final manuscript.

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Supplementary Files Legend

**Supplemental material**

Figure 1s Study flow.

Figure 2s Risk of bias graph

Figure 3s Risk of bias summary

Figure 4s ICU mortality

CI, confidence interval; SD, standard derivation

Figure 5s Hospital mortality

CI, confidence interval; SD, standard derivation

Figure 6s 28 day mortality

CI, confidence interval; SD, standard derivation

Figure 7s 90 day mortality

CI, confidence interval; SD, standard derivation
Figures

| Study or Subgroup | conservative | conventional | Risk Ratio |
|-------------------|--------------|--------------|------------|
| Events | Total | Events | Total | Weight | M-H. Fixed, 95% CI |
| Eastwood 2015 | 28 | 50 | 27 | 50 | 8.3% | 1.04 [0.75, 1.48] |
| Eastwood 2019 | 6 | 286 | 3 | 245 | 1.1% | 1.64 [0.42, 6.51] |
| Girardis 2016 | 52 | 216 | 74 | 218 | 24.2% | 0.71 [0.52, 0.98] |
| Mackie 2019 | 170 | 476 | 164 | 475 | 54.0% | 1.03 [0.87, 1.23] |
| Panwar 2015 | 21 | 52 | 19 | 51 | 8.3% | 1.08 [0.87, 1.36] |
| Suzuki 2014 | 9 | 54 | 16 | 51 | 5.4% | 0.53 [0.26, 1.09] |
| Total (95% CI) | 1146 | 1090 | 100.0% | 0.94 [0.82, 1.07] |

Heterogeneity: Chi² = 8.23, df = 5 (P = 0.14), P = 39%
Test for overall effect: Z = 0.98 (P = 0.34)

Figure 1

Overall Mortality. CI, confidence interval; SD, standard derivation

| Study or Subgroup | Conservative | Conventional | Mean Difference |
|-------------------|--------------|--------------|----------------|
| Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Eastwood 2015 | 4 | 3.7 | 50 | 5 | 3.7 | 50 | 8.4% | -1.00 [-2.45, 0.45] |
| Eastwood 2019 | 1.75 | 2 | 298 | 1.71 | 2 | 245 | 5.9% | 0.04 [-0.30, 0.38] |
| Girardis 2016 | 6 | 4.44 | 216 | 6 | 5.99 | 210 | 10.1% | 0.00 [-0.91, 0.91] |
| Mackie 2019 | 4.78 | 5.34 | 484 | 5.17 | 7.89 | 481 | 15.0% | -0.39 [-1.23, 0.47] |
| Panwar 2015 | 9 | 5.93 | 62 | 7 | 5.93 | 51 | 5.7% | 2.09 [-0.39, 4.29] |
| Total (95% CI) | 1100 | 1045 | 100.0% | -0.07 [-0.52, 0.38] |

Heterogeneity: Tau² = 0.08, Chi² = 5.55, df = 4 (P = 0.24), P = 28%
Test for overall effect: Z = 0.29 (P = 0.77)

Figure 2

ICU LOS CI, confidence interval; ICU, intensive care unit; LOS, length of stay; MD, mean difference; SD, standard derivation

| Study or Subgroup | Conservative | Conventional | Mean Difference |
|-------------------|--------------|--------------|----------------|
| Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| Eastwood 2015 | 9 | 10.37 | 50 | 9 | 14.81 | 50 | 2.3% | 0.00 [-15.01, 15.01] |
| Eastwood 2019 | 8 | 4.44 | 216 | 9 | 5.99 | 245 | 71.4% | -1.00 [-1.60, -0.40] |
| Girardis 2016 | 21 | 18.62 | 216 | 21 | 18.63 | 216 | 53% | 0.00 [-3.28, 3.28] |
| Mackie 2019 | 12.42 | 13.19 | 484 | 13.08 | 14.29 | 481 | 18.1% | -0.60 [-3.38, 1.17] |
| Panwar 2015 | 20 | 11.11 | 52 | 16 | 17.04 | 51 | 1.9% | 4.00 [1.57, 6.47] |
| Total (95% CI) | 1100 | 1045 | 100.0% | -0.77 [-1.52, 0.01] |

Heterogeneity: Chi² = 3.38, df = 4 (P = 0.49), P = 0%
Test for overall effect: Z = 1.93 (P = 0.05)

Figure 3

Hospital LOS CI, confidence interval; LOS, length of stay; MD, mean difference; SD, standard derivation
Figure 4

MV hours. CI, confidence interval; MD, mean difference; MV, mechanical ventilation; SD, standard derivation

| Study or Subgroup | Conservative Mean | SD | Total | Conventional Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|-------------------|-------------------|----|-------|-------------------|----|-------|--------|----------------------------------|
| Eastwood 2015     | 64                | 74.81 | 50    | 68                | 69.87 | 50    | 0.1%  | -6.08 [-32.76, 22.76] |
| Eastwood 2018     | 67                | 65.88 | 283   | 71                | 69.72 | 245   | 68.3% | -1.76 [-3.82, 0.30] |
| Mackie 2019       | 70.99             | 12.98 | 434   | 74.64             | 13.33 | 401   | 91.8% | -3.94 [-5.49, -2.39] |
| Total (95% CI)    | 776               | 100.0% | 832   | 2.38 [-3.31, 1.45] |

Heterogeneity: Chi² = 4.46, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 5.03 (P < 0.00001)

Figure 5

New organ failure during ICU stay. CI, confidence interval; ICU, intensive care unit; SD, standard derivation

| Study or Subgroup | conservative Events | conventional Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|---------------------|--------------|--------|-------------------------------|
| Grafatis 2016     | 41                  | 216                 | 257          | 71.7%  | 0.74 [0.52, 1.08] |
| Suzuka 2014       | 18                  | 51                  | 69           | 28.3%  | 0.73 [0.44, 1.12] |
| Total (95% CI)    | 267                 | 269                 | 536          | 100.0% | 0.74 [0.55, 0.99] |

Total events: 577
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0.0%
Test for overall effect: Z = 2.05 (P = 0.04)

Figure 6

New infection during ICU stay. CI, confidence interval; ICU, intensive care unit; SD, standard derivation

| Study or Subgroup | conservative Events | conventional Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|---------------------|--------------|--------|-------------------------------|
| Grafatis 2016     | 39                  | 216                 | 255          | 63.3%  | 0.79 [0.54, 1.14] |
| Suzuka 2014       | 31                  | 54                  | 85           | 36.7%  | 1.05 [0.75, 1.47] |
| Total (95% CI)    | 270                 | 269                 | 539          | 100.0% | 0.88 [0.68, 1.15] |

Total events: 579
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 0.94 (P = 0.35)

Supplementary Files

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supplemental material.docx