**Prone positioning during veno-venous extracorporeal membrane oxygenation: a systematic review and meta-analysis**

**Intensive Care Medicine**

Tommaso Pettenuzzo, Eleonora Balzani, Nicolò Sella, Marco Giani, Mara Bassi, Valentina Fincati, Rossella Cescon, Giorgia Pacchiarini, Giovanna Pandolfo, Roberta Ceccato, Lars Grønlykke, Dawid L. Staudacher, Nicolas Nesseler, Senta Jorinde Raasveld, Michele Carron, Elisa Pistollato, Giulia Mormando, Francesco Zarantonello, Alessandro De Cassai, Annalisa Boscolo, Emanuele Rezoagli, Giuseppe Foti, Paolo Navalesi

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**Online Resource**

**Online resource 1. Extensive study methodology**

## Combining randomized and non-randomized controlled trials

Combining randomized controlled trials (RCTs) and non-RCTs is controversial and requires careful consideration to ensure the credibility of results. As recommended by Cochrane, with respect to the inclusion of non-RCTs in systematic reviews [S1,S2], we scoped the available evidence on Pubmed and reasoned that: 1) the number of available RCTs addressing our participants, interventions, comparisons, and outcomes (PICO) question (i.e., association of prone positioning vs. no prone positioning with 28-day mortality in adult patients receiving veno-venous extracorporeal membrane oxygenation [ECMO] for acute hypoxemic respiratory failure [AHRF]) could have been insufficient, as we found no RCT assessing 28-day mortality; 2) most non-RCTs could have addressed the PICO question without critical risk of bias, as many employed a propensity score-based analysis to reduce the impact of confounding variables by matching individuals with similar likelihood of receiving the treatment in the two groups; 3) most non-RCTs could have addressed the PICO question directly with respect to the intervention, the comparator, the outcome, and the setting. After conducting the literature search and citation selection and applying the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool, we could confirm that no RCT reported on 28-day mortality and only 10% (2/20) of non-RCTs were considered at critical risk of bias. Therefore, we concluded that the inclusion of non-RCTs in our study was methodologically adequate.

## Data collection

Search results were merged and duplicate records of the same report were removed. The remaining studies were stored using Microsoft Excel software (Microsoft Corporation, Redmond, WA). Eight researchers (MB, RCes, RCec, GPan, VF, GPac, EP, GM) performed the citation selection based on titles, abstracts, and full texts and the subsequent data extraction in a blind independent fashion. Specifically, the eight researchers were split into four couples, each analyzing the same number of articles. Excluded full texts were listed and reasons for exclusions were detailed (Online Resource 4).

Data from included studies were extracted and recorded using a Microsoft Excel specific report form. Two researchers (TP, EB) independently verified all extracted data for accuracy. Any disagreement on both study selection and data extraction were resolved by referral to another author (NS), if necessary. The following information was collected: first author, year of the study, study design and setting, baseline patient characteristics in the prone positioning and no prone positioning groups, indications for prone positioning and details on the number and duration of proning sessions, and primary and secondary outcomes. For the ECMO duration, invasive mechanical ventilation duration, intensive care unit (ICU) length of stay, and hospital length of stay outcomes, we considered the absolute numbers of patients that, in the two groups, were successfully weaned from ECMO, were successfully weaned from invasive mechanical ventilation, survived in the ICU, and survived in the hospital, respectively, to pool data from individual studies. When data on any mortality outcome for the two groups were not detailed, we contacted the corresponding author of the original study with three subsequent e-mails, each one week apart from the previous one.

**Quality and certainty of evidence assessments**

Six researchers (EB, NS, ADC, MC, FZ, AB) were split into three couples and assessed the risk of bias of the same number of studies. Specifically, each member of the couple independently evaluated the quality of included RCTs and non-RCTs by using the risk of bias (RoB) 2 [S3] and the ROBINS-I assessment tools, respectively [S4]. Disagreements were resolved by discussion with another author (NS), if necessary.

The RoB2 examines five domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The study-level risk of bias is expressed on a three-grade scale, i.e., low, high or some concerns [S3]. The ROBINS-I considers seven domains of bias: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The study-level risk of bias is described on a four-grade scale, i.e., low, moderate, serious, and critical [S4].

The grades of recommendation, assessment, development and evaluation (GRADE) approach, addressing the domains of risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, plausible confounding, and dose-response gradient, was used to rate the certainty of evidence (CoE) related to the primary outcome and the following secondary outcomes: ICU, hospital, and 60-day mortality, ECMO duration, ECMO weaning, 28-day ventilator-free days, and hospital length of stay. To handle imprecision for qualitative outcomes, we verified whether the optimal information size (OIS) criterion was met for all conventional relative risk reductions (RRRs) of 20%, 25%, and 30%. For quantitative outcomes, we calculated the OIS with R version 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria) using the "pwr" packages with the varying standard deviations reported for control group by the studies assessing each outcome. Second, we assessed whether the 95% confidence interval (CI) excluded the null effect. If it did, we judged the precision as adequate. Otherwise, when the CI overlapped the null effect and failed to exclude important benefit or important harm, we downgraded the certainty of evidence for imprecision [S5].

**Data synthesis and analysis**

Meta-analyses were performed using a random-effects model to account for between-study heterogeneity [S6]. The treatment effect for dichotomous outcomes was analyzed with the Mantel-Haenszel method and expressed as odds ratio (OR) with 95% CI. The treatment effect for continuous outcomes was analyzed with the inverse variance method and expressed as mean difference (MD) or standardized mean difference (SMD) with 95% CI, as appropriate. When a non-randomized controlled trial (RCT) employed a propensity score matching analysis to balance confounding factors between the treatment groups, data from this analysis were used in the meta-analyses. Where necessary, we converted the reported median and interquartile range to estimated mean and standard deviation using a standard approach [S7]. When no events were observed in any of the groups in an individual study, a fixed value of 1 was added as a continuity correction to the cells corresponding to the number of events [S6]. When the number of studies for an outcome was ≥ 10 and no evidence for publication bias was found, the 95% prediction interval (PI) was reported alongside the 95% CI as an estimate of the dispersion of the true effect size across different study

conditions. A prediction interval represents the interval the mean effect of a new study will fall in when included [S6].

Statistical heterogeneity for the outcomes among studies was assessed using the $\chi^2$ test, the $I^2$ test, and $\tau^2$. We considered $I^2 \geq 75\%$ and $p < 0.100$ as considerable heterogeneity [S6]. Publication bias was assessed by visually inspecting a funnel plot for potential asymmetry and Egger's test was applied when the number of studies was ≥ 10 [S8]. The Doi plot, allowing better visual representation of asymmetry than the funnel plot, and the LFK index, demonstrating higher diagnostic accuracy than the Egger's regression result, were used as reference for publication bias detection, when the number of studies was ≥ 5 [S9].

Provided the number of studies reporting on the primary outcome was ≥ 10, meta-regression analyses were conducted to assess whether the strength of the association between the use prone positioning and lower 28-day mortality was significantly influenced by the following covariates [S6]: 1) qualitative variables used for subgroup analyses, i.e., pulmonary vs. extra-pulmonary AHRF, Coronavirus disease (Covid)-19 vs. non-Covid-19 AHRF, RCTs vs. non-RCTs, high- vs. low-volume ECMO centers [S10], number of proning cycles per patient > 1 vs. equal to 1; 2) quantitative variables potentially mediating the association between prone positioning and outcome, i.e., patients' age, gender, and body mass index, immunosuppression, the percent of patients with pneumonia as primary risk factor for acute respiratory distress syndrome, sequential organ failure assessment score, duration of invasive mechanical ventilation before ECMO cannulation, the percent of patients receiving prone ventilation before ECMO cannulation, arterial partial pressure of oxygen to fraction of inspired oxygen ratio before ECMO cannulation, and driving pressure and compliance of the respiratory system before ECMO cannulation [S11,S12]. We also investigated whether the duration of ECMO before prone positioning and the number and duration of proning cycles during ECMO mediated the association between prone positioning and 28-day mortality. The value of $R^2$, informing on the amount of the difference in true effect sizes that can be explained by each covariate, and the $I^2$ equivalent, corresponding to the residual variability attributable to the remaining between-study heterogeneity after inclusion of the covariate, were reported.

A trial sequential analysis was planned for 28-day and/or hospital mortality when at least two RCTs reported on mortality. We considered a type I error of 5%, a power of 90%, and a mortality proportion in the no prone positioning arm calculated as the event proportion in this group among the included studies [S13].

The two-sided α-spending boundaries and futility area were computed with the O'Brien-Fleming function. The OR reduction percentage was calculated based on a 10%-relative decrease in mortality (arbitrarily set as a clinically significant threshold) and the required information size was calculated accordingly [S13].

All analyses were performed with R version 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria) with the "meta", "metafor", and "metasens" packages and the Trial Sequential Analysis software version 0.9.5.10 Beta (The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen). For all analyses, two-sided p-values $< 0.05$ were considered significant.

**Online Resource 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [S14]**

| Topic | No. | Item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| **Title** | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT** | | | |
| **Abstract** | 2 | See the PRISMA 2020 for Abstracts checklist | Pages 2, 3 |
| **INTRODUCTION** | | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of existing knowledge. | Pages 5, 6 |
| **Objectives** | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 6 |
| **METHODS** | | | |
| **Eligibility criteria** | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 6,7 |
| **Information sources** | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 7 |
| **Search strategy** | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Online resource 3 |

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|---|---|---|---|
| **Selection process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Pages 7, 8<br>Online Resource 1 |
| **Data collection process** | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 8<br>Online Resource 1 |
| **Data items** | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 6, 7 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 7<br>Online resource 1 |
| **Study risk of bias assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8<br>Online resource 1 |
| **Effect measures** | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Online resource 1 |

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|---|---|---|---|
| **Synthesis methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)). | Pages 6-8<br>Online resource 1 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Online resource 1 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 9<br>Online resource 1 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Pages 9<br>Online resource 1 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Page 9<br>Online resource 1 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 9 |
| **Reporting bias assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 8, 9<br>Online resource 1 |
| **Certainty assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 8 |
| **RESULTS** | | | |

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|---|---|---|---|
| **Study selection** | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Pages 10, 11 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Online resource 4 |
| **Study characteristics** | 17 | Cite each included study and present its characteristics. | Online resource 5 |
| **Risk of bias in studies** | 18 | Present assessments of risk of bias for each included study. | Pages 12<br>Online resource 6 |
| **Results of individual studies** | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Pages 13-15<br>Online resource 8 |
| **Results of syntheses** | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Table 1 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Pages 13-15<br>Online resource 8 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Page 14<br>Online resources 10, 11 |

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|---|---|---|---|
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Page 13<br>Online resource 9 |
| **Reporting biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Page 12, Online resource 7 |
| **Certainty of evidence** | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Pages 13-15<br>Table 1 |
| **DISCUSSION** | | | |
| **Discussion** | 23a | Provide a general interpretation of the results in the context of other evidence. | Pages 15, 16 |
| | 23b | Discuss any limitations of the evidence included in the review. | Page 16, 17 |
| | 23c | Discuss any limitations of the review processes used. | Page 17, 18 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Pages 15-18 |
| **OTHER INFORMATION** | | | |
| **Registration and protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 6 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 6 |

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|---|---|---|---|
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Not applicable |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 4 |
| **Competing interests** | 26 | Declare any competing interests of review authors. | Page 3 |
| **Availability of data, code and other materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 4 |

**PRISMA Abstract Checklist**

| Topic | No. | Item | Reported? |
|---|---|---|---|
| **TITLE** | | | |
| **Title** | 1 | Identify the report as a systematic review. | Yes |
| **BACKGROUND** | | | |
| **Objectives** | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes |
| **METHODS** | | | |
| **Eligibility criteria** | 3 | Specify the inclusion and exclusion criteria for the review. | Yes |
| **Information sources** | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Yes |

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|---|---|---|---|
| **Risk of bias** | 5 | Specify the methods used to assess risk of bias in the included studies. | Yes |
| **Synthesis of results** | 6 | Specify the methods used to present and synthesize results. | Yes |
| **RESULTS** | | | |
| **Included studies** | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Yes |
| **Synthesis of results** | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Yes |
| **DISCUSSION** | | | |
| **Limitations of evidence** | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Yes |
| **Interpretation** | 10 | Provide a general interpretation of the results and important implications. | Yes |
| **OTHER** | | | |
| **Funding** | 11 | Specify the primary source of funding for the review. | Not applicable |
| **Registration** | 12 | Provide the register name and registration number. | Yes |

**Online Resource 3. Electronic search strategies**

**Ovid MEDLINE(R)** and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to September 19, 2024

Total citations: 534

| | | |
|---|---|---|
| 1 | exp Extracorporeal Membrane Oxygenation/ | 16629 |
| 2 | veno-venous extracorporeal membrane oxygenation.mp. | 926 |
| 3 | vv-ECMO.mp. | 1293 |
| 4 | veno-venous-ECMO.mp. | 436 |
| 5 | ECLS.mp. | 1991 |
| 6 | extracorporeal life support.mp. | 3353 |
| 7 | Extracorporeal Circulation/ | 13275 |
| 8 | Oxygenators, Membrane/ | 1833 |
| 9 | Oxygenators, Membrane.mp. | 1836 |
| 10 | Extracorporeal Circulation.mp. | 17364 |
| 11 | ECMO.mp. | 14667 |
| 12 | extra-corporeal life support.mp. | 87 |
| 13 | ecmo.mp. | 14667 |
| 14 | ecco2r.mp. | 249 |
| 15 | extra-corporeal CO2 removal.mp. | 7 |
| 16 | Heart-Lung Machine.mp. | 2593 |
| 17 | Heart-Lung Machine/ | 2117 |
| 18 | AV-ECMO.mp. | 22 |
| 19 | avECMO.mp. | 1 |
| 20 | VA-ECMO.mp. | 2129 |
| 21 | vaECMO.mp. | 36 |
| 22 | vvECMO.mp. | 76 |
| 23 | vav-ECMO.mp. | 23 |
| 24 | vva-ECMO.mp. | 7 |
| 25 | vvaECMO.mp. | 1 |
| 26 | ecpr.mp. | 947 |
| 27 | ECPR.mp. | 947 |
| 28 | E-CPR.mp. | 117 |
| 29 | cardiac lung machine.mp. | 0 |

| | | |
|---|---|---|
| 30 | cardiac pulmonary machine.mp. | 0 |
| 31 | CardioHelp.mp. | 32 |
| 32 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 | 43134 |
| 33 | Pronation.mp. | 5956 |
| 34 | Pronation/ | 1781 |
| 35 | prone position.mp. | 9566 |
| 36 | prone positioning.mp. | 2404 |
| 37 | proning.mp. | 332 |
| 38 | prone patient.mp. | 169 |
| 39 | prone patients.mp. | 451 |
| 40 | Patient Positioning/ | 8138 |
| 41 | face down.mp. | 548 |
| 42 | resupine.mp. | 2 |
| 43 | decubitus.mp. | 6318 |
| 44 | alternative decubitus.mp. | 0 |
| 45 | patient positioning.mp. | 11094 |
| 46 | patients positioning.mp. | 121 |
| 47 | posture.mp. | 90035 |
| 48 | Posture/ | 68502 |
| 49 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 | 119452 |
| 50 | 32 and 49 | 534 |

**Embase** 1974 to 2024 September 20

Total citations: 1771

| | | |
|---|---|---|
| 1 | exp Extracorporeal Membrane Oxygenation/ | 49337 |
| 2 | veno-venous extracorporeal membrane oxygenation.mp. | 1561 |
| 3 | vv-ECMO.mp. | 3165 |
| 4 | veno-venous-ECMO.mp. | 4589 |
| 5 | ECLS.mp. | 3466 |

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| 6 | extracorporeal life support.mp. | 5300 |
| 7 | Extracorporeal Circulation/ | 19621 |
| 8 | Oxygenators, Membrane/ | 1146 |
| 9 | Oxygenators, Membrane.mp. | 12 |
| 10 | Extracorporeal Circulation.mp. | 22835 |
| 11 | ECMO.mp. | 33129 |
| 12 | extra-corporeal life support.mp. | 247 |
| 13 | ecmo.mp. | 33129 |
| 14 | ecco2r.mp. | 433 |
| 15 | extra-corporeal CO2 removal.mp. | 17 |
| 16 | Heart-Lung Machine.mp. | 2094 |
| 17 | Heart-Lung Machine/ | 1476 |
| 18 | AV-ECMO.mp. | 61 |
| 19 | avECMO.mp. | 3 |
| 20 | VA-ECMO.mp. | 5251 |
| 21 | vaECMO.mp. | 318 |
| 22 | vvECMO.mp. | 288 |
| 23 | vav-ECMO.mp. | 70 |
| 24 | vva-ECMO.mp. | 20 |
| 25 | vvaECMO.mp. | 3 |
| 26 | ecpr.mp. | 1825 |
| 27 | ECPR.mp. | 1825 |
| 28 | E-CPR.mp. | 283 |
| 29 | cardiac lung machine.mp. | 0 |
| 30 | cardiac pulmonary machine.mp. | 0 |
| 31 | CardioHelp.mp. | 493 |
| 32 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 | 82428 |
| 33 | Pronation.mp. | 7176 |
| 34 | Pronation/ | 2497 |
| 35 | prone position.mp. | 15377 |
| 36 | prone positioning.mp. | 3595 |
| 37 | proning.mp. | 796 |
| 38 | prone patient.mp. | 227 |

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| 39 | prone patients.mp. | 616 |
| 40 | Patient Positioning/ | 24649 |
| 41 | face down.mp. | 703 |
| 42 | resupine.mp. | 3 |
| 43 | decubitus.mp. | 32024 |
| 44 | alternative decubitus.mp. | 0 |
| 45 | patient positioning.mp. | 26614 |
| 46 | patients positioning.mp. | 250 |
| 47 | posture.mp. | 85629 |
| 48 | Posture/ | 28208 |
| 49 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 | 173439 |
| 50 | 32 and 49 | 1771 |

**Pubmed**

Total citations: 1177

("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR ("veno"[All Fields] AND "venous"[All Fields] AND "extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "veno venous extracorporeal membrane oxygenation"[All Fields]) OR ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR ("vv"[All Fields] AND "ecmo"[All Fields]) OR "vv ecmo"[All Fields]) OR "veno-venous-ECMO"[All Fields] OR "ECLS"[All Fields] OR ("extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] OR ("extracorporeal"[All Fields] AND "life"[All Fields] AND "support"[All Fields]) OR "extracorporeal life support"[All Fields]) OR ("extracorporeal circulation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "circulation"[All Fields]) OR "extracorporeal circulation"[All Fields]) OR ("oxygenators, membrane"[MeSH Terms] OR ("oxygenators"[All Fields] AND "membrane"[All Fields]) OR "membrane oxygenators"[All Fields] OR "oxygenators membrane"[All Fields]) OR ("extracorporeal circulation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "circulation"[All Fields]) OR "extracorporeal circulation"[All

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position"[All Fields] OR "prone"[All Fields]) AND ("patient positioning"[MeSH Terms] OR ("patient"[All Fields] AND "positioning"[All Fields]) OR "patient positioning"[All Fields] OR "positioning"[All Fields] OR "position"[All Fields] OR "position s"[All Fields] OR "positional"[All Fields] OR "positioned"[All Fields] OR "positionings"[All Fields] OR "positions"[All Fields])) OR "proning"[All Fields] OR (("prone position"[MeSH Terms] OR ("prone"[All Fields] AND "position"[All Fields]) OR "prone position"[All Fields] OR "prone"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR (("prone position"[MeSH Terms] OR ("prone"[All Fields] AND "position"[All Fields]) OR "prone position"[All Fields] OR "prone"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("patient positioning"[MeSH Terms] OR ("patient"[All Fields] AND "positioning"[All Fields]) OR "patient positioning"[All Fields]) OR (("face"[MeSH Terms] OR "face"[All Fields]) AND "down"[All Fields]) OR "resupine"[All Fields] OR ("pressure ulcer"[MeSH Terms] OR ("pressure"[All Fields] AND "ulcer"[All Fields]) OR "pressure ulcer"[All Fields] OR "decubitus"[All Fields]) OR (("alternance"[All Fields] OR "alternances"[All Fields] OR "alternant"[All Fields] OR "alternants"[All Fields] OR "alternate"[All Fields] OR "alternated"[All Fields] OR "alternately"[All Fields] OR "alternates"[All Fields] OR "alternating"[All Fields] OR "alternation"[All Fields] OR "alternations"[All Fields] OR "alternative"[All Fields] OR "alternatively"[All Fields] OR "alternatives"[All Fields]) AND ("pressure ulcer"[MeSH Terms] OR ("pressure"[All Fields] AND "ulcer"[All Fields]) OR "pressure ulcer"[All Fields] OR "decubitus"[All Fields])) OR ("patient positioning"[MeSH Terms] OR ("patient"[All Fields] AND "positioning"[All Fields]) OR "patient positioning"[All Fields]) OR ("patient positioning"[MeSH Terms] OR ("patient"[All Fields] AND "positioning"[All Fields]) OR "patient positioning"[All Fields] OR ("patients"[All Fields] AND "positioning"[All Fields]) OR "patients positioning"[All Fields]) OR ("postural"[All Fields] OR "posturally"[All Fields] OR "posture"[MeSH Terms] OR "posture"[All Fields] OR "postures"[All Fields] OR "postured"[All Fields] OR "posturing"[All Fields]))

**Scopus**

Total citations: 1350

((Extracorporeal Membrane Oxygenation) OR (veno-venous extracorporeal membrane oxygenation) OR (vv-ECMO) OR (veno-venous-ECMO) OR (ECLS) OR (extracorporeal life support) OR (Extracorporeal Circulation) OR (Oxygenators, Membrane) OR (Extracorporeal Circulation) OR (ECMO) OR (extra-corporeal life support) OR (ecmo) OR (ecco2r) OR (extra-corporeal CO2 removal) OR (Heart-Lung Machine) OR (Heart-Lung Machine) OR (AV-ECMO) OR (avECMO) OR (VA-ECMO) OR (vaECMO) OR (vvECMO) OR (v-v ECMO) OR (v-vECMO) OR (vav-ECMO) OR

(vva-ECMO) OR (vvaECMO) OR (ecpr) OR (ECPR) OR (E-CPR) OR (cardiac lung machine) OR (cardiac pulmonary machine) OR (CardioHelp)) AND ((Pronation) OR (prone position) OR (prone positioning) OR (proning) OR (prone patient) OR (prone patients) OR (Patient Positioning) OR (face down) OR (resupine) OR (decubitus) OR (alternative decubitus) OR (patient positioning) OR (patients positioning) OR (posture))

**Web of Science**

Total citations: 1033

((Extracorporeal Membrane Oxygenation) OR (veno-venous extracorporeal membrane oxygenation) OR (vv-ECMO) OR (veno-venous-ECMO) OR (ECLS) OR (extracorporeal life support) OR (Extracorporeal Circulation) OR (Oxygenators, Membrane) OR (Extracorporeal Circulation) OR (ECMO) OR (extra-corporeal life support) OR (ecmo) OR (ecco2r) OR (extra-corporeal CO2 removal) OR (Heart-Lung Machine) OR (Heart-Lung Machine) OR (AV-ECMO) OR (avECMO) OR (VA-ECMO) OR (vaECMO) OR (vvECMO) OR (v-v ECMO) OR (v-vECMO) OR (vav-ECMO) OR (vva-ECMO) OR (vvaECMO) OR (ecpr) OR (ECPR) OR (E-CPR) OR (cardiac lung machine) OR (cardiac pulmonary machine) OR (CardioHelp)) AND ((Pronation) OR (prone position) OR (prone positioning) OR (proning) OR (prone patient) OR (prone patients) OR (Patient Positioning) OR (face down) OR (resupine) OR (decubitus) OR (alternative decubitus) OR (patient positioning) OR (patients positioning) OR (posture))

**CENTRAL**

Total citations: 649

((Extracorporeal Membrane Oxygenation) OR (veno-venous extracorporeal membrane oxygenation) OR (vv-ECMO) OR (veno-venous-ECMO) OR (ECLS) OR (extracorporeal life support) OR (Extracorporeal Circulation) OR (Oxygenators, Membrane) OR (Extracorporeal Circulation) OR (ECMO) OR (extra-corporeal life support) OR (ecmo) OR (ecco2r) OR (extra-corporeal CO2 removal) OR (Heart-Lung Machine) OR (Heart-Lung Machine) OR (AV-ECMO) OR (avECMO) OR (VA-ECMO) OR (vaECMO) OR (vvECMO) OR (v-v ECMO) OR (v-vECMO) OR (vav-ECMO) OR (vva-ECMO) OR (vvaECMO) OR (ecpr) OR (ECPR) OR (E-CPR) OR (cardiac lung machine) OR (cardiac pulmonary machine) OR (CardioHelp)) AND ((Pronation) OR (prone position) OR (prone positioning) OR (proning) OR (prone patient) OR (prone patients) OR (Patient Positioning) OR (face down) OR (resupine) OR (decubitus) OR (alternative decubitus) OR (patient positioning) OR (patients positioning) OR (posture))

**Grey literature**

Scholar
Total citations: 60

Medrxv
Total citations: 25

((Extracorporeal Membrane Oxygenation) OR (veno-venous extracorporeal membrane oxygenation) OR (vv-ECMO) OR (veno-venous-ECMO) OR (ECLS) OR (extracorporeal life support) OR (Extracorporeal Circulation) OR (Oxygenators, Membrane) OR (Extracorporeal Circulation) OR (ECMO) OR (extra-corporeal life support) OR (ecmo) OR (ecco2r) OR (extra-corporeal CO2 removal) OR (Heart-Lung Machine) OR (Heart-Lung Machine) OR (AV-ECMO) OR (avECMO) OR (VA-ECMO) OR (vaECMO) OR (vvECMO) OR (v-v ECMO) OR (v-vECMO) OR (vav-ECMO) OR (vva-ECMO) OR (vvaECMO) OR (ecpr) OR (ECPR) OR (E-CPR) OR (cardiac lung machine) OR (cardiac pulmonary machine) OR (CardioHelp)) AND ((Pronation) OR (prone position) OR (prone positioning) OR (proning) OR (prone patient) OR (prone patients) OR (Patient Positioning) OR (face down) OR (resupine) OR (decubitus) OR (alternative decubitus) OR (patient positioning) OR (patients positioning) OR (posture)) AND (clinical trial)

**Online Resource 4. Excluded full texts with reasons for exclusion**

Total 113 citations

**Duplicate publication:** 1 citation

1. Lyu G, Cai T, Jiang W, Liu M, Wang X. [Comparison of efficacy between veno-venous extracorporeal membrane oxygenation (VV-ECMO) and VV-ECMO combined with prone position ventilation for the treatment of acute respiratory distress syndrome]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2021 Mar;33(3):293-298. Chinese. doi: 10.3760/cma.j.cn121430-20200805-00563.

**Other study designs:** 16 citations

1. Goettler, C.E., Pryor, J.P., Hoey, B.A. et al. Prone positioning does not affect cannula function during extracorporeal membrane oxygenation or continuous renal replacement therapy. Crit Care **6**, 452 (2002). https://doi.org/10.1186/cc1814
2. Veld-Van Wingerden A, Maas J, Harinck HIJ, Mauritz R. Long-term extracorporeal membrane oxygenation in acute respiratory distress syndrome. Neth J Crit Care 2015;19(1).
3. Murphy C, Mc Mahon A, Parvanov P, Nguyen M, Pecak M, Mulvihill J, Dwyer R, Curley G. Worsened outcome of COVID-19 patients in Intensive Care during the pandemic second surge in cases versus the first ESICM LIVES 2021: Part 1. ICMx **9** (Suppl 1), 51 (2021). https://doi.org/10.1186/s40635-021-00413-8
4. Ong SL, Tantawy H, Assi R, Chichra A, Treggiari MM. Combined Use of ECMO, Prone Positioning, and APRV in the Management of Severe COVID-19 Patients. Clin Med Insights Circ Respir Pulm Med. 2022 Nov 17;16:11795484221134451. doi: 10.1177/11795484221134451. PMID: 36419562; PMCID: PMC9677293.
5. Saha S, Jebran AF, Leistner M, Kutschka I, Niehaus H. Turning Things Around: The Role of Prone Positioning in the Management of Acute Respiratory Failure After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2020 Jun;34(6):1434-1438. doi: 10.1053/j.jvca.2019.10.055. Epub 2019 Nov 9. PMID: 31812562.
6. van Minnen O, Jolink FEJ, van den Bergh WM, Droogh JM, Oude Lansink-Hartgring A; Dutch ECLS Study Group. International Survey on Mechanical Ventilation During Extracorporeal Membrane Oxygenation. ASAIO J. 2024 Apr 1;70(4):300-304. doi: 10.1097/MAT.0000000000002101. Epub 2023 Dec 5. PMID: 38051596; PMCID: PMC10977054.
7. Rossaint R, Lewandowski K, Pappert D, Slama K, Falke K. Die Therapie des ARDS. Teil 1: Aktuelle Behandlungsstrategien einschliesslich des extrakorporalen Gasaustauschs [Therapy of ARDS. 1. Current therapeutic strategy including extracorporeal gas exchange]. Anaesthesist. 1994 May;43(5):298-308. German. doi: 10.1007/s001010050061. PMID: 8042758.

8. Schindler M. Pflege bei Extracorporaler Membranoxigenierung (ECMO) [Care in extracorporeal membrane oxygenation]. Kinderkrankenschwester. 1995 Mar;14(3):120-2. German. PMID: 7703165.
9. Sud S, Friedrich JO, Adhikari NKJ, Fan E, Ferguson ND, Guyatt G, Meade MO. Comparative Effectiveness of Protective Ventilation Strategies for Moderate and Severe Acute Respiratory Distress Syndrome. A Network Meta-Analysis. Am J Respir Crit Care Med. 2021 Jun 1;203(11):1366-1377. doi: 10.1164/rccm.202008-3039OC. PMID: 33406009.
10. Tey SF, Cheng KC. Coronavirus disease 2019 (COVID-19): Medication treatment and management in critical illness. Journal of Internal Medicine of Taiwan 2020. doi: 10.6314/JIMT.202008_31(4).03
11. Valera, S. (2017). Mobilizing the ECMO Patients: Prone Positioning During Venovenous Extracorporeal Membrane Oxygenation (vvECMO). In: Mossadegh, C., Combes, A. (eds) Nursing Care and ECMO. Springer, Cham. https://doi.org/10.1007/978-3-319-20101-6_7
12. Wang Y, Meng Y, Ma L, Li P. [Advances in the diagnosis and treatment of acute respiratory distress syndrome induced by pancreatitis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2021 Sep;33(9):1149-1152. Chinese. doi: 10.3760/cma.j.cn121430-20210201-00188. PMID: 34839881.
13. Wei Zhang W, Pan C, Qing S. We should pay close attention to some issues in the process of lung injury therapy of critical severe COVID-19. Medical Journal of Chinese People's Liberation Army 2020;45(3):236-2020
14. Yadam S, Bihler E, Balaan M. Acute Respiratory Distress Syndrome. Crit Care Nurs Q. 2016 Apr-Jun;39(2):190-5. doi: 10.1097/CNQ.0000000000000111. PMID: 26919679.
15. Zhang, H., Liu, Z., Shu, H. et al. Prone positioning in ARDS patients supported with VV ECMO, what we should explore?. J Intensive Care **10**, 46 (2022). https://doi.org/10.1186/s40560-022-00640-5
16. Zhang Z, Gu WJ, Chen K, Ni H. Mechanical Ventilation during Extracorporeal Membrane Oxygenation in Patients with Acute Severe Respiratory Failure. Can Respir J. 2017;2017:1783857. doi: 10.1155/2017/1783857. Epub 2017 Jan 3. PMID: 28127231; PMCID: PMC5239989.

**Same data as another included publication:** 26 citations

1. Genty T, Cherel Q, Thes J, Roman C, Imbert A, Stephan F. Prone Positioning Under ECMO: A Retrospective Cohort of 34 Patients. J Heart Lung Transplant. 2022;41(4):S433. doi: 10.1016/j.healun.2022.01.1093
2. Binda F, Galazzi A, Marelli F, Bruno M, Vinci E, Mauri T, Adamini I, Laquintana D. Pressure ulcers following prone positioning in ARDS patients undergoing ECMO treatment. ESICM LIVES 2019. Intensive Care Med Exp. 2019 Sep 27;7(Suppl 3):55. doi: 10.1186/s40635-019-0265-y. Erratum in:

Intensive Care Med Exp. 2020 Jan 21;8(1):4. doi: 10.1186/s40635-019-0289-3. PMID: 31559498; PMCID: PMC6763544.

3. Binda F, Marelli F, Galazzi A, Gambazza S, Adamini I, Grasselli G, Laquintana D. Pressure ulcers onset in patients with ARDS undergoing ECMO: 5 years preliminary analysis. ESICM LIVES 2022: part 2. Intensive Care Med Exp. 2022 Oct 19;10(Suppl 2):40. doi: 10.1186/s40635-022-00469-0. PMID: 36258052; PMCID: PMC9579253.
4. Binda F, Marelli F, Galazzi A, Gambazza S, Vinci E, Roselli P, Adamini I, Laquintana D. Pressure ulcers after prone positioning in patients undergoing extracorporeal membrane oxygenation: A cross-sectional study. Nurs Crit Care. 2024 Jan;29(1):65-72. doi: 10.1111/nicc.12889. Epub 2023 Feb 5. PMID: 36740588.
5. Chommeloux J, Valentin S, Winiszewski H, Adda M, Pineton de Chambrun M, Moyon Q, Mathian A, Capellier G, Guervilly C, Levy B, Jaquet P, Sonneville R, Voiriot G, Demoule A, Boussouar S, Painvin B, Lebreton G, Combes A, Schmidt M. One-Year Mental and Physical Health Assessment in Survivors after Extracorporeal Membrane Oxygenation for COVID-19-related Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2023 Jan 15;207(2):150-159. doi: 10.1164/rccm.202206-1145OC. PMID: 36150112; PMCID: PMC9893333.
6. Giani M, Fossi F, Grasselli G, Garofalo E, Martucci G, Belliato M, Fanelli V, Simonetti U, Peroni N, Lucchini A, Navalesi P, Arcadipane A, Iotti GA, Pesenti A, Foti G. Prone positioning during veno-venous ECMO support for severe ARDS: A multicenter retrospective trial. ESICM LIVES 2019: Berlin, Germany. 28 September - 2 October 2019. Intensive Care Med Exp. 2019 Sep 27;7(Suppl 3):55. doi: 10.1186/s40635-019-0265-y. Erratum in: Intensive Care Med Exp. 2020 Jan 21;8(1):4. doi: 10.1186/s40635-019-0289-3. PMID: 31559498; PMCID: PMC6763544.
7. Giani M, Rezoagli E, Guervilly C, Rilinger J, Duburcq T, Petit M, Textoris L, Garcia B, Wengenmayer T, Bellani G, Grasselli G, Pesenti A, Combes A, Foti G, Schmidt M; European Prone positioning During Extracorporeal Membrane Oxygenation (EuroPronECMO) Investigators. Timing of Prone Positioning During Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. Crit Care Med. 2023 Jan 1;51(1):25-35. doi: 10.1097/CCM.0000000000005705. Epub 2022 Nov 9. PMID: 36519981.
8. Lang CN, Zotzmann V, Schmid B, Berchtold-Herz M, Utzolino S, Biever P, Duerschmied D, Bode C, Wengenmayer T, Staudacher DL. Intensive Care Resources and 60-Day Survival of Critically-Ill COVID-19 Patients. Cureus. 2021 Feb 7;13(2):e13210. doi: 10.7759/cureus.13210. PMID: 33728167; PMCID: PMC7946605.
9. Le Breton C, Besset S, Freita-Ramos S, Amouretti M, Billiet PA, Dao M, Dumont LM, Federici L, Gaborieau B, Longrois D, Postel-Vinay P, Vuillard C, Zucman N, Lebreton G, Combes A, Dreyfuss D, Ricard JD, Roux D. Extracorporeal membrane oxygenation for refractory COVID-19 acute respiratory distress syndrome. J Crit Care. 2020 Dec;60:10-12. doi: 10.1016/j.jcrc.2020.07.013. Epub 2020 Jul 16. PMID: 32731100; PMCID: PMC7365051.

10. Natanov R, Wiesner O, Haverich A, Kühn C. Mechanical circulatory support in coronavirus disease-2019-positive patients with severe respiratory failure. Interact Cardiovasc Thorac Surg. 2021 Aug 18;33(3):489-493. doi: 10.1093/icvts/ivab087. PMID: 33822952; PMCID: PMC8083392.
11. Noe C, Rottmann FA, Bemtgen X, Supady A, Wengenmayer T, Staudacher DL. Dual lumen cannulation and mobilization of patients with venovenous extracorporeal membrane oxygenation. Artif Organs. 2023 Oct;47(10):1654-1662. doi: 10.1111/aor.14604. Epub 2023 Jul 7. PMID: 37358935.
12. Guervilly C, Prud'homme E, Hraiech S, Pauly V, Bourenne J, Adda M, Rambaud R, Coiffard B. Daviet F, Roch A, Forel JM, Papazian L. Combination of prone position during veno venous extracorporeal membrane oxygenation: Effects on extra corporeal membrane oxygenation weaning and ICU survival. ESICM LIVES 2018. Intensive Care Med Exp. 2018 Oct 19;6(Suppl 2):40. doi: 10.1186/s40635-018-0201-6. PMID: 30341496; PMCID: PMC6195497.
13. Guervilly C, Xéridat F, Hraiech S, Adda M, Forel JM, Roch A, Papazian L. Safety and efficacy of prone positioning during venovenous extra corporeal membrane oxygenation in severe acute respiratory distress syndrome. Abstracts of the ESICM 26th Annual Congress, Intensive Care Med. 2013 Oct;39 Suppl 2:201-539. doi: 10.1007/s00134-013-3095-5. PMID: 24096313.
14. Jozwiak M, Chiche JD, Charpentier J, Ait Hamou Z, Jaubert P, Benghanem S, Dupland P, Gavaud A, Péne F, Cariou A, Mira JP, Nguyen LS. Use of Venovenous Extracorporeal Membrane Oxygenation in Critically-Ill Patients With COVID-19. Front Med (Lausanne). 2020 Dec 10;7:614569. doi: 10.3389/fmed.2020.614569. PMID: 33363190; PMCID: PMC7758460.
15. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, Lansac E, Sage E, Cholley B, Mégarbane B, Cronier P, Zarka J, Da Silva D, Besset S, Morichau-Beauchant T, Lacombat I, Mongardon N, Richard C, Duranteau J, Cerf C, Saiydoun G, Sonneville R, Chiche JD, Nataf P, Longrois D, Combes A, Leprince P; Paris ECMO-COVID-19 investigators. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. Lancet Respir Med. 2021 Aug;9(8):851-862. doi: 10.1016/S2213-2600(21)00096-5. Epub 2021 Apr 19. Erratum in: Lancet Respir Med. 2021 Jun;9(6):e55. doi: 10.1016/S2213-2600(21)00209-5. Erratum in: Lancet Respir Med. 2021 Jul;9(7):e62. doi: 10.1016/S2213-2600(21)00280-0. PMID: 33887246; PMCID: PMC8055207.
16. Nesseler N, Guervilly C, Mansour A, Porto A, Flécher E, Esvan M, Fougerou-Leurent C, Ross J, Vincentelli A, Massart N. Prone Position Is Beneficial in COVID-19 Patients on Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure. doi: 10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A3537
17. Park PK, SAGE Investigators. Variation in US Management Practices in Moderate-to-Severe ARDS: The Severe ARDS: Generating Evidence (SAGE) Study. American Journal of Respiratory and Critical Care Medicine 2018;197:A7376

18. Prud'Homme E, Guervilly C, Pauly V, Daviet F, Bourenne J, Coiffard B, Forel JM, Hraiech S, Adda M, Roch A, Persico N, Papazian L. Improved mortality associated with prone positioning during ECMO for ARDS: A retrospective study in 169 patients. Proceedings of Réanimation 2019, the French Intensive Care Society International Congress. Ann Intensive Care. 2019 Mar;9(Suppl 1):1-153. doi: 10.1186/s13613-018-0474-7. PMID: 30924032; PMCID: PMC6439134.
19. Qadir N, SAGE Investigators. Management of US patients with ards requiring ECMO: Results of the severe ards generating evidence (SAGE) study. Am J Respir Crit Care Med 2018;197:A5116
20. Qadir N, SAGE Investigators. Use of adjunctive therapy in ARDS: Results from the severe ARDS generating evidence (SAGE) study. Am J Respir Crit Care Med 2018;197:A5071
21. Raasveld SJ et al. Outcomes in patients with COVID-19 induced acute respiratory distress syndrome receiving venovenous extracorporeal membrane oxygenation: An inverse probability weighted analysis. Supplement for the 10th EuroELSO Congress 4-6 May 2022 London/UK. Perfusion. 2022 May;37(1_suppl):3-111. doi: 10.1177/02676591221089240. PMID: 35506394.
22. Rilinger J, Zotzmann V, Bemtgen X, Biever PM, Duerschmied D, Bode C, Staudacher DL, Wengenmayer T. Prone positioning while extracorporeal membrane oxygenation therapy in severe ARDS. Critical Care 2020, 24(Suppl 1):87. doi: 10.1186/s13054-020-2772-3
23. Rottmann FA, Noe C, Bemtgen X, Maier S, Supady A, Wengenmayer T, Staudacher DL. Survival outcomes and mobilization during venovenous extracorporeal membrane oxygenation: a retrospective cohort study. Front Med. 2023; 10:1271540. doi: 10.3389/fmed.2023.1271540
24. Schmidt M, Pham T, Arcadipane A, Agerstrand C, Ohshimo S, Pellegrino V, Vuylsteke A, Guervilly C, McGuinness S, Pierard S, Breeding J, Stewart C, Ching SSW, Camuso JM, Stephens RS, King B, Herr D, Schultz MJ, Neuville M, Zogheib E, Mira JP, Rozé H, Pierrot M, Tobin A, Hodgson C, Chevret S, Brodie D, Combes A. Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. An International Multicenter Prospective Cohort. Am J Respir Crit Care Med. 2019 Oct 15;200(8):1002-1012. doi: 10.1164/rccm.201806-1094OC. PMID: 31144997.
25. Zaaqoq A, Barnett A, Griffee M, MacLaren G, Jacobs J, Heinsar S, Suen J, Bassi G, Fraser J, Dalton H, Peek G. Prone position during veno-venous extracorporeal membrane oxygenation for COVID-19. EuroELSO 2021 Poster Abstracts Volume 36, Issue 1_suppl. doi: 10.1177/02676591211007763.
26. Zaaqoq A, Barnett AG, Griffee M, Maclaren G, Jacobs J, Heinsar S, Suen JY, Li Bassi G, Fraser J, Dalton HJ, Peek G. Beneficial effect of prone positioning during venovenous extracorporeal membrane oxygenation for COVID-19. ESICM LIVES 2021: Part 1. doi: 10.1186/s40635-021-00413-8.

**Studies not including patients supported with extracorporeal membrane oxygenation (ECMO):** 14 citations

1. Alser O, Mokhtari A, Naar L, Langeveld K, Breen KA, El Moheb M, Kapoen C, Gaitanidis A, Christensen MA, Maurer LR, Mashbari H, Bankhead-Kendall B, Parks J, Fawley J, Saillant N, Mendoza A, Paranjape C, Fagenholz P, King D, Lee J, Farhat MR, Velmahos GC, Kaafarani HMA. Multisystem outcomes and predictors of mortality in critically ill patients with COVID-19: Demographics and disease acuity matter more than comorbidities or treatment modalities. J Trauma Acute Care Surg. 2021 May 1;90(5):880-890. doi: 10.1097/TA.0000000000003085. PMID: 33891572.
2. Boddi M, Cianchi G, Cappellini E, Ciapetti M, Batacchi S, Di Lascio G, Bonizzoli M, Cozzolino M, Peris A. Cannula-related deep vein thrombosis during extracorporeal membrane oxygenation (ECMO) treatment do not affect mortality and length of stay in intensive care unit Critical Care 2017, 21(Suppl 1):57. doi: 10.1186/s13054-017-1628-y.
3. Cornejo R, Zamorano A, Diaz G, Romero C, Tobar E, Llanos O, Galvez LR, Fabrega L, Neira W, Arellano D, Repetto C, Aedo D, Gonzalez R, Goñi D. Effects of extended prone position ventilation in ards secondary to pneumonia due to the novel a (H1N1) influenza. 23rd ESICM Annual Congress. doi: 10.1007/s00134-010-2000-8
4. Duggal A, Rezoagli E, Pham T, McNicholas BA, Fan E, Bellani G, Rubenfeld G, Pesenti AM, Laffey JG; LUNG SAFE Investigators and the ESICM Trials Group. Patterns of Use of Adjunctive Therapies in Patients With Early Moderate to Severe ARDS: Insights From the LUNG SAFE Study. Chest. 2020 Jun;157(6):1497-1505. doi: 10.1016/j.chest.2020.01.041. Epub 2020 Feb 20. PMID: 32088180.
5. Kredel M, Bierbaum D, Lotz C, Küstermann J, Roewer N, Muellenbach RM. Therapie des akuten Lungenversagens : Umfrage an deutschen ARDS-Zentren und wissenschaftliche Evidenz [Therapy of acute respiratory distress syndrome : Survey of German ARDS centers and scientific evidence]. Anaesthesist. 2015 Apr;64(4):277-85. German. doi: 10.1007/s00101-015-0010-1. Epub 2015 Apr 1. PMID: 25824000.
6. Kulesza, A. and Galvin, I. ARDS in the Age of COVID-19 - A survey of Canadian Critical Care Physicians. Critical Care Canada Forum 2021 Abstracts. Can J Anesth/J Can Anesth 69 (Suppl 1), 1–146 (2022). https://doi.org/10.1007/s12630-022-02207-2
7. Liu S, Ding X, Cao J, Zhang S, Sun T. [Nationwide survey on clinical treatment of coronavirus disease 2019 in 9 provinces and municipalities]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020 Apr;32(4):397-400. Chinese. doi: 10.3760/cma.j.cn121430-20200313-00338. PMID: 32527340.
8. Magira, E. Time of Herpes Simplex-1 Virus Detection Among Critical-ill With COVID- 19 Pneumonia Patients. American Journal of Respiratory and Critical Care Medicine 2023;207:A3442. doi: 10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A3442
9. Moratelli G, Regaieg K, Nakaa S, Fraj N, Kallel M, Al Harach A, Gazaigne L, Goldgran-Toledano D. Characteristics and prognosis of mechanical ventilated patients with SARS CoV2 pneumonia: a

prospective analysis of 143 patients. Annals of Intensive Care 2022, 12(Suppl 1):54 https://doi.org/10.1186/s13613-022-01016-6

10. Rodríguez Villamizar P, Morales Varas G, Calle Flores A, Alonso Ciria E, Pedrosa Guerrero A, Alonso Gómez G, Padilla R, Lobo Valbuena B. Impact of the body mass index (BMI) in patients with COVID-19 acute respiratory distress syndrome (CARDS) in the intensive care unit (ICU). ICMx 2022, 10(Suppl 2):39 https://doi.org/10.1186/s40635-022-00468-1
11. Evaluating Potential Use of Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) Services in Patients with Saha B, Drapak S, Mailman J, Kassir S, Sy E. Severe Acute Respiratory Distress Syndrome (ARDS) at Regina General Hospital in Regina, Saskatchewan. Can J Anesth/J Can Anesth (2022) 69:S1–S146 https://doi.org/10.1007/s12630-022-02207-2.
12. Stutz MR, Pearson SD, Han X, Christian C, Ajmani G, Leonhard AG, Lecompte-Osorio P, Wolfe KS, Pohlman A, Hall JB, Patel BK, Kress JP. Predictors of Mortality in COVID 19 Associated Respiratory Failure Among Predominantly African American Patients American Journal of Respiratory and Critical Care Medicine 2021;203:A2499. doi: 10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A2499
13. Udi J, Zotzmann V, Lang CN, Fluegler A, Krueger K, Duerschmied D, Bamberg F, Bode C, Wengenmayer T, Staudacher DL. High incidence of barotrauma in patients with COVID-19 pneumonia during invasive mechanical ventilation. Critical Care 2020, 24(Suppl 2):P523. doi: 10.1186/s13054-020-03187-9.
14. Xu Y, Deng X, Han Y, Zhou L, He W, Chen S, Nong L, Huang H, Zhang Y, Yu T, Li Y, Liu X. A Multicenter Retrospective Review of Prone Position Ventilation (PPV) in Treatment of Severe Human H7N9 Avian Flu. PLoS One. 2015 Aug 28;10(8):e0136520. doi: 10.1371/journal.pone.0136520. PMID: 26317621; PMCID: PMC4552847.

**Studies on extracorporeal configurations different from veno-venous ECMO:** 1 citation

1. Mustafa AK, Alexander PJ, Joshi DJ, Tabachnick DR, Cross CA, Pappas PS, Tatooles AJ. Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure. JAMA Surg. 2020 Oct 1;155(10):990-992. doi: 10.1001/jamasurg.2020.3950. PMID: 32780089; PMCID: PMC7420824.

**Studies not including patients undergoing prone positioning:** 25 citations

1. Biondi S, Cianchi G, Bonizzoli M, Matano S, Anichini V, Franci A, Zagli G, Peris A. Requiem for xigris®: Its use in sepsis-associated ARDS requiring ECMO support. ESICM 2012 monday sessions

15 October, 2012. Intensive Care Med 38 (Suppl 1), 1–327 (2012). https://doi.org/10.1007/s00134-012-2683-0

2. Argudo E, Vaz A, Albacete C, Ricart P, Millán P, Blandino A, Santa-Teresa P, Fuset M, Chomón H, Martínez-Vega S, Huguet M, Jara R, Veganzones J, Gallart E, Resta P, Roncon-Albuquerque R, Riera J. Long ECMO runs in patients with COVID-19 disease. A subanalysis of the ECMOVIBER study. EuroELSO 2021 Poster Abstracts. Perfusion. 2021;36(1_suppl):4-81. doi:10.1177/02676591211007763
3. Çalışkan G, Kelebek Girgin N. Comparison of nutritional adequacy in adult patients with acute respiratory distress syndrome with and without veno-venous extracorporeal membrane oxygenation: a single-center experience. Eur Res J. September 2023;9(5):1114-1123. doi:10.18621/eurj.1310881
4. Dalton H, Desai M, Osborn E, Lantry J, King C, Singh R, Moran P, Speir A. Covid 19 care, ECMO usage and outcomes in a time of crisis at a major medical center. EuroELSO 2021 Poster Abstracts. Perfusion. 2021;36(1_suppl):4-81. doi:10.1177/02676591211007763
5. Delgado Tellez De Cepeda A, Renes Carreno E, PerezVela JL, Rubio Mateo-Sidron JA, Lesmes A, Grau Carmon T, Montejo-Gonzalez JC. Implementation of the veno-venous ExtraCorporeal Membrane Oxygenation (ECMO) Retrieval program in the region of Madrid (Spain). Experience of Hospital Universitario 12 de Octubre ECMO referral centre ESICM LIVES 2021: Part 1. ICMx 9 (Suppl 1), 51 (2021). https://doi.org/10.1186/s40635-021-00413-8. doi: 10.1186/s40635-021-00413-8
6. Dognon N, Gaudet A, Parmentier-Decrucq E, Normandin S, Vincentelli A, Moussa M, Poissy J, Duburcq T, Lille Intensive Care Covid-Group. Extracorporeal Membrane Oxygenation for COVID 2019-Acute Respiratory Distress Syndrome: Comparison between First and Second Waves (Stage 2). J Clin Med. 2021 Oct 21;10(21):4839. doi: 10.3390/jcm10214839. PMID: 34768359; PMCID: PMC8584595.
7. Garfield B, Bianchi P, Arachchillage D, Hartley P, Naruka V, Shroff D, Law A, Passariello M, Patel B, Price S, Rosenberg A, Singh S, Trimlett R, Xu T, Doyle J, Ledot S. Six Month Mortality in Patients with COVID-19 and Non-COVID-19 Viral Pneumonitis Managed with Veno-Venous Extracorporeal Membrane Oxygenation. ASAIO J. 2021 Sep 1;67(9):982-988. doi: 10.1097/MAT.0000000000001527. PMID: 34144551.
8. Natanov R, Kunkel ER, Wiesner O, Haverich A, Wiegmann B, Rümke S, Kühn C. Determinants of survival in patients on extracorporeal membrane oxygenation therapy due to severe covid-19. Perfusion. 2023 Oct;38(7):1393-1398. doi: 10.1177/02676591221113135. Epub 2022 Jul 4. PMID: 35786064; PMCID: PMC9260190.
9. Moreno Franco P, Rachmale S, Ding S, Wilson G, Li G. Rescue therapies in patients with refractory hypoxemia 10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A1643

10. Rich PB, Awad SS, Kolla S, Annich G, Schreiner RJ, Hirschl RB, Bartlett RH. An approach to the treatment of severe adult respiratory failure. J Crit Care. 1998 Mar;13(1):26-36. doi: 10.1016/s0883-9441(98)90026-0. PMID: 9556124.
11. Sami H, David G, Florence B, Saber B, Florence B, Daniel DS, Stéphane E, Olfa H, Antoine K, Jean-Claude L, Jean-Baptiste L, Philippe M, Gaël P, Atika Y, Grégoire M, Nadia A, Cerc C. Treatments and outcomes of severe hypoxemic patients in French speaking ICUs: A subgroup analysis from the SPECTRUM study. Proceedings of Réanimation 2018, the French Intensive Care Society International Congress. Ann Intensive Care. 2018 Feb 5;8(Suppl 1):13. doi: 10.1186/s13613-017-0345-7. Erratum in: Ann Intensive Care. 2019 Jul 4;9(1):80. doi: 10.1186/s13613-019-0555-2. PMID: 29404789; PMCID: PMC5799093.
12. Pereira JM, Basilio C, Sousa Dias C, Santos L, Sarmento A, Artur Paiva J. Pandemic influenza H1N1: How did we deal with it! ESICM 2010 WEDNESDAY SESSIONS 13 October 2010. Intensive Care Med 36 (Suppl 2), 326–433 (2010). doi: 10.1007/s00134-010-2001-7
13. Reddy R, Dovidio J, Baram M, Hirose H. Outcomes of extracorporeal membrane oxygenation in ARDS due to Covid-19: comparison of the first and the second wave. Chest 2021;160(4):A1065
14. Rezoagli E, Rilinger J, Duburq T, Guervilly C, Petit M, Wengenmayer T, Bellani G, Grasselli G, Combes A, Foti G, Schmidt M, Giani M. Timing of Prone Positioning during venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. ESICM LIVES 2022: part 1. ICMx 10 (Suppl 2), 39 (2022). doi: 10.1186/s40635-022-00468-1
15. Rozencwajg S, Tran Dinh A, Foubert A, Haye G, Seguin P, Dupont H, Guitard PG, Veber B, Godet T, Bazin JE, Montravers P. Acute pancreatitis complicated with refractory ARDS supported by ECMO: A French multicentric retrospective study (preliminary results). ESICM LIVES 2020. ICMx 8 (Suppl 2), 73 (2020). doi: 10.1186/s40635-020-00354-8
16. Seeliger B, Stahl K, Schenk H, Schmidt JJ, Wiesner O, Welte T, Kuehn C, Bauersachs J, Hoeper MM, David S. Extracorporeal Membrane Oxygenation for Severe ARDS Due to Immune Diffuse Alveolar Hemorrhage: A Retrospective Observational Study. Chest. 2020 Mar;157(3):744-747. doi: 10.1016/j.chest.2019.10.021. Epub 2019 Nov 9. PMID: 31711988.
17. Shah R, Said R, Christopher N. VV-ecmo in patients with Covid-19: survival prediction score comparison. Chest 2021;160(4):A1139. doi: 10.1016/j.chest.2021.07.1043
18. Wen J, Chen J, Chang J, Wei J. Pulmonary complications and respiratory management in neurocritical care: a narrative review. Chin Med J (Engl) 2022;135(7):779–789. doi: 10.1097/CM9.0000000000001930
19. Sousse L, Whitmore S, Cyr K, Cohen E, Schlauch D, Gidwani H, Sterling R, Kunavarapu C, DellaVolpe J. ECMO for acute respiratory failure due to Covid-19: a multicenter retrospective study. Crit Care Med 2023 51(1):448. doi: 10.1097/01.ccm.0000909372.09637.8b

20. Vahdatpour C, De Young S, Ayyoub J, Jaber JF, Nwankwo O, Kinniry P. ICU outcomes in patients with COVID-19 associated ARDS: A retrospective analysis. doi: 10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A2554
21. Wan DM, Kang XH, Bai W, Zeng ZG, Zhang W. [The clinical characteristics and prognosis of 20 patients with H7N9 avian influenza]. Zhonghua Jie He He Hu Xi Za Zhi. 2019 Oct 12;42(10):750-754. Chinese. doi: 10.3760/cma.j.issn.1001-0939.2019.10.007. PMID: 31594108.
22. Whitmore S, Cyr K, Cohen E, Schlauch D, Jarzembowski J, Kunavarapu C, Stell O, McRae T, Dellavolpe J. Extracorporeal membrane oxygenation (ECMO) vs conventional mechanical ventilation for severe acute respiratory failure due to Covid-19: a multicenter matched cohort study. Chest 2022;162(4):a978-a979. doi: 10.1016/j.chest.2022.08.771
23. Wong B, Shi E, Wang Y, Brovman E, Chweich H, Fieber SB, Fox J, Joyce M, Lussier L, Ortoleva J, Reich JA, Ruopp NF, Sekhar P, Ursprung E, Faugno A, Han, X. Pre-extracorporeal membrane oxygenation (ECMO) ventilatory ratio (VR) may predict mortality in severe acute respiratory distress syndrome (ARDS). Chest 2023;164(4):A1613-A1614. doi: 10.1016/j.chest.2023.07.1109
24. Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. Crit Care. 2020 Apr 15;24(1):148. doi: 10.1186/s13054-020-2840-8. PMID: 32293518; PMCID: PMC7156900.
25. Extracorporeal respiratory support of severe hypoxemic respiratory failure in COVID-19 pneumonitis. Zollei EV, Rudas L, Hankovszky P, Korsos A, Palfi A, Varga Z, Hegedus Z, Bari G, Lobozarne SB, Kiszel A, Babik B. ESICM LIVES 2022: part 1. ICMx **10** (Suppl 2), 39 (2022). doi: 10.1186/s40635-022-00468-1

**Studies with no comparison group:** 28 citations

1. Genty T, Cherel Q, Thès J, et al. Prone positioning during veno-venous or veno-arterial extracorporeal membrane oxygenation: feasibility and complications after cardiothoracic surgery. Crit Care 26, 66 (2022). https://doi.org/10.1186/s13054-022-03944-y
2. Baek M, Lee SM, Chung C, et al. Improvement in the survival rates of extracorporeal membrane oxygenation-supported respiratory failure patients: a multicenter retrospective study in Korean patients. Crit Care 23, 1 (2019). https://doi.org/10.1186/s13054-018-2293-5
3. Claxton A, Hodd J, Templeton R, Wong N, Garcia M. Nurse-led proning is safe in VV-ECMO patients. Abstracts for the 8th EuroELSO Congress on ECMO-ECLS, 10 – 13 April 2019, Barcelona, Spain. Perfusion. 2019;34(1_suppl):82-251. doi:10.1177/0267659119829686
4. Délgado Tellez de Cepeda AM, Renes Carreño E, Pérez-Vela JL, Lesmes González A, Grau Carmona T, Martín Delgado MC. Experience achieved after implementation of the Veno-Venous ExtraCorporeal Membrane Oxygenation(ECMO) retrieval program in the region of Madrid (Spain).

Hospital Universitario 12 de Octubre. Supplement for the EuroELSO 2023, 26-29 April 2023, Lisbon, Portugal. Perfusion. 2023;38(1_suppl):82-212. doi:10.1177/02676591231162023

5. Durak K, Zayat R, Grottke O, Dreher M, Autschbach R, Marx G, Marx N, Spillner J, Kalverkamp S, Kersten A. Extracorporeal membrane oxygenation in patients with COVID-19: 1-year experience. J Thorac Dis. 2021 Oct;13(10):5911-5924. doi: 10.21037/jtd-21-971. PMID: 34795939; PMCID: PMC8575858.
6. Foofuengmonkolkit K, Susupaus A, Udomkusonsri J, Songdechakraiwut T, Namchaisiri J, Sakiyalak P. Extracorporeal Membrane Oxygenation versus Conventional Ventilator Support in COVID-19 Patients with Acute Respiratory Distress Syndrome. J Med Assoc Thai 2022;106:1-6. DOI: 10.35755/jmedassocthai.2023.01.13728
7. Franchineau G, Bréchot N, Hekimian G, Lebreton G, Bourcier S, Demondion P, Le Guennec L, Nieszkowska A, Luyt CE, Combes A, Schmidt M. Prone positioning monitored by electrical impedance tomography in patients with severe acute respiratory distress syndrome on veno-venous ECMO. Ann Intensive Care. 2020 Feb 3;10(1):12. doi: 10.1186/s13613-020-0633-5. PMID: 32016593; PMCID: PMC6997307.
8. Georgovasilis G, Topciu T, Naldrett IA. Concurrent prone positioning and VV-ECMO treatment. EuroELSO 2020 Poster Abstracts. Perfusion. 2020;35(1_suppl):93-282. doi:10.1177/0267659120909723
9. Jäckel M, Rilinger J, Lang CN, Zotzmann V, Kaier K, Stachon P, Biever PM, Wengenmayer T, Duerschmied D, Bode C, Staudacher DL, Supady A. Outcome of acute respiratory distress syndrome requiring extracorporeal membrane oxygenation in Covid-19 or influenza: A single-center registry study. Artif Organs. 2021 Jun;45(6):593-601. doi: 10.1111/aor.13865. Epub 2020 Dec 18. PMID: 33188714; PMCID: PMC7753485.
10. Kim TH, Joon HK, Yang SH, Song MJ, Lim SY, Lee YJ, Cho YJ. Clinical outcomes and pulmonary function test of critically ill COVID-19 patients: Which firstly as rescue therapy? ESICM LIVES 2022: part 1. Intensive Care Med Exp. 2022 Oct 19;10(Suppl 2):39. doi: 10.1186/s40635-022-00468-1. PMID: 36258101; PMCID: PMC9579221.
11. Kon ZN, Smith DE, Chang SH, Goldenberg RM, Angel LF, Carillo JA, Geraci TC, Cerfolio RJ, Montgomery RA, Moazami N, Galloway AC. Extracorporeal Membrane Oxygenation Support in Severe COVID-19. Ann Thorac Surg. 2021 Feb;111(2):537-543. doi: 10.1016/j.athoracsur.2020.07.002. Epub 2020 Jul 17. PMID: 32687823; PMCID: PMC7366119.
12. Nie Q, Ye A, Wei S. Nursing Management of Severe COVID-19 Patients Undergoing Extracorporeal Membrane Oxygenation Combined with Prone Position Ventilation. Heart Surg Forum. 2020 Jun 15;23(4):E422-E425. doi: 10.1532/hsf.3045. PMID: 32726206.
13. Guervilly, C., Fournier, T., Chommeloux, J. et al. Ultra-lung-protective ventilation and biotrauma in severe ARDS patients on veno-venous extracorporeal membrane oxygenation: a randomized controlled study. Crit Care 26, 383 (2022). https://doi.org/10.1186/s13054-022-04272-x

14. Guervilly C, Hraiech S, Gariboldi V, Xeridat F, Dizier S, Toesca R, Forel JM, Adda M, Grisoli D, Collart F, Roch A, Papazian L. Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. Minerva Anestesiol. 2014 Mar;80(3):307-13. Epub 2013 Nov 21. PMID: 24257150.
15. Hagiwara Y, Ogura T, Fujita K. Early prone positioning under VV-ECMO in SARSCoV- 2-induced acute respiratory distress syndrome - a retrospective cohort study. Supplement for the 10th EuroELSO Congress 4-6 May 2022 London/UK. Perfusion. 2022 May;37(1_suppl):3-111. doi: 10.1177/02676591221089240. PMID: 35506394.
16. Lucchini A, De Felippis C, Pelucchi G, Grasselli G, Patroniti N, Castagna L, Foti G, Pesenti A, Fumagalli R. Application of prone position in hypoxaemic patients supported by veno-venous ECMO. Intensive Crit Care Nurs. 2018 Oct;48:61-68. doi: 10.1016/j.iccn.2018.04.002. Epub 2018 Jul 20. PMID: 30037534.
17. Obreja V, Chen W, Marcarian T, Murray K, Zakaryan A, Rodriguez M, Gonzalez A, Ortiz C. ASAIO Journal 2022. Process and Outcomes of Prone Position Therapy (PPT) for Extracorporeal Membrane Oxygenation (ECMO) Patients with COVID-19.
18. Oujidi Y, Bensaid A, Melhoaui I, Jakhjoukh DD, Kherroubi L, Bkiyar H, Housni B. Prone position during ECMO in patients with COVID-19 in Morocco: Case series. Ann Med Surg (Lond). 2021 Aug 28;69:102769. doi: 10.1016/j.amsu.2021.102769. PMID: 34484734; PMCID: PMC8403004.
19. Paparoupa M, Fischer M, Pinnschmidt HO, Grensemann J, Roedl K, Kluge S, Jarczak D. Impact of COVID-19 on Sedation Requirements during Veno-Venous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. Journal of Clinical Medicine. 2023; 12(10):3515. https://doi.org/10.3390/jcm12103515
20. Qadir N, Bartz RR, Cooter ML, Hough CL, Lanspa MJ, Banner-Goodspeed VM, Chen JT, Giovanni S, Gomaa D, Sjoding MW, Hajizadeh N, Komisarow J, Duggal A, Khanna AK, Kashyap R, Khan A, Chang SY, Tonna JE, Anderson HL 3rd, Liebler JM, Mosier JM, Morris PE, Genthon A, Louh IK, Tidswell M, Stephens RS, Esper AM, Dries DJ, Martinez A, Schreyer KE, Bender W, Tiwari A, Guru PK, Hanna S, Gong MN, Park PK; Severe ARDS: Generating Evidence (SAGE) Study Investigators; Society of Critical Care Medicine's Discovery Network. Variation in Early Management Practices in Moderate-to-Severe ARDS in the United States: The Severe ARDS: Generating Evidence Study. Chest. 2021 Oct;160(4):1304-1315. doi: 10.1016/j.chest.2021.05.047. Epub 2021 Jun 4. PMID: 34089739; PMCID: PMC8176896.
21. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351-63. doi: 10.1016/S0140-6736(09)61069-2. Epub 2009 Sep 15. Erratum in: Lancet. 2009 Oct 17;374(9698):1330. PMID: 19762075.

22. Pieri M, Donatelli V, Calabrò MG, Scandroglio AM, Pappalardo F, Zangrillo A. Eleven Years of Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: From H1N1 to SARS-CoV-2. Experience and Perspectives of a National Referral Center. J Cardiothorac Vasc Anesth. 2022 Jun;36(6):1703-1708. doi: 10.1053/j.jvca.2021.09.029. Epub 2021 Sep 24. PMID: 34686438; PMCID: PMC8461266.
23. Siuba M, Panitchote A, Krishnan S, Duggal A. Oxygenation index predicts need for prone positioning or ECMO in ARDS. Crit Care Med 2019;47(1):p 563. doi: 10.1097/01.ccm.0000551917.13369.79
24. Textoris L, Gragueb-Chatti I, Daviet F, Valera S, Sanz C, Papazian L, Forel J-M, Hraiech S, Roch A, Guervilly C. Response to Prone Position in COVID-19 and Non-COVID-19 Patients with Severe ARDS Supported by vvECMO. J Clin Med. 2023; 12(12):3918. https://doi.org/10.3390/jcm12123918
25. Textoris L et al. Prone position during veno-venous extracorporeal membrane oxygenation in COVID-19 ARDS. Proceedings of Reanimation 2022, the French Intensive Care Society International Congress. Ann. Intensive Care **12** (Suppl 1), 54 (2022). doi: 10.1186/s13613-022-01016-6.
26. Voelker MT, Jahn N, Bercker S, Becker-Rux D, Köppen S, Kaisers UX, Laudi S. Bauchlagerung von Patienten an der venovenösen ECMO ist möglich und sicher [Prone positioning of patients during venovenous extracorporeal membrane oxygenation is safe and feasible]. Anaesthesist. 2016 Apr;65(4):250-7. German. doi: 10.1007/s00101-015-0131-6. Epub 2016 Mar 23. PMID: 27007777.
27. Waybill K et al. Impact of proning on respiratory physiology in patients on veno-venous extracorporeal membrane oxygenation with acute respiratory distress syndrome due to Covid-19 pneumonia. Chest 2023;164(4):A1585-A1586
28. Zonies D, Creutzenberg M, Graf B, Hofmann H, Fang R, Bein T. Oxygenation improvement with prone positioning in ECMO patients during post-traumatic ARDS. Crit Care Med 2012;40(12):p 1-328. doi: 10.1097/01.ccm.0000424446.71482.21

**Studies with no data on mortality:** 2 citations

1. Lyu G, Cai T, Jiang W, Liu M, Wang X. [Comparison of efficacy between veno-venous extracorporeal membrane oxygenation (VV-ECMO) and VV-ECMO combined with prone position ventilation for the treatment of acute respiratory distress syndrome]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2021 Mar;33(3):293-298. Chinese. doi: 10.3760/cma.j.cn121430-20200805-00563. PMID: 33834969.
2. Templeman V, Caetano F, Georgovasilis G, Topciu T, Ledot S. Prone position (PP) on patients (pt) supported with veno-venous extracorporeal membrane oxygenation (VV-ECMO): a risk worth taking? Critical Care 2021, 25(Suppl 1): P179

**Online Resource 5. Characteristics of included studies**

**Table S1. General study characteristics**

| First author, year | Setting | Design | Risk of bias assessment |
|---|---|---|---|
| Combes, 2018 | France, USA, Australia, Canada (64 hospitals), 2011-Apr 2017 | Multi-center RCT (non-RCT for the purpose of the present study) | Serious |
| Guervilly, 2019 | France, January 2012-April 2017 | Single-center retrospective observational | Moderate |
| Garcia, 2020 | France | Single-center retrospective observational | Serious |
| Rilinger, 2020 | Germany, October 2010-May 2018 | Single-center retrospective observational | Moderate |
| Giani, 2021 | Italy (6 hospitals), January 2014-December 2018 | Multi-center retrospective observational | Moderate |
| Chaplin, 2021 | New Zealand, July 2014-July 2019 | Single-center retrospective observational | Serious |
| Laghlam, 2021 | France, March 2020-June 2021 | Single-center prospective observational | Serious |
| Martinez Martinez, 2021 | Spain, Portugal (25 hospitals), March-December 2020 | Multi-center retrospective observational | Serious |
| COVID-ICU Group, 2021 | France, Switzerland, and Belgium (138 hospitals), February-May 2020 | Multi-center prospective observational | Serious |
| Yang, 2021 | China (21 ICUs), January-May 2020 | Multi-center retrospective observational | Serious |
| Cheng, 2021 | China, January-May 2020 | Multi-center retrospective observational | Critical |
| Chang, 2022 | USA, March-May 2020 | Single-center retrospective observational | Critical |
| Chen, 2022 | China, April 2013-October 2020 | Single-center retrospective observational | Moderate |
| Zaaqoq, 2022 | International study (more than 370 hospitals), February 2020-October 2020 | Multi-center retrospective observational | Serious |
| Petit, 2022 | France, January 2012-January 2020 | Single-center retrospective observational | Moderate |
| Raasveld, 2022 | Belgium, Germany, The Netherlands, Spain, Sweden (15 ICUs), March-December 2020 (Covid-19 cohort), January 2018-July 2019 (non-Covid-19 cohort) | Multi-center retrospective observational | Serious |
| Adelsten, 2023 | Denmark (two hospitals), March 2020-December 2021 | Multi-center retrospective observational | Serious |
| Massart, 2023 | France (47 hospitals), April 2020-June 2021 | Multi-center retrospective observational | Serious |

| | | | |
|---|---|---|---|
| Schmidt, 2023 | France (14 hospitals), March-December 2021 | Multi-center RCT | Low |
| Giani, 2023 | Italy, March 2020-January 2022 | Single-center retrospective observational | Serious |
| Tong, 2024 | China (three hospitals), June 2021-July 2023 | Multi-center RCT | Some concerns |
| Wang, 2024 | China, November 2019-August 2023 | Single-center prospective observational | Moderate |
| Abbreviations: USA, United States of America; RCT, randomized controlled trial; ICU, intensive care unit; Covid, coronavirus disease. | | | |

**Table S2. General patient characteristics**

| First author, year | Number | | Age | | Female gender | | Body mass index | | Pneumonia | | Covid | Other causes of AHRF (prone; no prone) | Immunosuppression | | SOFA score | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | | | Prone | No prone | Prone | No prone |
| Combes, 2018 | 17 | 107 | | | | | | | | | No | | | | | |
| Guervilly, 2019 | 91 | 77 | 49 (15) | 53 (13) | 25 (27) | 25 (32) | | | | | No | | | | 10 (4) | 11 (4) |
| Garcia, 2020 | 14 | 11 | 59 (48-63) | 57 (48-66) | 2 (14) | 1 (9) | 31.5 (28.0-38.0) | 33.6 (28.4-37.6) | 14 (100) | 11 (100) | Yes | | | | | |
| Rilinger, 2020 | 38 | 120 | 51 (16) | 53 (14) | 10 (26) | 42 (35) | 26.5 (5.9) | 26.8 (8.2) | 33 (87) | 83 (69) | No | Aspiration (2; 13), sepsis (1; 9), other unspecified (2; 15) | 13 (34) | 44 (37) | 13 (3) | 14 (4) |
| Giani, 2021 | 107 | 133 | 50 (39-58) | 50 (41-59) | 34 (32) | 50 (38) | 27.8 (23.8-31.3) | 26.7 (23.4-31.2) | 99 (93) | 121 (91) | No | Aspiration (1; 0), sepsis (4; 6), trauma (1; 5), other unspecified (2; 1) | 15 (14) | 30 (23) | 8 (4-11) | 11 (8-13) |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chaplin, 2021 | 13 | 59 | 45 (34-48) | 46 (34-56) | 6 (46) | 20 (34) | 29.1 (26.7-35) | 31.3 (26.3-35.3) | 13 (100) | 49 (83) | No | Aspiration (0; 6), other unspecified (0; 4) | | | | |
| Laghlam, 2021 | 10 | 14 | 52 (37-59) | 52 (44-57) | 3 (30) | 3 (21) | 30 (29-35) | 26 (23-33) | 10 (100) | 14 (100) | Yes | | 1 (10) | 1 (7) | 11 (6-4) | 9 (5-15) |
| Martinez Martinez, 2021 | 43 | 285 | 58 (54-60) | 55 (46-61) | 4 (9) | 61 (21) | 30.7 (7.4) | 30.4 (5.9) | 43 (100) | 285 (100) | Yes | | | | | |
| COVID-ICU Group, 2021 | 184 | 85 | | | | | | | 184 (100) | 85 (100) | Yes | | | | | |
| Yang, 2021 | 51 | 22 | | | | | | | 51 (100) | 22 (100) | Yes | | | | | |
| Cheng, 2021 | 29 | 45 | | | | | | | 29 (100) | 45 (100) | Yes | | | | | |
| Chang, 2022 | 12 | 18 | 42 (37-26) | 39 (29-48) | 1 (8) | 3 (17) | 30 (27-38) | 33 (29-35) | 12 (100) | 18 (100) | Yes | | | | | |
| Chen, 2022 | 38 | 53 | 41 (31-50) | 58 (44-64) | 9 (24) | 18 (34) | 25.3 (22.3-28.5) | 24.6 (20.9-28.1) | | | No | | 7 (18) | 7 (13) | | |
| Zaaqoq, 2022 | 67 | 165 | 52 (43-60) | 53 (44-60) | 20 (30) | 52 (32) | 29 (26-33) | 31 (27-36) | 67 (100) | 165 (100) | Yes | | 34 (51) | 79 (48) | 7 (4-9) | 8 (5-10) |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Petit, 2022 | 64 | 234 | 53 (45-61) | 51 (39-60) | 21 (33) | 74 (32) | 31.2 (27-38.7) | 28.1 (24.2-33) | 52 (81) | 170 (73) | No | Other unspecified (12; 64) | 18 (28) | 65 (28) | 13 (9–16) | 14 (10-17) |
| Raasveld, 2022 | 96 | 97 | | | | | | | 96 (100) | 97 (100) | Yes | | | | | |
| Adelsten, 2023 | 44 | 24 | 54 (45-59) | 55 (45-62) | 13 (30) | 10 (42) | 29.5 (25.9-32.2) | 27.7 (25.7-33.1) | 44 (100) | 24 (100) | Yes | | | | 8 (6-10) | 7 (69) |
| Massart, 2023 | 364 | 153 | 54 (48-61) | 56 (46-62) | 82 (23) | 33 (22) | 30.1 (27.1-34.0) | 30.1 (27.5-35.0) | 364 (100) | 153 (100) | Yes | | 3 (1) | 1 (1) | 9 (8-12) | 9 (7-13) |
| Schmidt, 2023 | 86 | 84 | 52 (44-60) | 50 (41-58) | 24 (28) | 36 (43) | 32.7 (28.4-38.1) | 33.1 (28.8-36.8) | 86 (100) | 82 (98) | No | Sepsis (0; 1), other unspecified (0; 1) | 4 (5) | 3 (4) | 9 (8-13) | 9 (8-12) |
| Giani, 2023 | 38 | 11 | 55 (41-58) | 53 (48-59) | 13 (34) | 3 (27) | 31.1 (27.6-35) | 29.3 (24.5-37) | 38 (100) | 11 (100) | Yes | | 2 (5) | 0 (0) | 5 (3-7) | 5 (3-7) |
| Tong, 2024 | 49 | 48 | 53 (44-62) | 49 (40-58) | 22 (45) | 24 (50) | | | 42 (86) | 41 (85) | No | other unspecified (7; 7) | | | | |
| Wang, 2024 | 50 | 115 | 58 (14) | 55 (17) | 12 (24) | 40 (35) | 25.0 (22.9-26.4) | 24.2 (22.4-26.2) | 50 (100) | 115 (100) | No | | 11 (22) | 18 (16) | 12 (11-14) | 13 (11-14) |

Abbreviations: Covid, coronavirus disease; AHRF, acute hypoxemic respiratory failure; SOFA, sequential organ failure assessment. Quantitative variables are reported as mean (standard deviation) or median (first quartile-third quartile), as per the original study. Qualitative variable are reported as absolute number (percentage).

| **Table S3. Treatments before cannulation** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| First author, year | Prone positioning | | Duration of invasive mechanical ventilation | | Neuromuscular blockade | | Steroids | | Inhaled nitric oxide | |
| | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone |
| Combes, 2018 | | | | | | | | | | |
| Guervilly, 2019 | 69 (76) | 39 (51) | 5 (5) | 6 (7) | | | | | 31 (34) | 31 (40) |
| Garcia, 2020 | 14 (100) | 11 (100) | 6.5 (4.0-10.0) | 7 (4-13) | 14 (100) | 11 (100) | 1 (7) | 3 (27) | 12 (86) | 9 (82) |
| Rilinger, 2020 | 7 (18) | 19 (16) | 4.6 (5.4) | 3.3 (5.3) | 3 (8) | 14 (12) | | | 1 (3) | 1 (1) |
| Giani, 2021 | 34 (32) | 38 (29) | 2 (1-6) | 2 (1-6) | | | | | 8 (7) | 20 (15) |
| Chaplin, 2021 | | | | | | | | | | |
| Laghlam, 2021 | | | 5 (4-10) | 6 (3-12) | 10 (100) | 14 (100) | 10 (100) | 14 (100) | 4 (40) | 5 (36) |
| Martinez Martinez, 2021 | 39 (91) | 276 (97) | 5 (3-8) | 5 (3-9) | | | | | | |
| COVID-ICU Group, 2021 | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Yang, 2021 | | | | | | | | | | |
| Cheng, 2021 | | | | | | | | | | |
| Chang, 2022 | | | | | | | | | | |
| Chen, 2022 | 14 (37) | 17 (32) | 55.5 (20-132) | 45 (7.5-120) | | | | | | |
| Zaaqoq, 2022 | 49 (73) | 127 (77) | | | | | | | | |
| Petit, 2022 | 55 (86) | 141 (60) | 4 (1-9) | 4 (1-10) | 64 (100) | 233 (100) | 13 (20) | 48 (21) | 32 (50) | 124 (53) |
| Raasveld, 2022 | | | | | | | | | | |
| Adelsten, 2023 | | | 5 (3-6) | 3 (1-5.5) | 38 (86) | 21 (88) | 34 (77) | 16 (67) | 36 (82) | 13 (54) |
| Massart, 2023 | 349 (96) | 141 (92) | | | 353 (97) | 147 (96) | | | 140 (38) | 56 (37) |
| Schmidt, 2023 | 85 (99) | 79 (94) | 3 (1-6) | 5 (2-7) | 78 (91) | 65 (77) | 22 (28) | 20 (24) | 44 (51) | 35 (42) |
| Giani, 2023 | | | 6 (2.0-10) | 5 (1.0-8.0) | | | | | 8 (21) | 1 (9) |
| Tong, 2024 | 5 (10) | 7 (15) | 3 (2-4) | 4 (3-5) | | | | | | |
| Wang, 2024 | 50 (100) | 115 (100) | 2 (1–3) | 1 (1-4) | 7 (14) | 15 (13) | 11 (22) | 30 (26) | 3 (6) | 6 (5) |

Quantitative variables are reported as mean (standard deviation) or median (first quartile-third quartile), as per the original study. Qualitative variable are reported as absolute number (percentage).

**Table S4. Mechanical ventilation settings, respiratory mechanics, and arterial gas exchanges**

| First author, year | Tidal volume/kg PBW | | Respiratory rate | | Pplat | | PEEP | | Crs | | Driving pressure | | PaCO2 | | PaO2 | | pH | | PaO2/FiO2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone | Prone | No prone |
| Combes, 2018 | | | | | | | | | | | | | | | | | | | | |
| Guervilly, 2019 | | | 11 (2) | 11 (2) | 24 (4) | 24 (4) | 15 (3) | 14 (4) | 22 (12) | 21 (11) | 10 (4) | 10 (4) | | | | | | | 67 (21) | 67 (19) |
| Garcia, 2020 | | | 18 (13-25) | 12 (12-14) | 26 (25-29) | 26 (21-29) | 14 (12-20) | 14 (10-20) | 24 (14-30) | 28 (18-33) | 11 (10-14) | 9 (8-12) | | | | | | | 84 (67-96) | 87 (66-102) |
| Rilinger, 2020 | | | 26 (5) | 27 (7) | | | 15 (4) | 14 (4) | | | | | 66 (30) | 67 (32) | 69 (14) | 75 (31) | 7.24 (0.11) | 7.21 (0.15) | 83 (25) | 92(53) |
| Giani, 2021 | | | | | | | | | | | | | | | | | | | 65 (55-84) | 68 (55-87) |
| Chaplin, 2021 | | | | | | | | | | | | | | | | | | | | |
| Laghlam, 2021 | 5.9 (5.1-6.4) | 5.8 (4.9-6.1) | | | | | 14 (3) | 14 (5) | | | 19 (8) | 18 (6) | 61 (10) | 63 (12) | | | 7.34 (0.1) | 7.28 (0.1) | 63 (57-78) | 70 (63.81) |
| Martinez Martinez, 2021 | | | | | | | | | | | 17 (4.6) | 18.2 (4.9) | | | | | | | 70 (60-80) | 78 (65-91) |
| COVID-ICU Group, 2021 | | | | | | | | | | | | | | | | | | | | |
| Yang, 2021 | | | | | | | | | | | | | | | | | | | | |
| Cheng, 2021 | | | | | | | | | | | | | | | | | | | | |
| Chang, 2022 | | | | | | | | | | | | | | | | | | | | |
| Chen, 2022 | | | 27 (22-33) | 28 (23-34) | 27 (22-30) | 28 (22-33) | 10 (8-14) | 12 (8-15) | | | | | 49.4 (40.8-58.7) | 44.4 (35.2-57.4) | 65.6 (55.9-76.1) | (52.8-82.6) | 7.34 (7.24-7.42) | 7.35 (7.26-7.43) | 65.9 (55.9-82.6) | 63.3 (56-91.8) |
| Zaaqoq, 2022 | | | | | | | 14 (10-16) | 12 (10-16) | 21 (20-29) | 29 (22–37) | | | 49 (39-62) | 48 (35-58) | | | | | 85 (70-136) | 83 (61-124) |
| Petit, 2022 | | | | | | | | | 16 (11-24) | 14 (7–23) | | | | | | | | | 61 (54–70) | 65 (53–70) |
| Raasveld, 2022 | | | | | | | | | | | | | | | | | | | | |
| Adelsten, 2023 | 5.5 (4.58-6.65) | 5.98 (3.97-7.99) | 24 () | 21 (18-32) | | | 14 (12-16) | 13 (11-5) | 21.3 (15.2-29.8) | 24.4 (11.32-32.5) | | | 8.9 (7.6-11.8) | 8.9 (7.3-9.8) | 8.300 (7.325-9.250)* | 7.7 (6.35-8.60)* | 7.29 (0.13) | 7.28 (0.18) | 8.3 (7.3-9.3) | 7.7 (6.3-10.4) |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Massart, 2023 | 5.9 (5.1-6.3) | 5.9 (5.5-6.4) | 28 (18-30) | 27 (23-30) | 30 (26-32) | 30 (26-32) | 12 (10-14) | 12 (10-14) | 21.5 (16.4-30) | 21.2 (15.7-27.7) | | | 54 (45-64) | 55 (48-67) | | | | | 64 (54-76) | 61 (52-75) |
| Schmidt, 2023 | 5.9 (5.3-6.3) | 6.0 (5.2-6.4) | 30 (25-33) | 30 25-32) | 30 (29-33) | 31 (29-34) | 12 (10-15) | 12 (10-14) | 22.0 (16.0-29.5) | 20.5 (14.7-27.0) | | | 54 (48-64) | 59 (51-70) | | | 7.31 (7.26-7.40) | 7.3 (7.20-7.40) | 66 (55-77) | 67 (59-80) |
| Giani, 2023 | | | | | | | | | | | | | | | | | | | 75 (53-100) | 87 (74-114) |
| Tong, 2024 | | | 19 (18–22) | 20 (18–23) | 28 (27-29) | 29 (27-30) | 12 (10-dic) | 12 (10-13) | 16.1 (2.6) | 15.5 (2.9) | 17 (16-18) | 17 (16-19) | | | | | 7.18 (7.14–7.26) | 7.19 (7.15–7.25) | 109 (93-121) | 103 (93-116) |
| Wang, 2024 | 6.0 (0.9) | 6.0 (0.4) | 28.4 (4.0) | 28.8 (5.9) | 28.1 (3.9) | 28.5 (4.5) | 14.7 (2.9) | 14.2 (3.9) | 25.9 (6.9) | 25.4 (8.6) | 14.5 (4.1) | 14.3 (3.3) | 46.6 (12.3) | 47.8 (12.6) | 59.3 (10.6) | 59.1 (13.2) | 7.36 (7.32–7.43) | 7.37 (7.28–7.43) | 59.5 (10.5) | 59.6 (13.8) |

Abbreviations: PBW, predicted body weight; Pplat, plateau pressure; PEEP, positive end-expiratory pressure; Crs, compliance of the respiratory system; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaO_2$, arterial partial pressure of oxygen; $FiO_2$, fraction of inspired oxygen.

*$PaO_2$ is reported in KPa

Quantitative variables are reported as mean (standard deviation) or median (first quartile-third quartile), as per the original study.

| **Table S5. Details on prone positioning** | | | | | |
|---|---|---|---|---|---|
| First author, year | Duration of ECMO before PP | Duration of PP cycle | Number of PP sessions | Indications for prone positioning | Adverse events* |
| Combes, 2018 | | | | | |
| Guervilly, 2019 | 5 (4) | | 3 | • Persistent hypoxemia defined by $SpO_2$ < 88 % or $PaO_2$ < 55 mmHg despite 100% $FdO_2$ and $FiO_2$ with a maximal ECMO blood flow<br>• Failure of attempt to wean ECMO after at least 10 days of ECMO and the presence of lung consolidations on chest X-ray or lung ultrasounds<br>• According to the physician in charge of the patient. | |
| Garcia, 2020 | 1.5 | 16 | | • Severe hypoxemia ($PaO_2/FiO_2$ ratio below 80 mmHg) despite $FDO_2$ and $FiO_2$ both at 100%<br>• Extensive lung consolidation on chest imaging (>50% of lung volume). | • Pressure sores after 6 procedures: 1<br>• Minor hemorrhages at the injection cannula: 3<br>• Moderate drops in VV-ECMO flow requiring fluid resuscitation: 3 |
| Rilinger, 2020 | 3.2 (3.8) | 19.5 | 2 | Treating medical team's judgement | No relevant complications (e.g. decannulation) occurred during the positioning procedures. |
| Giani, 2021 | 4 (2-7) | 15 | 1.35 | Routine in 4 centers | Out of 21 total prone positioning procedures with complications:<br>• Desaturation: 8<br>• Bleeding: 4<br>• Decrease of extracorporeal blood flow: 4<br>• Hemodynamic instability: 2<br>• $PaCO_2$ increase: 1<br>• Thigh swelling: 1 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | • Face swelling: 1<br>• Vomiting: 1<br>• Aborted procedures: 6 |
| Chaplin, 2021 | 8 (5-18) | 11 | | | • Displacement of tracheal tubes/intravascular catheters/chest tubes: 0<br>• Grade 1 pressure injuries: six procedures (21% of total prone positioning sessions) |
| Laghlam, 2021 | | 17.4 | 4 | The decision to perform PP in patients under VV-ECMO was based on $PaO_2/FiO_2$ ratio value and left at the discretion of the attending physician, except in patients with persistent $PaO_2/FiO_2$ ratio <100, on whom PP was systematically performed according to local practices | No serious adverse events were reported for all the PP sessions |
| Martinez Martinez, 2021 | | | | | |
| COVID-ICU Group, 2021 | | | 3 | | |
| Yang, 2021 | | | | | |
| Cheng, 2021 | | | | | |
| Chang, 2022 | 12 (9-13) | | 7 | • Patients had increased sweep requirement, and worsening compliance<br>• Patients had no clinical improvement after 2 weeks, determined by inability to decrease sweep, decreased ECMO flow, continued low compliance, or no improvement on serial radiographs of the chest. | • No ECMO cannulas/chest tubes/invasive lines/endotracheal tubes were dislodged, no bleeding from the cannulation sites/chest tubes/invasive lines occurred, no recirculation events occurred<br>• Mucosal lacerations leading to bleeding: 2, with blood transfusion requirement in one patient.<br>• Cracked tracheostomy flange: 1 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | • Pressure sore on the chest after the third proning episode: 1 |
| Chen, 2022 | 2.0 (0.9–4.9) | 14 | 4 | • Difficulties in maintenance of oxygenation<br>• Requirement of aggressive sputum drainage<br>• Potential difficulties in weaning ECMO | • Pressure sores (Face): 4 (10%)<br>• Edema: 6 (15%)<br>• Vomiting: 1 (2%)<br>• Minimal bleeding: 3 (7%)<br>• Increase of CO2: 1 (2%)<br>• Decrease of $SpO_2$: 6 (15%)<br>• Decrease of systolic blood pressure: 1 (2%)<br>• Decrease of blood flow on ECMO: 7 (18%)<br>• Dislodgment: 0<br>• Severe bleeding: 0<br>• Difficult to correct hemodynamic instability: 0<br>• Malignant ventricular arrhythmia: 0 |
| Zaaqoq, 2022 | | | | | |
| Petit, 2022 | 3 (2–6) | | 2 | • Severe hypoxemia<br>• Extensive lung consolidation<br>• Difficult ECMO-weaning | |
| Raasveld, 2022 | | | | | |
| Adelsten, 2023 | 2 (2.0-4.5) | 16 | 5 | • Refractory hypoxia on V-V ECMO: $PaO_2/FiO_2$ < 11 kPa or 75 mmHg or so<br>• Unacceptable peak-/plateau pressure on V-V ECMO (> 30 mmHg)<br>• Failure to wean off V-V ECMO<br>• (Presumed) positive effect on lung function. | • Airway bleeding requiring surgical intervention and/or transfusion of blood products (33% of total 99 prone positioning sessions)<br>• Bleeding (other sites than airway and cannula) (5%)<br>• Circulation/hemodynamic collapse (9%)<br>• Severe hypoxia (20%) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | • Cannula/insertion sites/ECMO related (20%)<br>• Pressure sores and/or ulcers (38%) |
| Massart, 2023 | | | | | |
| Schmidt, 2023 | 1 (0-1) | | 4 | | |
| Giani, 2023 | 1 (1.0-1.0) | | | | |
| Tong, 2024 | | | 5 | Random assignment. PP was ceased when any of the following occurred: nonscheduled removal of endotracheal or ECMO tubes, endotracheal tube obstruction, hemoptysis, cardiac arrest, heart rate < 30 beats per minute for >1 min, systolic blood pressure < 60 mmHg for more than 5 min, and any life-threatening condition. | • ECMO flow drop: 3<br>• Pressure sores: 5<br>• Decreased blood pressure: 4<br>• Bleeding: 3<br>• Kinking of the endotracheal tube: 1<br>• Central vein catheter slippage: 1 |
| Wang, 2024 | 1 (14–22) | 15 | 5 | Routine. Patients with any of the following conditions were not to be placed in PP: facial or neck trauma; spinal instability; recent thoracic surgery; elevated intra- cranial pressure; hemoptysis; or hemodynamic instability (i.e., MAP < 65 mmHg and norepinephrine > 0.5 ug/kg/min). The criteria for stopping PP were any of the following: greater than 1 L/min increase of ECMO blood flow to achieve $SpO_2 \geq 92\%$; norepinephrine > 0.5 ug/kg/min to maintain MAP ≥ 65 mm Hg; frequent abrupt declines in blood flow; any other life-threatening reason for which the physician decided to stop the treatment. | • Accidental extubation: 0<br>• ECMO cannula dislodgement: 0<br>• Airway dislodgement: 4<br>• Endotracheal tube obstruction: 4<br>• Drop in ECMO flow: 3<br>• Cannula site bleeding: 5<br>• Hemodynamic instability: 3<br>• Vomiting: 2<br>• Facial swelling: 2 |

Abbreviations: PP, prone positioning; $SpO_2$, peripheral oxygen saturation; $FDO_2$, fraction of delivered oxygen; $PaO_2$, arterial partial pressure of oxygen; $FiO_2$, fraction of inspired oxygen; ECMO, extracorporeal membrane oxygenation; VV, veno-venous; $PaCO_2$, arterial partial pressure of carbon dioxide; MAP, mean arterial pressure.

*Overall, complications related to prone positioning were as follows:

- Pressure sores on the chest and/or face: 1/14 patients (Garcia), 1/12 patients (Chang), 4/38 patients (Chen), 5/49 patients (Tong), 6/29 prone positioning procedures (Chaplin) and 38/99 procedures (Adelsten);

- Moderate drops in VV-ECMO flow requiring fluid resuscitation: 3/14 patients (Garcia), 4/21 complicated procedures (Giani 2021), 7/38 patients (Chen), 3/49 patients (Tong), and 3/50 patients (Wang)
- Desaturation: 8/21 complicated procedures (Giani 2021), 6/38 patients (Chen), 20/99 procedures (Adelsten)
- Hemodynamic instability: 2/21 complicated procedures (Giani 2021), 1/38 patients (Chen), 4/49 patients (Tong), 3/50 patients (Wang), 9/99 procedures (Adelsten)
- PaCO2 increase: 1/21 complicated procedures (Giani 2021), 1/38 patients (Chen)
- Thigh swelling: 1/21 complicated procedures (Giani 2021)
- Edema: 1/21 complicated procedures (Giani 2021; face), 6/38 patients (Chen; unspecified), 2/50 patients (Wang; face)
- Vomiting: 1/21 complicated procedures (Giani 2021), 1/38 patients (Chen), 2/50 patients (Wang)
- Aborted procedures: 6/21 complicated procedures (Giani 2021)
- Mucosal lacerations leading to bleeding: 2/12 patients (blood transfusion requirement in one patient) (Chang);
- Cracked tracheostomy flange: 1/12 patients (Chang)
- Cannula/insertion sites/ECMO related complications, different from bleeding and sores: 20/99 procedures (Adelsten)
- Kinking/dislodgement/obstruction of the endotracheal tube: 1/50 patients (Tong), 8/49 patients (Wang)
- Central vein catheter slippage: 1/50 patients (Tong)

**Online Resource 6. Risk of bias assessments**

**Risk of bias assessments for non-randomized controlled trials**

# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Combes et al., 2018

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 28-day mortality in Figure 2A in Papazian L, Schmidt M, Hajage D, Combes A, Petit M, Lebreton G, Rilinger J, Giani M, Le Breton C, Duburcq T, Jozwiak M, Wengenmayer T, Roux D, Parke R, Loundou A, Guervilly C, Boyer L. Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med. 2022 Mar;48(3):270-280. doi: 10.1007/s00134-021-06604-x. Epub 2022 Jan 17. PMID: 35037993; PMCID: PMC8762989.

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control groups were not compared in the original study. The corresponding authors did not respond to our requests. Therefore, the outcome data were derived from a previous meta-analysis (doi: 10.1007/s00134-021-06604-x). However, the baseline characteristics of the subgroups were not described. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| **Bias in selection of participants into the study** | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "Patients were eligible for enrollment if their con- dition fulfilled the American–European Consensus Conference definition for ARDS,14 if they had undergone endotracheal intubation and had been receiving ventilation for less than 7 days, and if they met disease-severity criteria as outlined in Section II.1 of the Supplementary Appendix […]" | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| **Bias in classification of interventions** | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | According to Papazian et al. Intensive Care Med. 2022 Mar;48(3):270-280. doi: 10.1007/s00134-021-06604-x), data on vital status were likely complete. | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | Although research staff members were not blinded to the primary outcome, outcome assessors were blinded. They were likely also blinded to any intervention received during ECMO support, e.g., prone positioning. | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | PY |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Guervilly et al., 2019

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

30-day mortality. Prone positioning is hypothesized to reduce 30-day mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 30-day mortality in the unmatched cohorts (Table 1) and after the propensity score matching analysis (Supplementary)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Citation: "Patients in the prone ECMO group were more frequently turned to PP before ECMO." | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used multivariable logistic regression and matching. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | The matching method is not detailed. | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "we have performed a retrospective observational study to compare outcomes of severe ARDS patients under vvECMO according to the use of PP or lack thereof during their ECMO run." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "We have compared patients with a combination of PP during ECMO (prone ECMO group) to those maintained in supine position (ECMO alone group)." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Garcia et al., 2020

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce hospital mortality.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 28-day mortality (Table 2)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Patients in the "prone group" had significantly more frequent consolidations on chest imaging and significantly higher sweep gas flow. | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We performed a retrospective study of patients with SARS-CoV-2-induced ARDS submitted to PP during VV-ECMO." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "We assess the safety of PP and compare patients with PP under ECMO (prone ECMO group) to those maintained in the supine position (supine ECMO group)." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Favours comparator |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Rilinger et al., 2020

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

30-day mortality. Prone positioning is hypothesized to reduce 90-day mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 30-day mortality in the unmatched cohorts(Table 2) and following the propensity score matching analysis (Table E2)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Citation: "Patients with PP during ECMO support had a higher rate of pre-existing chronic renal failure and pneumonia- induced ARDS. Patients in the prone group displayed a different pulmonary pathogen spectrum […]<br>Patients with PP during ECMO support showed higher PEEP levels from day 4 and higher plateau pressures from day 4 to 8 […] patients with PP during ECMO support showed less spontaneous breathing on day 5 and day 8 to 10." | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used propensity score matching. Citation: “Thirty-eight propensity score matched pairs (76 patients) with similar baseline characteristics could be analysed”. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| **Bias in selection of participants into the study** | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We report retrospective data of a single-centre registry of patients with severe ARDS treated with VV ECMO." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| **Bias in classification of interventions** | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: “Patients receiving PP during ECMO support were allocated to the prone group, whereas the remaining patients formed the supine group.” | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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Yang et al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Data on hospital mortality stratified for the prone and no prone groups are not reported in the original study, but were derived from a previous meta-analysis.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality in Figure 3 in Papazian L, Schmidt M, Hajage D, Combes A, Petit M, Lebreton G, Rilinger J, Giani M, Le Breton C, Duburcq T, Jozwiak M, Wengenmayer T, Roux D, Parke R, Loundou A, Guervilly C, Boyer L. Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med. 2022 Mar;48(3):270-280. doi: 10.1007/s00134-021-06604-x. Epub 2022 Jan 17. PMID: 35037993; PMCID: PMC8762989.

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control subgroups were not compared in the original study. The corresponding authors did not respond to our requests. Therefore, the outcome data were derived from a previous meta-analysis (doi: 10.1007/s00134-021-06604-x). However, the baseline characteristics of the subgroups were not described. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We conducted this retrospective observational study on adult patients infected by SARS-CoV-2 who were treated with ECMO since January 1 in Hubei, China." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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Giani et al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study. However, the study was included after correspondence with the authors.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality in the unmatched cohorts (Table 4) and after the propensity score matching analysis (Table 6)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Citation: "SOFA score was higher in control subjects […]. Renal replacement therapy before ECMO was used more frequently in the prone group, and the use of nitric oxide before ECMO was higher in the control group. […] In the prone group, the proportion of patients referred from other centers and retrieved on ECMO was higher." | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used multivariable logistic regression and propensity score matching. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | PY |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "In this multicenter retrospective study, we enrolled patients treated in six Italian ECMO referral centers between January 2014 and December 2018. We included adult patients with a diagnosis of ARDS according to the Berlin definition […] and treated with V-V ECMO support." | PN |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | Although the selection of participants into the study was not based on any characteristic observed after the start of the intervention, all control patients came from the same centers. This unmeasured selection bias may have affected the association of the intervention with mortality.<br>Citation: "In the prone group, we enrolled consecutive ECMO patients who underwent PP in four centers in which PP is routinely performed during extracorporeal support. […] In the control group, we enrolled consecutive patients from two ECMO centers in which patients are routinely managed in the supine position without PP" | Moderate |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: “In the prone group, we enrolled consecutive ECMO patients who underwent PP in four centers in which PP is routinely performed during extracorporeal support (ASST Monza, Monza; Ospedale Maggiore Policlinico, Milano; Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo; and Azienda Ospedaliera Mater Domini, Catanzaro). In the control group, we enrolled consecutive patients from two ECMO centers in which patients are routinely managed in the supine position without PP (Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, and Azienda Ospedaliera Universitaria Citta` della Salute e della Scienza, Torino).” | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | Citation: "Six procedures (2%) were aborted because of respiratory or hemodynamic instability during PP." | N |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Absolute frequencies of hospital mortality are available for the whole cohort. The multivariable logistic model was performed on 226 patients, instead of 240. | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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Chaplin et al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| | |
|---|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles | |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| | |
|---|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings | |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study. However, the study was included because of the availability of data on hospital mortality after correspondence with the authors.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality (Table 1)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | No comparison was made between the prone and supine groups. Therefore, significant between-group differences may be present. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "All adult patients who received VV-ECMO at this centre between July 1, 2014, and July 1, 2019, were included." | PN |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "Patients were defined as having received prone positioning if they were documented as being in the prone position for more than 1 h. […]Patients who underwent lung transplant were excluded." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | Citation: "One patient was turned to the prone position for only 20 min and returned to the supine position urgently owing to an episode of desaturation and was therefore excluded from data analysis." | N |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Laghlam et al., 2022

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 28-day mortality (Table 1)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Although the prone positioning and no prone positioning groups were similar according to reported baseline characteristics, we cannot exclude the presence of unmeasured confounders. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| **Bias in selection of participants into the study** | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We included all consecutive patients under mechanical ventilation with the following inclusion criteria [...]." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| **Bias in classification of interventions** | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | No clear definition of the intervention groups. However, the assignment to the two groups is | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Martines Martines at al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

6-month mortality. Prone positioning is hypothesized to reduce 6-month mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 6-month mortality (Table)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Although the prone positioning and no prone positioning groups were similar according to reported baseline characteristics, we cannot exclude the presence of unmeasured confounders. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "All adult (>18 years old) COVID-19 patients requiring extracorporeal respiratory support between 1st March and 1st December 2020 were included." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | No clear definition of the intervention groups. However, the assignment to the two groups is | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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COVID-ICU, 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 28-day mortality in Figure 2A in Papazian L, Schmidt M, Hajage D, Combes A, Petit M, Lebreton G, Rilinger J, Giani M, Le Breton C, Duburcq T, Jozwiak M, Wengenmayer T, Roux D, Parke R, Loundou A, Guervilly C, Boyer L. Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med. 2022 Mar;48(3):270-280. doi: 10.1007/s00134-021-06604-x. Epub 2022 Jan 17. PMID: 35037993; PMCID: PMC8762989.

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control subgroups were not compared in the original study. The corresponding authors did not respond to our requests. Therefore, the outcome data were derived from a previous meta-analysis (doi: 10.1007/s00134-021-06604-x). However, the baseline characteristics of the subgroups were not described. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "All consecutive patients over 16 years of age admitted to the participating ICU between February 25, 2020, and May 4, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were included." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | According to figure S1 and S2, data on vital status were complete. | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Cheng et al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality stratified for the prone and no-prone groups in Table 3

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | No comparison was performed between the prone and no-prone groups. Therefore, we hypothesize the selection bias associated with the decision to offer prone positioning makes the potential for unmeasured confounding not negligible. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Critical |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "All confirmed COVID-19 patients admitted to 62 authorized hospitals in Wuhan from January 1, 2020, to May 1, 2020, were examined […] the patients who met the indications and had no contraindications of ECMO use were enrolled in this study." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Critical |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Chang et al., 2022

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality (Table 2)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Despite there being no significant differences in patient age, sex, body mass index, or pre-existing conditions between the two groups, the patients who were proned were found to have significantly longer ECMO duration, ventilator duration, and hospital length of stay, compared to patients who were not. Given that patients were proned due to minimal or no improvement in ECMO requirement after two weeks, proning was likely not the primary variable leading to these differences, but rather a marker for a more severe underlying disease. | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | N |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Critical |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We conducted a retrospective analysis of all patients admitted to New York University Langone Health (NYULH) Manhattan with severe ARDS requiring initiation of ECMO support between March 1 and May 31, 2020. All patients placed on ECMO for severe ARDS during this time had ARDS secondary to COVID-19." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "In this study, we will describe the patient population that was proned, evaluate pulmonary mechanics with resultant changes in ECMO settings, and report the safety of proning while on ECMO support." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | Extensive data on pronation complications are reported. Therefore, deviations from the intended intervention, such as need for acute supination for complications related to proning, is unlikely. | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Critical |
| Optional: What is the overall predicted direction of bias for this outcome? | | Favours comparator |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Chen et al., 2022

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study. However, the study was included because of the availability of data on hospital mortality.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality (Table 4)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Citation: "Before matching, we found statistical significance in age and the pathogen spectrum of ARDS induced by pneumonia." | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used propensity score matching. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| **Bias in selection of participants into the study** | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "This is a retrospective study enrolling patients treated in the 30-bed medical intensive care unit (MICU) of a teaching hospital at Beijing, China from April 2013 to October 2020. All 91 patients included in our study met the Berlin definition of ARDS [2] and were sup- ported with VV-ECMO. All participants were older than 14 years because otherwise they would be triaged to pediatric department. We did not include patients with COVID-19." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: “Patients who received at least one period of PP during ECMO were categorized into the prone group, while those without PP were defined as the supine group.” | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | N |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | N |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Zaaqoq et al., 2021

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality (Table 2)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| Extracorporeal membrane oxygenation centers | Extracorporeal membrane oxygenation centers | No | Yes | No information |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The respiratory compliance was lower in the prone position group, which may imply greater respiratory disease severity. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used a multistate survival analysis to examine patient outcomes over time to account for confounding related to time and patient severity. A Weibull survival model was used in the multistate model to examine the instantaneous cause-specific hazards of death, while adjusting for potential confounders. The potential confounders were identified based on previously published studies, the clinically relevant factors for decision making, and differences in baseline characteristics. Moreover, the authors adjusted for each intensive care unit using a random intercept. The effect of prone position was modeled as a time-dependent variable that accumulated during a patient's time on extracorporeal membrane oxygenation. Finally, different nonlinear transformations in the relationship between prone positioning and death were tested. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "The enrollment eligibility criteria were age of 18 years old or greater, confirmed COVID-19, and need for invasive mechanical ventilation and veno-venous ECMO support." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "[…] comparing patients who experienced prone positioning post-extracorporeal membrane oxygenation initiation versus those who were always supine" | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Citation: "There are more missing outcome data in the supine versus prone group. We attempted to overcome this limitation by applying multiple imputation and censoring patients at 90 days". | N |
| 5.2 Were participants excluded due to missing data on intervention status? | | PN |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | Citation: "There are more missing outcome data in the supine versus prone group. We attempted to overcome this limitation by applying multiple imputation and censoring patients at 90 days". | N |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | No sensitivity analyses with multiple imputations replacing missing data were used. | NI |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Petit et al., 2022

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

90-day mortality. Prone positioning is hypothesized to reduce 90-day mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 90-day mortality (Table S3)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Citation: "Before matching, PP-ECMO patients had significantly higher BMIs, lower SAPS II scores, more frequently prone-positioned pre-ECMO PP, and more frequent viral pneumonia." | Y |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used propensity score matching. Citation: “After PS matching, the absolute standardized mean difference was less than 0.1 for all variables except diabetes mellitus.” | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We retrospectively analyzed the database of our 26-bed ICU to identify all severe ARDS patients given VV-ECMO support (January 2012–2020)." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "we report the characteristics and outcomes of our ECMO-treated ARDS patients according to concomitant PP use or not." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Citation: “Missing data were not imputed to complete the PS.”. However, no further description on missing data is provided. | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| **Bias in selection of the reported result** | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| **Overall bias** | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Raasveld et al., 2022

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality. Twenty-eight-day mortality was not analyzed in the original study, but was obtained thanks to the correspondence with the authors.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Correspondence with the authors.

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control subgroups were not compared in the original study. The outcome data were derived from the correspondence with the authors. However, the baseline characteristics of the subgroups were not described. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| **Bias in selection of participants into the study** | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "This retrospective study consisted of two cohorts: a COVID-19 cohort and a non-COVID-19 cohort. Patients were included if they were 18 years old or older and received VV ECMO during ICU ad- mission. In the COVID-19 cohort, patients were included if they were admitted to one of the par- ticipating ICUs between March 2020 and December 2020 and had a polymerase chain reaction-proven severe acute respiratory syndrome coronavirus 2 infection. | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Citation: “the overall percentage of missing data within all variables was less than 5%” | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Adelsten et al., 2023

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality. Twenty-eight-day mortality was not analyzed in the original study, but was provided by the authors.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 28-day mortality (authors' correspondence)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control subgroups were not compared in the original study. Although the corresponding authors did respond to our requests, they provided aggregated data, therefore baseline characteristics of the subgroups could not be compared. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "We performed a nationwide retrospective cohort study, reporting data on adverse events in relation to PPV from all patients in Denmark with PCR confirmed SARS-Cov-2 ARDS, supported with V-V ECMO." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Data available from correspondence with the authors. | Y |
| 5.2 Were participants excluded due to missing data on intervention status? | | PN |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Massart et al., 2023

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles

### List co-interventions that could be different between intervention groups and that could impact on outcomes

Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Hospital mortality. Prone positioning is hypothesized to reduce hospital mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of hospital mortality (Table S3)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Although the prone positioning and no prone positioning groups were similar according to reported baseline characteristics, we cannot exclude the presence of unmeasured confounders. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used multivariable logistic regression and propensity score matching. | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Favours comparator |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "For the present study, we analyzed all consecutive patients included in the registry up to June 29, 2021, supported by venovenous ECMO for respiratory failure, and in whom prone position status while on ECMO (yes/no) and hospital mortality were known." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "After cannulation, 364 patients (70%) were proned at least once, while 153 (30%) remained in the supine position for the whole ECMO run." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| | | |
|---|---|---|
| **Bias due to deviations from intended interventions** | | |
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| Bias due to missing data | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | Citation: “143 (28%) patients had missing data”. | N |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | No sensitivity analyses with multiple imputations replacing missing data were used. | NI |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| Bias in measurement of outcomes | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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Giani et al., 2023

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

28-day mortality. Prone positioning is hypothesized to reduce 28-day mortality. Twenty-eight-day mortality was not analyzed in the original study, but was obtained thanks to the correspondence with the authors.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Correspondence with the authors.

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | The experimental and control subgroups were not compared in the original study. The outcome data were derived from the correspondence with the authors. However, the baseline characteristics of the subgroups were not described. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | | PN |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | NI |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Serious |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "2022. We included patients with a diagnosis of COVID-19–related ARDS treated with V-V ECMO support. Patients with other ECMO configurations were excluded. 2022. We included patients with a diagnosis of COVID-19–related ARDS treated with V-V ECMO support. Patients with other ECMO configurations were excluded." | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | The intervention groups were not defined in the study methods, as participants were not analyzed according to the prone positioning vs. no prone positioning characteristic. | N |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | PN |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| **Bias due to deviations from intended interventions** | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | PN |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NA |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Serious |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**

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## Wang et al., 2024

## ROBINS-I tool (Stage I): At protocol stage

### Specify the review question

| | |
|---|---|
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |
| Outcomes | 28-day mortality |

### List the confounding domains relevant to all or most studies

| |
|---|
| Patients' characteristics, etiology of acute hypoxemic respiratory failure, severity of acute hypoxemic respiratory failure, large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers; number of proning cycles |

### List co-interventions that could be different between intervention groups and that could impact on outcomes

| |
|---|
| Steroids, antibiotics, fluid therapy, mechanical ventilation settings, extracorporeal membrane oxygenation settings |

## ROBINS-I tool (Stage II): For each study

### Specify a target randomized trial specific to the study

| | |
|---|---|
| Design | Individually randomized |
| Participants | Patients with acute hypoxemic respiratory failure receiving veno-venous extracorporeal membrane oxygenation |
| Experimental intervention | Prone positioning |
| Comparator | No prone positioning |

### Is your aim for this study…?

X to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

### Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

60-day mortality. Prone positioning is hypothesized to reduce 60-day mortality. Twenty-eight-day mortality was not analyzed in the original study.

### Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Absolute frequency of 60-day mortality in the unmatched cohorts (Table 2) and in the propensity score matching analysis (Table 5)

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

*"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).*

| **(i) Confounding domains listed in the review protocol** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Patients' characteristics | Age, gender, comorbidities, severity of critical illness | No | Yes | No information |
| Etiology of acute hypoxemic respiratory failure | Etiology of acute hypoxemic respiratory failure | No | | |
| Severity of acute hypoxemic respiratory failure | Arterial partial pressure of oxygen to fraction of inspired oxygen ratio | No | | |
| Large-volume (>20 cases annually) vs. low-volume (≤20 cases annually) extracorporeal membrane oxygenation centers | Number of extracorporeal membrane oxygenation case per year | No | | |
| Number of proning cycles before cannulation | Number of proning cycles | No | | |

| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** | | | | |
|---|---|---|---|---|
| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary?* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |

| | | | | |
|---|---|---|---|---|
| None | | | | |

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

*"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.*

| **(i) Co-interventions listed in the review protocol** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| No important co-interventions were listed in the review protocol | | |

| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** | | |
|---|---|---|
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Steroids | No | No information |
| Antibiotics | No | No information |
| Fluid therapy | No | No information |
| Mechanical ventilation settings | No | No information |
| Extracorporeal membrane oxygenation settings | No | No information |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

| Signalling questions | Description | Response options |
|---|---|---|
| **Bias due to confounding** | | |
| 1.1 Is there potential for confounding of the effect of intervention in this study?<br>**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | Although there was no significant difference in baseline characteristics between the two groups (Table 1), the selection bias associated with the decision to offer prone positioning makes the potential for unmeasured confounding not negligible. | PY |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: | | |
| 1.2. Was the analysis based on splitting participants' follow up time according to intervention received?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, go to question 1.3. | | N |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?<br>**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)<br>**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8) | | NA |

| | | |
|---|---|---|
| **Questions relating to baseline confounding only** | | |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? | The authors used propensity score matching. Citation: "The dot-plot of covariates included in the PS (Figure S3) showed that the two groups were comparable." | PY |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | Y |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? | | N |
| **Questions relating to baseline and time-varying confounding** | | |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? | | NA |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? | | NA |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to confounding? | | Unpredictable |

| Bias in selection of participants into the study | | |
|---|---|---|
| 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?<br>**If N/PN to 2.1:** go to 2.4 | Citation: "All patients included in our study met the Berlin definition of ARDS and underwent PP before VV-ECMO" | N |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? | | NA |
| 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? | | NA |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | | Y |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? | | NA |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | | Unpredictable |

| Bias in classification of interventions | | |
|---|---|---|
| 3.1 Were intervention groups clearly defined? | Citation: "Patients were divided into the prone and supine groups according to whether early PP was combined with VV-ECMO." | Y |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | | Y |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | | N |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to classification of interventions? | | Unpredictable |

| Bias due to deviations from intended interventions | | |
|---|---|---|
| **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** | | |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | | PN |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? | | NA |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** | | |
| 4.3. Were important co-interventions balanced across intervention groups? | | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? | | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? | | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? | | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? | | Unpredictable |

| **Bias due to missing data** | | |
|---|---|---|
| 5.1 Were outcome data available for all, or nearly all, participants? | From Table S1, missing data were very limited. | PY |
| 5.2 Were participants excluded due to missing data on intervention status? | | NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | | NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? | | NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? | | NI |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing data? | | Unpredictable |

| **Bias in measurement of outcomes** | | |
|---|---|---|
| 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | | N |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | | PY |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | | Y |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | | N |
| **Risk of bias judgement** | | Moderate |
| Optional: What is the predicted direction of bias due to measurement of outcomes? | | Unpredictable |

| Bias in selection of the reported result | | |
|---|---|---|
| Is the reported effect estimate likely to be selected, on the basis of the results, from...<br>7.1. ... multiple outcome *measurements* within the outcome domain? | | N |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | | PN |
| 7.3 ... different *subgroups*? | | PN |
| **Risk of bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

| Overall bias | | |
|---|---|---|
| **Risk of bias judgement** | | Moderate |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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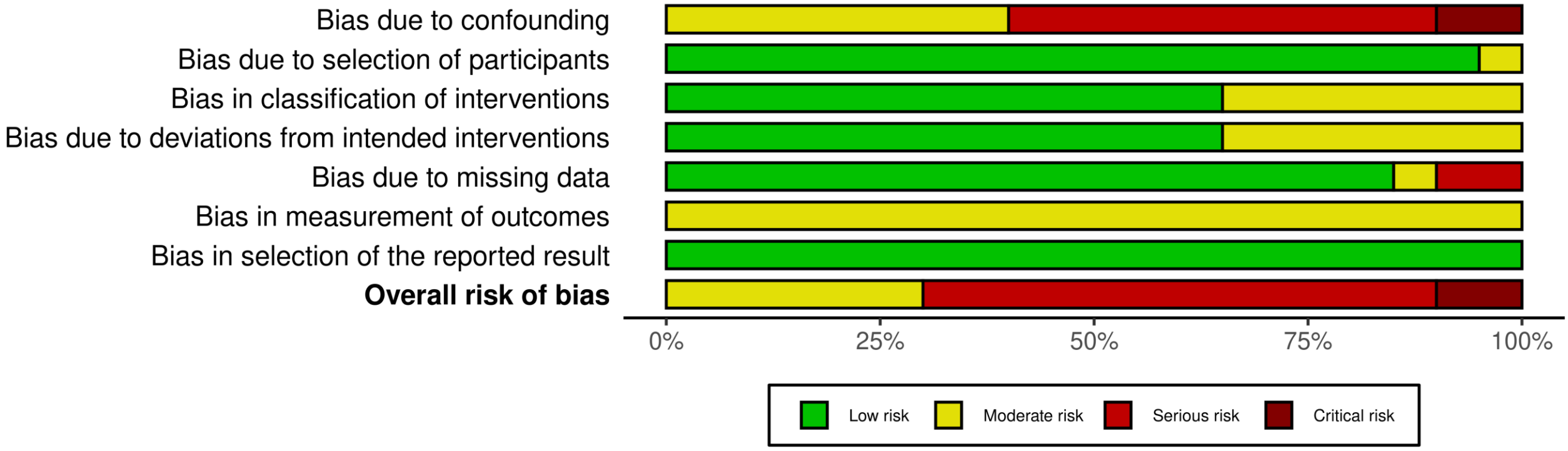
**Figure S1. Risk of bias in non-randomized studies of interventions (ROBINS-I) summary plot**



**Risk of bias assessments for randomized controlled trials**

# Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
# TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

**Version of 22 August 2019**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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**Study details**

| | |
|---|---|
| **Reference** | Tong H, Pan F, Zhang X, Jia S, Vashisht R, Chen K, Wang Q. Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a prospective multicenter randomized controlled study. J Thorac Dis. 2024 Feb 29;16(2):1368-1377. doi: 10.21037/jtd-23-1808. Epub 2024 Jan 15. PMID: 38505030; PMCID: PMC10944719. |

**Study design**

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

**For the purposes of this assessment, the interventions being compared are defined as**

Experimental: No prone positioning Comparator: Prone positioning

| | |
|---|---|
| **Specify which outcome is being assessed for risk of bias** | 30-day mortality |
| **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | Absolute value of 30-day survival in Table 5 |

**Is the review team's aim for this result…?**

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

**If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

**Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)**

X Journal article(s) with results of the trial
X Trial protocol
☐ Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

### Domain 1: Risk of bias arising from the randomization process

| Signalling questions | Comments | Response options |
|---|---|---|
| **1.1 Was the allocation sequence random?** | Citation: "One of the researchers (Qianqian Wang) used Stata software version 14 (StataCorp., College Station, TX, USA) to generate random numbers. A series of consecutively numbered, opaque, sealed envelopes were used to store the random numbers. After enrollment, the envelope was opened by the participant (patients' relatives and researchers); moreover, the patients were randomly allocated in a 1:1 ratio into PP and control groups based on the number in the envelope." | Y |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | | PY |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | Although the duration of mechanical ventilation before ECMO was significantly shorter in the experimental group, compared to the control group, all other baseline characteristics were similar. | PN |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias arising from the randomization process? | | Favours experimental |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

| Signalling questions | Comments | Response options |
|---|---|---|
| **2.1. Were participants aware of their assigned intervention during the trial?** | Citation: "[… ] the patients were unaware of the trial-group assignments." | N |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | Y |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** | Ninety-two percent of patients in the experimental group reached the duration target. Although no description of the reasons leading to the interruption of the prone positioning session is provided, the small percentage of patients not reaching the target is compatible with clinical practice. | PN |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** | | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** | | NA |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | No specifications are provided. However, all patients assigned to either group are analyzed as part of the assignment arm, | PY |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Unpredictable |

Domain 3: Missing outcome data

| Signalling questions | Comments | Response options |
|---|---|---|
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | | Y |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | | NA |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** | | NA |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? | | Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

| Signalling questions | Comments | Response options |
|---|---|---|
| **4.1 Was the method of measuring the outcome inappropriate?** | | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | | PN |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | As reported in the study protocol, outcome assessors were unaware of the intervention received by study participants | N |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | | NA |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | Unpredictable |

Domain 5: Risk of bias in selection of the reported result

| Signalling questions | Comments | Response options |
|---|---|---|
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | No pre-specified analysis plan was found in either the study protocol or the trial registration. | NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** | | |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | | N |
| **5.3 ... multiple eligible analyses of the data?** | | PN |
| **Risk-of-bias judgement** | | Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

Overall risk of bias

| | | |
|---|---|---|
| **Risk-of-bias judgement** | | Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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# Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
# TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

**Version of 22 August 2019**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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**Study details**

| | |
|---|---|
| **Reference** | Schmidt M, Hajage D, Lebreton G, Dres M, Guervilly C, Richard JC, Sonneville R, Winiszewski H, Muller G, Beduneau G, Mercier E, Roze H, Lesouhaitier M, Terzi N, Thille AW, Laurent I, Kimmoun A, Combes A; PRONECMO Investigators, the REVA Network, and the International ECMO Network (ECMONet). Prone Positioning During Extracorporeal Membrane Oxygenation in Patients With Severe ARDS: The PRONECMO Randomized Clinical Trial. JAMA. 2023 Dec 26;330(24):2343-2353. doi: 10.1001/jama.2023.24491. Erratum in: JAMA. 2024 Feb 6;331(5):446. doi: 10.1001/jama.2024.0231. PMID: 38038395; PMCID: PMC10692949. |

**Study design**

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

**For the purposes of this assessment, the interventions being compared are defined as**

Experimental: Prone positioning Comparator: No prone positioning

| | |
|---|---|
| **Specify which outcome is being assessed for risk of bias** | 60-day mortality |
| **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | Table 2 |

**Is the review team's aim for this result…?**

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

**If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

**Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)**

X Journal article(s) with results of the trial
X Trial protocol
X Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

### Domain 1: Risk of bias arising from the randomization process

| Signalling questions | Comments | Response options |
|---|---|---|
| **1.1 Was the allocation sequence random?** | Citation: "Eligible patients were randomly assigned in a 1:1 ratio to either prone positioning while undergoing ECMO (prone ECMO group) or supine positioning while undergoing ECMO (supine ECMO group) in permuted blocks of size 4 or 6. Randomization was performed through a secure web-based system using the minimization method […]:" | Y |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | | PY |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | The groups were similar, with respect to baseline patient characteristics. | N |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias arising from the randomization process? | | Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

| Signalling questions | Comments | Response options |
|---|---|---|
| **2.1. Were participants aware of their assigned intervention during the trial?** | Citation: "[…] the trial was unblinded due to the nature of the intervention, and this design may introduce bias." | PN |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | | Y |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** | Citations: "In the prone ECMO group, 17 patients (19.8%) discontinued the prone intervention before achievement of 4 prone position sessions […] Among patients randomized to the supine ECMO group, 2 (2.4%) were placed in prone position for refractory hypoxemia while undergoing ECMO"<br>The above-mentioned deviations occurred according to the trial protocol. | PN |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** | | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** | | NA |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | Citation: "The primary analysis will be performed with the intention to treat population." (from the statistical analysis plan) | Y |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | | Unpredictable |

Domain 3: Missing outcome data

| Signalling questions | Comments | Response options |
|---|---|---|
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | | Y |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | | NA |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** | | NA |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? | | Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

| Signalling questions | Comments | Response options |
|---|---|---|
| **4.1 Was the method of measuring the outcome inappropriate?** | | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | | PN |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Citation: "Patient safety was regularly monitored by an independent data and safety monitoring board, who analyzed adverse events in a blinded manner."<br>Although not clearly specified, it is reasonable to imagine that the Direction de la Recherche Clinique et du Développement, Assistance Publique–Hôpitaux de Paris, which performed statistical analyses, was also blinded. | PN |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | | NA |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | | NA |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias in measurement of the outcome? | | Unpredictable |

Domain 5: Risk of bias in selection of the reported result

| Signalling questions | Comments | Response options |
|---|---|---|
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | The statistical analysis plan was examined. | Y |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** | | |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | | N |
| **5.3 ... multiple eligible analyses of the data?** | | PN |
| **Risk-of-bias judgement** | | Low |
| Optional: What is the predicted direction of bias due to selection of the reported result? | | Unpredictable |

Overall risk of bias

| | | |
|---|---|---|
| **Risk-of-bias judgement** | | Low |
| Optional: What is the overall predicted direction of bias for this outcome? | | Unpredictable |

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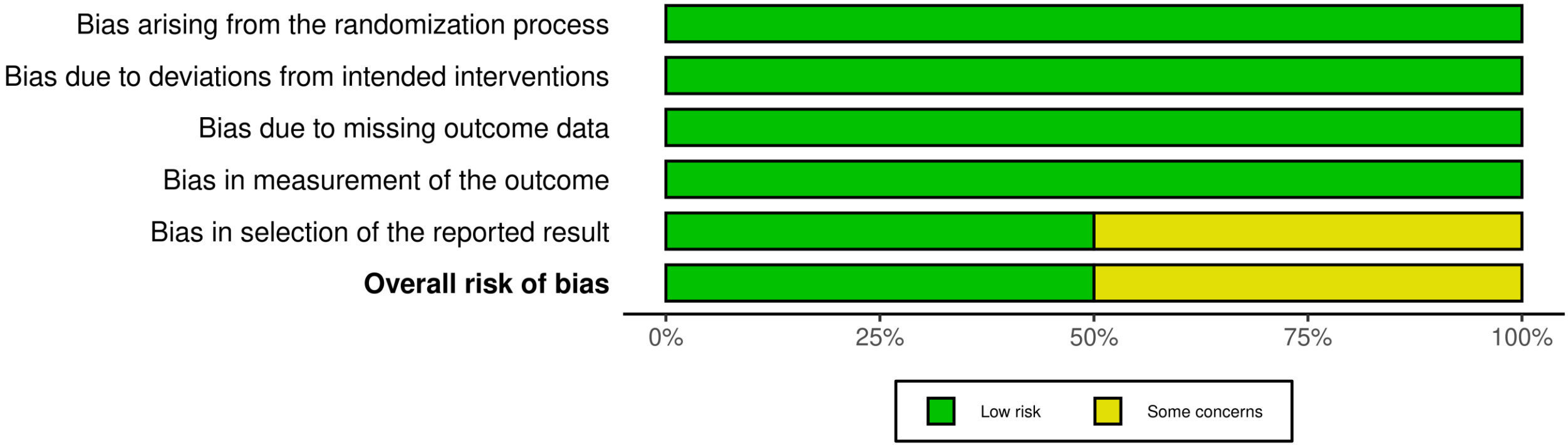
**Figure S2. Risk of bias (RoB) 2 summary plot**

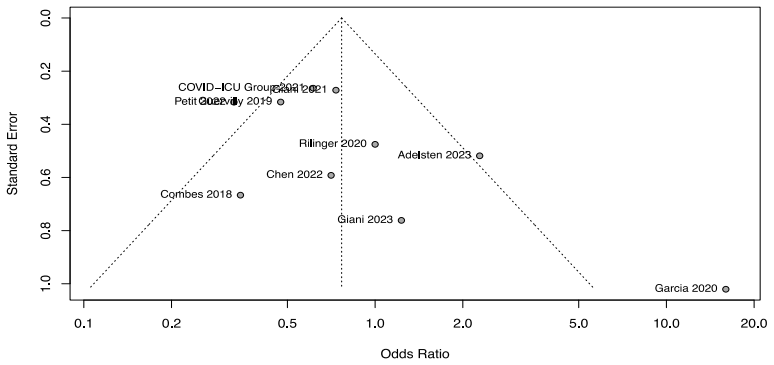


# Online Resource 7. The assessment of publication bias

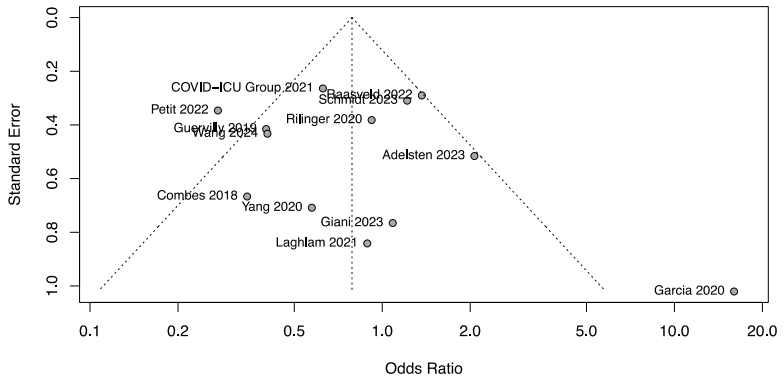
## A. Funnel plots

Funnel plots for the primary and secondary outcomes are reported. A funnel plot is a scatter plot of the intervention effect estimates from individual studies plotted on the horizontal axis, against the standard error of the estimated effect on the vertical axis. Abbreviations: ICU, intensive care unit, ECMO, extracorporeal membrane oxygenation.

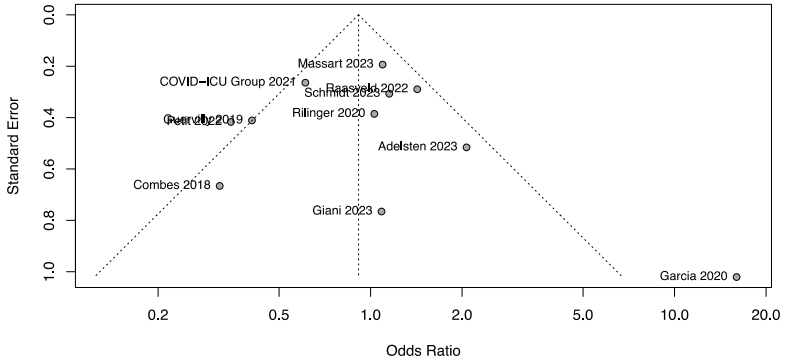
28-DAY MORTALITY



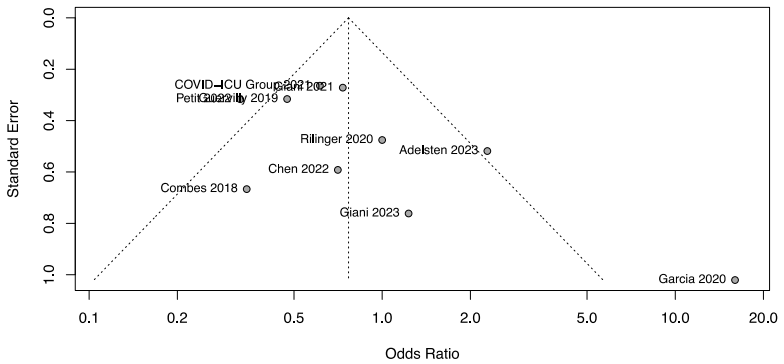

60-DAY MORTALITY



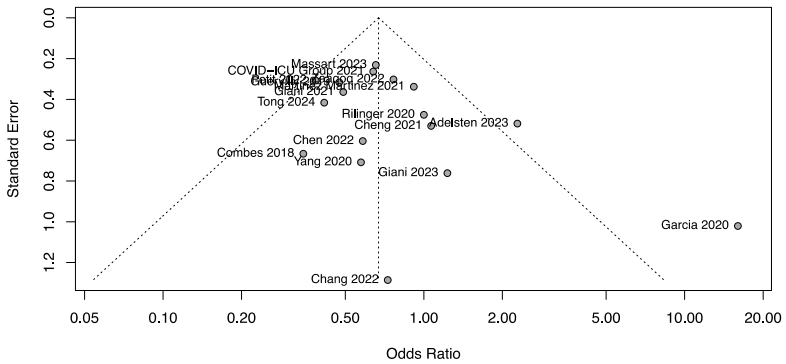

90-DAY MORTALITY



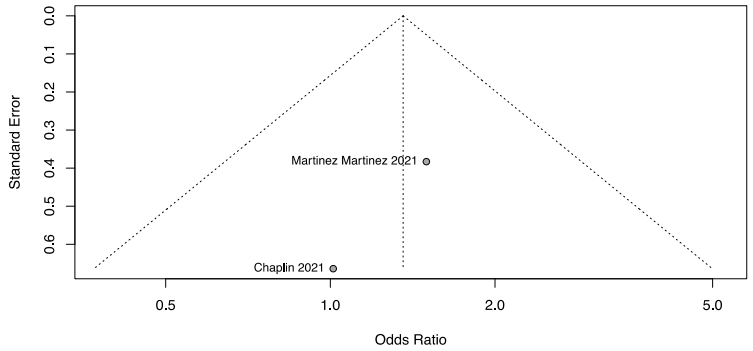

ICU MORTALITY



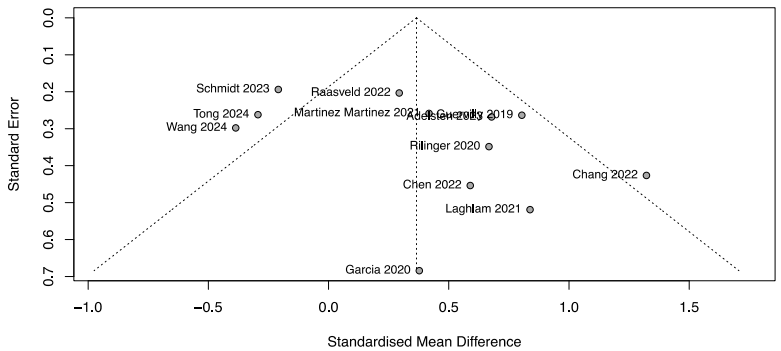

HOSPITAL MORTALITY



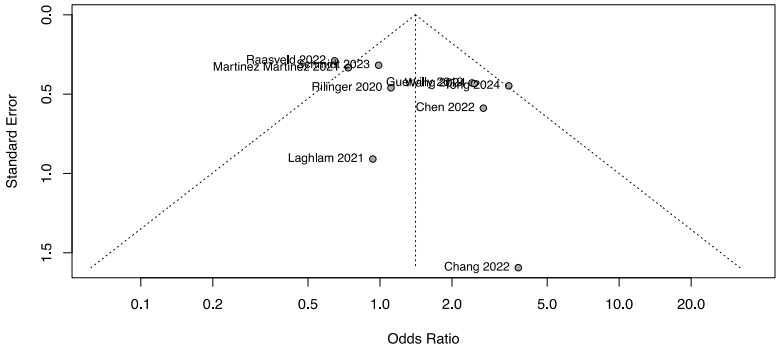
## 6-MONTH MORTALITY



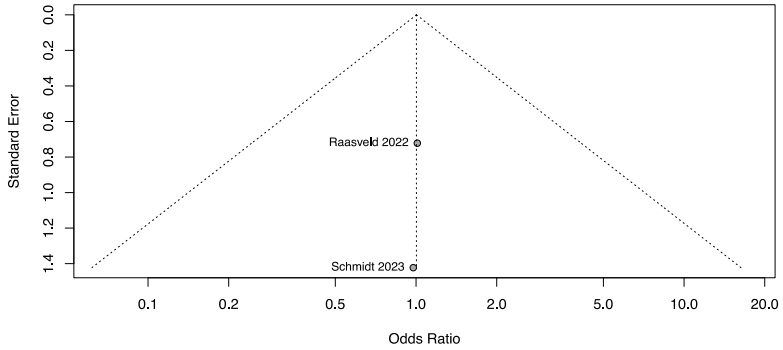

## ECMO DURATION



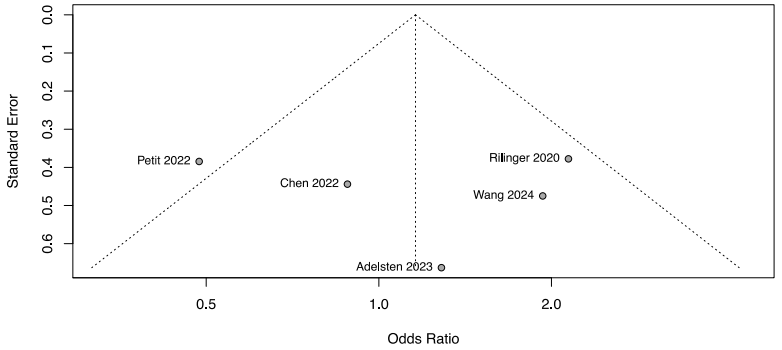

## ECMO WEANING



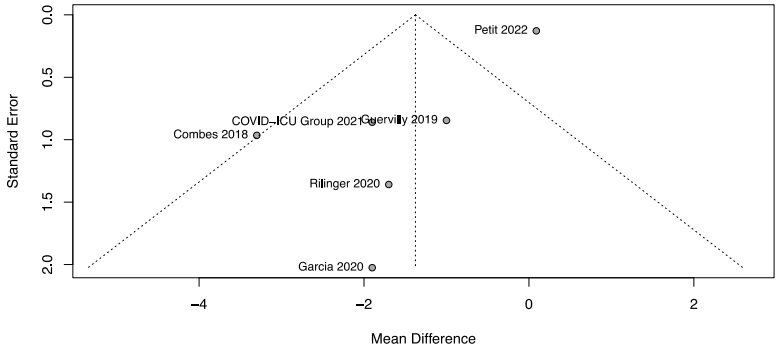

## RECANNULATION



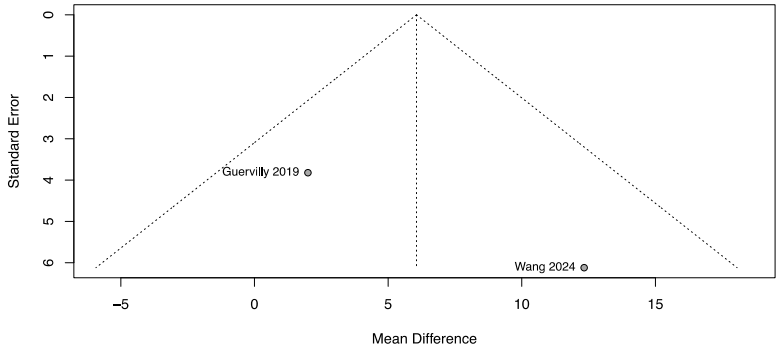

## TRACHEOSTOMY



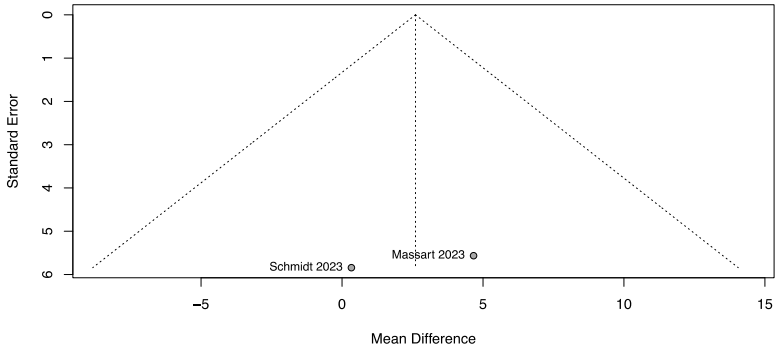

## 28-DAY VENTILATOR-FREE DAYS



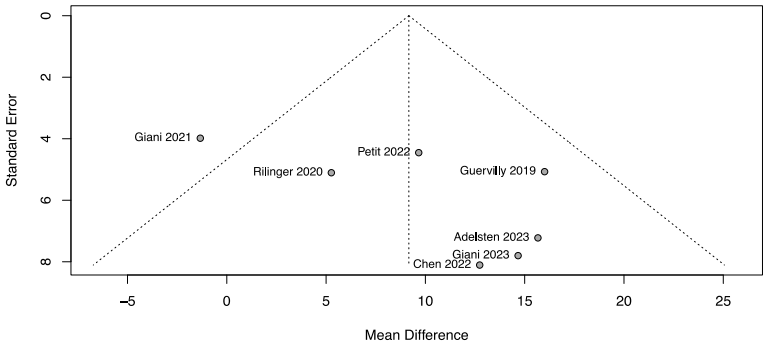

## 60-DAY VENTILATOR-FREE DAYS



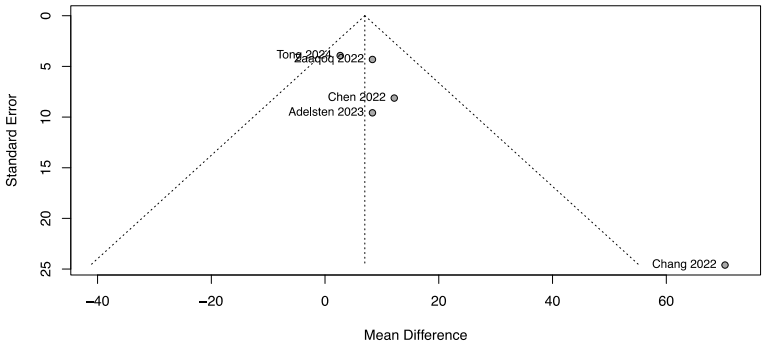

## 90-DAY VENTILATOR-FREE DAYS



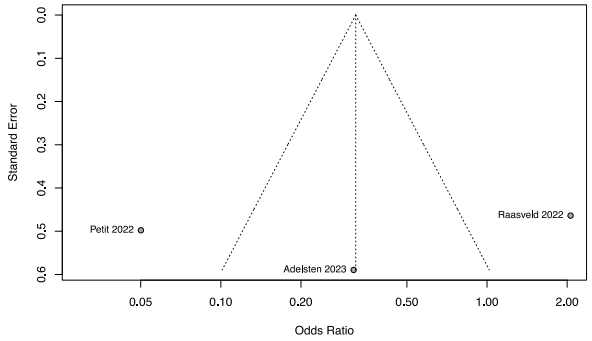
## ICU LENGTH OF STAY



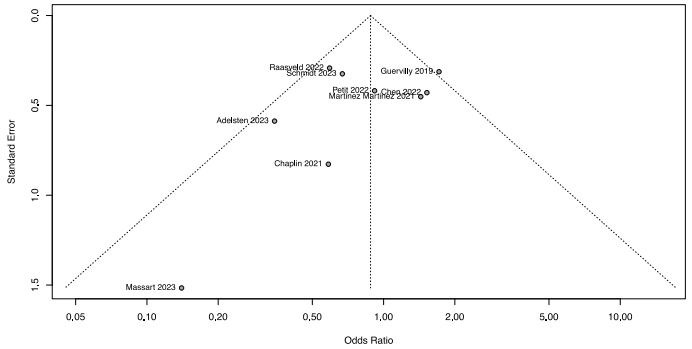

## HOSPITAL LENGTH OF STAY



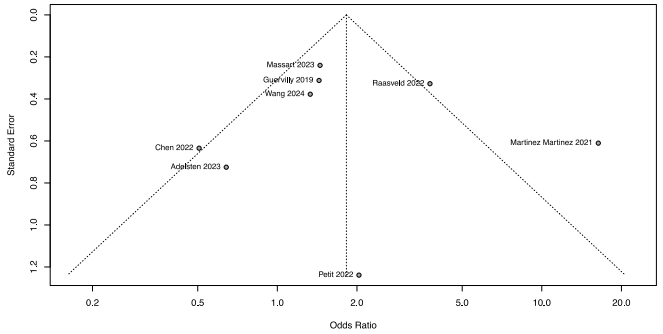

## BLEEDING AT CANNULA SITE



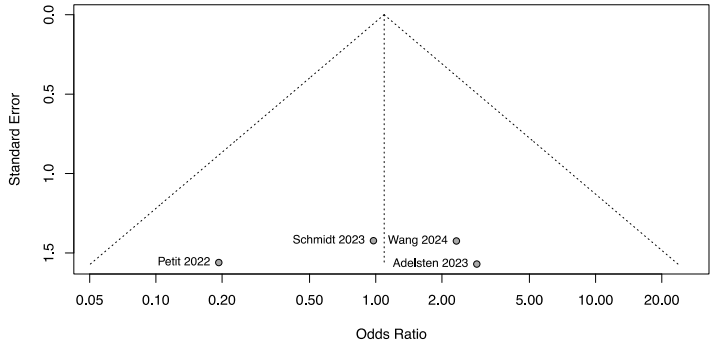

## TOTAL BLEEDING EVENTS



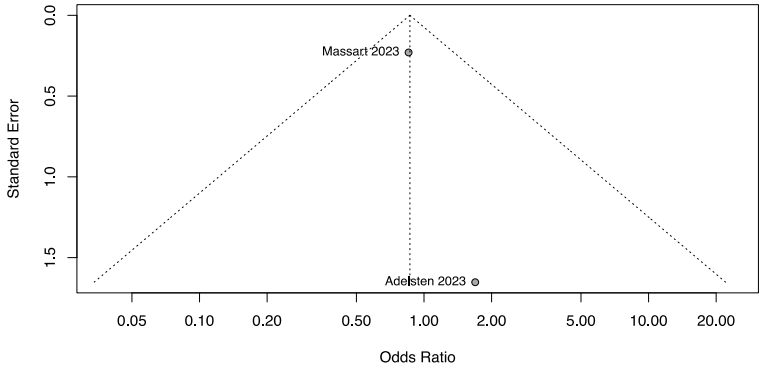

## TOTAL THROMBOEMBOLISM EVENTS



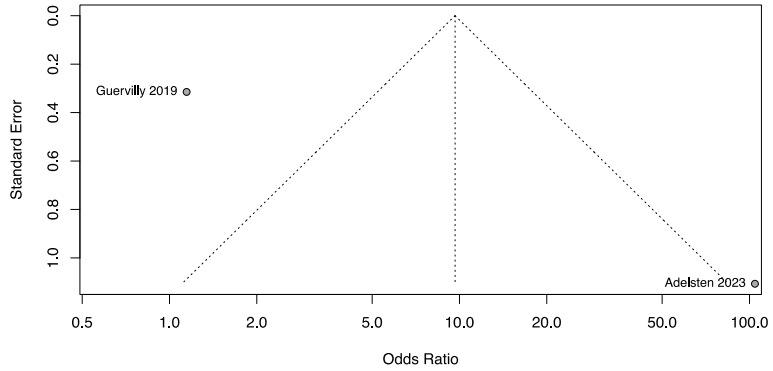

## CANNULA DISLODGEMENT




## LIMB ISCHEMIA




## CIRCUIT CHANGE




## INFECTION

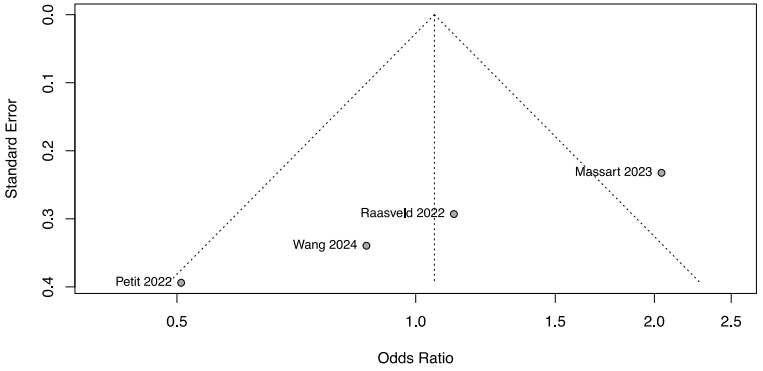
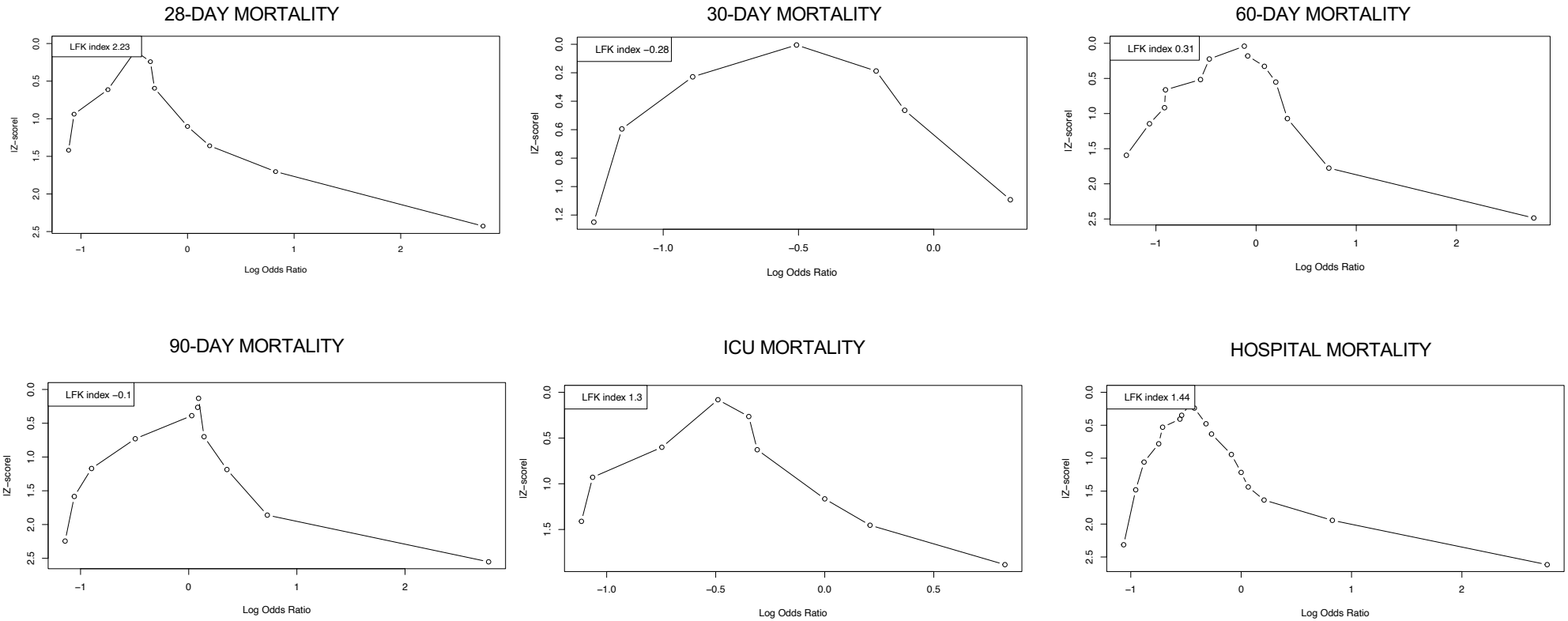


**Table S6. Regression tests for funnel plot asymmetry**

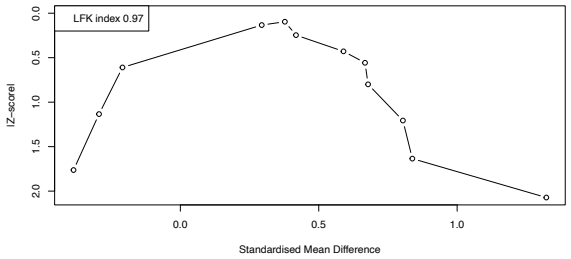
| Outcome | β (95% CI) | p-value |
|---|---|---|
| 28-day mortality | -0.5188 (-1.3855–0.3480) | 0.8475 |
| 60-day mortality | -0.9082 (-2.0062–0.1898) | 0.1903 |
| 90-day mortality | -0.9209 (-2.1901–0.3483) | 0.1680 |
| ICU mortality | -1.3804 (-2.2850–-0.4758) | 0.0124 |
| Hospital mortality | -0.8874 (-1.4008–-0.3740) | 0.0439 |
| ECMO duration | -0.2148 (-1.0212–0.5916) | 0.1373 |
| ECMO weaning | -0.3086 (-1.4104–0.7932) | 0.8793 |
| ICU length of stay | -7.2172 (-26.1411–11.7067) | 0.0865 |
| Abbreviations: CI, confidence interval; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation. | | |

# Doi plots

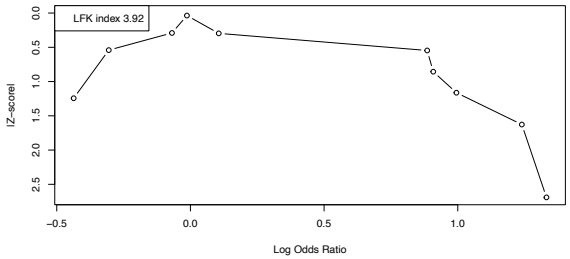
The Doi plot replaces the conventional scatter plot of precision versus effect with a normal quantile versus effect plot [S9]. Abbreviations: ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.



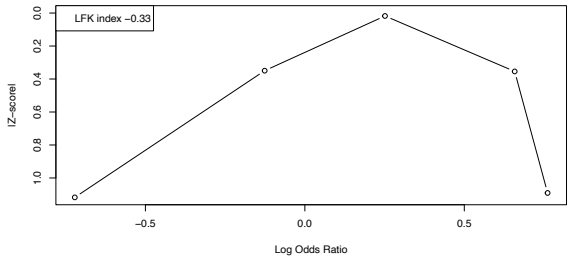
## ECMO DURATION



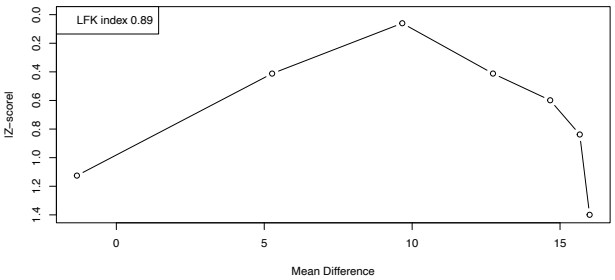

## ECMO WEANING



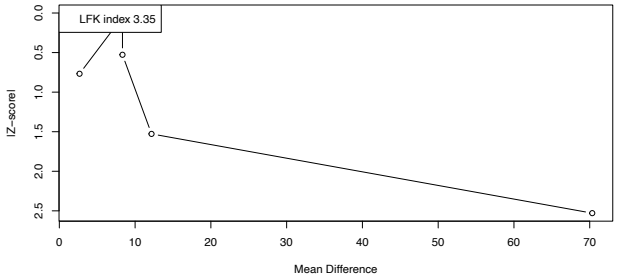

## TRACHEOSTOMY



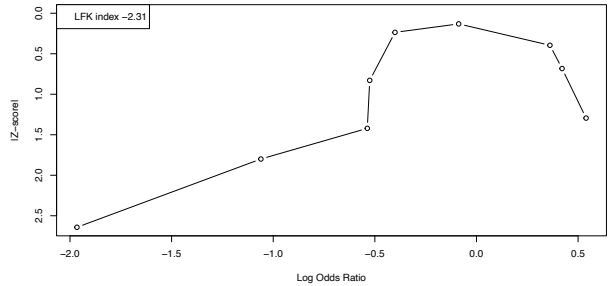

## ICU LENGTH OF STAY



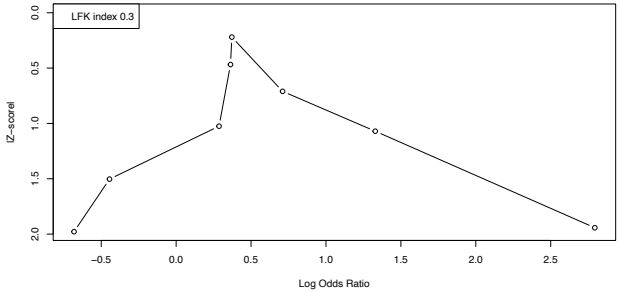

## HOSPITAL LENGTH OF STAY




## TOTAL BLEEDING EVENTS




## TOTAL THROMBOEMBOLISM EVENTS



**Online Resource 8. Other secondary outcomes**

**Table S7. Secondary outcomes not included in Figure 3**

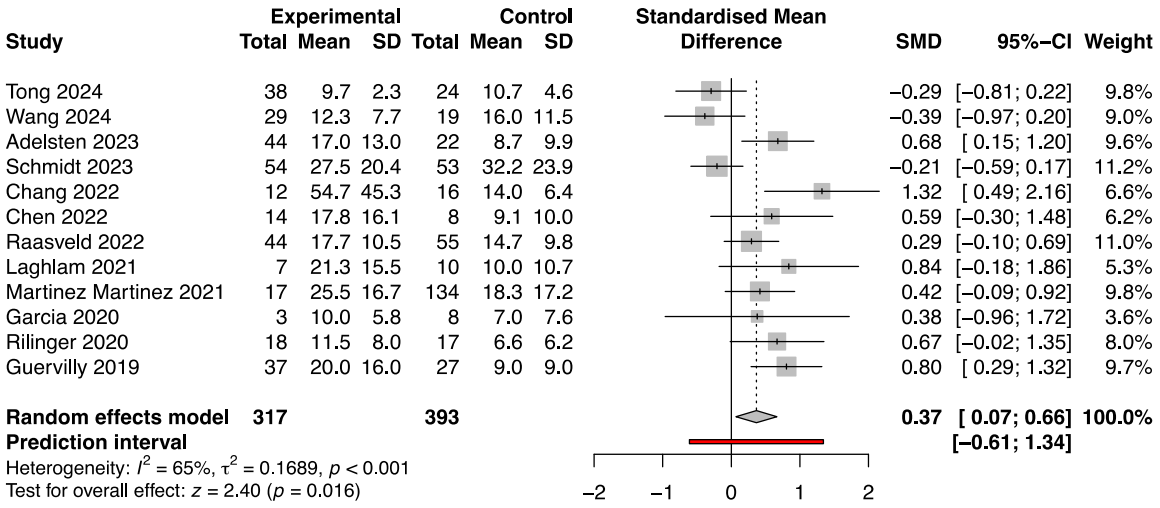
| Outcome | OR, MD, or SMD (95% CI) | p-value for overall effect | $I^2$ (%) | p-value for heterogeneity |
|---|---|---|---|---|
| ECMO duration | 0.37 (0.07-0.66) | 0.016 | 65 | < 0.001 |
| ECMO weaning | 1.26 (0.78-2.03) | 0.339 | 64 | 0.002 |
| Recannulation | 1.00 (0.28-3.55) | 0.995 | 0 | 0.983 |
| Tracheostomy | 1.16 (0.64-2.11) | 0.631 | 57 | 0.054 |
| 28-day ventilator-free days | -1.38 (-2.56–-0.20) | 0.022 | 76 | < 0.001 |
| 60-day ventilator-free days | 6.06 (-3.83–15.95) | 0.230 | 51 | 0.152 |
| 90-day ventilator-free days | 2.61 (-5.29–10.50) | 0.518 | 0 | 0.591 |
| ICU length of stay | 9.17 (3.55–14.79) | 0.001 | 43 | 0.101 |
| Hospital length of stay | 7.00 (1.75–12.24) | 0.009 | 52 | 0.079 |
| Bleeding at cannula site | 0.32 (0.04–2.69) | 0.295 | 93 | < 0.001 |
| Total bleeding events | 0.88 (0.60–1.29) | 0.517 | 43 | 0.078 |
| Total thromboembolism events | 1.82 (0.89–3.72) | 0.098 | 73 | < 0.001 |
| Cannula dislodgement | 1.09 (0.25–4.70) | 0.906 | 0 | 0.593 |
| Limb ischemia | 0.86 (0.55–1.35) | 0.523 | 0 | 0.682 |
| Circuit change | 9.66 (0.12–798.58) | 0.314 | 93 | < 0.001 |
| Infection | 1.06 (0.60–1.87) | 0.852 | 73 | 0.012 |

Abbreviations: OR, odds ratio; MD, mean difference; SMD, standardized mean difference; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

We could not perform the meta-analyses for the invasive mechanical ventilation duration, total and after de-cannulation, because no study reported the numbers of patients successfully weaned from invasive mechanical ventilation in the two groups.

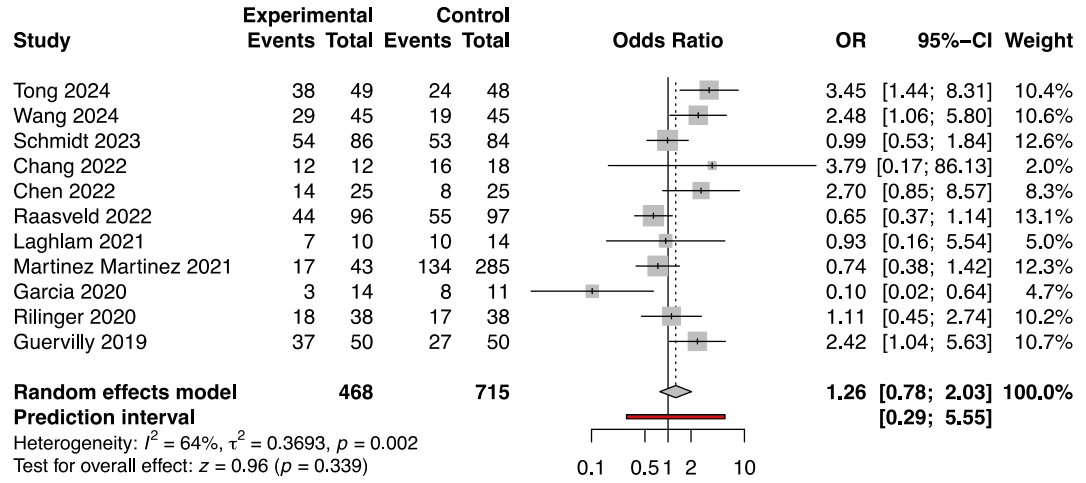
Forest plots. Forest plots for secondary outcomes not included in Figure 3 are depicted. Abbreviations: ECMO, extracorporeal membrane oxygenation; SMD, standardized mean difference; CI, confidence interval; OR, odds ratio; MD, mean difference; ICU, intensive care unit.

## ECMO DURATION



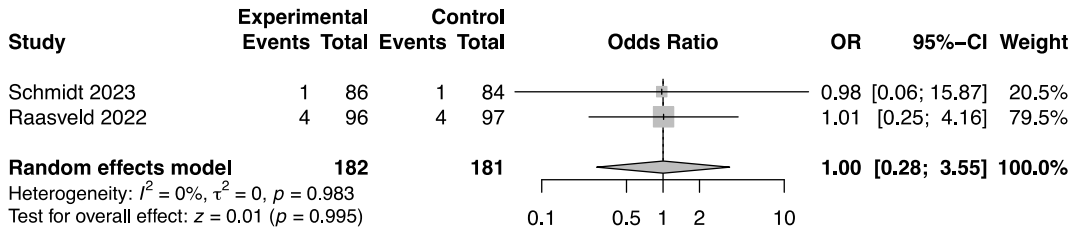

Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.1689$, $p < 0.001$
Test for overall effect: $z = 2.40$ ($p = 0.016$)

## ECMO WEANING



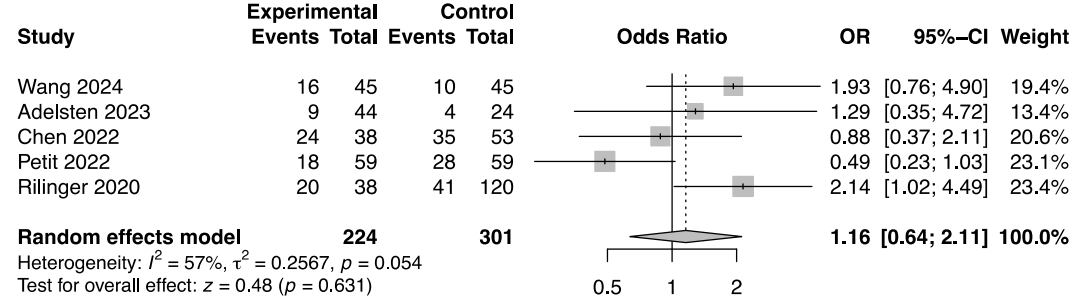

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.3693$, $p = 0.002$
Test for overall effect: $z = 0.96$ ($p = 0.339$)

## RECANNULATION



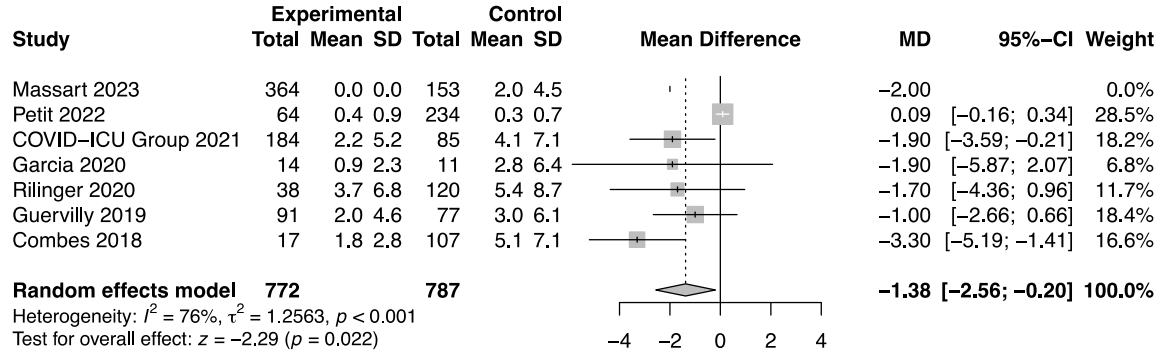

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.983$
Test for overall effect: $z = 0.01$ ($p = 0.995$)

## TRACHEOSTOMY

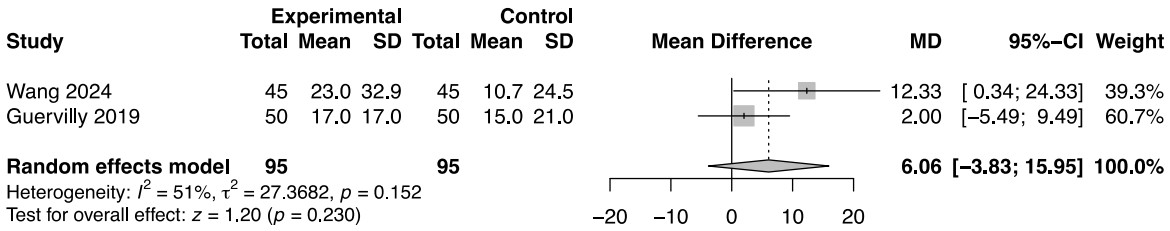



Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.2567$, $p = 0.054$
Test for overall effect: $z = 0.48$ ($p = 0.631$)

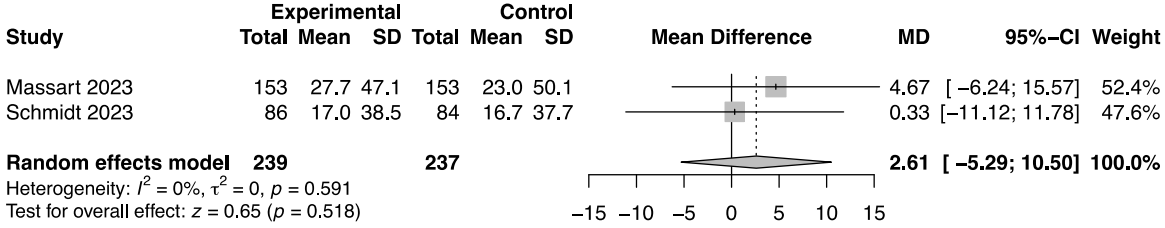
## 28-DAY VENTILATOR-FREE DAYS



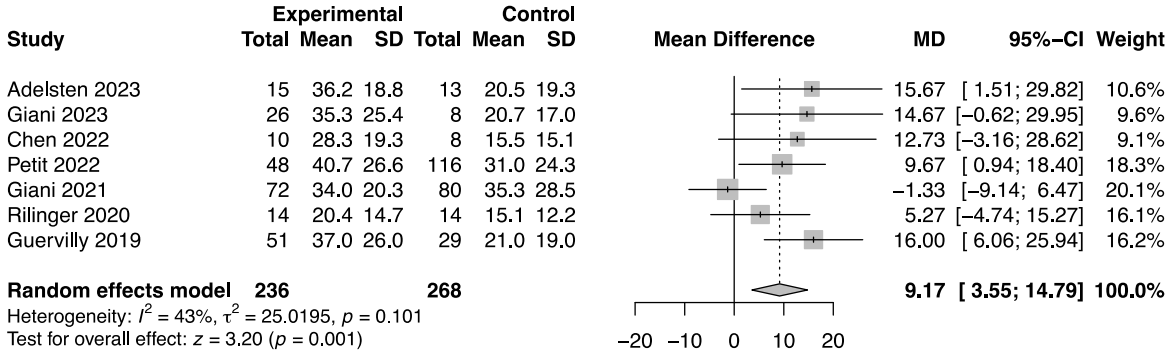

## 60-DAY VENTILATOR-FREE DAYS



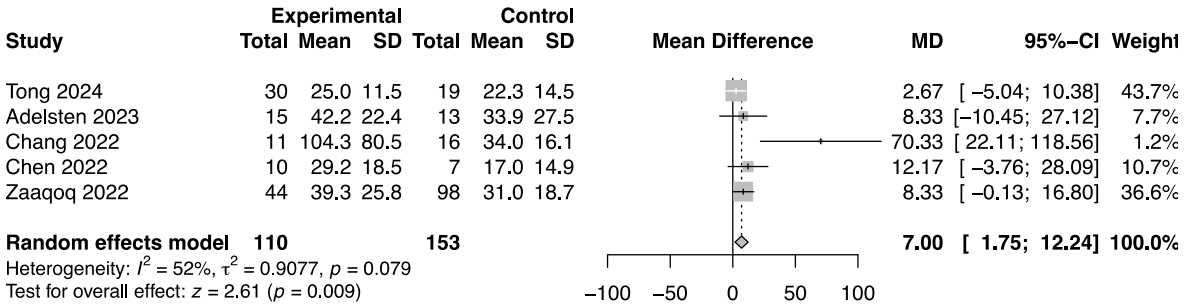

## 90-DAY VENTILATOR-FREE DAYS



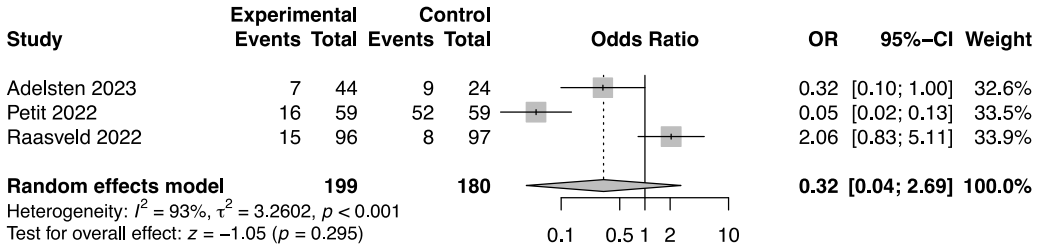

## ICU LENGTH OF STAY



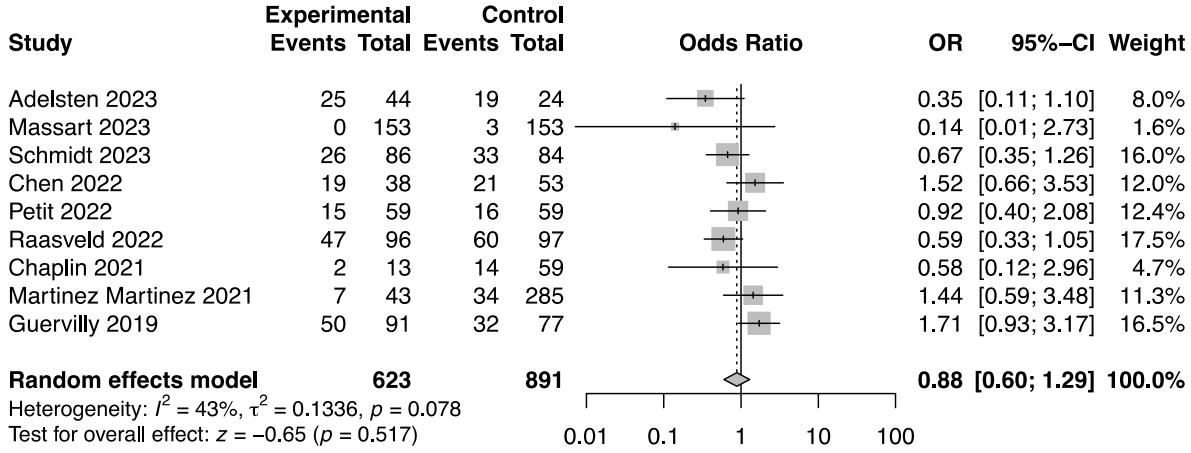
## HOSPITAL LENGTH OF STAY



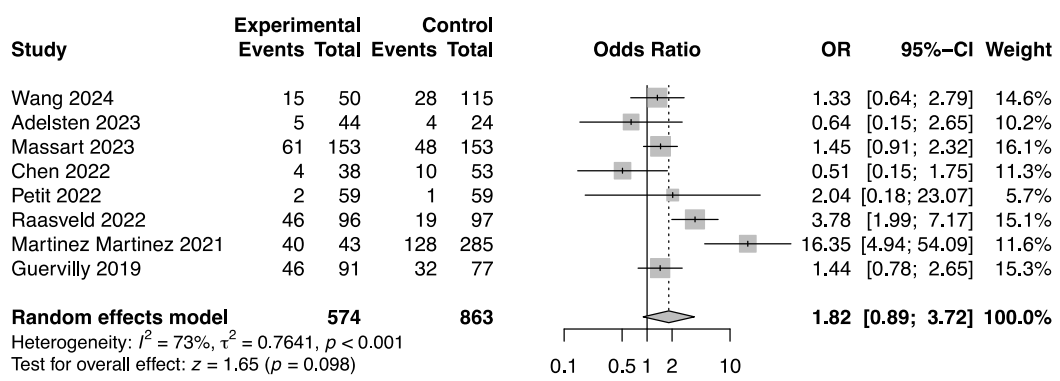

## BLEEDING AT CANNULA SITE



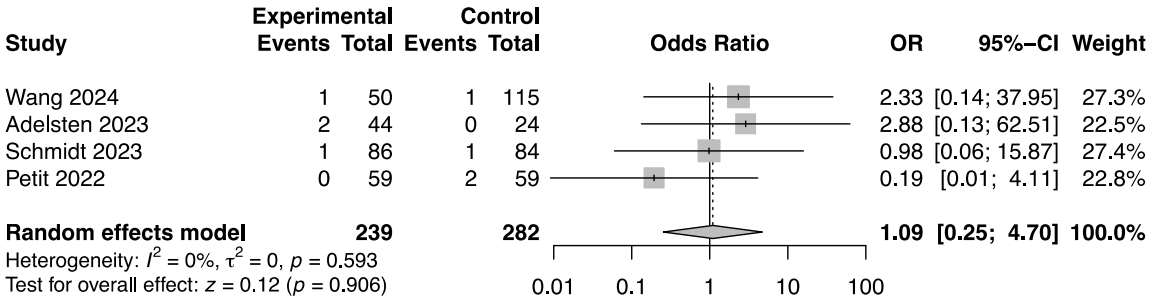

## TOTAL BLEEDING EVENTS



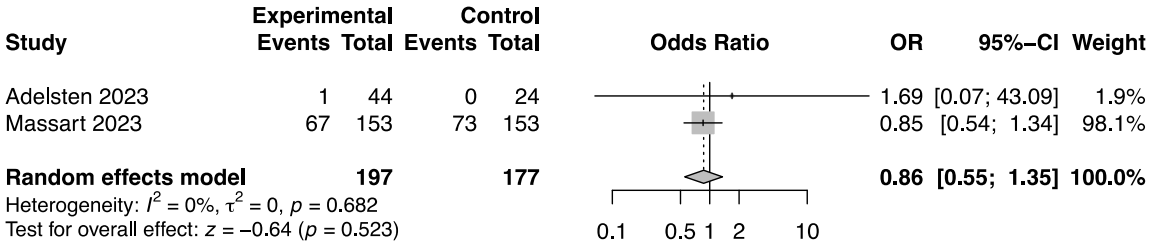

## TOTAL THROMBOEMBOLISM EVENTS



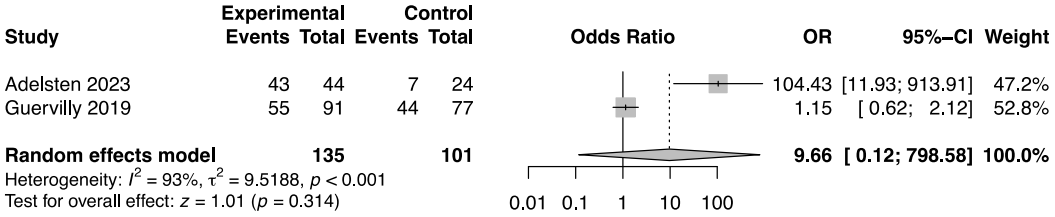
## CANNULA DISLODGEMENT



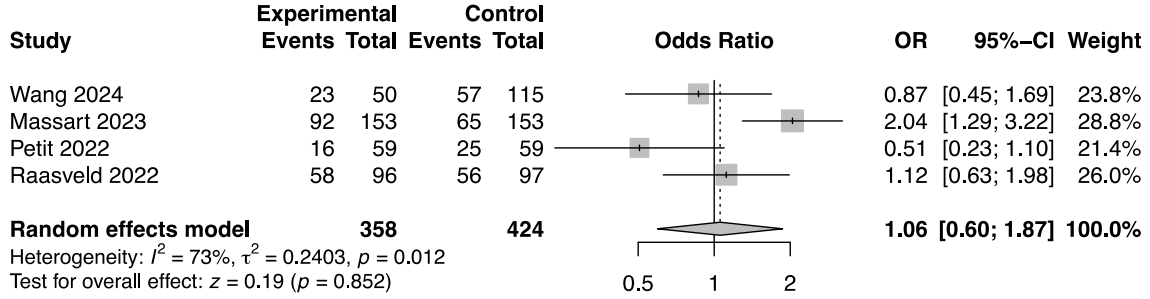

## LIMB ISCHEMIA




## CIRCUIT CHANGE

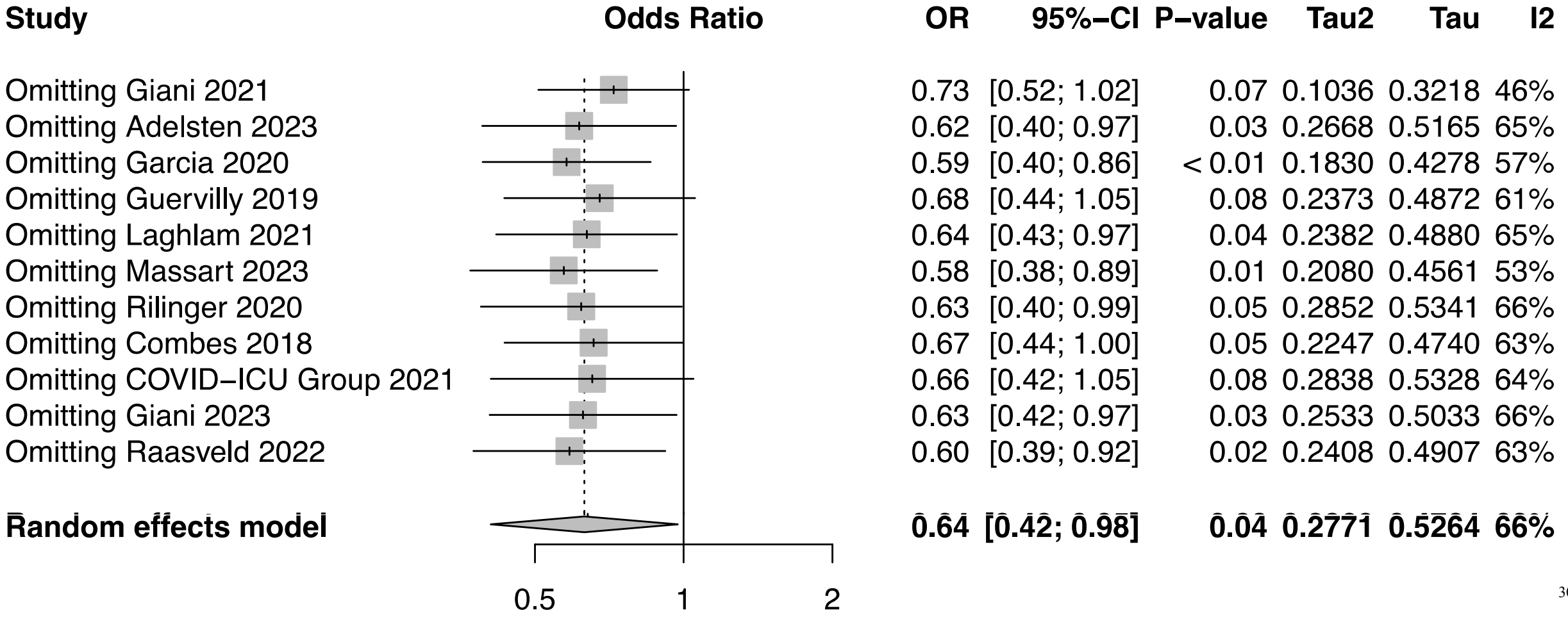



## INFECTION



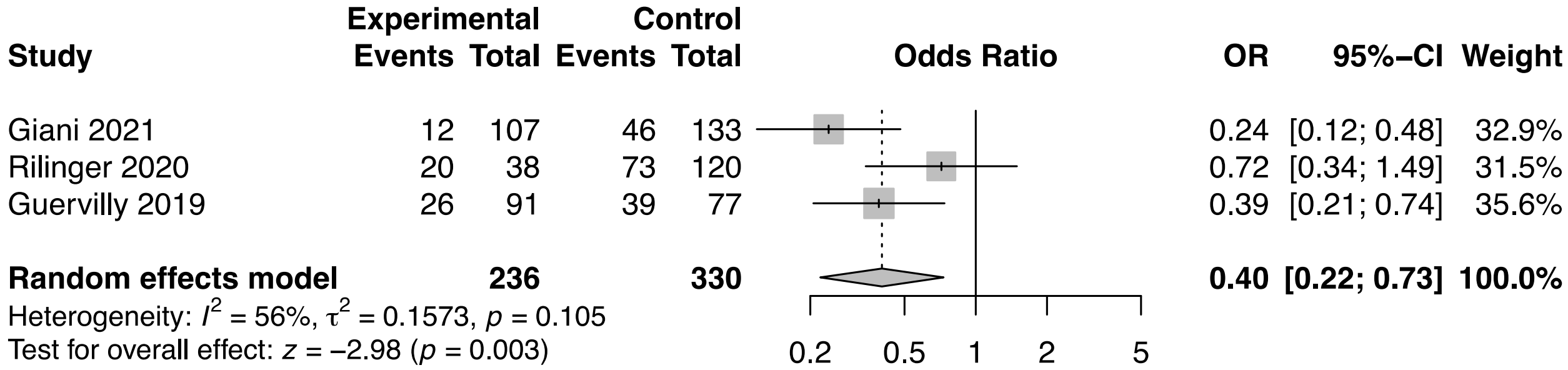
**Online Resource 9. Sensitivity analyses**

A. Sensitivity analysis serially excluding each study from meta-analysis. Abbreviations: OR, odds ratio; CI, confidence interval. The exclusion of the studies by Giani et al. (2021), Guervilly et al., and the COVID-ICU Group resulted in a non-significant association between prone positioning and the reduction of 28-day mortality.



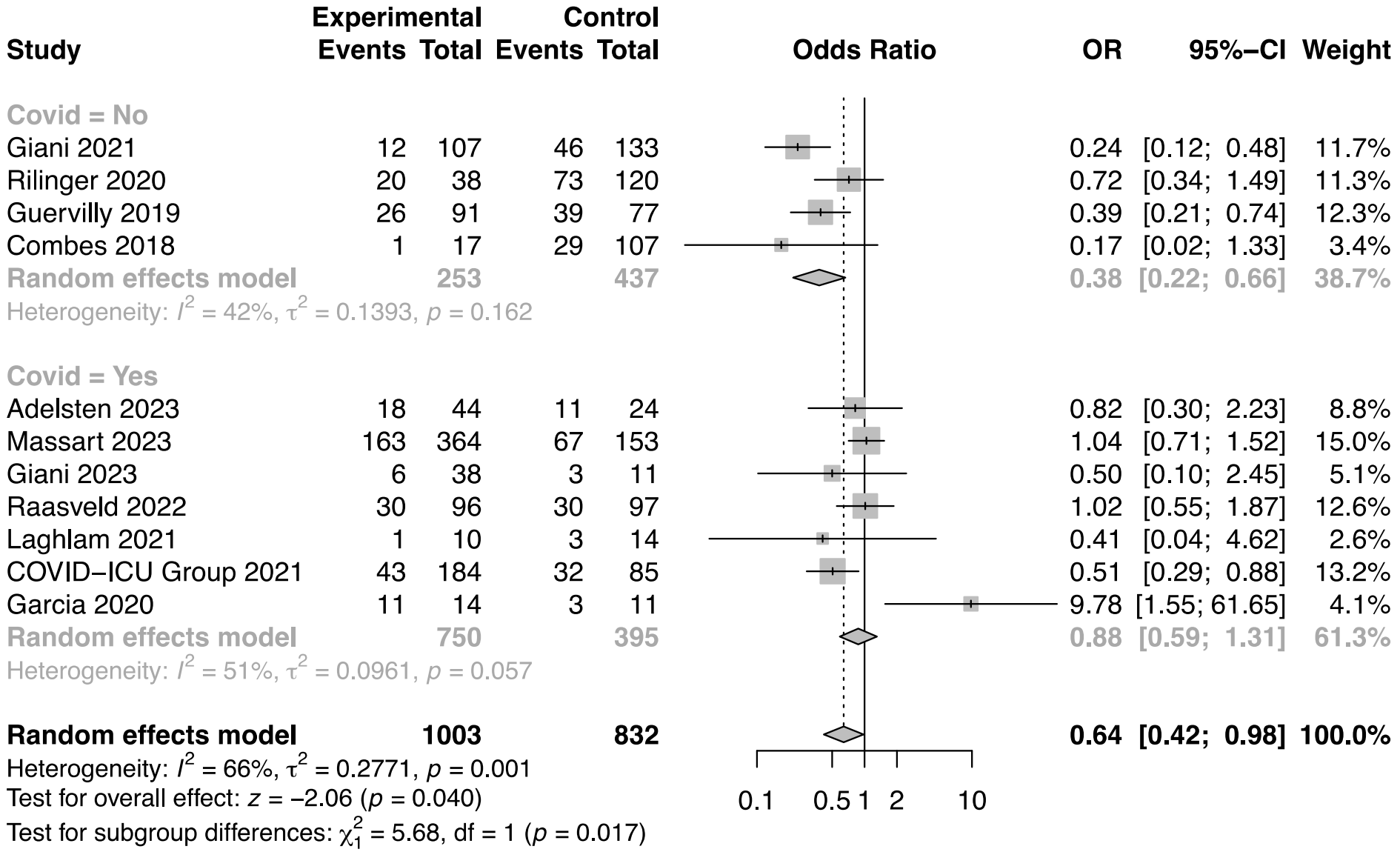
B. Sensitivity analysis excluding randomized controlled trials (RCTs) at high risk of bias and non-RCTs at serious or critical risk of bias. Abbreviations: OR, odds ratio; CI, confidence interval. No RCT reported on the primary outcome. Excluding non-RCTs at serious or critical risk of bias confirmed the significant association between prone positioning and the reduction of 28-day mortality.

The sensitivity analysis including data from non-matched patients' cohorts in those non-RCTs using propensity score matching was not feasible because 28-day mortality was not available for these cohorts across the studies.

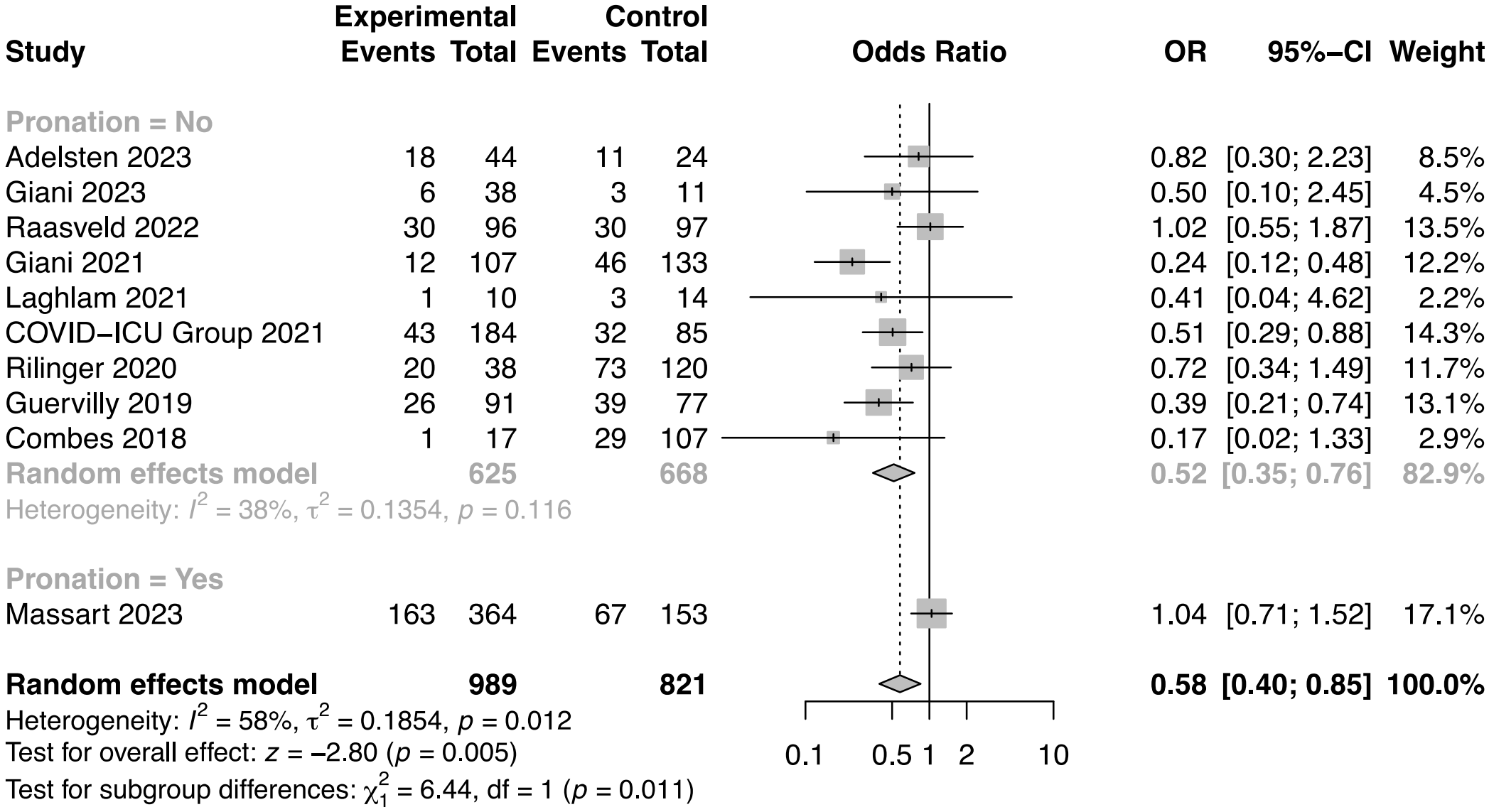


## Online Resource 10. Subgroup analyses

A. Subgroup analysis for the Coronavirus disease (Covid)-19 vs. non-Coronavirus disease-19 related acute hypoxemic respiratory failure subgroups. Abbreviations: OR, odds ratio; CI, confidence interval; Covid, coronavirus disease.



B. Subgroup analysis for the studies including ≥ 73% (Pronation = Yes) vs. < 73% (Pronation = No) of patients receiving prone positioning before ECMO. The 73% percentage was identified as the third quartile of the proportion of patients proned before ECMO across the studies. Abbreviations: OR, odds ratio; CI, confidence interval.



**Online Resource 11. Meta-regressions**

**Table S8. Meta-regressions' results**

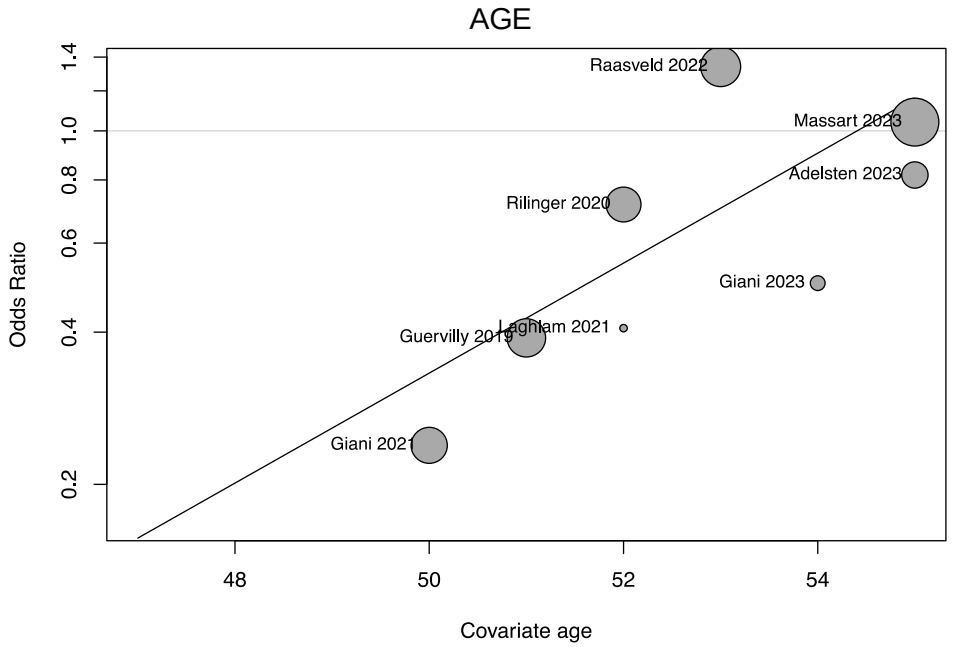
| Covariate | β (95% CI) | Standard error | p-value | $I^2$ (%) | $R^2$ (%) | $Q_E$ test (p-value) |
|---|---|---|---|---|---|---|
| Age | 0.250 (0.076–0.425) | 0.089 | 0.005 | 0.00 | 75.78 | 4.054 (0.669) |
| Body mass index | -0.378 (-1.388–0.632) | 0.515 | 0.464 | 0.00 | 0.00 | 0.558 (0.455) |
| Female gender | -0.085 (-0.141–-0.029) | 0.028 | 0.003 | 13.67 | 84.26 | 8.131 (0.321) |
| Immunocompromised patients | -0.021 (-0.070–0.028) | 0.025 | 0.394 | 62.86 | 0.00 | 12.043 (0.034) |
| SOFA score | -1.053 (-1.748–-0.357) | 0.355 | 0.003 | 0.00 | 100.00 | 0.006 (0.997) |
| $PaO_2/FiO_2$ before cannulation | -0.010 (-0.366–0.346) | 0.182 | 0.956 | 67.68 | 0.00 | 0.099 (0.753) |
| RCT | -1.309 (-3.616–0.999) | 1.177 | 0.266 | 59.40 | 2.64 | 19.546 (0.012) |
| Covid diagnosis | 0.788 (0.113–1.463) | 0.345 | 0.022 | 34.54 | 54.52 | 10.704 (0.219) |
| Year of publication | 0.242 (0.034–0.449) | 0.106 | 0.036 | 32.42 | 60.23 | 10.213 (0.250) |
| Percentage of patients with pneumonia | 0.004 (-0.048–0.0560) | 0.027 | 0.880 | 63.92 | 0.00 | 14.248 (0.014) |
| Duration of invasive mechanical ventilation before cannulation | -0.482 (-3.380–2.416) | 1.479 | 0.745 | 85.13 | 0.00 | 6.727 (0.010) |
| Percentage of patients receiving PP before cannulation | 0.010 (0.000–0.019) | 0.005 | 0.049 | 66.49 | 51.57 | 11.608 (0.021) |
| Duration of ECMO before PP | -0.218 (-0.589–0.154) | 0.190 | 0.252 | 33.18 | 28.17 | 4.200 (0.241) |
| Number of PP sessions | 0.044 (-0.365–0.452) | 0.209 | 0.834 | 0.00 | 0.00 | 2.283 (0.516) |

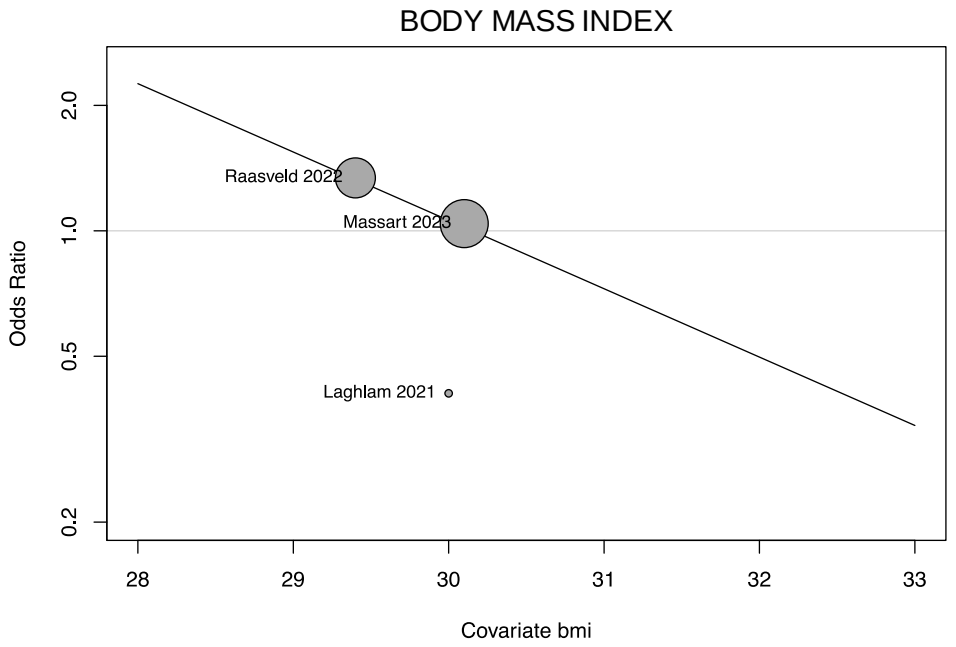
| | | | | | | |
|---|---|---|---|---|---|---|
| Duration of PP sessions | 0.182 (-0.179–0.542) | 0.184 | 0.323 | 40.18 | 8.39 | 2.853 (0.240) |

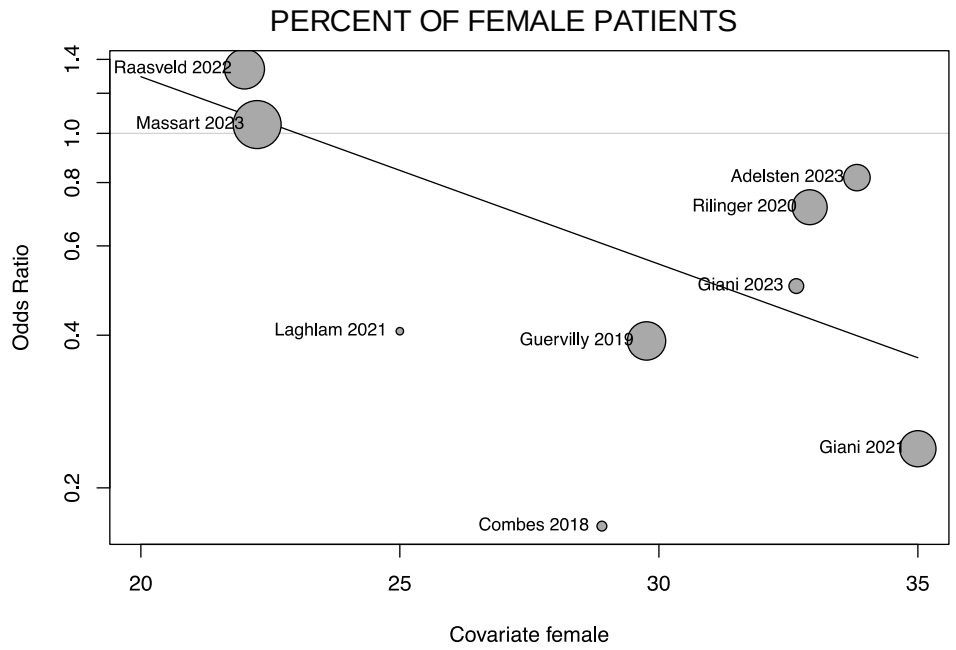
Abbreviations: CI, confidence interval; SOFA, sequential organ failure assessment; $PaO_2$, arterial partial pressure of oxygen; $FiO_2$, fraction of inspired oxygen; PP, prone positioning. $R^2$ is the amount of heterogeneity accounted for by the inclusion of the covariate in the model.

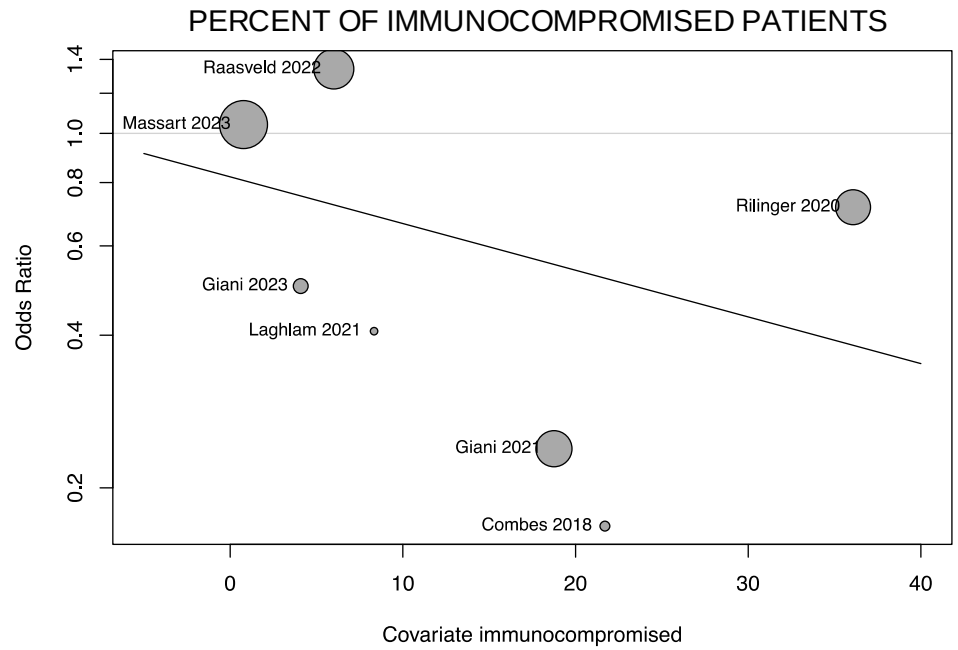
The meta-regressions using, as covariates, pulmonary vs. extra-pulmonary AHRF, high- vs. low-volume ECMO centers, number of proning cycles per patient > 1 vs. equal to 1, and driving pressure and compliance of the respiratory system before ECMO cannulation were not feasible because of lacking data in the original studies.

# Meta-regressions bubble plots

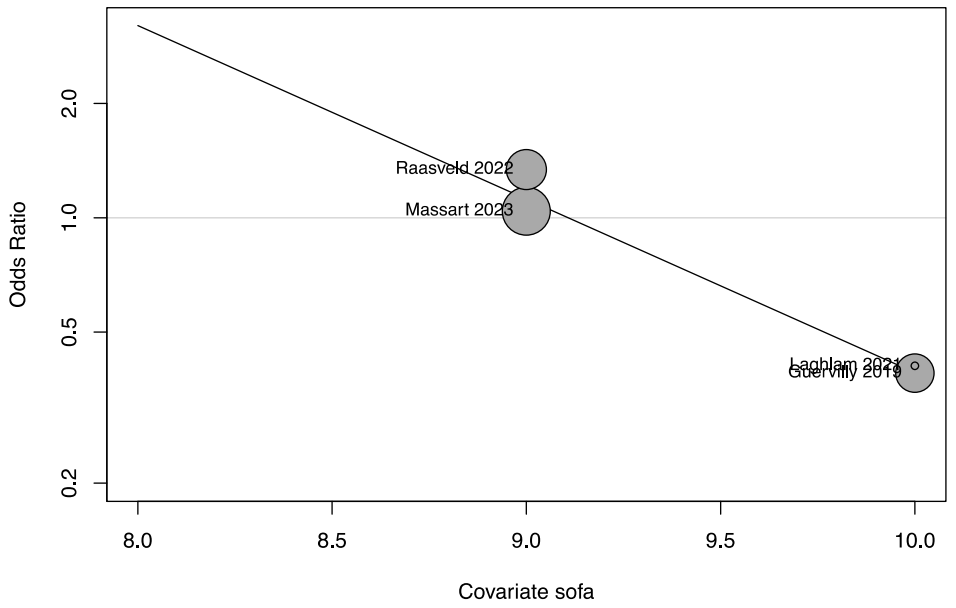


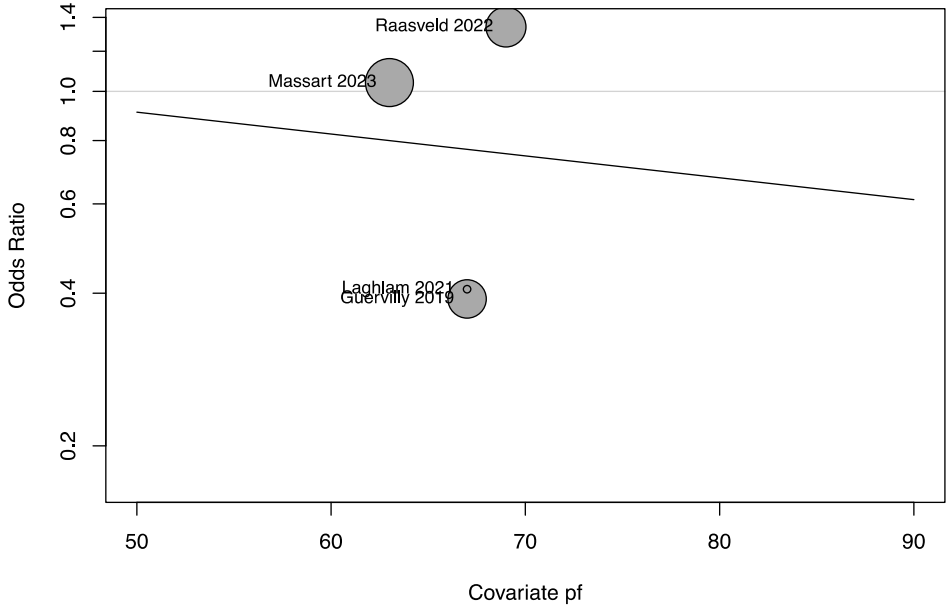



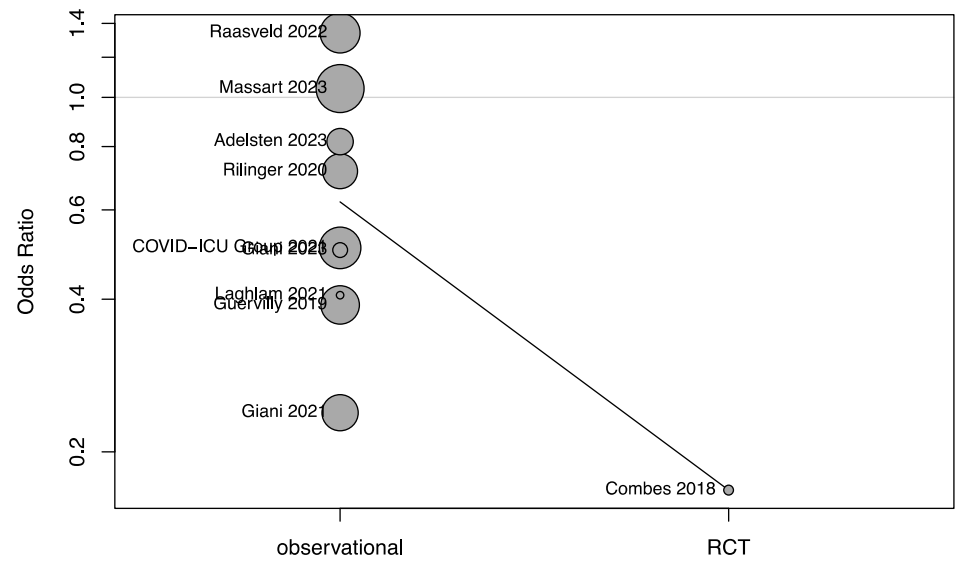
## SOFA



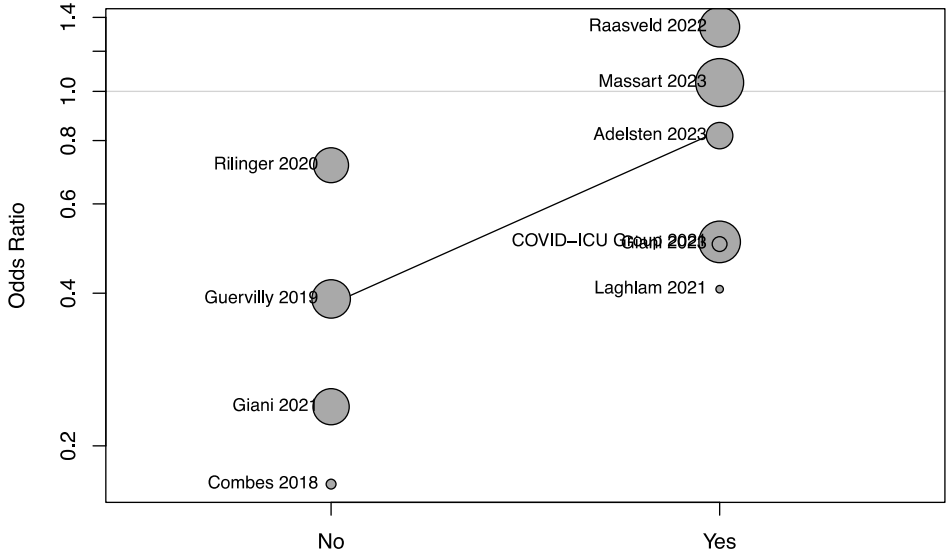

## ARTERIAL PARTIAL PRESSURE OF OXYGEN TO FRACTION OF INSPIRED OXYGEN RATIO BEFORE CANNULATION



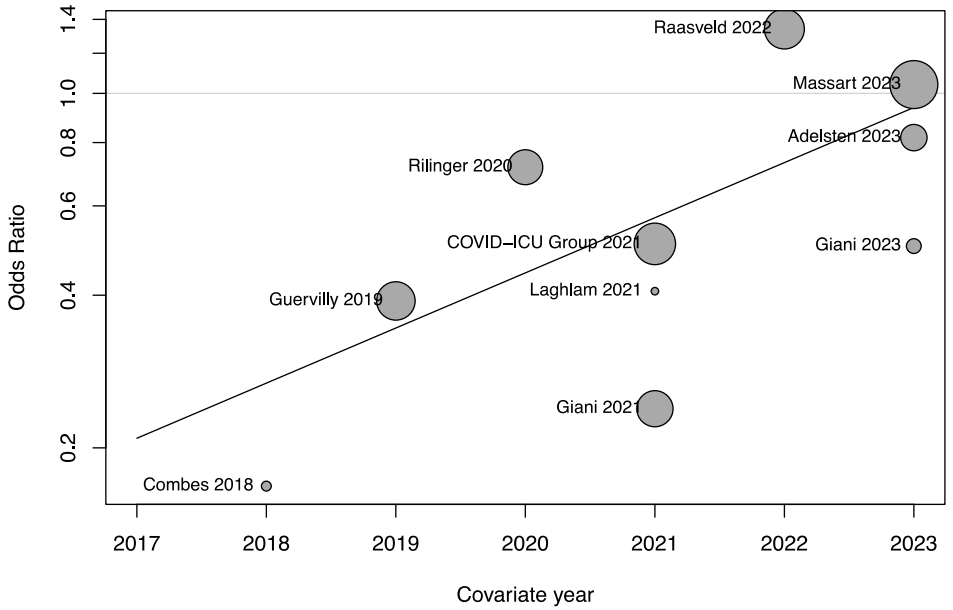

## DESIGN



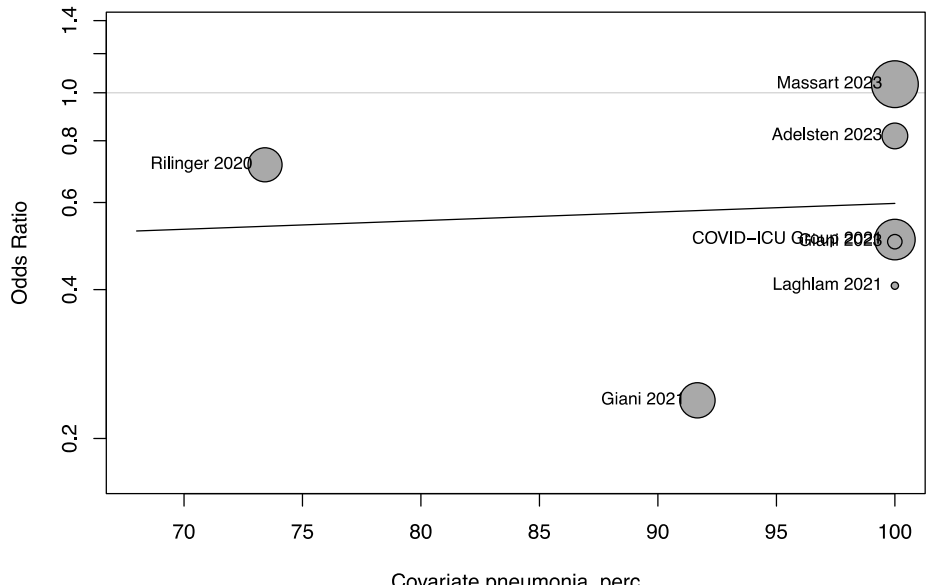

## CORONAVIRUS DISEASE-19



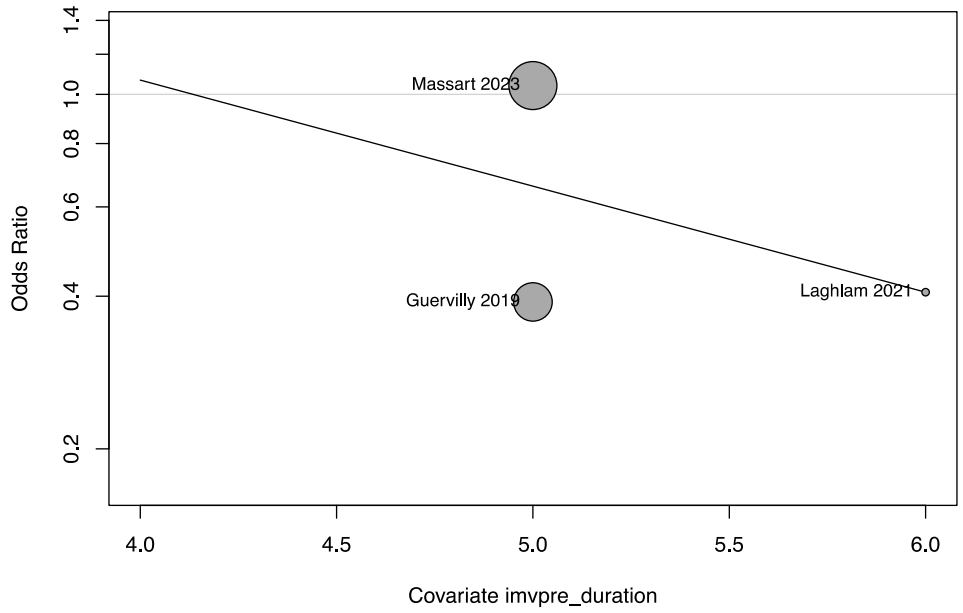
## YEAR



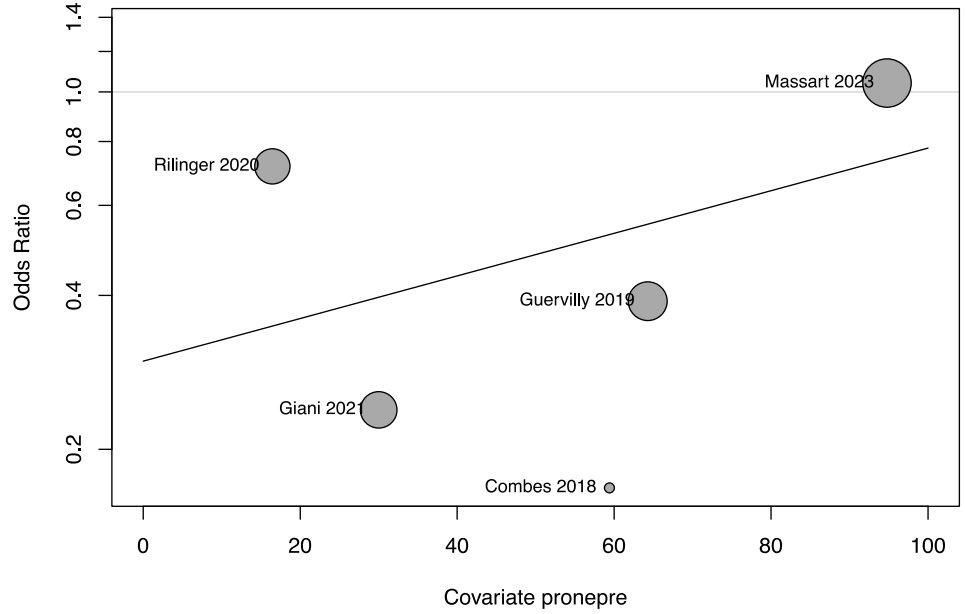

## PERCENT OF PATIENTS WITH PNEUMONIA



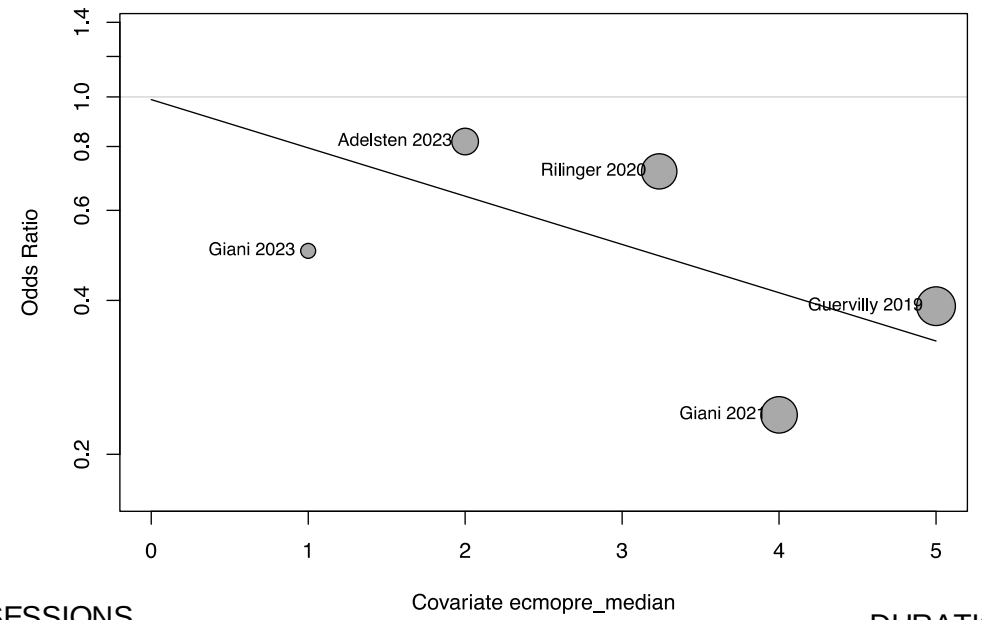

## DURATION OF INVASIVE MECHANICAL VENTILATION BEFORE CANNULATION



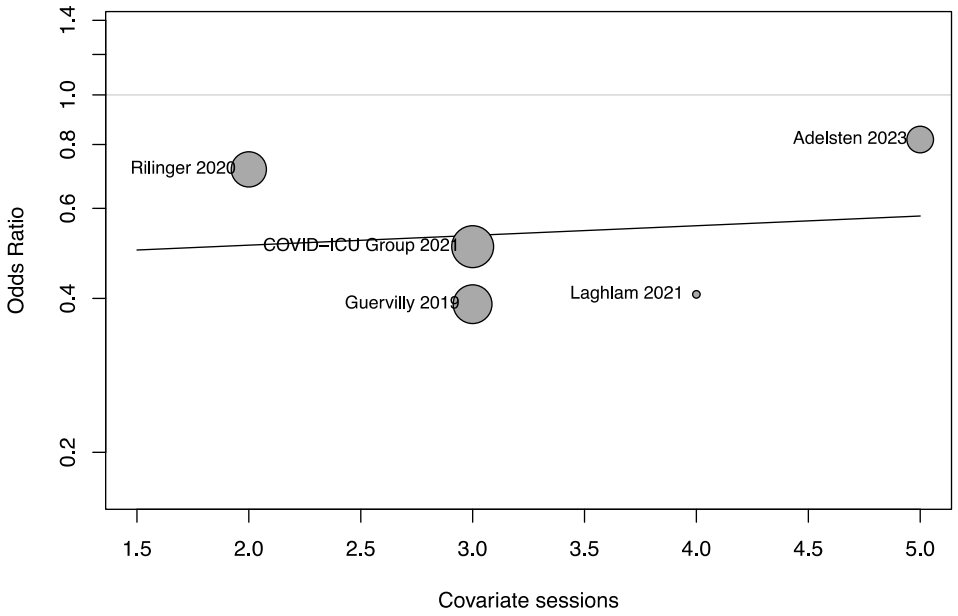

## PERCENT OF PATIENTS RECEIVING PRONE POSITIONING BEFORE CANNULATION



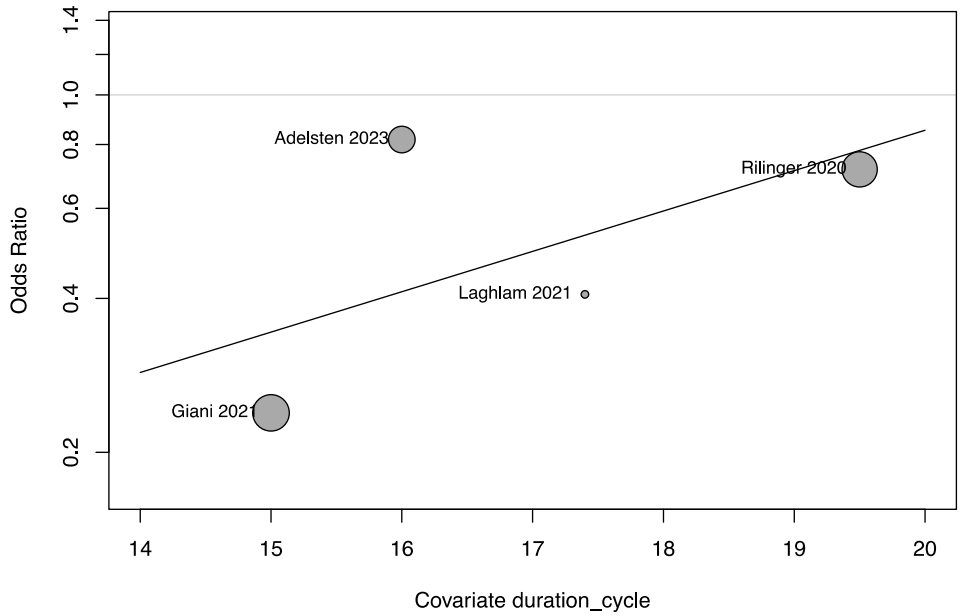
## DURATION OF ECMO BEFORE PRONE POSITIONING




## NUMBER OF PRONING SESSIONS




## DURATION OF PRONE POSITIONING CYCLES



**Supplementary digital content references**


S1. Reeves BC, Deeks JJ, Higgins JPT, et al. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, et al. (ed) Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Available from www.training.cochrane.org/handbook.

S2. Cuello-Garcia CA, Santesso N, Morgan RL, et al. (2022). GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. J Clin Epidemiol;142:200-208. https://doi.org/10.1016/j.jclinepi.2021.11.026

S3. Sterne JAC, Savović J, Page MJ, et al. (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ l4898. https://doi.org/10.1136/bmj.l4898

S4. Sterne JA, Hernán MA, Reeves BC, et al. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ i4919. https://doi.org/10.1136/bmj.i4919

S5. Guyatt GH, Oxman AD, Kunz R, et al. (2011) GRADE guidelines 6. Rating the quality of evidence—imprecision. Journal of Clinical Epidemiology 64:1283–1293. https://doi.org/10.1016/j.jclinepi.2011.01.012

S6. Deeks JJ, Higgins JPT, Altman DG (2023). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al. (ed) Cochrane Handbook for Systematic Reviews of Interventions version 6.4. Available from www.training.cochrane.org/handbook.

S7. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135. https://doi.org/10.1186/1471-2288-14-135

S8. Page MJ, Higgins JPT, Sterne JAC (2023). Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, et al. (ed) Cochrane Handbook for Systematic Reviews of Interventions version 6.4, Cochrane, 2023. Available from www.training.cochrane.org/handbook.

S9. Furuya-Kanamori L, Barendregt JJ, Doi SAR (2018) A new improved graphical and quantitative method for detecting bias in meta-analysis. Int J Evid Based Healthc 16:195–203. https://doi.org/10.1097/XEB.0000000000000141

S10. Combes A, Brodie D, Bartlett R, et al. (2014) Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med 190:488–496. https://doi.org/10.1164/rccm.201404-0630CP

S11. Cortegiani A, Madotto F, Gregoretti C, et al., for the LUNG SAFE Investigators and the ESICM Trials Group (2018) Immunocompromised patients with acute respiratory distress syndrome: secondary analysis of the LUNG SAFE database. Crit Care 22:157. https://doi.org/10.1186/s13054-018-2079-9

S12. Giani M, Rezoagli E, Guervilly C, et al. (2022) Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a pooled individual patient data analysis. Crit Care 26:8. https://doi.org/10.1186/s13054-021-03879-w

S13. De Cassai A, Tassone M, Geraldini F, et al. (2021) Explanation of trial sequential analysis: using a post-hoc analysis of meta-analyses published in Korean Journal of Anesthesiology. Korean J Anesthesiol 74:383–393. https://doi.org/10.4097/kja.21218

S14. Page MJ, McKenzie JE, Bossuyt PM, et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71