Supplemental Online Content

eAppendix 1. Study Protocol

Context

Brain injury is a widespread condition that significantly contributes to global mortality and disability. Following an initial insult—such as trauma, subarachnoid hemorrhage, or intracranial hematoma—secondary injuries may occur. These secondary lesions typically arise from an imbalance between the brain's oxygen requirements and its blood supply, often driven by intracranial hypertension or cerebral edema.

Anemia is also a frequent condition in the intensive care unit[1]resulting from various factors, including trauma, surgery, inflammation, or repeated blood sampling. Red blood cell transfusions can increase hemoglobin levels and, theoretically, enhance oxygen delivery, provided cardiac output remains stable. However, there are currently no universally accepted guidelines on the optimal hemoglobin threshold for transfusion in brain-injured patients[2].

Some studies have suggested that transfusion might improve neurological outcomes, which are commonly evaluated six months after the acute event[3,4].Recently, two major studies have been published on this topic, offering valuable insights to address this important question.

Objective

The primary objective of our study was to evaluate whether a liberal transfusion threshold rather than a restrictive one was associated with better neurological outcomes. Secondary outcomes included d180 mortality, early mortality, the incidence of thromboembolic events, duration of mechanical ventilation, ICU length of stay, incidence of ARDS, risk of secondary infections, and adverse events.

Methods

This systematic review and meta-analysis was prospectively registered on PROSPERO **ID:CRD42024601169**. The methodology adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Eligibility criteria

Population

- Adults patients (> 18 years) hospitalized in ICU for brain injury defined as: trauma, sub-arachnoidal hemorrhage, intracranial hematoma with a glasgow coma scale of 13 or less on admission.

- Patients needed to be included in study maximum 48h after ICU admission

Intervention

- Liberal transfusion: Transfusion threshold of 9–10 g/dL or higher.

Comparator

- Restrictive transfusion: Transfusion threshold of 7–8 g/dL.

The intervention period in both groups had to correspond to the acute phase of brain injury, typically within the first weeks. No strict timeline was applied.

Outcomes

1. **Primary Outcome : good neurological outcome**

Prevalence of a good neurological outcome at day 180:

- Good neurological outcome: Defined as a score of 6–8 on the Glasgow Outcome Scale–Extended (GOSE) or 4–5 on the Glasgow Outcome Scale (GOS).
- Poor neurological outcome: Defined as a score of 1–5 on the GOSE or 1–3 on the GOS.

2. **Secondary Outcomes**

- **Early mortality**: Death occurring within 90 days of admission or intervention.
- **Late mortality**: Mortality at day 180.
- **Length of stay in ICU**: Duration of a patient's admission to the intensive care unit, reported in days.
- **Mechanical ventilation duration**: Total time a patient required mechanical ventilatory support, expressed in days.
- **Infection rates**:
- **Any infection rate**: Overall incidence of infections during the ICU stay. Defined as :
    - Pneumonia: Incidence of ventilator-associated or hospital-acquired pneumonia.
    - Bacteremia: Documented bloodstream infections confirmed by positive blood cultures.
    - Sepsis/Septic shock: Cases meeting Sepsis-3 criteria, including organ dysfunction and/or shock.
    - Central nervous system infection: Diagnosed meningitis or encephalitis.
    - Catheter-related bloodstream infection: Infections associated with intravascular devices confirmed by culture and clinical criteria.
- **Number of RBC transfused**: Total number of red blood cell units transfused during the ICU stay.

- **Prevalence of ARDS**: Acute respiratory distress syndrome (ARDS) diagnosed per Berlin criteria. For information, acute respiratory failure was initially prespecified as a secondary outcome in the PROSPERO registration. However, as the included studies only reported data on ARDS, this was used as a substitute in our analysis.

- **Adverse events (transfusion related events)**: Any documented complications or undesired outcomes associated with transfusions or treatments. Documented transfusion reactions, such as febrile non-hemolytic reactions, allergic reactions, or hemolysis, occurring shortly after transfusion.

- **Post-HOC incidence of thromboembolic events**: Frequency of venous thromboembolism (deep vein thrombosis or pulmonary embolism).

Exclusion criteria

- **Observational studies**: Studies without randomization, including cohort, case-control, or cross-sectional designs.
- **Non-human studies**: Animal studies or laboratory research.

eAppendix 2. Electronic Search Strategy

EMBASE

Date of search : 24/10/2024

Database : EMBASE via EMBASE

1. Population (Patient)

1. 'traumatic brain injury':ab,ti
2. 'brain trauma':ab,ti
3. 'brain injur*':ab,ti
4. 'head injur*':ab,ti
5. 'cranial trauma':ab,ti
6. 'head trauma':ab,ti
7. 'TBI':ab,ti
8. 'intracerebral hemorrhag*':ab,ti
9. 'intracranial hemorrhag*':ab,ti
10. 'cerebral hemorrhag*':ab,ti
11. 'subarachnoid hemorrhag*':ab,ti
12. 'subdural hematoma':ab,ti
13. 'epidural hematoma':ab,ti
14. 'brain hemorrhag*':ab,ti
15. 'traumatic hemorrhag*':ab,ti
16. 'cerebral aneurysm*':ab,ti
17. 'ICH':ab,ti
18. 'SAH':ab,ti
19. 'SDH':ab,ti
20. 'brain hemorrhage'/exp
21. 'brain injury'/exp
22. #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

2. Intervention

23. 'transfusion':ab,ti
24. 'hemoglobin':ab,ti
25. 'red blood cells':ab,ti
26. 'RBC':ab,ti
27. 'erythrocyte':ab,ti
28. 'threshold':ab,ti
29. 'blood transfusion':ab,ti
30. 'blood transfusion'/exp
31. 'liberal':ab,ti
32. 'restrictive':ab,ti
33. 'conservative':ab,ti
34. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33

3. Dates

35. [2000-2024]/py

4. Study type ***Cochrane 2023 high sensitivity***

36. 'randomized controlled trial'/exp
37. 'controlled clinical trial'/de
38. random*:ti,ab,tt
39. 'randomization'/de
40. 'intermethod comparison'/de
41. placebo:ti,ab,tt
42. (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
43. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
44. (open NEXT/1 label):ti,ab,tt
45. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
46. 'double blind procedure'/de
47. (parallel NEXT/1 group*):ti,ab,tt
48. (crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
49. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
50. (assigned:ti,ab,tt OR allocated:ti,ab,tt)
51. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
52. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
53. 'human experiment'/de
54. trial:ti,tt
55. #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 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54

5. Exclusions

56. 'child'/exp OR 'pediatric'/exp OR 'infant'/exp OR 'newborn'/exp OR 'stroke'/exp OR 'cerebrovascular accident'/exp OR 'cerebral infarction'/exp OR 'myocardial infarction'/exp OR 'heart attack'/exp OR 'coronary artery disease'/exp

6. Final combination

57. #22 AND #34 AND #35 AND #55 NOT #56

MEDLINE
Date of search : 24/10/2024

Database : MEDLINE (via PubMed)

1. Population (Patient)

1. "traumatic brain injury"[tiab]
2. "brain trauma"[tiab]
3. "brain injur*"[tiab]
4. "head injur*"[tiab]
5. "cranial trauma"[tiab]
6. "head trauma"[tiab]
7. "TBI"[tiab]
8. "intracerebral hemorrhag*"[tiab]
9. "intracranial hemorrhag*"[tiab]
10. "cerebral hemorrhag*"[tiab]
11. "subarachnoid hemorrhag*"[tiab]
12. "subdural hematoma"[tiab]
13. "epidural hematoma"[tiab]
14. "brain hemorrhag*"[tiab]
15. "traumatic hemorrhag*"[tiab]
16. "cerebral aneurysm*"[tiab]
17. "ICH"[tiab]
18. "SAH"[tiab]
19. "SDH"[tiab]
20. "Intracranial Hemorrhages"[MeSH Terms]
21. "Craniocerebral Trauma"[MeSH Terms]
22. #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

2. Intervention

23. transfusion[tiab]
24. hemoglobin[tiab]
25. "red blood cells"[tiab]
26. RBC[tiab]
27. erythrocyte[tiab]
28. threshold[tiab]
29. "blood transfusion"[tiab]
30. "Blood Transfusion"[MeSH Terms]
31. liberal[tiab]
32. restrictive[tiab]
33. conservative[tiab]
34. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33

3. Dates

35. ("2000/01/01"[Date - Publication] : "2024/12/31"[Date - Publication])

4. Study type ***Cochrane 2008 high sensitivity***

36. randomized controlled trial[pt]

37. controlled clinical trial[pt]
38. randomized[tiab]
39. placebo[tiab]
40. "drug therapy"[sh]
41. randomly[tiab]
42. trial[tiab]
43. groups[tiab]
44. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
45. animals[mh] NOT humans[mh]
46. #44 NOT #45

5. Exclusions

47. child[tiab] OR pediatric[tiab] OR infant[tiab] OR newborn[tiab] OR stroke[tiab] OR "Brain Ischemia"[MeSH Terms] OR "myocardial infarction"[tiab] OR "heart attack"[tiab] OR "coronary artery disease"[tiab] OR "Child"[MeSH Terms] OR "Adolescent"[MeSH Terms]

6. Final combinaison

48. #22 AND #34 AND #35 AND #46 NOT #47

COCHRANE LIBRARY

Date of search **:** 24/10/2024

Base de données : Cochrane Central Register of Controlled Trials (CENTRAL)

1. Population (Patient)

1. "traumatic brain injury":ti,ab,kw
2. "brain trauma":ti,ab,kw
3. "brain injur*":ti,ab,kw
4. "head injur*":ti,ab,kw
5. "cranial trauma":ti,ab,kw
6. "head trauma":ti,ab,kw
7. "TBI":ti,ab,kw
8. "intracerebral hemorrhag*":ti,ab,kw
9. "intracranial hemorrhag*":ti,ab,kw
10. "cerebral hemorrhag*":ti,ab,kw
11. "subarachnoid hemorrhag*":ti,ab,kw
12. "subdural hematoma":ti,ab,kw
13. "epidural hematoma":ti,ab,kw
14. "brain hemorrhag*":ti,ab,kw
15. "traumatic hemorrhag*":ti,ab,kw
16. "cerebral aneurysm*":ti,ab,kw
17. "ICH":ti,ab,kw
18. "SAH":ti,ab,kw
19. "SDH":ti,ab,kw

20. #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

2. Intervention

21. transfusion:ti,ab,kw
22. hemoglobin:ti,ab,kw
23. "red blood cells":ti,ab,kw
24. RBC:ti,ab,kw
25. erythrocyte:ti,ab,kw
26. threshold:ti,ab,kw
27. "blood transfusion":ti,ab,kw
28. liberal:ti,ab,kw
29. restrictive:ti,ab,kw
30. conservative:ti,ab,kw
31. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30

3. Exclusions

32. child:kw OR pediatric:kw OR infant:kw OR newborn:kw OR stroke:kw OR "cerebrovascular accident":kw OR "cerebral infarction":kw OR "myocardial infarction":kw OR "heart attack":kw OR "coronary artery disease":kw

4. Final combinaison

33. #20 AND #31 NOT #32

eAppendix 3. Study selections

The study selection was conducted using Rayyan software. Duplicates were excluded based on DOI. Two reviewers (PL and MR) independently screened titles and abstracts in a blinded manner. Disagreements were resolved after unblinding by a third reviewer (RB). Full-text screening followed the same process, with independent evaluation and resolution of conflicts by the third reviewer when required. Summary of excluded studies is provided in eTable 1.

eAppendix 4. Data extraction and missing data

We extracted data on study characteristics, including first author, year, journal, DOI/reference, and trial registration. Study design details included the design type, blinding, setting (country, center type, trauma center level), number of centers, and funding source. Participant data included the total number of participants, numbers analyzed per group, inclusion and exclusion criteria, and baseline characteristics (age, gender, GCS, ISS, hemoglobin at admission, mechanism of injury, and comorbidities).

- The primary outcome, good neurological outcome at d180, was extracted as the number of events and total participants per group.

Secondary outcomes:

- ICU length of stay (days, mean ± SD or median with IQR)
- Mechanical ventilation duration (hours or days, mean ± SD or median with IQR)
- Infection rates (any infection, pneumonia, bacteremia, sepsis/septic shock, CNS infection, catheter-related bloodstream infection)
- RBC units transfused (total units, mean ± SD or median with IQR)
- Acute respiratory failure or ARDS (event counts and total participants)
- Early mortality defined as death within 90 days (event counts and total participants)
- Mortality at 180 days
- Transfusion related adverse events (e.g., transfusion reactions, event counts and total participants)
- Thromboembolic events (e.g., DVT, PE, arterial thrombosis, event counts and total participants)

We prioritized outcomes corresponding to ITT analyses wherever available.

For missing data, we contacted the corresponding authors by email, with follow-up reminders sent two weeks apart if no response was received. Additionally, we contacted authors of studies registered as clinical trials that were planned but not yet published to obtain additional data or results not yet available publicly.

eAppendix 5. Bias Assessment

Study risk of bias

The risk of bias for included randomized trials was assessed using the Cochrane Risk of Bias tool (RoB 2). The evaluation focused on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias.

The assessment process was conducted independently by two reviewers (PLB and MR). Discrepancies between reviewers were resolved through discussion. In cases where agreement could not be reached, a third reviewer (RB) was consulted for arbitration.

Bias related to missing outcome data (Domain 2) was specifically assessed based on an intention-to-treat (ITT) analysis framework. All assessments were documented, and decisions were cross-checked using Cochrane macro.

Publication bias

Coutour–enhanced funnel plots were constructed to assess publication bias or small-study effects. Egger's test for funnel plot asymmetry was not performed due to the limited number of studies included.

eAppendix 6. Statistical analysis

Frequentist analysis

Primary analysis

We report the absolute number of events and the corresponding proportions for both the liberal and restrictive groups. Data were extracted from eligible studies, including both binary and continuous outcomes. For binary outcomes, effect sizes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) and pooled using the Mantel-Haenszel method. For continuous outcomes, standardized mean differences (SMDs) were calculated (Cohen's method).

When studies reported medians and interquartile ranges (IQRs) instead of means and standard deviations (SDs), we estimated the means and SDs following the method recommended by the Cochrane Handbook, assuming a normal distribution for sample sizes greater than 100 patients (SD = IQR / 1.35). For smaller sample sizes, data were not converted unless additional evidence supported the assumption of normality.

The primary meta-analysis was conducted using random-effects models. The between-study variance (tau-squared, τ^2) was estimated using the DerSimonian and Laird method.

Heterogeneity among studies was assessed using Cochran's Q test, and the I^2 statistic was used to quantify the proportion of variation due to heterogeneity rather than chance. I^2 values were calculated based on the Q statistic and reported without decimal places.

Heterogeneity was assessed using the I^2 statistic, following Cochrane guidelines. The thresholds for interpretation are as follows (Cochrane Handbook):

- **0% to 40%**: Might not be important.
- **30% to 60%**: May represent moderate heterogeneity.
- **50% to 90%**: May represent substantial heterogeneity.
- **75% to 100%**: Considerable heterogeneity.

R package : meta / metafor

Trial sequential analysis

A non pre-speficified Trial Sequential Analysis (TSA) was performed as an exploratory analysis to assess the robustness of the primary outcome. This analysis was not pre-specified in the PROSPERO protocol. The TSA was conducted using a two-sided test with a significance level (alpha) of 0.05 and a statistical power (1 − beta) of 80%. An anticipated relative risk reduction of 20% (risk ratio of 0.8) was assumed as the minimal clinically significant effect. The O'Brien-Fleming alpha-spending function was applied.

R package : RTSA

Sensitivity analysis

We conducted a pre-specified sensitivity analysis based on studies with a low risk of bias. We analyzed binary outcomes using risk ratios (RRs) as pre-specified. However, because one study (Roberston et al.) had poor baseline adjustment and reported an adjusted odds ratio (OR), we also conducted a sensitivity analysis pooling ORs to include this adjusted OR. Due to the limited number of studies included in the analysis, a no speficified post-hoc analysis was performed using the Hartung-Knapp method to adjust the confidence intervals in the random-effects model.

Sub-group analysis

We performed subgroup analyses based on predefined criteria:

- Traumatic brain injury, excluding non-traumatic intracranial hemorrhages.
- Glasgow Coma Scale (GCS) score stratification: >8 or ≤8.
- Intracranial pressure (ICP) value-based analysis.

These analyses were conducted as per the predefined protocol.

However, due to the lack of available data or refusal by authors to share their data, subgroup analyses for GCS and ICP could not be performed.

Post-Hoc Analysis

We decided to include a recent randomized controlled trial published after our initial data collection10. Although it did not fully meet our predefined PICO criteria, we conducted a post-hoc analysis to incorporate its findings. This subarachnoid hemorrhage study reported only one-year outcomes using the modified Rankin Scale (mRS). Since mRS correlates with the Glasgow Outcome Scale–Extended (GOSE), we combined the trial's one-year mRS data with our six-month GOSE results22. A DerSimonian-Laird random-effects model was used for this frequentist analysis.

Bayesian Analysis

A Bayesian analysis was performed as a sensitivity analysis using a random-effects model. Markov Chain Monte Carlo (MCMC) algorithms were utilized using the rstan package in R. Convergence diagnostics were assessed through the calculation of the maximum Rhat values and the minimum Effective Sample Size (ESS), with a minimum ESS threshold of 400 considered acceptable. Visual inspection of trace plots was conducted to verify that the chains were well mixed and converged appropriately.

Priors were selected based on different assumptions:

- **Neutral weakly informative prior**: The log odds ratio (θ) was assigned a normal distribution with mean 0 and variance 0.5 ($\theta \sim N(0, 0.5)$). Baseline risks (μ) were assigned non-informative priors with mean 0 and variance 10 ($\mu \sim N(0, 10)$). Heterogeneity (τ) was assigned a non-informative prior with standard deviation of 0.5 (half-normal distribution).
- **Favorable priors**: Based on the estimated log odds ratio from Taccone et al.[4], as their effect estimate had higher statistical power compared to Gobatto et al.[5], and included spontaneous hemorrhages, making it more representative of our meta-analysis compared to Turgeon et al.
    - **Weakly informative favorable prior**: $\theta \sim N(-0.4615, 0.5)$, $\mu \sim N(0, 10)$, $\tau \sim 0.5$
    - **Moderately informative favorable prior**: $\theta \sim N(-0.4615, 0.2)$, $\mu \sim N(0, 10)$, $\tau \sim 0.5$
- **Unfavorable prior**: Based on the estimated log odds ratio from Robertson et al.[6], as it was the only study that estimated an unfavorable effect.
    - **Weakly informative unfavorable prior**: $\theta \sim N(0.4080, 0.2)$ $\mu \sim N(0, 10)$, $\tau \sim 0.5$
    - **Moderately informative unfavorable prior**: $\theta \sim N(0.4080, 0.5)$ $\mu \sim N(0, 10)$, $\tau \sim 0.5$

The same analyses were performed under the assumption of lower heterogeneity with $\tau = 0.2$. This assumption was justified by the subgroup analysis excluding Robertson et al. ($I^2 = 0$), the similarity of transfusion protocols, and the standardized measurement of outcomes.

For each analysis, the posterior distribution of θ (log odds ratio) was computed, and its credible interval was defined. Predictive distributions for potential new studies were also generated based on the posterior distributions. Bayes Factors were calculated to compare the evidence supporting different prior models.

Bayes Factor Definition and Interpretation

Bayes Factors were calculated to compare the evidence supporting different prior models. The Bayes Factor (BF_A/B) is defined as the ratio of the marginal likelihoods of two competing models, Model A and Model B:

$$BF_{A/B} = P(\text{Data} \mid \text{Model A}) / P(\text{Data} \mid \text{Model A})$$

Where :

- P(Data | Model A) is the marginal likelihood of the data under Model A
- P(Data | Model A) is the marginal likelihood of the data under Model A

Marginal likelihoods were estimated using bridge sampling.

Interpretation of Bayes Factors:

- **BF_A/B > 1**: Evidence in favor of Model A over Model B.
- **0 < BF_A/B < 1**: Evidence in favor of Model B over Model A.
- **BF_A/B = 1**: Data are equally likely under both models; no preference.

Strength of Evidence Based on BF_A/B Values:

- **1 – 3**: Anecdotal evidence supporting Model A.
- **3 – 10**: Moderate evidence supporting Model A.
- **10 – 30**: Strong evidence supporting Model A.
- **30 – 100**: Very strong evidence supporting Model A.
- **>100**: Extreme evidence supporting Model A.

R packages : rstan, metastan, bridgesampling.

All statistical analyses were performed using R software (version 4.3.2)

Data availability

All extracted data are available in supplementary.

eAppendix 7. Assessment of Certainty of Evidence (GRADE Approach)

The certainty of evidence was assessed using the GRADE framework. Evidence was evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome was categorized as high, moderate, low, or very low certainty based on the cumulative assessment of these domains. This process was conducted using the GRADEpro GDT tool (RB and LC).

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	✓
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	✓
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	✓
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	✓
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	✓
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.	✓
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	✓
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.	✓
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.	✓
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.	✓
	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.	✓
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.	✓
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.	✓
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)).	✓
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	✓
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	✓
	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.	✓
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	✓

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	✓
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	✓
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	✓
RESULTS			
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.	✓
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	✓
Study characteristics	17	Cite each included study and present its characteristics.	✓
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	✓
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.	✓
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	✓
	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.	✓
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	✓
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	✓
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	✓
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	✓
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	✓
	23b	Discuss any limitations of the evidence included in the review.	✓
	23c	Discuss any limitations of the review processes used.	✓
	23d	Discuss implications of the results for practice, policy, and future research.	✓
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	✓

Section and Topic	Item #	Checklist item	Location where item is reported
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	✓
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	✓
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	✓
Competing interests	26	Declare any competing interests of review authors.	✓
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.	✓

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi

eTable 1. Excluded Reports and Reasons for Exclusion

Study	Reasons for exclusion
McIntyre et al, 2006	Post-hoc analysis of a 1999 study, too many missing data
Audibert et al, 2014	Abstract only. Outcomes focusing on metabolism with no clinical data, short time of intervention (3 days), too many missing data
De Georgia et al, 2007	Observational study
Yamal et al, 2015	Post-hoc analysis of Robertson et al, 2014 with no relevant additional data
Zygun et al, 2009	Outcomes focusing on metabolism with no clinical data, short time of intervention (3 hours)
Xia et al, 2017	Observational study

eTable 2. Unpublished Outcome Data Obtained From Robertson Study

	Liberal strategy	Restrictive strategy
Secondary outcomes		
Ventilator-free days during first month, mean (SD)	12.2 (10.3)	14.6 (10.3)
ICU length of stay, mean (SD)	17.7 (11.1)	16.3 (10.0)
ARDS, No./total (%)	25/101 (24.7)	16/99 (16.2)
Thromboembolic events, No./total (%)	22/101 (21.8)	8/99 (8.1)

*Data requests were sent to all authors. Only Robertson et al. accepted to share unpublished data. Other authors did not respond to our sollicitations.

eTable 3. Narrative Literature Overview

TRAIN Study – Taccone et al. 2024

Study Identification

- First author: Fabio Taccone
- Year of publication: 2024
- Journal: JAMA
- DOI/Reference: 10.1001/jama.2024.20424
- Trial registration: NCT02968654

Study Design and Setting

- Study design: Randomized Controlled Trial
- Study dates: Sept 2017 – Dec 2022
- Blinding: Open-label, outcome assessor–blinded
- Setting: 22 countries, 72 ICUs
- Number of centers: 72
- Funding sources: ESICM NeXT grant & La Fondation des Gueules Cassées

Participants

- Total number of participants: 820
- Number analyzed for each group: 397 in the liberal strategy group & 423 in the restrictive strategy group
- Inclusion criteria: ICU patients, age older than 18 y.o., TBI/SAH/ICH, GCS ≤ 13
- Exclusion criteria: active bleeding, ICH due to tumor or AVM, previously known neurological disorder, brain death expected in <24H, DNE orders.
- Baseline characteristics for each group:
  - Liberal: Age 52 ± 16, Male 54.9%, Female 45.1%, GCS median at 7 [4–11], APACHE II 19 (8), mGCS 3 [1–5], Hb at randomization at 8.5 [7.9–8.8], TBI in 60.5%, SAH in 21.7%, ICH in 17.9%, Comorbidities (Diabetes 6.3%, COPD 5.3%, Cancer 2.5%, CHF 2.0%), Salvage therapies for elevated ICP in 27.7%
  - Restrictive: Age 51 ± 16, Male 53.4%, Female 46.6%, GCS median 8 [4–12], APACHE II 19 (8), mGCS 3 [1–5], Hb at randomization at 8.5 [8.0–8.8], TBI in 58.2%, SAH in 24.6%, ICH in 17.3%, Comorbidities (Diabetes 5.7%, COPD 5.2%, Cancer 3.5%, CHF 1.9%), Salvage therapies for elevated ICP in 31.9%

Interventions

- Liberal transfusion group: Transfusion should be given at Hb concentration < 9g/dL. 1 unit of packed red blood cells at a time. No protocolization for the timing of transfusion.
- Restrictive transfusion group: Transfusion should be given at Hb concentration < 7g/dL. 1 unit of packed red blood cells at a time. No protocolization for the timing of transfusion.
- Cointerventions: none
- Treatment duration: the allocated transfusion thresholds were maintained for a maximum of 28 days after randomization or until hospital discharge or death, whichever event occurred first

Outcomes

- Primary outcome: proportion of patients with unfavorable neurological outcome at 6 months after randomization assessed using GOS-E (unfavorable GOS-E score of 1-5, favorable GOS-E score of 6-8)
- Secondary outcomes: 28-day survival, distribution of GOS-E scores in the 2 groups at 6 months, ICU and hospital LOS, presence of organ failure during the ICU stay, composite outcome

including death and/or organ failure at 28 day, daily fluid balance during ICU stay, adverse events (ARDS, sepsis, venous thromboembolic events)

Methodological Quality (Risk of Bias Assessment)

- Randomization process: Adequate
- Allocation concealment: Adequate
- Blinding: Outcome assessment: Adequate
- Incomplete outcome data: Adequate
- Selective reporting: No
- Overall risk of bias (Rob-2): Low

Data for Meta-Analysis

- Effect size for primary outcomes: absolute difference, −10.0% [95% CI, −16.5% to −3.6%]; unadjusted relative risk, 0.86 [95% CI, 0.78-0.95]; adjusted relative risk, 0.86 [95% CI, 0.79-0.94]; P = .002).
- Effect size for secondary outcomes:
  - 28-day survival: (82/397 [20.7%] vs 94/418 [22.5%]; relative risk, 0.95 [95% CI, 0.74-1.22]
  - Distribution of GOS-E scores in the 2 groups at 6 months: significantly higher in the liberal strategy group ods ratio, 1.37 [95% CI, 1.07-1.75]; P = .01
  - Other secondary outcomes: not significantly different
  - Adverse events:
    - Cerebral ischemic events: 5 (8.8%) of 397 patients had at least 1 cerebral ischemic event compared with 57 (13.5%) of 423 in the restrictive strategy group (relative risk, 0.65 [95% CI, 0.44-0.97]
    - No difference in other adverse events
- Missing data: 2%

Additional Notes

- Study limitations: open label, some patients may have received blood transfusion before randomization (reduction of the differences in Hb values and transfusion exposure between the groups), inclusion of patients with different types of brain injury (different susceptibility to cerebral ischemia from anemia), no recommendation for screening VTE events
- Author conclusions: patients with anemia and ABI randomized to a liberal strategy of RBCT at a hemoglobin threshold of 9 g/dL had a lower probability of unfavorable neurological outcome at 180 days than patients randomized to a restrictive strategy of transfusion at a hemoglobin threshold of 7 g/dL.
- Reviewer comments and synthesis: Strengths, Limitations, Impact on overall findings

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HEMOTION Study – Turgeon et al. 2024

Study Identification

- First author: Alexis Turgeon
- Year of publication: 2024
- Journal: NEJM
- DOI/Reference: 10.1056/NEJMoa2404360
- Trial registration: NCT03260478

Study Design and Setting

- Study design: Randomized Controlled Trial
- Study dates: Sept 2017 – April 2023
- Blinding: Open-label, outcome assessor–blinded

- Setting: 4 countries, 34 ICUs
- Number of centers: 34
- Funding sources: Canadian Institutes of Health Research, Ottawa ON and Canadian Accelerating Clinical Trials.

Participants

- Total number of participants: 736
- Number analyzed for each group: 369 in the liberal strategy group & 367 in the restrictive strategy group
- Inclusion criteria: ICU patients, age older than 18 y.o., severe to moderate TBI (GCS ≤ 12), and Hb level ≤ 10 g/dL
- Exclusion criteria: transfusion after ICU admission, before randomization, CI or objection to transfusion, bleeding, brain death, decision to WLST, GCS3 with bilateral fixed dilated pupils.
- Baseline characteristics for each group:
  - Liberal: Age 48.9 ± 18.8, Male 75.9%, moderate TBI in 26.6%, Hb at admission 13.8±1.8 g/dL, Hb at randomization 9.1 ± 0.8 g/dL, ISS 30 ± 11, mGCS 1 [4–5], motor vehicle in 15.7%, pedal/motorcycle/scooter/all-terrain collision in 20.3%, vehicle-pedestrian in 10.6%, assault in 4.1%. Comorbidities (chronic anemia 0.5%, ischemic heart disease or myocardial infarction 5.4%, CHF 0.5%), Hyperosmolar therapy in 39.8%, active cooling in 20.9%, craniectomy in 14.1%.
  - Restrictive: Age 48.4 ± 19.0, Male 69.5%, moderate TBI in 27%, Hb at admission 13.1±1.7 g/dL, Hb at randomization 9.1 ± 0.8 dL, ISS 32 ± 11, mGCS 1 [4–5], motor vehicle in 19.6%, pedal/motorcycle/scooter/all-terrain collision in 19.3%, vehicle-pedestrian in 10.9%, assault in 6.8%. Comorbidities (chronic anemia 1.4%, ischemic heart disease or myocardial infarction 6.5%, CHF 1.4%,), Hyperosmolar therapy in 39.8%, active cooling in 20.9%, craniectomy in 14.1%

Interventions

- Liberal transfusion group: triggered by a hemoglobin level of ≤10 g/dL, leukoreduced red cells, 1 unit at a time, transfusion within 3 hours after threshold was reached.
- Restrictive transfusion group: triggered by a hemoglobin level of ≤7 g/dL, leukoreduced red cells, 1 unit at a time, transfusion within 3 hours after threshold was reached
- Cointerventions: none
- Treatment duration: the transfusion strategy was applied until the patient's discharge from the ICU

Outcomes

- Primary outcome: unfavorable outcome assessed by the score on GOS-E at 6 months (unfavorable GOS-E score of 1-5)
- Secondary outcomes: mortality in the ICU, mortality at 6 months, score on the Functional Independence Measure, score on EQ-5D-5L, score on the Qolibri scale and the PHQ-9 to evaluate depression
- Tertiary outcomes: number of units of RCT in the ICU, lowest daily Hb level, infections, complications related to transfusion, duration of MV, ICU and hospital LOS

Methodological Quality (Risk of Bias Assessment)

- Randomization process: Adequate
- Allocation concealment: Adequate
- Blinding: Outcome assessment: Adequate
- Incomplete outcome data: Adequate
- Selective reporting: No
- Overall risk of bias (Rob-2): Low

Data for Meta-Analysis

- Effect size for primary outcomes: 68.4% in the liberal-strategy group versus 73.5% in the restrictive-strategy group, adjusted absolute difference, restrictive strategy vs. liberal strategy, 5.4 percentage points; 95% confidence interval [CI], −2.9 to 13.7. Overall relative risk of an unfavorable outcome in the liberal group vs restrictive group was 0.93 (95% CI, 0.83 to 1.04)
- Effect size for secondary outcomes:
  - Mortality at 6 months: 26.8% in the liberal-strategy group versus 26.3% in the restrictive-strategy group (hazard ratio for death, 1.01; 95% CI, 0.76 to 1.35)
  - Functional scores:
    - FIM: median difference between liberal-strategy and restrictive-strategy groups of 4.34 points (95%CI, 0.22–9.86)
    - EuroQol: median difference between liberal-strategy and restrictive-strategy groups of 5.19 points (95% CI, 0.52–9.86)
    - EQ-5D-5L: median difference between liberal-strategy and restrictive-strategy groups of 0.06 points (95% CI, 0.01–0.10)
    - Qolibri: median difference between liberal-strategy and restrictive-strategy groups 3.72 (IQR, -1.13–8.56]
    - PHQ-9: median difference between liberal-strategy and restrictive-strategy groups -0.51 points (95% CI, -1.91–0.90)
    - Depression: RR in the liberal group as compared with the restrictive group was 0.85 (95% CI, 0.63–1.17)
- Effect size for tertiary outcomes:
  - Reaction to the transfusion: 1.6% in the liberal-strategy group and 0.7% in the restrictive-strategy group
  - VTE: 8.4% (31/369) in the liberal-strategy group versus 8.4% (31/367) in the restrictive-strategy group
  - ARDS: 3.3% (12/369) in the liberal-strategy group versus 0.8% (3/367) in the restrictive-strategy group
- Missing data: 5.2% of missing data. Sensitivity analysis did not reveal any imbalance between groups

Additional Notes

- Study limitations: severity of TBI patients included by recruiting solely patients with anemia, imbalances between the groups at baseline with better prognosis at baseline in the liberal-strategy group, open-label
- Author conclusions: liberal transfusion strategy did not decrease the risk of an unfavorable neurologic outcome at 6 months as measured with the GOS-E in critically ill patients with traumatic brain injury

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Gobatto et al. 2019

Study Identification

- First author: André L N Gobatto
- Year of publication: 2019
- Journal: Crit Care
- DOI/Reference: 10.1186/s13054-018-2273-9
- Trial registration: NCT02203292

Study Design and Setting

- Study design: Randomized Controlled Trial
- Study dates: Aug 2014 – June 2016
- Blinding: Open-label

- Setting: 1 country, 2 ICUs
- Number of centers: 1
- Funding sources: The study was not financially supported by any funding source

Participants

- Total number of participants: 44
- Number analyzed for each group: 21 in the liberal strategy group & 23 in the restrictive strategy group
- Inclusion criteria: ICU patients, age older than 18 y.o., severe or moderate TBI (GCS ≤ 12), and Hb levels < 9 g/dL within 7 days from hospital admission.
- Exclusion criteria: GCS of 3, with dilated pupils bilaterally, previous neurological sequelae, pregnancy, Jehovah's witnesses, hemorrhagic shock at randomization, moribund.
- Baseline characteristics for each group:
    - Liberal: Age 33 ± 11, Male 95%, ISS 29 ± 9, SAPS2 at ICU admission 55 ± 12, IMPACT 47 (17), Hb at admission 12 ± 2.3 g/dL, Hb at randomization 7.9 ± 0.6 g/dL , motorcycle crash in 29%, fall in 33% and run over in 14%, GCS at admission 4 [3–7], compressed citerns on CT in 17 (85%), midline deviation ≥ 5 mm in 10 (48%), decompressive craniectomy in 7 (33%).
    - Restrictive: Age (36 ± 15), Male 87%, ISS 31 ± 9, SAPS2 at ICU admission 57 ± 12, IMPACT 52 (14), Hb at admission 12.5 ± 1.8 g/dL, Hb at randomization 8.2 ± 1.0 g/dL, motorcycle crash in 35%, fall in 44% and run over in 9%, GCS at admission 4 [3–7], compressed citerns on CT in 18 (78%), midline deviation ≥ 5 mm in 16 (70%), decompressive craniectomy in 10 (44%).

Interventions

- Liberal transfusion group: patients were transfused if the hemoglobin concentration was less than 9 g/dL
- Restrictive transfusion group: patients were transfused if the hemoglobin concentration was less than 7 g/dL.
- Single units of cross-matched, pre-storage non-leuko-reduced RBCs. After every RBC transfusion, hemoglobin concentrations were checked one hour after transfusion and a single unit of RBCs was provided.
- Treatment duration: the transfusion strategy was respected for 14 days or until death or ICU discharge
- Cointerventions: none

Outcomes

- Primary outcome: difference in mean hemoglobin concentration between the liberal and restrictive groups during the 14 days after hospital admission
- Secondary outcomes: numbers of transfused patients, number of RBC pack transfused, ICU mortality, hospital mortality, mortality at 6 months after hospital discharge, adverse events, presence of elevated ICP, intensity of ICH treatment, cerebral hemodynamic findings on TCD, ICU LOS, hospital LOS, ICU-free days, duration of MV, MV free days, neurological status at hospital discharge and 6 months after hospital discharge.

Methodological Quality (Risk of Bias Assessment)

- Randomization process: Adequate
- Allocation concealment: Adequate
- Blinding: Outcome assessment: Adequate
- Incomplete outcome data: Adequate
- Selective reporting: No
- Overall risk of bias (Rob-2): low

Data for Meta-Analysis

- Effect size for primary outcome: 9.3 ± 1.3 g/dL in the liberal group versus 8.4 ± 1.0 g/dL in the restrictive group with $p < 0.01$, mean difference of 0.9 +/- 0.2 g/dL.
- Effect size for secondary outcomes:
  - Transfusion: All 21 patients in the liberal group were transfused, compared with 13 (57%) patients in the restrictive group with a mean of 3.1 ± 1.6 vs. 1.5 ± 1.7 units per patient, respectively ($p < 0.01$).
  - Complications: no differences in the numbers of complications: 4.2 ± 1.8 vs. 4.1 ± 1.7, respectively ($p = 0.86$)
  - Neurological status: no significant difference between groups in GOS outcomes at hospital discharge. At 6 months the liberal group trended to have a better neurological status ($p=0.06$).
  - Hospital mortality was lower in the liberal group (n = 1 patient (5%) vs. n = 7 patients (30%), respectively; $p = 0.048$).
- Missing data: no missing data

Additional Notes

- Study limitations: pilot study, difference in mean Hb concentration as a primary outcome, secondary outcomes are exploratory, small sample size and underpowered to detect small differences between groups, no standardization for assessment at 6 months, single-center, slow recruitment.
- Author conclusions: trial reached feasibility criteria. The restrictive group had lower hemoglobin concentrations and received fewer RBC transfusions. Hospital mortality was lower in the liberal group.

Robertson et al. 2014

Study Identification

- First author: Claudia S. Robertson
- Year of publication: 2014
- Journal: JAMA
- DOI/Reference: 10.1001/jama.2014.6490
- Trial registration: NCT00313716

Study Design and Setting

- Study design: Randomized Controlled Trial using a factorial (2x2) design compared administration of erythropoietin or placebo and hemoglobin thresholds separately
- Study dates: May 2006 – August 2012
- Blinding: Double blinded for erythropoietin, Open-label for transfusion threshold assignment. Personnel conducting outcome assessments were blinded to both drug treatment assignment and transfusion threshold.
- Setting: 1 country, 2 US level 1 trauma centers
- Number of centers: 2
- Funding source: supported by grand PO1-NS38660 from the National Institute of Neurological Disorders and Stroke

Participants

- Total number of participants: 200
- Number analyzed for each group: 99 patients in the restrictive strategy group, 101 patients in the liberal strategy group
- Inclusion criteria: closed head injury, admitted to 1 of 2 level I trauma centers, within 6 hours following injury.

- Exclusion criteria: GCS score of 3 and fixed/dilated pupils, penetrating trauma, pregnancy, life-threatening systemic injury, severe preexisting disease
- Baseline characteristics for each group:
  - Liberal: Age 31 [24–45], Male 87.1%, Female 11.9%, ISS 29 [25–35], GCS ≤ 5 in 31.7%, GCS 6-8 in 21.8%, prehospital hypotension in 13.9%, prehospital hypoxemia in 20.8%, no pupilar reactivity in 33.7%, Hb ad admission 14.6 [12.8–15.5], intracerebral hematoma or contusion in 2%, automobile crash in 57.4%
  - Restrictive: Age 28 [21–48], Male 85.9%, ISS 29 [25–38], GCS ≤ 5 in 34.3%, GCS 6-8 in 23.2%, prehospital hypotension in 11.1%, prehospital hypoxemia in 18.2%, no pupilar reactivity in 22.2%, Hb ad admission 14.4 [13.0–15.6], intracerebral hematoma or contusion in 2%, automobile crash in 58.6%

Interventions

- Liberal transfusion group: Transfusion should be given at Hb concentration ≤10g/dL
- Restrictive transfusion group: Transfusion should be given at Hb concentration ≤ 7g/dL
- Cointerventions: erythropoietin in a factorial 2x2 design
- Treatment duration: until ICP and MV weaning

Outcomes

- Primary outcome: neurological recovery at 6 months measured using GOS, dichotomized into favorable outcome (GOS 4-5) or unfavorable outcome (GOSE 1-3)
- Safety outcomes for transfusion: mortality, incidence of ARDS, incidence of infections
- Secondary transfusion outcomes: Disability Rating Scale (31-point scale).

Methodological Quality (Risk of Bias Assessment)

- Randomization process: Some concerns
- Allocation concealment: Adequate
- Blinding: Outcome assessment: Some concerns
- Incomplete outcome data: Adequate
- Selective reporting: No
- Overall risk of bias (Rob-2): some concerns

Data for Meta-Analysis

- Effect size for primary outcomes: 37 (42.5%) patients in the restrictive group recovered to a favorable outcome versus 31 (33%) patients in the liberal transfusion (95% CI, -0.06 to 0.25). No significant difference in the multiple imputation of missing GOS scores in outcome detected between the 2 threshold groups (95% CI for difference, −0.07 to 0.20; P = .34). No difference after adjustment for prespecified covariates (OR, 0.75 [95% CI, 0.36-1.55]; P = .43).
- Disability Rating Scale Score: median at 5 [2.25–9.75] in the restrictive group versus 8 [4–17] in the liberal group with p=0.06.
- Safety outcomes:
  - Mortality at 6 months: 14 deaths in the restrictive group versus 17 in the liberal group (log-rank test p=0.72)
  - ARDS: 16.2% in the restrictive versus 24.7% in the liberal with p=0.16. In the final Cox regression model, transfusion threshold of 10g/dL was not associated with ARDS (HR 1.79 [95% CI, 0.93–3.45], p=0.08).
  - Infections: 27 patients in the restrictive versus 36 patients in the liberal group (95% CI for difference in proportions, −0.22 to 0.05, P = .26).
  - Thromboembolic events: patients in the liberal group had a significantly greater incidence of 1 or more thromboembolic events (22 patients [21.8%] vs 8 patients [8.1%] compared to patients in the restrictive group; OR, 0.32 [95% CI, 0.12-0.79], P = .009).
- Missing data: 7% of lost to follow up

Additional Notes

- Study limitations: factorial design with erythropoietin, only 2 centers (limit the ability to generalize the results), long time for enrollment
- Author conclusions: in patients with TBI, neither the administration of erythropoietin nor maintaining hemoglobin concentration of at least 10 g/dL resulted in improved neurological outcome at 6 months. These findings do not support either approach in patients with traumatic brain injury.

eTable 4. Explanation of MCMC Diagnostics

Theta Prior Mean	Theta Prior Variance	Theta Posterior Mean	Theta Posterior Median	Theta Lower 95% CI	Theta Upper 95% CI	ESS	Rhat (max)
0.00	0.5	-0.21	-0.22	-0.59	0.28	1,133	1.005808
-0.46	0.2	-0.36	-0.36	-0.66	-0.09	1,569	1.002369
-0.46	0.5	-0.30	-0.30	-0.74	0.10	1,285	1.001941
0.41	0.2	0.18	0.17	-0.18	0.55	1,394	1.001732
0.41	0.5	-0.13	-0.17	-0.52	0.42	1,137	1.003104
0.00	0.5	-0.25	-0.26	-0.55	0.08	1,662	1.001849
-0.46	0.2	-0.35	-0.35	-0.59	-0.12	1,321	1.002526
-0.46	0.5	-0.30	-0.30	-0.60	0.01	1,607	1.003624
0.41	0.2	0.06	0.05	-0.23	0.41	1,401	1.001865
0.41	0.5	-0.21	-0.22	-0.51	0.16	1,342	1.002118

eTable 5. GRADE assessment of the certainty of evidence

Author(s): Rayan BRAÏK, Lucie COLLET

Question: Liberal threshold transfusion (9g/dl or higher) compared to Restrictive threshold transfusion (7g/dl or higher) for Brain Injury

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Liberal threshold transfusion (9g/dl or higher)	Restrictive threshold transfusion (7g/dl or higher)	Relative (95% CI)	Absolute (95% CI)		
Favorable neurological outcome (follow-up: 180 days; assessed with: GOSE score or GOS score)												
4	randomised trials	very serious	serious[a]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	273/872 (31.3%)	223/881 (25.3%)	**OR 0.84** (0.65 to 1.09)	**32 fewer per 1 000** (from 73 fewer to 17 more)	⨁⨁◯◯ Low[a]	CRITIQUE
Death occurring at 180 days (follow-up: 180 days; assessed with: death)												
4	randomised trials	serious[b]	not serious	not serious	not serious	none	230/877 (26.2%)	246/890 (27.6%)	**OR 1.05** (0.90 to 1.22)	**10 more per 1 000** (from 21 fewer to 41 more)	⨁⨁⨁◯ Moderate[b]	IMPORTANT
Risk of infection (follow-up: 180; assessed with: - Any infection rate: Overall incidence of infections during the ICU stay. - Pneumonia: Incidence of ventilator-associated or hospital-acquired pneumonia. - Bacteremia: Documented bloodstream infections confirmed by positive blood cultures. - Sepsis/Septic shock: Cases meeting Sepsis-3 criteria, including organ dysfunction and/or shock. - Central nervous system infection: Diagnosed meningitis or encephalitis. - Catheter-related bloodstream infection: Infections associated with intravascular devices confirmed by culture and clinical criteria.)													
4	randomised trials	serious[b]	not serious	not serious	not serious	none	299/926 (32.3%)	298/941 (31.7%)	**OR 0.98** (0.84 to 1.15)	**4 fewer per 1 000** (from 36 fewer to 31 more)	⨁⨁⨁◯ Moderate[b]	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Liberal threshold transfusion (9g/dl or higher)	Restrictive threshold transfusion (7g/dl or higher)	Relative (95% CI)	Absolute (95% CI)		
Transfusion related events (follow-up: 180 days; assessed with: Any documented complications or undesired outcomes associated with transfusions or treatments. Documented transfusion reactions, such as febrile non-hemolytic reactions, allergic reactions, or hemolysis, occurring shortly after transfusion.)												
3	randomised trials	not serious	serious[c]	not serious	extremely serious[d]	none	5/813 (0.6%)	11/787 (1.4%)	**OR 0.43** (0.07 to 2.67)	**8 fewer per 1 000** (from 13 fewer to 22 more)	⨁◯◯◯ Very low[c,d]	IMPORTANT
Respiratory distress syndrome (follow-up: 180 days; assessed with: Cases requiring respiratory support due to oxygenation or ventilation failure, including acute respiratory distress syndrome (ARDS) diagnosed per Berlin criteria.)												
4	randomised trials	serious[b]	serious[e]	not serious	serious[f]	none	67/888 (7.5%)	56/912 (6.1%)	**OR 0.72** (0.39 to 1.32)	**16 fewer per 1 000** (from 37 fewer to 18 more)	⨁◯◯◯ Very low[b,e,f]	IMPORTANT
Mechanical ventilation duration (assessed with: Total time a patient required mechanical ventilatory support)												
2	randomised trials	not serious	serious[g]	not serious	extremely serious[h]	none	766	790	-	SMD 0.07 SD higher (0.07 lower to 0.21 higher)	⨁◯◯◯ Very low[g,h]	IMPORTANT
Thromboembolic events (follow-up: 180 days; assessed with: Frequency of venous thromboembolism (deep vein thrombosis or pulmonary embolism) or arterial thrombosis.)												
4	randomised trials	serious[b]	serious[i]	not serious	not serious	none	75/888 (8.4%)	56/912 (6.1%)	**OR 0.68** (0.39 to 1.19)	**19 fewer per 1 000** (from 37 fewer to 11 more)	⨁⨁◯◯ Low[b,i]	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

Explanations

a. The primary analysis results are characterized by high heterogeneity (I^2 = 58%). Sensitivity analysis identifies the study by Robertson et al. as the main contributor to this heterogeneity. Study-specific factors are likely to explain these findings and could account for the high heterogeneity. Indeed, the hemoglobin levels in the restrictive group of Robertson et al.'s study reached values comparable to those of the liberal group in other studies. Furthermore, the study included a co-intervention with erythropoietin, which does not reflect standard clinical practice. The combination of erythropoietin and transfusion at higher liberal thresholds may account for the observed differences in outcomes and contribute to the elevated heterogeneity. Additionally, the sensitivity analysis excluding Robertson et al.'s study reveals a significant effect with an OR of 0.74 (95% CI 0.63–0.87) and no detected heterogeneity.

b. The analysis includes Robertson et al.'s study, where hemoglobin levels in the restrictive group were similar to those in the liberal groups of other studies. The use of erythropoietin in this study does not reflect standard clinical practice. Excluding this study would not significantly change the overall effect estimate.

c. A notable heterogeneity was observed in the analysis, with an statistic of 53%

d. The imprecision bias for adverse events is justified because the confidence interval (CI) of 0.07 to 2.67 is wide. It shows uncertainty, ranging from a large reduction to a big increase, making conclusions unclear. Moreover, the definition of adverse events varied between studies, and the low incidence further limits the reliability of the results, reducing precision and confidence in the estimates.

e. A notable heterogeneity was observed in the analysis, with an statistic of 52%

f. The imprecision bias for the risk of respiratory failure is justified because the confidence interval (CI) ranges from 0.39 to 1.32, which includes the null value of 1. This indicates that the true effect is uncertain and could range from a potential reduction in risk to a slight increase. Since the suspected effect is modest, the current evidence is not sufficient to draw definitive conclusions.

g. A notable heterogeneity was observed in the analysis, with an statistic of 49%

h. The imprecision bias for the risk of infection is justified because the confidence interval (CI) ranges from -0.07 to 0.21, which includes the null value of 1. This indicates that the true effect is uncertain and could range from a potential reduction in risk to a slight increase. Since the suspected effect is modest, the current evidence is not sufficient to draw definitive conclusions.

i. A notable heterogeneity was observed in the analysis, with an statistic of 52%

GRADE assessment of the certainty of evidence for primary and secondary outcomes. This figure evaluates risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty of evidence is categorized as high, moderate, low, or very low.

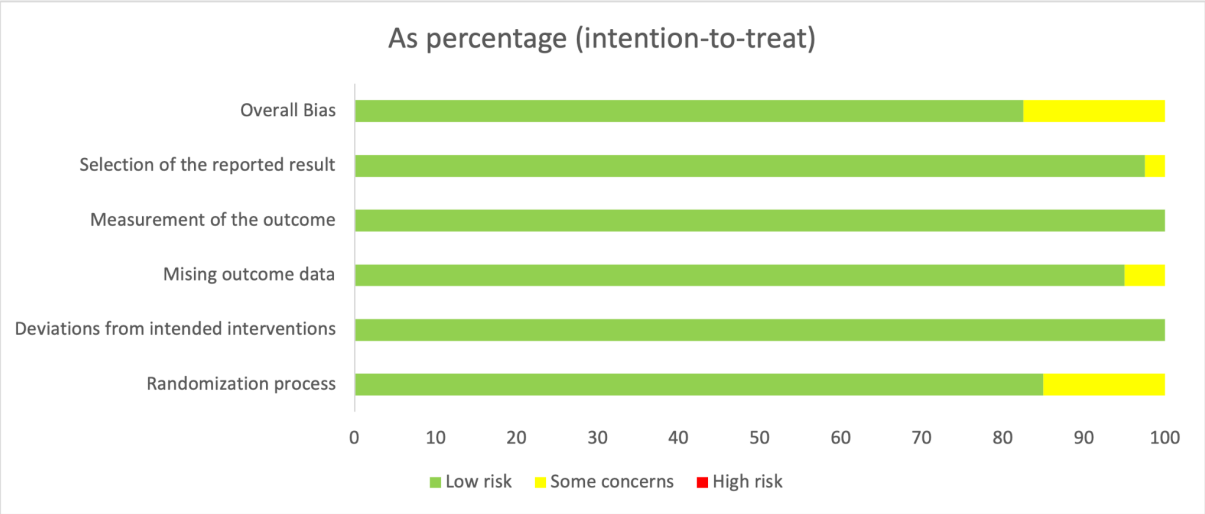
eFigure 1. Risk of Bias Assessments

A.

	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Turgeon 2024	7g/dL	10g/dL	Neurological outcome	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Neurological outcome	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	Neurological outcome	+	+	+	+	+	+
Robertson 201	7g/dL	10g/dL	Neurological outcome	!	+	!	+	+	!
English 2024	8g/dL	10g/dL	Neurological outcome	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Mortality at 180 days	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Mortality at 180 days	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	Mortality at 180 days	+	+	+	+	+	+
Robertson 201	7g/dL	10g/dL	Mortality at 180 days	!	+	!	+	+	!
English 2024	8g/dL	10g/dL	Mortality at 180 days	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Early mortality (<d90)	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Early mortality (<d90)	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	Early mortality (<d90)	+	+	+	+	+	+
Robertson 201	7g/dL	10g/dL	Early mortality (<d90)	!	+	+	+	+	!
English 2024	8g/dL	10g/dL	Early mortality (<d90)	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Lenght of stay	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Lenght of stay	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	Lenght of stay	+	+	+	+	+	+
English 2024	8g/dL	10g/dL	Lenght of stay	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Mechanical ventilation	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Mechanical ventilation	+	+	+	+	+	+
English 2024	8g/dL	10g/dL	Mechanical ventilation	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Infection rate	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Infection rate	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	Infection rate	+	+	+	+	+	+
Robertson 201	7g/dL	10g/dL	Infection rate	!	+	+	+	+	!
English 2024	8g/dL	10g/dL	Infection rate	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	Adverse event	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	Adverse event	+	+	+	+	+	+
English 2024	8g/dL	10g/dL	Adverse event	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	ARDS	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	ARDS	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	ARDS	+	+	+	+	+	+
Robertson 201	7g/dL	10g/dL	ARDS	!	+	+	+	+	!
English 2024	8g/dL	10g/dL	ARDS	+	+	+	+	+	+
Turgeon 2024	7g/dL	10g/dL	VTE	+	+	+	+	+	+
Taccone 2024	7g/dL	9g/dL	VTE	+	+	+	+	+	+
Gobatto 2019	7g/dL	9g/dL	VTE	+	+	+	+	!	!
Robertson 201	7g/dL	10g/dL	VTE	!	+	+	+	+	!
English 2024	8g/dL	10g/dL	VTE	+	+	+	+	+	+

+	Low risk
!	Some concerns
-	High risk
D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

B.

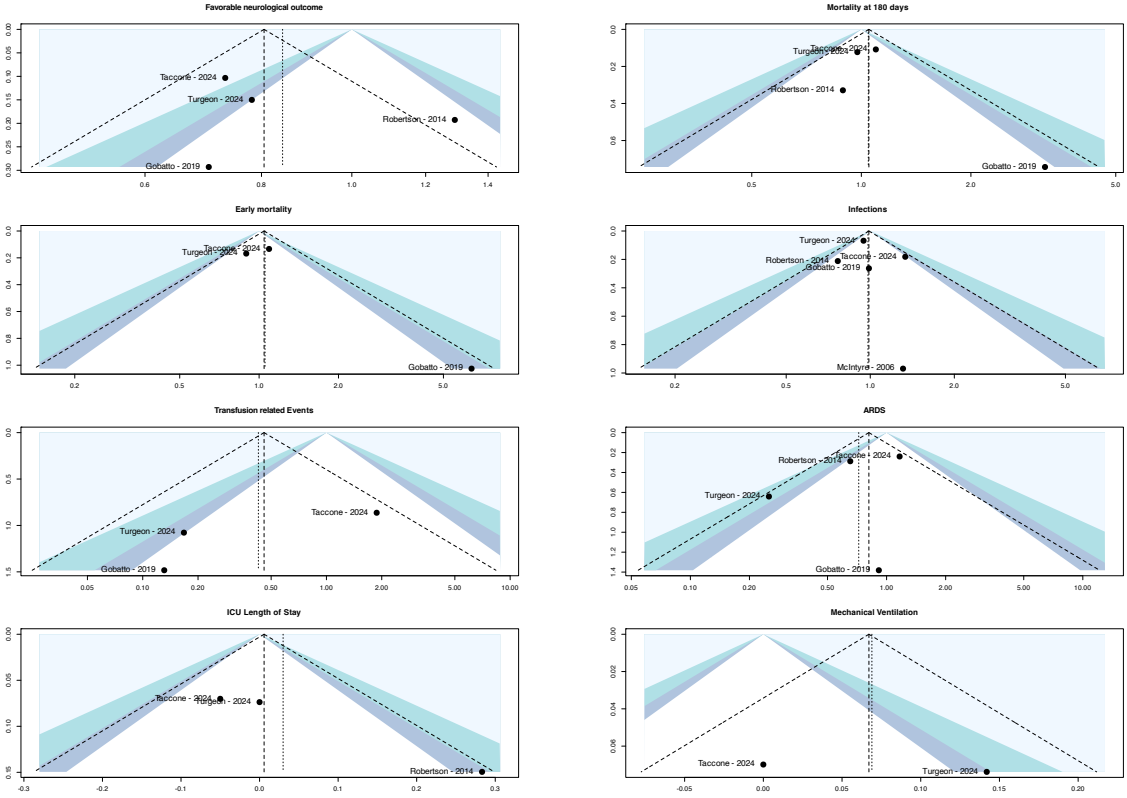


eFigure 2A: risk of bias assessment for each outcome.

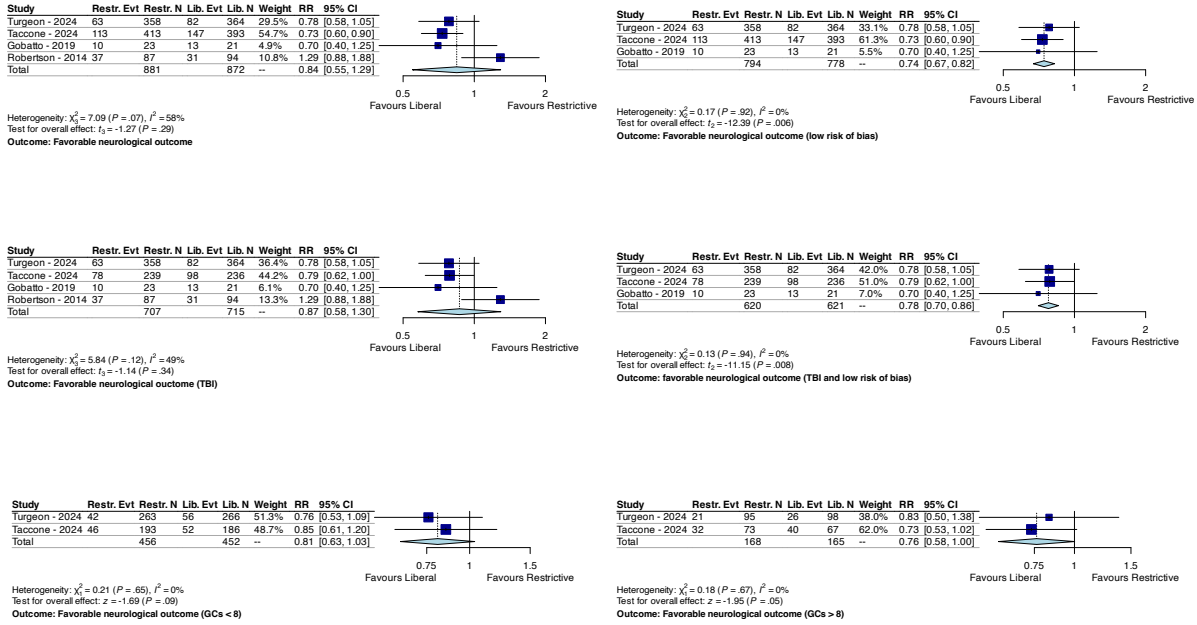
eFigure 2B: summary of risk of bias represented as percentage.

ARDS: acute respiratory distress syndrome; VTE: venous thromboembolic events.

eFigure 2. Bias of publications (Funnel Plot)

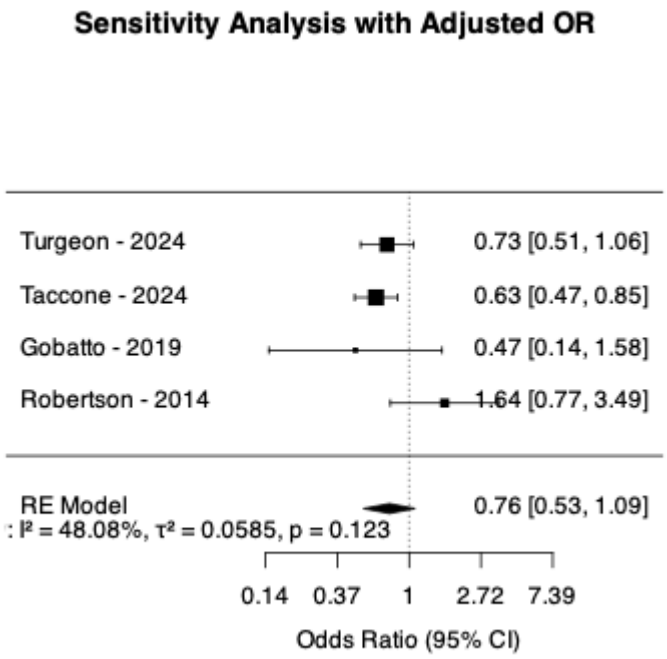


eFigure 3. Forest plots using the Hartung-Knapp random-effects model for neurologic outcomes



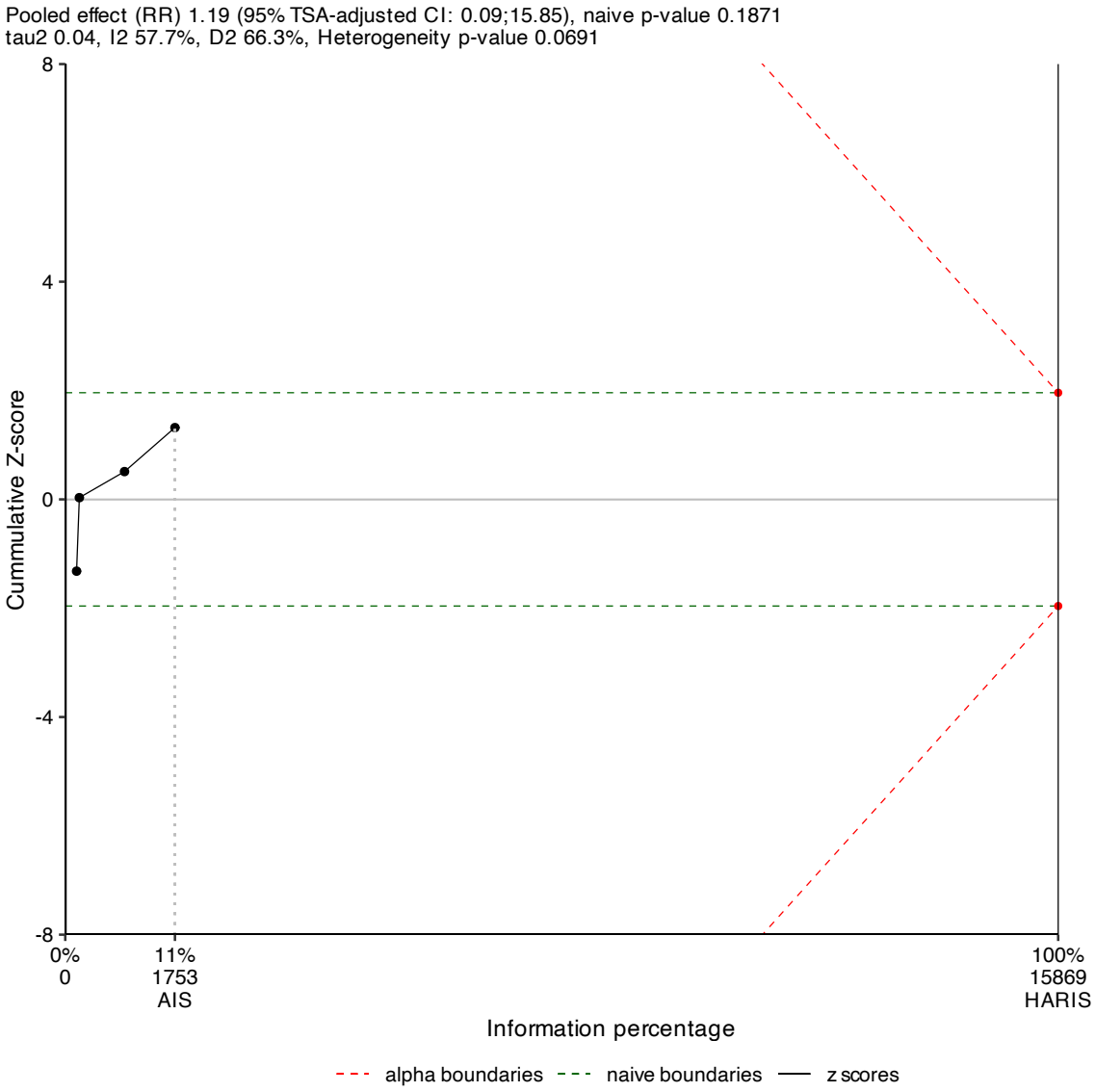
Forest plots of risk ratios (RR) for unfavorable neurologic outcomes using the Hartung-Knapp (HK) random-effects model. The top-right panel excludes Robertson et al. (low risk-of-bias subgroup). Other panels present analyses including all TBI patients, only low risk-of-bias TBI studies, and GCS-based subgroups (<8 vs. >8). Each panel provides study-level and pooled estimates with 95% confidence intervals and relative weights. Heterogeneity was assessed by I^2 and the Cochrane Q test (P<0.05). Favorable neurological outcomes were defined as Glasgow Outcome Scale (GOS) scores of 4–5 or Glasgow Outcome Scale Extended (GOSE) scores of 6–8 at 180 days. Abbreviations: GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale Extended; RR, risk ratio

eFigure 4. Forest plot of adjusted odds ratios for unfavorable neurologic outcomes



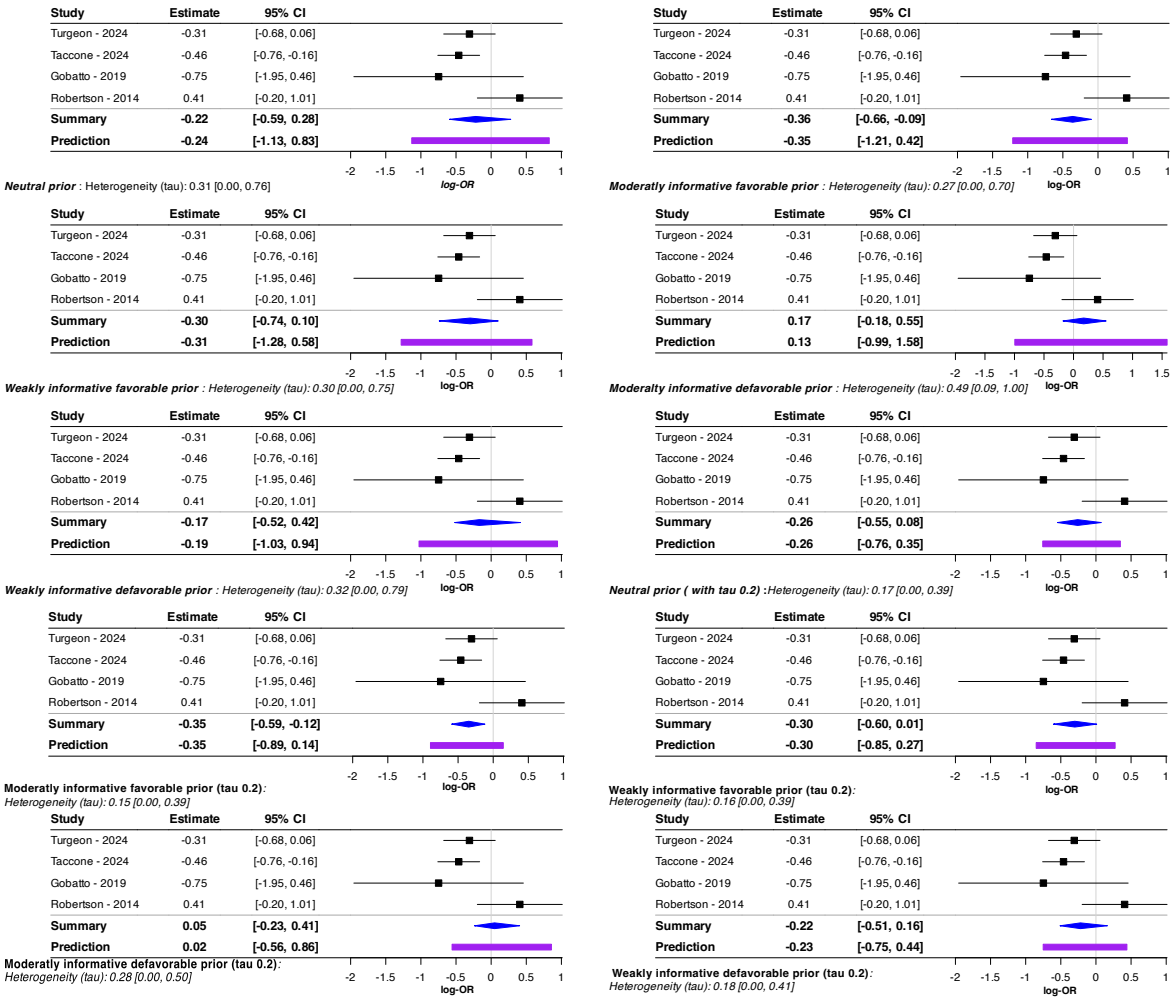
Forest plot of adjusted odds ratios (OR) for unfavorable neurologic outcomes using a random-effects model (DerSimonian-Laird). The pooled analysis incorporates the baseline-adjusted OR from Robertson et al. to account for imbalances in initial patient characteristics. Favorable neurological outcomes were defined as Glasgow Outcome Scale (GOS) scores of 4–5 or Glasgow Outcome Scale Extended (GOSE) scores of 6–8 at 180 days. The plot displays study-specific and pooled OR estimates with corresponding 95% confidence intervals. Abbreviations: OR, odds ratio.

eFigure 5. Trial sequential analysis



This figure illustrates the Trial Sequential Analysis (TSA) conducted for the primary outcome. The cumulative Z-curve (black solid line) represents the progression of evidence as studies are added sequentially. The horizontal green dashed line denotes the Z-threshold for statistical significance (alpha = 0.05). The descending red lines are the trial sequential monitoring boundaries based on the O'Brien-Fleming alpha-spending function. The vertical red line represents the required information size, indicating the estimated sample size needed to reliably confirm or refute the hypothesized treatment effect.

eFigure 6. Bayesian Analysis Forest Plots : Posterior Distribution, Heterogeneity, and Prediction



Forest plots from a Bayesian sensitivity analysis conducted using MCMC methods in a random-effects model. Different priors represent varying assumptions: neutral (θ~N(0,0.5)), favorable (θ~N(−0.46,0.5) or θ~N(−0.46,0.2)), and favorable (θ~N(0.41,0.5) or θ~N(0.41,0.2)). The top section shows study-specific log-OR estimates with 95% credible intervals, and the bottom section provides pooled estimates and predictive intervals. Analyses were performed with standard (τ=0.5) and reduced heterogeneity (τ=0.2). These results highlight the influence of prior assumptions and heterogeneity on the estimated treatment effect.

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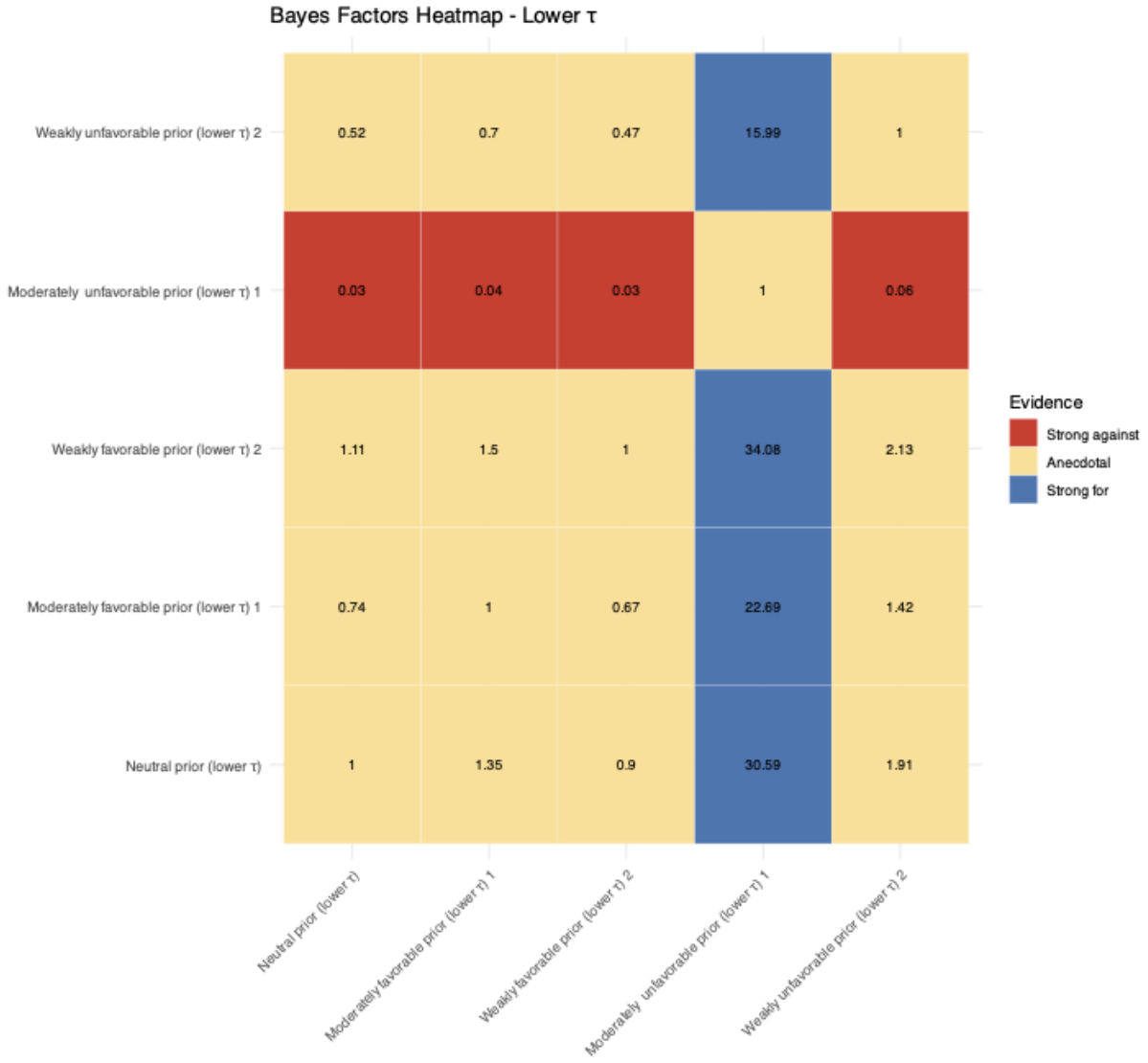
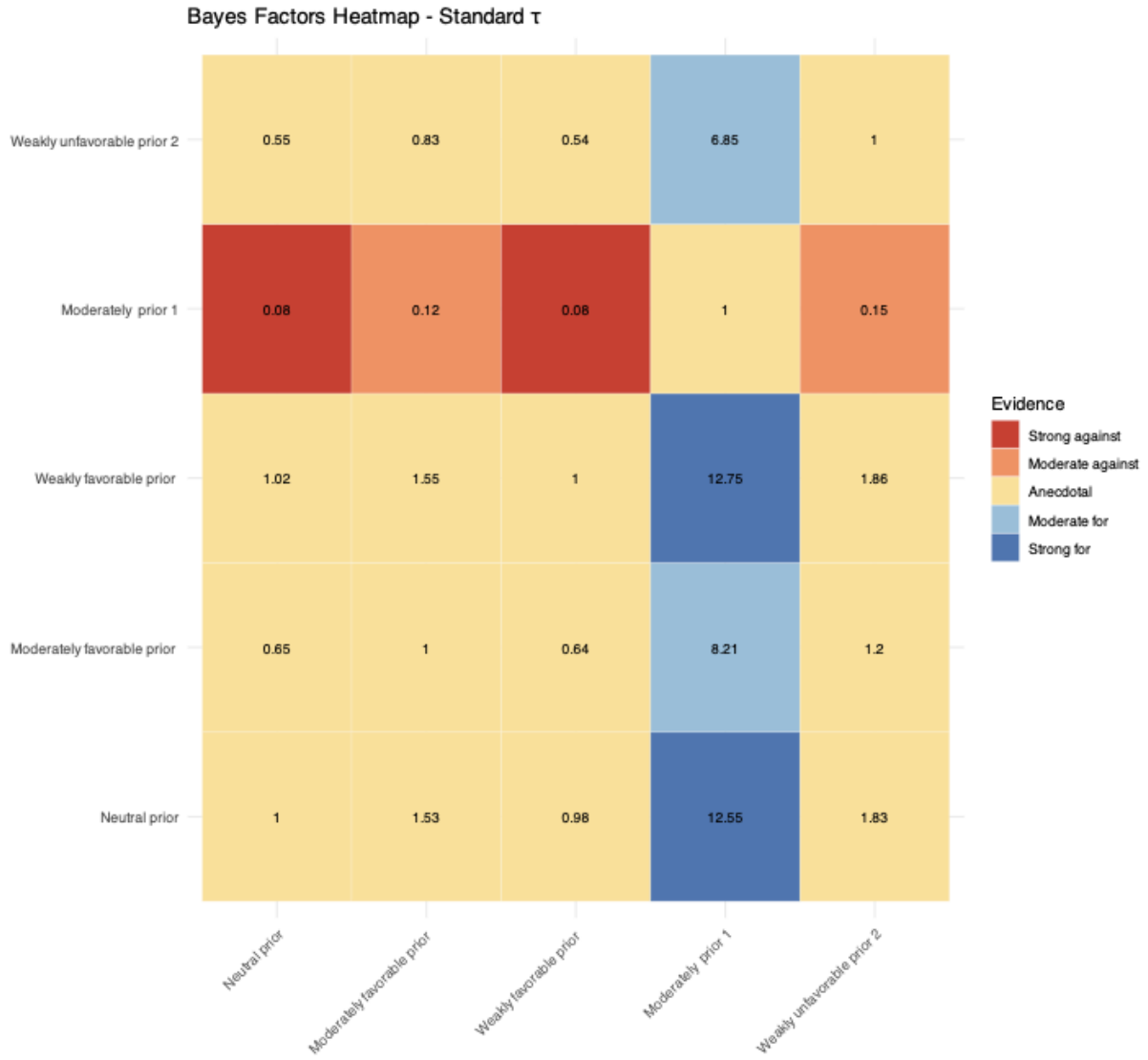
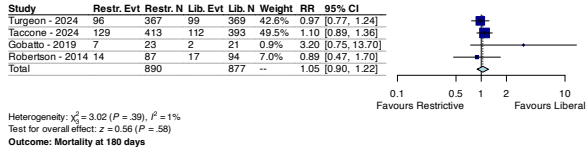
eFigure 7. Model Comparison Using Bayes Factor





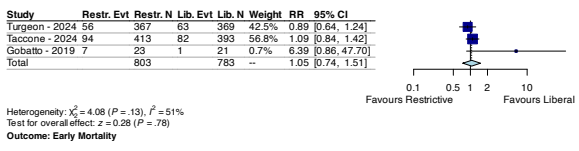
Heatmaps of Bayes Factors (BF) comparing models under different prior and heterogeneity assumptions (τ=0.5 in Figure 5; τ=0.2 in Figure 6). Neutral, favorable, and unfavorable priors are derived from prior studies. BF >1 favors the row model over the column model. Colors indicate the strength of evidence, with darker shades representing stronger support. These figures offer a visual comparison of model performance under various Bayesian priors and heterogeneity conditions.

eFigure 8. Forest plots of secondary outcomes using the DerSimonian-Laird model



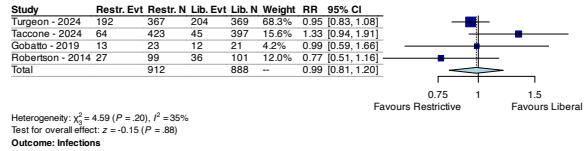
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	96	367	99	369	42.6%	0.97	[0.77, 1.24]
Taccone - 2024	129	413	112	393	49.5%	1.10	[0.89, 1.36]
Gobatto - 2019	7	23	2	21	0.9%	3.20	[0.75, 13.70]
Robertson - 2014	14	87	17	94	7.0%	0.89	[0.47, 1.70]
Total		890		877	--	1.05	[0.90, 1.22]

Heterogeneity: $\chi^2_3 = 3.02$ ($P = .39$), $I^2 = 1\%$
Test for overall effect: $z = 0.56$ ($P = .58$)
Outcome: Mortality at 180 days



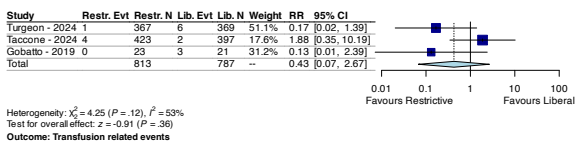
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	56	367	63	369	42.5%	0.89	[0.64, 1.24]
Taccone - 2024	94	413	82	393	56.8%	1.09	[0.84, 1.42]
Gobatto - 2019	7	23	1	21	0.7%	6.39	[0.86, 47.70]
Total		803		783	--	1.05	[0.74, 1.51]

Heterogeneity: $\chi^2_2 = 4.08$ ($P = .13$), $I^2 = 51\%$
Test for overall effect: $z = 0.28$ ($P = .78$)
Outcome: Early Mortality



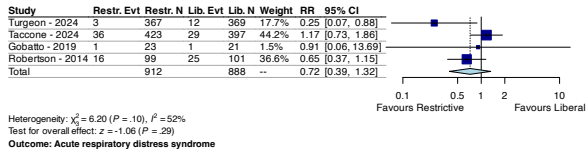
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	192	367	204	369	68.3%	0.95	[0.83, 1.08]
Taccone - 2024	64	423	45	397	15.6%	1.33	[0.94, 1.91]
Gobatto - 2019	13	23	12	21	4.2%	0.99	[0.59, 1.66]
Robertson - 2014	27	99	36	101	12.0%	0.77	[0.51, 1.16]
Total		912		888	--	0.99	[0.81, 1.20]

Heterogeneity: $\chi^2_3 = 4.59$ ($P = .20$), $I^2 = 35\%$
Test for overall effect: $z = -0.15$ ($P = .88$)
Outcome: Infections



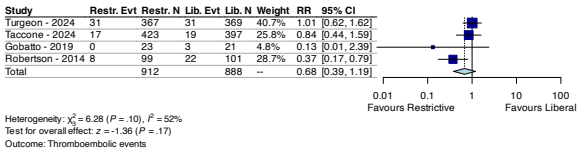
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	1	367	6	369	51.1%	0.17	[0.02, 1.39]
Taccone - 2024	4	423	2	397	17.6%	1.88	[0.35, 10.19]
Gobatto - 2019	0	23	3	21	31.2%	0.13	[0.01, 2.39]
Total		813		787	--	0.43	[0.07, 2.67]

Heterogeneity: $\chi^2_2 = 4.25$ ($P = .12$), $I^2 = 53\%$
Test for overall effect: $z = -0.91$ ($P = .36$)
Outcome: Transfusion related events



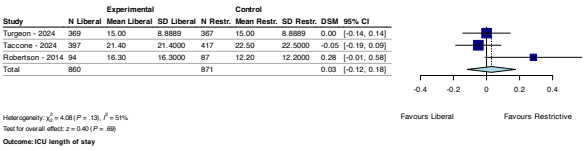
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	3	367	12	369	17.7%	0.25	[0.07, 0.88]
Taccone - 2024	36	423	29	397	44.2%	1.17	[0.73, 1.86]
Gobatto - 2019	1	23	1	21	1.5%	0.91	[0.06, 13.69]
Robertson - 2014	16	99	25	101	36.6%	0.65	[0.37, 1.15]
Total		912		888	--	0.72	[0.39, 1.32]

Heterogeneity: $\chi^2_3 = 6.20$ ($P = .10$), $I^2 = 52\%$
Test for overall effect: $z = -1.06$ ($P = .29$)
Outcome: Acute respiratory distress syndrome



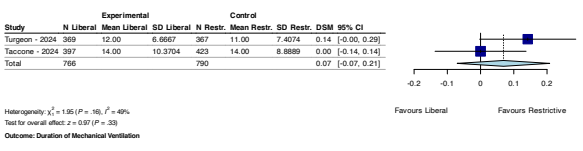
Study	Restr. Evt	Restr. N	Lib. Evt	Lib. N	Weight	RR	95% CI
Turgeon - 2024	31	367	31	369	40.7%	1.01	[0.62, 1.62]
Taccone - 2024	17	423	19	397	25.8%	0.84	[0.44, 1.59]
Gobatto - 2019	0	23	3	21	4.8%	0.13	[0.01, 2.39]
Robertson - 2014	8	99	22	101	28.7%	0.37	[0.17, 0.79]
Total		912		888	--	0.68	[0.39, 1.19]

Heterogeneity: $\chi^2_3 = 6.28$ ($P = .10$), $I^2 = 52\%$
Test for overall effect: $z = -1.36$ ($P = .17$)
Outcome: Thromboembolic events



Study	Experimental N	Liberal Mean	Liberal SD	Control N	Restr. Mean	Restr. SD	DSM	95% CI
Turgeon - 2024	369	15.00	8.8889	367	15.00	8.8889	0.00	[-0.14, 0.14]
Taccone - 2024	397	21.40	21.4000	417	22.50	22.5000	-0.05	[-0.19, 0.09]
Robertson - 2014	94	16.30	16.3000	87	12.20	12.2000	0.28	[-0.01, 0.58]
Total	860			871			0.03	[-0.12, 0.18]

Heterogeneity: $\chi^2_2 = 4.08$ ($P = .13$), $I^2 = 51\%$
Test for overall effect: $z = 0.40$ ($P = .69$)
Outcome: ICU length of stay

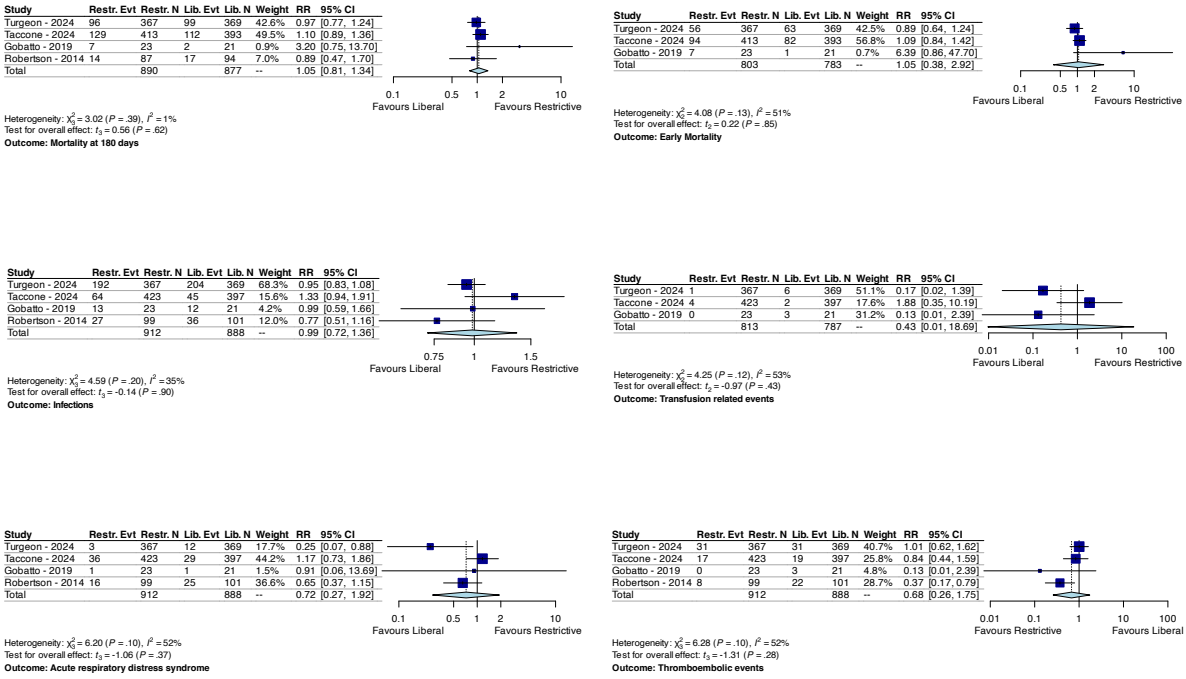


Study	Experimental N	Liberal Mean	Liberal SD	Control N	Restr. Mean	Restr. SD	DSM	95% CI
Turgeon - 2024	369	12.00	6.6667	367	11.00	7.4074	0.14	[-0.00, 0.29]
Taccone - 2024	397	14.00	10.3704	423	14.00	8.8889	0.00	[-0.14, 0.14]
Total	766			790			0.07	[-0.07, 0.21]

Heterogeneity: $\chi^2_2 = 1.95$ ($P = .16$), $I^2 = 49\%$
Test for overall effect: $z = 0.97$ ($P = .33$)
Outcome: Duration of Mechanical Ventilation

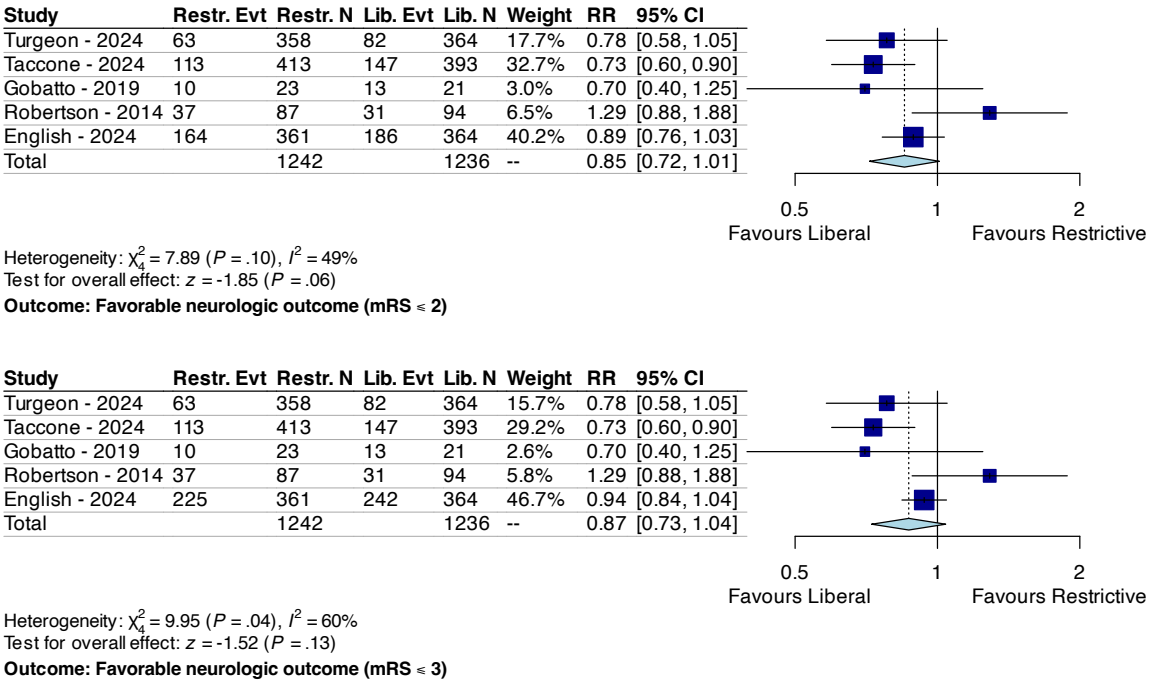
Forest plots of secondary outcomes (e.g., mortality, infections, thrombotic events, transfusion-related complications, ICU length of stay, duration of mechanical ventilation) using a DerSimonian-Laird random-effects model. Standardized mean differences (SMD) are reported for continuous outcomes. Each plot includes study-specific estimates, 95% confidence intervals, and relative weights. Heterogeneity was assessed by I^2 and the Cochrane Q test ($P<0.05$). Abbreviations: RR, risk ratio; SMD, standardized mean difference; LOS, length of stay; MV, mechanical ventilation.

eFigure 9. Forest plots of secondary outcomes using the Hartung-Knapp model Hartung-Knapp model



Forest plots of secondary outcomes (e.g., mortality, infections, thrombotic events, and transfusion-related complications) using the HKSrandom-effects model. Standardized mean differences (SMD) are reported for continuous outcomes. Each plot includes study-specific estimates, 95% confidence intervals, and relative weights. Heterogeneity was assessed by I^2 and the Cochrane Q test ($P<0.05$). Abbreviations: RR, risk ratio; SMD, standardized mean difference.

eFigure10: Post-HOC analysis



Forest plots of neurological outcomes, including data from the English et al. trial, are shown. Neurological outcomes were defined by the Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale–Extended (GOSE) in all studies except for the English et al. trial, which used the modified Rankin Scale (mRS). Favorable neurological outcomes were defined as Glasgow Outcome Scale (GOS) scores of 4–5 or Glasgow Outcome Scale Extended (GOSE) scores of 6–8 at 180 days. In the upper panel, favorable neurological outcome was defined as mRS ≤2, and in the lower panel, unfavorable outcome was defined as mRS ≥3. All outcomes were assessed at 6 months, except for those from the English et al. trial, which were assessed at 1 year. Analyses were conducted using a DerSimonian-Laird random-effects model. Standardized mean differences (SMD) are presented for continuous outcomes. Each plot displays study-specific estimates, 95% CIs, and relative weights. Heterogeneity was assessed using the I^2 statistic and the Cochrane Q test (P<.05).

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