Association Between Lack of Blinding and Mortality Results in Critical Care Randomized Controlled Trials

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Association between lack of blinding and mortality results in critical-care randomized controlled trials: a meta-epidemiological study

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ABSTRACT (268 words)

Objective: To investigate whether intervention effect estimates for mortality differ between blinded and non-blinded randomized controlled trials (RCTs) conducted in critical care.

Design: Meta-epidemiological study, comparing effect estimates between blinded and non-blinded RCTs for the same research question.

Data sources: Systematic reviews and meta-analyses of RCTs evaluating a therapeutic intervention on mortality in critical care, published between January 2009 and March 2019 in high impact factor general medical or critical-care journals and by Cochrane.

Data extraction: For each RCT included in eligible meta-analyses, we evaluated whether the trial was blinded (ie, double-blinded and/or reporting adequate methods) or not (ie, open-label, single-blinded or unclear). We collected risk of bias evaluated by the review authors and extracted trial results.

Data synthesis: Within each meta-analysis, we compared intervention effect estimates between blinded and non-blinded RCTs by using a ratio of odds ratio (ROR) (ROR<1 indicates larger estimates in non-blinded than blinded RCTs). We then combined RORs across meta-analyses to obtain the average relative difference between non-blinded and blinded trials.

Results: Among 467 RCTs included in 36 meta-analyses, 267 (57%) were considered blinded and 200 (43%) non-blinded. Intervention effect estimates were statistically significantly larger in non-blinded than blinded trials (combined ROR 0.91 [95% CI 0.84–0.99]). We found no heterogeneity across meta-analyses (p=0.72, I^2=0%, τ^2=0). Sensitivity analyses adjusting the main analysis on risk of bias items yielded consistent results.

Conclusions: Intervention effect estimates of mortality were slightly larger in non-blinded than blinded RCTs conducted in critical care, but confounding cannot be excluded. Blinding of both patients and personnel is important to consider when possible in critical-care trials, even when evaluating mortality.

Trials registration: Not applicable. This is a research-on-research study.

INTRODUCTION

Mortality is one of the most important outcomes to evaluate in clinical trials and considered one of the most objective because not subject to interpretation. Most meta-epidemiological studies showed no difference in intervention effect estimates between blinded and non-blinded trials evaluating mortality, whereas for subjective outcomes, effects were significantly larger in non-blinded trials(1–3). A more recent study suggested that the situation may not be simple(4), highlighting the need for additional methodological research across a variety of contexts(5).

In critical care, mortality is a peculiar outcome because physicians often have to limit life-sustaining treatments to preserve patient dignity in end-of-life care, which is nowadays the most common death scenario in many intensive care units (ICUs)(6–11). Physicians also have access to life-support techniques to prolong life via artificial cardiac and respiratory assistance(12,13). Without blinding, belief in a favourable effect of novel experimental interventions might influence physicians, even unconsciously, when making these decisions, which may affect the timing of death(14,15). This situation could lead to biased intervention effect estimates on mortality if such decisions differ between randomisation arms. This issue might be of particular importance in these times of pandemic : many prominent COVID-19 trials were open-label(16,17). The association between lack of blinding and mortality estimates in critical-care clinical trials was explored in 2 studies(18,19), with inconsistent results. These studies compared effect estimates between blinded and non-blinded trials mixing different research questions, which might bias their results. Meta-epidemiological studies are the reference method to identify bias(20) as they evaluate within meta-analyses of the same intervention how a trial characteristic is associated with intervention effect.

In this study, we investigated whether intervention effect estimates for mortality differ between blinded and non-blinded randomized controlled trials (RCTs) conducted in critical care.

METHODS

Study design

We performed a meta-epidemiological study based on a sample of meta-analyses evaluating the effect of a therapeutic intervention on mortality in critical care.

Data sources

In April 2019, we conducted a search on PubMed using an algorithm combining MeSH terms and free-text words to identify systematic reviews and meta-analyses of RCTs conducted in critical care (**Supplemental Digital Content**).

We restricted the search to articles published from January 2009 to March 2019 to rely on recent systematic reviews. We also restricted the search to the five highest impact factor (IF) general medical journals according to the *Journal of Citation Reports* (*The New England Journal of Medicine*, *The Lancet*, *The Journal of the American Medical Association*, *The BMJ*, *Annals of Internal Medicine*), the *Cochrane Database of Systematic Reviews* and the six highest IF critical-care journals (*Lancet Respiratory Medicine*, *American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine*, *Chest*, *Critical Care Medicine*, *Critical Care*).

Identification of eligible meta-analyses

We screened titles and abstracts, and full texts whenever necessary, to identify reports of systematic reviews with meta-analyses of RCTs conducted in critical care that assessed an experimental intervention against placebo or standard-care and including mortality as an outcome. We chose not to include comparisons between experimental interventions because of the uncertainty in the direction of bias. We focused on adult populations and did not include reviews concerning paediatric populations because the issue of end-of-life may be more complex. Because some reviews may include both adult and paediatric trials, we selected them if they included a maximum 20% of paediatric RCTs per meta-analysis. We then identified reviews with meta-analyses of mortality

including ≥3 RCTs (3 is the minimum to conduct a meta-epidemiological analysis) and evaluated blinding.

Two reviewers (GLM and TT) independently selected reviews with disagreements resolved by discussion, referring to a third opinion (AD) when necessary.

Evaluation of blinding in RCTs

We searched the full-text report of each RCT included in selected meta-analyses. We first evaluated the article presenting the main findings, and if information on blinding was not reported or unclear, we searched for additional references such as the protocol or trial registration. We considered an RCT blinded if it was described as a double-blinded trial (defined as unknown intervention by both patients and personnel) and/or mentioned the use of adequate methods for double-blinding (eg, matched placebo). We considered an RCT non-blinded if it was described as a single-blind or open-label trial, had distinguishable interventions or no information was reported.

Two reviewers (GLM and TT) independently evaluated blinding with disagreements resolved by discussion, referring to a third opinion (AD) when necessary.

Final selection of meta-analyses and exclusion of overlaps

To conduct the meta-epidemiological analysis, we selected only meta-analyses including at least one blinded and one non-blinded trial. When an individual systematic review had multiple eligible meta-analyses because of different time points evaluated, we selected the meta-analysis evaluating short-term (≤ 31 days) mortality and in case of several such meta-analyses, the one including the highest number of RCTs. If short-term mortality was not available, we included the meta-analysis with the highest number of RCTs. We chose short-term mortality as the preferred outcome because it was the most frequently reported in critical-care RCTs(21), but planned to conduct a subgroup analysis for different outcome timing (see below).

Finally, we identified and removed overlapping meta-analyses, defined as those sharing ≥3 RCTs. In case of overlap, we kept the meta-analysis with the highest number of RCTs.

Data extraction

One reviewer (GLM) extracted data using extraction forms, referring to a second opinion (AD) when necessary. Another reviewer (TT) independently extracted data for half of the meta-analyses chosen at random for quality insurance. We collected the following data on meta-analyses: general characteristics, medical condition, interventions evaluated, time-point for mortality and the following data for each RCT: general characteristics, blinding as described above, risk of bias (RoB) and results (numbers of events and of patients analysed in each group).

Statistical methods

Estimation of intervention effects within meta-analyses

We estimated the intervention effects within each meta-analysis as odds ratios (OR) and 95% confidence intervals (CIs). Outcomes were recoded when necessary so that an OR<1 indicated a beneficial effect of the experimental intervention on mortality. We used random-effects models to combine intervention effects across RCTs within each meta-analysis. RCTs with no event or all events in both groups did not contribute to the analysis. When necessary, we used a continuity-correction to deal with zero cell-counts in one arm(22). Heterogeneity across RCTs was assessed with the Cochran Q chi-square test, I^2 statistic, and between-study variance τ^2.

Meta-epidemiological analysis

Using a two-step approach(23), we first calculated, within each meta-analysis, the ratio of ORs (ROR) — the ratio of the intervention-effect OR in non-blinded RCTs to the OR in blinded RCTs by using a random-effects meta-regression model. An ROR<1 indicates larger intervention effect estimates for mortality for non-blinded than blinded trials. Second, we calculated a combined ROR across all meta-analyses by using a random-effects meta-analysis model. This combined ROR

represents the average relative difference between non-blinded and blinded trials across included meta-analyses. Heterogeneity across meta-analyses was quantified with the Cochran Q chi-square test, I^2 statistic, and between–meta-analysis variance τ^2.

Subgroup, sensitivity and secondary analyses

As previously mentioned, a pre-specified subgroup analysis concerned the timing of the mortality outcome (*short-term*, defined as in ICU or ≤31 days, vs *long-term*, defined as >31 days, in-hospital, overall or longest follow-up). We used an interaction test to assess whether the combined ROR varied between subgroups.

To control for confounding, sensitivity analyses were performed by adjusting the meta-regression models for sample size and each item of the RoB tool using the review author's evaluation (*high or unclear risk* vs *low risk*), except the item "blinding of participants and personnel" because of collinearity with our assessment of blinding. Meta-analyses had to include ≥4 RCTs to contribute to the sensitivity analyses (accounting for the additional co-variable(24)).

As a secondary analysis, with the same sample, we performed a meta-epidemiological analysis using the review authors' evaluation of RoB for the item "blinding of participants and personnel", instead of our manual assessment of blinding.

All analyses involved use of R v3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Selection and general characteristics

Among 720 references identified, 186 reports of systematic reviews were selected, with their relevant meta-analyses assessed for eligibility. We found 84 eligible meta-analyses including at least 3 RCTs with one blinded and one non-blinded trial. Among these, 47 meta-analyses overlapped and 1 had unusable data (computed mean-differences, without additional data available), so 36 meta-analyses remained in our sample. **Figure 1** lists reasons for exclusion.

Table 1 presents detailed characteristics of the included meta-analyses. Briefly, 20 meta-analyses were published in critical-care journals, 2 in general medical journals and 14 by Cochrane. Most meta-analyses evaluated pharmacological interventions (97.2%). They covered a wide range of critical-care pathologies. In most meta-analyses (75%), the authors used the Cochrane tool to assess RoB. Different time-points were evaluated for mortality, with short-term time-points evaluated in 17 meta-analyses and longer-term time-points in 19 meta-analyses. Only one meta-analysis showed substantial heterogeneity ($I^2 \geq 50\%$) (**Supplemental Digital Content – Table 1)**. The meta-analyses included 467 RCTs (total of 116,678 patients) contributing to the analysis. The median number of RCTs per meta-analysis was 11.5 (range 3 to 36).

Comparison of blinded and non-blinded trials

Table 2 presents characteristics of blinded and non-blinded trials. Among the 467 RCTs included, 267 (57%) were blinded and 200 (43%) non-blinded. The median sample size was smaller in non-blinded than blinded trials (60 [interquartile range (IQR) 34.8–104.8] vs 96 [IQR 45.5–249]). Non-blinded RCTs were less frequently judged as low RoB than were blinded RCTs for random sequence generation (45.5% vs 61.0%) and allocation concealment (39.5% vs 55.4%). For RoB related to blinding of participants and personnel, 15.5% of non-blinded RCTs were judged at low risk by review authors, and 6% of blinded RCTs were judged at high or unclear risk.

Non-blinded and blinded RCTs did not differ in year of publication: 145 (72.5%) and 203 (76%), respectively, had results published after year 2000. The median publication year was 2007 for both groups.

Comparison of intervention effect estimates between blinded and non-blinded trials

Figure 2 shows the difference in intervention effect estimates for mortality between blinded and non-blinded trials. Intervention effect estimates were significantly larger for non-blinded than blinded trials, with a combined ROR of 0.91 (95% CI 0.84–0.99). We found no heterogeneity across meta-analyses (p=0.70, I^2=0%, τ^2=0).

Subgroup, sensitivity and secondary analyses

On subgroup analysis, for the 17 meta-analyses reporting short-term mortality, the combined ROR was 0.88 (95% CI 0.79–0.99) with no heterogeneity (**Figure 2**). For the 19 meta-analyses reporting longer-term mortality, the combined ROR was 0.94 (95% CI 0.83–1.10), with no heterogeneity. The interaction test was not statistically significant (p=0.44).

Figure 3 shows the results of the sensitivity analyses. For adjustments on random sequence generation, results were consistent with the primary analysis. For the other items of the RoB tool and sample size, the orientation of the adjusted ROR remained in favour of non-blinded trials, although no longer significant.

Supplemental Digital Content - Figure 1 shows the results of the secondary analysis. Among the 32 meta-analysis eligible for this analysis, the combined ROR was 0.93, consistent with the primary analysis, although no longer significant (95% CI 0.83–1.03).

DISCUSSION

In this meta-epidemiological study comparing intervention effect estimates for mortality between blinded and non-blinded RCTs in critical care, we analysed 36 meta-analyses, including 467 RCTs. The intervention effect estimate for mortality was statistically significantly larger for non-blinded than blinded RCTs, with a combined ROR of 0.91.

Our selection of meta-analyses covered most eligible critical-care topics, providing a generalizable sample of the discipline. We selected recent meta-analyses published in high IF general medical and critical-care journals or published by Cochrane, because these are more likely to be well reported(25,26) and concern subjects that are important to a large readership. In addition, we used a meta-epidemiological approach, which has become the reference method to identify bias(20).

Our study has some limitations. First, regarding selection, some meta-analyses might have been missed with our search strategy. Nevertheless, our aim was not to be exhaustive but to obtain a representative sample of meta-analyses, and we see no reason why this could have biased our results. Second, because blinding is difficult to ensure for non-pharmacological interventions, our sample included mostly pharmacological interventions. Another limitation is related to meta-confounding(27). Although we tried to limit it with sensitivity analyses adjusted for each RoB item and sample size, meta-confounding cannot be excluded. We only evaluated blinding in individual RCTs and did not re-evaluate RoB for the other items. There may be discrepancies between RoB definitions, tools, or authors' judgments across meta-analyses. Finally, because this is the first critical-care focused meta-epidemiological study on this subject, results should be confirmed in future studies.

Lack of blinding has for long been considered a potential source of bias in RCTs because knowing which intervention is received by the patient might affect follow-up and outcome assessment. Many meta-epidemiological studies(1–3,28–31) assessed blinding, however evidence was not consistent across them. Recent studies(1–3) analysed the effect of blinding according to the type of outcome: lack of blinding was significantly associated with larger intervention estimates in trials

with subjective outcomes. When the outcome was mortality or objectively assessed, blinded and non-blinded trials did not differ. Accordingly, the previous version of the Cochrane RoB tool(32), published in 2011, indicated that bias related to blinding could be judged at low risk in non-blinded studies if knowledge of the assigned intervention was not likely to affect the outcome, such as mortality. This definition may explain the discrepancies between our evaluation of blinding and assessment by review authors. Our secondary analysis considering assessment related to blinding by review authors was consistent though, but the difference was slightly lower. Anthon et al.(18) previously had a similar approach comparing RCTs in critical-care Cochrane reviews, using the review authors' assessment for blinding. They found no evidence that RCTs judged at high or unclear risk for blinding affected intervention estimates for mortality, but they did not use a meta-epidemiological approach and included fewer studies. Many non-blinded trials might also have been judged at low risk, considering the previous version of the Cochrane RoB tool(32). The tool was revised in 2019(33). In the new version, any deviations arising from lack of blinding, regardless of their supposed impact, should be judged "some concerns" or "high risk" of bias. Another study assessed the association of blinding with mortality in critical care. Baiardo et al.(19) selected critical-care RCTs published between 2000 and 2015 with statistically significant results for mortality, and calculated the median number-needed-to-treat for blinded and non-blinded RCTs. The authors found that the number-needed-to-treat was higher for blinded than non-blinded RCTs, but they did not use a meta-epidemiological approach and compared RCTs of different topics.

We found that non-blinded trials seem to favour intervention effect for mortality, with a ROR of 0.91. Several reasons might explain this result. First, it may be explained by the higher RoB associated with non-blinded trials, known to exaggerate intervention effect estimates(28,34–37). Non-blinded trials in our study also had a smaller sample size than blinded trials, and our sensitivity analysis adjusted on sample size largely reduced the difference. This suggests that our results may be explained by small-study effect(38–41), the tendency for small studies to show larger intervention effect than larger studies within meta-analyses, which may be explained by publication and other

reporting bias but also differences in methodological quality (including blinding) between small and large trials. Another possible explanation may be related to differences in end-of-life or life-support practices and their timing between groups in non-blinded RCTs. A belief in a favourable effect of novel experimental interventions might influence physicians, even unconsciously, in the timing of such decisions. This situation might be particularly true in RCTs evaluating mortality in the short-term, which are the most common in critical care(21). In such trials, different timing of end-of-life decisions could let some patients cross the mortality evaluation time-point and thus impact intervention estimates. Compatible with this hypothesis, our subgroup analysis showed larger difference between non-blinded and blinded trials evaluating mortality on the short-term than on the long-term, although the interaction was not significant, possibly due to a lack of power. This should be explored in further studies.

Overall, the pooled ROR of 0.91 seems small, but is similar to that observed for inadequate or unclear random sequence generation(2,42). Such small difference may have an impact on trial results and conclusions when the fragility index is high, which is frequent in critical care(43). Our results provide an important argument for blinding in critical-care trials evaluating mortality. Blinding may be difficult to achieve though: it is costly, can discourage recruitment and continuation in clinical trials(4,44), or can simply be unfeasible in critical-care settings. Our findings showing an association between lack of blinding and higher intervention estimates for mortality suggest open-label critical-care trials should be considered at high RoB, but does not mean their conclusions are inevitably wrong. A more nuanced approach might be needed to improve the reliability of their results. First, reporting longer-term mortality as the preferable primary outcome should be encouraged(45): it is clinically more relevant and seems less influenced by lack of blinding. Second, the reporting of end-of-life decisions in short-term trials should be improved. Recent systematic reviews of critical-care trials(15,46) found that only 9-18.5% reported end-of-life decisions. The Consolidated Standards of Reporting Trials (CONSORT) statement, updated in 2010(47) and adopted by most medical journals, does not require reporting these decisions. In light of our findings, we further the call by Messika et

al.(15), asking for a mandated report in critical-care trials of numbers and timing of end-of-life and life-support decisions. Future studies could then investigate whether an imbalance of practices exists between groups in non-blinded critical-care RCTs and if these could bias the results.

CONCLUSION

In this meta-epidemiological study, we found statistically significantly larger intervention effects for mortality in non-blinded than blinded trials in critical care, but confounding cannot be excluded. Our results suggest that double-blinding is important to consider when possible in critical-care trials, even when evaluating mortality. If not possible, the use of longer-term mortality as primary outcome and the better reporting of end-of-life and life-support decisions should be considered.

Ethics approval: Not applicable. This is a research-on-research study.

Availability of data and materials: The datasets, code and analysis are available from the corresponding author on request and on the following link: https://github.com/GuillaumeMartinMD/blinding_mortality_ICU.

Competing interests: The authors declare that they have no competing interests.

Author's contribution:

GLM participated in the design of the study, selection and acquisition of data, conducted statistical analyses, interpreted the data and wrote the manuscript.

TT was involved in the selection and acquisition of data and critically reviewed the manuscript.

SG participated in the interpretation of data and critically reviewed the manuscript.

FT participated in the interpretation of data and critically reviewed the manuscript.

DH participated in the interpretation of data and critically reviewed the manuscript.

AD participated in the design of the study, interpretation of data and writing of the manuscript. She is the guarantor. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1: Flow chart of the selection of reviews.

Figure 2: Comparison of intervention effects between blinded and non-blinded randomized controlled trials in eligible critical-care meta-analyses.

Figure 3: Sensitivity analyses adjusted on sample size and each item of the risk of bias tool.

Supplemental Digital Content – Figure 1: Comparison of intervention effects between randomized controlled trials judged at low risk and high or unclear risk for blinding of participants and personnel in eligible critical-care meta-analyses.

LIST OF ABBREVIATIONS

CI: Confidence Interval

ICU: Intensive Care Unit

IF: Impact Factor

IQR: Interquartile range

OR: Odds Ratio

RCT: Randomized Controlled Trial

RoB : Risk of Bias

ROR: Ratio of Odds Ratio