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REVIEW ARTICLE

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Systematic overview and critical appraisal of meta-analyses of interventions in intensive care medicine

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Rationale: Meta-analysed intervention effect estimates are perceived to represent the highest level of evidence. However, such effects and the randomized clinical trials which are included in them need critical appraisal before the effects can be trusted.

Objective: Critical appraisal of a predefined set of all meta-analyses on interventions in intensive care medicine to assess their quality and assessed the risks of bias in those meta-analyses having the best quality.

Methods: We conducted a systematic search to select all meta-analyses of randomized clinical trials on interventions used in intensive care medicine. Selected meta-analyses were critically appraised for basic scientific criteria, (1) presence of an available protocol, (2) report of a full search strategy, and (3) use of any bias risk assessment of included trials. All meta-analyses which qualified these criteria were scrutinized by full "Risk of Bias in Systematic Reviews" ROBIS evaluation of 4 domains of risks of bias, and a "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" PRISMA evaluation.

Results: We identified 467 meta-analyses. A total of 56 meta-analyses complied with these basic scientific criteria. We scrutinized the risks of bias in the 56 meta-analyses by full ROBIS evaluation and a PRISMA evaluation. Only 4 meta-analyses scored low risk of bias in all the 4 ROBIS domains and 41 meta-analyses reported all 27 items of the PRISMA checklist.

Conclusion: In contrast with what might be perceived as the highest level of evidence only 0.9% of all meta-analyses were judged to have overall low risk of bias.

KEYWORDS
evidence-based medicine, intensive care, meta-analyses, risk of bias

1 | INTRODUCTION

The amount of available evidence to be read in medicine is growing rapidly.[1] Evidence is summarized and aggregated in systematic reviews with meta-analyses to facilitate overview and increase power.[1-4] Systematic reviews of randomized clinical trials represent the highest level of evidence and frequently inform guidelines and practice protocols.[5,6]

While inappropriate, terminology of "reviews", "systematic reviews" and "meta-analyses" are frequently used interchangeably, and many may consider the meta-analysed intervention effect estimate to represent the most valid intervention effect.[4] Any paper reporting a meta-analysed effect may be perceived to represent the highest level of evidence, whilst after critical appraisal serious conflicts with established quality criteria may appear, and it may in fact fail to reach the highest level of evidence.[7-9] Significant intervention effects from such flawed evidence may be launched into medical practice, either by original reports or propagated via practice guidelines and may in fact be futile or directly harm patients.[10-13]

Authors of systematic reviews focus increasingly on prevention of potential biases by developing explicit expectations for their conduct and reporting, such as the Methodological Expectations of Cochrane Intervention Review (MECIR), the Preferred Reporting

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Items for Systematic Reviews and Meta-Analyses (PRISMA), and PRISMA-Protocol (PRISMA-P).[14-17] Recently, the Risk Of Bias In Systematic Reviews (ROBIS) has been developed for assessment of the risk of bias in systematic reviews.[18]

The highest level of evidence qualification in the evidence pyramid is conditional on adherence to all high standard criteria which translate from sound general principles of reproducible science and final conclusions ought to be based on adherence to all quality criteria.[4,19]

Editorial comment

In this systematic overview and critical appraisal of meta-analyses of ICU interventions, <1% of the available meta-analyses were judged as having low risk of bias, that is, had been designed and reported according to standards for trustworthy systematic reviews and meta-analyses.

1.1 | Objective

We hypothesized that many of the reports that may be perceived to represent the highest level of evidence (eg level 1A) are actually not qualified for this label.[5] We aimed to conduct a systematic overview of all studies that are potentially perceived to be meta-analyses on interventions in intensive care patients and we aimed to assess the quality of all these studies according to established criteria for systematic reviews.

2 | METHODS

This meta-epidemiologic study was conducted following our prepublished protocol (http://www.ctu.dk/media/6144/2013-Protocol-TSA-ICU.pdf) and addendum (http://www.ctu.dk/media/12769/2013-Protocol-TSA-ICU_addendum.pdf).

Quality assessment of all meta-analyses may lead to reclassification of studies into a lower level of evidence when they fall short on requirements for the highest level of evidence label (level 1A).[5] Reclassifications may lead to a set of systematic reviews of randomized clinical trials on interventions in intensive care medicine which can and should be used for guiding clinical practice or future research efforts.

2.1 | Selection criteria

2.1.1 | Types of studies

Statistically significant intervention effects from meta-analysis are increasingly drivers for implementation of interventions into clinical practice, which can be found in a variety of reports and may be taken for granted despite many potential pitfalls. As a result of perceived confusions in terminology including "systematic reviews", "reviews", and "meta-analyses", they all may be mistaken to represent the highest level of evidence.[5] We therefore intended to include all meta-analyses, independent of review or systematic review classifications, to acknowledge potential misperceptions.

We selected all meta-analyses irrespective of quality or reporting items, such as advocated by *The Cochrane Handbook for Systematic Reviews of Interventions* or the PRISMA statement.[4,5,16] We used no restrictions on the numbers of meta-analyses for each type of intervention. If a meta-analysis was updated, and published in the same journal, we included only the most recent version. We applied no language restrictions. We excluded meta-analyses of observational studies.[5]

2.1.2 | Types of patients

The criteria for the patients of the trials included in the meta-analyses had to be critically ill adult patients. We excluded meta-analyses of randomized clinical trials with patients below 18 years of age. Meta-analyses that included randomized trials in adults as well as in children were included.

2.1.3 | Types of interventions

Only meta-analyses which evaluated interventions used for patients in intensive care medicine and performed or authorized by intensivists were included. For example, inotrope or vasopressor therapies are typical interventions used by intensivists. Interventions performed by other medical specialists were excluded, if the intervention was not continued on the intensive care unit (ICU). For example, a decompressive craniectomy is indicated by the neurosurgeon, yet patients in need for a decompressive craniectomy may be admitted to the ICU. Another example, the decision to use a cardiopulmonary bypass during coronary artery bypass grafting is made by the thoracic surgeon and lies outside the competence of any intensivist, so meta-analyses on the use of a cardiopulmonary bypass were excluded as well.

Meta-analyses on interventions initiated in another location and continued in the ICU were included, eg Early Goal Directed Therapy (EGDT) or use of antibiotics in septic patients initiated in the emergency room and continued in the ICU were included. Some other interventions are most frequently used in other wards and incidentally also in the ICU; any such interventions were excluded when the majority of such interventions were used outside the ICU, for example early enteral feeding in patients with pancreatitis.

All included meta-analyses were categorized according to the organ system in which the intervention was mainly supposed to target.

2.1.4 | Types of control interventions

We included all meta-analyses independent of the type of the control group intervention, including an active comparator, placebo, usual care or no intervention.

2.1.5 | Types of outcomes

Following the recommendations on the grading of outcomes according to the perspective of patients made by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group we focused on outcomes critical or important for decision-making.[5,20,21] The outcomes reported in a meta-analysis can be numerous while patient-important outcomes are typically dichotomous. We included all meta-analyses that reported at least one dichotomous outcome to guarantee the patient-centeredness of the outcomes evaluated in the meta-analysis and up to a maximum of 3 outcomes.

2.2 | Search strategy

We searched the databases "Cochrane Reviews" and "Other Reviews" in *The Cochrane Library*, *PubMed/MEDLINE* and *EMBASE*. The search strategies are provided in the prepublished protocol with the time span of the searches until August 29th, 2017 (Appendix S1).

2.3 | Quality assessment

2.3.1 | General principles of sound reproducible science

There are 3 very basic requirements originating from sound general principles of reproducible science before any meta-analysis can be considered sufficiently scientifically rigorous for qualifying to be systematic: (1) the reference to and public availability of *any prepublished protocol* prior to the conduct of the (systematic) review and/or meta-analysis[4]; (2) the reference to and availability of a *full database specific search string exploring more than two databases* either available in the full manuscript, or as additional material or (preferably) published in the referenced protocol[4]; and (3) the reporting of the use of *any evaluation of the risk of bias* and the results originating from these assessments of the included trials/studies, independent of the tool or method used to evaluate bias risk.[4]

If a meta-analysis did not fulfil all these 3 basic requirements it was considered at high risk of bias. If the selected meta-analysis fulfilled these 3 basic requirements we further assessed for potential risks of bias according to ROBIS (see below).

2.3.2 | Risk of bias in systematic reviews (ROBIS)

Recently, the Risk Of Bias In Systematic Reviews (ROBIS) tool (www.robis-tool.info) has been developed for evaluation of the risks of bias of systematic reviews and is currently aimed at 4 broad categories of interventions, diagnosis, prognosis and aetiology.[18] ROBIS involves assessment of study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. These domains of ROBIS identify areas of potential concern to help judge overall risk of bias. The signalling questions are answered as "Yes", "Probably Yes", "Probably No", "No" and "No Information", with "Yes" indicating low concerns. The subsequent level of concern about bias associated with each domain is then judged as "low," "high" or "unclear". If the answers to all signalling questions for a domain are "Yes" or "Probably Yes", then the level of concern can be judged as low. If any signalling question is answered "No" or "Probably No", potential for concern about bias exists. Assessments of the ROBIS domains were performed by two authors independently and disagreements were resolved through discussions.

2.3.3 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA)

The PRISMA statement was introduced for complete and transparent reporting of systematic reviews and is currently endorsed by many medical journals.[16] While PRISMA includes some items that relate to bias risk issues, it is, however, not a tool for bias risk assessment of systematic reviews. We used the PRISMA checklist for evaluation of completeness of reporting of all selected studies that fulfilled the 3 general principles of reproducible science. The items were scored positive when either part or all of the issue(s) in that item were reported and only negative if none of those issues were reported.

2.4 | Data inclusion and extraction

Study selection was divided between two authors. Any minimal uncertainties were resolved through discussions.

For each meta-analysis we recorded the author, year of publication, the numbers of included randomized clinical trials and the total number of randomized patients, the type of intervention evaluated, and the dichotomous outcomes up to a maximum of 3.

3 | RESULTS

The search strategy identified 23 822 hits (Figure 1). After removal of duplicates and screening based on title and abstract, 714 remained. After full text evaluation another 222 were excluded (Table S1) and 492 fulfilled our inclusion criteria. As a result of the restricted translation resources, we had to exclude 25 hits (Chinese n = 23; Spanish n = 2). Accordingly, we critically appraised 467 meta-analyses.

3.1 | Characteristics of included meta-analyses

The 467 meta-analyses included an overall total of 8231 randomized clinical trials with 2 199 462 randomized patients. From these meta-analyses, a total of 1087 outcomes were selected. A median of 6 trials (Interquartile range [IQR] 3-10) with a median total of 966 patients (IQR 434-1911) provided data for each selected outcome.

3.1.1 | Characteristics of the content of the meta-analyses: patients, interventions and comparators

A wide variety of interventions were evaluated in critically ill patients suffering from various illnesses (Table S2). We classified the

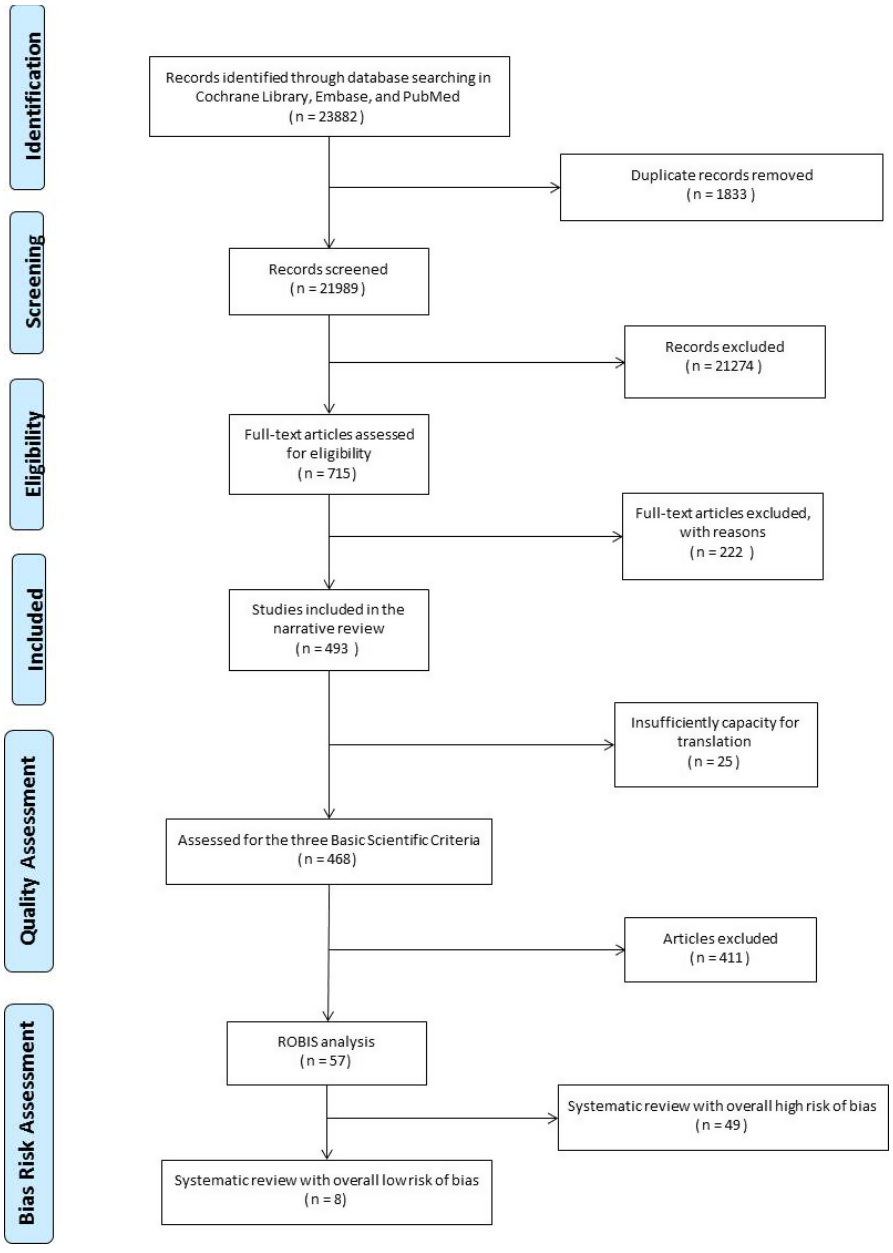

FIGURE 1 Modified PRISMA flow chart of search results and quality assessment [Colour figure can be viewed at wileyonlinelibrary.com]

interventions evaluated in all included meta-analyses to 11 organ systems, which the interventions were mainly supposed to target, and one additional miscellaneous category (Table 1). Most interventions were supposed to impact the pulmonary system (n = 111 meta-analyses; 24%), followed by the infection/inflammatory system (n = 78 meta-analyses; 19%) and the cardiovascular organ system (n = 60 meta-analyses; 13%). The most frequently evaluated intervention was the use of steroids (n = 20 meta-analyses; 5%).

3.1.2 | Characteristics of the content of the meta-analyses: outcomes

A total of 1087 dichotomous primary outcomes were selected: 254 meta-analyses reported 3 co-primary dichotomous outcomes, 112 meta-analyses reported two co-primary dichotomous outcomes and 101 meta-analyses reported one. Mortality was chosen as primary outcome in 393 meta-analyses (84.2%; Table S3).

3.2 | Quality assessment of meta-analyses

3.2.1 | Basic scientific requirements for any systematic review

The 3 basic scientific requirements of the availability of a protocol, the availability of a full search strategy, and the use of any bias risk assessment were evaluated in all 467 meta-analyses (Table S3). Unfortunately the conduct of meta-analyses has improved less than expected in recent years (Figure 2). Only 56 meta-analyses (12%) fulfilled all the 3 basic scientific requirements. Accordingly, 411 meta-analyses were considered at high risks of bias.

TABLE 1 Numbers of meta-analyses per main category according to target organ of the intervention

Target organ system of the intervention evaluated	"Meta-analyses" selected for inclusion
Airway	17
Pulmonary	111
Cardiovascular	60
Infection/Inflammation	87
Renal	38
Gastroenterology	71
Coagulation	12
Endocrinology	13
Haematology/Oncology	17
Neurology	9
Sedation/pain management	20
Miscellaneous	12
Total	467

The "use of a protocol" was claimed in 151 meta-analyses (32%), of which 96 meta-analyses (21%) actually referenced to an available protocol.

Any "search strategy" was reported in 461 meta-analyses (99%). Five meta-analyses (1%) did not report the numbers of databases searched; 18 meta-analyses (4%) searched only one database; 27 meta-analyses (6%) searched two databases; and 417 meta-analyses (89%) searched 3 or more databases. A total of 131 meta-analyses (28%) reported a full database-specific search string for 2 or more databases either in the main text or in the Supporting information.

The "use of any risk of bias assessment" was reported and conducted in 443 meta-analyses (96%). A total of 228 meta-analyses (49%) performed the risk of bias assessment using the Cochrane Collaboration tool.

3.2.2 | ROBIS evaluation

A full ROBIS evaluation was conducted in the 56 meta-analyses fulfilling the basic scientific requirements for any systematic review (Table 2 and for details Table S4). Independent assessments were in agreement on 207/224 (92%) domains.

A total of 53 meta-analyses (95%) were assessed to be at low risk of bias on the "study eligibility criteria" domain and 3 meta-analyses were assessed as having high risk of bias.

A total of 54 meta-analyses (96%) were assessed to be at low risk of bias on the "identification and selection of studies" domain, one meta-analysis was assessed as having unclear risk of bias and one meta-analysis as having high risk of bias.

A total of 48 meta-analyses (86%) were assessed to be at low risk of bias on the "data collection and study appraisal" domain, 4 meta-analyses (7%) were assessed as unclear risk of bias, and 4 meta-analyses (7%) were assessed as having high risk of bias.

Four meta-analyses (7%) were assessed to be at low risk of bias on "synthesis and findings" domain, one meta-analysis (1.8%) was assessed as unclear risk of bias, and 51 meta-analyses (91%) were assessed as having high risk of bias. The large majority of the meta-

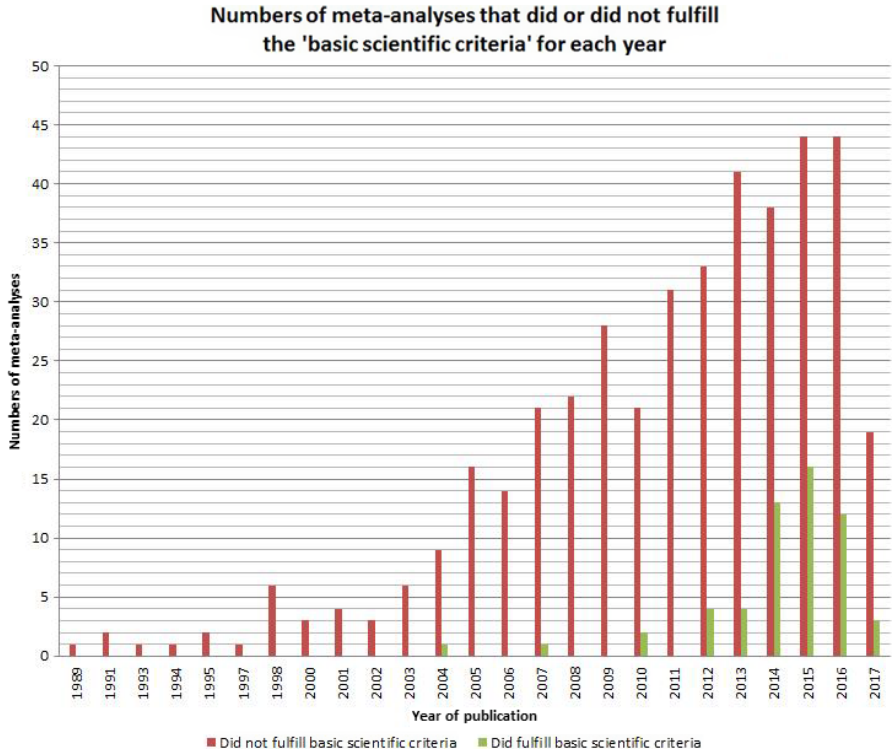

FIGURE 2 Numbers of meta-analyses that did or did not fulfill the "basic scientific criteria" for each year [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 ROBIS domains assessment

Year	Author	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
2004	Adhikari	☺	☺	☹	☹	☹
2007	Rabindranath	☺	☺	☹	☹	☹
2010	Dart	☺	☺	☺	☹	☹
2010	Kelly	☺	☺	?	☹	☹
2011	Pugh	☺	☺	☺	☹	☹
2012	Marti-Carvajal	☺	☺	☺	☹	☹
2012	Szakmany	☺	☺	☺	☹	☹
2012	Berton	☺	☺	☺	☹	☹
2012	Arrich	☺	☺	☹	☹	☹
2012	Ma	☺	☺	☺	☹	☹
2013	Sud	☺	☺	☺	☹	☹
2013	Haase	☺	☺	☺	☺	☺
2013	Ker	☺	☺	☺	☹	☹
2013	Shi	☺	☺	☺	☹	☹
2013	Santa Cruz	☺	☺	☺	☹	☹
2014	Blackwood	☺	☺	☺	☹	☹
2014	Ireland	☹	☺	?	☹	☹
2014	Ladeira	☺	☺	?	☹	☹
2014	López-Briz	☺	☺	?	☹	☹
2014	Burry	☺	☺	☺	☹	☹
2014	Tao	☺	☺	☺	☹	☹
2014	Burns	☺	☺	☺	☹	☹
2014	Bo	☺	☺	☺	☹	☹
2014	Strametz	☺	☺	☺	☹	☹
2014	Hermans	☺	☺	☺	☹	☹
2014	Huang	☺	?	☹	☹	☹
2014	Koster	☺	☺	☺	☺	☺
2014	Singh	☺	☺	☺	☹	☹
2015	Unverzagt	☺	☺	☺	☹	☹
2015	Andriolo	☺	☺	☺	☹	☹
2015	Bruder	☺	☺	☺	☹	☹
2015	Chen	☺	☺	☺	☹	☹
2015	Chacko	☺	☺	☺	☹	☹
2015	Aitken	☺	☺	☺	☹	☹
2015	Tian	☹	☺	☺	☹	☹
2015	Bloomfield	☺	☺	☺	☹	☹
2015	Hua	☹	☺	☺	☹	☹
2015	Alkhawaja	☺	☺	☺	☹	☹
2015	Tokmaji	☺	☺	☺	☹	☹
2015	Hu	☺	☺	☺	☹	☹
2015	Volbeda	☺	☺	☺	☺	☺
2015	Faria	☺	☺	☺	☹	☹
2015	Ruan	☺	☺	☺	☹	☹
2016	Allingstrup	☺	☺	☺	☹	☹

(Continues)

TABLE 2 (Continued)

Year	Author	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
2016	Hodgson	☺	☺	☺	☹	☹
2016	Wang	☺	☺	☺	☹	☹
2016	Cortegiani	☺	☺	☺	☹	☹
2016	Brass	☺	☺	☺	☹	☹
2016	Arthur	☺	☺	☺	☹	☹
2016	Fayad	☺	☺	☺	☹	☹
2016	Lai	☺	☺	☺	☹	☹
2016	Cruickshank	☺	☹	☺	☹	☹
2016	Wikkelsø	☺	☺	☺	☹	☹
2017	Mesgarpour	☺	☺	☺	☹	☹
2017	Corley	☺	☺	☺	☺	☺
2017	Borthwick	☺	☺	☺	☹	☹

☺ = low risk; ☹ = high risk; ? = unclear risk.

analyses failed to report their findings in the perspective of the bias risk assessments of the included randomized clinical trials.

The overall ROBIS bias risk assessment resulted in 4 meta-analyses (0.9%) of a total of 467 evaluated which were at low risk of bias in all 4 domains of the ROBIS assessment.

3.2.3 | PRISMA reporting

All 27 items from the PRISMA checklist were evaluated for each of the 56 meta-analyses fulfilling the basic scientific requirements for a systematic review. The median score of the meta-analyses reports was 27 (range 24-27). A total of 41 meta-analyses (73%) reports scored positive on all 27 items of the PRISMA checklist (Table S5).

4 | DISCUSSION

We identified a total 467 meta-analyses of interventions used in intensive care medicine to be potentially perceived as reaching for the highest level of evidence. A total of 56 (12%) of 467 meta-analyses fulfilled the 3 basic requirements for a systematic review. Moreover, only 4 of these meta-analyses or 0.9% of the total were evaluated to be overall low risk of bias by a full ROBIS assessment.

No previous study has critically appraised all meta-analyses of interventions in intensive care medicine. We found that the chances are 99.1% that any meta-analysis on an intervention in intensive care medicine does not reach for the highest level of evidence. Therefore, caregivers and authorities should be warned not automatically to implement conclusions of a meta-analysis, as the requirements for a well-performed systematic review are rarely fulfilled.[22] Especially, the consideration of the fourth domain of ROBIS, ie synthesis and findings, is of key importance. We suggest that authors consider the ROBIS criteria before the conduct of each systematic review, and that editors of journals demand fulfilment of overall low risk of bias of ROBIS criteria mandatory for publication. Such a measure could serve as a quality mark and reduce the large numbers of non-systematic and flawed meta-analyses. Focusing attention towards overall low risk of bias of systematic reviews may reduce harm as flawed meta-analyses do not sufficiently emphasize the reliable results of well-performed randomized trials but may purport biased intervention effect estimates that overestimates beneficial effects and underestimates harmful effects.[7,23] This may be one way to prevent evidence-based medicine being hijacked and systematic reviews being devaluated.[1,24,25]

Intensive care medicine involves acutely and severely ill patients with high mortality and morbidity rates. Even small relative risk reductions may have large clinically relevant effects and statistical significance is far more easily obtained in the presence of large control event rates when using conventional statistical methods for meta-analysing data. We consider this important since positive results are far more easily published compared to neutral or negative results.[26,27] So, specifically the medical specialty of critical care is at risk for implementing statistically significant intervention effects if insufficiently critically appraised. The last decades intensive care medicine has been faced with increasing number of interventions initially considered beneficial, propagated by guidelines and implemented in practice. Numerous examples of initially adopted interventions in intensive care were abandoned again once trials with low risk of bias emerged.[10-13] Our study confirms that some interventions have been evaluated far more extensively compared to other less popular interventions while some other accepted treatments have never been tested by randomized trials.[28] Large control event rates increase the risk of identifying interventions with potentially false positive premature effects explaining previous erroneous implementations. In 1999 Ferreira et al[29] showed that perceptions of critical care physicians were frequently not in line with the evidence. Apparently, physicians are not appropriately aware which interventions have been rigorously evaluated by systematic reviews, but in turn this does not help when intensivists have insufficient skills for recognition and critical appraisal of the evidence.

There are several studies suggesting that the risk of bias of trials and studies has decreased, and quality has improved over the years, while at the same time there remains ample room for improvement.[21,30] Several initiatives such as the Cochrane Collaboration improved reporting and PRISMA have promoted such improvements. Others argue that the large majority of current research efforts are wasted.[31-36] Not only methods and reporting fall short, but also evaluation by peer-review and doubtful incentives to publish contribute.[27] Figure 2 illustrates that even in recent years, after guidelines for sound conduct and reporting of systematic reviews have emerged, many reviews do still not fulfil the basic scientific criteria. Not only authors need to improve, but maybe it is more important that editors raise the bar of quality criteria.

Preferred reporting items for systematic reviews and meta-analyses has contributed to improved reporting of systematic reviews by improving awareness of methodological flaws among review authors.[16] Although all PRISMA items improve transparency, most PRISMA items, however, do not relate to risk of bias of systematic reviews. All 56 meta-analyses were evaluated by PRISMA checklist and 41 meta-analyses (73%) scored all 27 items of the PRISMA checklist positive. Though, we might have judged adherence to PRISMA items rather mild as we judged positive when only part of an item was reported. While 41 meta-analyses had a full PRISMA score, only 4 meta-analyses had an overall low risk of bias ROBIS score. Apparently, the PRISMA checklist is insufficiently capable of distinguishing between systematic reviews with overall low or high risk of bias. The incorporation of a bias risk assessment in the main analysis appeared to be the major discriminating quality domain in the ROBIS tool. We would strongly argue that both PRISMA-Protocol and PRISMA should be revised to incorporate a separate item explicitly requiring authors that the primary analyses and conclusions of a systematic review are based on the results of the trials with overall low risk of bias, or equally important that this needs to be acknowledged, in the presence of insufficient or no such data.

There are several limitations associated with this systematic overview and critical appraisal. First, we have used two steps for assessment of the risk of bias of systematic reviews. The first step of 3 basic scientific requirements including a published protocol, a full search strategy and any bias risk assessment may seem common sense since a protocol is essential for any scientific endeavour, a full search strategy is key for being reproducible and systematic, and evaluation of bias risk is necessary to acknowledge potential overestimation of benefit and underestimation of harm. These 3 basic requirements have, however, never been suggested as merged criteria in any milestone publication.

Second, ideally all selected meta-analyses should have been scrutinized by a full ROBIS evaluation. However, we deemed this as a superfluous workload easily reduced by the previous suggested basic set of requirements. Any meta-analysis not passing these minimal requirements would by definition fail to qualify for overall low risks of bias on all 4 ROBIS domains.

Third, we have evaluated all systematic reviews according to the PRISMA checklist. Many items on this list include several issues. The items were scored positive when part of or all the issue(s) in that item were reported and negative if none of those issues were reported. Maybe we should have been harsher and only have scored positive when all issues of one item were reported. However, frequently some issues were considered not applicable or not used for a specific meta-analysis which would have complicated such a method of scoring.

Fourth, we could have selected to use AMSTAR in our assessments of the reviews.[37,38] Future studies should compare our methods of assessment with AMSTAR II. However, both methodologies lack proper assessment of the risks of imprecision (GRADE) and none of them recommend methods like Trial Sequential Analysis to control random errors.[39,40]

Fifth, in the protocol we aimed to include all studies without any language restrictions. Unfortunately, we had insufficient capacity for translations so that we were forced to exclude 25 reports.

Sixth, the selection of studies and data-extraction were not conducted by two researchers independently. This might have led to errors.

5 | CONCLUSIONS

Basic requirements for sound reproducible science were not fulfilled in 411 (88%) of all meta-analyses in intensive care medicine, and another 52 meta-analyses (11%) had overall high risk of bias. Eventually, only 4 (0.9%) of meta-analyses of interventions in intensive care medicine have overall low risk of bias based on ROBIS assessments. We suggest that any recommendation considering intensive care medicine should be revised for the content being based on flawed meta-analyses potentially lowering the level of evidence for specific interventions.

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The manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and discrepancies from the study as planned have been explained.

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHORS' CONTRIBUTION

All authors: contributed to the design of the protocol, data analysis and writing of the manuscripts.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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